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Assessment of circulatory and pulmonary endothelin-1 levels in a lavage-induced surfactant-depleted lung injury rabbit model with repeated open endotracheal suctioning and hyperinflation

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ABSTRACT

Aims:: Endothelin-1 (ET-1) is a mediator of various physiological and pathological processes, including vascular inflammation, cell proliferation and vasoconstriction. Attenuation of ET action using ET-1 antagonists reduces pulmonary vascular leakage and inflammation in several models of lung injuries and experimental acute respiratory distress syndrome (ARDS). Based on these earlier reports, the current study investigates the patterns of ET-1 levels in circulation and pulmonary tissues in an experimental model of lavage-induced surfactant-depleted lung injury. Additionally, we also test the effects of open endotracheal suctioning (OES) and hyperinflation (HI) as recruitment maneuver following OES on ET-1 levels.
Main methods:: Briefly, 24 Japanese white rabbits were anesthetized and intubated. Normal saline was instilled into the lung and washed mildly. After instillation, rabbits were ventilated at definite settings at a total duration of 3 hours. OES and HI were performed every 15 minutes from the beginning of the protocol.
Key findings:: Here, we show that both circulatory and pulmonary ET-1 levels increased in models with lung injury induced by saline lavage compared to healthy control group. No further aggravation in expression of pulmonary ET-1 was seen after OES and HI, although OES and HI worsened arterial hypoxygenation and severity of lung injury. In contrast, circulatory ET-1 levels significantly decreased after OES and HI but were not associated with blood pressure changes.
Significance:: We conclude that in a saline lavage-induced lung injury model, both circulatory and pulmonary ET-1 levels increased. Further, OES and HI exerted differential effects on ET-1 expression at both circulatory and pulmonary levels.

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Introduction

Mechanical ventilation is an indispensable tool for providing basic life support and in major surgical procedures of intensive care patients. This is particularly the case for patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). However, ventilator-induced lung injury (VILI) is a common complication in intubated and mechanically-ventilated patients (Dreyfuss and Saumon, 1998; Slutsky, 2005; Albaiceta and Blanch, 2011). The causes of VILI are multifactorial and it has been suggested that they may play a crucial role in the pathogenesis of the disease by releasing factors into the systemic circulation from the lung. Collectively, these events may subsequently lead to distal organ failure (Wheeler and Bernard, 2007). In view of this, it has been proposed that development of protective ventilation strategies for VILI is key in the management of ALI and ARDS (The Acute Respiratory Distress Syndrome Network, 2000).

Endotracheal suctioning is one of the major procedures frequently performed by nurses for patients during mechanical ventilation. The purpose of this procedure is to directly clean the airway secretions, as patients in this state are unable to cough up the sputum. Specifically, open endotracheal suctioning (OES) is one of the methods of endotracheal suctioning, which requires disconnecting the ventilator from the patient before insertion of a suction catheter into the trachea (Maggiore et al., 2002). It is clear that more airway secretion is removed in OES than in closed endotracheal suctioning of both animal models and patients (Lindgren et al., 2004; Lasocki et al., 2006; Copnell et al., 2007). However, disconnecting from the mechanical ventilator in OES leads to severe hypoxygenation and lung injury (Suh et al., 2002;

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Maggiore et al., 2003; Caramez et al., 2006). Notably, the induced repeated recruitment and de-recruitment by OES can induce a cytokine response in ARDS patients (Ranieri et al., 1999).

Hyperinflation (HI) is one of the recruitment maneuvers (RM) used to stimulate a cough, recover oxygenation and improve compliance, following OES in mechanically-ventilated subjects (Hodgson et al., 2000; Patman et al., 2000; Berney and Denehy, 2007). Previous studies have demonstrated an association between RM and cytokine release (Talmor et al., 2007) and that RM directly promotes cytokine releases, increases lung stress and compromises lung function (Santiago et al., 2010). If indeed this is the case, the release of inflammatory mediators from the injured lung into the systemic circulation could lead to distal organ failure (Wheeler and Bernard, 2007).

Endothelin-1 (ET-1), a family of 21 amino acid peptide (three isoforms exist; ET-1, ET-2, ET-3), is a mediator of various physiological and pathological processes, including vascular inflammation, cell proliferation and fibrosis. The involvement of ET-1 in the pathogenesis of lung injuries, as well as in ARDS, has been well documented (Filip et al., 1991; Horgan et al., 1991; Jesmin et al., 2011). Furthermore, another study has demonstrated the involvement of ET-1 in VILI (Lai et al., 2010).

To date, there is no study that has examined the expression profile of ET-1 in circulation and pulmonary tissues of a saline lavage-induced surfactant-depleted lung injury model, with or without repeated OES or HI during mechanical ventilation. Thus, the current study attempts to use an experimental model of lavage-induced surfactant-depleted lung injury to investigate the pattern of circulatory and pulmonary expression of ET-1. In addition, we also tested the effects of OES and RM, such as HI, on ET-1 levels. Lastly, we explore whether ET-1 is also involved in lung injury, as well as arterial hypoxygenation during mechanical ventilation, under conditions of repeated OES or OES and HI.

Methods

Animals

The study was performed using 24 Japanese White Rabbits, weighting between 2.5 and 3.2 kg and fed with a standard diet and water ad libitum. This study was pre-approved by the Ethics Committee of the Animal Resource Center of the University of Tsukuba and the rabbits were cared for in accordance with the guidelines of ethical animal research.

Animal preparation

Rabbits were sedated using 1.0% lidocaine solution (0.25 mg/kg, intramuscularly) and sodium pentobarbital (75–150 mg, bolus infusion) and then restrained in a supine position. The anesthesia was maintained during the experiment by a continuous infusion of sodium pentobarbital (5 mg/kg/h) and pancuronium (0.1 mg/kg/h) administered through the ear vein via an infusion pump. Also, the body fluid in the animals was maintained by a continuous infusion of normal saline (5 mL/kg/h).

The anterior neck was then carefully dissected, followed by a tracheotomy, insertion of an endotracheal tube (3.5 mm internal diameter) in the trachea and mechanical ventilation in pressure-controlled mode (LTV-1000 ventilator; Care Fusion, San Diego, CA). Since no lung lavage was induced, the ventilator settings for the baseline were as follows: inspired oxygen fraction (F_IO_2) 1.0; peak end-expiratory pressure (PEEP) of 2 cmH_2O; and inspiratory time of 0.5 second. Airway pressure and respiratory rate were adjusted to maintain constant expiratory tidal volume of 6 to 8 mL/kg (around the criteria range of protective ventilation strategy), and initial respiratory rate was set to achieve normocarbia. In the current study, the essential parameters of protective ventilation strategy were carefully followed, including: 1) low tidal volume (6 mL/kg), 2) expiratory plateau pressure <30 cmH_2O, 3) permissive hypercapnia, and 4) set up of PEEP to prevent alveolar collapse (The Acute Respiratory Distress Syndrome Network, 2000). Mechanical ventilation was continued in the same manner throughout the experiment, except for the adjustments of PEEP level, described later.

In order to monitor systemic arterial pressure and sampling blood gas, a catheter was carefully inserted into the right carotid artery. Blood was then drawn using heparinized syringe for determining baseline levels of PaO_2, $PaCO_2$, arterial pH and lactate (ABL 720; Radiometer Copenhagen, Copenhagen, Denmark). Baseline readings for lung mechanics were also measured (baseline). Lastly, body temperature was monitored continuously and maintained between 38 °C and 39 °C using a rectal probe and a heating pad, respectively. When arterial blood pressure in the current experimental protocol dropped to life-threatening levels, intravenous saline infusion was gradually increased, up to a maximum of 1.5 times in order to restore the blood pressure back to normal.

Lung injury

After 30 minutes of stability, we recorded the baseline data of hemodynamics, gas exchange and lung mechanics. Acute lung injury was induced by lavaging the whole lung using a modified technique, described earlier by Lachman et al. (1980). With the rabbit in the supine position, warm sterile saline (28 mL/kg, average number of lavages were 3–4 times with some variations to obtain PaO_2 < 100 mmHg) was administered into the trachea via the endotracheal tube. The rabbits were then gently rocked from side to side in order to perform mechanical ventilation and the saline solution was gravity-drained and then actively suctioned with a suctioning catheter. The lavage process was repeated until adequate injury was evident (defined as PaO_2 < 100 mmHg) and each lavage was performed at 5 minutes intervals. After 30 minutes, the blood gas was sampled to monitor the stability of the animal before the experimental ventilation protocol was begun.

Experimental protocol

In the current study, 4 groups of animals were used. The healthy control group (control, $n = 6$) was mechanically ventilated but without saline lavage. The rest of the animals were first lavaged, and randomly assigned to three groups ($n = 6$/each), namely: a) lung injury group (lung injury): in this group the animals with lung injury were mechanically-ventilated for 3 hours; b) open endotracheal suctioning group (OES): animals here were also mechanically-ventilated for 3 hours. However, in addition, OES was performed every 15 minutes after the protocol was started. For endotracheal suctioning, 6 French suctioning catheters were used (TrachCare, Ballard Medical products, Draper, Utah). Suction depth was of 2 cm (length of adapter) plus length of tracheal tube and a negative pressure of −150 cmH_2O was applied for 15 seconds, while withdrawing the catheter; c) hyperinflation group (HI): in this group suctioning was performed, as described earlier in the OES group. Further, animals were considered manually hyperinflated by changing the ventilator mode with PEEP of 0 cmH_2O and positive airway pressure of +5 cmH_2O for 1 minute. After the protocol was started, the rabbits were ventilated by pressure-controlled ventilation with a PEEP of 10 cmH_2O, inspiratory time of 0.5 second and inspired oxygen fraction of 1.0. Airway pressure and respiratory rate were adjusted to maintain constant expiratory tidal volume of 6 to 8 mL/kg, according to the protective ventilation strategy (The Acute Respiratory Distress Syndrome Network, 2000). The inspiratory pressure limit was set at 25 cmH_2O and respiratory rate limit was 55/min. Blood gas sampling as well as hemodynamics and pulmonary parameters data were performed every 30 minutes and blood samples (plasma and serum) taken every hour. Finally, the rabbits were euthanized with bolus injection of sodium pentobarbital and lungs were processed for morphological examination.

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