Review Article

Inhalation therapies in acute respiratory distress syndrome

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Abstract: The defining features of acute respiratory distress syndrome (ARDS) are an excessive inflammatory respiratory response associated with high morbidity and mortality. Treatment consists mainly of measures to avoid worsening lung injury and cannot reverse the underlying pathophysiological process. New pharmacological agents have shown promising results in preclinical studies; however, they have not been successfully translated to patients with ARDS. The lack of effective therapeutic interventions has resulted in a recent interest in strategies to prevent ARDS with treatments delivering medications directly to the lungs by inhalation and nebulization, hopefully minimizing systemic adverse events. We analyzed the effect of different aerosolized drugs such as bronchodilators, corticosteroids, pulmonary vasodilators, anticoagulants, mucolytics and surfactant. New therapeutic strategies and ongoing trials using carbon monoxide (CO) and AP301 peptide are also briefly reviewed.

Keywords: Acute respiratory distress syndrome (ARDS); acute lung injury (ALI); nebulization; inhalation; treatment; prevention

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Introduction

In acute respiratory distress syndrome (ARDS), overproduction of inflammatory factors in lung tissue is followed by pulmonary edema and severe hypoxemia and an increase in pulmonary dead space. Despite significant advances in our understanding and management of patients with ARDS, the morbidity and mortality associated with ARDS remains high. Few measures have been proven to improve outcomes in ARDS. Treatment consists mainly of measures to avoid worsening lung injury, such as lung-protective mechanical ventilation (1), prone positioning (2), and neuromuscular blockers (3); these are the only strategies that proved effective in reducing mortality. However, these approaches are unable to reverse the pathophysiological processes that underlie ARDS.

ARDS can result from direct or indirect insult, such as infection or trauma. Specific hallmarks of the disease include dysregulation of inflammation, accumulation of leukocytes and platelets with the activation of coagulation pathways, and disruption of the endothelial and epithelial barriers in the alveoli increasing their permeability to proteins (4). Decades of research have failed to find effective therapies that reduce mortality in established ARDS, and preclinical studies suggest that therapies that prevent lung injury when employed before the injury have lesser or no beneficial effects after lung injury develops (5). In recent years, new pharmacological agents designed to decrease the release of pro-inflammatory cytokines have shown

promising results in preclinical studies; moreover, these studies have furthered our understanding of the mechanisms involved in the pathogenesis and resolution of lung injury (6). However, clinical studies have failed to extend these results to humans and no pharmacological treatment for ARDS has been successful in a controlled trial (7).

Given that relatively few therapeutic measures have proven effective in ARDS, intravenous treatments can result in systemic side effects, and early treatment is crucial in critically ill patients, the focus has started to shift toward seeking strategies to prevent ARDS. One such strategy aims to develop local pulmonary treatments that deliver medications directly to the lungs by nebulization, with the aim of increasing local efficacy and minimizing systemic adverse effects.

This review discusses inhalational therapies (aerosols or gases) in the prevention and treatment of ARDS.

Aerosol delivery in mechanical ventilated patients

The medical use of aerosols dates back to ancient times (8). Two factors make therapeutic aerosols inherently attractive. Drugs can be delivered directly to the respiratory tree, to the alveolar epithelium, or both; moreover, the lungs' huge capacity for absorption and diffusion ensures that inhaled drugs reach the systemic circulation quickly.

Aerosols are colloidal suspensions of particles in gas. The size, shape, and density of particles together with the density and viscosity of the gas determine the extent to which particles can remain suspended. Two variables are often used to characterize aerosols. The first, the mass median aerodynamic diameter reflects the size of the particles; whereas the second, the geometric standard deviation, reflects the degree of variation in the size of the particles. These properties make it possible to predict where the particles will be deposited within the tracheobronchial tree/ventilator circuit (*Figure 1*). The efficiency of an aerosol generator can be determined if the rate of particle production and the geometric standard deviation are known. The ventilator circuit and settings have a bigger impact than the aerosol generator on time required for drugs to reach their targets and on the proportion of drugs that reach these targets.

In patients receiving mechanical ventilation, it can be a challenge to ensure that a generator delivers aerosolized particles to distal airways to reach the alveoli, and the proportion of the drug that reaches the target site depends on various factors (*Table 1*). Delivery depends on the ventilator settings and the physiological/pathophysiological factors of the patient's airflow. To ensure peripheral drug deposition, the ventilator should be set for: (I) low bias flow; (II) higher tidal volume and/or recruitment maneuver to distribute the drug more extensively; (III) a long, slow, continuous inspiratory profile; (IV) a long pause at end-inspiration to maximize the impaction/dropout of particles in peripheral regions; and (V) positive end-expiratory pressure (PEEP) to prevent alveolar collapse during expiration. Modern ventilators all synchronize aerosol production with inspiration to improve drug delivery (9).

Aerosolized drugs

Bronchodilators

In patients undergoing mechanical ventilation, the drug most often prescribed for nebulization is albuterol (racemic salbutamol). This β2-agonist is not only a bronchodilator; it also seems to improve fluid clearance (10,11) and favor mucociliary clearance (12).

Most patients with ARDS have impaired fluid clearance from the alveoli, and increased impairment is associated with increased mortality (13). Alveolar fluid clearance can be improved by stimulating pulmonary β2-adrenergic receptors, which upregulates and activates sodium and chloride transport proteins through cyclic adenosine monophosphate (14). One study in mice with lung injury due to the aspiration of acid found that clinically relevant concentrations of β2-agonists resulted in clearance of fluid from alveoli dependent on cyclic adenosine monophosphate and decreased pulmonary edema (15). Albuterol levels reached therapeutic levels in the pulmonary edema fluid of mechanically ventilated ARDS patients (16). More importantly, inhaling salmeterol prophylaxis prevents high-altitude pulmonary edema (17).

However, two randomized multicenter trials testing selective β2-agonists for established ARDS found that these drugs not only failed to provide clinical benefits but actually seemed to worsen outcomes when given intravenously (18,19). Thus, it may be that β2-agonists increase fluid clearance only in patients without damage to the alveolar epithelium before the onset of ARDS. Perkins *et al.* (20) studied 362 patients undergoing esophagectomy in 12 centers in the United Kingdom to determine whether inhaling salmeterol could prevent ARDS. They found no difference in the incidence of ARDS between salmeterol and

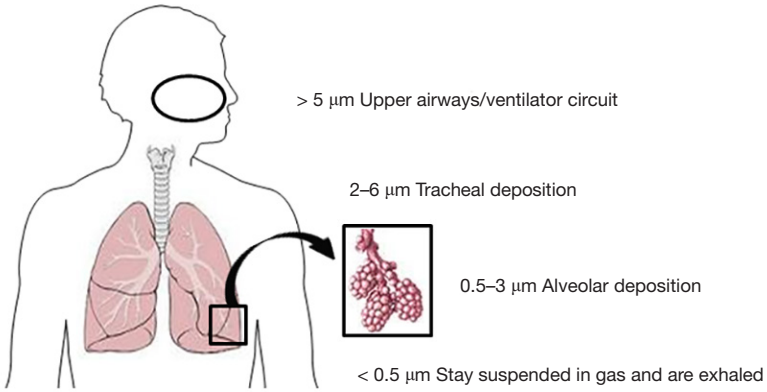

Figure 1 Probable site of aerosol deposition related to particle size

Table 1 Factors that affect the delivery of aerosol to the distal airways/alveoli in mechanically ventilated patients

Ventilator
Bias flow
Tidal volume
Respiratory rate
Inspiratory profile-time, flow rate
End inspiratory pause
Positive end expiratory pressure (PEEP)
Gas composition
Circuit
Method, location and efficiency humidification
Presence of any restrictions distal to aerosol generator
Temperature
Geometry of entire circuit
Position of nebulizer within the circuit
Patient
Proximal airway geometry
Degree and pattern of ventilator heterogeneity
Airway and/or parenchymal pathology
Ventilation-perfusion matching
Body position
Spontaneous respiratory efforts and ventilator synchrony

placebo (OR, 1.25; 95% CI, 0.71–2.22), but postoperative adverse events (mainly pneumonia) were less frequent in patients receiving salmeterol. A sub-study of 53 patients found that several biomarkers of alveolar inflammation and epithelial injury were lower in patients receiving salmeterol.

Despite extensive, supportive preclinical data and sound physiologic rationale, clinical trials have failed to improve outcome in established ARDS, but why? There are several plausible explanations, including lack of fidelity in preclinical models, substantial heterogeneity of ARDS in human trials, and changes in critical care practices (conservative fluid management and lower tidal volumes). However, timing of intervention and suboptimal dosing may be most critical, as data from preclinical and observational studies suggest.

Recently, Festic *et al.* (21) took an important first step toward answering this question with the "Lung Injury Prevention Study with Budesonide and Beta agonist (LIPS-B)" phase II randomized clinical trial comparing blinded treatment with aerosolized corticosteroids (budesonide 0.5 mg/2 mL) in combination with a long-acting beta agonist (formoterol 20 mcg/2 mL) to placebo administered twice daily during 5 days for ARDS prevention among at-risk patients. Patients were approached for consent in the emergency department and the treatment was administered within 9 hours, demonstrating that the early intervention for ARDS prevention is feasible. Standardization of ICU best practices was recommended and the most common reasons for exclusion were the use of steroids or β-agonists prior to enrollment and inability to obtain consent within 12 hours. The high rate of exclusion, including smokers with chronic obstructive pulmonary disease who often use inhaled steroids and β-agonists, could limit the generalizability of the study; this is particularly

important given that smokers have a higher risk of developing ARDS. The investigators found a significant improvement in oxygenation as measure by the oxygen saturation divided by inspired oxygen fraction (S/F ratio) in the group treated with inhaled budesonide/formoterol that became evident on days 2 and 4 of the protocol, but did not persist to day 5. Secondary outcomes included the development of ARDS, hospital and ICU length of stay, and the need for mechanical ventilation, which were not significantly different after adjusting for baseline differences in the rate of shock. Subjects in the treatment group appeared to be less acutely ill with lower LIPS and had less shock compared to subjects in the placebo group (13% *vs.* 47%). However, the improvement in oxygenation as measured by the S/F ratio remained statistically different between groups after logistic regression adjusting for LIPS or the presence of shock. In addition to the longitudinal improvement in oxygenation, the study demonstrated that it is feasible to rapidly enroll and safety treat these patients in the emergency department. These results support further studies to test the efficacy of inhaled corticosteroids and beta agonists for ARDS prevention. A phase 2 trial could address some of the limitations of the present study, such as unbalanced ARDS risk in the treatment arm, and could determine if more sustained improvements in gas exchange, survival, and ventilator-free days are achievable with the use of inhaled steroids and long-acting β-agonists in patients at risk of ARDS.

After salbutamol, ipratropium bromide, an anticholinergic bronchodilator, is the drug most commonly administered in mechanically ventilated patients by nebulization, even though, like salbutamol, its effectiveness has yet to be demonstrated in clinical trials.

ARDS survivors frequently present a decrease in expiration flow rate with airway hyperreactivity and air trapping due to small airways disease, indicating a need to maintain bronchodilator treatment for 6 months after hospital discharge (22).

Corticosteroids

Given the role of unregulated inflammation in ARDS, there has been interest in inhaled corticosteroids for treatment and prevention of ARDS in patients in whom systemic steroid administration may not be desirable (23-26). Corticosteroids have proven beneficial in many lung injuries of different origins, such as diffuse alveolar hemorrhage, that progress to ARDS. Animal models of lung injury have consistently shown amelioration of histologic injury, and improvement in oxygenation and respiratory mechanics in animals treated with inhaled corticosteroids even with heterogeneity in timing treatment and mechanisms of inciting injury.

Although studies in patients with severe influenza pneumonia showed no benefit for corticosteroids, other studies in patients hospitalized with pneumonia found that systemic steroids reduced treatment failure, including in patients with ARDS (27-29). Although limited clinical data exist, a secondary analysis of the LIPS cohort found that the use of inhaled corticosteroids prior to hospitalization was associated with a decreased risk of developing ARDS (OR, 0.39; 95% CI, 0.14–0.93) (30). A recent trial demonstrated that nebulized budesonide (1 mg/2 mL) improved oxygenation and peak and plateau airway pressures, and significantly reduced inflammatory markers (TNFα, IL-1β, and IL6) without affecting hemodynamics (31).

However, point-of-care measurements will be needed to integrate with clinical criteria to identify patients who might benefit based on a more pro-inflammatory phenotype (32).

Pulmonary vasodilators

Inhaled nitric oxide (iNO) decreases pulmonary artery pressure and improves oxygenation significantly, but fails to reduce mortality in patients with ARDS no matter how severe their hypoxemia is; moreover, iNO might increase the risk of renal impairment (33). A recent meta-analysis of 1,142 patients in nine homogeneous randomized trials found no reduction in mortality in patients with severe ARDS who received iNO (RR, 1.01; 95% CI, 0.78–1.32) (34). Furthermore, analyzing subgroups of patients with PaO2/FIO2 ratios (70–200 mmHg) failed to find a cutoff for which iNO reduces mortality. A retrospective study carried out in a single center that examined the effectiveness, safety, and cost of inhaled epoprostenol (iEPO) versus iNO in 105 patients found no differences between the two treatments in several clinical and outcome measures (35). The greatest benefits for iEPO have been reported in ARDS patients with right ventricular heart failure at the outset. A potential effect of inhaled prostaglandins could be derived from their antiplatelet and anti-inflammatory properties, but further studies are needed to analyze their impact on outcome (36).

In surveys, 29% to 44% of intensivists from UK and Germany report administering iNO in ARDS (37,38). However, the LUNG SAFE study found that physicians

prescribed inhaled vasodilators much less often: only 7.7% of all patients with ARDS and only 13.0% of those with severe ARDS received these drugs (39). Although inhaled vasodilators improve hemodynamic parameters and oxygenation in ARDS patients, they should be used mainly as a rescue therapy only after traditional treatments fail, rather than as standard care in ARDS.

Anticoagulants

Dysregulated coagulation, mediated by the tissue factor (TF) pathway, is another pathophysiological hallmark of ARDS, and agents targeting the coagulation cascade are putative candidates for ARDS treatment and prevention. Pulmonary coagulation is evident in increased markers of thrombin generation, soluble TF, and factor VIIa activity found in bronchoalveolar lavage fluid from ARDS patients, together with an increased release of plasminogen activator inhibitor-1 (PAI-1) decreasing fibrinolytic activity (40). The deposition of intravascular and extravascular fibrin as a result of activated coagulation and impaired fibrinolysis may contribute to lung inflammation, endothelial cell activation, and disruption of the alveolar capillary membrane barrier. Local administration of nebulized anticoagulants to the lungs allows higher dosages and increases local efficacy, reduces the risk of systemic bleeding, and is more effective than intravenous administration (41). In addition to its anticoagulant activity, intravenously administered heparin had anti-inflammatory effects, ameliorating the injury induced by lipopolysaccharide in a model of acute lung injury (ALI) (42). Heparin reduces the expression of proinflammatory mediators in human alveolar macrophages injured by lipopolysaccharide and decreases the NF-kβ pathway in alveolar cells (43). Furthermore, nebulized heparin decreases pro-inflammatory cytokines in lung tissue and the expression of NF-kB and TGF-β effectors in alveolar macrophages (44).

In smoke inhalation-related lung injury, preclinical and clinical studies have suggested that administration of inhaled anticoagulants improves oxygenation, reduces lung injury severity, and improves survival without altering systemic markers of clotting and anticoagulation (45). In a clinical trial in 50 patients requiring extended mechanical ventilation for any reason, the group randomized to inhaled heparin required fewer days of mechanical ventilation compared to the placebo group, although no improvements in oxygenation or outcomes were observed (46). Hofstra *et al.* (47) showed that local treatment with recombinant human activated protein C (APC), plasma-derived antithrombin, heparin, and danaparoid attenuated pulmonary coagulopathy, but not inflammation, in rats with endotoxemia-induced lung injury. A recent multicenter trial to investigate the efficacy and safety of nebulized heparin (HEPBURN) in burn patients with inhalation trauma was stopped earlier due to adverse events and futility (48).

The protein C anticoagulant pathway limits the activation of homeostasis and has anti-inflammatory effects (49,50). Thus, the activation of this pathway in the alveolar epithelium could modulate the deposition of fibrin in the alveoli. Inhaled protein C also decreases the recruitment of neutrophils into airspaces, resulting in an antiapoptotic effect; this, together with its anticoagulant, profibrinolytic, and anti-inflammatory effects, make inhaled protein C ideal to counteract the pathophysiological changes seen in ARDS. Another advantage is that it appears that inhaled APC does not interfere with pulmonary host defense. Aerosolized APC might be optimal for treating ARDS because in this inflammatory lung condition the normal conversion of protein C into APC in the lungs is disrupted and targets in the distal airspaces mediate inhaled APC's effects. Preclinical and limited clinical experience support this possibility (49,51,52). Unfortunately, this hypothesis cannot be tested in larger series of ARDS patients due to the negative PROWESS-Shock trial and the removal of APC from the market (53).

Mucolytic agents

Normal respiratory tract secretions are mainly made up of gel-forming mucin glycoproteins that form large oligomeric structures. Sputum or pathological respiratory mucus also contain other elements and have a much higher viscosity, which favors clearance through coughing but makes mucociliary clearance less efficient (54). In mechanically ventilated patients, both cough and mucociliary clearance are reduced, so treatments targeting sputum viscosity might be useful. N-acetylcysteine is the most widely recommended mucolytic, but its efficacy has yet to be confirmed for pathological condition (54,55). By contrast, strong evidence for the efficacy of nebulized hypertonic (3–14%) saline has been presented (54,56). Animal studies of nebulized hypertonic saline suggest that the preadministration of hypertonic saline attenuates the severity of lung injury, reduces matrix metalloproteinase activity, and decreases cytokine production from macrophages and epithelial

cells (57,58). A phase I clinical trial is currently recruiting patients with post-traumatic ARDS to investigate nebulized hypertonic saline [registered with www.clinical.trials.gov (NTCO1667666)].

Surfactant

Pulmonary surfactant is produced by type II alveolar epithelial cells; it is composed of phospholipids, proteins, and neutral lipids. Surfactant plays important roles in maintaining alveolar surface tension and in the host immune response (59). Surfactants in ARDS patients' bronchoalveolar lavage fluid have alterations in phospholipid composition and lower concentrations of surfactant proteins (60-62). Although exogenous surfactant confers clinical benefits in pediatric patients, several phase III clinical trials have failed to find beneficial effects in adult ARDS patients (63). However, these studies had various shortcomings, such as the failure to deliver enough surfactant or to incorporate hydrophilic surfactant proteins; moreover, these studies might not have target the groups of patients with the greatest probability of deriving benefits from this treatment. Newer approaches that assess surfactant synthesis and metabolism by stable isotope labeling of surfactant precursors (64) might make it possible to target patients who synthesize insufficient amounts of surfactant and are therefore likely benefit from treatment with exogenous surfactant. For the time being, however, no added value can be attributed to the use of exogenous surfactant in adult ARDS patients, although improved delivery methods may make it possible to retest surfactant in selected patients with ARDS such as aspiration and pneumonia.

Inhaled carbon monoxide (CO)

CO produced by inducible enzyme heme oxygenase-1 (HO-1) during heme catabolism functions as a signaling molecule. In response to cellular stress, the HO-1/CO system activates anti-inflammatory, antioxidant, and anti-apoptotic defensive mechanisms while stimulating mitochondrial quality control programs and biogenesis. Pharmacological activation of the HO-1/CO system by inhaling low doses of CO results in protective effects against inflammation, oxidative stress, ischemia/reperfusion injury, sepsis, lung inflammation, ALI, and other pathological conditions. Thus, low-dose inhaled CO might be useful in critically ill patients, especially in those with sepsis and pneumonia-induced ARDS. However, some hurdles must be overcome before low-dose inhaled CO can be routinely used in patients; for instance, a ventilator-compatible system to deliver the gas and a safe, evidence-based dosing strategy must be devised. Fredenburgh *et al.* (65) proved that inhaled CO gas can be administered safely during mechanical ventilation; their clinically relevant nonhuman primate pneumonia model also provides preliminary evidence that this treatment might lead to earlier resolution of ALI by reducing extravascular fluid in the lungs. They found that inhaling CO at a concentration of 200 ppm for 60 minutes was able to achieve 6–8% COHb levels with ambient CO levels ≤1 ppm and was well tolerated. A phase II clinical trial is underway to test inhaled CO gas in critically ill patients with ARDS.

Novel peptide activating pulmonary edema clearance

Fluid homeostasis in the lung depends on Na+ ions being absorbed through apical epithelial sodium channels (ENaC). ENaC initiates transepithelial transport of Na+ ions on the surface and Na+/K+-ATPase drives excess fluid from the alveoli (14). Thus, activating ENaC is a useful approach to restore lung fluid homeostasis. Ware and Matthay (13) found that most ARDS patients have impaired alveolar fluid clearance and that maximal alveolar fluid clearance is associated with better clinical outcomes.

Recently, AP301, a synthetic peptide, has been reported to activate ENaC, promoting lung alveolar fluid clearance through a novel mechanism of ENaC activation. This peptide directly binds to intracellular carboxy-terminal of the α-subunit of ENaC, which increases the likelihood of the channel being open and thus enhances Na+ absorption (66,67). In a phase IIa randomized trial in 40 mechanically ventilated patients with pulmonary permeability edema, inhaled AP301 resulted in earlier and more pronounced reduction in extravascular lung water compared to placebo, indicating that the peptide activated alveolar clearance (68). A phase IIB/III trial will soon assess the safety and determine doses and efficacy for future phase III trials.

Future directions

Since the 1980s, several pharmacologic agents have failed in clinical trials for ARDS. Why have so many rationally chosen drugs proved ineffective? Reasons include the heterogeneity of underlying pathology, the heterogeneous

patient population, and the lack of an ideal animal model and specific biomarkers for early diagnosis. ARDS faces three relatively unique pharmacological challenges: (I) ARDS patients are vulnerable due to concomitant multiple organ dysfunction, so they may not tolerate off-target effects of drugs; (II) inhaled drug delivery is impeded by the proteinaceous fluid in the injured alveoli and the inhomogeneous ventilation distribution where the damaged lung area is not ventilated; (III) ARDS is heterogeneous in its underlying pathophysiology, so targeting one pathway is unlikely to improve most patients' outcomes. To find solutions for these three unique pharmacological challenges for the diverse ARDS population, a drug should concentrate in alveoli and target multiple alveolar cell types and cell processes. Nanomedicine primarily involves the use of nano-scale (usually 100 nm) drug carriers to improve the localization, kinetics, and sometimes pharmacodynamics of drugs. Pulmonary nanomedicine has the long-term potential to benefit nearly all lung diseases by increasing local concentrations of drugs in the lung and expanding the repertoire of drug formulations that can be used with attractive efficacy and safety profiles. Most nanomedicine-enhanced applications are likely to employ delivery by inhalation (69,70).

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Footnote

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