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Biomarkers in Acute Respiratory Distress Syndrome

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Abstract

Purpose of review—This article provides an overview of protein biomarkers for acute respiratory distress syndrome (ARDS) and their potential use in future clinical trials.

Recent findings—The protein biomarkers studied as indices of biological processes involved in the pathogenesis of ARDS may have diagnostic and/or prognostic value. Recently, they also proved useful for identifying ARDS phenotypes and assessing heterogeneity of treatment effect in retrospective analyses of completed clinical trials.

Summary—This article summarizes the current research on ARDS biomarkers and provides insights into how they should be integrated as prognostic and predictive enrichment tools in future clinical trials.

Keywords

Acute respiratory distress syndrome; biomarker; pathogenesis; prognostic enrichment; predictive enrichment

Introduction

Acute respiratory distress syndrome (ARDS), a severe form of acute inflammatory lung injury and alveolar edema, is associated with high mortality and has important physical and cognitive consequences in survivors (1–4). ARDS is characterized by marked clinical and pathophysiologic heterogeneity (5,6), contributing to both underdiagnosis and undertreatment. Therefore, a key challenge in ARDS management, treatment, and prevention remains the establishment of a consensus clinical definition for ARDS that addresses this heterogeneity. The use of biomarkers can provide major insights into the

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pathophysiologic mechanisms underlying ARDS and can be helpful for diagnosis, risk stratification, and identification of candidate therapeutic targets (7–10). In addition, biomarkers have been crucial in identifying subgroups of patients (or phenotypes) with shared biological features that have prognostic and therapeutic implications in retrospective analyses and in providing a better pathophysiologic understanding of ARDS heterogeneity.

In this article, we review the current use of protein biomarkers for diagnostic, prognostic, and phenotype evaluation in patients with or at risk for ARDS and propose strategies for using biomarkers for predictive and/or prognostic enrichment in future precision ARDS trials.

Biomarkers in ARDS: from pathogenesis insights to diagnosis and risk stratification

Recent reviews summarize how the study of protein biomarkers has provided important insights into the pathophysiologic mechanisms of ARDS (7,8,11–15). These include disruption of the alveolar–capillary barrier (as assessed by elevated protein levels in pulmonary edema fluid) (16,17), exaggerated inflammatory responses (18,19), and lung endothelial (20–22) and epithelial injury determined by measurements of impaired alveolar fluid clearance (23,24) or the presence of specific markers of alveolar epithelial cell injury (e.g., surfactant protein D [SP-D] (25,26) and the soluble form of the receptor for advanced glycation end-products [sRAGE] (27–29)). In this article, we will focus on how plasma biomarkers can inform diagnosis and risk stratification in patients, with or at risk of ARDS, while also reducing heterogeneity and providing a tool for assessing heterogeneity of treatment effects in ARDS clinical trials.

Biomarkers for ARDS diagnosis

RAGE is abundantly expressed on alveolar epithelial type 1 cells; the extracellular domain of this multiligand receptor is released in the setting of lung epithelial injury (27). Plasma levels of sRAGE are elevated in patients with ARDS and are associated with the severity of lung injury and the degree of impairment of alveolar fluid clearance (27–30). Plasma sRAGE also increases in trauma patients who develop ARDS (31) and is associated with ARDS diagnosis (9,32). A high plasma sRAGE at intensive care unit (ICU) admission may also identify patients likely to develop ARDS among those with at least one clinical ARDS risk factor (33). Plasma levels of SP-D, another marker of lung epithelial injury, are also increased in patients with ARDS (26,34).

Elevated plasma angiopoietin-2 (Ang-2), a marker of lung endothelial barrier dysfunction, has predictive value for ARDS development in ICU patients under mechanical ventilation (35,36) or admitted for trauma (31). Notably, the predictive performance of plasma Ang-2 is improved when combined with the clinical Lung Injury Prediction Score (LIPS) (36,37).

Other plasma biomarkers with potential value for ARDS diagnosis include von Willebrand factor (vWF) (another marker of endothelial injury) and proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-8 (31,32,36,38).

Combining multiple biomarkers also has diagnostic value, as panels that include sRAGE, Ang-2, IL-8, IL-10, TNF-α, procollagen peptide III, and brain natriuretic peptide (31) or sRAGE, SP-D, IL-6, IL-8, and club cell secretory protein (26) show better performance for ARDS diagnosis than each biomarker measured alone.

Biomarkers for Risk Stratification in ARDS

Elevated levels of plasma SP-D (25), vWF (38), soluble tumor necrosis factor receptor I and II (sTNFrI; sTNFr2) (18), soluble intercellular adhesion molecule-1 (sICAM-1) (39), and plasminogen activator inhibitor-1 (PAI-1) (40) are all independently associated with worse outcomes in ARDS.

High plasma sRAGE levels are associated with increased lung injury severity, fewer ventilator-free days, and increased mortality in patients with ARDS (41). A meta-analysis of individual patient data from eight studies confirmed an independent association between high baseline plasma sRAGE and high 90-day ARDS mortality (42). Other mortality-associated ARDS biomarkers include Ang-2, IL-6, IL-8, IL-4, IL-2, and Krebs von den Lungen-6 (32,43,44). Low levels of the endogenous anticoagulant protein C were also associated with increased mortality and fewer ventilator-free days (40), whereas high plasma levels of IL-2 receptor and of procalcitonin were associated with increased mortality in unselected patients with ARDS (45) and patients with ARDS due to community-acquired pneumonia (46), respectively.

Models that combine multiple clinical variables and biomarkers have been computed to improve risk stratification. For example, one model combining six clinical variables and eight biomarkers was better at predicting mortality than a model based only on clinical variables or only on biomarkers in a secondary analysis of patients previously enrolled in the ARDS Network ALVEOLI trial (47). A simplified model combining two clinical variables (age, APACHE III) and two biomarkers (SP-D, IL-8) also had good performance and was subsequently validated in three additional cohorts (48).

Enriching future clinical trials with biomarkers

ARDS is a clinically and biologically complex, heterogeneous syndrome with a variety of underlying etiologies including etiologies that are pulmonary and directly injure the lung (such as viral or bacterial pneumonia, aspiration of gastric contents) and etiologies that are non-pulmonary and indirectly injure the lung (such as non-pulmonary sepsis, severe traumatic injuries, transfusion of blood products). The failure of most randomized clinical trials in ARDS to improve patient outcomes may be explained by such heterogeneity; better identification of appropriate subsets of patients to target with novel therapies is still needed (49). In this context, biomarkers could be used both to understand heterogeneity in clinical trial populations and as enrichment strategies in future trials (4,43). Determining how biomarker-derived approaches should be integrated to improve future ARDS research remains a major challenge.

Identification of ARDS phenotypes

The use of biomarkers has already been crucial in addressing ARDS heterogeneity (5,6,14,50). For example, a secondary clinical analysis revealed that patients with ARDS from direct lung injury had higher lung epithelial injury (as assessed by plasma sRAGE and SP-D) and lower lung endothelial injury (as assessed by plasma Ang-2) and inflammation (as assessed by plasma vWF, IL-6, and IL-8) compared to patients with ARDS arising from indirect lung injury (43).

Latent class analysis (LCA) has also been used to study ARDS heterogeneity. This novel approach is unbiased, making no a priori assumptions as to whether there are distinct biological subsets among groups of heterogeneous patients with ARDS arising from different underlying conditions. LCA has consistently identified distinct phenotypes of ARDS characterized by specific combinations of biomarkers and clinical characteristics in secondary analyses of multiple clinical trial cohorts (51–53). A “hyperinflammatory” phenotype, with elevated serum levels of inflammatory markers, was identified in approximately one-third of the patients, while a “hypoinflammatory” phenotype was identified in the remaining patients. Mortality was higher and ventilator-free days were higher in the hyperinflammatory phenotype, as further validated in secondary analyses of three additional clinical trials (54–56). These molecular phenotypes could be reliably identified with a three-biomarker model (plasma IL-8, sTNFr, and serum bicarbonate) (54). Parsimonious three-variable (IL-8, protein C, and bicarbonate) and four-variable (three-variable plus vasopressor use) models were also recently validated for phenotype classification (57). Preliminary studies also suggest that these phenotypes can be identified among patients with ARDS due to SARS-CoV-2 infection (58). Bos et al. confirmed the presence of two molecular phenotypes of ARDS using cluster analysis of data from the MARS cohort (59); these phenotypes could be distinguished by distinct serum IL-6, Ang-1/2, PAI-1, and interferon-gamma levels. Gene expression profiles in peripheral blood leukocytes were used to evaluate the distinct biology underlying these phenotypes including upregulation of pathways of oxidative phosphorylation or mitochondrial dysfunction in the hyperinflammatory (or “reactive”) subgroup (60).

Interestingly, application of these analytic approaches to patients at risk of developing ARDS has revealed the presence of similar inflammatory phenotypes among ICU patients with a clinical risk factor for ARDS (61) and those with an increased risk of postoperative pulmonary complications after elective abdominal surgery (62).

Heterogeneity of treatment effect and enrichment strategies

The concept of “heterogeneity of treatment effects” is attributable to the variability in therapeutic responses among distinct phenotypes. Protein biomarkers could be helpful to overcome this issue and facilitate biomarker-based selection of patients to target in “enriched” trials. Prospective enrichment strategies can include both predictive and prognostic enrichment. The overall aim of predictive enrichment is to personalize treatments for subjects with shared biologic profiles rather than searching for treatments that are applicable to everyone (63,64). Trials that utilize predictive enrichment enroll a smaller and

more homogeneous subgroup more likely to respond to an intervention targeting a specific biologic mechanism (50,64,65).

The overall aim of prognostic enrichment is to identify a subset of patients that is more likely to develop an outcome of interest (such as mortality) who can be selected to increase the power to detect a benefit from a therapeutic intervention (50,64,65). These enrichment strategies can be used to guide the enrollment of selected patients such as those most likely to develop the outcome or to respond to a given therapy.

Biomarkers may be useful for prognostic, predictive, or both forms of enrichment. For example, severe hypoxemia can have value for both prognostic (higher risk of death) and predictive (better response to prone position) enrichment in patients with ARDS (1,66).

Treatment responsive subgroups have been reported within the context of completed clinical trials through retrospective analysis of LCA-identified phenotypes.

A secondary analysis of the ALVEOLI trial of two levels of positive end-expiratory pressure (PEEP) for treatment of ARDS (52) showed a decreased 90-day mortality (from 50% to 40%) in patients with the hyperinflammatory phenotype exposed to higher versus lower PEEP (53). By contrast, mortality was higher when higher levels of PEEP were used in the hypoinflammatory phenotype (53), although the original trial found no difference. Similarly, ARDS mortality was lower in the hyperinflammatory phenotype with a liberal rather than a conservative fluid strategy in the Fluid and Catheter Treatment Trial (FACTT) for ARDS (54), whereas the original trial found no effect of fluid strategy on mortality and more ventilator-free days with the conservative fluid strategy (67). Similar distinct effects have also been reported for simvastatin in a secondary analysis of the HARP-2 trial of simvastatin in ARDS (68). The original trial found no difference in clinical outcomes between simvastatin and placebo, whereas a secondary analysis showed better survival in the hyperinflammatory phenotype with simvastatin but no difference in therapeutic response among patients with the hypoinflammatory phenotype. To summarize, inflammatory ARDS phenotypes have been consistently identified in secondary analyses of clinical trial cohorts and hold great promise for application as tools for both predictive and prognostic enrichment. However, they should now be prospectively validated and rapid biomarker measurement methods are still needed to allow practical incorporation into future enriched trials (see the Challenges and limitations section below).

Other ARDS phenotypes have also been described, such as radiographic phenotypes of focal and nonfocal ARDS based on the extent of loss of aeration apparent in lung CT scans (69). Radiographic phenotypes are thought to identify patients with different lung physiology who may have distinct responses to mechanical ventilation (5). A French prospective observational multicenter study showed higher plasma sRAGE and PAI-1 levels in radiographically nonfocal compared to focal ARDS (70). Nonfocal ARDS was also associated with increased mortality (70) and with greater impairment of alveolar fluid clearance (71), implicating sRAGE as a useful correlate of radiographic ARDS phenotypes (72). The multicenter randomized controlled Lung Imaging for Ventilator Setting in ARDS (LIVE) trial evaluated different mechanical ventilation strategies tailored to radiographic

phenotypes in 400 patients with moderate-to-severe ARDS (73). No between-group differences in 90-day mortality were seen in the intention-to-treat analysis of the primary endpoint; however, a prespecified post-hoc analysis revealed misclassification of 21% of the radiographic phenotypes assigned at the time of randomization (73,74). It would now be interesting to evaluate whether measurement of plasma sRAGE, reported as higher in nonfocal compared to focal ARDS (28,70,72), might improve “real-time” radiographic phenotyping in future trials.

Another approach to predictive enrichment is currently under investigation in patients with moderate-to-severe ARDS unresolved between day 5 and day 14 after onset. Here, elevated BAL procollagen III, a marker of lung fibroproliferation, is used as an entry criteria to the Procollagen-3 Driven Corticosteroids for Persistent Acute Respiratory Distress Syndrome (ProCoCo) multicenter randomized controlled trial of methylprednisolone versus placebo (ClinicalTrials.gov Identifier: NCT03371498) (75,76).

In summary, both predictive and prognostic enrichment strategies may improve the efficiency of randomized controlled trials by increasing the likelihood of detecting a beneficial effect from a targeted therapeutic intervention in patients who are more likely to develop the outcome of interest (50,77,78). The main plasma protein biomarkers that have been evaluated in patients at risk of developing ARDS and those with ARDS, and their potential applications to enrich future clinical trials are summarized in the Table and the Figure.

Challenges and limitations

Studies incorporating biomarker-driven strategies for ARDS management are unfortunately scarce, but they should be further evaluated to assess the full potential of biomarkers, in addition to their use as enrichment tools. A major potential application of biomarkers is the identification of biologic pathways to target in future interventional trials (79). For example, measuring plasma sRAGE could be useful in selecting patients with increased lung epithelial injury who may benefit from epithelial-targeted therapies, such as beta-agonists, keratinocyte growth factor, or anti-RAGE therapies, to prevent or treat ARDS (28,29,42,80–85). Conversely, ARDS patients with pronounced lung endothelial injury (e.g., as assessed by plasma Ang-2) may benefit more from candidate therapies, such as recombinant Ang-1, that target the endothelium (35,43).

Ideally, biomarkers should be useful for monitoring the progression or repair of lung injury, as well as the therapeutic response in ARDS (86). For instance, the use of a lung-protective, low-tidal volume ventilation strategy was associated with a decrease (or smaller increase) in plasma lung epithelial injury markers SP-D and sRAGE (25,41,87). A recent preliminary report of a secondary analysis of longitudinal sRAGE plasma levels in patients previously enrolled in the LIVE trial revealed an association between changes in plasma sRAGE over the first week after ARDS onset and 90-day survival. Similarly, a strategy of maximal alveolar recruitment (with higher PEEP and repeated recruitment maneuvers) was associated with increasing plasma sRAGE levels, suggesting increased injury to the lung alveolar epithelium due to this strategy in focal ARDS. Thus, plasma sRAGE may have potential

value as a surrogate outcome for monitoring responses to ventilator settings in patients with ARDS (72,88). These approaches warrant further validation in prospective clinical studies, as they hold the promise for developing novel precision therapies that are effective in specific phenotypes (89).

The major limitations of biomarker-driven approaches to ARDS trials include the urgent need for prospective validation of most phenotypes described in secondary analyses of previous studies. The lack of a point-of-care assay for evaluating the candidate biomarkers at the bedside also limits the current application of biomarker-based enrichment strategies in "real time". The Clinical Evaluation of a Point of Care Assay to Identify Phenotypes in the Acute Respiratory Distress Syndrome (PHIND) study is currently enrolling patients with ARDS for prospective identification of hyperinflammatory and hypoinflammatory phenotypes using a novel POC assay of serum IL-6 and sTNFr1 (ClinicalTrials.gov Identifier: NCT04009330). This POC assay has been recently used to identify phenotypes in patients with ARDS due to coronavirus disease 2019 (COVID-19) (58).

The hyperinflammatory and hypoinflammatory phenotypes of ARDS could be driven by genetic and/or environmental factors, and this deserves further investigation. This review has focused only on plasma protein biomarkers, as they have been most studied; however, measurements of biomarkers in the alveolar compartment (44,90), as well as the study of genetic variants, DNA methylation, transcriptomics (60,91,92), or metabolomics (93–96), may also be very important in meeting the challenge of precision ARDS medicine (49). In particular, examining the exhaled breath as a source of volatile organic compounds that can serve as ARDS biomarkers (97,98) or measuring biomarkers in the fluid collected from heat-and-moisture-exchange filters (as commonly used in mechanically ventilated patients) (99) represent promising, non-invasive methods for sampling the distal airspace in patients with ARDS. However, these methods and their potential value in ARDS management need to be further assessed.

Conclusion

Biomarker research has promise in elucidating the pathobiology of acute lung injury and repair, and protein biomarkers have been investigated for diagnosis and risk stratification in ARDS. Several biomarkers, such as proinflammatory cytokines and markers of lung epithelial and endothelial injury, can aid in establishing ARDS patient phenotypes and identifying potential biological treatment targets. Numerous challenges remain, but recent advances in both biomarker research and trial design open up opportunities for using biomarkers to facilitate more personalized approaches in future ARDS clinical trials.

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Key points

- Biomarkers can provide major insights into the pathophysiologic mechanisms involved in ARDS, thereby aiding the diagnosis, risk stratification, and identification of candidate therapeutic targets.
- The recent use of biomarkers has identified distinct phenotypes among patients with ARDS, with potential implications for assessment of prognosis and therapeutic responses in patients with ARDS or at risk of developing the syndrome.
- Biomarkers should now be integrated as prognostic and predictive enrichment tools in future clinical trials to account for the heterogeneity of treatment effect observed in a number of negative ARDS clinical trials to date.

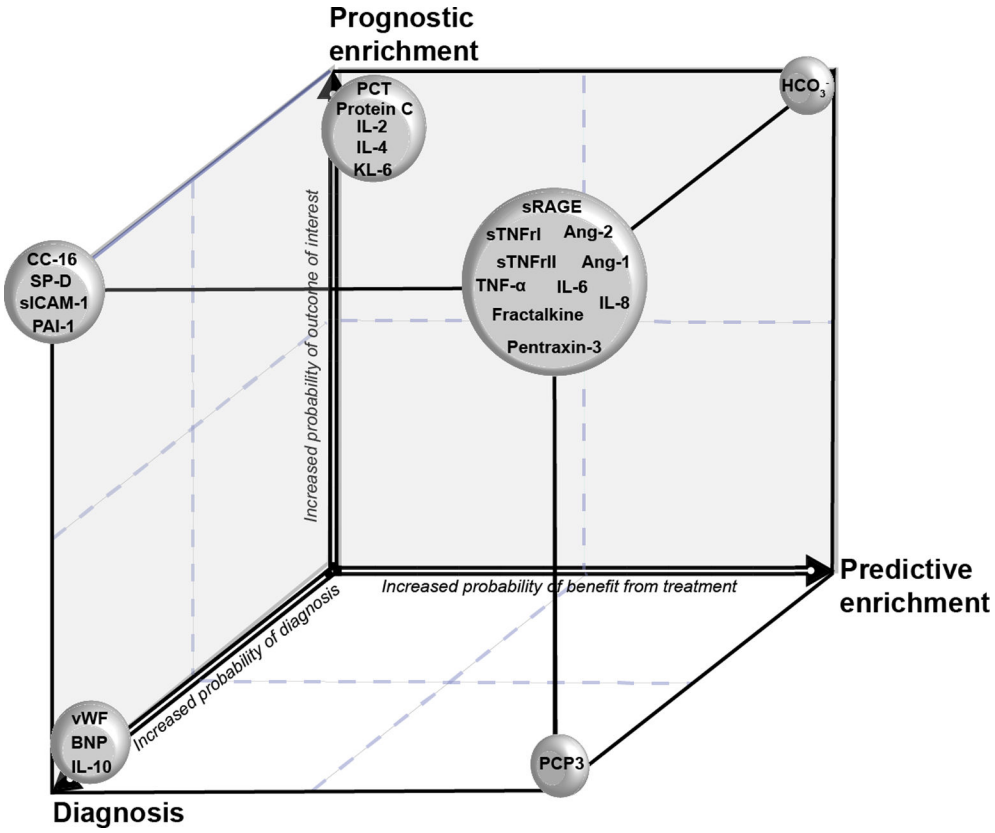

Figure. Schematic representation of the value of selected protein biomarkers for diagnosis of acute respiratory distress syndrome and potential application for predictive and prognostic trial enrichment.

KL-6: Krebs von den Lungen 6. PCT: procalcitonin. IL: interleukin. SP-D: surfactant protein D. sICAM-1: soluble intercellular adhesion molecule-1. CC16: club cell secretory protein. PAI-1: plasminogen activator inhibitor-1. vWF: von Willebrand factor. BNP: brain natriuretic peptide. sRAGE: soluble receptor for advanced glycation end-products. sTNFr: soluble tumor necrosis factor receptor. Ang: angiopoietin. TNF: tumor necrosis factor. PCP3: procollagen peptide III.

Table

Selected plasma protein biomarkers that have been evaluated in patients at risk of developing and those with ARDS, and their potential applications to enrich future clinical trials.

ARDS: acute respiratory distress syndrome. Ang: angiopoietin. sRAGE: soluble receptor for advanced glycation end-products. IL: interleukin. sTNFr: soluble tumor necrosis factor receptor. TNF: tumor necrosis factor. ICU: intensive care unit. SP-D: surfactant protein D. PEEP: positive end-expiratory pressure. ST: suppression of tumorigenicity. PAI: plasminogen activator inhibitor.

Plasma biomarker(s)	Potential application(s)	Reference(s)
Patients at risk of ARDS		
Ang-2	• Risk prediction for ARDS development	(36)
sRAGE	• Predictive enrichment for the evaluation of therapies targeting the lung endothelium or epithelium for ARDS prevention • Prognostic enrichment for ARDS preventive measures and targeted therapies	(33)
IL-6, IL-8, IL-10, sTNFr1, ST-2, fractalkine, sRAGE, Ang-2, procalcitonin, pentraxin-3	• Identification of phenotypes with distinct outcomes among mechanically ventilated ICU patients with acute respiratory failure • Predictive enrichment for the evaluation of therapies targeting specific mechanisms of lung injury for ARDS prevention • Prognostic enrichment for ARDS preventive measures and targeted therapies	(59)
sRAGE, Ang-2, IL-8, IL-10, TNF-α, procollagen peptide III, and brain natriuretic peptide	• Biomarker panel with value for ARDS diagnosis in ICU patients with severe trauma • Predictive and prognostic enrichment for the evaluation of interventions or targeted therapies for trauma-related ARDS	(31)
sRAGE, SP-D, IL-6, IL-8, and club cell secretory protein	• Biomarker panel with value for ARDS diagnosis in ICU patients with sepsis • Predictive and prognostic enrichment for the evaluation of therapies targeting lung epithelial injury and inflammation for sepsis-related ARDS	(26)
TNF-α, IL-6, IL-8	• Preoperative identification of inflammatory phenotypes with distinct risks of developing postoperative pulmonary complications among patients undergoing abdominal surgery • Predictive enrichment for the evaluation of therapies targeting inflammation to prevent postoperative ARDS • Prognostic enrichment for the evaluation of interventions for postoperative ARDS prevention	(60*)
Patients with ARDS		
IL-8, sTNFr, bicarbonate	• Identification of hypoinflammatory and hyperinflammatory phenotypes with distinct outcomes and therapeutic responses (such as to PEEP, fluid therapy, and simvastatin) among patients with ARDS • Predictive enrichment for the evaluation of therapies targeting inflammatory pathways in ARDS • Prognostic enrichment for the evaluation of therapeutic interventions, including targeted therapies, in ARDS	(53**)
IL-8, protein C, bicarbonate		(56)
IL-6, Ang-1/2, PAI-1		(57**)
sRAGE	• Identification of radiographic phenotypes of focal and nonfocal ARDS • Predictive enrichment for the evaluation of therapies targeting lung epithelial injury and inflammation in ARDS	(28*,29,42*,69*,71,88)

Plasma biomarker(s)	Potential application(s)	Reference(s)
	• Prognostic enrichment for the evaluation of therapeutic interventions, including epithelial-targeted therapies, in ARDS • Monitoring the “biological” response to some interventions in ARDS, such as recruitment maneuvers or ventilation strategies	