Low-frequency assessment of airway and tissue mechanics in ventilated COPD patients

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Low-frequency assessment of airway and tissue mechanics in ventilated COPD patients. J Appl Physiol 107: 1884–1892, 2009. First published October 15, 2009; doi:10.1152/japplphysiol.00151.2009.—Low-frequency forced oscillations have increasingly been employed to characterize airway and tissue mechanics separately in the normal respiratory system and animal models of lung disease; however, few data are available on the use of this method in chronic obstructive pulmonary disease (COPD). We studied 30 intubated and mechanically ventilated patients (COPD, n = 9; acute exacerbation of COPD, n = 21) during short apneic intervals at different levels of positive end-expiratory pressure (PEEP), with small-amplitude forced oscillations between 0.4 and 4.8 Hz. In 16 patients, measurements were made before and after inhalation of fenoterol hydrobromide plus ipratropium bromide (Berodual). Newtonian resistance and coefficients of tissue resistance (G) and elastance (H) were estimated from the respiratory system impedance (Zrs) data by model fitting. Apart from some extremely high Zrs data obtained primarily at relatively low PEEP levels, the model yielded a reasonable partitioning of the airway and tissue parameters, and the inclusion of further parameters did not improve the model performance. With increasing PEEP, Newtonian resistance and the ratio G/H decreased, reflecting the volume dependence of the airway caliber and the improved homogeneity of the lungs, respectively. Bronchodilation after the administration of Berodual was also associated with simultaneous decreases in G and H, indicating recruitment of lung units. In conclusion, the low-frequency Zrs can be accomplished in ventilated COPD patients during short apneic periods and offers valuable information on the mechanical status of the airways and tissues.

forced oscillation; respiratory resistance; respiratory elastance; mechanical ventilation; bronchodilation

THE FORCED OSCILLATION TECHNIQUE (FOT) has increasingly been used as a lung function test method in both health and disease (26). A variant of the FOT, involving low oscillation frequencies comparable with the breathing rate (LFOT) and a model-based evaluation of respiratory system impedance (Zrs), has been shown to provide a noninvasive method for partitioning of the total respiratory or pulmonary mechanics into airway and respiratory tissue properties. The LFOT has been employed extensively in infants during Hering-Breuer reflex apnea (e.g., Refs. 14, 32) and in perioperative studies on adults (2, 3, 8, 25) and children with normal lung function (28). In these studies, the interpretation of the measured Zrs data via a mechanical model consisting of a simple airway model connected to a constant-phase tissue impedance (16) resulted in physiologically meaningful parameters. Although this approach has been implemented in numerous investigations on different animals both under normal conditions and in disease models, few LFOT measurements have been made in patients with respiratory diseases.

In ventilated chronic obstructive pulmonary disease (COPD) patients, Farré et al. (9) compared the Zrs data derived from end-inspiratory occlusion maneuvers with those measured directly via the LFOT and demonstrated the potential of the wide frequency content of the oscillation method in monitoring the mechanical status of the ventilated respiratory system. Kaczka et al. (21) studied the inspiratory lung impedance in COPD patients undergoing lung volume reduction surgery and interpreted the indications and effects of the surgical procedure in terms of impedance data. In both studies (9, 21), the impedance data were presented in terms of resistance and elastance as functions of oscillation frequency, and the partitioning of these measures into airway and tissue components was not addressed. In the present study, we measured low-frequency small-amplitude Zrs in COPD patients mechanically ventilated because of the acute exacerbation of their illness (AECOPD) or for other reasons, at different levels of positive end-expiratory pressure (PEEP) and before and after bronchodilator administration. We were interested in the question of whether the simple homogeneous model of low-frequency respiratory mechanics (16) is consistent with the measured Zrs data and in clarifying whether the model parameters can yield reasonable estimates of the mechanical status of the airways and tissues as functions of PEEP and bronchoactive treatment.

METHODS

The 30 patients involved in this study were hospitalized because of respiratory insufficiency. The demographic, anthropometric, and clinical characteristics of the patients are detailed in Table 1. The patients were classified on the basis of their previous clinical records, with the COPD documented as involving AECOPD (n = 21) or requiring ventilatory support for different reasons (n = 9); however, as a consequence of the status of the patients, no lung function tests could be performed at the time of the admission. The study was approved by the Semmelweis University local ethical committee in agreement with the Hungarian Medical Research Council Scientific and Human Research Ethical Committee. Informed consent was obtained from all patients or their relatives.

Patients were sedated for mechanical ventilation with propofol (1.5–4 mg·kg⁻¹·h⁻¹) to establish a sedation level around Ramsay score 2–3 (29). A cuffed endotracheal tube (ETT) in the 7- to 9-mm-inner diameter range (Portex, Hythe, UK) was introduced, and mechanical ventilation was maintained. A pressure control mode with a 50% inspired oxygen fraction, a PEEP level between 5 and 10 cmH₂O, a tidal volume of 8 ml/kg, and an inspiratory time between 0.8 and 1.2 s was employed. The respiratory rate was adjusted to between 14 and 20 breaths/min to achieve a pH of ~7.37. Patients were in a supine position with a 30° upper body elevation and did not
receive any bronchoactive therapy for 3 h before the LFOT measurement. Arterial blood gases (ABL 800 Flex Radiometer, Copenhagen, Denmark), end-tidal carbon dioxide, arterial saturation, ECG, and blood pressure were monitored continuously. For the LFOT measurement, deep sedation was introduced with propofol (a 0.5- to 1.5-kg infusion as required). Anesthesia alone was not sufficient to provide a total apnea of 12 s in 24 patients, in whom muscle relaxation was achieved with vecuronium (a 4- to 8-mg bolus, with supplementary fractional boluses for maintenance as needed). Ventilation was stopped for the 12-s intervals of ventilation resumed between the recordings, and the respirator Y-tube via a pneumotachograph and ventilated loudspeaker-in-box system was connected to the junction of the ETT.

Table 1. Demographic, anthropometric, and clinical characteristics of the patients

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<th>Patient No.</th>
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(BMI, body-mass index; F, female; M, male; COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of COPD; GOLD, the Global initiative for chronic Obstructive Lung Disease (www.goldcopd.com); *Inverse reaction to broncholytics; †failure of the constant-phase model to describe respiratory system impedance; ‡excluded from the study because of technical problems.)

patients, the measurements of Zrs were repeated at 7 and 10 cmH2O after administration of 2 ml of nebulized fenoterol hydrobromide plus ipratropium bromide (Berodual) solution. 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.

Estimation of Zrs parameters. The mean Zrs spectra were evaluated by fitting a model of the low-frequency respiratory mechanics (16) that yields estimates for a frequency-independent (Newtonian) resistance (RN), inertance (I), and the constant-phase coefficients of tissue damping (G) and elastance (H). G and H characterize the properties of dissipation and energy storage, respectively, in a frequency-independent manner, and their ratio G/H = ε is called tissue hysteresitivity (10). In the standard fitting procedure of this model commonly called “constant phase” (CP), a nonnegativity constraint was applied to all parameters except I. The mean Zrs data were also evaluated with the nonnegativity constraint expanded to I (CP I ≥ 0 model) and with the addition of a lumped central shunt compliance (Cs) in parallel (CP + Cs model). Extended models (18, 33), including Cs and either a hyperbolic distribution of parallel airway resistances (33) ranging from a minimum to a maximum value, or parallel tissue units with elastance ranging from a minimum to a maximum value subtended by identical airway elements (30) were also employed. In these distributed models, I elements with identical values were placed in the
parallel branches. The parameters of these distributed-resistance (DR + Cs) and distributed-elastance (DH + Cs) models were estimated by means of a global optimization procedure (15). The model performance was characterized by the root-mean-squares differences between the measured and model data, normalized by the impedance magnitude at the corresponding frequency and expressed as a percentage (F%). Since the CP + Cs, DR + Cs, and DH + Cs models are associated with multiple parameter sets that provide similarly good fits to the measured data, the parameter estimation algorithm was run ≥8 times on every Zrs spectrum, and the parameter sets with the lowest F% were selected.

Statistical analysis. Two-way repeated-measures ANOVA was employed to evaluate the effects of PEEP and the model version on the mechanical parameters, and the separate effects of PEEP in the COPD and AECOPD. Since the normality of data distribution was not fulfilled, logarithmic transformation of the variables was introduced. The effects of broncholytic intervention in the two patient groups and at the two levels of PEEP were analyzed with three-way repeated-measures ANOVA; for these sets of parameters, the normality of distribution was acceptable. 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.

RESULTS

Figures 1 and 2 illustrate typical average Zrs data in different measurement conditions in two subjects. Elevation of PEEP resulted in progressively lower respiratory system resistance (Rrs) values at all frequencies (Fig. 1), accompanied by smaller increases in respiratory system reactance (Xrs). An example of the effects of administration of Berodual at PEEP levels of 7 and 10 cmH2O is depicted in Fig. 2. Bronchodilation was manifested in a marked fall in Rrs and an increase in Xrs at both PEEP levels and an apparent decrease in the pressure dependence of Zrs.

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 cmH2O in particular). Poor model performances, occurring typically in the AECOPD group, were a decline in Rrs with decreasing PEEP (often resulting in values Rrs ≈ 0) and abnormally high values (e.g., >0.8) of η. The Zrs spectra remained inconsistent with the CP model at ≥5 cmH2O in four AECOPD patients, whose data were analyzed separately. Data from two patients were discarded because of technical problems during the PEEP dependence measurements. Figure 3 illustrates the mean data of the remaining 24 patients at PEEP levels of 3, 5, 7, 10, and 13 cmH2O from the different model fittings. The parameter values are not plotted where the lumped representation of the parameters was not available (Rrs and H in the DR and DH models, respectively, and η for both models); for Rrs and H, the distributions are characterized by the averages of the minimum and maximum values. Repeated-measures ANOVA revealed significant dependences on PEEP, the model version and their interaction for Rrs, 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 Rrs, H, and η merely at 3 cmH2O, except for the values of η from the CP + Cs model at 5 and 7 cmH2O. 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 RN values, as expressed by the coefficient of variation (SD/mean), was on the average 0.76 for the different models at 3 cmH₂O (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 cmH₂O, respectively. There was a similarly large drop between 3 and 5 cmH₂O 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 cmH₂O, only the Zrs data obtained at ≥5 cmH₂O were retained for further analyses, and the number of patients included from the AE-COPD group decreased to 14. 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 AE-COPD groups.

The mean values of the mechanical parameters of the respiratory system at PEEP levels of 5, 7, 10, and 13 cmH₂O are plotted in Fig. 4. 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 cmH₂O PEEP. For either group and the combined data, the PEEP dependences were highly significant for RN, G, and η (two-way repeated-measures ANOVA; P < 0.001). The values of I were scattered around zero, and there was no dependence on PEEP (data not shown). H decreased between 5 and 7 cmH₂O and remained fairly constant at higher PEEP in both groups, although the two-way repeated-measures ANOVA indicated a significant PEEP dependence (P = 0.001). The between-group difference in H was small and statistically not significant.

Administration of Berodual resulted in marked decreases in RN at both levels of PEEP (Fig. 5). RN decreased slightly more in the COPD group than in the AECOPD patients at 7 cmH₂O (−51% vs. −32%) and 10 cmH₂O (−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 AE-COPD patients, administration of Berodual led to an increase in RN (average 52%; range 20–90%), which was accompanied by marked elevations in G, H, and η; the data on these inversely responding patients are not included in the results summarized in Fig. 5.

The failure of the CP model in the description of the Zrs data in the four AE-COPD patients was indicated by RN values close to zero at PEEP levels as high as 10 cmH₂O (see Fig. 6).
consequence, all Rs had to be accounted for by the tissue resistance term $G/\omega^2$, which in turn resulted in abnormally high $G$ and $\eta$ values, accompanied by large negative values of $I$. The example given in Fig. 7 reveals that the failure in model fitting is most obvious in the Xrs data, where the parameter $I$ has a major compensatory effect. Analysis of these Zrs spectra with different model versions indicated that 1) a nonnegativity constraint imposed on $I$ markedly impaired the fitting quality (Fig. 6), 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) $\eta$ remained unrealistically high.

**DISCUSSION**

The majority of the Zrs spectra collected with the LFOT technique in intubated COPD patients during short apneic intervals were consistent with the simple four-parameter description of the oscillatory mechanics of the respiratory system, and the estimated airway and tissue parameters revealed sys-
tematic and physiologically meaningful changes with varying transrespiratory pressure and following a broncholytic intervention. The LFOT offers an alternative to the rapid end-inspiratory flow interruption technique (4, 6, 12) in the partitioning of airway and tissue mechanics, with similar concepts in bronchial resistance, as both methods estimate the RN of the respiratory system (contributed to mostly by the airway resistance), and they would give comparable results under similar flow conditions (5). However, the approaches to tissue viscoelasticity are fundamentally different, although both methods claim to cover the phenomena of stress relaxation and interregional flows. With the occlusion method, the slow decay in the postinterruption pressure is interpreted via the classical time-constant approach involving “static” elastance and an ideal viscoelastic unit of resistance and elastance (4, 6), whereas the two CP tissue parameters establish a dissipation-storage energy relationship (10) valid in a wide frequency range of deformation (16). From the measurement aspect, the Zrs data obtained with the small-amplitude LFOT address the mechanical properties at around a preset level of transrespiratory pressure, in an assumed steady state, whereas the end-inspiratory occlusion method measures the mechanical response to the changes in flow and volume of a preceding dynamic maneuver.

Assessment of the airway and tissue mechanical parameters obtained in the present study is hampered by the lack of normative data on the low-frequency impedance parameters in healthy adults. Babik et al. (2) measured LFOT Zrs data in 30 patients with mean anthropometric data similar to those in our present study (age: 68 vs. 65 years, weight: 81 vs. 76 kg, and height: 168 vs. 173 cm), who underwent cardiopulmonary

Fig. 6. Summary of fitting results for 4 patients in whose impedance data the constant-phase model provided unrealistic values of $R_N$ and $\eta$. For model definitions, see legend to Fig. 3. Lumped representations of $R_N$ and $H$ are not available for the DR+Cs and DH+Cs models, respectively. Columns and bars, respectively, indicate mean and SD values from pooled data measured at PEEPs of 5, 7, and 10 cmH2O. $P$ values indicate the results of paired $t$-tests between the CP model and the other models. Broken lines relate to average data from Babik et al. (2).

Fig. 7. Mean values of total Rrs and Xrs obtained in an AECOPD patient at a PEEP of 5 cmH2O (symbols) and fittings with different models (lines). Model definitions are shown in Fig. 3. Inset: parameter values corresponding to the model fittings. $F_b$, fitting error. $R_N$ given in cmH2O·s·L$^{-1}$; $G$ and $H$ given in cmH2O·L$^{-1}$·s$^{-1}$; $I$ given in cmH2O·L$^{-1}$·s$^{-2}$; $C_s$ given in cmH2O·L$^{-1}$·s$^{-1}$·L$^{-1}$·s$. The fitting curves from the DR+Cs and DH+Cs models are visually indistinguishable.
bypass surgery. Although their health status may have included pulmonary circulation impairments and although these patients had a mixed smoking history, they did not display any chronic or acute respiratory disease. This was corroborated by the reasonably normal spirometry data at the time of hospitalization: the average forced vital capacity was 101% predicted (range: 61–141) and forced expiratory volume in 1 s was 98% predicted (69–134). The medications for anesthesia and paralysis in that investigation (2) were different from those in our present study (fentanyl in addition to propofol and pipercuronium instead of vecuronium). More importantly, perhaps, the measurement conditions differed in that the Zrs measurements in the earlier study (2) were made in a 0° supine position and at a transrespiratory pressure of 0 cmH₂O. Despite the latter facts, the average RN values were much lower than those obtained at a PEEP of 5 cmH₂O in the combined AECOPD and COPD groups (2.78 vs. 6.58 cmH₂O·s⁻¹·l⁻¹). Large differences can also be observed in the values of G (8.6 vs. 14.8 cmH₂O/l), whereas there is no difference in H (30.2 vs. 29.4 cmH₂O/l) between the two studies. The elevated hysteresivity in the present study (0.41 vs. 0.29) may indicate differences in the intrinsic parenchymal properties (10) or, as documented in bronchoconstriction studies in dogs (16) and rats (22), an increased peripheral inhomogeneity accompanying the elevation of the overall bronchial resistance, both consistent with the altered frequency dependence of the pulmonary mechanics in COPD (11, 27). This comparison appears to reveal a marked difference in the low-frequency mechanical properties of the respiratory system between ventilated subjects with normal lungs and COPD patients.

It should be noted that the Zrs parameters include the contributions from the chest wall, which may somewhat mask the alterations occurring in the lungs in COPD. There is a Newtonian component in RN that originates from the rib cage-abdomen compartment, which amounts to ~0.5 cmH₂O·s⁻¹·l⁻¹ (15, 24), a relatively small value compared with the elevated airway resistance in COPD patients; consequently, RN would be sufficiently sensitive in the detection of decreases in airway resistance due to recruitment maneuvers or bronchodilator intervention. In contrast, in low-frequency measurements in healthy subjects during mechanical ventilation (1, 17) or voluntary apnea (15), the chest wall elastance has been found to be comparable with or even higher than the lung elastance. In COPD, however, the positive frequency dependence of lung elastance is enhanced (9, 21, 23), in accord with the conventional medium-frequency (e.g., 2–32 Hz) FOT measurements (26, 34, 35). Thus, although the lowest frequency elastance values in COPD can be similar to, or even smaller than, those of a healthy respiratory system (2, 21), indicating the decreased elasticity resulting from emphysematous changes (21), at higher frequencies lung elastance will predominate. Nevertheless, the contribution of chest wall properties to the Zrs parameters would be appropriately assessed by direct partitioning based on the measurement of esophageal pressure (15, 21, 24).

The selection of the CP model with unrestrained I for the detailed analysis of PEEP dependence and the bronchodilator response may be argued against because physically unrealistic, negative values of I were occasionally associated with the best fit with this model. Although the decrease in I has been shown to indicate the increased peripheral inhomogeneity during experimental bronchoconstriction in dogs (16) and rats (22), we can only hypothesize that the heterogeneous pathway resistances were the mechanism underlying the negative I at low PEEP in some of our COPD patients. Independent bedside techniques that assess ventilation distribution need to be employed to confirm this hypothesis. Although the physiological importance of I is rather limited in the LFOT studies that exclude the upper airways, and hence I is usually not reported (31), under circumstances such as those in the present study I may serve as an indicator of the developing inhomogeneity and consequent model failure.

The decrease in RN with the elevation of the premeasurement PEEP level reflected the increase in airway caliber, which is consistent with the data obtained by Guerin et al. (13) with the end-inspiratory occlusion technique in ventilated COPD patients. The subjects involved in the present study were classified into two groups, depending on whether AECOPD or other reasons necessitated the application of mechanical ventilation. The AECOPD patients exhibited less improvement in airway function with increasing PEEP than did the COPD group, although a statistically significant difference between the groups was not established for RN for any PEEP. The improvement in airway function with increasing PEEP was accompanied by marked decreases in G and η, which appeared to be more pronounced in the COPD patients. Also, on the basis of animal studies on experimental bronchoconstriction (16, 22), we assume that these parallel changes reflected the improved homogeneity of the peripheral airways rather than changes in the tissue properties, although measurements of ventilation homogeneity would be necessary to validate this assumption. Concerning the changes in H with PEEP, the two groups behaved similarly: they both exhibited a slight initial decrease, which can be attributed to recruitment processes; however, in the AECOPD group, there was no decrease in H at higher PEEP levels, probably because the improvement in the elastic properties due to recruitment was compensated by the overdistension of the open lung units (7). The differences in parameter values between our study groups can also be attributed to different levels of hyperinflation, which may have been more serious in the AECOPD patients; however, in our study protocol, the premeasurement PEEP was standardized and the actual lung volumes were not known. We note that, although there is agreement between the results of Guerin et al. (13) and those of the present study in regard to the decrease in RN, Guerin et al. observed an unchanged viscoelastic behavior of the respiratory system with increasing PEEP. This is in sharp contrast with the decline in G with increasing PEEP in the present study, indicating that the two modeling approaches do not account for the combined effects of stress relaxation and ventilation inhomogeneity in a similar manner. Further studies involving the use of both techniques in the same patients would be needed to identify the causes of this apparent discrepancy.

Marked decreases in RN were also documented following the broncholytic intervention in both groups of patients and at both levels of PEEP. These changes were associated with similar falls in G and H but milder and statistically not significant decreases in η. In terms of the CP mechanical parameters (16) and the manifestation of the inhomogeneous constriction of the bronchi in the apparent tissue mechanics (22), with the provision we made above in connection with the improved homogeneity of the airways with increasing PEEP, we interpret these findings in that the reopening of closed terminal lung units was the major com-
ponent in the bronchoactive response, and the improvement in the homogeneity of the communicating resistance pathways was of secondary importance.

A number of Zrs spectra were either of poor quality or, despite their reproducibility and smooth course, inconsistent with the CP model. The former case was frequently encountered at low levels of PEEP, where the temporal invariance of Zrs was not fulfilled, due to deroentration processes taking place between or even during the oscillatory recordings. Indeed, we were able to detect changes in the oscillatory excursions in the pressure and flow recordings, together with an unstable mean airway opening pressure. We assessed the performance of the CP model by involving certain extensions of the CP model (18, 20, 30, 33) featuring distributions of resistances in parallel pathways (20, 33) or of the terminal elastic units (18, 30) and the placement of a central shunt element. Although this analysis was restricted for practical reasons to a few model configurations, it revealed that, together with the appearance of unrealistic R₉ and η values, the parameters obtained at PEEP of 3 cmH₂O were strongly model dependent and of increased variability. As a consequence, the study on the PEEP dependence of Zrs had to be restricted to PEEP levels ≥5 cmH₂O. Although this seems to be a limitation of the small-amplitude LFOT technique in patients receiving ventilatory support because of respiratory diseases, it should be pointed out that the results of the end-inspiratory occlusion measurements are also associated, by definition, with elevated lung volumes. Of more concern, therefore, were the reproducible Zrs data measured in four patients, the CP model fitting of which resulted in an acceptable F%, but unrealistic parameter values, such as R₉ ≈ 0 and η ≥ 0.8, even at high PEEP levels. The fitting trials on these Zrs spectra with the extended models did not lead to physically meaningful parameter sets, in contrast with the vast majority of the measurements at PEEP levels ≥5 cmH₂O, where the parameter variabilities consolidated and the dependences on the model topology became minor.

In conclusion, 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, which is in accord with numerous observations based on the LFOT in experimental bronchoconstriction in different animals (16, 19, 20, 22, 33). 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 behavior consistent with the models with a single-generation airway system featuring only parallel inhomogeneities.

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REFERENCES


