Regional Time Constants Determined by Electrical Impedance Tomography are Affected by Ventilatory Parameters

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Abstract. *Electrical impedance tomography (EIT) is a non-invasive radiation free imaging modality that enables bedside monitoring of regional lung aeration dynamics. Recently published study has shown that EIT-derived time constants (τ) can be obtained from the data acquired during mechanical ventilation. Moreover, it suggested that τ could be used to distinguish lung pathologies. The aim of our study is to investigate whether setting of ventilatory parameters can affect the values of τ. An animal trial (n=3) with anesthetized mechanically ventilated pigs was conducted. In one animal, acute respiratory distress syndrome was induced by repeated whole lung lavage. Changes of tidal volume (V_T), respiratory rate (RR) and inspiratory-to-expiratory (I:E) ratio were performed. For each ventilatory setting, 20 consecutive breath cycles were used for analysis. EIT data were segmented in spatial domain and mean breath cycles were calculated. Regional values of τ were obtained for each ventilatory setting. The main result of this study is that values of τ are significantly affected by settings of ventilatory parameters. In a consequence, assessment of lung pathologies by means of τ may be compromised when various ventilatory settings are applied.*

Keywords

Electrical impedance tomography, mechanical ventilation, respiratory mechanics, time constants.

1. Introduction

In the last two decades, electrical impedance tomography (EIT) made a big leap from a research technology to imaging modality for intensive care units. It is a safe, radiation-free technique that enables long-term bedside monitoring of patients. The principle of EIT is based on application of small alternating currents using skin electrodes attached to the patient's chest, measurement of the resulting voltages and consequent calculation of the distribution of tissue impedance within the selected body cross-section. Many studies have shown that EIT could offer a considerable alternative to computed tomography (CT), especially in monitoring of lung ventilation and perfusion [1], [2]. Unfortunately, when compared to CT, EIT suffers from low spatial resolution and the provided information may be rather difficult to interpret [3]. Therefore, it still seeks new approaches of data processing and visualization.

Monitoring of regional lung aeration dynamics is probably one of the most promising areas for clinical use of EIT. It has been shown that in patients with chronic obstructive pulmonary disease (COPD) the values of expiratory time constant derived from pneumotachometer data are significantly higher when compared to patients without COPD [4]. However, these pulmonary function tests provide values that are representative for the whole lungs only. To assess regional dynamics of lung aeration, a concept of regional EIT-derived time constants (τ) was introduced [5]. In this approach, EIT data are recorded continuously during spirometry and τ is calculated from a forced expiration maneuver. Subsequently, color-coded maps representing regional values of τ are generated. Moreover, recently published feasibility study [6] suggested that τ obtained in mechanically ventilated patients can be used to distinguish lung pathologies such as acute respiratory distress syndrome (ARDS) or COPD.

Hence the original idea for determination of τ uses EIT data that were recorded during defined ventilatory maneuver (forced expiration performed in Tiffeneau test), ventilatory parameters are set individually for each mechanically ventilated patient. Therefore, we hypothesized that the values of τ calculated from EIT data acquired in mechanically ventilated patients may be influenced by setting of ventilatory parameters.

The aim of this study is to investigate whether setting of ventilatory parameters can affect the values of EIT-derived regional time constants.

2. Methods

The study protocol was approved by the Institutional Review Board of the First Faculty of Medicine, Charles

University in Prague (FFM CU) and is in accordance with Act No. 246/1992 Coll., on the protection of animals against cruelty. The measurements were performed at an accredited animal laboratory of the FFM CU.

Three crossbred Landrace female pigs (*Sus scrofa domestica*) with a body weight of 47 ± 2 kg were used in the study.

2.1. Anesthesia and preparation

The animals were premedicated with azaperone (2 mg/kg IM), followed by anesthesia with ketamine hydrochloride (20 mg/kg IM) and atropine sulphate (0.02 mg/kg IM). When placed on the operating table, initial boluses of morphine (0.1 mg/kg IV) and propofol (2 mg/kg IV) were administered. A cuffed endotracheal tube (I.D. 7.5 mm) was used for intubation. Anesthesia was maintained with propofol (8 to 10 mg/kg/h IV) in combination with heparin (40 U/kg/h IV) and morphine (0.1 mg/kg/h IV). Myorelaxant pipecuronium bromide (4 mg boluses every 45 min) was administered during mechanical lung ventilation to suppress spontaneous breathing. Initial rapid infusion of 1 000 mL of normal saline was administered intravenously, followed by a continuous IV drip of 250 mL/h to reach and maintain central venous pressure of 6 to 7 mmHg.

Heart rate, arterial blood pressure, central venous pressure, body temperature and ECG were monitored using MU-631 RK (Nihon Kohden, Tokyo, Japan) patient monitor. Continuous cardiac output and mixed venous blood oxygen saturation were measured by Vigilance (Edwards Lifesciences, Irvine, CA, USA) monitor. Arterial blood gases, i.e. arterial partial pressure of oxygen, carbon dioxide ($PaCO_2$) and pH, were measured continuously by CDI 500 (Terumo, Tokyo, Japan). The arterio-venous extracorporeal circuit for CDI 500 monitor was established between the femoral artery and the femoral vein using peristaltic roller pump with a blood flow set to 400 mL/min.

In one animal, repeated whole lung lavage (normal saline, 40 mL/kg, 37 °C) was performed to induce surfactant deficiency similar to ARDS [7].

2.2. Ventilation

Conventional ventilator Engström (Datex-Ohmeda, GE Healthcare, Finland) was used in the VCV mode with the following initial setting: respiratory rate (RR) 18 min^{-1}, FiO_2 21%, inspiratory-to-expiratory ratio (I:E) 1:2, positive end-expiratory pressure (PEEP) of 5 cmH_2O and pressure limit set to 40 cmH_2O. Tidal volume (V_T) was set to 8.5 mL/kg of the actual body weight and was titrated to reach normocapnia ($PaCO_2$ 40 ± 3 mmHg).

2.3. EIT measurements

PulmoVista 500 (Dräger Medical, Lübeck, Germany) was used for continuous EIT data acquisition during the whole study protocol. The electrode belt of size S was attached to the chest of the animal at the level of the 6^{th} intercostal space. The frequency of the applied current was set to 110 kHz and the frame rate to 50 Hz.

2.4. Study protocol

After animal preparation, myorelaxation and instrumentation, calibration of the EIT system was performed. A steady phase of 30 minutes was introduced. The study protocol consisted of three phases separated by stabilization periods. In each phase, several different settings of a selected ventilatory parameter were used while keeping the values of remaining ventilatory parameters unchanged. Each setting was kept at least for 2 minutes. The stabilization periods lasted from 3 to 4 minutes. In the first phase, the values of V_T were set in a range from 6 to 12 mL/kg with a step of 2 mL/kg. In the second phase, six different values of RR were used, ranging from 12 to 22 breaths per minute with a step of 2. Changes of I:E were performed in the third phase, setting the values of the parameter to 1:1, 1:1.5, 1:2, 1:2.5 and 1:3. The study protocol is summarized in the scheme in Fig. 1.

In the ARDS subject, different setting of ventilatory parameters was used to prevent severe hypercapnia and hypoxemia. PEEP was set to 15 cmH_2O during the whole protocol. In the first phase, RR was set to 30 min^{-1} and the highest value of V_T (12 mL/kg) was omitted. In the second phase, RR was set to 30, 35, 40, 45 and 50 min^{-1} with V_T of 8 mL/kg. The third phase was performed with RR set to 30 min^{-1} and V_T of 8 mL/kg.

2.5. Data analysis and statistics

The acquired EIT data were pre-processed using Dräger EIT Data Analysis Tool 6.1 (Dräger Medical, Lübeck, Germany). Reference frames (often referred to as baseline frames) were set automatically for each animal as frames that corresponds with the global minima of the global impedance waveforms. Reconstructed data were processed in MATLAB 2014b (MathWorks, Natick, MA, USA). For each ventilatory setting, a data set representing 20 consecutive breaths was created and used for analysis.

Functional region of interest (ROI) was determined in each data set, based on the approach of linear regression coefficient [8]. For each pixel, the relative impedance values in time (impedance waveforms) were used as a dependent variable while the global impedance waveform, determined

Time →

	Steady phase	Phase 1: Changes of V_T				Stabilization	Phase 2: Changes of RR						Stabilization	Phase 3: Changes of I:E				
V_T (mL/kg)	8	6	8	10	12	8	10	10	10	10	10	10	8	10	10	10	10	10
RR (min^{-1})	20	20	20	20	20	20	12	14	16	18	20	22	20	20	20	20	20	20
I:E (-)	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:1	1:1.5	1:2	1:2.5	1:3

Fig.1. Study design and the settings of ventilatory parameters during the protocol. For each phase, the changes in parameter setting are highlighted by light gray background of the parameter value. V_T—tidal volume; RR—respiratory rate; I:E—inspiratory-to-expiratory time ratio.

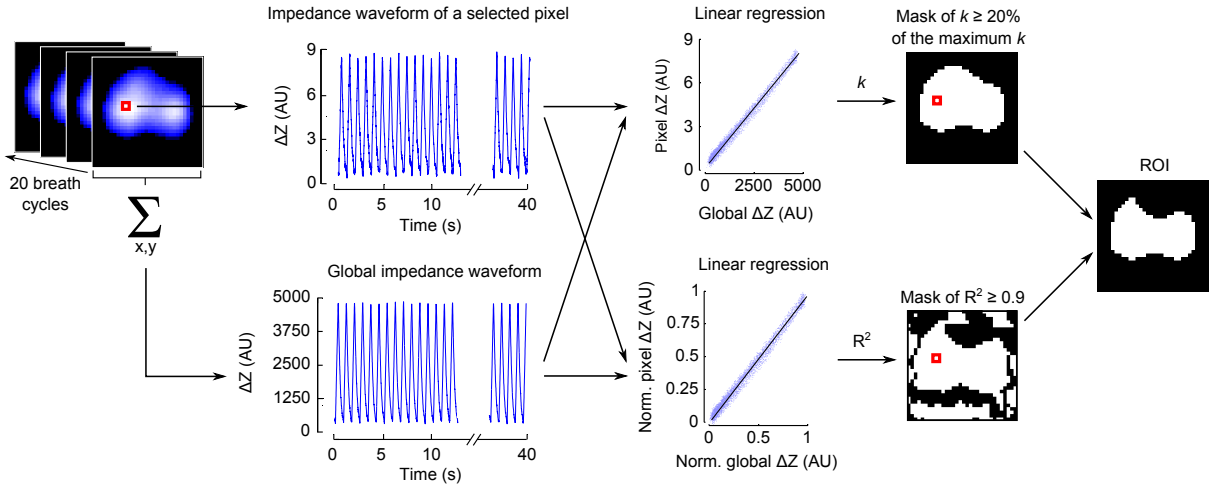

Fig.2. Determination of the region of interest (ROI). For each pixel, impedance waveform represents a time course of the relative impedance (ΔZ). Global impedance waveform is obtained as a sum of impedance waveforms of all pixels. Linear regression coefficient (k) is determined using the pixel and the global impedance waveform as a dependent and independent variable, respectively. Similarly, coefficient of determination (R^2) is calculated when the normalized values are used. Based on the given criteria, two masks are obtained from the values of k and R^2. The final ROI is obtained as an intersection of both masks.

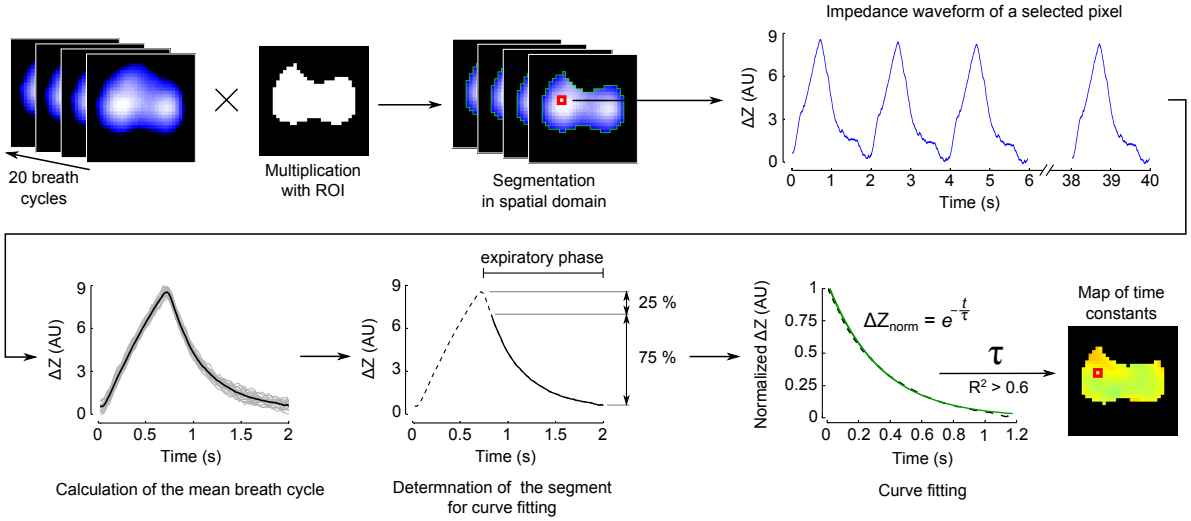

Fig.3. Data processing scheme. EIT data set is segmented in a spatial domain by multiplication of each frame with the region of interest (ROI). Impedance waveform of each pixel within the ROI is divided in 20 separated breath cycles from which one mean breath cycle is calculated. The expiratory phase of the mean breath cycle is determined and the part with the values lower than 75% of the mean breath amplitude is fitted with an exponential curve. The values of time constants (τ) obtained from the curve fitting with coefficient of determination (R^2) higher than 0.6 are visualized as a map of time constants.

as a sum of impedance waveforms of all pixels, was used as an independent variable. Consequently, linear regression coefficient was calculated. The set of all pixels with the values of regression coefficient larger than 20% of the maximum resulted in a segmentation mask. For the purposes of this study, this approach was enhanced by computation of another mask, based on the values of coefficient of determination (R^2). For each image point, both pixel and global impedance waveforms were normalized and R^2 of linear regression was calculated. The final ROI was obtained as an intersection of both masks. Determination of the ROI is schematically depicted in Fig. 2.

The ROI was applied to the data set and the segmented data were further processed. For each pixel, impedance waveform was segmented in time domain, resulting in 20 separated breath cycles from which one mean breath cycle was calculated. An expiratory phase was determined in the mean breath cycle and the part with the values higher than 75% of the mean breath amplitude was cropped [6]. The resulting part of the expiratory phase was normalized and fitted with an exponential curve:

$$\Delta Z_{\mathrm{norm}} = e^{-\frac{t}{\tau}} \tag{1}$$

where ΔZ_{norm} is normalized relative impedance, t is time and τ is a time constant. Only the values of τ that resulted from a curve fitting with $R^2 > 0.6$ were considered [6]. The whole procedure of obtaining the time constants is depicted in Fig. 3.

For each ventilatory setting the values of τ were visualized as a color-coded maps and as a box-and-whisker-plot. To enable pairwise comparisons within each pig, only the pixels with nonzero τ for all ventilatory settings were considered for statistical analysis. The Shapiro-Wilk test was used to confirm the normality of evaluated data. The differences between the values of τ were assessed by repeated measures ANOVA. A value of $p<0.05$ was considered as statistically significant. The statistical analysis was performed with STATISTICA (StatSoft, Inc., Tulsa, OK, USA).

3. Results

EIT data from 3 animals were analyzed according to the study protocol. In one healthy animal the values of RR were set to 12, 15, 18, 20, 22 and 24 min^{-1} in the second phase of the protocol to investigate greater range of settings. In total, 44 data sets were analyzed.

In general, the values of τ differed significantly in each phase of the protocol as shown in Fig. 4. There were only three cases where the changes in τ were statistically insignificant with $p>0.05$ and one case with $p>0.01$. The box plots in Fig. 4 show that V_T has an increasing effect upon values of τ while the effect of RR is exactly the opposite. Similarly, the values of τ are higher when the value of I:E is increased on the side of expiratory time. In the ARDS animal, τ was significantly lower as shown in Fig. 4 and in the color-coded maps presented in Fig. 5 and 6.

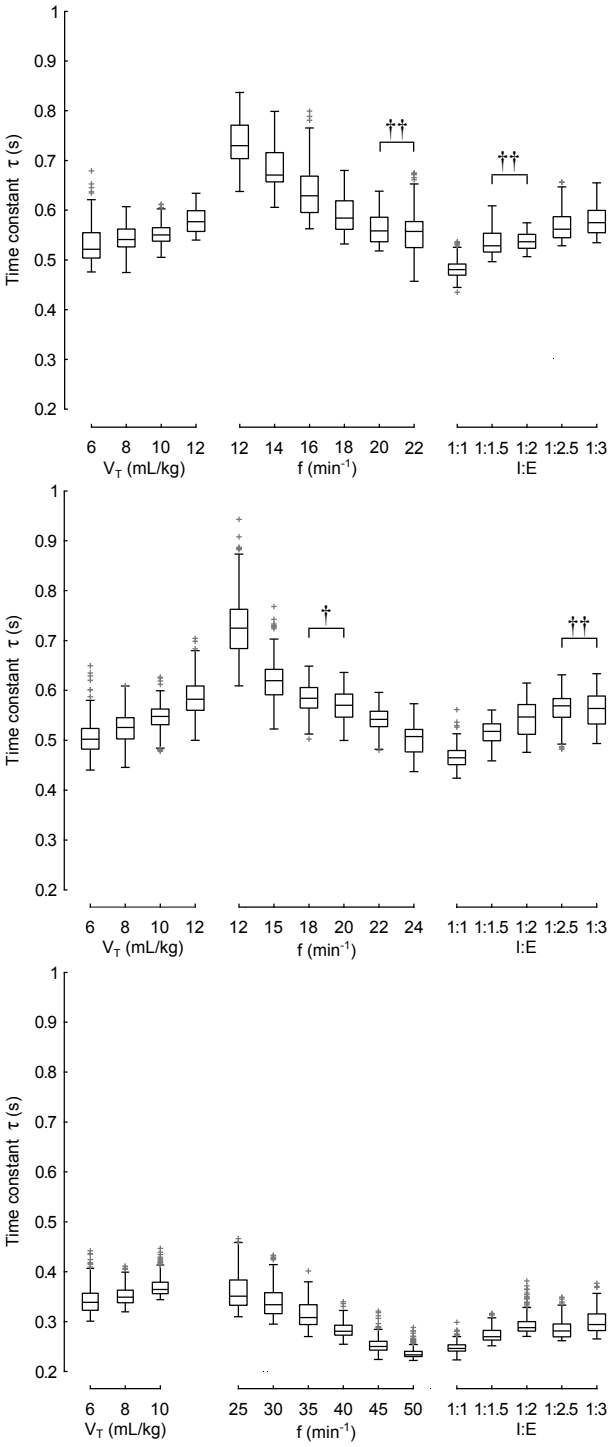

Fig. 4. Values of regional time constants (τ) for different ventilatory settings. The top and the middle graph represent the values obtained in healthy animals, the bottom graph presents τ calculated in the animal with induced acute respiratory distress syndrome. Statistically insignificant differences are marked as † ($p>0.01$) and †† ($p> 0.05$). V_T, tidal volume; RR, respiratory rate; I:E, inspiratory-to-expiratory ratio.

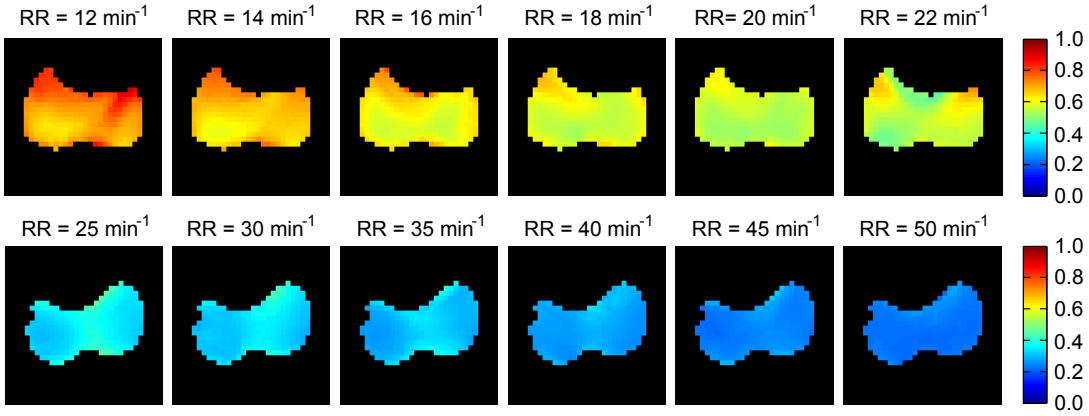

Fig.5. Color-coded maps of time constants obtained during the second phase of the study protocol. Top row: changes of respiratory rate (RR) in healthy animal—positive end-expiratory pressure (PEEP) 5 cmH_2O, tidal volume (V_T) 10 mL/kg, inspiratory-to-expiratory ratio (I:E) 1:2. Bottom row: animal with induced acute respiratory distress syndrome—PEEP 15 cmH_2O, V_T 8 mL/kg, I:E 1:2.

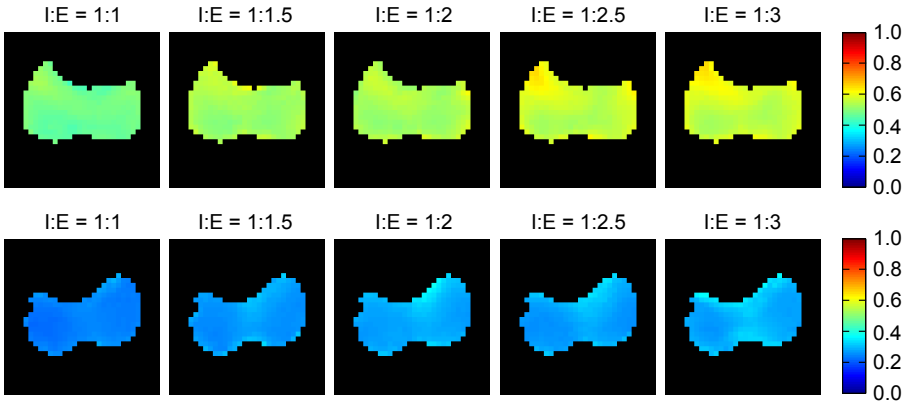

Fig.6. Color-coded maps of time constants obtained during the third phase of the study protocol. Top row: changes of inspiratory-to-expiratory ratio (I:E) in healthy animal—positive end-expiratory pressure (PEEP) 5 cmH_2O, tidal volume (V_T) 10 mL/kg, respiratory rate (RR) 20 min^{-1}. Bottom row: animal with induced acute respiratory distress syndrome—PEEP 15 cmH_2O, V_T 8 mL/kg, RR 30 min^{-1}.

4. Discussion

The main result of this study is that values of regional EIT-derived time constants τ are affected by setting of ventilatory parameters. Statistically significant changes of τ were observed for different settings of V_T, RR and I:E in healthy animals as well as in the animal with artificially induced ARDS.

The values of τ obtained in healthy animals are comparable with the values presented in recently published study [6]. However, we observed more pronounced decrease of τ in the ARDS animal. This was probably caused by the setting of RR which was relatively high during the whole study protocol. Because the results show that RR has a decreasing effect upon τ, it is rather difficult to distinguish how much the values of τ are affected by the ventilatory setting and what is the effect of the lung injury itself.

Despite the observed dependency of τ upon settings of ventilatory parameters, we do not reject the idea that different lung pathologies could be distinguished by assessment of regional dynamics of lung aeration as determined by EIT. However, the results of our study indicate that a defined ventilatory maneuver or ventilatory setting is necessary to obtain comparable values for different subjects.

The are numerous outliers above the box plots depicted in Fig. 4, especially in the graph of the ARDS animal. Analysis of the maps of time constants presented in Fig. 5 and 6 showed that the corresponding pixels are predominantly located at the ventral edge of the ROI. Therefore, we speculate that the high values of τ in these pixels are caused by the presence of cardiac-related artifacts in the impedance waveforms.

Although the original idea of regional time constants considered calculation of τ on a breath-to-breath basis, we decided to use mean breath cycles for our calculations. The main advantage of this approach is that averaging attenuates the artifacts in the impedance waveforms that are related to cardiac activity and lung perfusion.

In this study we used a modified approach for calculation of ROI. Multiplication of the original ROI with the mask that is based on the values of R^2 resulted in most of the cases in neglecting of cardiac-related pixels. In a consequence, there were only few pixels where the value of τ was omitted due to poor curve fitting ($R^2 < 0.6$).

Despite the fact the study was performed using data from three animals only, we do not consider this number as insufficient. Rather than evaluation of τ in individual animals, we wanted to assess the changes caused by different ventilatory settings. Thus, the applied range of selected ventilatory parameters was more important for the study design than the total number of evaluated subjects. For this reason, we considered higher number of animals involved in the study as ethically inappropriate.

5. Conclusion

This study shows that setting of ventilatory parameters significantly affects the values of EIT-derived regional time constants. In a consequence, assessment of lung pathologies by means of regional time constants may be compromised when various ventilatory settings are applied.

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