offered to those with one or more risk factors. Prestroke risk assessment is simple and feasible, being supported by recent publications validating that the high prestroke CHA_2DS_2-VASc score predicts worse long-term outcome even in patients with sepsis but without AF.[9,10]

Finally, Walkey et al[3] also highlight the potential of upstream therapy to tackle sepsis-associated new-onset AF. Sepsis triggers an inflammatory response, and this may directly increase the risk of AF via increased catecholamine release. Previous work has demonstrated the significant rise in C-reactive protein level prior to the onset of sepsis-induced AF.[2] Thus, potential suppression of overwhelming inflammation may have a role in reducing the incidence of, or even preventing, subsequent arrhythmia. For example, the potential of perioperative use of corticosteroids in cardiac surgery to prevent AF has been promising.[11] In sepsis, systemic steroids, however, may be counterproductive, so other options need to be found. Given the high prevalence of AF, the challenge is to accurately identify those patients who have an increased propensity for developing AF and those at particular risk of complications. Indeed, sepsis may simply be the catalyst to expose the vulnerability of developing this arrhythmia (and its complications).

In conclusion, Walkey et al[3] demonstrate a high incidence of occurrence of further AF in sepsis survivors who had previously experienced acute sepsis-associated AF. These patients also exhibited higher rates of mortality and stroke, and heart failure risk. As survival of sepsis improves, there is the need to diligently identify those at risk for AF recurrence and its complications.

References

1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7):1303-1310.
2. Meierhenrich R, Steinhilber E, Eggermann C, et al. Incidence and prognostic impact of new-onset atrial fibrillation in patients with septic shock: a prospective observational study. *Crit Care*. 2010; 14(3):R108.
3. Walkey AJ, Hammill BG, Curtis LH, Benjamin EJ. Long-term outcomes following development of new-onset atrial fibrillation during sepsis. *Chest*. 2014;146(5):1187-1195.
4. Lowres N, Neubeck L, Redfern J, Freedman SB. Screening to identify unknown atrial fibrillation. A systematic review. *Thromb Haemost*. 2013;110(2):213-222.
5. Cotter PE, Martin PJ, Ring L, Warburton EA, Belham M, Pugh PJ. Incidence of atrial fibrillation detected by implantable loop recorders in unexplained stroke. *Neurology*. 2013;80(17):1546-1550.
6. Franks Z, Campbell RA, Vieira de Abreu A, et al. Methicillin-resistant *Staphylococcus aureus*-induced thrombo-inflammatory response is reduced with timely antibiotic administration. *Thromb Haemost*. 2013;109(4):684-695.
7. De Caterina R, Husted S, Wallentin L, et al. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis—Task Force on Anticoagulants in Heart Disease. *Thromb Haemost*. 2013;110(6):1087-1107.
8. Pisters R, Nieuwlaat R, Lane DA, Crijns HJ, Lip GY. Potential net clinical benefit of population-wide implementation of apixaban and dabigatran among European patients with atrial fibrillation. A modelling analysis from the Euro Heart Survey. *Thromb Haemost*. 2013;109(2):328-336.
9. Ntaios G, Lip GY, Makaritsis K, et al. $CHADS_2$, $CHA_2S_2DS_2$-VASc, and long-term stroke outcome in patients without atrial fibrillation. *Neurology*. 2013;80(11):1009-1017.
10. Tu HT, Campbell BC, Meretoja A, et al. Pre-stroke CHADS2 and CHA2DS2-VASc scores are useful in stratifying three-month outcomes in patients with and without atrial fibrillation. *Cerebrovasc Dis*. 2013;36(4):273-280.
11. Dieleman JM, van Paassen J, van Dijk D, et al. Prophylactic corticosteroids for cardiopulmonary bypass in adults. *Cochrane Database Syst Rev*. 2011;(5):CD005566.

Fibroproliferative ARDS in the Era of Low-Tidal-Volume Ventilation

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Though mortality in ARDS has been improving, in unselected populations, mortality may still be as high as 40%.[1] Patients with ARDS infrequently die of refractory hypoxemia and more often die due to sepsis and multiorgan failure, both complications of prolonged mechanical ventilation (MV). Inability to discontinue MV likely reflects disordered lung repair which may in part be due to excessive fibroblast activation. Markers of fibroblast activation such as procollagen III[2] and transforming growth factor-β are elevated early in ARDS[3] and are associated with increased mortality. Factors that have contributed to better ARDS outcomes include less-injurious MV strategies, judicious fluid management, and generally improved supportive care.[4,5] As more patients with ARDS are surviving their acute illness, long-term outcomes for these patients have garnered increased attention. It has been shown in multiple studies that survivors of ARDS continue to have reduced health-related quality of life (HRQoL)

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for years after their acute illness.[6] The cause of reduced HRQoL has most often been attributed to neuromuscular and psychosocial dysfunction.[6] The contributions of residual pulmonary dysfunction have received less attention and a National Institutes of Health-sponsored ARDS workshop failed to identify fibroproliferation as a significant contributor to morbidity and mortality in the era of low-tidal-volume ventilation.[7]

However, there is accumulating data that despite low-tidal-volume ventilation, persistent pulmonary dysfunction in survivors of ARDS is a significant contributor to reduced HRQoL. The incidence of persistent pulmonary dysfunction in survivors of ARDS depends on how it is defined. If radiologic abnormality is used as the basis of defining persistent pulmonary dysfunction, the incidence is significantly higher. CT scanning of survivors of ARDS demonstrates reticular infiltrates, often with an anterior distribution, in up to 85% of patients, which persist out to at least 5 years.[8,9] If one uses physiologic assessment with pulmonary function testing to define persistent pulmonary dysfunction, the incidence is smaller though not trivial. Multiple studies have reported that while the median FVC is normal in long-term survivors of ARDS, about 25% will have values below the normal range.[6] Similar findings were reported for FEV_1, total lung capacity, and diffusing capacity for carbon monoxide. The data relating pulmonary dysfunction to diminished HRQoL is conflicting. Some studies have been able to demonstrate associations of decreased pulmonary function testing parameters with poorer scores on components of the Short-Form 36 as well as the St. George's Respiratory Questionnaire[10] while others have attributed much of the HRQoL changes to neuromuscular weakness.[6] One study that measured respiratory muscle strength in survivors of ARDS found it to be normal.[8]

To improve long-term outcomes, several investigators have attempted to identify factors during the acute illness that are associated with adverse long-term outcomes. With respect to this issue, Burnham and colleagues[11] publish data in this issue of *CHEST* (see page 1196) that supplements previous evidence linking physiologic abnormalities present on the day of ARDS onset with long-term outcomes. In a retrospective analysis of prospectively collected data from an ARDS clinical trial, they found static respiratory system compliance measured on the first day or averaged over the first 14 days of MV had an inverse correlation with the severity of reticular changes on chest high-resolution CT (HRCT) scan. HRCT scan reticular changes are thought to most often reflect areas of tissue fibrosis. This study complements data previously published by the same group in which they showed that HRCT scanning at day 14 correlated with poorer HRQoL at 6 months.[12] The strengths of the present study include a prospective collection of data, an explicit protocol for low-tidal-volume MV and weaning, as well as a defined protocol for performance of HRCT scan and interpretation by blinded readers. One significant limitation of the study is that the included subjects were a "convenience cohort" that was substantially different than the cohort of patients who were eligible but were not enrolled. The excluded patients had more severe physiologic derangements, which precluded safe transport for an HRCT scan and much higher 28-day mortality. This limits generalizability of the studies' findings and raises the question of whether a noninvasive physiologic measure that could be assessed at the bedside, such as dead-space fraction or oxygenation index, would work as well as an HRCT scan in identifying patients destined for long-term morbidity. In addition, it is not clear from this work whether compliance abnormalities measured in the first 14 days reflect pulmonary edema, an exuberant fibroproliferative response,[3] or most likely a combination of both.

Nevertheless, the studies by Burnham and colleagues[11,12] suggest that the severity of physiologic derangement in early ARDS impacts long-term HRQoL in survivors despite use of low-tidal-volume ventilation. Prior studies have identified speed of lung-injury resolution, duration of MV, corticosteroids, neuromuscular blocking agents, glycemic control, and sedatives as contributors to adverse long-term outcomes in survivors of ARDS. These observations highlight the importance of appropriate decision-making in the early phase of ARDS in an effort to not just improve survival for patients with ARDS but optimize HRQoL for the long-term, even in the era of low-tidal-volume ventilation. A second inference from the studies by Burnham and colleagues[11,12] is that HRCT scanning may be useful in identifying patients at risk for poorer long-term HRQoL. However, at this time, identifying such patients has no obvious therapeutic implications and so it is difficult to endorse routine HRCT scanning in the management of survivors of ARDS. That would have to be reconsidered if effective interventions targeting fibroproliferation are identified in the future.

References

1. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med*. 2005;353(16):1685-1693.

2. Clark JG, Milberg JA, Steinberg KP, Hudson LD. Type III procollagen peptide in the adult respiratory distress syndrome. Association of increased peptide levels in bronchoalveolar lavage fluid with increased risk for death. *Ann Intern Med*. 1995;122(1): 17-23.
3. Synenki L, Chandel NS, Budinger GR, et al. Bronchoalveolar lavage fluid from patients with acute lung injury/acute respiratory distress syndrome induces myofibroblast differentiation. *Crit Care Med*. 2007;35(3):842-848.
4. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000;342(18):1301-1308.
5. Wiedemann HP, Wheeler AP, Bernard GR, et al; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354(24):2564-2575.
6. Herridge MS, Tansey CM, Matté A, et al; Canadian Critical Care Trials Group. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364(14):1293-1304.
7. Spragg RG, Bernard GR, Checkley W, et al. Beyond mortality: future clinical research in acute lung injury. *Am J Respir Crit Care Med*. 2010;181(10):1121-1127.
8. Masclans JR, Roca O, Muñoz X, et al. Quality of life, pulmonary function, and tomographic scan abnormalities after ARDS. *Chest*. 2011;139(6):1340-1346.
9. Wilcox ME, Patsios D, Murphy G, et al. Radiologic outcomes at 5 years after severe ARDS. *Chest*. 2013;143(4):920-926.
10. Heyland DK, Groll D, Caeser M. Survivors of acute respiratory distress syndrome: relationship between pulmonary dysfunction and long-term health-related quality of life. *Crit Care Med*. 2005; 33(7):1549-1556.
11. Burnham EL, Hyzy RC, Paine R III, et al. Detection of fibroproliferation by chest high-resolution CT scan in resolving ARDS. *Chest*. 2014;146(5):1196-1204.
12. Burnham EL, Hyzy RC, Paine R III, et al. Chest CT features are associated with poorer quality of life in acute lung injury survivors. *Crit Care Med*. 2013;41(2):445-456.

Choosing Wisely in Critical Care

Maximizing Value in the ICU

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Overuse of medical tests and treatments wastes health-care resources and leads to unnecessary complications, while underuse results in delayed or missed diagnoses and treatment opportunities.[1] Such problems are well recognized, and there have been multiple attempts to correct inappropriate diagnostic testing and treatment over the past several decades.[2] However, sustainable solutions have proven to be elusive.[3]

Several years ago, medical ethicist Howard Brody, MD, PhD, suggested that physicians take leadership in declaring what tests and interventions should be used less commonly. He recommended that professional societies develop a specialty's top five list of "diagnostic tests or treatments that are very commonly ordered, that are among the most expensive services provided, and that have been shown by the currently available evidence not to provide any meaningful benefit to at least some major categories of patients."[4] Dr Brody's vision gave rise to the Choosing Wisely Campaign, an effort designed to empower providers and patients by charging professional societies to develop lists of five common medical services "that patients and physicians should question."[5]

The top five list for critical care medicine was developed by the Critical Care Societies Collaborative (CCSC), a consortium representing the four professional societies

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Detection of Fibroproliferation by Chest High-Resolution CT Scan in Resolving ARDS

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BACKGROUND: In ARDS, the extent of fibroproliferative activity on chest high-resolution CT (HRCT) scan has been reported to correlate with poorer short-term outcomes and pulmonary-associated quality of life. However, clinical factors associated with HRCT scan fibroproliferation are incompletely characterized. We questioned if lung compliance assessed at the bedside would be associated with fibroproliferation on HRCT scans obtained during the resolution phase of ARDS.

METHODS: We used data from a published randomized, controlled clinical trial in ARDS. All patients were cared for using a low tidal volume strategy. Demographic data and ventilator parameters were examined in association with radiologic scores from chest HRCT scans obtained 14 days after diagnosis.

RESULTS: Data from 82 patients with ARDS were analyzed. Average static respiratory compliance over the first 14 days after diagnosis was inversely associated with chest HRCT scan reticulation ($\rho = -0.46$); this relationship persisted in multivariable analysis including APACHE (Acute Physiology and Chronic Health Evaluation) II scores, initial Pao_2/Fio_2, pneumonia diagnosis, and ventilator days. Average static respiratory compliance was also lower among patients with bronchiectasis at day 14 ($P = .007$). Initial static respiratory compliance obtained within the first day after ARDS diagnosis was correlated inversely with the presence of HRCT scan reticulation ($\rho = -0.38$) and was lower among patients who demonstrated bronchiectasis on the day 14 HRCT scan ($P = .008$).

CONCLUSIONS: In patients with ARDS, diminished lung compliance measured bedside was associated with radiologic fibroproliferation 14 days post diagnosis. Establishing factors that predispose to development of excessive fibroproliferation with subsequent confirmation by chest HRCT scan represents a promising strategy to identify patients with ARDS at risk for poorer clinical outcomes.

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ABBREVIATIONS: APACHE = Acute Physiology and Chronic Health Evaluation; Cstat = static respiratory compliance; GGO = ground-glass opacification; HRCT = high-resolution CT; IPO = intense parenchymal opacification; PEEP = positive end-expiratory pressure; PPlat = plateau pressure; SOFA = Sequential Organ Failure Assessment; $\dot{V}_E corr$ = corrected minute ventilation; V_T = tidal volume

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Although mortality in ARDS has improved with the use of a low tidal volume (V_T) ventilator strategy,[1] pulmonary fibroproliferation remains an observable clinical phenomenon in a subset of patients,[2] in whom it has been associated with higher mortality and ventilator dependence.[2-5] Moreover, recent data support a negative relationship between fibroproliferation and health-related quality of life in ARDS survivors.[6] Nevertheless, factors influencing the development of fibroproliferation are not well understood.

Previous investigations have used chest high-resolution CT (HRCT) scans as a tool in very early ARDS (< 1 week)[7-9] to identify patients with fibroproliferative radiologic abnormalities who are likely to suffer poorer short-term outcomes, such as mortality. However, studies to systematically assess fibroproliferation via HRCT scan during resolving ARDS (> 1 week after diagnosis) have not been performed. Therefore, the specific patient and clinical factors that underlie the development of radiologic fibroproliferation have not been clearly established. It is possible that certain clinical factors associated with fibroproliferation are modifiable and that novel treatment modalities could be developed to limit excessive fibroproliferation. Moreover, using HRCT scanning during the resolution phase of ARDS to identify patients who have excessive fibroproliferation may be a useful strategy to predict who will have an impaired quality of life after hospital discharge.

The mechanical ventilation strategy used to care for patients with ARDS is one clinical factor that may be implicated in the fibroproliferative response. In laboratory investigations focused on characterizing ventilator-associated lung injury, mechanical ventilation has been linked to increased inflammation, altered extracellular matrix composition, enhanced production of profibrotic molecules, and promotion of frank fibrosis within the lung.[10-12] Analogous observations have been reported in mechanically ventilated patients with ARDS.[13-15] Although large clinical trials have reassured clinicians that a low V_T strategy[1] and judicious use of positive end-expiratory pressure (PEEP)[16,17] promote improved short-term outcomes in ARDS, including survival, their effects on early development of fibroproliferation remain unclear. Importantly, recent investigations using chest CT scanning have suggested that lung inhomogeneities typical of ARDS function as "stress raisers" that may locally increase the susceptibility to ventilator-induced lung injury from externally applied pressure or volume,[18] highlighting the need to further delineate and characterize the effects of mechanical ventilation on ARDS pathophysiology.

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We sought to characterize clinical factors associated with the development of fibroproliferative changes on 14-day chest HRCT scan in a cohort of patients with ARDS enrolled in a multicenter clinical trial.[19] We hypothesized that patients with ARDS with the poorest respiratory compliance, who were exposed to an increased duration and intensity of PEEP and plateau pressure (PPlat), would display evidence of increased chest HRCT scan fibroproliferation, as evidenced by increased reticulation and bronchiectasis, 14 days after diagnosis.

Materials and Methods

Data were derived from a National Institutes of Health-sponsored double-blind randomized controlled trial for acute lung injury of granulocyte macrophage-colony stimulating factor[19] that enrolled patients from 2004 to 2009. The study was conducted in accordance with the amended Declaration of Helsinki. Local institutional review boards approved the protocol (institutional review board of the University of Michigan Medical School approval number 2003-0430, Emory University institutional review board approval number 734-2004, Colorado Multiple Institutional Review Board, approval number 06-0573), and written informed consent was obtained from all patients.

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Subjects Examined

Individuals meeting criteria for ARDS using the American-European Consensus Conference definition were considered for enrollment in the parent study.[20] Patients who had evidence of preexisting lung disease (GOLD [Global Initiative for Chronic Obstructive Lung Disease] stages III or IV COPD, or interstitial lung disease from any cause) were excluded. Subjects received standardized ventilator management according to the ARDS Network protocol, targeting a V_T of 6 mL/kg ideal body weight and PPlat < 30 cm H_2O.[1] Weaning was similarly based upon protocols developed through the ARDS Network and implemented by respiratory therapists.

For the present study, parent study data were included from patients with chest HRCT scans who were followed clinically for 28 days after diagnosis (or until death or discharge). Clinical data from the parent trial were used in our analyses. Detailed information regarding patients from the parent study who were excluded from the present investigations may be found in e-Table 1. Predicted body weight was calculated using patient height and sex by established methods.[1] Ventilator parameters, including V_T (mL), PEEP (cm H_2O), and PPlat (cm H_2O) were recorded

daily in patients on mechanical ventilation, along with the number of mechanically ventilated days. Average V_T, PEEP, and PPlat exposures prior to chest HRCT scan were calculated by summing all available daily values for these parameters while patients were on mechanical ventilation and dividing by the total number of mechanically ventilated days prior to the chest HRCT scan. Static respiratory compliance (Cstat) (mL/cm H_2O) was calculated using collected ventilator variables.

HRCT Scans

Chest HRCT scans were performed at 14 (SD, 2) days post ARDS diagnosis. Enrolled patients who were mechanically ventilated at the time of the chest HRCT scan were placed on ≥ 10 cm H_2O PEEP during the HRCT scan[21]; all images were obtained at end-inspiration. Chest HRCT scan sections were obtained with 1.25-mm collimation and reconstructed using a high-spatial-frequency algorithm. All images were viewed at window settings optimized for assessment of lung parenchyma (window width, 1,300 Hounsfield units; window level, −500 Hounsfield units). Completed HRCT scans were evaluated by two chest radiologists using established methods.[8,22] Radiologists had previously calibrated their scoring strategy by concomitantly reading chest HRCT scans obtained early in the study (n = 8) to ensure consistent grading of subsequently performed HRCT scans. Five levels of imaging were assessed: aortic arch, 1 cm above the dome of the right hemidiaphragm, and three additional levels equally spaced between these two levels. At each level, lungs were divided into anterior and posterior zones by drawing a horizontal line across the image, creating four quadrants for analysis per level. Radiologic patterns that were quantified in each quadrant included reticulation, ground-glass opacification (GGO), and intense parenchymal opacification (IPO). Reticulation was defined as evidence of innumerable interlacing shadows that were fine, intermediate, or coarse, with associated distortion of the lung architecture, and taken to represent fibrosis. GGO was defined as a hazy increase in lung attenuation with preservation of bronchovascular markings. IPO was characterized by a homogeneous increase in lung attenuation with obscuration of the bronchovascular structures in which an air bronchogram may have been present. The extent of involvement for each pattern was assigned a numerical score, where 0 = no involvement; 1 = < 5% involvement/minimal/not normal; 2 = 5% to 25% involvement; 3 = 26% to 49% involvement; 4 = 50% to 75% involvement; and 5 = > 75% involvement. For each radiologic pattern, the average score (range, 0-20) was calculated by summing all quadrant values for each slice, adding these values together, and dividing by the number of slices with complete data. Bronchiectasis was scored as present (1) or absent (0) on each slice, with the total bronchiectasis score calculated by summing values over all slices (range, 0-5). Missing data were scored as 0.[6]

Statistical Analyses

Analyses with continuous data were performed with Student *t* test or the Wilcoxon rank sum test. Categorical data were analyzed using Fisher exact test. Correlation coefficients between continuous data were calculated using Spearman correlation coefficient. Linear or logistic regression was used to determine the association between clinical variables, including ventilator parameters, and HRCT scan scores at the 14-day time point. Two-sided *P* values of < .05 were deemed to be significant. JMP software (version 9) was used in analyses.

TABLE 1] Baseline Characteristics of Patients With ARDS

Feature	Value
Age, y	47 (14)
Sex, % men	56
BMI, kg/m²	30 (7)
Race, % white	87
ARDS severity, %	
Mild (300 ≤ Pao_2/FIo_2 < 200)	13
Moderate (200 ≤ Pao_2/FIo_2 < 100)	49
Severe (Pao_2/FIo_2 ≤ 100)	38
Minute ventilation, L/min (corrected for $Paco_2$)[a]	11.6 (4.3)
Percentage of patients with severe ARDS according to minute ventilation, corrected	64
Static compliance, mL/cm H_2O[b]	40 (22)
Percentage of patients with severe ARDS according to static compliance	68
Primary ARDS risk factor, %	
Sepsis	28
Aspiration	13
Pneumonia	35
Other	24
SOFA, wk 1	10.7 (4.0)
APACHE II	18 (7)
Survival at 28 d, %	96
Ventilator-free d	12 (8)
ICU-free d	8 (8)
Hospital-free d	5 (6)

N = 82 with 14-d chest HRCT scans and complete follow-up. Values are means (SD) unless otherwise noted. Earliest values available for patients after initiation of mechanical ventilation presented. APACHE = Acute Physiology and Chronic Health Evaluation; HRCT = high-resolution CT; SOFA = Sequential Organ Failure Assessment.

[a]Minute ventilation calculated correcting for $Paco_2$ using the following equation: [minute ventilation × $Paco_2$]/40. Severe ARDS categorized as minute ventilation > 10 L/min.

[b]Static compliance calculated with plateau, positive end-expiratory pressure, and tidal volume values collected within 24 h of ARDS diagnosis. Severe ARDS categorized as static compliance < 40.

Results

The parent study enrolled 132 patients. Eight patients died before the 14-day HRCT scan could be completed. In 42 of the patients, HRCT scan was not performed because of the patient's being unable to safely tolerate the procedure, the attending physician being unwilling to proceed with study, or investigator withdrawing the patient from the study. Therefore, the cohort included 82 patients who had a chest HRCT scan completed at day 14.

Baseline characteristics for the patients who had chest HRCT scans available are highlighted in Table 1. A similar number of women and men were in the cohort; the majority of patients were white. Survival at 28 days was 96%. On enrollment, the majority of patients had either moderate or severe ARDS by Pao_2/FIo_2 criteria.[23] Using an initial Cstat value of < 40, 68% (36 of 53) of patients were categorized as having severe ARDS, whereas initial corrected minute ventilation ([$\dot{V}Ecorr$] > 10 L/min)

categorized 64% (47 of 73) as having severe ARDS. Twelve of the initial 82 patients (15%) had a Pao_2/Fio_2 ratio of ≤ 100 and $\dot{V}Ecorr$ of ≥ 13 L/min, which would place them in the higher-risk ARDS subgroup.[23] At 14 days, in the 42 patients who remained on mechanical ventilation, 5% had a Pao_2/Fio_2 ratio of ≤ 100, whereas 79% had $\dot{V}Ecorr$ that would place them in the severe ARDS category.

For comparison, characteristics of patients from the parent study who were excluded from these investigations indicated nonsignificant differences in terms of age, sex, and ARDS risk factors; excluded patients were significantly less likely to be white. ARDS severity by either initial Pao_2/Fio_2 or $\dot{V}Ecorr$ did not differ; however, a higher percentage of patients with severe ARDS based on Cstat ($P = .01$) was observed in the excluded group. APACHE (Acute Physiology and Chronic Health Evaluation) II and Sequential Organ Failure Assessment (SOFA) scores indicated a greater severity of illness in excluded patients, with significantly poorer 28-day survival (61%, $P < .0001$ vs included patients). Please see e-Table 1 for additional details.

In terms of ventilator measurements, the average Vt exposure indexed to predicted body weight (7.2 mL/kg) was increased relative to the goal of 6 mL/kg (Table 2). Both the initial and average Cstat at day 14 would categorize these patients as having severe ARDS. We did not observe significant associations between initial or average Cstat with BMI, ARDS severity, or ARDS risk factor. Comparing physiologic data between included and excluded patients revealed nonsignificant differences in terms of Vt (with or without indexing to predicted body weight) and PEEP values obtained within the first 24 h of ARDS diagnosis. Notably, initial PPlat was higher ($P = .04$) and initial Cstat was lower ($P = .01$) in excluded patients.

No direct correlations with baseline clinical characteristics including age, sex, race, APACHE II, total SOFA score at week 1, and Pao_2/Fio_2 ratio on date of enrollment and individual day HRCT scan scores were observed. A diagnosis of pneumonia as a primary or secondary ARDS risk factor (yes or no) correlated with higher 14-day HRCT scan reticulation (5.1 [SD, 3.3] vs 3.3 [SD, 3.2], $P = .04$) and bronchiectasis (1.3 [SD, 1.8] vs 0.4 [SD, 0.98], $P = .01$) scores. Reticulation was observed in 87% (71 of 82), whereas bronchiectasis was observed in 34% of all patients (28 of 82) (Table 3). Average reticulation and bronchiectasis scores were most elevated in the basilar regions of the chest (Fig 1).

Analyses were performed examining mechanical ventilation characteristics in relationship to 14-day chest HRCT scan individual scores (Table 4). Average daily PPlat exposure was associated with both HRCT scan reticulation ($\rho = 0.52$) and bronchiectasis ($\rho = .42$) (Figs 2A-2C). Average Cstat was similarly associated with HRCT scan reticulation ($\rho = -0.46$) but less strongly with bronchiectasis ($\rho = -0.31$) (Figs 2D-2F). Both PPlat exposure and Cstat were also associated with HRCT scan GGO ($\rho = 0.48$ and $\rho = -0.44$, respectively). Days on the ventilator correlated only with HRCT scan IPO scores ($\rho = 0.55$). Average daily PEEP correlated weakly with HRCT scan scores, whereas average daily Vt exposure did not correlate with any radiologic pattern.

Secondary analyses were performed examining correlations between highest single recorded ventilator measurement obtained during the first 14 days after ARDS diagnosis and the HRCT scan scores. Similar to what was observed with average exposure values, the single highest PPlat measurement was associated with 14-day reticulation ($\rho = 0.33$) and bronchiectasis ($\rho = 0.33$) scores (Fig 3A, Table 5). The highest single recorded PPlat value was also greater among patients with ARDS

TABLE 2] Ventilator Characteristics of Enrolled Patients

Characteristic	Vt, mL	Vt Indexed to Predicted Body Weight, mL/kg	PPlat, cm H_2O	PEEP, cm H_2O	Cstat, mL/cm H_2O
Unique value within 24 h of ARDS diagnosis	555 (137)	8.6 (2.2)	24 (6)	8.5 (3.6)	40 (22)[a]
Highest unique value prior to day 14	622 (138)	9.6 (2.3)	29 (6)	12.3 (3.7)	n/a
Average value prior to day 14	465 (93)	7.2 (1.5)	23 (4)	8.2 (2.1)	34 (13)

Values are means (SD). Cstat = static respiratory compliance; n/a = not applicable; PEEP = positive end-expiratory pressure; PPlat = plateau pressure; Vt = tidal volume.
[a]Data from 53 subjects with ARDS available at this time point.

TABLE 3] Scores for Individual Chest HRCT Scan Patterns Obtained at 14 Days After ARDS Diagnosis

Pattern	Mean Value (SD)	Median Value (IQR)
Reticulation	4.4 (3.9)	3.4 (0.6, 6.8)
Ground-glass opacification	6.6 (4.8)	5.8 (3.5, 8.8)
Intense parenchymal opacification	4.2 (3.5)	3.4 (1.1, 6.7)
Bronchiectasis	0.9 (1.6)	0 (0, 1)

IQR = interquartile range. See Table 1 legend for expansion of other abbreviation.

who exhibited any bronchiectasis ($P < .01$) (Figure 3B). Finally, we assessed the earliest ventilator measurements obtained after enrollment in association with the 14-day HRCT scan scores. Modest correlations between the earliest PPlat ($\rho = 0.32$) and Cstat ($\rho = -0.38$) values and HRCT scan reticulation were observed (Figs 3C, 3E, Table 5). Similarly, the first recorded PPlat value was higher, and first Cstat lower, among patients who exhibited any bronchiectasis on the 14-day HRCT scan (Figs 3D, 3F).

Multiple linear regression analyses were performed to clarify the relationship between mechanical ventilation characteristics and individual chest HRCT scan scores. In the first model, average Cstat prior to chest HRCT scan remained independently associated with reticulation ($\beta = -0.13$, $P < .0001$), accounting for APACHE II scores, number of ventilator days, initial Pao_2/Fio_2 ratio, and diagnosis of pneumonia ($R^2 = 0.33$ for model). In a separate model containing average PEEP, PPlat, and V_T, along with these same clinical variables, PPlat exposure remained independently associated with reticulation after accounting for other variables in the model ($\beta = 0.095$, $P < .0001$; $R^2 = 0.36$ for model). In multiple logistic regression analysis, average PPlat exposure ($\beta = 0.29$, $P = .001$) and a diagnosis of pneumonia ($\beta = 0.74$, $P = .04$) were associated with the finding of any HRCT scan bronchiectasis, accounting for these same clinical variables in the model ($R^2 = 0.25$ for model).

Finally, given prior correlations between excessive fibroproliferation and poorer ARDS outcomes, we examined HRCT scan reticulation and bronchiectasis scores in conjunction with outcome data from patients with ARDS who remained on the ventilator > 14 days (n = 40), excluding spontaneously breathing patients from these analyses. Fourteen-day chest HRCT scan reticulation scores did not correlate with ventilator-free ($\rho = 0.12$) or ICU-free ($\rho = -0.17$) days. Similarly, bronchiectasis scores did not correlate with either ventilator-free ($\rho = -0.23$) or ICU-free ($\rho = -0.27$) days.

Discussion

Our present investigations in a cohort of patients with ARDS who were closely managed on a low V_T ventilator protocol in the context of a clinical trial[19] revealed associations between measured PPlat and respiratory compliance with 14-day chest HRCT scan reticulation and bronchiectasis. Associations were consistent whether

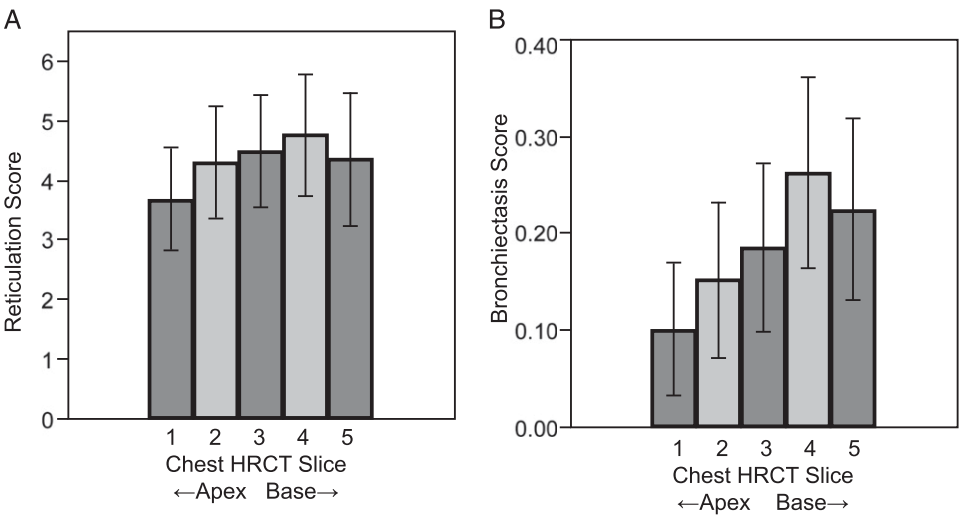

Figure 1 – *Evidence of fibroproliferative changes on chest HRCT scan were quantitated by radiologists from the level of the aortic arch (slice 1) to 1 cm above the dome of the right hemidiaphragm (slice 5) and at three additional levels spaced equally between these two levels (slices 2-4). On average, fibroproliferative changes were most prominent in slices 3, 4, and 5 although they were observed in all slices examined. A, Bars represent mean scores for reticulation, with 95% CIs. B, Bars represent mean scores for bronchiectasis, with 95% CIs. HRCT = high-resolution CT.*

TABLE 4] Correlations Between Composite Ventilation Parameters Obtained During First 14 Days After ARDS Diagnosis and Chest HRCT Scan Scores

Relationship Between Variables	Average daily V_T Exposure, mL	Average Daily PEEP Exposure, cm H_2O	Average Daily PPlat Exposure, cm H_2O	Average Cstat, mL/cm H_2O	Days on Ventilator (Prior to 14-d HRCT Scan)
Reticulation score	−0.18	0.27[a]	0.52[b]	−0.46[b]	0.21
Bronchiectasis score	−0.06	0.22	0.42[b]	−0.31[a]	0.07
Ground glass opacification score	−0.19	0.19	0.48[b]	−0.44[b]	0.26[a]
Intense parenchymal opacification score	−0.07	0.28[a]	0.37[b]	−0.26[a]	0.55[b]

See Table 1 and 2 legends for expansion of abbreviations.
[a]$P \leq .02$.
[b]$P \leq .0007$.

average PPlat or unique PPlat values were used and in multivariate analyses. Our observations suggest that poor lung compliance, reflected in higher PPlats within days after ARDS diagnosis, corresponds with evidence of enhanced fibroproliferative activity, manifest by increased radiographic reticulation and bronchiectasis on HRCT scan. This work is distinct from previous investigations in which chest CT imaging has been used to assess lung recruitability in the setting of ARDS to adjust the application of PEEP.[21,24,25] Our findings suggest the potential of early HRCT scan evaluation in patients with ARDS with the poorest lung compliance to identify individuals who may be at risk for complications related to excessive fibroproliferation.[6]

Emerging evidence suggests that HRCT scan scores measured very early (within days) after ARDS diagnosis using validated methods[7,8] may be helpful in prognosticating short-term outcomes, illustrated in a

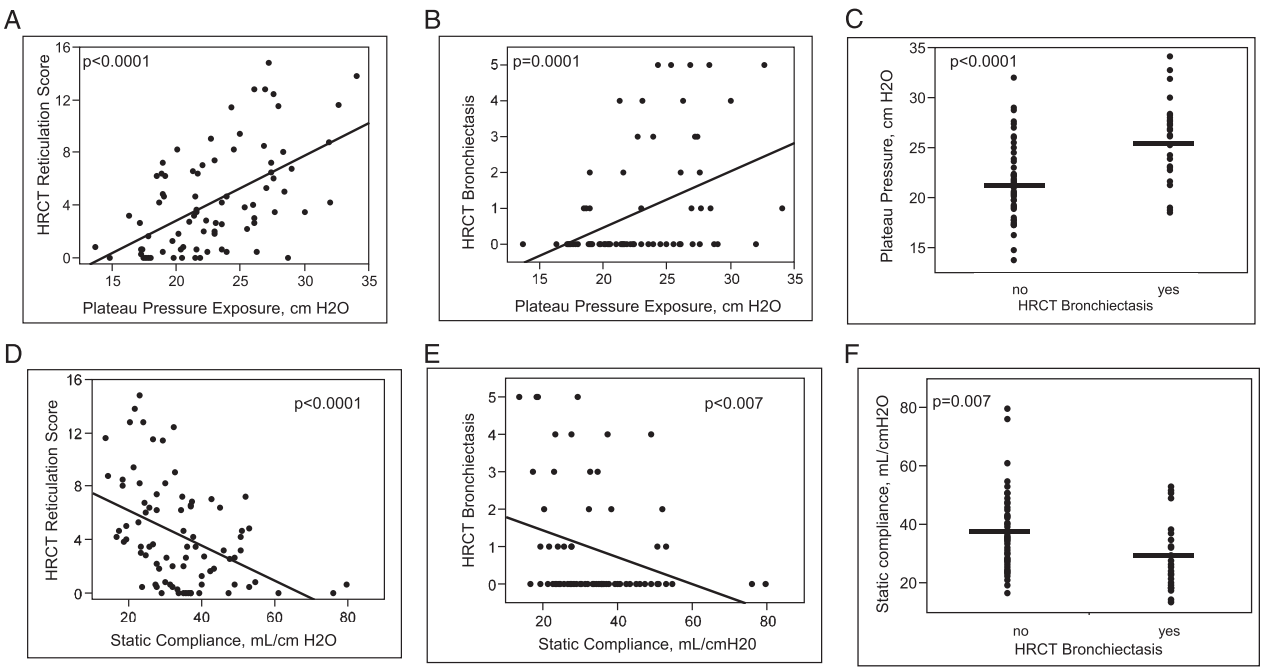

Figure 2 – *Ventilator parameters recorded during the first 14 d after ARDS diagnosis were examined in conjunction with HRCT scan radiologic involvement present at 14 (SD, 2) d after ARDS diagnosis. A, B, In this cohort of patients, the average plateau pressure exposure during the first 14 d after diagnosis correlated positively with HRCT scan reticulation scores (A, ρ = 0.52) and bronchiectasis scores (B, ρ = 0.42). C, If patients were stratified according to having no bronchiectasis vs any bronchiectasis, average plateau pressure exposure among the group with any bronchiectasis was significantly higher (P < .0001). D, E, Complementary to this, the average static compliance for patients over the first 14 d after diagnosis calculated using tidal volume, plateau pressure, and positive end-expiratory pressure correlated inversely with HRCT scan reticulation scores (D, ρ = −0.46) and bronchiectasis scores (E, ρ = −0.31). F, The presence of any bronchiectasis on HRCT scan was associated with a lower average static compliance (P = .007). Horizontal bars indicate mean values; diagonal bars are regression lines. See Figure 1 legend for expansion of abbreviation.*

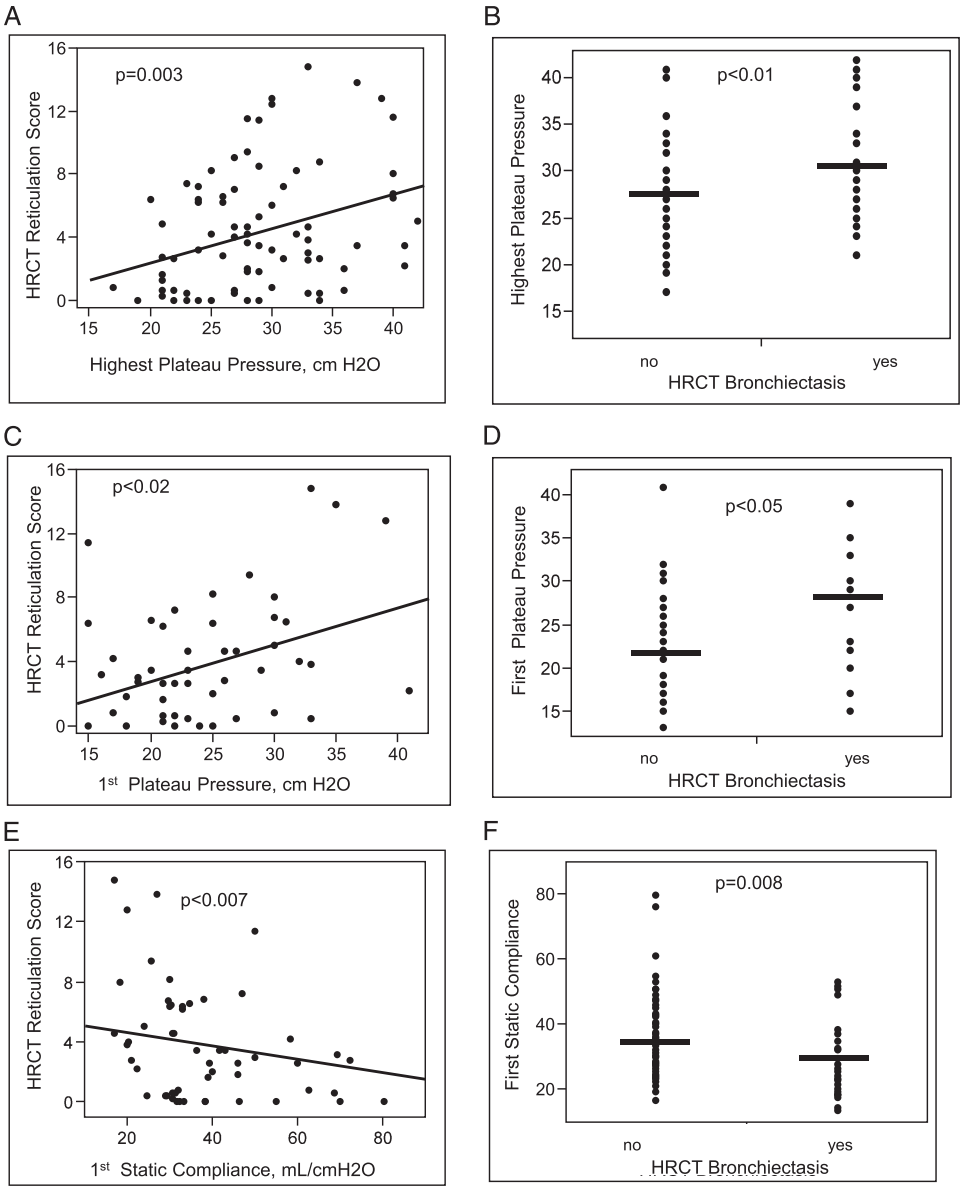

Figure 3 – *The highest single plateau pressure, and the first available recorded plateau pressure or static compliance within 24 h of ARDS diagnosis, were examined in conjunction with HRCT scan reticulation and bronchiectasis present at 14 d (SD, 2) after ARDS diagnosis. A, In this cohort of patients, the highest plateau pressure exposure was associated with 14-d chest HRCT scan reticulation score (ρ = 0.33). B, Among patients who exhibited any bronchiectasis on their 14-d HRCT scan, on average, the highest single plateau pressure value recorded in the days prior to the HRCT scan was higher (P < .01). C, D, Similar relationships between the earliest single plateau pressure exposure obtained within 24 h of ARDS diagnosis and reticulation (C, ρ = 0.32) or bronchiectasis (D, P < .04) were also observed. E, F, Complementary to the earliest plateau pressure/HRCT scan relationships, the first recorded static respiratory compliance was inversely associated with HRCT scan reticulation (E, ρ = −0.38) and was also determined to be lower in patients with evidence of bronchiectasis (F, P = .008). Horizontal bars indicate mean values; diagonal bars are regression lines. See Figure 1 legend for expansion of abbreviation.*

prospective observational study[9] in which evidence for chest HRCT scan fibroproliferation present on the first day of ARDS diagnosis was associated with 60-day mortality. However, our recent investigations suggest that chest HRCT scans obtained at 14 days post ARDS diagnosis identifies a subset of patients who will have persistent radiographic fibroproliferation much later, at 180 days, and also poorer pulmonary-specific quality of life.[6] Data from our present work complement these prior observations by demonstrating an association between poor respiratory compliance measured in the first days after ARDS diagnosis with radiographic fibroproliferation at 14 days. These data are clinically meaningful in suggesting that simple bedside ventilator measurements early in ARDS may help to identify and target patients who are most likely to have

TABLE 5] Correlations Between Single Time Point Mechanical Ventilation Parameters Obtained During the First 14 Days After ARDS Diagnosis and Chest HRCT Scan Scores

Relationship Between Variables	Highest[a] Exposure			First[b] Exposure			
	V_T, mL	PEEP, cm H_2O	PPlat, cm H_2O	V_T, mL	PEEP, cm H_2O	PPlat, cm H_2O	Static Compliance, mL/cm H_2O
Reticulation score	−0.04	0.05	0.33[c]	−0.12	0.24[d]	0.32[d]	−0.38[c]
Bronchiectasis score	−0.04	−0.01	0.33[c]	−0.07	0.22	0.25	−0.20
Ground-glass opacification score	−0.02	0.10	0.34[c]	−0.11	0.27[d]	0.30[d]	−0.29[d]
Intense parenchymal opacification score	0.05	0.27[d]	0.35[c]	−0.07	0.27[d]	0.12	−0.05

See Table 1 and 2 legends for expansion of abbreviations.
[a]Highest values recorded on any single day up until the 14-d chest HRCT scan.
[b]First values recorded within the first 24 h after ARDS diagnosis. Complete data available for 53 subjects at this first time point.
[c]$P \leq .006$.
[d]$P \leq .04$.

radiologic fibroproliferation during the resolution of their acute illness; that is, patients with the poorest respiratory compliance. If substantial fibroproliferation is in fact evident on HRCT scan, appropriate follow-up and therapy may be implemented in this selected subset of ARDS survivors to optimize health-related quality of life. In contrast, patients who have relatively normal or rapidly improving respiratory compliance would not be targeted for HRCT imaging, as their likelihood of future pulmonary compromise would likely be low.

Our present work is not without limitations. Although the data support associations between ventilator parameters and radiologic fibroproliferation, this does not indicate causality. The observation that poorer compliance was also associated with HRCT scan GGO and IPO suggests that factors other than fibroproliferation, such as specific ARDS risk factors (eg, pneumonia) may play a role. Moreover, biologic evidence of excessive profibrotic activity would help substantiate a cause-and-effect relationship between the ventilator and fibroproliferation. Patients we included from the parent study were racially homogeneous and had a high survival rate compared with general patients with ARDS. In comparison, patients from the parent study who were excluded from the current investigation had a significantly greater severity of illness, poorer initial lung compliance, and higher mortality. However, the distribution of ARDS severity by initial Pao_2/Fio_2 values between patients included or excluded from the parent study did not differ and was relatively comparable to other ARDS studies. Moreover, both included and excluded patients were cared for using a stringent ventilator management and weaning strategy as part of a larger randomized controlled trial; this should provide further confidence in the validity of the observations. In summary, the unique characteristics of our study population raise at least two important clinical considerations. First, the fact that the more severely ill patients with ARDS with poorer lung compliance, and those who died before day 14, were excluded from our investigations suggests the possibility that the magnitude of the relationship we report between lung compliance and chest HRCT scan fibroproliferation is an underestimation. Second, the inability to safely perform HRCT imaging in the sickest patients with ARDS perhaps indicates a limitation in the use of this technology for prognostication to a subset of patients who are less ill and who can, therefore, travel safely to obtain the imaging study.

Conclusions

In our cohort of patients with ARDS, diminished respiratory compliance was associated with evidence of increased chest HRCT scan reticulation and bronchiectasis at 14 days after ARDS diagnosis. Specific factors in ventilator management, biologic mediators, and patient characteristics driving fibroproliferation remain to be established. However, HRCT imaging represents a promising tool to identify and quantify fibroproliferative activity in the acute setting and to help predict who may be at risk for poorer outcomes or impaired quality of life.

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Additional information: The e-Table can be found in the Supplemental Materials section of the online article.

References

1. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301-1308.
2. Papazian L, Doddoli C, Chetaille B, et al. A contributive result of open-lung biopsy improves survival in acute respiratory distress syndrome patients. *Crit Care Med*. 2007;35(3):755-762.
3. Meduri GU, Headley AS, Golden E, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 1998;280(2):159-165.
4. Steinberg KP, Hudson LD, Goodman RB, et al; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med*. 2006;354(16):1671-1684.
5. Martin C, Papazian L, Payan MJ, Saux P, Gouin F. Pulmonary fibrosis correlates with outcome in adult respiratory distress syndrome. A study in mechanically ventilated patients. *Chest*. 1995;107(1):196-200.
6. Burnham EL, Hyzy RC, Paine R III, et al. Chest computed tomography features are associated with poorer quality of life in acute lung injury survivors. *Crit Care Med*. 2013;41(2)445-456.
7. Ichikado K, Suga M, Müller NL, et al. Acute interstitial pneumonia: comparison of high-resolution computed tomography findings between survivors and nonsurvivors. *Am J Respir Crit Care Med*. 2002;165(11):1551-1556.
8. Ichikado K, Suga M, Muranaka H, et al. Prediction of prognosis for acute respiratory distress syndrome with thin-section CT: validation in 44 cases. *Radiology*. 2006;238(1):321-329.
9. Ichikado K, Muranaka H, Gushima Y, et al. Fibroproliferative changes on high-resolution CT in the acute respiratory distress syndrome predict mortality and ventilator dependency: a prospective observational cohort study. *BMJ Open*. 2012;2(2):e000545.
10. Cabrera-Benítez NE, Parotto M, Post M, et al. Mechanical stress induces lung fibrosis by epithelial-mesenchymal transition. *Crit Care Med*. 2012;40(2):510-517.
11. Caruso P, Meireles SI, Reis LF, Mauad T, Martins MA, Deheinzelin D. Low tidal volume ventilation induces proinflammatory and profibrogenic response in lungs of rats. *Intensive Care Med*. 2003;29(10):1808-1811.
12. Hirsch J, Hansen KC, Sapru A, et al. Impact of low and high tidal volumes on the rat alveolar epithelial type II cell proteome. *Am J Respir Crit Care Med*. 2007;175(10):1006-1013.
13. Budinger GR, Chandel NS, Donnelly HK, Eisenbart J, Oberoi M, Jain M. Active transforming growth factor-beta1 activates the procollagen I promoter in patients with acute lung injury. *Intensive Care Med*. 2005;31(1):121-128.
14. dos Santos CC, Slutsky AS. Protective ventilation of patients with acute respiratory distress syndrome. *Crit Care*. 2004;8(3):145-147.
15. Marshall RP, Bellingan G, Webb S, et al. Fibroproliferation occurs early in the acute respiratory distress syndrome and impacts on outcome. *Am J Respir Crit Care Med*. 2000;162(5):1783-1788.
16. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA*. 2010;303(9):865-873.
17. Santa Cruz R, Rojas JI, Nervi R, Heredia R, Ciapponi A. High versus low positive end-expiratory pressure (PEEP) levels for mechanically ventilated adult patients with acute lung injury and acute respiratory distress syndrome. *Cochrane Database Syst Rev*. 2013;6:CD009098.
18. Cressoni M, Cadringher P, Chiurazzi C, et al. Lung inhomogeneity in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2014;189(2):149-158.
19. Paine R III, Standiford TJ, Dechert RE, et al. A randomized trial of recombinant human granulocyte-macrophage colony stimulating factor for patients with acute lung injury. *Crit Care Med*. 2012;40(1):90-97.
20. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med*. 1994;149(3 pt 1):818-824.
21. Crotti S, Mascheroni D, Caironi P, et al. Recruitment and derecruitment during acute respiratory failure: a clinical study. *Am J Respir Crit Care Med*. 2001;164(1):131-140.
22. Desai SR, Wells AU, Rubens MB, Evans TW, Hansell DM. Acute respiratory distress syndrome: CT abnormalities at long-term follow-up. *Radiology*. 1999;210(1):29-35.
23. Ranieri VM, Rubenfeld GD, Thompson BT, et al; ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307(23):2526-2533.
24. Chiumello D, Marino A, Brioni M, et al. Visual anatomical lung CT scan assessment of lung recruitability. *Intensive Care Med*. 2013;39(1):66-73.
25. Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med*. 2006;354(17):1775-1786.