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Is There a Role for β-Adrenoceptor Agonists in the Management of Acute Lung Injury and the Acute Respiratory Distress Syndrome?

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Abstract

Despite improvements in general supportive care and ventilatory strategies designed to limit lung injury, no specific pharmacological therapy has yet proven to be efficacious in the management of acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS). Based on experimental studies, as well as studies of the *ex-vivo* human lung, pulmonary edema fluid clearance from the alveolar space can be augmented by both inhaled and systemic β_2-adrenoceptor agonists (β_2-agonists). Additionally, in the presence of lung injury, β_2-agonists may reduce lung vascular permeability. Treatment with β_2-agonists may also increase the secretion of surfactant and have anti-inflammatory effects. In view of these potentially beneficial effects, β_2-agonist therapy should be evaluated for the treatment of lung injury in humans, particularly because they are already in wide clinical use and do not seem to have serious adverse effects in critically ill patients.

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are characterized by a constellation of clinical, radiological and physiological abnormalities, resulting in acute respiratory failure due to alveolar epithelial and lung endothelial injury (figure 1).

Two well-designed epidemiological studies estimating the incidence of ALI and ARDS have been published recently. The Australia and New Zealand Intensive Care Society Clinical Trials Group have estimated the incidence of ALI and ARDS as 34 and 28 cases per 100 000 per year, respectively.[1] The second study reported the incidence of ALI/ARDS in hospitals that participated in the ARDS Network low tidal volume trial[2] and extrapolated these results to estimate incidence rates for the US. The average incidence of ALI/ARDS in the ARDS network registry was 2.2 cases per intensive care unit (ICU) bed per year.[2] The incidence of ALI in the US has been estimated as 22–64 cases per 100 000 per year.[3] Although improvements in general supportive care have contributed to a decrease in mortality over the last 10 years,[4,5] mortality associated with ARDS remains high, between 30% and 65% depending on the population that has been studied.[2,4,6]

A recent review provided a comprehensive overview of the potential role of pharmacotherapy in the management of ARDS.[7] In their initial description, Ashbaugh et al.[8] described using "a clinical trial of a variety of drugs, respirators and fluid regimen" with limited success. Despite active investigation over the past 30 years, little progress has been made in identifying an effective pharmacological agent for the treatment of this condition. However, there is increasing evidence that β-adrenoceptor agonists (β-agonists) may have a potential role in the management of ARDS. This review will discuss the pathophysiological basis for the mechanism of action of β_2-agonists in ARDS and review the evidence supporting a potential role for their use in the management of this condition. The potential beneficial and adverse effects of β_2-agonists in the treatment of patients with ALI/ARDS are presented in tables I and II.

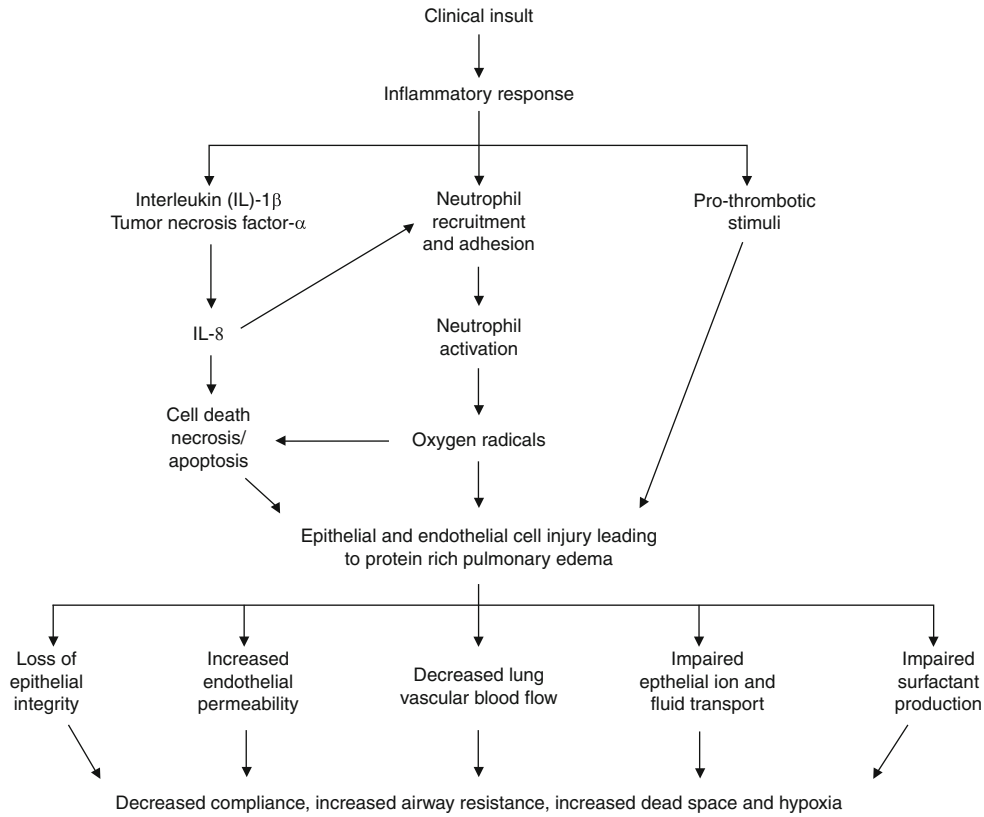

Fig. 1. Clinical and physiological abnormalities leading to the development of acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) following pulmonary epithelial and endothelial damage.

1. Lung Epithelial and Endothelial Function

1.1 Alveolar Epithelial Fluid Clearance

The normal alveolar epithelium acts as a tight barrier to prevent alveolar flooding and has an important role in the active transport of fluid from the alveolar to the interstitial space. Alveolar fluid clearance is dependent on active sodium and chloride transport. The alveolar type II cell appears to be responsible for most of the ion transport via the apical sodium and chloride conductive pathways and the basolateral sodium-potassium activated adenosine triphosphatase (Na^+, K^+-ATPase) activity, although the alveolar type I cell and distal airway epithelium may also contribute to sodium and chloride ion transport.[9]

Early ALI/ARDS is characterized by diffuse alveolar epithelial and endothelial injury with increased pulmonary endothelial permeability and pulmonary edema. In the majority of patients with ALI/ARDS alveolar fluid clearance is impaired; maximal alveolar fluid clearance was associated with better clinical outcomes (figure 2).[10] The ability of the alveolar epithelium to remove edema fluid is an important first step in recovery from ALI/ARDS and the degree of alveolar epithelial injury is an important predictor of outcome.[10-12] The normal mechanisms regulating alveolar fluid clearance appear to be intact in mild-to-moderate lung injury[13,14] (figure 3) and in some instances are upregulated.[15,16]

Several experimental studies in animals, as well as in the *ex-vivo* human lung, have demonstrated that β_2-agonists accelerate the rate of alveolar fluid clearance.[17-19] It has been hypothesized that the mechanism underlying increased alveolar fluid clearance induced by β_2-agonists is due to an increase in intracellular cyclic adenosine monophosphate (cAMP), which results in increased sodium transport across alveolar type II cells by upregulation of the apical sodium and chloride pathways and Na^+, K^+-ATPase and probably the cystic fibrosis transmembrane conductance regulator (CFTR) activity.[9] Suggested mechanisms for the upregulation of sodium transport proteins by cAMP include augmented sodium channel open probability, increases in Na^+, K^+-ATPase α-subunit phosphorylation, as well as increased trafficking of epithelial Na^+ channels (ENaC) to the apical membrane and Na^+, K^+-ATPases to the basolateral membrane.[9] β_2-Agonists have been shown to increase both the expression[20] and activity[21] of sodium transport channels in the type II alveolar cells, as well as CFTR.

Table I. Potential beneficial effects of β_2-adrenoceptor agonists in the treatment of acute lung injury/acute respiratory distress syndrome

Target	Action
Lung epithelial and endothelial function	Increases alveolar fluid clearance; reduces pulmonary endothelial permeability; epithelial cytoprotection
Neutrophil function	Decreases neutrophil adhesion via inhibition of neutrophil Mac-1 cell surface expression and reduced epithelial intercellular adhesion molecule-1 expression; decreases neutrophil chemotaxis; decreases release of neutrophil mediators via neutrophil membrane stabilization; down-regulation of neutrophil priming and decreased release of neutrophil oxidative products; induces neutrophil apoptosis
Cytokine production	Inhibits nuclear factor-kappa B activation and translocation; decreases pro-inflammatory cytokine production; increases interleukin-10 production
Coagulation	Decreases activation of coagulation system; increases fibrinolysis
Surfactant	Increases surfactant secretion
Respiratory mechanics	Reduces airflow resistance and peak airway pressure; reduces plateau pressure with improvement in respiratory system compliance

cAMP stimulation has also been shown to upregulate fluid transport in the presence of septic or hypovolemic shock,[16,22] hydrostatic edema,[23-25] and experimental hyperoxic lung injury[14,26,27] (figure 3). β-Adrenergic stimulation restores alveolar fluid clearance in an animal model of ventilator-associated lung injury.[28] In addition, β_2-agonists can overcome the depressant effects of hypoxia on alveolar fluid clearance.[29,30] Also, salmeterol, a long-acting β_2-agonist, has been associated with a reduction in the incidence of high altitude pulmonary edema in susceptible patients.[31] Patients susceptible to high altitude pulmonary edema have impaired basal transepithelial sodium and fluid transport, suggesting a genetic defect of sodium and fluid transport, which is likely to be further impaired by hypoxia. One possible mechanism for the beneficial effect of salmeterol may be upregulation of alveolar fluid clearance.[31]

Denopamine, a β_1-agonist, causes a dose-dependent increase in alveolar fluid clearance in *ex vivo* rat and guinea pig lungs.[32] Although high concentrations of denopamine increased intracellular cAMP levels, at lower concentrations, which caused an increase in alveolar fluid clearance, denopamine failed to increase cAMP levels, suggesting that the mechanism of action for improved alveolar fluid clearance is, at least in part, cAMP independent.[32] However, β_2-adrenergic stimulation is more important in increasing alveolar epithelial sodium and fluid transport. Dopamine, at doses associated with only a β_1-agonist effect, whether given intra-alveolar or intravenously, had no effect on alveolar fluid clearance *in vivo* in rats.[33] Additionally, the increase in alveolar fluid clearance induced by dobutamine was blocked by selective β_2-antagonists.[33]

1.2 Pulmonary Endothelial Permeability

β-Adrenergic stimulation reduces pulmonary vascular endothelial permeability in animal models of ALI.[34-37] It has also been reported that activation of β-adrenergic receptors can reduce vascular endothelial permeability in the systemic circulation.[38] Isoproterenol (isoprenaline) has also been shown to attenuate the increase in endothelial permeability induced by high vascular pressure.[39] One study demonstrated that β_2-agonists reduced lung edema in isolated rat lungs subjected to ischemia/reperfusion injury both by restoring pulmonary endothelial permeability and upregulating alveolar fluid transport.[36] In this study, edema formation was maximal when epithelial fluid transport was inhibited. Isoproterenol reduced edema formation when epithelial fluid transport was inhibited, indicating improvement in endothelial permeability, but reduced edema formation further when epithelial fluid transport was not inhibited, indicating an additional effect on upregulation of alveolar fluid transport.[36] In acid aspiration-induced lung injury, clinically relevant airspace concentrations of

Table II. Potential adverse effects of β_2-adrenoceptor agonists in the treatment of acute lung injury/acute respiratory distress syndrome

Tachycardia and arrhythmia
Hypokalemia
Hyperglycemia
Increased risk of nosocomial infection
Lack of effect due to extensive alveolar epithelium and endothelial injury
β-Adrenoceptor down-regulation with attenuation of effect
β-Adrenoceptor genetic polymorphisms associated with variable effect
Pulmonary edema in pregnancy associated with the use of β_2-agonists as tocolytics

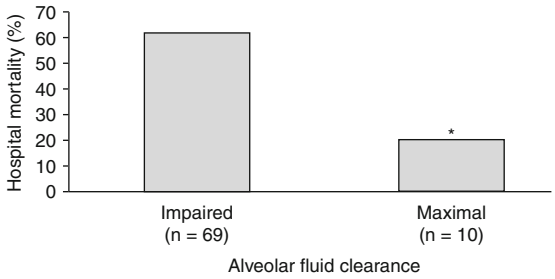

Fig. 2. Plot of hospital mortality in two groups of patients with acute lung injury or acute respiratory distress syndrome; those with maximal alveolar fluid clearance (i.e. >14% per hour), and those with impaired alveolar fluid clearance (i.e. <14% per hour). The mean rate of alveolar fluid clearance in the maximal clearance group was 34 ± 28% per hour. These threshold levels were determined on the basis of extrapolations from studies in the *ex vivo* human lung. Alveolar fluid clearance was measured from the change in protein concentration between two pulmonary edema fluid samples during the first 4 hours after intubation. Columns represent the hospital mortality rate in each group (* $p < 0.02$ vs impaired alveolar fluid clearance) [reproduced from Ware and Matthay,[10] with permission].

albuterol (salbutamol), administered following acid injury, reduce pulmonary edema both by increasing alveolar fluid clearance and decreasing endothelial permeability.[40]

1.3 Hemodynamic Effects and Lung Edema Formation

In addition to causing vascular smooth muscle relaxation β_2-agonists have positive chronotropic and inotropic effects.[41] The resultant hemodynamic effect is an increase in cardiac output with an associated increase in systemic and pulmonary arterial pressure.[42] Pulmonary edema formation increases as pulmonary arterial blood flow and pressure increases.[43] It is possible that β_2-agonists, by increasing pulmonary artery pressure or blood flow, an effect that occurs in animals in response to β_2-agonists delivered to the airspaces,[44] may increase edema formation. However, the net effect is an overall reduction in lung edema due to increased alveolar fluid resorption and a reduction in endothelial permeability.

1.4 Epithelial Cytoprotection and Repair

There is also some evidence that β_2-agonists have a cytoprotective action. β_2-agonists cause a reduction in ultrastructural epithelial damage caused by bacteria, bacterial toxins and inflammatory mediators such as elastase, probably by maintaining intracellular levels of cAMP.[45,46] The process of cell migration and wound repair involves cAMP-dependent mechanisms. Isoproterenol increases migration of bovine epithelial cells and accelerates closure of mechanically and enzymatically induced injury of monolayers.[47]

2. Neutrophil Function, Oxidative Stress and Inflammatory Mediators

The acute phase of ALI/ARDS is characterized by infiltration and activation of neutrophils and inflammatory cytokines. It is likely that neutrophils have a central role in the development of lung injury.[48] Pulmonary neutrophil sequestration occurs early in the development of ALI/ARDS[49] and neutrophil activation seems to be an important step in mediating tissue damage.[50] There is considerable evidence of oxidative damage in ALI/ARDS,[51,52] and activated neutrophils secrete a variety of oxidants and granular enzymes that probably contribute to the endothelial and epithelial injury.[53,54] Furthermore, neutrophil-dependent oxidant injury to the alveolar epithelium can inhibit β-adrenergic dependent alveolar fluid clearance.[55-57]

2.1 Neutrophil Function

2.1.1 Neutrophil Adhesion

β-Adrenergic induced elevation of intracellular cAMP inhibits neutrophil adhesion to bronchial epithelial cells[58] and vascular endothelium[59] through inhibition of neutrophil Mac-1 cell surface expression. In addition, β_2-agonists reduce intercellular adhesion molecule (ICAM)-1 expression in stimulated bronchial epithelial cells.[60] Furthermore, in animal models, β_2-agonists have been shown to inhibit neutrophil adhesion to the vascular endothelium.[61]

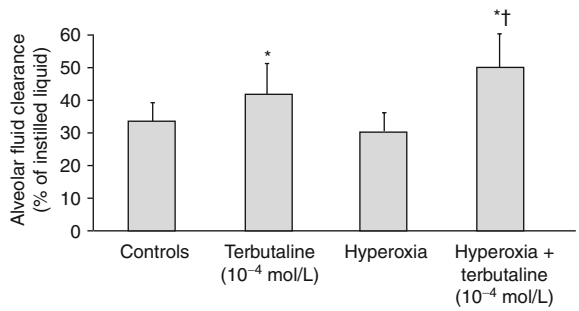

Fig. 3. The effects of terbutaline on alveolar fluid clearance in rats exposed to 100% oxygen (hyperoxic) compared with rats exposed to room air. Amiloride reduced the rate of active sodium transport by approximately 50% in both groups (data not shown). Alveolar fluid clearance increased to 42 ± 7% in rats exposed to room air and to 50 ± 10% in hyperoxic-injured rats after terbutaline stimulation (* $p < 0.05$ vs control rats, † $p < 0.05$ vs hyperoxia). These findings indicate that in a rat model of moderate hyperoxic lung injury alveolar epithelial fluid clearance mechanisms are intact and up-regulated by β-adrenoceptor agonists (reproduced from Garat et al.,[14] with permission).

2.1.2 Neutrophil Accumulation

β_2-Agonists decrease systemic blood neutrophilia in rats[62] and pulmonary neutrophil sequestration *in vivo* in humans[63] in response to platelet-activating factor. Although not all studies are consistent,[64] the majority show that β_2-agonists inhibit neutrophil chemotaxis.[65-68] One study has demonstrated a dose-dependent effect, with therapeutic concentrations of β_2-agonists increasing and supratherapeutic concentrations inhibiting neutrophil chemotaxis.[69] The mechanism by which β_2-agonists inhibit chemotaxis may be due, only in part, to increased levels of cAMP.[67]

2.1.3 Neutrophil Function and Mediator Release

The production of neutrophil oxidant products and oxidant-mediated cytotoxicity is reduced by β-adrenergic stimulation,[70-72] although the dose of β_2-agonists required to achieve this effect may be supratherapeutic.[71] In addition, there is evidence that β_2-agonists may have a biphasic effect on release of oxidative products with lower concentrations increasing and supratherapeutic concentrations inhibiting release of oxidative products.[69,73] The mechanism by which β_2-agonists reduce oxidative stress appears to be via both β-adrenoreceptor stimulation and intrinsic reactive oxygen scavenging ability.[71,74,75] There is also evidence that β-adrenergic stimulation may have a differential effect on intra- and extracellular oxidant production, with one study demonstrating that adrenaline (epinephrine) reduces the generation of extracellular oxygen metabolites likely to mediate tissue injury while maintaining intracellular oxidant production for phagocytosis.[76] β-Adrenergic stimulation also causes down-regulation of neutrophil priming.[77,78]

2.1.4 Apoptosis

When neutrophils fail to undergo apoptosis and die by necrosis, they induce an inflammatory response that contributes to tissue injury. There is some preliminary evidence that β_2-agonists induce apoptosis in neutrophils. Apoptosis, as measured by nuclear morphology, was increased in isolated neutrophils incubated with salmeterol for 20 hours.[79] The action of salmeterol was completely reversed by both a non-selective and a selective β_2-antagonist. Similar effects were seen with a phosphodiesterase-4 inhibitor. These findings suggest the effect of salmeterol is mediated by β_2-adrenergic receptor activation and elevation of cAMP.[79]

2.2 Cytokines

A complex network of cytokines, pro-inflammatory and anti-inflammatory, are involved in the inflammatory response in ALI/ARDS. The balance between pro- and anti-inflammatory cytokines is likely to be critical in the development and persistence of ALI/ARDS.[80,81] Levels of bronchoalveolar lavage (BAL) fluid interleukin (IL)-8, are increased in patients at risk of ALI/ARDS who subsequently develop ALI/ARDS. Furthermore, pulmonary macrophages from patients who developed ARDS contained higher levels of IL-8 than those who did not, suggestive of the fact that pulmonary macrophages were, in part, the cellular source of IL-8. Levels of IL-8 in blood did not predict development of ALI/ARDS.[82,83] Tumor necrosis factor (TNF)-α and IL-1β activity have also been found to be increased in pulmonary edema fluid in the early phase of ALI/ARDS.[84] High initial plasma or BAL fluid levels of TNFα, IL-1β, IL-2, IL-6 and IL-8 are associated with a poor outcome. Furthermore, persistent elevation of these cytokines was associated with increased mortality.[85,86] IL-8 is important in the recruitment of neutrophils to the injured lung.[80,83,87] Treatment with anti-IL-8 monoclonal antibody in experimental animal models of ALI/ARDS decreases the magnitude of ALI.[88,89]

β-agonists modulate the release of a range of cytokines. β-agonists decrease lipopolysaccharide (LPS)-stimulated release of TNFα in bovine alveolar macrophages and HL-60 cells differentiated to macrophages,[90] rat myocardial cells,[91] in human blood and promonocytic THP-1 cells,[92-94] *in vivo* in mice[95] and *in vivo* in healthy humans.[94] Adrenaline and exogenous cAMP inhibit LPS stimulated IL-1β production from mouse peritoneal macrophages.[96] LPS-stimulated release of IL-6 from rat myocardial cells[91] and human whole blood[97] is also inhibited by β-agonists. In a murine model of endotoxin-induced lung injury, intravenous treatment with the β-agonists, dobutamine and dopexamine, reduced IL-6 and macrophage inflammatory protein-2 mRNA expression and caused a reduction in neutrophil infiltration in BAL.[98] In one study, however, isoproterenol increased the release of IL-6 *in vivo* in mice.[95]

Studies examining the effect of β_2-agonists on IL-8 production suggest that they may have a cell specific effect with an increase in IL-8 production from bronchial epithelial cells[99,100] and a decrease in IL-8 production from neutrophils[101] and monoctyes.[93] LPS-induced production of IL-10, an anti-inflammatory cytokine, is increased from human whole blood[94] and *in vivo* in mice.[95] These effects are predominately mediated through a β-adrenoreceptor stimulated increase in cAMP,[91-93,96,97,99] although increased IL-10 production is mediated through a combined effect on α- and β-adrenergic receptors.[94] This effect may be mediated, at least in part, through inhibition of nuclear factor-κB activation and translocation.[93]

3. Coagulation

According to some pathological studies, microvascular thrombosis is a characteristic feature of clinical lung injury.[102] ALI/ARDS is characterized by local abnormalities of fibrin turnover with an increased procoagulant response and depressed fibrinolytic activity resulting in abnormal fibrin. In the lungs, tissue factor can also be produced by the endothelial cells on stimulation with IL-6 and other inflammatory factors, creating a hypercoaguable environment.[103-105] The finding that an early increase in pulmonary deadspace, which may reflect, in part, pulmonary microvascular thrombosis, is associated with higher mortality in ALI/ARDS, indicates this procoagulant state may be an important etiological factor in the development of ALI/ARDS.[106] β-Adrenergic stimulation can inhibit the procoagulant effects of endotoxin. Adrenaline has been shown to reduce activation of the coagulation system as measured by decreased circulating thrombin-anti-thrombin complexes and enhances fibrinolysis as measured by increased plasma levels of tissue-type plasminogen activator (TPA).[107] Isoproterenol has also been shown to stimulate increased secretion of TPA in dogs and healthy humans, an effect which can be blocked by a non-selective β-antagonist.[108,109] These data suggest β-agonists may have beneficial effects on the procoagulant state potentially attenuating coagulation-dependent lung injury.

4. Surfactant

Alveolar type II epithelial cells produce surfactant, which has an important role in reducing the surface tension at the alveolar air-liquid interface, stabilizing alveoli and terminal airways at low lung volumes to allow efficient gas exchange. In addition to the mechanical properties of surfactant, the surfactant associated proteins have other important functions, which include antibacterial host defense.[110] There is increasing evidence that dysfunction of the alveolar epithelial type II cells may be an important mechanism of injury in ALI/ARDS, as reflected by a worse outcome in patients with a reduced level of surfactant protein-D (SP-D) in the alveolar edema fluid within 24 hours of the onset of ALI.[111] One prior study[112] found that lower levels of SP-D in fluid of patients with ALI/ARDS was associated with a higher mortality rate. The lower levels of surfactant proteins in the distal airspaces of the lung early in the course of ALI suggest that the alveolar type II epithelial cells are not producing or releasing surfactant proteins normally. Alternatively, it is possible there is an increase in lung epithelial permeability and accelerated loss of SP-D from the airspaces in the more injured patients. Surfactant proteins may also be nitrated and inactivated in patients with ALI/ARDS.[113] Interestingly, β_2-agonists improve surfactant release *in vitro* from animal type II pneumocytes[114-116] and the human fetal lung.[117]

5. Respiratory Mechanics

Reduced lung compliance is characteristic of ALI/ARDS. However, increased airflow resistance has also been documented in animal models and in patients with ALI/ARDS.[118] Furthermore, there is evidence of expiratory flow limitation.[119] There is data to suggest that β_2-agonists have a beneficial role in improving respiratory mechanics. Not surprisingly, β_2-agonists reduce airflow resistance and peak airway pressure.[120-122] In addition, in some but not all studies,[120] β_2-agonists reduce plateau pressure.[121,122] The reduction in plateau airway pressure suggests an improvement in respiratory system compliance, possibly because of a reduction in alveolar edema and/or increased surfactant secretion.

6. Dosage and Delivery

Experimental studies demonstrate that β_2-agonists stimulate alveolar fluid clearance in animal models and healthy *ex-vivo* human lungs when drug concentrations of 10^{-5} – 10^{-6} mol/L are achieved in alveolar fluid.[19,44] Plasma and edema fluid concentrations of adrenaline and noradrenaline, measured in mechanically ventilated patients with pulmonary oedema due to ALI/ARDS are significantly below this therapeutic level for up regulating alveolar fluid clearance.[123] This suggests it might be possible to pharmacologically produce further increases in the rate of edema clearance by administration of exogenous β-agonists. In a retrospective observational study in intubated, ventilated patients with pulmonary edema albuterol levels were measured in the pulmonary edema fluid from mechanically ventilated patients with pulmonary edema. After a total aerosolized dose of 3.5 ± 2.6mg albuterol in the previous 6 hours patients with ALI (9 patients, 11 samples) had a median albuterol level of 1240 ng/mL, which is equivalent to $>10^{-6}$ mol/L.[124] Therefore, administration of salbutamol either by inhalation or intravenously, at these doses, is likely to achieve physiologically efficacious levels to upregulate fluid clearance.

7. Differences Among β_2-Adrenoceptor Agonists (β_2-Agonists)

Salmeterol is more potent than albuterol in upregulating alveolar fluid clearance *in vivo* in rats but the maximal rate of alveolar fluid clearance was similar with both agents.[40] In the *ex vivo* human lung, salmeterol was more potent than terbutaline in enhancing alveolar fluid clearance.[19] The effect of β_2-agonists in

the modulation of neutrophil function appears variable. Salmeterol appears to be inhibiting neutrophil recruitment and degranulation more effectively.[68,125-127] In contrast, although albuterol can inhibit neutrophil recruitment, in comparison to other β_2-agonists, it does not inhibit neutrophil oxidant generation.[72,127] Another study showed adrenaline was approximately 100-fold more potent in inhibiting formation of oxygen radicals compared with dobutamine or dopamine.[75] Because adrenaline has alpha effects, α-adrenergic stimulation may contribute to effects on neutrophil function. α-Adrenergic stimulation inhibits neutrophil accumulation and activation in the lungs attenuating the severity of ALI.[128] On the basis of these findings, salmeterol theoretically might be more effective than other β_2-agonists in the treatment of ALI/ARDS, although the studies are limited.

8. Potential Problems in the Use of β-Agonists to Treat Acute Lung Injury (ALI)/Acute Respiratory Distress Syndrome (ARDS)

It is possible that an extensively injured, denuded alveolar epithelium might make it difficult for any pharmacologic intervention aimed at improving epithelial function to be effective because of the extent of epithelial injury. However, this appears less likely since the normal mechanisms regulating alveolar fluid clearance are maintained in at least moderate lung injury.[13] In addition, some experimental models indicate that neutrophil-dependent oxidant injury to the alveolar epithelium is more resistant to β-adrenergic-dependent upregulation of alveolar fluid clearance.[55-57] However, because β_2-agonists may inhibit neutrophil function, they may still improve clinical outcome by reducing neutrophil mediated tissue damage. Prolonged treatment with β_2-agonists may lead to down-regulation of β-adrenoreceptors and subsequently attenuate the effect on stimulating the rate of alveolar fluid clearance.[129-131] Although β-adrenoreceptor down-regulation has been a concern in patients with asthma treated long-term with β_2-agonists, it is less likely that this would be a significant issue with short-term usage (7 days) of β_2-agonists in patients with ALI/ARDS. In a recent mouse study in which high-dose albuterol was administered over 6 days, there was no reduction in the rate of alveolar fluid clearance.[132]

β_2-Agonists may also be associated with potential adverse effects. Tachycardia and arrhythmias could develop. However, in a randomized, controlled trial of intravenous albuterol there was no increase in incidence of significant hemodynamic instability.[133] The risk of cardiovascular adverse effects is likely to be reduced if the drug is given as a metered dose inhaler or nebulizer where the systemic concentration will be significantly lower.[124] Hypokalemia and hyperglycemia, are other potential adverse effects which would need to be monitored and treated, particularly given recent evidence demonstrating the importance of strict glycemic control in improving outcome in critically ill patients.[134] Finally, given the inhibitory effects of β_2-agonists on neutrophil function, it is possible that the incidence of nosocomial infection may be increased. However, despite these potential concerns, experience with β_2-agonists in the critically ill indicates that these drugs are usually well tolerated and suggests they are not likely to be associated with serious adverse effects if used in the treatment of ALI/ARDS.

In patients with asthma, it is well recognized that there is some inter-individual variation in response to β_2-agonists[135] that is, at least in part, due to genetic variation in the β_2-adrenergic receptor and its related modulatory protein.[136,137] Genetic polymorphisms are associated with bronchodilator response and tachyphylaxis to β_2-agonists in patients with asthma, and it is possible that a similar association may occur with responses to albuterol therapy in patients with ALI.[138,139]

Pulmonary edema occurs rarely in pregnancy and has been associated with the use of β_2-agonists as tocolytics. However, the underlying mechanism is not clearly understood. It is difficult to resolve the experimental evidence that β_2-agonists accelerate alveolar fluid clearance with the association between β_2-agonists and maternal pulmonary edema.[140] However, in one large series of 86 pregnant patients the development of pulmonary edema was not associated with β_2-agonists.[141]

9. Conclusions

In summary, therapy with β_2-agonists is an attractive potential strategy in the treatment of ALI/ARDS for several reasons. They may (i) improve alveolar fluid clearance and hasten the resolution of alveolar edema; (ii) reduce pulmonary endothelial permeability; (iii) modulate neutrophil function and the inflammatory response; and (iv) perhaps increase surfactant secretion. Hypothetically, β_2-agonists may reduce the severity of lung injury, improve gas exchange and respiratory mechanics and reduce the need for mechanical ventilation, and improve survival. Assuming that β_2-agonists modulate mechanisms which are more important in the development and early exudative phase of ARDS we speculate that these agents are more likely to be effective if they are commenced early after the onset of ALI/ARDS. Since these drugs do not seem to modulate the later fibroproliferative phase of ALI/ARDS, it is proposed treatment should be for 7 days, since

treatment periods longer than this are unlikely to be associated with additional benefit.

The concept of treating ALI/ARDS patients with β_2-agonists merits further study. A phase II study examining the role of intravenous albuterol in ALI/ARDS has recently been completed in the UK. In this prospective, double-blind, placebo-controlled study, 40 patients were randomized within 48 hours of onset of ALI/ARDS to intravenous albuterol or placebo for 7 days. Extravascular lung water, a measure of pulmonary edema, was reduced with a trend towards reduced mortality in the albuterol-treated group. Furthermore, the treatment was well tolerated. This study provides the first proof of principle that in humans with ALI/ARDS, sustained treatment with an intravenous β-agonists may be beneficial.[133] Also the NIH sponsored ARDS network in the US is currently considering undertaking a phase III prospective, randomized, double-blind, placebo-controlled study of nebulized albuterol. In this study patients will be enrolled within 48 hours of onset of ALI/ARDS to nebulized albuterol or placebo for 7 days with mortality at 60 days as the primary outcome measure.

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