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Role of endothelin-1 in acute lung injury

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Abstract

The alveolar–capillary membrane serves as a barrier that prevents the accumulation of fluid in the alveolar space and restricts the diffusion of large solutes while facilitating an efficient gas exchange. When this barrier becomes dysfunctional, patients develop acute lung injury (ALI), which is characterized by pulmonary edema and increased lung inflammation that leads to a life-threatening impairment of gas exchange. In addition to the increase of inflammatory cytokines, plasma levels of endothelin-1 (ET-1), which is a primarily endothelium-derived vasoconstrictor, are increased in patients with ALI. As patients recover, ET-1 levels decrease, which suggests that ET-1 may not only be a marker of endothelial dysfunction but may have a role in the pathogenesis of ALI. While pulmonary edema accumulates, alveolar fluid clearance (AFC) is of critical importance, as failure to return to normal clearance is associated with poor prognosis in patients with pulmonary edema. AFC involves active transport mechanisms where sodium (Na^+) is actively transported from the alveolar airspaces, across the alveolar epithelium, and into the pulmonary circulation, which creates an osmotic gradient that is responsible for the clearance of lung edema. In this article, we review the relevance of ET-1 in the development of ALI, not only as a vasoconstrictor molecule but also by inhibiting AFC via the activation of endothelial ET-B receptors and generation. Furthermore, this review highlights the therapeutic role of drugs such as beta-adrenergic agonists and, in particular, of endothelin receptor antagonists in patients with ALI.

The alveolar-capillary barrier facilitates efficient gas exchange and restricts the accumulation of fluid and large solutes in the alveolar space. When this barrier becomes dysfunctional, patients develop acute lung injury (ALI), which is clinically defined by a ratio of arterial partial pressure of oxygen to a fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) of up to 300 and bilateral infiltrates on chest radiographs in the absence of left atrial hypertension. The more severe form of ALI is known as acute respiratory distress syndrome (ARDS), which has a similar definition as ALI except for a $\text{PaO}_2/\text{FiO}_2$ ratio of up to 200.^{1,2} This syndrome of acute respiratory failure affects ~190,000 patients per year in the United States with a mortality rate of 40% to 50%.³ Moreover, the costs of care for ALI in the United States per patient was approximately \$48,000 in 2005.⁴

It is now widely accepted that the pathophysiology of ALI is driven by an aggressive inflammatory reaction that increases the permeability of the alveolo-capillary unit after events such as sepsis, pneumonia, aspiration, and trauma.^{5–8} Several cytokines, such as tumor necrosis factor alpha, interleukin (IL)-1, IL-6, and IL-8, have been found to be increased in bronchoalveolar lavage (BAL) fluid and in the plasma of patients with ALI.^{9–11} The development of lung injury seems to include the activation of the coagulation and inflammatory cascades, increased leukocyte rolling, adhesion and transmigration, fibrin

deposition, as well as dysfunction of the epithelial and endothelial barrier.¹² The precise sequence of events that lead to ALI remains elusive and are likely to vary between clinical syndromes and individual patients; however, the dysfunction of the epithelial and endothelial barrier is crucial for the development of ALI.^{13–16}

Patients with ALI have increased alveolar epithelial dysfunction markers such as KL-6¹⁷ and receptor for advanced glycation end-products,¹⁸ as well as endothelial dysfunction markers such as endothelin-1 (ET-1). Interestingly, as these patients recover, ET-1 levels decrease, which suggests that ET-1 may not only be a marker of endothelial dysfunction, but also may have a role in the pathogenesis of ALI.^{19,20} Furthermore, Sartori et al²¹ reported that in another form of ALI known as high-altitude pulmonary edema (HAPE), susceptible mountaineers have augmented release concentrations of ET-1, potentially representing one of the mechanisms contributing to HAPE.

ENDOTHELIN SYSTEM

The endothelins are a family of 21 amino acid peptides, of which 3 distinct isoforms exist (ET-1, ET-2, and ET-3). These potent vasoactive peptides are released from biologic inactive precursors (big endothelin) by the endothelin-converting enzymes, which are a subgroup of membrane-bound zinc metalloproteases.²² ET-1 is the most abundant isoform and the best characterized,²³ and it is the only one released constitutively by the vascular endothelium. Its activity contributes to the maintenance of endogenous vasomotor tone by producing a long-lasting vasoconstriction of the underlying smooth muscle cells.²⁴ In addition, ET-1 is also produced by smooth muscle cells,²⁵ cardiomyocytes,²⁶ leukocytes,²⁶ macrophages,²⁷ mesangial cells,^{28,29} airway epithelium,^{30–32} and alveolar epithelial cells (AECs).^{33,34} ET-1 is released during various injurious stimuli, including shear stress, thrombin, angiotensin II, cytokines, and free radicals, whereas atrial natriuretic peptide, prostacyclin, and NO inhibit its synthesis and release.^{35,36}

ET-1 mediates all its different effects via activation of the ET-A and ET-B G-protein coupled receptors.^{23,36,37} When ET-1 binds to ET-A receptors, it activates phospholipase C (PLC), leading to the generation of the second messenger inositol triphosphate and diacylglycerol (DAG), which in turn stimulates calcium release and protein kinase C activation.³⁸ Other signaling pathways described for ET-A receptors include phospholipase D (PLD)-mediated DAG generation, phospholipase A2 (PLA2)-induced arachidonic acid release, and activation of the mitogen-activated protein kinase cascade. These signaling pathways are involved in the short-term regulation of vascular smooth muscle tone as well as in the long-term control of cell growth in the vasculature and the heart.³⁹ However, the ET-B receptor is expressed characteristically in cells that participate in several physiologic processes besides the modulation of vascular resistance, such as natriuresis, hepatic function, and neuronal activities.^{40–44} Moreover, the physiologic role of ET-1 is modulated by the location of the ET-B receptor. For example, its activation on smooth muscle cells mediates the vasoconstrictor responses of ET-1, whereas ET-B receptors located on endothelial cells stimulate the release of NO and prostacyclin, which causes a vasodilatory response.^{24,45,46} ET-B receptors are coupled to Gq/G11 proteins, and their activation recruits pathways dependent on PLC, PLA2, PLD, Na⁺/H⁺ exchanger, adenylate and guanylate cyclases, intracellular Ca²⁺ mobilization, phosphatidylinositol 3-kinase, and G-protein $\beta\gamma$ subunits.^{47–49} In addition, ET-1 is cleared from the circulation via ET-B receptors, primarily in the lung and secondarily in the kidney and liver.⁵⁰

ET-1 IN ACUTE LUNG INJURY

As mentioned, 1 marker of endothelial dysfunction in patients with ALI is the presence of high ET-1 concentrations.^{19,23,51} However, it is uncertain whether ET-1 by itself increases

protein or fluid transport into the lung.^{52–54} In a prospective observational study, Kuzkov et al⁵⁵ demonstrated that extravascular lung water index (EVLWI) correlated directly with markers of ALI. The authors also showed that patients with increased EVLWI had significantly higher ET-1 concentrations, which suggests that ET-1 is involved in the evolution of pulmonary edema. The mechanisms involved in endothelin-induced pulmonary edema formation remain uncertain but may include alterations in vascular reactivity with an increase in capillary hydrostatic pressure; recruitment of inflammatory cells, which disrupts the endothelial/epithelial barrier; and upregulation of mediators that increase vascular permeability, such as vascular endothelial growth factor (VEGF), which is part of a family of angiogenic peptides that increase permeability of the endothelial barrier.⁵⁶ ET-1 increases capillary hydrostatic pressure via a direct effect on the vascular bed by inducing systemic and pulmonary hypertension,^{57,58} while indirectly causing cardiac failure secondary to the development of bradycardia and depression of the myocardial function through a combination of systemic and coronary vasoconstriction.⁵⁸ In addition, ET-1 increases capillary permeability via postcapillary vasoconstriction, which is dependent on the presence of inflammatory cells.⁵² Interestingly, several *in vitro* studies suggest that ET-1 promotes VEGF expression in different cell types, including alveolar epithelial and lung endothelial cells.^{59–61} The role of VEGF in the development of pulmonary edema was first established by Kaner et al,⁶² who demonstrated that overexpression of VEGF via an adenovirus gene transfer vector mediated high permeability pulmonary edema in C57Bl/6 mice. Subsequently, Carpenter et al⁶⁰ showed that endothelin increases VEGF in the lung, which contributes to the formation of pulmonary edema.

Another piece of evidence that points toward the role of the endothelin system in the development of ALI is the fact that several endothelin receptor antagonists have been reported to exert protective effects in different models of ALI.^{63,64} As reported by Wang et al,⁶⁵ the endothelin system is involved in chlorine-gas-induced lung injury as circulating ET-1 increased with chlorine gas exposure, which shows a significant relationship between circulating ET-1 and lung function variables. In this study, a blockade of endothelin receptors A & B with a nonselective inhibitor, Tezosentan, ameliorated chlorine-gas-induced lung injury. Also, Kuklin et al⁵⁸ designed a series of experiments to evaluate the role of Tezosentan in treated sheep with endotoxin-induced lung injury. Results showed that treated animals had decreased pulmonary hypertension, cardiac dysfunction, pulmonary edema, and hypoxemia. Furthermore, Carpenter et al⁶⁶ reported that rats pre-treated with another nonselective endothelin receptor antagonist, Bosentan, and infected with Sendai virus followed by exposure to hypoxia ($\text{FiO}_2 = 0.1$) for 24 h, developed less lung water accumulation, less lung lavage fluid protein, and less perivascular fluid cuffing than untreated animals.

Although most nonselective endothelin receptor antagonists prevent the development of ALI, studies that examined the effects of blocking specific endothelin receptors A or B have revealed contradictory results. Ishizaki et al⁶⁷ reported that pretreatment of isolated rat lungs with the ET-A receptor antagonist, BQ-123, significantly attenuated the ET-1-induced increase in pulmonary arterial pressure and pulmonary capillary pressure. It also prevented the ET-1-induced and leukotoxin-induced lung edema. Conversely, Albertini et al⁶⁸ reported that pretreatment of rats with another selective ET-A receptor antagonist, ABT-627, prevented endotoxin-induced mortality and significantly attenuated an increase of wet/dry ratios of the heart, liver, kidney, but not the lungs. In regard to the role of ET-B receptor, Guimaraes et al⁶⁹ reported that pretreatment of mice with the ET-B receptor antagonist, Ro 46-8443, reduced oleic acid-induced increase permeability to Evans blue in mouse lungs and decreased the total number of neutrophils in the BAL. However, Carpenter et al⁷⁰ reported that ET-B transgenic rats, which do not express ET-B receptors except in adrenergic tissues,^{71,72} were predisposed to develop pulmonary edema under hypoxic conditions via an

increase in lung expression of VEGF. These discrepancies can be potentially explained by several factors, which include the type of injury, whether the experiments were done *in vivo* or in isolated lungs, the animal species used, and the type and class of pharmacologic antagonists. It is also conceivable that the ET-A and ET-B play different roles in the development of ALI. These roles include (1) direct effects that increase endothelial and/or epithelial permeability, (2) indirect effects that increase migration of inflammatory cells into the lung parenchyma, and (3) impairment of the mechanisms that are involved in alveolar fluid clearance (AFC), such as active sodium transport and lymphatic drainage.

These results suggest that both ET-A and ET-B are involved in the development of ALI, and therefore, blocking both is required as a strategy to prevent the development of ET-1-induced lung injury.

AFC

In ALI, an increase occurs in the permeability of the alveolar-capillary barrier, which in combination with changes in hydrostatic and oncotic pressures leads to the formation of pulmonary edema.⁷³ However, once alveolar edema is fully formed, decreasing the preload does not affect the overall amount of edema.⁷⁴

Approximately 3 decades ago, it was revealed that fluid balance in the lung was regulated by active ion transport mechanisms,^{75,76} whereas sodium (Na^+) is actively transported from the alveolar airspaces, across the alveolar epithelium, and into the pulmonary circulation creating an osmotic gradient that is responsible for the clearance of lung edema.^{77–79} The clinical relevance of this mechanism is illustrated by the fact that failure to return to normal clearance is associated with poor prognosis in patients with pulmonary edema.^{80,81}

As shown in Fig 1, the alveolar space consists of a monolayer of squamous type I cells [alveolar type 1 cell (ATI)] and cuboidal type II cells (ATII). The ATI cells cover 95% of the alveolar surface, whereas the ATII cells are responsible for the secretion of surfactant. Both cell types are involved in vectorial transport of Na^+ from the apical to the basolateral surface. Although Na^+ uptake is driven by several Na^+ transport mechanisms, which include amiloride-sensitive (ENaC), amiloride-insensitive Na^+ channels and co-transporters of Na^+ , the only transporter by which AEC actively extrude Na^+ out of the cell is the sodium–potassium–adenosine triphosphatase (Na, K-ATPase).^{16,82}

The Na, K-ATPase is a transmembrane protein expressed on the basolateral surface of most mammalian epithelial cells that maintains an electrochemical gradient across the plasma membrane by pumping Na^+ out of the cell and K^+ into the cell against their respective concentration gradients in an ATP-dependent process. It is composed of a catalytic α -subunit that comprises approximately 1000 amino acid residues, which spans the plasma membrane 10 times, and of the β subunit, which seems to contribute to the stability of the $\alpha\beta$ complex and its insertion into the baso-lateral membrane. In addition, the α -subunit contains sites for cleavage of high-energy phosphate bonds and binding of the classic Na, K-ATPase inhibitor, ouabain.^{83,84}

A decrease in the number of Na, K-ATPase molecules at the plasma membrane, via endocytosis and subsequent protein degradation, results in inhibition of Na^+ transport and, thus, decreased AFC.^{85–88} Multiple pathophysiologic stimulus alter the Na, K-ATPase function in ALI, and these include, although are not limited to, hyperoxia,^{89,90} hypocapnic alkalosis,⁹¹ hypercapnia,⁸⁵ ischemia/reperfusion injury,⁹² inflammatory events,⁹³ and hypoxia.^{86,87,94} Therefore, regulation of the Na, K-ATPase represents an important and fundamental mechanism to modulate alveolar epithelial function.^{74,86}

ROLE OF ET-1 IN AFC

The endothelium provides the interface between the blood and the extravascular tissue of the lungs, and normally, it restricts movement of water and protein.⁹⁵ Sources of ET-1 include the endothelium and epithelium, and as mentioned, ET-1 is increased in serum and BAL of patients with ALI, which suggests the presence of a lung endothelial–epithelial dysfunction.^{23,51,96,97} Also, an important stimulus for ET-1 release is hypoxia,⁹⁸ and recent evidence, both *in vivo* and *in vitro*, suggests that hypoxia significantly reduces the capacity for active Na⁺ transport across the alveolar epithelium.^{99–101} Because the alveolar epithelium is not accessible in humans, the nasal epithelium, which has Na⁺ transporters that are similar to those of the alveolar epithelium, has been used to estimate alveolar epithelium Na⁺ transport activity.¹⁰² Accordingly, hypoxia was found to inhibit nasal epithelial Na⁺ transport in HAPE-susceptible but not in HAPE-resistant mountaineers.^{103,104} In addition, endothelin receptor antagonists have been studied in patients with HAPE. Modesti et al⁹⁷ in a randomized double-blind placebo clinical trial determined the role of the nonselective ET-A and ET-B receptor antagonist bosentan in mountaineers with HAPE. The authors found that compared with placebo, bosentan induced a significant reduction of systolic pulmonary artery pressure and improved arterial oxygen saturation. In contrast, reports using other vasodilators, such as NO¹⁰⁵ and Sildenafil,¹⁰⁶ did not show beneficial effects. These differences may be explained by our recent report, where we describe that ET-1 activates endothelial ET-B receptors and increases NO concentrations, which in turn decreases Na, K-ATPase activity in AEC, reducing AFC.³⁴ Moreover, Berger et al¹⁰⁷ recently reported similar results, showing that ET-B receptors are involved in the ET-1 induced AFC reduction in anesthetized rats.

It is well known that NO downregulates ENaC and Na, K-ATPase activity in AEC, which impairs AFC.^{108–113} For instance, Guo et al¹⁰⁸ showed inhibition of the Na, K-ATPase in ATEC cells after exposure to a NO donor PAPA NONOate, and Kaestle et al¹¹² reported that acute elevation of hydrostatic pressures in isolated perfused rat lungs caused an increase in endothelial NO levels, which lead to a decrease in AFC. However, researchers have debated whether the mechanisms involved in the NO induced AFC reduction, as several reports have described that NO downregulates active sodium transport in AEC via a cGMP-mediated inhibition of epithelial cation channels.^{109,111,112} Conversely, other authors have reported that NO decreases sodium absorption across AEC monolayers by inhibiting both ENaC and the Na, K-ATPase through a cGMP independent mechanism.^{34,76,108} Based on these studies, the data suggest that ET-1 is involved in the development of pulmonary edema, in part by activating endothelial ET-B receptors and NO generation, which in turn downregulates the different Na⁺ transport mechanisms that are responsible for AFC in AEC (Fig 1).

BETA-ADRENERGIC AGONIST ROLE IN PREVENTING ET-1-INDUCED AFC REDUCTION

Beta-adrenergic agonists have been proposed as a potential therapy for ALI and were among the 1st agents shown to accelerate Na⁺ transport by increasing the activity of Na⁺ and Chloride (Cl⁻) channels and the Na, K-ATPase in the alveolar epithelium.^{82,114–118} Short-term stimulation of β_2 -adrenergic receptors by Isoproterenol (Iso) have been found to result in receptor-dependent activation of G proteins, which successively stimulates adenylyl cyclase, resulting in enhanced cyclic adenosine monophosphate (cAMP) generation and consequent activation of protein kinase A.^{119–122} In addition, β_2 -receptor agonists have been shown to stimulate alveolar epithelial Na⁺ and fluid transport in animal models,^{94,101} and to promote pulmonary edema reabsorption in patients with ALI.¹²³ In a double-blind, randomized, placebo-controlled study, the prophylactic inhalation of salmeterol, which is a

β_2 adrenergic receptor agonist, decreased the incidence of HAPE in susceptible subjects from 74% to 33%.¹²⁴ The authors of this study suggested that AFC may have played a part in this beneficial effect, because beta-adrenergic agonists upregulate the clearance of alveolar fluid by stimulating transepithelial Na^+ transport. Based on the above studies, we tested in a previously described model of isolated and perfused rat lung³⁴ to determine whether Iso instillation in the airspace prevents the ET-1 induced AFC reduction. These experiments were conducted in accordance with both local institutional guidelines and the Guide for the Care and Use of Laboratory Animals (National Institutes of Health). As shown in Fig 2, instillation of ET-1 decreased AFC by ~50%, whereas Iso increased AFC by ~120%. When Iso was instilled in the airspace, followed then by perfusion with ET-1, it prevented the ET-1 induced AFC reduction and increased AFC to similar levels of the Iso alone treated group. Interestingly, when isolated and perfused rat lungs were pretreated with ET-1, perfused for 30 minutes in the vascular circulation, and then followed by Iso instillation in the airspace, the AFC was similar to the control conditions, and it did not achieve the same level as in the Iso-treated group. This finding suggests that pretreatment of ET-1 partially impairs the mechanisms involved in the β -adrenergic-induced increase in AFC.

Although the results of clinical trials for pharmacologic treatment of ARDS have been disappointing, several promising treatment strategies are still evolving, which include agents that enhance edema clearance. It is conceivable that in some patients, the extent of alveolar epithelial injury and the severity of endothelial lung injury may preclude a therapeutic benefit of β -adrenergic agonists, at least in the early stages of the lung injury. However, as repair of the alveolar epithelium occurs, it is possible that the epithelial barrier may become responsive to cAMP stimulation, which hastens the resolution of alveolar edema. Currently, well-designed clinical studies are under way to test the potential therapeutic value of β_2 -agonist therapy in patients with ARDS.¹²⁵

CONCLUSION

In summary, clinical data suggest that ET-1 plays a role in the development of ALI, and experimental data, both *in vivo* and *in vitro*, demonstrates that ET-1 induces the formation of pulmonary edema via both ET-A and ET-B receptors. Also, endothelin receptor antagonists prevent the development of ALI, either via decreasing the permeability of the endothelial and epithelial barrier, or via reconstituting the ability of the alveolar epithelium to clear edema. Finally, based on all these findings, we propose that additional clinical trials will consider the use of endothelin receptor antagonists as a therapeutic tool in the treatment of patients with ALI.

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Abbreviations

AEC	alveolar epithelial cells
AFC	alveolar fluid clearance
ALI	acute lung injury
ARDS	acute respiratory distress syndrome
BAL	bronchoalveolar lavage

cAMP	cyclic adenosine monophosphate
DAG	diacylglycerol
EVLWI	extravascular lung water index
ENaC	amiloride sensitive sodium channel
ET-1	endothelin-1
FiO₂	fraction of inspired oxygen
HAPE	high-altitude pulmonary edema
Iso	isoproterenol
Na,K-ATPase	sodium, potassium-adenosine triphosphatase
PaO₂	arterial partial pressure of oxygen
PLA2	phospholipase A2
PLC	phospholipase C
PLD	phospholipase D
VEGF	vascular endothelial growth factor

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Biography

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Fig 1.

Schematic representation of the effect of both ET-1 and β -adrenergic agonist on the Na, K-ATPase abundance at the basolateral membrane in alveolar epithelial cells. ET-1 activates endothelial ET-B receptors that lead to NO generation, which in turn causes endocytosis of the Na, K-ATPase in alveolar epithelial cells. Conversely, activation of β -adrenergic receptors by isoproterenol leads to the translocation of the Na, K-ATPase to the basolateral membrane in alveolar epithelial cells. β -AR, beta-adrenergic receptor.

Fig 2.

Iso prevents ET-1 decrease in alveolar fluid clearance in isolated perfused rat lungs. Isolated rat lungs were treated for 1 h with vehicle (CT), ET-1 (10^{-7} mol/L in perfusate), Iso (10^{-6} mol/L in the instillate); Iso in the instillate (10^{-6}) for 30 min, followed by ET-1 in the perfusate (10^{-7}) for 30 min (Iso + ET-1); and ET-1 in the perfusate (10^{-7}) for 30 min, followed by Iso in the instillate (10^{-6}) for 30 min. AFC was measured as described previously^{34,126} ($n = 6$). Graph represents mean $\pm$ standard error of the mean. ** $P < 0.01$. NS = nonstatistically significant.