

## Commentary

# $\beta_2$ adrenergic agonists in acute lung injury? The heart of the matter

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## Abstract

Despite extensive research into its pathophysiology, acute lung injury/acute respiratory distress syndrome (ALI/ARDS) remains a devastating syndrome with mortality approaching 40%. Pharmacologic therapies that reduce the severity of lung injury *in vivo* and *in vitro* have not yet been translated to effective clinical treatment options, and innovative therapies are needed. Recently, the use of  $\beta_2$  adrenergic agonists as potential therapy has gained considerable interest due to their ability to increase the resolution of pulmonary edema. However, the results of clinical trials of  $\beta$  agonist therapy for ALI/ARDS have been conflicting in terms of benefit. In the previous issue of *Critical Care*, Briot and colleagues present evidence that may help clarify the inconsistent results. The authors demonstrate that, in oleic acid lung injury in dogs, the inotropic effect of  $\beta$  agonists may recruit damaged pulmonary capillaries, leading to increased lung endothelial permeability.

In their manuscript, Briot and colleagues [1] assessed the role of terbutaline, a  $\beta_2$  agonist, on lung microvascular permeability in an acute lung injury (ALI) *in vivo* model to uncover the underlying mechanisms of therapeutic benefit. The authors used a recently developed broncho-alveolar lavage technique [2] to repeatedly measure (every 15 minutes) the time-course of capillary-alveolar leakage of a macromolecule, fluorescein-labeled dextran (FITC-D70), in 19 oleic acid (OA) lung injured dogs. With OA injury, the transport rate of coefficient of FITC-D70, used as a measure of permeability, from blood to alveoli increased sharply and peaked at 30 minutes. Thereafter, FITC-D70 leakage decreased gradually until the end of the experiment at 4 hours. Surprisingly, the infusion of terbutaline, given following 90 minutes of OA injury, interrupted the recovery phase, further aggravating FITC-D70 leakage. The authors discovered that with the onset of terbutaline infusion at 0.25  $\mu\text{g}/\text{kg}/\text{minute}$ , the  $\beta_2$  inotropic

effect of the drug significantly [3] increased the cardiac output and pulmonary artery pressure by 50% and 30%, respectively, while decreasing the pulmonary vascular resistance by 40%. With increased pulmonary vascular recruitment, the authors surmised that the terbutaline infusion increased perfusion surface area or recruited leaking capillaries from hypoxic vasoconstriction, which led to an aggravation of FITC-D70 leakage into the alveoli.

Previously,  $\beta_2$  agonist therapy was considered promising for ALI based on several characteristics seen in both animal and human models: the ability to increase the rate of vectorial salt and water transport by increased intracellular cAMP, leading to improved alveolar fluid clearance (AFC) [4,5] - clinically, impaired AFC in patients with ALI is associated with higher mortality [6]; the ability to improve lung endothelial permeability to protein [7]; and the anti-inflammatory properties of  $\beta_2$  agonists. Maris and colleagues [8] demonstrated that pre-treatment with an inhaled  $\beta_2$  agonist markedly reduced neutrophil influx, neutrophil degranulation and accumulation of tumor necrosis factor  $\alpha$  in the airspaces of human volunteers exposed to inhaled endotoxin.

However, the results of clinical trials of  $\beta$  agonist therapy for ALI/acute respiratory distress syndrome (ARDS) have been inconsistent. In a randomized placebo controlled clinical trial of 40 patients with ALI (Beta-Agonist Lung Injury Trial (BALTI)), Perkins and colleagues [9] found that salbutamol (albuterol) given intravenously at a dose of 15  $\mu\text{g}/\text{kg}/\text{h}$  reduced extravascular lung water in patients with ALI/ARDS as measured by thermodilution (PiCCO) at day 7 compared to placebo control subjects. Whereas Matthay and colleagues [10] in another randomized, placebo-controlled

AFC = alveolar fluid clearance; ALI = acute lung injury; ARDS = acute respiratory distress syndrome; OA = oleic acid.

trial (Albuterol for the Treatment of ALI (ALTA)) by the ARDS Network of an aerosolized  $\beta_2$  adrenergic agonist (albuterol) for ALI found no significant difference in their primary study endpoint of ventilator free days (to 28 days) or 60-day mortality between treatment groups. The study was stopped by the Data Monitoring Board at the first interim analysis for futility following 279 patients who received the study drug. The study by Briot and colleagues [1] suggests that the inotropic effect of  $\beta$  agonist therapy may influence outcome by increasing perfusion surface area, further aggravating pulmonary edema.

The strength of their paper is the development of an *in vivo* technique to measure lung endothelial permeability in ALI models across the capillary endothelial, interstitial and alveolar epithelial monolayers without the influence of AFC on the measurement. In ALI, changes in AFC rate do not necessarily correlate with changes in lung endothelial permeability [11]; however, either parameter can influence the measurement of the other. The broncho-alveolar lavage sampling process avoids this potential error by ensuring supra-maximal AFC rate (48%/h) in their calculations, allowing the authors to measure the effect of OA on permeability and the perfusion surface area of the lung capillaries in isolation. However, the major limitations are the severity and short time period of OA injury reflecting an early phase of ALI and the inability to use the *in vivo* technique beyond 4 hours due to a spontaneous aggravation of lung permeability in the control lung. The beneficial effect of  $\beta$  agonists on the capillary-alveolar membrane may take longer to become apparent than their effects on inflammation [8] and wound healing [12].

In the future, the significance of the inotropic effect of  $\beta$  agonists for ALI patients will need to be clarified. However, studies like that of Briot and colleagues highlight a major limitation of using pharmacological monotherapy such as  $\beta$  agonists or activated protein C [13] in ARDS: the complex and inter-related interactions in the pathophysiology of ARDS, such as the relationship between impaired AFC and lung endothelial permeability, and the inability of one therapy to address all simultaneously.

## Competing interests

The author declares that he has no competing interests.

## References

- Briot R, Bayat S, Anglade D, Martiel JL, Grimbert F: **Increased cardiac index due to terbutaline treatment aggravates capillary-alveolar macromolecular leakage in oleic acid lung injury in dogs.** *Crit Care* 2009, **13**:R166.
- Briot R, Bayat S, Anglade D, Martiel JL, Grimbert F: **Monitoring the capillary-alveolar leakage in an A.R.D.S. model using broncho-alveolar lavage.** *Microcirculation* 2008, **15**:237-249.
- Schäfers RF, Adler S, Daul A, Zeitler G, Vogelsang M, Zerkowski HR, Brodde OE: **Positive inotropic effects of the beta 2-adrenoceptor agonist terbutaline in the human heart: effects of long-term beta 1-adrenoceptor antagonist treatment.** *J Am Coll Cardiol* 1994, **23**:1224-1233.
- Matthay MA, Folkesson HG, Clerici C: **Lung epithelial fluid transport and the resolution of pulmonary edema.** *Physiol Rev* 2002, **82**:569-600.
- Sartori C, Allemann Y, Duplain H, Lepori M, Egli M, Lipp E, Hutter D, Turini P, Hugli O, Cook S, Nicod P, Scherrer U: **Salmeterol for the prevention of high-altitude pulmonary edema.** *N Engl J Med* 2002, **346**:1631-1636.
- Ware LB, Matthay MA: **Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome.** *Am J Respir Crit Care Med* 2001, **163**:1376-1383.
- McAuley DF, Frank JA, Fang X, Matthay MA: **Clinically relevant concentrations of beta2-adrenergic agonists stimulate maximal cyclic adenosine monophosphate-dependent air-space fluid clearance and decrease pulmonary edema in experimental acid-induced lung injury.** *Crit Care Med* 2004, **32**:1470-1476.
- Maris NA, de Vos AF, Dessing MC, Spek CA, Lutter R, Jansen HM, van der Zee JS, Bresser P, van der Poll T: **Antiinflammatory effects of salmeterol after inhalation of lipopolysaccharide by healthy volunteers.** *Am J Respir Crit Care Med* 2005, **172**:878-884.
- Perkins GD, McAuley DF, Thickett DR, Gao F: **The beta-agonist lung injury trial (BALTI): a randomized placebo-controlled clinical trial.** *Am J Respir Crit Care Med* 2006, **173**:281-287.
- Matthay M, Brower R, Thompson BT, Schoenfeld D, Eisner MD, Carson S, Moss M, Douglas I, Hite D, MacIntyre N, Liu KD: **Randomized, placebo-controlled trial of an aerosolized beta-2 adrenergic agonist (albuterol) for the treatment of acute lung injury.** *Am J Respir Crit Care Med* 2009, **179**:A2166.
- Wiener-Kronish JP, Albertine KH, Matthay MA: **Differential responses of the endothelial and epithelial barriers of the lung in sheep to *Escherichia coli* endotoxin.** *J Clin Invest* 1991, **88**:864-875.
- Perkins GD, Gao F, Thickett DR: **In vivo and in vitro effects of salbutamol on alveolar epithelial repair in acute lung injury.** *Thorax* 2008, **63**:215-220.
- Liu KD, Levitt J, Zhuo H, Kallet RH, Brady S, Steingrub J, Tidswell M, Siegel MD, Soto G, Peterson MW, Chesnutt MS, Phillips C, Weinacker A, Thompson BT, Eisner MD, Matthay MA: **Randomized clinical trial of activated protein C for the treatment of acute lung injury.** *Am J Respir Crit Care Med* 2008, **178**:618-623.