

Review

Science review: Mechanisms of beta-receptor stimulation-induced improvement of acute lung injury and pulmonary edema

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Published online: 25 May 2004

Critical Care 2004, **8**:234-242 (DOI 10.1186/cc2875)

This article is online at <http://ccforum.com/content/8/4/234>

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Abstract

Acute lung injury (ALI) and the acute respiratory distress syndrome are complex syndromes because both inflammatory and coagulation cascades cause lung injury. Transport of salt and water, repair and remodeling of the lung, apoptosis, and necrosis are additional important mechanisms of injury. Alveolar edema is cleared by active transport of salt and water from the alveoli into the lung interstitium by complex cellular mechanisms. Beta-2 agonists act on the cellular mechanisms of pulmonary edema clearance as well as other pathways relevant to repair in ALI. Numerous studies suggest that the beneficial effects of beta-2 agonists in ALI include at least enhanced fluid clearance from the alveolar space, anti-inflammatory actions, and bronchodilation. The purposes of the present review are to consider the effects of beta agonists on three mechanisms of improvement of lung injury: edema clearance, anti-inflammatory effects, and bronchodilation. This update reviews specifically the evidence on the effects of beta-2 agonists in human ALI and in models of ALI. The available evidence suggests that beta-2 agonists may be efficacious therapy in ALI. Further randomized controlled trials of beta agonists in pulmonary edema and in acute lung injury are necessary.

Keywords acute lung injury, acute respiratory distress syndrome, alveolar fluid clearance, beta-agonists

Introduction

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are important because of the continued high mortality and costs of care of these conditions. Beta adrenergic agonists are inexpensive and are actually often used in the treatment of patients who have ALI or ARDS for reasons not related to attempts to improve resolution of lung injury. For example, inhaled beta-2 adrenergic agonists are used to decrease airway resistance when it is increased in ALI and ARDS. Intravenously infused beta adrenergic agonists are used when the circulation requires inotropic support because of shock or ventricular dysfunction, both of which are common in ALI and ARDS. It is unknown whether beta adrenergic agonists used for these other reasons also improve the resolution of ALI.

We have chosen to focus on the evidence that beta-2 adrenergic agonists act through three mechanisms (increased

clearance of salt and water from alveoli, anti-inflammatory effects, and bronchodilation) to improve the pathophysiology, and possibly the rate and success of resolution, of pulmonary edema and ALI. This leads to the hypothesis that beta-2 adrenergic agonists may be beneficial therapy for patients with ALI or with ARDS.

Definitions

Different definitions and scoring systems have been developed since the "adult respiratory distress syndrome" was first described by Ashbaugh and colleagues in 12 patients in 1967 [1]. The most current consensus conference definition of ALI is acute onset of acute respiratory failure characterized by $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg, bilateral infiltrates, and pulmonary capillary wedge pressure ≤ 18 mmHg, or by no clinical evidence of left atrial hypertension. The definition of ARDS differs only in that the oxygenation criterion is more severe: $\text{PaO}_2/\text{FiO}_2 \leq 200$ mmHg [2].

ALI = acute lung injury; AQP = aquaporin; ARDS = acute respiratory distress syndrome; FiO_2 = fractional inspired concentration of oxygen; IL = interleukin; PaO_2 = partial pressure of oxygen; $\text{TNF-}\alpha$ = tumor necrosis factor alpha.

Current therapeutic strategies

The mortality of ALI has decreased over the past 20 years to 30–35%. This reduction is due to advances in ventilation, in management of sepsis, and in general support. Only recently has class-one evidence (adequately powered, randomized controlled trials) become available to guide management of patients with ALI/ARDS. A National Heart, Lung, and Blood Institute-supported, ARDS network, randomized controlled trial demonstrated that ventilation using low tidal volumes (6 ml/kg lean body weight) and a limited plateau pressure (<30 cmH₂O) reduced the mortality of ARDS from 40% to 31% [3]. This has changed the ventilator management of these patients. Ongoing investigation of the mechanisms of lung stretch-induced injury may contribute to further improvement of outcomes [3].

Improved management of sepsis, which is the commonest predisposing condition that initiates ALI and ARDS, is also supported by class-one evidence. The PROWESS Trial demonstrated that a 96-hour infusion of activated protein C in patients with severe sepsis reduces mortality from 31% to 26% [4]. Recent positive randomized controlled trials are thus leading to improved management of ALI and ARDS.

Pathophysiology of ALI relevant to beta agonists

The pathophysiology of ARDS occurs in three phases: the initial exudative phase (up to 6 days after the initial event), the second proliferative phase (4–10 days after the initial injury), and a third fibrotic phase (the second and third weeks after the initial lung injury) [5]. After the acute phase of ALI, resolution can be rapid with complete recovery or complete resolution, or the ALI can evolve into fibrosis. Key features of the pathophysiology of ALI are inflammation, impaired fluid clearance, increased airway resistance, and surfactant dysfunction.

ALI/ARDS evolves from an initial trigger of inflammation [6]. The trigger of inflammatory pathways may be infection in the lung or infection elsewhere that initiates a systemic inflammatory response. Alternatively, a systemic inflammatory response may be triggered by trauma, by pancreatitis, by ischemia reperfusion injury, by burns, and by surgery. Once a systemic inflammatory response is triggered, circulating monocytes and alveolar macrophages secrete cytokines including tumor necrosis factor alpha (TNF- α), IL-1, IL-6, and IL-8. These pro-inflammatory cytokines activate leukocytes and endothelial cells so that these cells increase expression of surface adhesion molecules. Neutrophils, other leukocytes, and platelets adhere via cognate receptors to the pulmonary endothelium. Production of IL-8 and other chemokines within the lung leads to recruitment of neutrophils and of other leukocytes into the interstitial and alveolar spaces of the lung. Activated neutrophils release proteases, leukotrienes, reactive oxygen intermediates, and other inflammatory molecules that amplify the inflammatory response. Reactive oxygen intermediates and proteases directly damage alveolar-capillary membrane integrity.

This pro-inflammatory cascade is regulated by anti-inflammatory mediators such as IL-10, IL-1 receptor antagonist, and soluble TNF receptors [7,8]. Propagation of ALI can also lead to microthrombosis and impaired fibrinolysis of the microvasculature of the acutely injured lung. All of these pathways can lead to further release of mediators into the systemic circulation so that the systemic inflammatory response is amplified and leads to dysfunction of remote organ systems.

This inflammatory response in the lung in ALI decreases the capacity of the epithelium to remove edema fluid from the distal airspaces of the lung. Disruption of the integrity of the alveolar-capillary membrane results in increased permeability, and as a result the air spaces are flooded with protein-rich edema fluid. Histologically, the development of pulmonary edema is related to injury of the alveolar-capillary barrier. The alveolar-capillary barrier is comprised of capillary endothelium and of alveolar epithelium. The alveolar epithelium is composed of type I cells (90–95%) and of type II cells (5–10%). Type II cells are more resistant to initial injury. Injury to the alveolar type I epithelial cells leads to increased permeability, to impairment of fluid and salt transport, and to disorganized epithelial repair. In addition to edemagenesis, impaired alveolar-capillary barrier function may increase permeability to bacteria and bacterial products.

After the initial injury, alveolar edema can be cleared by active transport of salt and water into the lung interstitium through a number of cellular mechanisms. Active transport of sodium, and perhaps chloride, from the air spaces to the lung interstitium is a primary mechanism driving clearance of alveolar fluid. Water passively follows this sodium gradient.

Injury of the alveolar epithelium also reduces the production and turnover of surfactant by type II cells, which further exacerbates the lung injury. Surfactant is a complex of lipids and proteins that reduces alveolar surface tension, has antibacterial properties, and prevents pulmonary edema formation.

Mechanisms of clearance of edema from the lung

Sodium transport through the alveolar epithelium plays a major and active role in the clearance of alveolar fluid in both normal and pathological conditions. The mechanisms of sodium transport include participation of amiloride-sensitive sodium channels on the apical membrane of alveolar type II cells, followed by the extrusion of sodium from the basolateral surface by the Na,K-ATPase pump. Alveolar type I cells may also have an important role in sodium transport through the alveolar epithelium, which is important because type I cells comprise more than 90% of alveolar surface area.

Johnson and colleagues [9] discovered that there is expression of three amiloride-sensitive epithelial sodium channel subunits (α , β and γ) and two subunits (α and β) of the Na,K-ATPase in type I cultured cells isolated from adult rat lungs. Ridge and

colleagues [10] found that alveolar type I cells express both the $\alpha 1$ and $\alpha 2$ Na,K-ATPase isoforms. Of note, the $\alpha 2$ isoform plays a major role in active sodium transport. Borok and colleagues [11] found $\alpha 1$ and $\beta 1$ Na,K-ATPase subunits in cultured type I cells using antibodies specific to type I and type II alveolar cells. These observations emphasize the importance of alveolar type I cells in sodium transport.

Sodium transport can be upregulated by both catecholamine-dependent mechanisms and catecholamine-independent mechanisms. For example, endogenous epinephrine release during sepsis and ALI increases the rate of edema clearance from alveolae [12]. Catecholamine-independent mechanisms include corticosteroids, thyroid hormone, insulin, and several growth factors [7,13–16].

Chloride is also an important ion that follows the electrochemical gradient using the cystic fibrosis transmembrane conductance regulator [17]. Reddy and colleagues [18] and Jiang and colleagues [19] reported that the enhancement of sodium transport mediated by beta agonist-induced stimulation of cAMP also increases chloride conductance. Furthermore, O'Grady and colleagues suggested that apical membrane chloride channel activation responds to adrenergic agonists to cause transepithelial sodium absorption [20,21]. The transepithelial sodium absorption requires amiloride-sensitive sodium channels.

Water follows the osmotic gradient passively and is absorbed through water channels called aquaporins (AQPs) [7,16,22]. AQP channels are distributed along bronchopulmonary tissues, although they are not essential to achieve a maximal epithelial fluid transport [23]. AQP1 is expressed in microvascular endothelium, while AQP3 and AQP4 are expressed in large airways. AQP4 is also present in small airways. AQP5 is present in type I alveolar cells and in submucosal gland acinar cells. The principal functional AQP water channels are AQP1 and AQP5. Deletion of AQP5 in submucosal glands in the upper airways is the only AQP deletion that reduces the fluid transport.

Injury to the epithelial alveolar barrier disrupts the integrity of mechanisms of sodium, chloride, and water clearance because ion transport pathways are downregulated, thus reducing edema clearance. Hypoxia, a common feature of ALI/ARDS, may in addition contribute to impaired edema clearance because hypoxia decreases expression of subunits of the sodium channel and of the Na,K-ATPase pump [24]. These mechanisms are important in the role of beta-2 agonists in the clearance of alveolar edema.

Effects of beta agonists on alveolar fluid clearance

Many studies have been carried out to determine the mechanisms of resolution of alveolar edema in lung injury. Table 1 highlights numerous experimental studies that

demonstrate the positive role of beta agonists in the improvement of alveolar edema clearance.

Type II alveolar epithelial cells are mainly responsible for the mechanism of alveolar edema clearance and are resistant to a variety of insults. In mild to moderate lung injury, therefore, the mechanism of active transport of sodium (and water, because it follows passively) through the epithelium can be up-regulated. In severe cases of lung injury, where the damage to the epithelium is extensive, there is often a decrease in alveolar fluid removal [25].

Beta-2 adrenergic agonists modulate the expression of the epithelial apical sodium channel as well as the expression of the Na,K-ATPase pump. Berthiaume and colleagues [25] and Matthay and colleagues [26] have published relevant reviews of animal models on resolution of edema in ALI. Pittet and colleagues [12] demonstrated that endogenous catecholamines stimulate alveolar fluid clearance of a rat model of septic ALI. When amiloride (which inhibits sodium uptake) and the beta blocker propranolol were added, the rate of edema fluid removal decreased. Laffon and colleagues [16] showed that intravenous lidocaine, a sodium channel inhibitor, decreased baseline alveolar epithelial fluid clearance by 50% in rats when albumin solution was instilled into distal air spaces, and that this effect was reversed by terbutaline. This strongly suggested the importance of increased transport of sodium across the alveolar epithelium and of beta adrenergic receptor stimulation in stimulating alveolar fluid clearance.

Tibayan and colleagues [27] found that dobutamine (a beta-1 and beta-2 agonist) increased alveolar edema clearance but dopamine (a beta-1 agonist) had no effect on alveolar edema clearance in anesthetized rats. Consistent with other studies [28–31], the addition of amiloride reduced the beneficial effects of dobutamine on edema clearance. Interestingly, Wang and colleagues [32] found that alveolar edema clearance was increased by keratinocyte growth factor because it may have increased proliferation of alveolar type II cells. Secondary treatment with the beta agonist terbutaline enhanced the upregulation of fluid transport in these studies, providing evidence that both treatments increase the ability of alveolae to clear edema fluid.

Several different beta agonists have been shown to increase alveolar edema clearance in several different models of ALI. This suggests that beta agonists could be efficacious in human ALI caused by many different triggers. Alveolar epithelial fluid clearance mechanisms are intact after moderate hyperoxic lung injury in rats [33]. However, Saldias and colleagues found that the beta agonist isoproterenol improves clearance of pulmonary edema in hyperoxic rat lungs [34]. Furthermore, alveolar liquid clearance and arterial oxygen tension due to hydrostatic pulmonary edema were increased by aerosolized salmeterol because salmeterol decreased the left atrial pressure [35].

Table 1**Selected studies of alveolar fluid clearance by beta agonists**

Study	Model	Beta-2 agonist	Effect
Sartori and colleagues, 2002 [43]	High-altitude edema in humans	Salmeterol	+
Ware and colleagues, 2002 [61]	Human donor lung	Terbutaline	+
Sakuma and colleagues, 1994 [29]	Resected human lung	Terbutaline	+
Atabai and colleagues, 2002 [45]	Ventilated patients (ARDS)	Albuterol	+
Sakuma and colleagues, 1997 [62]	<i>Ex vivo</i> human and rat	Salmeterol	+
Suzuki and colleagues, 1995 [63]	Cultured rat alveolar type II	Terbutaline	+
Minakata and colleagues, 1998 [36]	Cultured rat alveolar type II	Terbutaline	+
Planes and colleagues, 2002 [37]	Cultured rat alveolar type II	Terbutaline	+
Icard and Saumon, 1999 [64]	Mice	Terbutaline	+
Tibayan and colleagues, 1997 [27]	Rats	Dobutamine	+
Barnard and colleagues, 1997 [28]	Rats	Dopamine	+
Charron and colleagues, 1999 [65]	Rats	Epinephrine	+
Saldias and colleagues, 1999 [34]	Rats	Isoproterenol	+
Morgan and colleagues, 2002 [39]	Rats	Prolonged isoproterenol	-
Lasnier and colleagues, 1996 [66]	Rats	Terbutaline	+
Norlin and colleagues, 2001 [31]	Rats	Terbutaline	+
Jayr and colleagues, 1994 [30]	Rats	Terbutaline	+
Saldias and colleagues, 2000 [67]	Rats	Terbutaline + isoproterenol	+
Pittet and colleagues, 1994 [12]	Rats	Epinephrine	+
	Rabbit	Epinephrine	-
Smedira and colleagues, 1991 [68]	Rabbit	Terbutaline	-
Effros and colleagues, 1987 [69]	Rabbit	Terbutaline	-
Campbell and colleagues, 1999 [70]	Sheep	Salmeterol	+
Berthiaume and colleagues, 1987 [71]	Sheep	Terbutaline	+
Berthiaume and colleagues, 1988 [72]	Sheep (faster) > dog	Terbutaline	+
Frank and colleagues, 2000 [35]	Sheep and rats	Salmeterol	+
Grimme and colleagues, 1997 [73]	Dogs	Terbutaline	+
Sugita and colleagues, 2003 [74]	Transplanted dogs	Terbutaline	-

ARDS, acute respiratory distress syndrome; +, increased alveolar edema clearance; -, no effect.

The mechanisms that explain the beneficial effect of beta adrenergic agonists on edema clearance are complex, and they include cAMP, amiloride-sensitive nonselective cation channels, and highly selective cation channels. Beta adrenergic stimulation acts in part by an intracellular cAMP-dependent mechanism [16,26,36]. Planes and colleagues [37] showed that terbutaline reverses the hypoxia-induced decrease in sodium transport by amiloride-sensitive sodium channel activity because terbutaline activates cAMP and increases apical expression of the sodium channel subunits. Terbutaline enhances the insertion of the epithelial sodium channel subunits into the membrane of hypoxic alveolar epithelial cells.

Chen and colleagues [38] studied the beta adrenergic regulation of amiloride-sensitive lung sodium channels and discovered that beta adrenergic stimulation activates protein kinase A through the increment of intracellular cAMP. Protein kinase A increases highly selective cation channel numbers and the intracellular calcium, which then increases the nonselective cation channel open probability. Beta adrenergic stimulation therefore increases both the highly selective cation channel number and the nonselective cation channel by increasing cAMP.

There are potentially important differences between short-term and long-term beta adrenergic stimulation in the lung

that are relevant to consideration of beta agonists as therapy because of desensitization after long-term stimulation. Short-term (minutes to hours) desensitization does occur and involves receptor phosphorylation, leading to uncoupling from the stimulatory G proteins. Short-term desensitization plays a minor role in alveolar edema clearance. In contrast, long-term effects (hours to days) cause internalization and degradation of beta agonist receptors. Long-term stimulation of beta adrenergic receptors leads to desensitization.

Berthiaume [17] proposed different pathways that increase sodium transport after acute stimulation (hours) compared with long-term stimulation (days). Acutely, sodium transport is enhanced by increased activity of cationic channels and the Na,K-ATPase pump, by membrane insertion of epithelial sodium channel subunits, and by changes in chloride transport. In contrast, after long-term stimulation by beta agonists, there is increased expression of apical channels and the Na,K-ATPase pump, and there is stimulation of epidermal growth factor, leading to increased normal cell growth that may also enhance edema clearance.

Morgan and colleagues, however, found differences in long-term administration compared with acute beta agonist administration [39]: prolonged administration of high doses of beta agonists reduced the alveolar epithelial response to beta agonist stimulation. The resolution of alveolar edema decreased in a dose-dependent manner after 48 hours of isoproterenol infusion. Morgan and colleagues also showed that desensitization limits alveolar type II cells' capacity to produce cAMP [40]. Desensitization by long-term stimulation using higher dose beta agonist decreased the adenylate cyclase function. It would therefore appear that prolonged beta stimulation in the lung may cause important desensitization and downregulation of beta adrenergic receptors in alveolar type II cells, which impairs beta-2 agonist stimulation of fluid removal from lung. This has relevance to the design of randomized controlled trials of beta agonists in human ALI.

To summarize, beta-2 adrenergic receptor stimulation increases sodium, chloride, and fluid absorption by increasing the activity of the Na,K-ATPase pump and by increasing the activity of epithelial apical sodium channels in type I and type II alveolar cells. Beta agonists enhance the clearance of sodium and of edema fluid in a wide range of animal models of hydrostatic pulmonary edema and of ALI. There appears to be beta receptor desensitization to long-term beta adrenergic stimulation that could influence the design of clinical studies in human ALI.

Human studies of beta agonists in ALI

There are relatively few studies of the effects of beta-2 adrenergic agents on measures of edema clearance in humans who have ALI or ARDS. Ware and Matthay [41] found that the net alveolar fluid clearance was impaired in

56% of patients, particularly in septic patients, who had ALI/ARDS. Those patients who had maximal alveolar clearance had better outcomes (more days alive and free of ventilation and lower mortality) than those who had suboptimal edema clearance. However, this is evidence of association of edema clearance and outcome only, and does not prove cause and effect.

Impairment of the sodium, chloride, and water pathways also plays a central role in the pathophysiology of high-altitude pulmonary edema [42,43]. Salmeterol prevented high-altitude pulmonary edema, and Sartori and colleagues [43] suggested that the benefit was explained by upregulation of the alveolar epithelial clearance of alveolar fluid. People susceptible to high-altitude pulmonary edema may have genetic differences in the amiloride-sensitive sodium channel because they have a higher incidence of HLA-DR6 and HLA-DQ4 antigens [24,42].

Basran and colleagues treated 10 patients who had ARDS with intravenous terbutaline [44]. Terbutaline inhibited the increased plasma protein extravasation and accumulation in the lung, suggesting improved lung vascular permeability. Atabai and colleagues demonstrated that standard doses of aerosolized albuterol enhanced clearance of alveolar fluid in acute pulmonary edema if edema fluid levels of albuterol were greater than 10^{-6} M [45]. Indeed, they found that they were able to achieve therapeutic levels of albuterol in the edema fluid in human ALI. This is important for two reasons. First, if inhaled beta-2 agonists are to be effective for edema clearance in ALI, then there must be therapeutic levels in the alveolae. Second, there could be impaired delivery of inhaled beta-2 agonists into the exact alveolae that require treatment – the flooded alveolae. Atabai's study is therefore an important study of the local pharmacokinetics of albuterol in human ALI.

Anti-inflammatory actions of beta agonists in ALI

ALI is characterized by neutrophil accumulation in the lung, by production of pro-inflammatory mediators, including cytokines, by increased activation of cAMP, by disruption of epithelial integrity, and by interstitial and alveolar edema. Anti-inflammatory activity of beta agonists may be important in the resolution of ALI by beta-2 agonists (Table 2).

Beta agonists reduce pulmonary neutrophil sequestration, reduce pro-inflammatory cytokines (TNF- α , IL-6, IL-8), increase the anti-inflammatory cytokine IL-10, reduce neutrophil adhesion to bronchial epithelial and endothelial cells, inhibit chemotaxis, and reduce oxygen free radical formation.

Dhingra and colleagues [46] found that intravenous beta adrenergic agonists (dobutamine and dopexamine) attenuated the inflammatory response, particularly the pro-inflammatory cytokine expression, the induction of chemokines, and the infiltration of the lung by neutrophils in a septic rat model

Table 2**Selected studies of anti-inflammatory effects of beta agonists in acute lung injury**

Study	Model	Treatment	Effect
Perkins and colleagues, 2003 [54]	Human neutrophils	Salbutamol	Inhibited chemotaxis
Sekut and colleagues, 1995 [47]	Lipopolysaccharide-activated THP1 cells	Salmeterol, salbutamol	Inhibited TNF- α
Dhingra and colleagues, 2001 [46]	Murine sepsis	Dobutamine, dopexamine	Attenuated inflammatory cytokine expression and chemokines induction
Van der Poll and colleagues, 1994 [48]	Lipopolysaccharide-stimulated macrophages	Norepinephrine	Decreased TNF- α , IL-6
Van der Poll and Lowry, 1997 [49]	Human endotoxemia	Epinephrine	Increased IL-10

TNF- α , tumor necrosis factor alpha.

Table 3**Selected studies of bronchodilator effects of beta agonists in acute lung injury**

Study	Cohort	Treatment	Effect
Morina and colleagues, 1997 [56]	Human ARDS	Salbutamol	Decreased airway resistance, increased compliance
Pesenti and colleagues, 1993 [55]	Human ARDS	Salbutamol	Decreased airway resistance
Wright and colleagues, 1994 [57]	Human ARDS	Metoprolerol	Decreased airway resistance

ARDS, acute respiratory distress syndrome.

of ALI. Sekut and colleagues [47] showed that salmeterol inhibited TNF- α secretion by lipopolysaccharide-activated THP1 cells, and that this inhibition is reversed by oxprenolol (a beta-2 antagonist). This cytokine downregulation suggests an anti-inflammatory property of salmeterol.

Van der Poll and colleagues showed that noradrenaline decreases TNF- α and IL-6 expression that is increased by lipopolysaccharide stimulation of macrophages [48]. Epinephrine increased IL-10 and inhibited TNF- α production [49]. Nakamura and colleagues [50] also found that beta-2 receptor stimulation using terbutaline in cultured rat renal mesangial cells in the presence of lipopolysaccharide prevented TNF- α production because of mitogen-activated protein kinase inhibition and enhanced cAMP generation. The aforementioned studies suggest an anti-inflammatory effect of beta agonists.

It is interesting, however, to note that the pro-inflammatory cytokine TNF- α increases fluid clearance. Fukuda and colleagues [51] found that the combination of TNF- α and terbutaline did not have an effect on increasing alveolar fluid clearance in TNF- α -instilled rats. This discovery suggests that TNF- α -induced fluid transport is not mediated by endogenous release of beta agonists and probably does not depend on a cAMP-mediated process. Borjesson and colleagues [52] found that the increase in alveolar edema clearance in a model of intestinal ischemia reperfusion was not mediated by endogenous catecholamine release because propranolol had no effect and there was no stimulation of

cAMP. The increase in alveolar fluid clearance during ischemia reperfusion is therefore possibly mediated by translocation of intestinal bacteria and subsequent activation of monocytes and macrophages to secrete TNF- α . Arcaroli and colleagues [53] also noted that alpha adrenergic (but not beta adrenergic) stimulation modulated the severity of ALI after hemorrhage and endotoxemia.

Beta adrenergic agents also act on neutrophils to modulate ALI. Salbutamol decreases neutrophil chemotaxis, but not activation of neutrophils or adhesion molecule expression [54].

In summary, beta agonists exhibit anti-inflammatory properties that may be relevant in the severity and progression of ALI/ARDS. However, the role of increased fluid clearance with inflammatory cytokines such as TNF- α remains to be determined.

Bronchodilator effects of beta-2 agonists in ALI

Beta agonists decrease respiratory system resistance [55–57] and increase both the dynamic compliance and the static compliance of patients with ARDS [56] (Table 3).

The increase of dynamic compliance is consistent with bronchodilator effects of salbutamol. The increase in static compliance is intriguing because it suggests other nonbronchodilator effects of salbutamol in these patients, such as changes in the quantity of tissue edema. It has been shown that both nebulized salbutamol (1 mg through an

endotracheal tube) [56] and continuous intravenous infusion (15 µg/min for at least 30 min) [55] decrease respiratory system resistance and the abnormal high airway pressure of ARDS patients, and may attenuate the risk of barotraumas. Wright and colleagues [57] also showed that endotracheal metoprolol (5 mg) decreased high airway resistance of ARDS patients with a tendency to improve oxygenation.

Effects of beta-2 agonists on surfactant

Surfactant deficiency plays an important secondary role in the pathogenesis of ALI by altering alveolar surface tension and by altering antibacterial defenses of the lung. Surfactant deficiency may be important in the propagation of adult ALI. Beta agonists have some favorable effects on surfactant in ALI.

von Wichert and colleagues [58] studied the effect of fenoterol on the lung phospholipid metabolism in septic rats. Fenoterol increased the incorporation of choline by 80% in normal lungs and by 35% in septic lungs. Fenoterol restored phosphatidylcholine to normal in bronchoalveolar lavage fluid and in lung tissue.

Polack and colleagues [59] showed that prolonged exposure to hyperoxia decreases surfactant synthesis and that beta adrenergic stimulation enhances the release of newly synthesized surfactant into the alveoli in neonatal lungs. The beta agonists terbutaline and salmeterol increased phosphatidylcholine secretion by adult and fetal type II cells [60] in a dose-dependent manner.

Summary

Many experimental studies of the physiopathology of alveolar edema in ALI indicate that cellular mechanisms are important in the resolution of ALI. Several of these mechanisms are amenable to improvement by beta-2 agonists. Specifically, beta-2 antagonists increase sodium transport, and thus edema clearance, they are anti-inflammatory, and they induce bronchodilation. The preclinical studies of the effects of beta-2 adrenergic agonists in models of ALI/ARDS open an exciting horizon of therapeutic implications. A limited number of studies of beta agonists in human ALI show that respiratory mechanics are improved, that therapeutic levels of albuterol can be achieved in the edema fluid, and that edema fluid clearance is increased. This challenges investigators to study the safety and efficacy of beta-2 agonists for the treatment of human ALI/ARDS. This strategy may be particularly advantageous because beta-2 agonists may be relatively safe, inexpensive, and easy to administer in this setting. Well-designed, randomized controlled trials of beta agonists for ALI/ARDS are now warranted.

Competing interests

None declared.

Acknowledgement

KRW is a Michael Smith Foundation for Health Research Distinguished Scholar.

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