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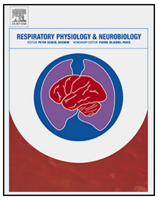

Effects of superimposed tissue weight on regional compliance of injured lungs[☆]

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ABSTRACT

Computed tomography (CT), together with image analysis technologies, enable the construction of regional volume (V_{REG}) and local transpulmonary pressure ($P_{TP,REG}$) maps of the lung. Purpose of this study is to assess the distribution of V_{REG} vs $P_{TP,REG}$ along the gravitational axis in healthy (HL) and experimental acute lung injury conditions (eALI) at various positive end-expiratory pressures (PEEPs) and inflation volumes.

Mechanically ventilated pigs underwent inspiratory hold maneuvers at increasing volumes simultaneously with lung CT scans. eALI was induced via the iv administration of oleic acid. We computed voxel-level V_{REG} vs $P_{TP,REG}$ curves into eleven isogravitational planes by applying polynomial regressions.

Via F-test, we determined that V_{REG} vs $P_{TP,REG}$ curves derived from different anatomical planes (p-values < 1.4E-3), exposed to different PEEPs (p-values < 1.5E-5) or subtending different lung status (p-values < 3E-3) were statistically different (except for two cases of adjacent planes).

Lung parenchyma exhibits different elastic behaviors based on its position and the density of superimposed tissue which can increase during lung injury.

1. Introduction

Respiratory system compliance (C_{RS}) is an indicator of the severity of acute respiratory distress syndrome (ARDS) and is used for titrating ventilatory settings for ARDS treatment (Matamis et al., 1984). A growing body of evidence shows that intrapulmonary differences in the elastic proprieties of the lung are also potential sources of ventilator-induced lung injury (VILI) due to the increased strain between neighboring groups of alveoli with different time constants (Steinberg et al., 2004).

Several studies have demonstrated that the healthy lung is inherently inhomogeneous because of gravitational (Milic-Emili, 1986) and local forces (Ma et al., 2013). This results in vertical but opposing gradients of alveolar distension (Simon et al., 2005) and relative ventilation (i.e., the ratio between ventilated gas and the volume of gas already present in a lung region) (Milic-Emili et al., 1966 and Milic-Emili, 1986). More recent findings showed that along the gravitational axis, lung density, quantified via computed tomography (CT) and estimated superimposed pressure, increases from nondependent to dependent zones in both normal and ARDS lungs (Gattinoni et al., 1991; Pelosi et al., 1994).

Our group has recently defined a method of assessing the topographic distribution of lung compliance (Perchiazzi et al., 2014) by using a series of CT images obtained at different inflation volumes. One relevant message of that study was that compliance, measured at the airway opening, is a lumped parameter that does not necessarily reflect the extent of regional differences of lung elasticity. Moreover, it provided a reliable method with which to compute

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a distribution map of volume and pressure inside the lung at the voxel level.

We have previously shown that regional strain is posture-dependent in healthy lungs and that intrapulmonary differences between dependent and non-dependent planes are less pronounced in the prone than in the supine position (Perchiazzi et al., 2011). Considering that global lung compliance measured at the airway opening is used to both assess the degree of lung impairment and titrate respiratory support, we deemed it relevant to explore the effects of weight force on the distribution of the elastic properties in the lung.

The purpose of the present study was to determine the relationship between regional lung compliance and the compression from superimposed tissue weight, by using two-dimensional maps of the distribution of pressure and volume variation in healthy lung conditions and an experimental model of human ARDS (eALI) at two levels of applied positive end-expiratory pressure (PEEP) and twelve inflation volumes. We hypothesize that the effect of gravity on regional lung compliance is moderated by the superimposed weight of the lung itself.

2. Methods

After approval by the local animal ethics committee at Uppsala University, the present study was executed in agreement with the National Research Council guide regarding the “Principles of laboratory animal care” (NIH publication no. 86-23, revised 1985).

2.1. Animal preparation

Five healthy pigs with a mean weight of 26.0 ± 2.8 kg after sedation underwent general anesthesia. Anesthesia induction was achieved via an intramuscular injection of atropine (0.04 mg/kg), tiletamine-zolazepam (5 mg/kg, Zoletil; Boeringer Ingelheim, Copenhagen, Denmark), and medetomine (5 μg/kg, Dormitor Vet; Orion Pharma, Sollentuna, Sweden). Before the injection of the muscle relaxant, endotracheal intubation was guaranteed via surgical tracheostomy by using a cuffed tube (6.0 Hi-Contour; Mallinckrodt Medical, Athlone, Ireland).

An intravenous infusion of ketamine (20 mg/kg/h, Ketaminol; Vetpharma, Zurich, Switzerland), fentanyl (5 mg/kg/h, Pharmalink, Spånga, Sweden), and pancuronium (0.24 mg/kg/h, Pavulon; OrganonTeknika, Gothenburg, Sweden) in buffered glucose 2.5% (Rehydrex; Fresenius Kabi, Uppsala, Sweden) delivered at a rate of 7 ml/kg/h was used to maintain anesthesia.

Mechanical ventilation was provided by a mobile ventilator (Servo-I, Maquet, Solna, Sweden) that delivered a baseline ventilation using a volume-controlled, constant flow modality with a tidal volume (V_T) of 9 ml/Kg and a respiratory rate (RR) of 20 bpm; the inspiratory-to-expiratory (I:E) ratio was 1:2, and there was a PEEP of 5 cm H_2O, with a fraction of inspired oxygen (FiO_2) equal to 0.5.

Oxyhemoglobin saturation (SpO_2) was continuously measured via a transcutaneous sensor placed at the animal’s ear. An esophageal catheter (Oesophageal catheter, Erich Jaeger GmbH, Höchberg, Germany) was positioned in the distal third of the esophagus, using the Baydur technique (Baydur et al., 1982) to obtain continuous measurements of esophageal pressure (P_{ESO}). A second balloon catheter was located lower within the gastrointestinal duct to continuously measure gastric pressure (P_{GA}). Pressure (P_{AW}) and flow (V'_{AW}) were continuously measured at the airway opening. Three pressure transducers (Digimaclic Pressure Transducers, Special Instruments GmbH, Nördlingen, Germany) were used to measure P_{AW}, P_{ESO}, and P_{GA}, while V'_{AW} was acquired via a Fleisch pneumotacograph (Laminar Flow Element type PT, Special Instruments GmbH, Nördlingen, Germany) positioned between the endotracheal tube and the ventilator and connected to a differential pressure transducer (Diff-Cap Pressure Transducer, Special Instruments GmbH, Nördlingen, Germany).

All respiratory signals were acquired via an analog-to-digital converter card (DAQ-card AI-16XE50, National Instruments Corp., Austin, USA) controlled by the Biobench Software (ver.1.0, National Instruments Corp., Austin, USA) at a sampling frequency of 200 Hz. The inspiratory and expiratory airway volumes (V_{AW}) were obtained via flow integration. After instrumentation, the animals were mechanical ventilated for 60 min to stabilize the pigs’ hemodynamic and respiratory conditions.

eALI was induced via an injection of oleic acid (OA) 0.1 ml/kg (Apoteksbolaget, Göteborg, Sweden) through a central venous catheter at repeated doses of 0.5 ml. The target index of lung injury was a SpO_2 value less than or equal to 80%. During OA injection, adrenalin, in boluses of 0.01 mg, was used to avoid decreases in systemic arterial pressure.

2.2. Image acquisition and analysis protocol

The procedure used to generate two-dimensional maps of pressure and volume distribution from the CT images has been recently published by our group (Perchiazzi et al., 2014) and will only be summarized here (Fig. 1).

After a recruitment maneuver (RM) consisting of a constant airway pressure of 40 cm H_2O for 40 s, the inspiratory capacity (IC) of each animal was calculated. The entire IC was divided into twelve iso-volumetric steps, which were used to define the gas volumes to be delivered to the lungs before taking each CT scan ($VT = (IC/12) \times 1, (IC/12) \times 2, (IC/12) \times 3\ldots$ up to IC).

The animals underwent inspiratory hold maneuvers (IHMs) corresponding to the twelve inspiratory volumes, which were administered as monotonically increasing volumes. In order to restore a steady-state condition, each IHM was separated from the following ones via 2–3 min of tidal breathing. Whole-lung spiral CT scans (Somatom Sensation 16, Siemens, Erlangen, Germany) were performed for each IHM (120 KV, 80 mAs). At the end of the procedure, a CT acquisition at the zero end expiratory pressure (ZEEP) was performed. Each CT scan of the whole lung required less than 6 s of apnea. The described sequence, composed of RM, twelve IHM steps, and ZEEP, was performed in each animal at two levels of PEEP before and after the induction of eALI. Hence, the studied conditions were as follows: healthy lungs at a PEEP of 5 cm H_2O (HL5), healthy lungs at a PEEP of 10 cm H_2O (HL10), injured lungs at a PEEP of 5 cm H_2O (eALI5), and injured lungs at a PEEP of 10 cm H_2O (eALI10).

For each studied condition and sequence of IHMs, five transverse planes were selected among the whole-lung CT scans, covering the lung from the para-diaphragmatic to the apical level. The five transverse planes had 25 mm of distance between them along the longitudinal axis. Hence, the distance between the most para-diaphragmatic CT plane and the most apical one was fixed at 100 mm. The slice thickness was 5 mm.

Customized scripts for the Image Processing and Statistics Toolboxes of MatLab R2010 (MatLab, The MathWorks, Natick, USA) were purposely created by one of the authors (G.P.) in order to perform the image analysis.

In each slice, the perimeter of the lung parenchyma was manually selected in order to avoid potential flaws that are typical of automatic segmentation algorithms, which may not distinguish atelectatic areas from chest-wall structures, due to their similar HU density values.

The collected CT images of the lung underwent an *image registration* process, the details of which have been described previously (Flusser and Zitova, 2003; Perchiazzi et al., 2014). The process of image registration aims to enable comparisons between images