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Continuous Noninvasive Monitoring of Lung Recruitment during High-Frequency Oscillatory Ventilation by Electrical Impedance Measurement: An Animal Study

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Key Words
High-frequency oscillatory ventilation · Quadrant impedance measurement · Residual impedance

Abstract
Background: Ventilatory pressures should target the range between the upper and lower inflection point of the pressure volume curve in order to avoid atelecto- and volutrauma. During high-frequency oscillatory ventilation (HFOV), this range is difficult to determine. Quadrant impedance measurement (QIM) has recently been shown to allow accurate and precise measurement of lung volume changes during conventional mechanical ventilation. ***Objectives:*** To investigate if QIM can be used to determine a static pressure-residual impedance curve during a recruitment-derecruitment manoeuvre on HFOV and to monitor the time course of alveolar recruitment after changing mean airway pressure (MAP). ***Methods:*** An incremental and decremental MAP trial (6 cm H_2O to 27 cm H_2O) was conducted in five surfactant-depleted newborn piglets during HFOV. Ventilatory, gas exchange and haemodynamic parameters were recorded. Continuous measurement of thoracic impedance change was performed. ***Results:*** Mean residual impedance (RI) increased with each stepwise increase of MAP resulting in a total mean increase of +26.5% (±4.0) at the highest MAP (27 cm H_2O) compared to baseline ventilation at 6 cm H_2O. Upon decreasing MAP levels, RI fell more slowly compared to its ascent; 83.4% (±19.1) and 84.8% (±16.4) of impedance changes occurred in the first 5 min after an increase or decrease in airway pressure, respectively. ***Conclusions:*** QIM could be used for continuous monitoring of thoracic impedance and determination of the pressure-RI curve during HFOV. The method could prove to be a promising bedside method for the monitoring of lung recruitment during HFOV in the future.

Introduction

Alveolar overdistension and repetitive opening and closing of atelectatic lung units are two important determinants for the development of ventilator-induced lung injury [1]. This process of secondary lung injury is considered one of the major risk factors for the development of bronchopulmonary dysplasia in mechanically ventilated preterm infants [2]. Lung protective ventilation strategies aim at reducing this volu- and atelectotrauma

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by targeting the optimal area on the pressure volume curve of the respiratory system above the point where atelectatic lung regions begin to open (lower inflection point) and below the point where alveolar overdistension occurs (upper inflection point) [3]. According to this, during high-frequency oscillatory ventilation (HFOV), alveolar recruitment and stabilization have been proposed as important determinants for the attenuation of lung injury (i.e. the open lung strategy) [4, 5]. In clinical application of HFOV, the oxygenation response to increasing mean airway pressures (MAP) can be used in order to monitor alveolar recruitment and to determine the optimal pressure-volume range for ventilation [6]. Yet, such recruitment manoeuvres may be difficult to perform, require repeated blood samplings and offer only indirect information about the recruited lung volume [7].

Electrical impedance measurement is a non-invasive, radiation-free bedside technique which allows to evaluate pulmonary gas distribution and to monitor lung recruitment continuously [8–11]. Quadrant impedance measurement (QIM), an application of impedance measurement which has been specifically developed for use in neonatology, has recently been shown to allow accurate and precise estimation of lung volume changes during conventional mechanical ventilation in an animal model [12]. In the present study, QIM was used for the continuous measurement of residual impedance (RI) change, i.e. thoracic impedance change corresponding to the change of residual lung volume, in order to monitor pulmonary recruitment and derecruitment at different MAP levels during HFOV in surfactant-depleted animals. The study was performed to answer the following questions: (1) 'Can QIM be used to determine a static pressure-RI curve during a recruitment and derecruitment manoeuvre?' and (2) 'What is the time course of impedance change after changes in MAP?'

Materials and Methods

Animals

The study was performed in 5 anaesthetized newborn piglets and all experiments were approved by the university and the state committee for animal care, and adhered to the national law and to institutional standards on the care and use of laboratory animals. Animals were treated as previously described [12, 13]. In short, following intramuscular pre-medication (20 mg/kg ketamine, 5 mg/kg azaperone), intravenous anaesthesia was induced with morphine (2 mg/kg) and lorazepam (1 mg/kg), and subsequently maintained with morphine (20 μg/kg/h), lorazepam (0.2 mg/kg/h) and rocuronium (2 mg/kg/h). An arterial line was placed in the femoral artery, connected with a pressure transducer and kept open with a continuous infusion of heparin-saline mixture (1 ml/h). Continuous monitoring of vital parameters was performed using a neonatal patient monitor (HP, Palo Alto, Calif., USA). Animals were intubated via tracheotomy (tube with a 3.0-mm inner diameter with a side port; Vygon, Ecouen, France) and placed on a mechanical ventilator (Stephanie, Fa. Stephan, Dresden, Germany).

Ventilatory Protocol

Following initial ventilation in volume controlled mode (FiO_2 1.0; tidal volume 6 ml/kg; positive end-expiratory pressure 4 cm H_2O; inspiratory time 0.4 s, respiratory rate 60 breaths/min), surfactant depletion was performed by repetitive lung lavage with warmed saline (30 ml/kg) as described previously [14]. The lavage procedure was repeated until PaO_2 remained below 100 mm Hg for at least 30 min. Thereafter, HFOV was started with a ventilatory frequency of 10 Hz, MAP 6 cm H_2O and amplitude adjusted to achieve a volume of 2 ml/kg. The fixed-orifice pneumotachograph of the Stephanie ventilator was used for volume measurements, and calibration with the built-in test-lung of the ventilator was performed prior to all experiments. After a stabilization period of 15 min, baseline measurements were performed. MAP was increased by steps of 3 cm H_2O until reaching a MAP of 27 cm H_2O and subsequently decreased in steps of 3 cm H_2O until a MAP of 6 cm H_2O was achieved.

After each change in MAP, ventilatory settings were kept stable for 15 min except at 27 cm H_2O, where it was decreased after 5 min in order to avoid severe cardiopulmonary impairment of the animals. After each stabilization period, blood gases were obtained (ABL 500; Radiometer, Copenhagen, Denmark) and vital parameters were recorded prior to changing the MAP.

Electrical Impedance Measurement

Impedance measurements were performed using the QIM device of EMS Biomedical (Korneuburg, Austria) as previously described [12]. A constant current source which generates a sinus wave output current of 400 μA at a frequency of 2 KHz applied via a ventral and a dorsal current electrode was used. Voltage measurements were performed in four regions of the thorax, cephalic left, cephalic right and caudal left and right, at a frequency of 500 Hz. One ventral and one dorsal electrode per region were placed and disposable EEG needle electrodes were used for both current injection and voltage measurement (Technomed S43-438; Technomed, Berlin, Germany). A switchable high-pass filter (0.5 Hz) and a fixed frequency low pass filter (20 Hz) were used to process incoming biosignals of the four channels. Data was transferred to a PC via a USB interface and analyzed with EIM client 4.0 software. Mean thoracic impedance during 5-second time intervals was recorded separately in the four quadrants via four channels and total RI was subsequently calculated as the sum of thoracic impedance from all four channels and expressed in arbitrary units (AU). Relative impedance change at each MAP step was calculated for every animal as RI at the respective MAP step divided by individual RI at baseline (6 cm H_2O) and expressed in percent.

Statistical Analysis

The data of impedance measurements was exported to MS excel and JMP (JMP 7.0; SAS Institute Inc., N.C., USA) via EIM client 4.0 software data export. Data are expressed as means (±SD) if normal distribution was assumed or median (IQR) in case no

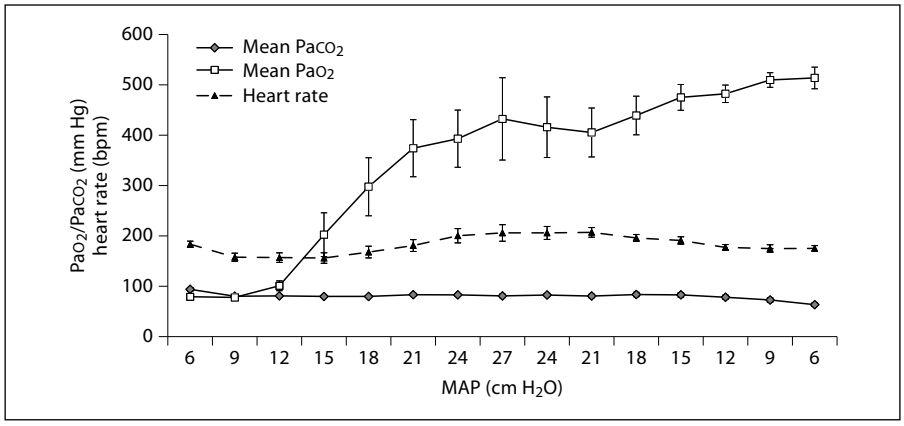

Fig. 1. Blood gases and heart rate: mean (±SEM) values of PaO_2, $PaCO_2$ and heart rate at different MAP levels.

normal distribution was assumed. Standard errors of the mean (SEM) are indicated instead of SD in the diagrams in order to improve visibility and clarity of data. Differences between RI values at the respective MAP levels were assessed by paired t tests at a two-sided significance level of $\alpha = 0.05$. Statistical analysis was performed using JMP (JMP 7.0; SAS Institute Inc., N.C., USA).

Results

Animals had a median (IQR) age of 2 (1–2) days of life and mean bodyweight of 1.4 kg (±0.2). All 5 animals remained stable during the experimental period with no additional interventions necessary. A median (IQR) of 4 (3–5) bronchoalveolar lavages were required to achieve post-lavage PaO_2 levels below 100 mm Hg.

Blood Gases and Vital Parameters

As shown in figure 1, PaO_2 increased with raising MAP levels during HFOV starting from 79 (±7) mm Hg at a MAP of 6 cm H_2O after lavage to 432 (±183) mm Hg at the highest MAP of 27 cm H_2O. Upon decreasing MAP levels, PaO_2 remained high and even showed a further increase to 513 (±48) mm Hg at the end of the experimental period. Mean $PaCO_2$ levels were 94 (±8) mm Hg after start of HFOV. They remained stable throughout the experimental period and showed a slight decrease towards the end of the study to 63 (±8) mm Hg.

Animals had a mean heart rate of 183 (±13) bpm at baseline, which during the course of HFOV first decreased to 156 (±23) bpm at a MAP of 15 cm H_2O. Subsequently heart rates increased with rising MAP levels to 205 (±37) bpm at 27 cm H_2O. With decreasing MAP values, heart rates decreased resulting in a mean heart rate of 175 (±12) bpm at the end of the experimental period (fig. 1).

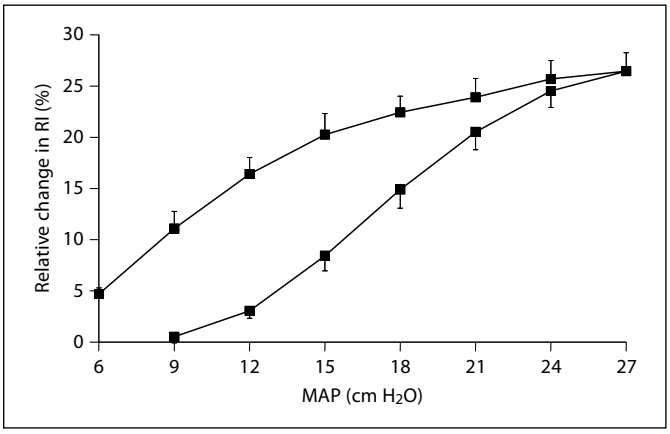

Fig. 2. Changes of RI: relative mean (±SEM) changes in RI compared to baseline measurements after changes in ventilatory pressure at different MAP levels.

Residual Impedance

Figure 2 shows mean relative changes in RI at different MAP levels during recruitment and derecruitment. Compared to baseline measurements at 6 cm H_2O, mean RI increased with each stepwise increase of MAP resulting in a total mean increase of +26.5% (± 4.0) at *27* cm H_2O. Upon decreasing MAP levels, RI fell more slowly compared to its ascent. At the MAP stages of 18, 15, 12, and 9 cm H_2O, RI levels were significantly higher than RI levels at the respective MAP stages on the inflation limb (all $p < 0.01$).

Time Course of RI Change

Repeated measurements of RI during 15 min after each alteration in MAP showed that changes in RI occurred mainly in the first few minutes after increase or decrease in airway pressure (fig. 3). For increasing MAP

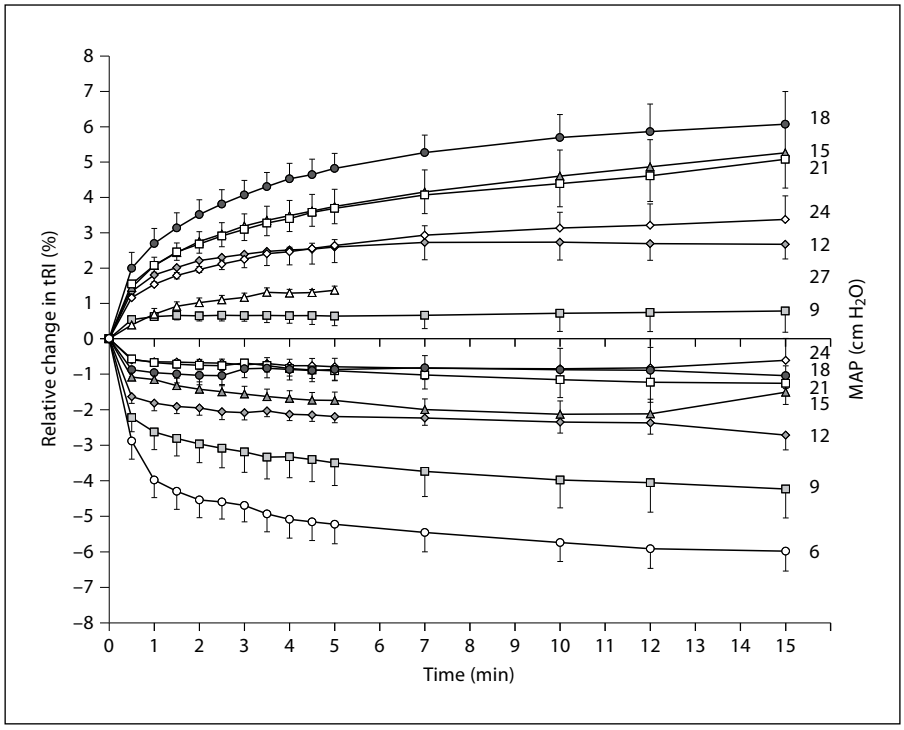

Fig. 3. Time course of changes in RI: mean relative (±SEM) changes in RI following the first 15 min after changes in ventilatory pressure at different MAP levels.

levels, mean impedance change after 2.5, 5 and 10 min was 69.9% (±13.5), 83.4% (±19.1) and 93.4% (±13.2) of total change, respectively. For decreasing MAP levels, mean impedance change was 77.4% (±19.3), 84.8% (±16.4) and 94.5% (±14.2) of total change after 2.5, 5 and 10 min, respectively.

Discussion

In the present study, QIM was used during a recruitment-derecruitment manoeuvre on HFOV to determine a static pressure-RI curve which showed the characteristic upward concavity on the inflation limb and marked lung volume hysteresis. Visual examination of the obtained curves suggests a MAP of approximately 12 cm H_2O as a lower inflection point on the inflation limb and an upper inflection point on the deflation limb in the region of 16–18 cm H_2O (fig. 2). Numerous studies have demonstrated linearity between lung volume and impedance change in healthy and in ventilated subjects [11, 15–17] as well as in several animal models [9, 12, 18, 19]. Miedema et al. [20] recently reported on a study using EIT to assess lung volume changes during a HFOV recruitment manoeuvre in preterm infants of 25–31 weeks of gestational age. Reported pressure ranges of lower and upper inflection points were very similar to the data obtained in the present study.

Due to methodological difficulties, the determination of lung volumes during HFOV poses a problem. For conventional wash out methods, HFOV has to be interrupted. The possibility of continuous assessment of pulmonary recruitment after changing MAP is therefore a major benefit from impedance measurement. In the present study more than 80% of impedance change occurred within the first 5 min after change of MAP. This is again very similar to what the group of Miedema et al. [21] found in 22 preterm infants on HFOV using EIT. Employing a SF6 wash out method with interruption of HFOV, Thome et al. [22] found a stabilization of lung volume after a median time of 9 min in premature children with respiratory distress syndrome after modification of MAP. During the course of our study, increasing MAP levels resulted in constantly rising PaO_2 levels as a sign of improved oxygenation through alveolar recruitment, which was similarly reflected by the pressure-impedance curve. Interestingly, oxygenation exhibited a further increase after decreasing the MAP below 21 cm H_2O. The improved oxygenation after lowering pressure levels during HFOV could possibly be partly explained by cardiocirculatory impairment at high MAP levels which improved after lowering MAP [23]. In addition, it most

likely expresses the recovery and stabilization of the lungs through production and spill out of new surfactant, which is a major limitation of the used animal model. In infants, decrease in MAP and subsequent derecruitment would most likely result in deterioration in gas exchange, showing that transferability of the presented results from the animal model to clinical understanding is limited. The missing concordance between oxygenation and pulmonary ventilation reflects the difficult interaction between ventilation and perfusion. Thus, an optimal ventilatory regulation requires not only monitoring of oxygenation, but also of pulmonary ventilation.

Compared to other methods of impedance measurement such as electrical impedance tomography, the reduced number of electrodes required for QIM and therefore the improved clinical practicability are a clear advantage of this method, especially in the field of neonatology. The high temporal resolution of 500 measurement points per second is another striking advantage of this method, which makes it particularly suitable for measurements during HFOV. The improved temporal resolution and clinical practicability is, however, at the expense of a reduced spatial resolution. Compared to devices with more electrodes such as EIT, QIM does not allow to determine lung volume changes in dependent and non-dependent lung regions, for example.

As for all techniques based on impedance change, there remains the problem that impedance is influenced not only by the content of air, but also by water or other liquids. Measurements can for instance be affected by alveolar oedema due to ventilatory injury [24]. To minimize the impact of ventilatory-induced oedema, the study duration was limited to a maximum of 6 h. Moreover, measurements are influenced by the type of electrodes used for impedance measurement. The present study employed needle electrodes, which are not convenient for clinical use and further studies using QIM should focus on electrodes suitable for clinical application, such as self-adhesive electrodes.

The correlation between impedance change and change in functional residual capacity during HFOV has not been finally proven for QIM so far. We also did not obtain a pressure/volume curve in the animals to which the impedance pressure/volume curve could be related to. Results from the former methodological study using QIM during conventional mechanical ventilation can, moreover, only cautiously be transferred to the present study and further validation of the technique before a potential application in a clinical setting is warranted.

In summary, the present study reports on a promising bedside method for online monitoring of lung recruitment during HFOV. In addition, data on the time course of pulmonary recruitment and derecruitment is provided.

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