Respiratory mechanics in ventilated patients studied with low-frequency forced oscillations

PhD thesis

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Introduction

The rapid development of medicine has exerted a great impact on the possibilities and instrumental support of the intensive therapy. Marked advancements have been observed in the field of the mechanical ventilation where the ventilatory modalities and parameters target at the pathophysiological conditions and can be adapted to the actual conditions of the patient. Any injury of the respiratory system and the associated dysfunction or failure of other organs will inevitably lead to changes in the mechanical properties of the respiratory system. Monitoring the mechanical parameters of the respiratory system is therefore crucial for the establishment of the differential diagnosis and also the selection of the appropriate ventilatory parameters during mechanical ventilation. In the case of respiratory diseases, the complexity of the mechanical structures and the system functions increases, the enhanced heterogeneity the nonlinearity and interdependence of the mechanical parameters make the descriptions and modelling difficult. The mechanical properties need to be characterized by equations or feature curves, instead of a single number. The parameters derived from measurement techniques based on simple models may be unreliable and mislead the clinical decision making. For the calculation of the mechanical parameters, the flow and pressure tracings of the mechanical ventilation are used as the signals of excitation and response, which is plausible but far from the ideal. We can apply a specially designed deformational signal *per se* or superimpose it on the ventilatory waveforms. This is the bottom line of the forced oscillatory technique (FOT) described by DuBois and co-workers in 1956. The FOT uses small-amplitude signals for the measurement of the impedance. In accordance with the unique frequency responses of the substructures, detailed information can be achieved when a wide frequency range is used in the excitation signal. Modern computing technology enables the use of a composite signal containing several frequency components simultaneously (as e.g. the pseudorandom signal), in order to map the frequency dependence of the respiratory mechanics. Spontaneous breathing or mechanical ventilation may confound the measurement if the frequency range of the measurement contains the fundamental frequency of the respiratory rate and some harmonics. In practice, this means that oscillatory measurements superimposed on spontaneous breathing can be achieved only at a few Hz and above. However, with increasing frequency, the signal is unlikely to reach the level of the tissues (as its penetration through the airway tree decreases), and also the upper airways will increasingly dominate in the measurements. To be able to assess the tissue properties, we have to decrease the measuring frequency down to the slow spontaneous breathing rate (0,125 – 0,25 Hz),

which in turn assumes strict apneic conditions. The low-frequency forced oscillatory technique (LFOT) described in 1986 by the Szeged respiratory research team, reveals the tissue and airway properties of the human respiratory system in a balanced manner. In 1989, Barnas et al. further separated the mechanical characteristics of the extrapulmonary compartment to the rib cage and the diaphragm-abdominal components. The next important step was the formulation of the "constant-phase model", which is still the fundamental model used for the LFOT measurements in rodents and humans nowadays. The advantages and disadvantages of the LFOT are quite clear. The LFOT gives a more detailed picture from the lung periphery, about the viscous and elastic behaviour of the tissues, and about the Newtonian resistance, although it observes the respiratory system in a steady-state, and disregards the non-linearity of the parameters. Volume or pressure dependences can be assessed easily, by repeating the measurements at different volume or pressure points, but the parameters will reflect static conditions even in this way. The technique requires total apnoea and a relatively complicated equipment for the measurements and intelligent computational tools for the evaluation of measurements. Sedated, intubated and mechanical ventilated patients are an ideal population for the LFOT studies, while other routine techniques can hardly be used.

The vast majority of the LFOT studies have been performed in rodents and small animals. Investigations in humans are relatively scarce, and most of them have been carried out in infants and healthy adults undergoing surgical interventions.

Aims

Since there are hardly any data on the low-frequency oscillation mechanics of ventilated patients suffering from pneumonia/ARDS or COPD we aimed

1. to describe the mechanical properties and the PEEP dependence of the human respiratory system in humans, intubated and mechanically ventilated because of respiratory failure and
2. to assess the effects of a bronchoactive intervention (inhalation of Berodual) on the airway and tissue parameters on; in each study, separating the patients according to the underlying disease (COPD, acute exacerbation of COPD, pneumonia, and severe pneumonia).

3. to determine the impedance of the lower respiratory system (that is distal to the level of the carina) via the measurement of the impedance spectra of the endotracheal tubes and tracheostomy cannulas of different sizes and their subtraction from the total impedance.

4. to analyse the impedance spectra, in addition to the CP model, with two more complex models containing either airway or tissue heterogeneity. Whereas mechanical heterogeneity is a feature of the underlying diseases (pneumonia and COPD), these models contain one extra parameter to describe the heterogeneity, the impact of the additional parameter was assessed in a subgroup where a comparison was made with the CP model using the Akaike criterion.

Methods

In these studies, we investigated 44 intubated and mechanically ventilated patients in the Semmelweis University, Department of Anaesthesiology and Intensive Therapy.

The pneumonia patients (n = 14) were admitted to the ICU because of severe community acquired pneumonia leading to respiratory insufficiency, and they were grouped according to the LIS score. Patients with a score more then 2.5 were the most severe cases and classified as group 2, and patients with 2.5 or less to the group 1. The COPD patients (n = 30) were admitted to the ICU because of respiratory insufficiency; according to the origin of the respiratory failure they were grouped to the AECOPD group when the acute exacerbations of the underlying disease caused the failure, or to the COPD group when any other reason led to respiratory insufficiency (mostly postoperative respiratory failure).

Patients were sedated and relaxed for the LFOT measurements, and ventilation was stopped for 12 s to provide apneic conditions required by the technique. To assess the pressure dependences of the parameters, at least 2 min before each set of measurements one of the PEEP levels (3, 5, 7, 10, or 13 cmH_2O) was adjusted in a variable sequence. In order to investigate the affect of nebulisation 2 ml of Berodual (ipratopium-bromide and fenoterol hydrobromide), we re-measured the impedance spectrum at PEEP 3, 7 and 10 cmH_2O respectively, in a subgroup of patients (10 pneumonia and 19 COPD).

Measurement of respiratory system impedance

A loudspeaker-in-box system delivered pseudorandom pressure oscillations (peak-to-peak size < 3.5 cmH_2O) with frequencies between 0.4 and 4.8 Hz into the ETT for 12 s of endexpiratory pause. The pneumotachograph pressure difference (flow signal) and the transrespiratory pressure were sensed with identical transducers, and Zrs was computed from these signals as follows. The outputs of the transducers were low-pass filtered at 25 Hz, and digitized at a sample rate of 256 Hz. The input impedance of the respiratory system was calculated as a spectral ratio of the transrespiratory pressure to the resulting flow. The Z_{rs} spectrum was calculated with fast Fourier transformation with a time window of 5 s and 95% overlapping. At least three measurements were collected at each PEEP level, with >1 min intervals of ventilation resumed between the recordings, and the Z_{rs} spectra were ensemble averaged. The impedance of every ETT was determined separately, under flow conditions similar to those prevailing in situ, and the corresponding spectrum was subtracted from the measured Zrs data. Cardiogenic components of the pressure and flow signals often corrupted the estimates of Zrs at oscillation frequencies coinciding with or close to the heart rate and its harmonics; these Zrs data were characterized by large coefficients of variation in the repeated measurements and were excluded from further analysis. The change in the resistance of the ETT was < 5 % between 50 and 150 % of the flow amplitude that was similar to the one measured in the patients, which showed that the ETT behaved fairly linearly in our small-amplitude LFOT measurements.

Modelling and parameter estimation

The mean Zrs spectra were first evaluated by fitting the single compartment constant-phase model of Zrs at low frequencies, which yields estimates for a frequency-independent (Newtonian) resistance (R_N), inertance (I), and the constant-phase coefficients of tissue damping (G) and elastance (H). In the CP model, the tissue impedance (Z_{ti}) is calculated as

$$Z_{ti}(\omega) = (G - jH)/\omega^{\alpha}, \quad \text{and} \quad \alpha = 2/\pi \arctan(H/G) \tag{1}$$

where ω is the circular frequency and j is the imaginary unit. The exponent α describes the frequency dependence of tissue resistance ($R_{ti} = G/(\omega)^{\alpha}$) and tissue elastance ($E_{ti} = H(\omega)^{1-\alpha}$).

The respiratory system impedance can then be obtained by adding the impedance of the airway tree (Z_{aw}) in series to the tissue impedance where Z_{aw} is given by:

$$Z_{aw} = R_N + j\omega I_{aw} \quad (2)$$

Consequently, the Z_{rs} was calculated in the CP model as:

$$Z_{rs} = R_{aw} + j\omega I_{aw} + (G - jH)/\omega^{\alpha} = R_{rs} + jX_{rs} \quad (3)$$

where the X_{rs} is the reactance of the respiratory system.

Accordingly, G and H is a frequency independent coefficient of tissue damping and elastic function, their ratio stands for tissue hysteresivity η=G/H.

To test whether airway heterogeneities influenced Z_{rs} , the airway tree was modelled as a set of parallel pathways each composed of a Newtonian resistance R, and an inertance, I, connected in series with a tissue compartment. The values of G and H were the same in each pathway, while R was varied according to a hyperbolic distribution function defined as n(R) = B/R where B is a normalizing constant and R was allowed to vary between a minimum (R_{min}) and a maximum (R_{max}) value. In this model, five parameters (G, H, R_{min}, R_{max} and I) were determined. Total resistance of the model, R_N, can be calculated from n(R). Because R is not normally distributed, we used the median value of n(R) defined as the value R_m of n(R) which separates n(R) into two regions each having the same area, 0.5. This calculation yields the following:

$$R_m = \sqrt{R_{min} R_{max}} \quad (4)$$

In order to characterize the heterogeneity of the model, we introduced an index, the coefficient of variability, defined as:

$$COV=(R_{max} - R_{min})/R_m \quad (5)$$

This model is referred to as the distributed-resistance (DR) model. To test for the presence of tissue elastance heterogeneities, the airway tree was represented by a set of parallel pathways

each composed of an in series connection of R_N , I and a tissue compartment. In each pathway, R_N and I were the same while the values of the elastance H were different. Since H was distributed, α in Eq. (1) would also be distributed which would not allow for a simple solution of the network. To avoid this difficulty, Eq. (1) is written as:

$$Z_{ti}(\omega_n) = (\eta - j)H'/\omega_n^{\alpha} \text{ and } \alpha = 2/\pi \arctan(1/\eta) \quad (6)$$

By assuming that each tissue compartment had the same η, α would not depend on H in Eq. (5). Similar to the DR model, the distribution function n(H) was also hyperbolic, n(H)=B/H, between a minimum (H_{min}) and maximum (H_{max}) value. In this model, five parameters (R_N , I, η, H_{min}, and H_{max}) were determined. The median (H_m) and the COV of the elastance of the network are analogous to the expressions in Eqs. (3) and (4), respectively. The parameter G was calculated as $G= \eta H_m$. This model is referred to as the distributed-elastance model (DH).
In both the DR and DH models, the total input impedance of the networks can be analytically obtained as described previously, which allows a formal fitting of these models to measured impedance spectra. The parameters in all three models were then estimated by using a global optimization procedure. The model performance was characterized by the root-mean-square differences between measured and model data, normalized by impedance magnitude at the corresponding frequency and expressed as percentage (F%). Since the DR and DH models are associated with multiple parameter sets that provide similarly good fits to the measured data, the parameter estimation algorithm was run $\geq$50 times (in some cases 2-300 times) on every Z_{rs} spectrum, and the parameter sets with the lowest F% were selected.
In addition, to test whether upper airway compliance plays an important role, we added a central lumped shunt compliance unit (Cs) to all models.
Parameter estimation in the distributed parameter models is time-consuming, stochastic and as a result the reliability and reproducibility is not 100%. Consequently, we used only some specific models accordingly to the underlying pathological changes in each group of disease. In pneumonia patients we applied the CP, DR and DH models, as in the preliminary studies the addition of a Cs parameter was not worthwhile. We applied a nonnegative constraint to all parameters. In the COPD patients where airway collapse is a main feature we added the Cs to the distributed and CP models, and we used a variant of the CP model, where I did not have the nonnegative constraint.

Statistical analysis

Two-way repeated measures ANOVA was employed to evaluate the dependences of the CP model parameters and the COV values of the distributed models on PEEP in the two pneumonia and COPD subject groups. Where the normality of data distribution was not fulfilled, logarithmic transformation of the variables was introduced.

.Three-way repeated measures ANOVA were used initially in both groups (pneumonia and COPD) to study the effects of bronchodilator inhalation and PEEP on the CP model parameters in the two subgroups. Since the effect of the patient group and all interactions with groups were not significant, the final analysis was performed with a two-way repeated measures ANOVA with two within-subject factors (PEEP and inhalation). The Holm–Sidak test was used for pairwise comparisons. Three-way repeated measures ANOVA was employed for the comparison of the lumped model parameters obtained from different models and at different levels of PEEP in the pneumonia gruop. In the COPD group the Holm-Sidak method was used for the pairwise multiple comparison procedures. For the comparison of CP model parameters with those obtained via the extended models in a subset of data, Student's paired *t*-test or Wilcoxon signed rank test was employed.

Since the extended models contain one extra parameter compared to the CP model, we used the Akaike criterion in order to verify that the improvement in F% also occurred at the level of individual impedances, i.e. whether or not the benefit of the additional parameter was significant.

Results

Model fitting

The CP model was consistent with the majority of the Zrs spectra in both groups. Nevertheless, in a few cases, systematic fitting errors characterizing the underlying disease could be observed .

COPD patients

The CP model was consistent with the majority of the Zrs spectra; however, physically unrealistic parameter values, with or without systematic fitting errors, were occasionally observed at low PEEP levels (at 3 cmH_2O in particular). Poor model performances, occurring typically in the AECOPD group, were a decline in R_N with decreasing PEEP (often resulting in values $R_N \approx 0$) and abnormally high values (e.g., >0.8) of η. The Z_{rs} spectra remained inconsistent with the CP model at >5 cmH_2O in four AECOPD patients (also these patients clinically belonged to the most severe cases), whose data were analyzed separately. Data from two patients were discarded because of technical problems during the PEEP dependence measurements. Repeated-measures ANOVA revealed significant dependences on PEEP, the model version and their interaction for R_N, H, I, and η, whereas the F% values exhibited only a model dependence. Pairwise comparisons with the CP model parameters indicated statistically significant differences for R_N, H, and η merely at 3 cmH_2O, except for the values of η from the CP+Cs model at 5 and 7 cmH_2O. F% was higher for the CP I≥0 and CP+Cs models than for the other models, whose performances in turn were not significantly different from one another. The variability of the R_N values, as expressed by the coefficient of variation (SD/mean), was on the average 0.76 for the different models at 3 cmH_2O (range: 0.62– 0.86), and it decreased to 0.50 (0.45– 0.56), 0.52 (0.49–0.55), 0.47 (0.44–0.48), and 0.51 (0.47– 0.55) at PEEP levels of 5, 7, 10, and 13 cmH_2O, respectively. There was a similarly large drop between 3 and 5 cmH_2O in the average coefficient of variation of H (from 0.81 to 0.51) and η (from 1.49 to 0.62), with no significant further changes at higher pressures.

Because of the higher variability, the associated unrealistic values, and the enhanced model dependence of parameters at 3 cmH_2O, only the Zrs data obtained at ≥5 cmH_2O were retained for further analysis.

Because the performance of the CP model was closest to that of the distributed periphery models, the CP model parameters will be reported in the studies of the PEEP dependence and bronchodilator response in the separate COPD and AECOPD groups.

All parameter values were higher at all PEEP levels for the AECOPD group than for the COPD patients, although a statistically significant difference was found only for G and η at 10 and 13 cmH_2O PEEP. For either group and the combined data, the PEEP dependences were highly significant for R_N, G and η. The values of I were scattered around zero, and there was no dependence on PEEP. H decreased between 5 and 7 cmH_2O and remained fairly constant at higher PEEP in both groups, although the two-way repeated measures ANOVA indicated a significant PEEP dependence. The between-group difference in H was small and statistically not significant.

The failure of the CP model in the description of the Zrs data in the four AECOPD patients was indicated by R_N values close to zero at PEEP levels as high as 10 cmH_2O. As a consequence, all R_{rs} had to be accounted for by the tissue resistance term (G/ω^{α}), which in turn resulted in abnormally high G and η values, accompanied by large negative values of I.

Analysis of these Z_{rs} spectra with different model versions indicated that *1*) a nonnegativity constraint imposed on I markedly impaired the fitting quality, *2*) inclusion of Cs decreased F% but left the values of R_N close to zero, and *3*) both distributed models further decreased F% and the DH+Cs model recovered large R_N values, whereas *4*) η remained unrealistically high.

Pneumonia patients

CP model

Generally, the parameters in the CP model tended to show an inverse relation with PEEP with higher values in Group 2, although the differences did not always reach a statistically significant level. The CP model fits the data similarly in both groups at all PEEP levels since there were no differences in F% between groups or PEEP levels, nor was there any interaction between group and PEEP.

With regard to R_N, two-way repeated measure ANOVA revealed a significant overall PEEP dependence ($p < 0{,}001$). Individually, we found significant differences only in Group 1 with R_N being significantly lower at PEEPs of 10 and 13 than at 3 cmH_2O. While the median R_N was higher in Group 2 at every PEEP, due to the large inter-subject variability in both groups, this difference did not reach the level of statistical significance.

A strong inverse relation was also seen between G and PEEP ($p < 0.001$), which was primarily due to the significant decrease in G with PEEP in Group 2 as demonstrated by the pairwise comparisons. Although the values of G tended to be higher in Group 2 which was statistically significant at the PEEP of 3 cmH_2O, overall significance between the two groups was not reached.

H was markedly higher in Group 2 ($p = 0.014$) and also displayed a strong overall PEEP dependence ($p < 0.001$). However, there was no interaction between group and PEEP despite the fact that the PEEP dependence reached statistical significance only in Group 2.

η showed a significant PEEP dependence ($p = 0.003$), but there was no difference between the groups and there was no interaction either.

I exhibited a PEEP dependent behaviour ($p = 0.007$) with significant interaction between group and PEEP ($p = 0.016$); however, the I in the two groups did not differ from each other.

DH and DR models

Comparison of the three different models using three-way repeated measure ANOVA showed a statistically significant dependence of F% on model type ($p = 0.001$) but not on PEEP. Pairwise comparisons revealed a slight but significant improvement in F% at nearly all PEEP levels when the DH or DR model was fitted to the data instead of the CP model ($p = 0.003$ for both). There was no statistically significant difference between the performances of the two distributed models. Also note that even though the reductions in F% by the distributed models were statistically significant, the actual improvements were small, always less than 0.5 %.

The non-distributed parameters in the distributed models (R_N in the DH model, H in the DR model) were similar to those estimated by the CP model. The regression between R_N from the CP and the DH models had a slope of 0.95 with $r^2 = 0.956$ with only a few data points falling significantly below the line of identity. Similarly, the regression between H from the CP and the DR models was very strong with a slope of 1.02 and $r^2 = 0.995$ and with no outliers.

With regard to η, the relations between the distributed and the CP models were considerably weaker ($r^2 = 0.848$ and $r^2 = 0.564$ for the DH and DR models, respectively). The deterioration of these relations was a result of significant scatter in the data due primarily to the fact that the distributed models sometimes produced unrealistically low estimates of η.

The distributed models also provide information on model based heterogeneity of airway resistance (DR model) or tissue elastance (DH model). Generally, COV appears to be larger in Group 1 with both models and at most PEEP levels. However, due to large inter-individual variations, there was no difference between the two groups and the PEEP dependence was not

significant. Nevertheless, it is interesting to note that with the DH model, COV was nearly significantly larger in Group 1 ($p = 0.061$).

Bronchodilator therapy

In the AECOP/COPD group the administration of Berodual resulted in marked decreases in R_N at both levels of PEEP. R_N decreased slightly more in the COPD group than in the AECOPD patients at 7 cmH_2O (-51% vs. -32%) and 10 cmH_2O (-45% vs. -38%). The changes in the tissue parameters G and H were also marked and fairly similar in the two groups; their parallel changes resulted in small and statistically not significant decreases in η. In three AECOPD patients, administration of Berodual led to an increase in R_N (average 52%; range 20–90%), which was accompanied by marked elevations in G, H, and η.

As mentioned above, no separate analyses were carried out for Groups 1 and 2. Also, because the improvement by the DH and DR models was minor, the results are reported only in terms of the CP model. The statistical analysis showed that bronchodilator inhalation significantly decreased G ($p = 0.009$), but no change occurred in R_N , H, η and F%. The PEEP dependence before and after of inhalation was significant for G ($p = 0.001$), H ($p = 0.004$), R_N ($p = 0.003$) and for η ($p = 0.05$). Additionally, we found a significant interaction between PEEP and bronchoactive therapy for the parameter G ($p = 0.048$), whereas for H, the interaction was close to significant ($p = 0.055$). These results indicate a more dominant effect of the bronchodilator Berodual at low PEEP compared to practically no effect at 10 cmH_2O PEEP.

Conclusions

In this study, we have extended the application of LFOT to intubated and ventilated ICU patients with ARF due to pneumonia or COPD. The steady-state conditions required for the appropriate measurements could be established in most of the cases; however, ongoing (de)recruitment might have had a negative impact on data quality, especially at low PEEP levels. The LFOT provides impedance spectra rich in information on the mechanical condition of the patient, including tissue and airway properties in steady-state conditions at different pressure levels. Pressure or volume dependences of the parameters can be easily assessed by repeated measurements. It appears that the simple homogeneous four-parameter model can adequately characterize the low-frequency oscillation mechanics of the obviously inhomogeneous lung structure in COPD and pneumonia. On the other hand, in severe COPD, the pathological conditions may reach such a degree that even elevated transrespiratory pressures are insufficient to maintain a lung structure and mechanical behaviour consistent with the models with a single-generation airway system featuring only parallel inhomogeneities.

The extended variants of the CP model (+Cs, DR and DH) use an extra parameter to describe the heterogeneity at a cost of significantly decreased reliability of the estimated parameter values. Further analysis with the Akaike criterion showed that both the DR and DH models brought statistically significant improvements over the CP model only in 10% of the data sets. In conclusion, it appears that this little benefit is not in balance with its cost .

In the GOLD III-IV stage AECOPD/COPD patients ventilated because of acute exacerbation or other reason, we described the respiratory mechanical parameters as functions of the transrespiratory pressure. . There were marked differences in the values and their pressure dependencies between the AECOPD and COPD groups.

We also described the changes in respiratory mechanical parameters with transrespiratory pressure of the pneumonia – ARDS patients. Parameters were separately evaluated in the bronchopneumonia and lobar pneumonia group (group 1) and in those patients who had severe diffuse infiltrates and their state was comparable to those of patients with ARDS (group 2).

The effect of inhalative Berodual was also assessed. Berodual inhalation could decrease the peripheral inhomogeneity (pneumonia) or recruit collapsed small airways (COPD) beyond

decreasing bronchoconstriction, according to the disease. We have demonstrated that LFOT is a reliable technique in the monitoring of bronchoactive therapy.

Publications

Publications that form the basis of the doctoral dissertation

Full papers:

1. **András Lorx,** Barna Szabó, Magdolna Hercsuth, István Pénzes, Zoltán Hantos *Low-frequency assessment of airway and tissue mechanics in ventilated COPD patients.* **J** Appl Physiol, October 15, 2009. **107**(6): p. 1884-92. **IF.: 3.566**

2. **András Lorx**, Béla Suki, Magdolna Hercsuth, Barna Szabó, Krisztina Boda, István Pénzes, Zoltán Hantos. *Airway and tissue mechanics in ventilated patients with pneumonia.* Respir Physiol Neurobiol, 2010. **171**(2): p. 101-9. **IF.: 2.035**

Abstracts:

1. **A. Lorx**, B. Szabó, M. Hercsuth, I. Pénzes, Z. Airway and tissue mechanics in mechanically ventilated COPD patients Eur Respir J 2006; 28: Suppl. 50, 831s
2. **A. Lorx**, B. Szabó, M. Hercsuth, Z. Hantos. Changes in airway and tissue mechanics in ventilated COPD patients after nebulized bronchodilator agent Eur. Respir. J. 30 (Suppl. 51): 259s (2007).
3. **A. Lorx**, B. Szabó, M. Hercsuth, Z. Hantos Changes in airway and tissue mechanics in ventilated acute lung injury (ALI) patients after nebulized bronchodilator agent, ESICM 2007. (Intensive Care Med. Volume 33, Supplement 2 / September, 2007)
4. Z. Hantos, **A. Lorx**, G. Albu, C. Thamrin, and P.D. Sly., Broadband Oscillatory Mechanics of the Respiratory System in Tracheostomized COPD Patients. Am. J. Respir. Crit. Care Med. 2009; 179 p. A6069