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Lung mechanical changes following bronchoaspiration in a porcine model: Differentiation of direct and indirect mechanisms

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ABSTRACT

Bronchoaspiration results in local deterioration of lung function through direct damage and/or indirect systemic effects related to neurohumoral pathways. We distinguished these effects by selectively intubating the two main bronchi in pigs while a PEEP of 4 or 10 cm H_2O was maintained. Gastric juice was instilled only into the right lung. Lung mechanical and ventilation defects were assessed by measuring unilateral pulmonary input impedance ($Z_{L,s}$) and the third phase slope of the capnogram (S_{III}) for each lung side separately before the aspiration and for 120 min thereafter. Marked transient elevations in $Z_{L,s}$ parameters and S_{III} were observed in the affected lung after aspiration. Elevating PEEP did not affect these responses in the $Z_{L,s}$ parameters, whereas it prevented the S_{III} increases. None of these indices changed in the intact left lung. These findings furnish evidence of the predominance of the local direct damage over the indirect systemic effects in the development of the deterioration of lung function, and demonstrate the benefit of an initially elevated PEEP following aspiration.

1. Introduction

Management of the adverse pulmonary consequences of bronchoaspiration poses a major challenge for health professionals during general anaesthesia and intensive care (Marik, 2001, 2011). This syndrome has been reported to cause a high incidence of morbidity and mortality, involving up to 90% of the affected patients, depending on the extent of the involved lung regions (Cameron et al., 1973; Engelhardt and Webster, 1999; LeFrock et al., 1979; Olsson et al., 1986; Warner et al., 1993). Inhalation of the gastric contents into the lower respiratory tract induces a number of pulmonary syndromes, described originally by Mendelson et al., including acute aspiration pneumonitis caused by the acidity subsequent to chemical injury (Mendelson, 1946), and aspiration pneumonia resulting from the inhalation of pathogenic bacteria (Marik, 2001, 2011; Raghavendran et al., 2011).

The mechanisms responsible for the acute deterioration of lung function following aspiration of the gastric contents have not been fully clarified. Earlier results demonstrated the involvement of direct physiochemical processes leading to mucosal damage and desquamation (Kennedy et al., 1989; Wynne et al., 1981). Another direct effect of gastric juice aspiration may be related to pepsin being cytotoxic to bronchial epithelial cells (Bathoorn et al., 2011). A further direct mechanism of lung injury following bronchoaspiration may be subsequent to the induced surfactant dysfunction (Lamonica et al., 2014). Besides these direct mechanisms, indirect pathways have also been reported to be involved in the course of aspiration, since the lung injury has been found to be mediated by capsaicin-sensitive vagal sensory afferent nerves (Kennedy et al., 1989; Kollarik et al., 2007; Martling and Lundberg, 1988; Nemzek and Kim, 2009). Another indirect route may be due to the activation of systemic inflammatory processes originating from the affected lungs, including the release of endogenous mediators by neutrophils, alveolar macrophages or by activation of the complement system leading to vascular leakage and oedema formation (Goldman et al., 1991; Kennedy et al., 1989; Knight et al., 1992; Nader-Djalal et al., 2007; Nishizawa et al., 1996; Weiser et al., 1997). Although the effective prevention and/or treatment of the bronchoaspiration would require the identification of the roles of these individual mechanisms, no previous studies have attempted to clarify the involvement of the direct and indirect pathways in the adverse functional changes in the lung during the acute phase of gastric juice inhalation.

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Another important factor that may affect the severity of the lung damage and the outcome of bronchoaspiration is the application of a raised positive end-expiratory pressure (PEEP). While an elevated PEEP is beneficial for the recruitment of lung regions and maintaining them open during mechanical ventilation (Colmenero-Ruiz et al., 1997; Ko et al., 2008), a significant haemodynamic impairment characterized by a deterioration in cardiac function may also occur during a PEEP increment (Marumo et al., 2009).

The aims of the present study were therefore to quantify the separate roles of direct and indirect mechanisms of the deterioration of lung mechanics following acid aspiration. Acidic gastric content was unilaterally administered into one lung and changes of lung mechanics were measured alternately in the affected and intact lungs. A further aim was to investigate the effects of different PEEP levels on the respiratory and circulatory outcomes during and following the inhalation of gastric juice.

2. Materials and methods

The work was carried out in accordance with EU Directive 2010/63/EU relating to animal experiments. The experimental protocol was approved by the institutional Animal Care Committee of the Faculty of Medicine at the University of Szeged (No. XIV/152/2013), and was performed in accordance with the National Institutes of Health guidelines for animal use.

2.1. Animal preparations

Male Vietnamese mini-pigs ($n = 13$) weighing 28.2 ± 0.9 kg (21–33 kg) were used in the present study. Anaesthesia was induced by an intramuscular injection of ketamine (20 mg/kg, CP-ketamin 10%, Produlab Pharma, Raamsdonksveer, Netherlands) and xylazine (2 mg/kg, CP-xylazin 2%, Produlab Pharma, Raamsdonksveer, Netherlands) until an i.v. line was secured into the ear. A continuous infusion of propofol (6 mg/kg/h, propofol 2% MCT/LCT, Fresenius-Kabi, Bad Homburg, Germany) was then maintained throughout the study via the ear vein. The mini-pigs were tracheostomized and a double-lumen cannula (Broncho-cath right 35 Fr, Mallinckrodt Medical, Athlone, Ireland) was introduced into the distal trachea. The double lumen tracheostomy tube was positioned to achieve separate support of the left and right lung sides and the tips were sealed by inflating a cuff. The pigs were then mechanically ventilated (Model 900C; Siemens-Elema, Solna, Sweden) in volume-controlled mode with a tidal volume of 7–8 ml/kg at a frequency of ~20/min and an inspired oxygen fraction (FiO_2) of 0.3 in air. A femoral artery was prepared surgically in a sterile manner and cannulated for blood sampling and the measurement of arterial blood pressure and cardiac output by thermodilution (PiCCO Catheters; Pulsion Medical Systems, Feldkirchen, Germany). The jugular vein was prepared in the same way as the femoral artery and cannulated for fluid and drug administration. Muscle relaxation was achieved by regular i.v. administration of pipecuronium (0.1 mg/kg, every 30 min, Arduan, Richter-Gedeon, Budapest, Hungary). The thorax was opened by means of a midline thoracotomy following an i.v. bolus of sufentanyl (25 μg/kg, Sufentanil Torrex, Chiesi Pharmaceuticals, Vienna, Austria) and the ribs were widely retracted. Following chest opening, the pigs were randomly assigned to maintain a PEEP of 4 or 10 cm H_2O.

Arterial blood samples were analyzed radiometrically (Cobas b221; Roche Diagnostics, Basel, Switzerland). The Horowitz quotient (HQ) was calculated as the ratio of the arterial partial pressure of oxygen and FiO_2.

A small incision was made in the stomach and 10–20 ml of gastric juice was obtained via a catheter introduced into the stomach. This gastric juice was filtered to remove solid particles. The pH of the remaining fluid was determined and hydrochloric acid was added to reach a pH of 2 if needed.

2.2. Measurement of lung mechanics

2.2.1. Forced oscillations

The measurement system for collection of the input impedance spectra of the right or left lung ($Z_{L,s}$) in the mini-pigs was similar to that used previously for the whole lungs (Petak et al., 2006). Briefly, the mechanical ventilation was ceased at end-expiration and the cannula of the measured lung was connected to a loudspeaker-in-box system while the cannula of the other lung was occluded. Thus, during these 8-s long apnoeic periods, the forced oscillatory signal was introduced only to either the left or the right lung. Prior to the measurements, the pressure in the loudspeaker box chambers was set to the level of the PEEP to keep the mean transpulmonary pressure constant. The loudspeaker delivered a computer-generated small-amplitude (<±1 cm H_2O) pseudo-random signal in the interval 0.5–21 Hz through a screen pneumotachograph (11 mm ID), which was used to measure the gas flow (V') with a differential pressure transducer (model 33NA002D; ICSensors, Malpitas, CA, USA). An identical pressure transducer was used to measure the pressure in the left or right main bronchi with reference to the atmosphere ($P_{L,s}$).

The $P_{L,s}$ and V' signals were low-pass filtered at 25 Hz and sampled with an analogue–digital board of a microcomputer at a rate of 256 Hz. Fast Fourier transformation with 4-s time windows and 95% overlapping was used to calculate the unilateral $Z_{L,s}$ spectra ($Z_{L,s} = P_{L,s}/V'$).

2.2.2. Estimation of airway and parenchymal parameters

The airway and parenchymal mechanical properties for the individual lungs were separated by fitting a model to the $Z_{L,s}$ spectra by minimizing the differences between the measured and modelled impedance values. The model consisted of an airway compartment containing airway resistance (Raw) and airway inertance (Iaw), and a constant-phase tissue unit (Hantos et al., 1992) characterized by tissue damping (G) and elastance (H):

$$Z_{L,s} = \mathrm{Raw} + j\omega \mathrm{Iaw} + \frac{G - jH}{\omega^{\alpha}}$$

where j is the imaginary unit, ω is the angular frequency ($2\pi f$), and α is $(2/\pi)$ arctan (H/G).

2.3. Capnography

Changes in partial CO_2 pressure in the exhaled gas during mechanical ventilation were measured with a calibrated sidestream capnometer (Cardiocap II; Datex/Instrumentarium, Helsinki, Finland). CO_2 traces were recorded alternately from each lung by closing one lumen of the endotracheal tube, at a time while the tidal volume was decreased by one-third by elevating the ventilation frequency. The 8-s CO_2 traces obtained from the aspirated or the intact lung were imported into custom-developed signal analysis software. The third phase of the expiratory CO_2 curves in each expiration was identified by selecting the CO_2 traces from its peak end-tidal value back to 60% of the total length of its linear temporal change. Linear regression analysis was applied to these phases to obtain slope of the third phase of the expiratory capnogram (S_{III}). S_{III} was normalized by dividing each slope by the average values of the corresponding CO_2 concentration in the mixed expired gas to obtain normalized time domain third phase slopes (S_{nIII}). Four to six expiratory traces were analyzed in each recording.