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Mathematical Models for Measuring Mechanical Properties in Experimental Animal Lung: A Literature Review

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Statistical Analysis C
Data Interpretation D
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The mechanical properties of the respiratory system are important determining factors of their function and might be impaired in lung disease. Mathematical models are used for studying the physiology and pathology of human respiratory mechanics, but these parameters can also be used in animal testing with small animals, such as mice or rats. Depending on the experiment, a tracheostomy or endotracheal intubation should be performed: the tracheal cannula is connected to a pneumotachograph and a mechanical ventilator, which allows minute volume control, airflow, and positive end-expiratory pressure (PEEP). After stabilizing the ventilatory parameters, the mechanicals properties are measured 10–15 times in each animal, and can be used in the equation of motion as the end-inspiration occlusion method. All data were analyzed using specific software. The lungs and the chest wall are usually treated as linear dynamic systems that can be expressed by differential equations, and thereby allow the determination of system parameters that reflect the mechanical properties. The unicompartmental linear model is sufficient to detail the mechanical behavior of the respiratory system in different physiological conditions. The use of mice to create a model of airway diseases has been essential to better understand the mechanical action of lung diseases.

MeSH Keywords: **Bioengineering • Biomedical Engineering • Lung • Respiratory Mechanics**

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Background

The lungs and the chest wall are usually treated as a linear dynamic system that can be expressed by differential equations, and thereby allow the determination of system parameters that reflect the mechanical properties. However, different models that include nonlinear characteristics and multiple compartments have been used in several approaches, especially in patients with acute lung injury requiring mechanical ventilation [1].

Bates et al. proposed the viscoelastic 2-compartment model, based on studies by Mount. The mechanical properties of the tissues, however, are now represented by 3 elements: a resistor (R1, known as a *dashpot*) and 2 springs. The 3 elements – *Rt*, *E*1, and *E*2 – together constitute what is known as a *Kelvin body*. The stiffness of the spring *E*1 represents the static elastic behavior of the lung, and the series combination of *Rt* and *E*2 (which together constitute a *Maxwell body*) account for its viscoelastic behavior. This is different from the principle of the single compartment proposed by Otis in 1956, which does not consider the slower pressure drop observed after occlusion of the airway at the end of inspiration, as described in Figure 1 [2–4].

Ventilatory volume, flow, and pressure measurements of the respiratory system in physiological and pathological conditions allow the evaluation of the mechanical behavior of the system, and of its components in isolation [5,6].

Pulmonary ventilation requires mechanical work to overcome opposing forces. These forces include elastic and viscoelastic lung tissue resistive forces generated by the flow of air in the airways. This air flow is also responsible for plastic-elastic hysteresis forces, inertial forces (e.g., dough-dependent tissues and gases), and gravitational forces (which are typically included in the measurements of elastic forces) [7].

The main determinants of the mechanical integrity of lung tissue fibers are collagen, elastin, and proteoglycans, but cells may also contribute to the mechanical tissue [8]. However, 2 main structures contribute to the elastic behavior of the pulmonary parenchyma: tissue fibres and alveolar lining. The lungs always tend to shrink and collapse because of the elastic recoil force resulting from elastin and collagen fibers and their geometrical arrangement, which tends to return them to their minimum volume [9].

Another important factor contributing to the elastic characteristics of lung tissue is the surface tension of the liquid film lining the alveoli. The surfactant causes a change in the surface tension as a function of the alveolar volume, and contributes to increased lung compliance and decreased respiratory activity [9].

Tissue resistance is determined by the energy losses caused by viscosity (i.e., friction) relative to the movement of the lungs and by the speed of displaced air. The larger the dissipated power to overcome frictional resistance of the fabric during expiration, the lower the elastic force available to overcome the pulmonary resistance. In normal individuals, tissue resistance corresponds to 20% of lung resistance and airway resistance accounts for the remainder [10].

Mathematical Models

Mathematical models seek to represent the behavior of the respiratory system in different physiological conditions, and have contributed to a better understanding of respiratory mechanics. Using complex models, especially in the presence of disease, allows better interpretation of physical mechanisms that enable detailed analysis of signals [10].

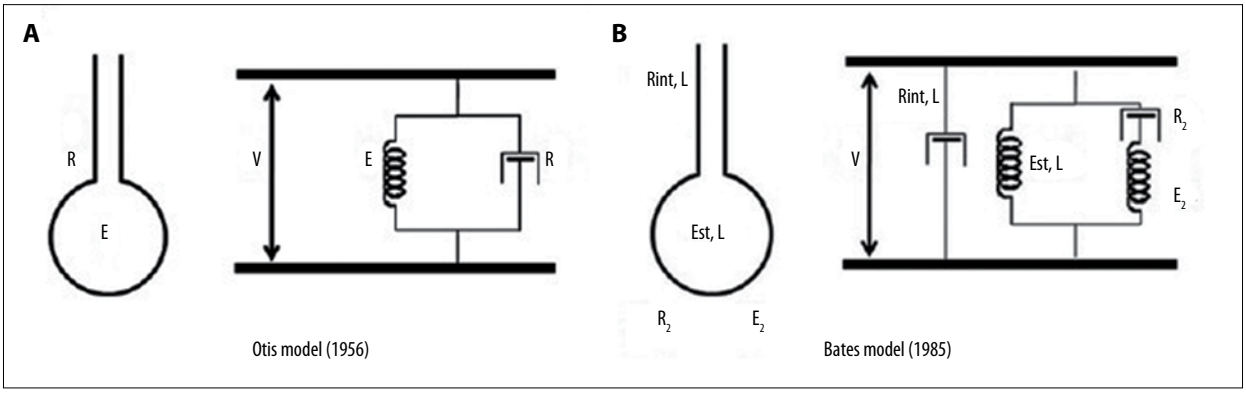

Figure 1. Anatomical and viscoelastic representation. (**A**) Single-compartment linear lung model; (**B**) Bicompartmental lung model with 2 degrees of freedom.

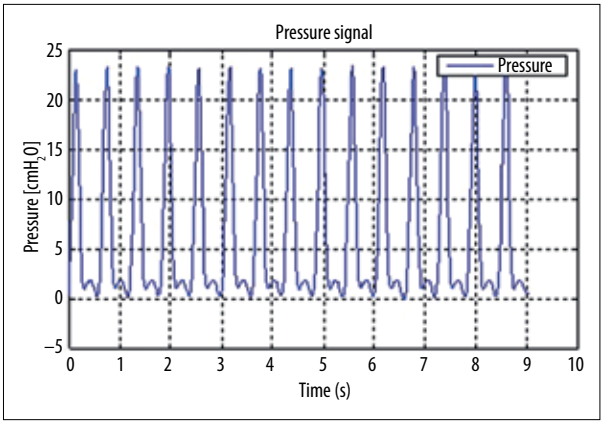

Figure 2. Tracheal pressure curve in related to time – Equation of motion.

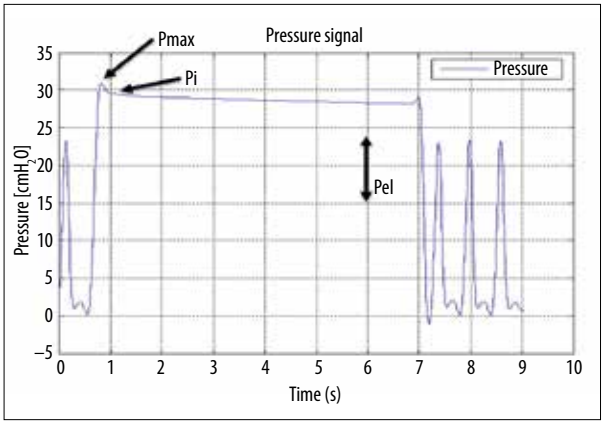

Figure 3. Tracheal pressure curve related to time – End-inspiratory airway occlusion.

Equation of Motion

In the early 20th century, Rohrer analyzed the influence of elastic and resistive inertive components to study the physical phenomena involved in the mechanical motion of the respiratory system [11].

The equation of motion (Equation 1, Figure 2) is the sum of resistive pressure (P_{res}) in relation to airflow in the airways; inertive pressure (P_{iva}) in relation to the time derivative of the flow; the elastic pressure (P_{el}) in relation to the volume (V) above the functional residual capacity (FRC); and residual end-expiratory pressure (P_o). This constitutes the unicompartmental linear model in which P_{ava} is the opening pressure of airway, R is the resistance, E is the elastance, In is inertance of the respiratory system, V' is the flow, and Po is the time derivative of the flow [12].

$$P_{ava} = R.\ V' + E \times V' + In \times V' + Po$$

The pressure applied to the respiratory system of a patient under mechanical ventilation is the sum of the pressure generated by the ventilator – measured at the airway opening (i.e. mouth) – and the pressure generated by the respiratory muscles, which can be described by the movement equation as follows:

$$P_{SR} = P_{AO} + P_{mus} = V' \times R + V'/C + k$$

in which P_{SR} is the pressure of the respiratory system, P_{AO} is the pressure at the airway opening, P_{MUs} is the pressure generated by the respiratory muscles, V is the volume, V' is the flow, R is the airway resistance, C is the compliance of the respiratory system, and *k* is a constant representing the positive end-expiratory pressure (PEEP) or, when associated with auto-PEEP, PEEP full.

When the respiratory activity of the patient is entirely passive (i.e., ventilation is controlled), the pressure developed by the respiratory muscles is negligible and the pressure required to move the air into and outside of the respiratory system can be described by the following simplified motion equation:

$$P_{SR} = P_{AO} = V' \times R + V'/C + k$$

Based on the characteristics of the forces to be overcome, the motion equation can be split into 2 components: the resistive component and the elastic component.

"V' × R" corresponds to the pressure dissipated through the air and the endotracheal tube that overcomes the friction forces generated by the flow of gas, which with the V determines the resistance of the respiratory system.

"V/C" corresponds to the pressure that must be applied to the system to overcome the elastic forces; V/C depends on inflation in excess of the residual volume, and reflects the compliance of the respiratory system volume.

End-Inspiratory Airway Occlusion

Respiratory mechanics are evaluated by the viscoelastic properties analyzed using parameters obtained by mechanical ventilation, based on the end-inspiratory airway occlusion method, described by Bates et al. [13,14]. After connecting the tracheostomy on a ventilator with a constant tidal volume (VT), airflow (V'), and PEEP, the lungs will be ventilated and subjected to 10 inspiratory pauses, with each lasting 6 seconds for the measurements.

According to Figure 3, after the occlusion of the end-inspiratory airway, a sudden fall in tracheal pressure from the maximum value (Pmax) to a turning point (Pi) occurs in which the

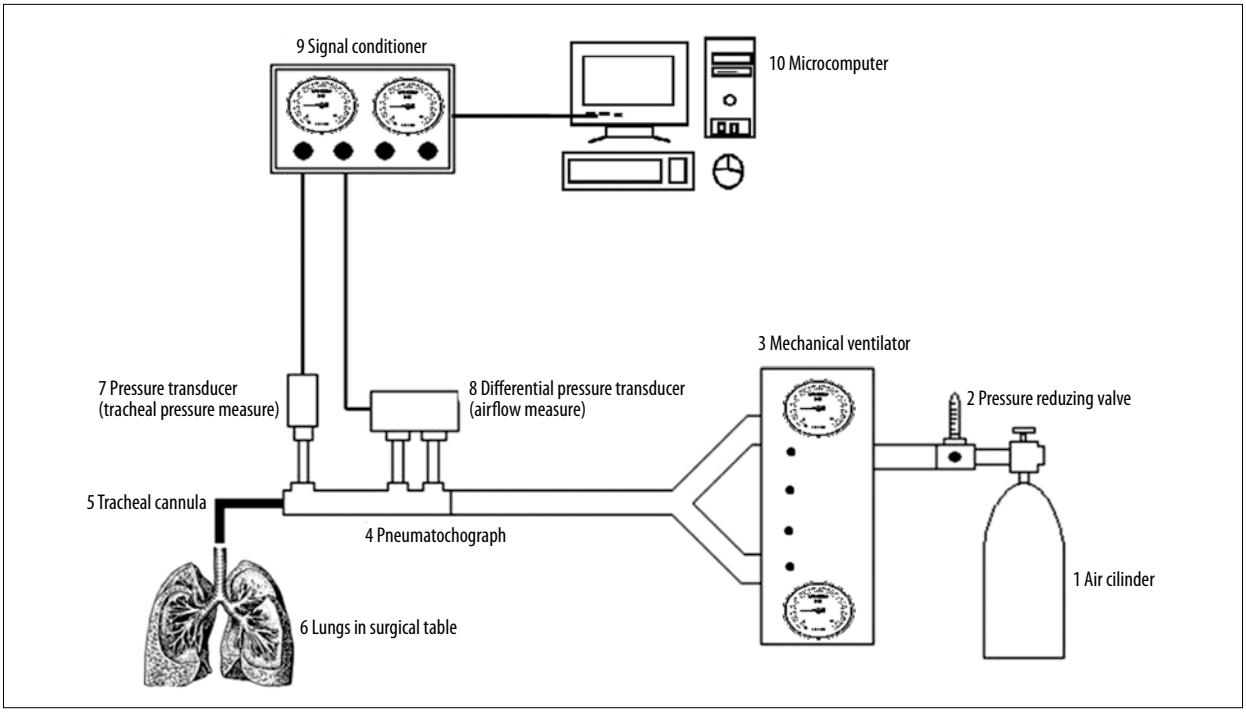

Figure 4. Respiratory mechanics study model setup.

pressure decay slows and reaches a plateau. This plateau phase corresponds to the elastic recoil pressure of the lungs (Pel). The pressure difference (ΔP1), which characterizes the initial rapid decline represented by the difference between the initial Pmax and Pi, is the viscous component [15].

Briefly, after end-inspiratory occlusion, there is an initial fast drop in PL (ΔP1) from the pre-occlusion value down to an inflection point (Pi) followed by a slow pressure decay (ΔP2) until an apparent plateau is reached [3]. ΔP1 selectively reflects pressure dissipated against pulmonary resistance in normal animals and humans and ΔP2 reflects viscoelastic properties (stress relaxation) and/or homogeneities of lung tissues, together with a miniscule contribution from the pendelluft in normal situations [16].

The second variation of pressure (ΔP2), represented by the slow fall of Pi to the plateau (Pel), reflects the pressure dissipated to overcome the viscoelastic component. The sum of ΔP1 and ΔP2 provides the total pressure in the lungs (ΔPtot). The static elastance (Est) and dynamic elastance (Edyn) can then be obtained by dividing Pel and Pi, respectively, by tidal volume; Δ is the difference between Edyn (i.e., static compliance) and Est (i.e., dynamic compliance) [17].

To obtain the Pi, the nonlinear fit to 2-exponential decay curves, which determine the time of fast decay and slow decay, and the pressure value at the time of passage ΔP1 + ΔP2 are used. To this end, *MicrocalOrigin* 6.0 software is used for analysis.

To obtain the analyzed parameters, the following formulas are used:

$$D\Delta P1 = Pmax - Pi\ Est = Pel/VC$$
$$\Delta P2 = Pi - Pel\ Edyn = Pi/VC$$
$$\Delta Ptot = \Delta P1 + \Delta P2\ \Delta E = Edyn - Est$$

Multiple Occlusion Method

In the multiple occlusion technique, airway occlusion is performed several times at different expiration points. From the moment the Hering-Breuer reflex is triggered, the pressure graph shows that a plateau is the elastic recoil pressure at the time of occlusion.

When the volume remaining in the lung is above the FRC at the time of occlusion, this volume is plotted against the other pressures. The slope of the resulting plot of the volume and pressure, which is calculated by linear regression, represents the intercept, and compliance of the respiratory system (Crs) represents the axis of the volume, and shows how much lung volume was increased at the end of expiration. Thus, to evaluate passive respiratory mechanics, it is necessary to accurately measure volume, flow, and pressure [18]. The absence of muscle relaxant administration is the main advantage of this method [19].

Expiration Relaxed Method

This technique consists of the occlusion of air at the end of each inhalation pathway, which may be spontaneous. While occlusion is maintained, the relaxation of the elastic pressures of the respiratory muscles is measured, and is used to obtain the values of complacency. When the airway opens and relaxes, expiration occurs, but if no other forces are being generated, the resistive pressure can be calculated [20]. It has been demonstrated that cardiac surgery increases the pulmonary complacency, thus altering the expiratory flow [21].

When the occlusion is released, relaxed exhalation and a single compartment may represent the respiratory system. The downward portion of the cycle, when flow volume has increased, is the expiratory time constant of the respiratory system, which indicates the time needed to vent 63% of the lung volume [20,21].

Forced Oscillation Technique

The forced oscillation technique (FOT) is a complementary tool that allows translational and experimental evaluation of pulmonary function in rats. This technique is comprehensive, detailed, accurate, and reproducible, and provides mechanical measurements of the respiratory system by analyzing pressure – volume signals obtained in response to predetermined criteria, a small amplitude, and waveform oscillating flow (also referred to as the disturbance or input signal) that are typically applied in opening the patient's airway [22].

Its simplest form would be a single sinusoidal waveform with a well-defined frequency. More complex disorders typically consist of a superposition of a selection of specific waveforms of (mutual) frequencies that cover a broad spectrum. The decomposition of the input signals and output to the multi-frequency components using the Fourier transformation allows the calculation of the input impedance of the respiratory system (Zrs; the transfer function between the input signals and the output in each frequency) [22].

Therefore, the forced oscillation technique allows simultaneous evaluation of respiratory mechanics in a range of frequencies in a single manoeuvre. Advanced mathematical models (e.g., the constant phase model) for impedance data allow a division of the response-dependent parameters (central and peripheral) airways and lung parenchyma tissue [23].

Experimental Protocol

Small animals such as mice or rats can be used in this experimental model. The animals must first be sedated and anaesthetized, and then placed on a surgical table where a tracheostomy and/or endotracheal intubation are performed.

For the tracheostomy procedure, a small longitudinal incision is created in the anterior neck. The tissues surrounding the trachea are exposed where the longitudinal incision is made between the 2 fibrous cannulae to introduce the appropriate length and diameter tubes for the individual animal (e.g., 0.5 mm in diameter for mouse rings and 2.1 mm in diameter for rats). Then, the animals were paralyzed with pancuronium bromide (0.1 mg/kg i.v.), and ventilated with frequency of 100 breaths/min, tidal volume of 0.2 ml, and flow of 1 ml/s, and PEEP 2 cmH_2O, and a constant-flow for mice and for rats with frequency of 100 breaths/min, tidal volume of 0.2 ml, and flow of 2 ml/s and PEEP 2 cmH_2O.

A pneumotachograph (1.5 mm ID, length=4.2 cm, distance between side ports=2.1 cm) was connected to the tracheal cannula for the measurement of fair flow (V'). The pneumotachograph is connected to a ventilator (Samay MVR17, Universidad de la Republica, Montevideo, Uruguay or Harvard Model 683, Harvard Apparatus, South Natick, MA) [16]. A pressure transducer (–P23 Db Statham Gould, Oxnard, CA) measures the tracheal pressure and a differential pressure transducer (PT5A; Grass, Quincy, MA) measures airway flow (V'). These devices are attached to the pneumotachograph, as illustrated in Figure 4.

The signal transducers are connected to a signal conditioner (EMG System Sao Paulo, Brazil), which has an 8-channel analogue input, 1000× amplification, sampled at 250 Hz with an analogue-digital 12-bit converter used in signal processing with the aid of a microcomputer, and data acquisition software Windaq/Pro (DATAQ Instruments, Akron, OH). The ventilator flow is generated by a compressed air source connected to the fan by a pressure-reducing valve. The flow resistance produced by the system (req), including the endotracheal tube, must be taken into consideration.

The pressure resistance of the equipment is subtracted from pulmonary resistive pressure so that the intrinsic values are real. After the tracheotomy, muscle relaxation is achieved with curare, and the tracheal cannula is connected to a pneumotachograph. A fan controls the tidal volume, air flow (V), and PEEP. After stabilizing the ventilatory parameters, the mechanicals properties were measured 10–15 times in each animal. All data were analyzed using specific software.

Model of Acute Lung Injury Using Venom and Respiratory Mechanics

A previous study investigated the pulmonary mechanics [i.e., static (Est) and dynamic (Edyn) elastances, resistive (DeltaP1)

and viscoelastic pressures (DeltaP2)], measured by the occlusion method at the end of inspiration from BALB/c mice at 1, 24, 48, and 72 h after intravenous injection of saline or *Bothrops jararaca* crude venom [0.3 (V0.3) or 1 (V1) microg·g(–1)]. [23]

Est, Edyn, and DeltaP2 increased at 1 h in both V groups, being significantly higher in V1 than in V0.3, decreasing progressively, reaching control values at 48 h in V0.3, but remaining altered in V1 at 72 h. DeltaP1 augmented in V1 at 1 h, and returning to normal at 72 h. This model allows a better understanding of the pathophysiological effects of different toxins in the respiratory system, which leads to faster and more efficient clinical interventions [23].

Another study investigated the effects of venom of the rattlesnake *Crotalus durissus terrificus* (CdtV) on the events of pulmonary mechanics [static compliance and dynamic resistance (DP1) and viscoelastic pressures (DP2)] and histology after intramuscular injection of saline (control) or venom (0.6 mg/g) [24]. The values of static and dynamic elastance were significantly increased after 3 h of venom inoculation, but were reduced to the control values in other periods that were studied. The DP1 values, which correspond to the resistive properties of the lung tissue, showed a significant increase 6 h after the CdtV injection and decreased to the basal levels 12 h after venom injection. In the DP2 analysis, viscoelastic components had a corresponding increase 12 h after the injection of the venom, and returned to the control values within 24 h. The CdtV also increased leukocyte recruitment (3–24 h) in the wall of the lung parenchyma and air routes [24].

A recent study evaluated the effects of an intramuscular injection of venom of the scorpion *Tityus serrulatus* (TsV) (0.67 mg/g) on lung mechanics and lung inflammation at 15, 30, 60, and 180 min after inoculation. The TsV injection increased lung elastance, compared to the lung elastance in the control group (P<0.001). These values were significantly higher at 60 min than at 15 min and 180 min (P<0.05) [25].

The values of resistive pressure (DP1) decreased significantly by 30, 60, and 180 min after TsV injection (P<0.001). The TsV injection increased lung inflammation, which was characterized by an increased density of mononuclear cells 15, 30, 60, and 180 min after the TsV injection, compared to lung inflammation in the control group (P<0.001) [25].

The TsV injection also increased the density of lung polymorphonuclear cells 15, 30, and 60 min after injection, compared to the polymorphonuclear cell density in the control group (P<0.001)[25]. A study involving blooms of toxic cyanobacteria due to microcystin exposure investigated the mechanical changes through the occlusion method at the end of inspiration at 2: 08 h and at 1, 2, and 4 days after the injection of the toxin. The authors concluded that microcystin led to a rapid rise in lung impedance and an inflammatory response with interstitial edema and inflammatory cell recruitment in mice [26].

Experimental Model of Respiratory Mechanics and Chronic Lung Disease

A study in rats using TOF methacholine-induced bronchospasm (12.5 mg/mL) showed increased resistance of the baseline end-expiratory pressure when measurements were performed with increasing pressures of 3–9 cmH_2O. When bronchodilators were administered, airway resistance was reduced as an effect of higher volume and pressure; this finding reflects the viscoelasticity of the tissue parameter and possibly lower resistance of the airway [27].

In a study by Fernandes et al. [28], 12 adult Wistar rats were randomly divided into 2 groups of 6 animals each: a Pentobarbital (PENTO group) and a Dexmedetomidine (DMED group). During mechanical ventilation, the respiratory mechanical parameters were similar in both groups. The absence of histological changes supported these results. For analysis, the lung mechanical occlusion method at the end of inspiration was used. The average constant inspiratory flows and volumes, as well as lung, and chest wall Est, Ptot, P1, and P2, were similar in both groups. Dexmedetomidine does not alter the parameters of respiratory mechanics and lung histology in normal rats, but caused respiratory depression with hypercapnia and hypoxemia.

Lino et al. [29] investigated a potential correlation between formaldehyde (FA) inhalation and asthma; however, the exact role of the FA remains controversial. The effects of FA inhalation after ovalbumin (OVA) sensitization were investigated using a parameter of respiratory function, as assessed by the end-inspiratory occlusion method. They concluded that exposure to FA before OVA sensitization reduces respiratory mechanics.

In a study by Aristoteles et al. [30], guinea pigs were exposed to repeated OVA inhalation to obtain an experimental model of asthma. For 4 days, the animals were administered 1400 W [specific inducible nitric oxide synthase (iNOS) inhibitor], commencing on the last inhalation. A slice of the distal lung respiratory function was evaluated using the oscillatory force technique wherein the tissue resistance (Rt) and tissue elastance (Et) were evaluated before and after the OVA challenge (0.1%); the lung slices were subjected to histopathological studies. The authors found that animals that had been exposed to OVA showed an increased response in Rt and maximum Et in the distal lung tissue (P<0.001). The 1400 W administration reduced all of these responses in the alveolar septa (P<0.001). Exposed animals that received ovalbumin alpha-amino acid

N(omega)-hydroxy-nor-l-arginine (nor-NOHA) decreased by Rt, Et after challenge with antigen-positive iNOS cells, and 8-isoprostane and NF-κB (P<0.001) in lung tissue [30].

Hyperinflation reduces elastic recoil and expiratory airflow limitation. It also increases respiratory work and oxygen demand, thereby hurting gas exchange and increasing the consumption of oxygen by cells, which leads to a progressive inability to perform physical activities.

Fusco et al. [31] evaluated pulmonary function before and after lung volume reduction surgery in an experimental rat model. The equation of motion, adapted to the respiratory system, was used to obtain the values of resistance and elastance of the respiratory system. They found that the elastance of animals subjected to bi-lobectomy and papain was higher than the elastance of animals subjected to papain without undergoing surgery; it was statistically equal to the physiological solution with and without surgery. The authors conclude that the elasticity of the respiratory system of animals with emphysema undergoing lung volume reduction through bi-lobectomy returned to levels equivalent to the control group values.

Experimental Model of Respiratory Mechanics and Atelectasis

An experimental model of atelectasis was created in rats, in which a sphygmomanometer is wrapped around the thorax or abdomen of the animal and the cuff is inflated for 5 s. The pulmonary mechanics were obtained through the occlusion technique at the end of inspiration before and after compression. The sample was divided into 2 groups: group A and group B atelectasis (control). The authors showed that in group A the respiratory mechanics remained unchanged, but in group B there was an increase in the resistive and viscoelastic pressures and increased static and dynamic elastance [32].

Trauma Induced by Mechanical Ventilation and Respiratory Mechanics

In 1994, Kano [12] proposed an index characterized by the percentage of dependent elastance in the total volume elastance (% E2), which identifies recruitment when this index is less than zero and hyperinflation when the index is greater than 30. Use of this index is important in preventing injury induced by mechanical ventilation. However, these studies did not consider the influence of the presence of 1 element or an inertive element. Dependent flow resistance may result in estimated elastance indexes and may be derived from them [33].

Pulmonary Mechanics in Animals Exposed to Environmental Pollution

A study published in 2014 aimed to investigate the time-dependency of lung impairment in animals that underwent a single exposure to residual oil fly ash (ROFA), simulating the situation of someone visiting a polluted place for a day. In conclusion, the authors demonstrated that the exposure to low doses of ROFA rapidly compromised pulmonary mechanics and histology, and the pathophysiological findings resolved 5 days after exposure [34]. In this study, the end-inspiratory pressure occlusion was used to evaluate lung mechanics.

Arsenic is a significant global environmental health problem. Exposure to arsenic in early life has been shown to increase the rate of respiratory infections during infancy, reduce childhood lung function, and increase the rates of bronchiectasis in early adulthood. In this article, lung mechanics were measured using the forced-oscillation technique and that technique generates measures of airway resistance (Raw), tissue damping (G), and elastance (H). Further details are provided in the Supplemental Material (pp. 3–4). The authors conclude in animals developmentally exposed to both arsenic and influenza had additive deficits in lung mechanics in early life and additive effects on airway responsiveness in adulthood [35].

Organs Bioengineering and Mechanical Properties

Study involving bioengineered organs, based on the scaffold of decellularized organs and using cycles of freeze/thaw in a conventional decellularization protocol, showed a slight increase in static elastance (15%) and dynamic elastance (15.7%). Fifteen lungs were decellularized and measured using the motion equation technique, so that the resistance (p<0.01) and elastance (p<0.05) increased significantly. The percentage of variation reached 79% resistance to A and reached a range of 28–35% for elastance E (34.3%), EL static (28.1%), and EL dyn (30.1%). However, data obtained using the technique of end-inspiratory occlusion, as well as static and dynamic elastance, showed no significant increase [36].

However, the increase in elastance has physiological implications in the performance of the scaffold when subjected to conventional lung ventilation during repopulation. This small change in elastance can be attributed to a small, induced formation of ice crystals at a non-uniform rate with changes within the scaffold, which determine the 3D architecture in most bronchi and alveoli with volume changes during breathing. Studies indicate that the technique of freezing/thawing has no relevant small effect on lung mechanical properties in decellularized lung scaffolds using the equation of motion technique

as the end-inspiratory occlusion method for assessing pulmonary mechanical properties [37].

The significant increase in resistance and elastance parameters observed after the first wash with sodium dodecyl sulphate (SDS), in which the lung becomes more translucent as the cellular material was washed out, can be attributed to the presence of cellular debris, which generated the apparent mucus [36]. Use of the equation of motion model containing the volume-dependent elastance can help unravel the elastic nonlinearities when subjected to opening and closing cycles of the airways in the respiratory system [38,39].

A study by Uriarte et al. [40] aimed to evaluate the effects of sterilization by gamma irradiation of lung scaffolds on the mechanical properties of an acellular organ when subjected to mechanical ventilation manoeuvres in bioreactors. The mechanical properties of decellularized lungs were measured before and after irradiation using the occlusion method at the end of inspiration. The lungs showed higher resistance (RL) and elastance (EL) after irradiation than before irradiation.

The RL increased 41.1% with room temperature irradiation and 32.8% with frozen irradiation, and EL increased by 41.8% with room temperature irradiation and 31.8% with frozen irradiation. Irradiation induced similar increases in static and dynamic elastance. Gamma radiation applied at a conventional dosage to ensure sterility modifies the mechanical properties of a decellularized organ and has potential implications for lung bioengineering [40].

Conclusions

Mathematical models represent the intrinsic nature of the system and the unicompartmental linear model sufficiently explains the mechanical behavior of the respiratory system in different physiological conditions. The use of mice to create a model of airway disease has been essential in better understanding the mechanisms of lung diseases.

Conflicts of interest

The authors declare no financial or other conflict of interest regarding this article.

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