

Pharmacological Therapy for Acute Lung Injury

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Abstract: Many pharmacological therapies have been investigated for use in acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS). These therapies can broadly be classified as being either anti-inflammatory or physiology based. Despite promising pre-clinical and small clinical studies almost all therapies have been shown to be unsuccessful in large scale randomized controlled trials. The evidence for pharmacological treatment for ALI/ARDS is reviewed. Potential future treatments are also presented.

Keywords: Acute lung injury (ALI), acute respiratory distress syndrome (ARDS), pharmacological treatment, anti-inflammatory, ventilation, alveolar function.

INTRODUCTION

Mechanical ventilation, as a supportive treatment for respiratory failure, was popularised by Ibsen in Copenhagen during the polio epidemic in 1952. As polio caused neuromuscular failure the replacement of endogenous ventilation with mechanical ventilation was logical. However, for pulmonary pathologies which cause alveolar failure mechanical ventilation, although currently essential as supportive care, does not directly address alveolar failure and is potentially injurious. Delivering gases to the alveoli is only one component of the respiratory process. Gaseous diffusion and alveolar perfusion still need to occur and a ventilator does not target these mechanisms specifically. The options for alveolar failure are either alveolar replacement, *via* some form of extracorporeal gas exchange device, or a strategy for maximising endogenous alveolar function. This review will focus on pharmacological methods of maximising endogenous alveolar function, and will review the evidence for past, present and potential future pharmacological therapies for ALI/ARDS.

BASIS FOR PHARMACOLOGICAL TREATMENT STRATEGIES

ALI/ARDS are acute inflammatory conditions of the lung. The inflammatory process can be targeted for manipulation anywhere from the genome through to leukocyte activation and reactive oxygen species release (Fig. 1). This inflammation can injure all 3 major components of the alveolus; the airspace (epithelium), the interstitium, and the capillary (endothelium). Structural damage leads to functional impairment of each component and these component dysfunctions combine to result in alveolar failure (Fig. 2). Although an oversimplification,

therapy can thus be classified as being either anti-inflammatory or physiological in nature. Physiology based therapies seek to optimise individual component processes and can be classified as drugs affecting ventilation, diffusion or perfusion.

Anti-inflammatory therapy dampens the excessively harmful host response and can be classified as general anti-inflammatory therapy, inflammatory signalling modification or cellular response modification. Although it is theoretically attractive to pharmacologically decrease the inflammatory response, the complexity of the inflammatory process, and its interdependency with other homeostatic mechanisms such as coagulation, means this approach could potentially be detrimental. For any individual it is difficult to ascertain which components of inflammation are functional and necessary, and which components are dysfunctional and harmful. Immuno-paralysis, with the consequent development of infection, is a risk and makes the timing of potential anti-inflammatory therapy important.

Many therapies may mechanistically overlap and could potentially act synergistically. This has been comprehensively reviewed elsewhere [1]. Ultimately treatment of the cause is required, with mechanical ventilation being necessary for life saving respiratory support.

Anti-Inflammatory Therapy

(I) General Anti-Inflammatory Therapy

1. Glucocorticoids

Steroids act at many levels throughout the inflammatory process. Several early trials demonstrated that short course, high dose methylprednisolone is ineffective in preventing the development of ARDS in high risk patients [2-5]. Although an initial trial of high dose steroids early in the course of ARDS was negative [6], a recent study using prolonged low dose methylprednisolone showed reduced durations of mechanical ventilation and ICU stay [7].

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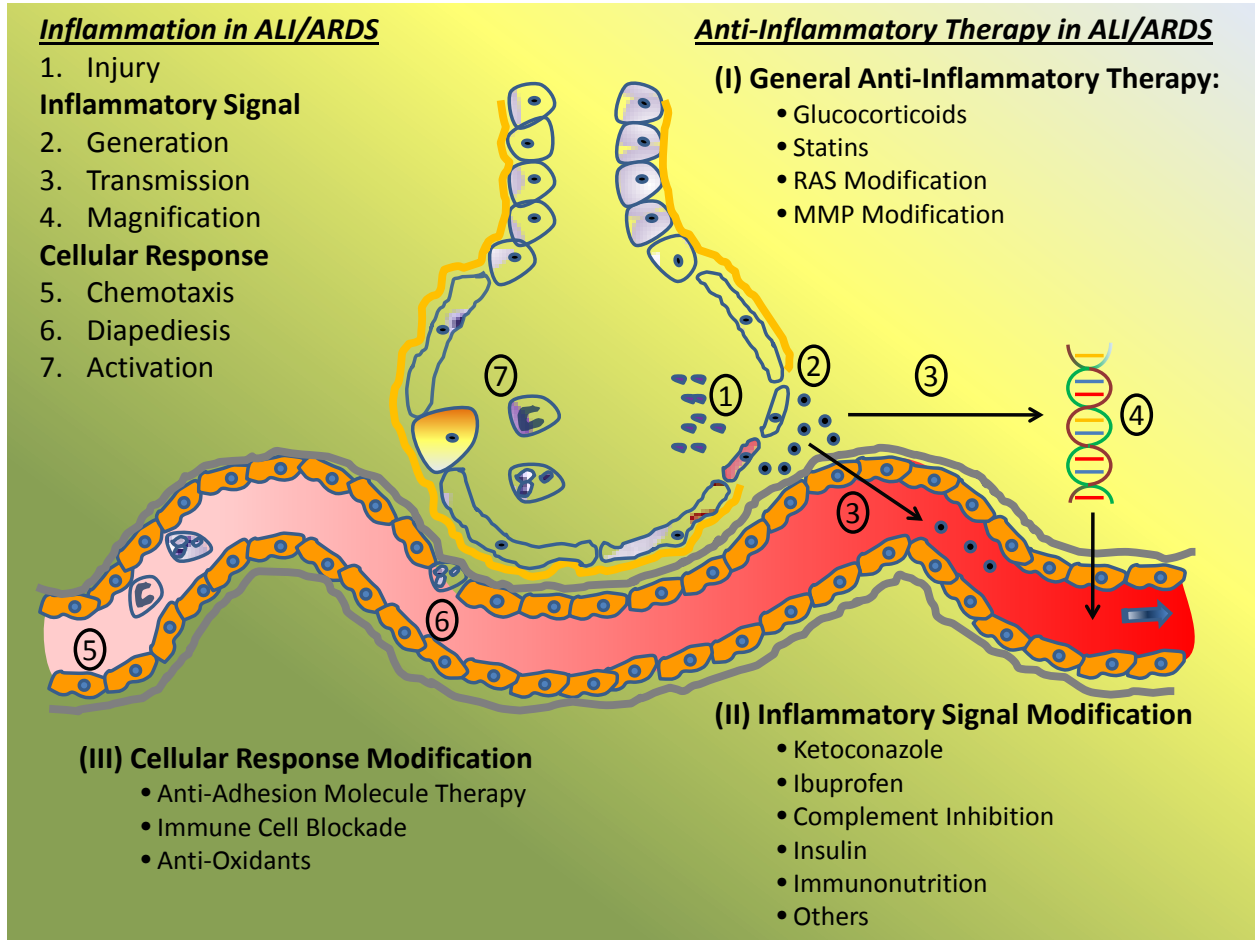


Fig. (1). Rationale for anti-inflammatory based drug therapies in ALI/ARDS. The diagram depicts an alveolus suffering a bacterial injury and generating an inflammatory response.

The anti-fibrotic properties of steroids have been investigated in the later stages of ARDS. Observational studies [8-11] and a small randomized controlled trial had positive results [12]. However, the subsequent multicentre Late Steroid Rescue Study conducted by the ARDSnet group demonstrated no effect on mortality [13]. More recently a meta-analysis [14] and a systematic review [15] have both concluded that steroids do not prevent ARDS but could be useful for treating ARDS. Further studies of low dose steroids in early ARDS are planned.

2. Statins

In addition to their cholesterol lowering effects statins improve epithelial and endothelial function to reduce alveolar capillary permeability and decrease pulmonary oedema. They also modulate the inflammatory cascade; regulate inflammatory cell recruitment, activation and apoptosis; and lessen cytokine and protease activity [16]. This may improve outcomes, as high levels and persistence of inflammatory mediators in ALI/ARDS are associated with poor outcome [17].

Observational studies of patients with sepsis suggest that prior statin use is associated with better outcomes [18-21]. Similarly, observational studies have suggested a beneficial

effect of prior statin therapy in patients with pneumonia, supporting a potential role for statins in modulating pulmonary inflammation [22-24].

Retrospective studies suggest prior statin therapy was associated with improved survival in sepsis and pneumonia [18-21, 24]. A prospective randomized controlled trial showed pre-treatment with statins reduced pulmonary markers of inflammation in a human experimental model of lung injury [25]. In a recent retrospective study statin use in patients with ALI/ARDS was associated with increased ventilator-free days and reduced mortality, although this was not statistically significant [26]. The recently completed HARP study (ISRCTN70127774) is investigating the effect of simvastatin in the prevention and treatment of ALI/ARDS and will further inform this area. Several groups, including ARDSnet and the Irish Critical Care Trials group, are currently considering undertaking multicentre studies to address the role of statins in ALI/ARDS.

3. Renin-Angiotensin System Modification

The SARS outbreak in 2003 affected over 8000 people in 25 countries across 5 continents killing 774 people worldwide in a matter of weeks [27]. It was due to infection with a novel coronavirus [28], the receptor for which was

discovered to be a variant of the angiotensin converting enzyme (ACE), termed ACE2 [29]. ACE2 functions to divert a local renin-angiotensin system (RAS) signal from the angiotensin 1 receptor (AT1R) to the angiotensin 2 receptor (AT2R). AT1R mediates vasoconstriction, alveolar permeability and fibrosis whilst the AT2R opposes these actions *via* vasodilation, decreased alveolar permeability, and apoptosis [30]. It was hypothesised that the SARS coronavirus downregulated ACE2 and impeded the counter-regulatory side of the RAS in the lung causing ARDS [29]. Several animal studies have implicated the RAS in the development of ARDS [31-35].

Genetic observational studies in humans have also implicated the RAS system in the development and outcome of ARDS [36, 37]. ACE activity correlates with the severity of lung injury in ARDS [38]. In a retrospective study prior treatment with an ACE inhibitor was associated with decreased mortality in patients requiring hospitalization for community acquired pneumonia [24]. Therapeutic modulation of the RAS has been investigated in rodents with recombinant ACE2, AT1R inhibition and ACE inhibitor studies all demonstrating amelioration of ARDS [29, 39-41]. Losartan, an AT1R antagonist, may reduce the damage caused by ventilator induced lung injury [42]. Human studies are awaited.

4. Matrix Metalloprotease Modification

The matrix metalloproteases (MMPs) are a group of structurally related zinc-dependent enzymes which together are capable of degrading all the components of the extracellular matrix (ECM). Many cell types in the lung are capable of MMP secretion, including alveolar macrophages, monocytes, neutrophils, endothelial cells, epithelial cells, and fibroblasts. In addition to regulation of ECM breakdown, MMPs may modulate the immune response and cell survival and may be pro-inflammatory. As MMPs are secreted from a variety of cells involved in the pathogenesis of ALI/ARDS, and have an important regulatory role on the ECM as well as inflammatory and immune function modulation, it follows that they may have a role in the evolution of ALI/ARDS.

Animal studies of lung injury suggest that MMP activity is up-regulated [43]. Similarly high levels of MMPs have been shown in ARDS patients [44-46]. Previous animal studies of MMP inhibition in ALI suggest that MMP inhibition is a potentially useful therapeutic option early in the course of ARDS [47]. However, up-regulation of MMP-9 activity at day 4 is associated with a reduction in pulmonary oedema [46]. These data caution against broad-spectrum MMP inhibition in ARDS. The timing of the intervention may be important. Early intervention may decrease proteolytic damage but later in the course of ALI, MMPs and in particular MMP-9, may be important in repair.

(II) Inflammatory Signalling Modification

1. Ketoconazole

Ketoconazole is an imidazole antifungal agent with anti-inflammatory properties. It blocks the synthesis of pro-inflammatory mediators such as the eicosanoid leukotrienes and thromboxane A2 and also reduces macrophage pro-inflammatory cytokine production [48]. Early small studies were successful in preventing ARDS in high risk patients

[49-51], however a later study by the ARDSnet group of ketoconazole in 234 patients with ARDS was negative [52].

2. Ibuprofen

Ibuprofen is a non-steroidal anti-inflammatory agent which inhibits cyclo-oxygenase. In a large sepsis study of 448 patients Ibuprofen diminished prostanoid production and was associated with trends towards decreased duration of pulmonary dysfunction and ARDS, but this did not reach statistical significance [53]. Modulation of other inflammatory mediators has also been investigated [54].

3. Complement Inhibition

Complement can contribute to ALI/ARDS by both propagating inflammation, *via* the generation of pro-inflammatory mediators [55], and also causing cellular injury *via* the production of the membrane attack complex, C5b-9 [56]. Complement receptor 1 is a cell surface receptor on erythrocytes and leukocytes which can inhibit both classical and alternative complement pathways. Initial animal studies [57, 58] and a small human phase 1 study [56] have confirmed that recombinant soluble cytokine receptor 1 is safe and can inhibit the complement cascade. Clinical trials are awaited.

4. Insulin

Insulin has anti-inflammatory effects *via* inhibition of the pro-inflammatory transcription factor NFkB [59]. A landmark trial of intensive insulin therapy (IIT) in critical care reported a large decrease in mortality by maintaining serum glucose levels between 80 and 110 mg/dL [60]. Subsequent critical care studies have had mixed results [61-63], and a significant risk of hypoglycaemia was apparent upon meta-analysis of intensive insulin therapy studies [64]. In a rat model of endotoxin induced ALI tight glycaemic control to 90-110mg/dl reduced the severity of lung injury [65]. The role of intensive insulin therapy in preventing ALI/ARDS by maintaining tight glycaemic control (80 to 110 mg/dL) is currently being studied in New York (NCT00605696).

5. Immunonutrition

Fish oils, which contain the omega 3 poly unsaturated fatty acids eicosapentaenoic acid (EPA), gamma-linolenic acid (GLA) and docosahexaenoic acid (DHA), can lessen the production of pro-inflammatory arachidonic acid metabolites. Clinical studies using fish oils in ALI/ARDS have demonstrated reduced inflammation in the form of decreased pulmonary neutrophil infiltration, improved physiology in the form of decreased microvascular permeability and pulmonary vascular resistance and improved outcomes in the form of reduced duration of ventilation and ICU stay and improved mortality [66-70]. The beneficial effects of fish oil supplementation in ALI/ARDS have been reiterated in a recent systematic review on immunonutrition [71]. The OMEGA trial, investigating omega 3 fatty acids, GLA and anti-oxidants in ALI has recently been presented at meeting level and reported negative findings. Full publication is awaited. Further studies of fish oils in ALI/ARDS are underway in Spain (ISRCTN63673813) and America (NCT00351533).

Additional uses for immunonutrition are the manipulation of the generation of carbon dioxide, *via* a low carbohydrate, high fat feed, resulting in decreased ventilator requirements [72]. Feeding enterally, rather than parenterally, can stimulate lung and gut IgA defences [73]. The early use of enteral nutrition by itself may improve outcomes in ALI [74].

6. Others

Interleukin 8 (IL-8) is a chemoattractant for neutrophil migration into the alveolus [75]. In a rat model of gastric aspiration anti-IL-8 antibody significantly reduced neutrophil recruitment to the alveolus and reduced the severity of lung injury [76]. Similarly, a rabbit model of acute pancreatitis induced lung injury was attenuated with anti-IL-8 antibody [77]. As IL-8 levels are elevated in at risk patients who subsequently develop ARDS [78] and in early ARDS [75, 79, 80] this represents a potential therapeutic target.

Other current studies of potential anti-inflammatory treatments include a trial investigating the safety, tolerability and efficacy of recombinant human interferon beta in ALI/ARDS (NCT00789685) and a phase 2 trial of IC14, a recombinant chimeric monoclonal antibody to CD14, to block CD14 mediated cellular activation in patients with sepsis-induced ALI (NCT00233207). This trial has recently been terminated and results are awaited.

(III) Cellular Response Modification

1. Anti-Adhesion Molecule Therapy

Transfer of immune cells from the vascular to the extravascular space is vital in the process of tissue inflammation. Blockage of CD18, a neutrophil adhesion molecule necessary for diapedesis, reduces the severity of experimental lung injury [81, 82]. Human data is awaited.

2. Immune Cell Blockade

Pentoxifylline [83-85] and its derivative lisofylline [86-89] have various inhibitory effects on immune cell function [83-85]. A small study using pentoxifylline in ARDS failed to show physiological improvements in either gas exchange or haemodynamics [90]. A large multicentre ARDSnet study of lisofylline in 235 patients with ALI/ARDS was negative [91].

Granulocyte-macrophage colony stimulating factor (GM-CSF) plays a role in the control of both alveolar macrophages and epithelial cells [92]. Alveolar macrophage tumour necrosis factor- α initiates alveolar epithelial repair by inducing autocrine epithelial GM-CSF signalling [93]. Higher GM-CSF levels in bronchoalveolar lavage fluid in ARDS patients correlates with improved survival [94]. Recombinant human GM-CSF improved oxygenation in a small placebo controlled study of 18 patients with sepsis related pulmonary dysfunction [95]. A further study of this agent in ARDS is ongoing in the USA (NCT00201409).

Neutrophil elastase, which is released by activated neutrophils, contributes to alveolar endothelial injury, increased permeability and airspace flooding [96, 97]. Sivelestat, a neutrophil elastase inhibitor, has had mixed results in clinical trials. A Japanese study demonstrated improved pulmonary function and reduced duration of ICU

stay with trends towards reduction in both duration of mechanical ventilation and mortality [98]. The subsequent larger international STRIVE study was stopped after an interim analysis due to an increase in 6 month all cause mortality [99]. Additionally, pulmonary function did not improve and 28 day mortality was not reduced.

3. Anti-Oxidants

Free radicals are highly reactive molecules due to the presence of unpaired electrons. Immune cells partly exert their injurious effects *via* the generation of these substances. Pulmonary levels of glutathione, an antioxidant, are known to be low in ARDS [100]. N-acetylcysteine and procysteine are precursors for this molecule and their administration can replete pulmonary glutathione levels in ARDS [101]. N-acetylcysteine has had mixed success in small ALI/ARDS studies [101-104], while a study of procysteine in lung injury was stopped early due to increased mortality (unpublished data). Additionally, N-acetylcysteine can also downregulate NF κ B, a pro-inflammatory transcription factor, with ensuing reductions in inflammatory markers.

Albumin exerts antioxidant effects *via* its thiol group. Non-survivors of ARDS have reduced thiol values [105]. The infusion of albumin is associated with increased plasma thiol levels in sepsis [106] and ARDS [107] and decreased markers of oxidant injury

Vitamins C & E may reduce the duration of mechanical ventilation and ICU stay, but not prevent the development of ARDS [108]. Based on the evidence to date routine use of anti-inflammatory therapy for ALI/ARDS is not recommended.

Physiological Derangement

(I) Ventilation

1. Surfactant

Surfactant is a multifunctional substance secreted by alveolar type 2 cells. It decreases alveolar surface tension preventing alveolar collapse during expiration, and has anti-inflammatory and antimicrobial properties¹. Local ventilation is hindered by surfactant deficiency during ALI/ARDS. This deficiency is both qualitative and quantitative, with reduced amounts of less functional surfactant produced during ALI/ARDS¹.

Although respiratory distress syndrome, the infantile form of ALI/ARDS, has been successfully treated with exogenous surfactant, adult studies have been disappointing. Small studies have shown physiological improvements [109-115], but subsequent larger studies have demonstrated no change in mortality [116, 117]. These findings have been confirmed in a recent meta-analysis, with improved oxygenation without improved duration of ventilation or mortality being the conclusion [118]. Further studies using different formulations, methods of delivery, timing of initiation of therapy, and duration of therapy are underway in response to criticisms of the earlier studies (NCT00682500), (NCT00215553) and (NCT00742482).

¹ Frerking I, Gunther A, Seeger W, Pison U. Pulmonary surfactant: functions, abnormalities and therapeutic options. *Intensive Care Med* 2001; 27: 1699-717.

2. Bronchodilators

Three small studies of inhaled beta-agonists demonstrated beneficial effects on lung mechanics by reducing airflow resistance, peak and plateau airway pressure, and improving lung compliance [119-121]. The BALTI trail, a phase 2 trial of the effect of intravenous salbutamol on the clearance of alveolar oedema, also demonstrated reduced peak airway pressures [122].

3. Mucolytics

Dornase alfa reduces sputum viscosity and improves sputum clearance by cleaving extracellular DNA released by degenerating leukocytes. Mucolytics improve lung function in cystic fibrosis [123-125] and have been investigated in other respiratory conditions. Dornase alfa reduced the duration of mechanical ventilation in children after cardiac surgery [126]. The successful use of Dornase alfa in patients undergoing mechanical ventilation for asthma [127] and ARDS [128] has been published only as case reports.

(II) Gas Diffusion

ALI/ARDS are forms of increased permeability pulmonary oedema. Strategies to minimise alveolar oedema include measures to limit the generation of alveolar flooding and measures to increase the resolution of this oedema.

1. Limitation of Generation of Alveolar Oedema

Alveolar flooding is primarily dependent on three factors, as described by Starlings law: capillary hydrostatic pressure, oncotic pressure and permeability. Capillary permeability is increased in ALI/ARDS, with the reflection coefficient being reduced from the normal 0.7-0.9 to about 0.5 [129]. In this setting potentially reducing hydrostatic pressure and/or increasing oncotic pressure may ameliorate the development of pulmonary oedema [130].

Hydrostatic pressure may be manipulated in a number of ways. Fluid intake can be restricted or fluid output increased, either with diuretics or renal replacement therapy. Vasomotor tone can be decreased with vasodilators. Cardiac filling pressures can be used to guide the above measures.

The ARDSnet FACTT study showed improved duration of ventilation and ICU stay with a restrictive fluid strategy [131]. Fluid management was governed by a complex protocol of diuretic therapy based on filling pressures. Patients in the fluid restrictive arm of the study averaged approximately a net fluid balance over 7 days of 0mls. Those in the liberal fluid arm averaged approximately plus 7000mls. Of note there was no increase in renal failure or organ hypoperfusion with the fluid restrictive strategy. Mortality was unchanged between the groups.

The reduction of both central venous [131] and pulmonary capillary wedge [132] pressures may be associated with improved outcomes in ALI/ARDS. However the use of a pulmonary artery catheter is not superior to the use of a central venous catheter for managing ALI/ARDS [133]. A positive fluid balance [134-137] and increased extravascular lung water (EVLW) [138] are both associated with poor outcomes. Using EVLW measurements with a PiCCO device to direct fluid management may be better than pulmonary artery wedge pressure based management [139]. As lung size is dependent on height rather than weight the

use of EVLW indexed to predicted body weight is superior to EVLW indexed to actual body weight (Craig - in press Critical Care Medicine, ISRCTN70127774).

Renal replacement therapy has been shown to reduce pulmonary oedema *via* reductions in pulmonary vascular pressures and permeability in experimental models of lung injury. Human experience has been limited to two small observational studies. 10 children with ALI/ARDS after bone marrow transplantation or chemotherapy treated with RRT had an 80% survival rate in contrast to a historical survival of 15% [140]. Thirty seven adults with renal failure and ALI/ARDS treated with RRT and a zero fluid balance had no pulmonary improvements within the first 24 hours of treatment [141]. The role of RRT in the management of ALI/ARDS remains uncertain.

The choice of fluid for resuscitation in ALI/ARDS remains unclear. Theoretically a colloid with higher oncotic pressure would be more suitable than a crystalloid, but this has not been borne out in a large comparative study of saline versus albumin for fluid resuscitation in critical illness [142].

Hypoproteinaemia is associated with the development of lung injury and is a marker of weight gain and death [143, 144]. Two small studies have investigated the use of furosemide with albumin infusions in hypoproteinaemic patients with acute lung injury. Both showed increases in total serum protein and more negative fluid balances with furosemide and albumin administration. This was associated with improvements in oxygenation, but without improving mortality [145, 146].

An Oregon based study is presently investigating whether minimising EVLW, as measured by PiCCO and directed by the FACTT diuretic algorithm, is superior to central venous pressure guided therapy (NCT00624650). A phase 2 study investigating the role of recombinant human atrial natriuretic peptide (Carperitide) in minimising pulmonary oedema in ARDS has recently completed and its report is awaited (NCT00030121).

Lung injury is often heralded by a rise in pulmonary vascular resistance², with an imbalance between pulmonary vasoconstrictors and vasodilators being seen in animal endotoxin shock models^{3,4}. Intravenous adenosine reduces EVLW⁵, whilst intravenous nitroprusside and nitroglycerin also reduce pulmonary oedema generation, but at the expense of increasing V/Q mismatch^{6,7}. To date there is no

² Nakazawa H, Noda H, Noshima S, *et al.* Pulmonary transvascular fluid flux and cardiovascular function in sheep with chronic sepsis. *J Appl Physiol* 1993; 75(6): 2521-8.

³ Hales CA, Sonne L, Peterson M, Kong D, Miller M, Watkins WD. Role of thromboxane and prostacyclin in pulmonary vasomotor changes after endotoxin in dogs. *J Clin Invest* 1981; 68: 497-505.

⁴ Ichinose F, Zapol WM, Sapirstein A, *et al.* Attenuation of Hypoxic Pulmonary Vasoconstriction by Endotoxemia Requires 5-Lipoxygenase in Mice. *Circ Res* 2001; 88(8): 832-8.

⁵ Kutzsche S, Lyberg T, Bjertnaes LJ. Effects of adenosine on extravascular lung water content in endotoxemic pigs. *Crit Care Med* 2001; 29: 2371-6.

⁶ Gottlieb SS, Wood LDH, Hansen DE, Long GR. The Effect of Nitroprusside on Pulmonary Edema, Oxygen Exchange, and Blood Flow in Hydrochloric Acid Aspiration. *Anesthesiology* 1987; 67(2): 203-10.

⁷ Radermacher P, Santak B, Becker H, Falke KJ. Prostaglandin E1 and Nitroglycerin Reduce Pulmonary Capillary Pressure but Worsen Ventilation-Perfusion Distributions in Patients with Adult Respiratory Distress Syndrome. *Anesthesiology* 1989; 70(4): 601-6.

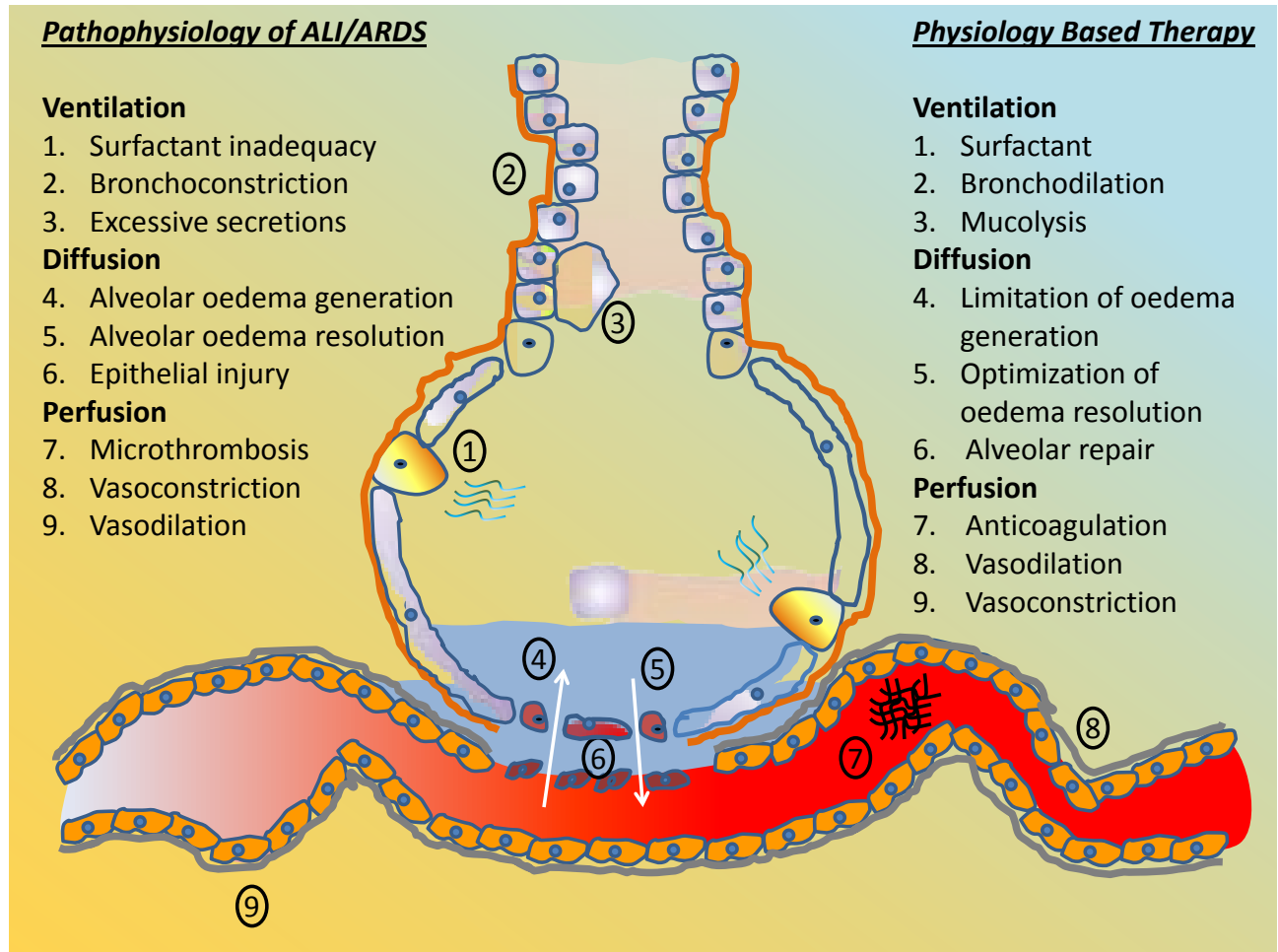


Fig. (2). Rationale for physiology based drug therapies for ALI/ARD. The diagram depicts the bronchoalveolar pathophysiological consequences of the inflammatory process of ALI/ARD.

clear evidence to support the role of vasodilator treatment targeted to decrease hydrostatic pressure in ALI/ARDS.

2. Maximising Clearance of Alveolar Oedema

Alveolar fluid clearance (AFC) is impaired in over 50% of those with ALI/ARDS, with this group having higher mortality rates [147]. Beta-agonists upregulate AFC *via* an effect on sodium ion movement [148]. Aerosolized salbutamol has been shown to accelerate the resolution of pulmonary oedema after lung resection [149]. A clinical trial of intravenous salbutamol in ARDS demonstrated reduced extravascular lung water and a trend towards increased survival [150]. A retrospective study of salbutamol exposure in ALI suggested an association between higher exposure and improved outcome [151]. Beta 2 agonists may exert several other beneficial effects in ALI/ARDS including increased surfactant secretion, decreased lung endothelial permeability, decreased airway resistance and decreased airway pressures [150]. A large phase 3 UK multicentre study is currently in progress examining the effects of intravenous salbutamol on outcome in ARDS (ISRCTN38366450). The ARDSnet group have recently terminated a multicentre, randomized, placebo controlled study investigating albuterol for the treatment of ALI (ALTA

trial) [152]. This study was halted early for futility after studying 279 patients who received the active drug. There was no reduction in duration of ventilation or 60 day mortality with albuterol. It has been speculated that this result may be due to 2 factors [153]. Firstly, this study was performed in a less sick ALI population likely to have retained an ability to clear alveolar fluid without the need for exogenous upregulation, rather than a sicker ARDS population. Additionally, inadequate delivery of the drug to the alveolus may have contributed to this failure.

The alveolar epithelium contains active glucose-sodium co-transporters [154] and alveolar glucose levels correlate with experimental alveolar fluid clearance [155]. In the setting of increased permeability higher alveolar glucose levels could theoretically improve AFC, however higher airway glucose concentrations are associated with increased risk of nosocomial infection in critically ill patients [156]. The effect of tight blood glucose control in critically ill patients on AFC is unclear and requires evaluation.

Gene therapy to increase the expression of the ion channels and pumps needed for AFC is another possible future therapy. An animal study investigating overexpression of the beta-1 subunit of the sodium-potassium ATPase pump

demonstrated increased rates of AFC and improved survival [157]. If the alveolar epithelium is badly injured then cellular regeneration may be required before a functioning epithelial layer can be manipulated.

3. Epithelial Repair

Stem cells have the capacity for limitless self-renewal and differentiation. Embryonic stem cells are pluripotent and have the ability to differentiate into any cell type in the body, whilst adult stem cells are multipotent and have the ability to differentiate into several cell types, including cell types of other organ systems [158].

Stem cells provide 3 therapeutic opportunities [158]. Firstly, endogenous stem cells may be stimulated *via* exogenously administered growth factors. Hepatocyte growth factor [159] and transforming growth factor α (TGF α) [160] have been shown to reduce the effects of acute lung injury in animal models. Epidermal growth factor [161, 162], TGF α [163] and KGF [164, 165] can all up regulate AFC. Vascular endothelial growth factor (VEGF) promotes angiogenesis and regulates vascular permeability [166]. Genetic polymorphisms of the VEGF gene are associated with lower levels of VEGF and increased mortality in ARDS [167]. The administration of VEGF enhances alveolar repair in both cell [168] and animal models [169] and its role in ARDS is currently being studied at Cornell University (NCT00319631). The administration of exogenous growth factors has not yet been directly studied in human trials of ALI/ARDS.

Keratinocyte growth factor (KGF) is a heparin-binding growth factor that is secreted by fibroblasts and is known to act *via* a receptor specific to epithelial cells [170]. It induces potent proliferative activity in a variety of epithelial cells including alveolar type 2 cells. Other potentially useful effects include cytoprotection, augmented surfactant secretion and an antioxidant effect [171-172]. KGF reduces the severity of lung injury in experimental models [171, 173-174]. A phase 2 study investigating the effects of KGF pre-treatment in adults using an inhaled LPS model of lung injury is currently underway (ISRCTN98813895).

Secondly, administration of exogenous stem cells, either embryonic or adult, can provide repair to an injured alveolus. In an LPS induced ALI model bone marrow progenitor cells localised to the site of injury and differentiated into endothelial and epithelial cells [175]. Embryonic stem cells have the ability to produce a fully differentiated airway epithelium when cultured in an air-liquid interface [176]. Patients with pneumonia [177] and ALI/ARDS [178] have higher levels of endothelial progenitor cells and this higher level correlates with outcome. Autologous transplantation of endothelial progenitor cells preserves endothelial function and maintains the integrity of the pulmonary alveolar-capillary barrier in an animal study [179]. Mesenchymal stem cells were originally thought to act as a source of regenerative cells by differentiating into, and locally replacing, lethally injured cells. However their primary mechanism of action is *via* the secretion of growth factors, cytokines and other signalling molecules to cause the trophic modulation of inflammation, cell death, fibrosis and tissue repair [180].

The third role of stem cells is their ability to deliver gene therapy to the injured lung. Endothelial progenitor cells have been used to deliver vasodilatory genes to the pulmonary vasculature with resultant decreases in pulmonary artery pressures in experimental pulmonary hypertension [181, 182]. Human studies are awaited.

(III) Perfusion

1. Vasodilators

Nitric oxide (NO) is an endogenous vasodilator produced by the endothelium. When administered by inhalation it vasodilates the circulation of ventilated alveoli thus reducing shunt and pulmonary hypertension. Its short half life and apparent lack of side-effects made it an attractive therapy. Early studies demonstrated physiological improvements with NO in ARDS [183-187], however mortality remained unchanged. Two meta-analyses showed no mortality benefit [188-189] and reported possible harm due to methaemoglobinaemia, toxic nitrogen compounds, increased pulmonary oedema, rebound pulmonary hypertension and renal failure. As NO is expensive, possibly harmful, and without a mortality benefit, its routine use is not recommended although it may have a place as rescue therapy for severe hypoxaemia given its ability to improve oxygenation [190].

Prostacyclins are derivatives of arachadonic acid and have potentially beneficial effects including vasodilation, inhibition of platelet aggregation, reduction of neutrophil adhesion, and inhibition of both macrophage and neutrophil activation [191]. Inhaled PGI₂ (prostacyclin) has been compared to inhaled NO in ARDS [192-194]. PGI₂ has similar efficacy and some advantages including minimal systemic effects, absence of platelet dysfunction, easy administration, harmless metabolites and no requirement for monitoring [195]. No placebo controlled randomized trial has yet studied PGI₂ in ARDS, but a current Pakistani study aims to show that nebulized PGI₂ (iloprost) decreases pulmonary hypertension selectively and improves oxygenation in ARDS (NCT00314548).

Intravenous prostacyclin in the form of PGE₁ has also been investigated in ARDS. Although vasodilatory effect can cause hypotension and increase pulmonary shunting [196], prostacyclin is anti-inflammatory and can increase both cardiac output and oxygen delivery [197] and improve oxygen extraction during reduced oxygen delivery [198]. Early studies [199-201] in ARDS showed no significant benefit although the dose delivered was questioned [202]. PGE₁ was reformulated as liposomal PGE₁ in order to increase pulmonary drug delivery and minimise side effects. Again despite a promising preclinical study [203] further studies were negative [204, 205].

Endothelin 1 is a potent vasoconstrictor which has been implicated in the pathophysiology of lung injury [206-208]. Tezosentan, an endothelin receptor antagonist, has been investigated in animal models of lung injury and with mixed results thus far [209, 210].

2. Vasoconstrictors

Almitrine is a pulmonary vasoconstrictor which may increase hypoxic pulmonary vasoconstriction and reduce shunt. In a small ARDS study oxygenation was improved

with minimal increase in pulmonary vascular pressures [211]. The combination of intravenous almitrine to decrease blood flow to hypoxic lung units and inhaled NO, to increase blood flow to ventilated lung units, has been investigated in both experimental lung injury⁸, and a small clinical study [212]. Both found the combination superior than either therapy alone at increasing PaO₂ with a minimal rise in pulmonary artery pressure. Further research is required.

3. Coagulation

An imbalance between fibrinogenesis and fibrinolysis in ARDS results in widespread fibrin deposition in the alveolar airspace, interstitium and blood vessels [213]. Pulmonary intravascular thrombosis and vasoconstriction can lead to the development of dead space, a known independent predictor of mortality in ARDS [214]. Several anticoagulants have been proposed as potential therapies in ALI/ARDS and have undergone investigation in animal models. Tissue factor pathway inhibitor (TFPI), factor VIIa, heparin, antithrombin III, activated protein C (APC) and thrombomodulin have all been shown to have beneficial effects at this level of investigation [215].

Protein C levels are lower in patients with ARDS than normal controls and the level of protein C correlates with clinical outcome [216]. However, a small randomized controlled trial of APC in ARDS did not reduce either duration of ventilation or mortality. (156) A Dutch study investigating APC in inflammatory and infectious ALI/ARDS is currently in progress (ISRCTN52566874). A phase 2 trial of recombinant TFPI demonstrated improvements in lung dysfunction score and survival [217]. Antithrombin III has had mixed results on pulmonary function in sepsis studies [218-220].

Reasons why Pharmacological Therapy is Ineffective in ALI/ARDS

Despite repeated promising pre-clinical and clinical phase 1 and 2 studies of therapies for ALI/ARDS, no non-ventilatory strategy has yet convincingly improved outcomes. This situation is not unique to lung injury. Over the past 30 years just 3 out of 38 new therapies evaluated for sepsis returned positive results [221]. All three therapies have since been seriously questioned and their place is presently unclear.

There are many reasons for the scientific failure of translation from bench to bedside [222]. Animal studies, which inform higher levels of clinical study, suffer from numerous limitations including the lack of generalization of inter-species physiology, immunology, genetics and host response to injury. The use of young healthy animals and pre-treatment before injury models directly contradicts true clinical practice. Large randomized controlled trials suffer from a heterogeneous study population which usually lacks identification of the phenotype most likely to receive a beneficial effect from the study drug. Allied with a small signal from the study intervention in comparison with the large signal from the multiple co-morbidities suffered by

most elderly patients, genuine positive interventional effects may be difficult to recognise. The use of outcome measures such as oxygenation in a condition in which only a small minority die from refractory hypoxemia [223, 224] makes this signal even more difficult to recognise.

The use of pharmacological agents as adjuncts to increase oxygenation allowing the limitation of injurious ventilation may be associated with improved outcomes but this remains to be tested.

CONCLUSION

Despite promising scientific advances, non-ventilatory strategies for ALI/ARDS remain elusive. The best evidence we have is for minimising pulmonary oedema *via* fluid restriction when appropriate. Other therapies may occasionally be justified as salvage therapy in severe ALI/ARDS, but with the knowledge that their risk benefit ratio remains unclear.

CONFLICT OF INTEREST

The authors have no conflicts of interest to report. This review article is based upon a book chapter entitled "Non-ventilatory strategies for acute lung injury and the acute respiratory distress syndrome" due to be published in "An Evidence Based Practice of Critical Care" (Deutschman CS, Neligan P (Editors), Elsevier (Publisher).

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