

Review

Lung hysteresis: a morphological view

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Summary. The lung is an imperfect elastic body and for this reason dissipates energy. The energy applied to the lung in inspiration is not recovered in expiration. The property of dissipating energy receives the name of hysteresis. Lung hysteresis can be quantified because it applies to the area between the ascending and descending portions of the pressure-volume curve. Lung hysteresis comprises parenchymal hysteresis and bronchial hysteresis. Each point on the pressure-volume applies to a different morphology of the lung parenchyma. The changes that take place in the lung architecture during expiration are related to alveolar recruitment: in inspiration the lung volume increases by the opening of distal air units. In expiration the lung volume decreases due to derecruitment. The energy is dissipated mainly in the alveolar recruitment process, in which forces of molecular adhesion, such as surface tension, are at work. Bronchial hysteresis involves the dead space and the bronchial wall being greater in expiration.

Key words: Alveolar recruitment, Parenchyma, Bronchus, Hysteresis, Lung

Introduction

The pressure difference that exists within and outside the thorax receives the name of transpulmonary pressure (T_{pp}) and is positive during inspiration but negative in expiration. For the study of the lung during the respiratory cycle, a respiratory cycle model was proposed, beginning with T_{pp} at zero and the minimum possible lung volume (L_v), followed by a maximum inspiration, total lung capacity (TLC) and finally expiration, with the zero T_{pp} once again. When a respiratory cycle is represented on a graph on which each L_v is made to correspond with its T_{pp} , the pressure-volume curve (p-v) is obtained (Maggiore and Brochard, 2001).

This curve has certain features that can be observed

in Figure 1. Among these, we would point out that the L_v - T_{pp} relation is not linear (Peslin et al., 1996; Yuan et al., 2000), that the ascending part (inspiration) does not correspond with the descending part (expiration) and that the L_v at the end of expiration does not coincide with the L_v observed during inspiration. These peculiarities in the p-v curve are due to the fact that the lung dissipates energy: part of the energy transmitted in inspiration is not recovered during expiration. The property of dissipating energy is characteristic of imperfect elastic bodies (Pellegrino et al., 1998). Due to the existence of lung hysteresis a lower T_{pp} is required to maintain the same lung volume in expiration as that which is required in inspiration. Hysteresis (H) applies to the surface area found between the ascending and descending portions of the p-v curve (Fig. 1); according to Bachofen and Hildebrandt (1971) lung hysteresis can be quantified, as it is directly proportional to tidal volume (T_v) and to pressure increase (ΔP) ($H=K \cdot T_v \cdot \Delta P$; K is a constant whose value is approximately 0.12). It has been demonstrated morphologically that at a single T_{pp} the volume of lungs fixed in inflation is lower than that of those fixed in deflation (Radford, 1963). Two different lung behavior models were proposed to explain the behavior of the lung in relation to hysteresis: the viscoelastic model and the protoelastic model. The viscoelastic model consists of a spring connected in parallel to a dashpot (Fig. 2B). The protoelastic model is composed of a spring and a dry friction element (Fig. 2C). In both models, the behavior of the dashpot or the friction element is responsible for the non-linear relation (Fig. 1) because their job is to dissipate energy (Brusasco and Pellegrino, 1995; Peslin et al., 1996). The viscoelastic model is the one most commonly used because 67-75 % of lung behavior can be compared with that of a viscoelastic body (D'Angelo et al., 1989; Brusasco and Pellegrino, 1995). However, there are other proposals for the behavior of the respiratory system, such as that based on a Newtonian unit (Beydon et al., 1996).

Alveolar recruitment

The modifications that take place in lung volume during respiratory movements are reflected at structural

level. Mead et al. (1957) described lung hysteresis on the p-v curve and related lung expansion with a sequential opening of “units”. Smaldone et al. (1983), after studying excised dog lobes filled with monodisperse aerosol, reached the conclusion that lung hysteresis is related to the number of alveoli that are open. These results have led to hysteresis being related to lung parenchyma modifications and, in particular, with alveolar recruitment.

The concept of alveolar recruitment proposes that during inflation/deflation the lungs expand and retract due to a sequential opening and closing of the peripheral

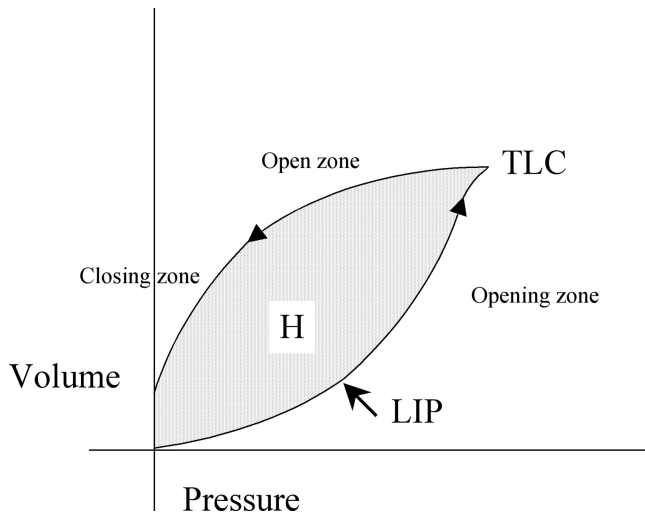


Fig. 1. Representation of the pressure-volume curve. The ascending part applies to inspiration and the descending part to expiration. The dotted area is the hysteresis area. TLC: Total Lung Capacity. H: Hysteresis area. LIP: Lower Inflexion Point. Beginning of the opening zone. Opening zone: first part of inspiration; the peripheral airways are opened exponentially. Open zone: second part of expiration, the peripheral airways remain open. Closing zone: third part of expiration; the peripheral airways close.

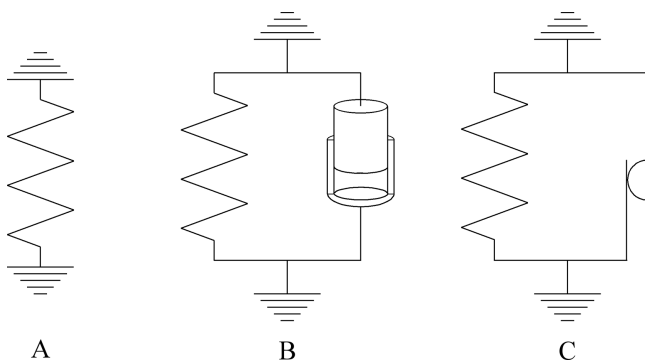


Fig. 2. Diagram of three bodies with different properties. **A:** Elastic body, spring. **B:** Viscoelastic body, spring connected in parallel to a dashpot. **C:** Protoelastic body, spring connected in parallel to a dry friction element.

airspace (PAS) (Fig. 3). The opening and closing of the PAS that takes place during the respiratory cycle has been associated with different parts of the p-v curve (Fig. 1) (Glaister et al., 1973; Frazer et al., 1985; Cheng et al., 1995; Ingimarsson et al., 2001). In the initial phases of inspiration, up to approximately 50% of the TLC, the lung increases in size because the number of PAS increases linearly. When the lung reaches 50% of the TLC, the p-v curve displays a lower inflection point or knee, which marks the beginning of the opening zone. In the opening zone the pressure/volume relation changes from being linear to becoming exponential, as a clear PAS opening takes place. The opening zone ends when the lung reaches TLC, at the end of inflation. Deflation is comprised of two phases: the first coincides with the open zone, in which the lung volume decreases without the PAS closing. The second phase is the closing phase, in which the lung retracts as the PAS close.

Different morphological studies have measured PAS size at different stages in the respiratory cycle, the results of which are somewhat disparate. For one group of authors, when the lung becomes distended, the PAS undergo a size increase (Storey and Staub, 1962; D’Angelo, 1972), while for others the lung volume increases through alveolar recruitment. Gil and Weibel (1972) described the fact that the lung distended and the lung surface area increased with the increase in T_{pp} , which coincided with the descriptions given by most researchers (Storey and Staub, 1962; Dunnill 1967; Forrest, 1970; Gil et al., 1979; Escolar et al., 2000; Butler et al., 2002). Gil and Weibel (1972) proposed that the alveolar surface area increased due to unfolding of septa, which they in turn related to the opening and closing of PAS. It was later described that the thickness of the alveolar wall was modified with changes in T_{pp} (Tsunoda et al., 1974; Bachofen et al., 1987; Escolar et al., 2002). This can be interpreted in two ways: that when the alveolar walls are unfolded they become

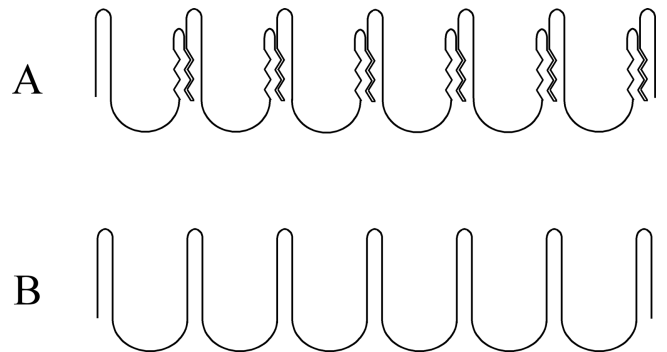


Fig. 3. Schematic representation of alveolar recruitment. At the beginning of inspiration the lung is partially swollen. Microscopically, there are more closed than open (derecruited than recruited) alveoli. **A:** At the beginning of inspiration the walls of the closed alveoli are stuck to one another. **B:** When the transpulmonary pressure is increased, the lung volume increases and the alveoli are recruited by unfolding their walls.

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thinner (Escobar et al., 2002), or that the capillaries of the walls collapse (Bachofen et al., 1987). Different morphometric studies have been carried out in which it has been concluded that PAS size is not modified when T_{pp} is increased (Carney et al., 1999; Escobar et al., 2002). In an experimental respiratory cycle model, it was observed that, between 10 and 20 cm of H_2O of T_{pp} in inspiration and between 20 and 10 cm in expiration, the PAS size was not modified, but their number was in directly relation to the T_{pp} (Escobar et al., 2002). Although morphological studies largely coincide with functional studies regarding the concept of alveolar recruitment, there are some divergences between them: Carney et al. (1999), having measured the PAS size at different T_{pp} , proposed that the exponential opening of the PAS takes place from 20% of the TLC and not at 50%, as is proposed by the studies carried out on the p-v curve (Glaister et al., 1973; Frazer et al., 1985).

It has been suggested that the shape of the PAS may be modified during respiration. Forrest (1970) and Klingele and Staub (1970) measured the mouth and depth of the PAS at different points during inspiration and concluded that a small increase in the bottom of the alveolus takes place with respect to the diameter of the mouth; these modifications are not significant. Gil and Weibel (1972) demonstrated that the curvature of the alveolar wall is smaller during the inspiration phase than in expiration; these differences are particularly outstanding at 40% of the TLC. The alveolus model with the shape of a regular dodecahedron suggests that the alveolus becomes spherical in shape during inspiration (Fig. 4) (Linhartova et al., 1986). The recruitment

hypothesis proposes that the lung increases in size due to PAS opening; however, it should not be forgotten that an increase takes place in the size of the alveolus in recruitment.

Alveolar recruitment/derecruitment is the most widely accepted hypothesis to explain how the lung parenchyma architecture is modified with respiratory movements. Gil et al. (1979) proposed four possible ways in which PAS may be modified during respiration: sequential recruitment/derecruitment (Fig. 3); a sequential change in shape and size, change from dodecahedron to sphere (Fig. 4); balloon-like increase/reduction in alveolar size (Fig. 5 A); and crumpling of the alveolar surface, similar to the folding of an accordion (Fig. 5 B).

Lung parenchyma forces

The major stress-bearing elements of the lung parenchyma are the surface lining layer, the extracellular matrix and the contractile apparatus (Yuan et al., 1997). The surface tension forces are governed by Laplace's Law, according to which surface tension is inversely proportional to the radius of the bubble. Therefore, the surface tension of the walls of small alveoli is greater than that of the walls of large alveoli (Bachofen et al., 1970, 1987) (Fig. 6).

Elastic and collagen fibers are grouped in the interstice forming a network that endows the lung with significant properties relating to stiffness, camping distortion (Yuan et al., 2000) and elasticity (Stamenovic

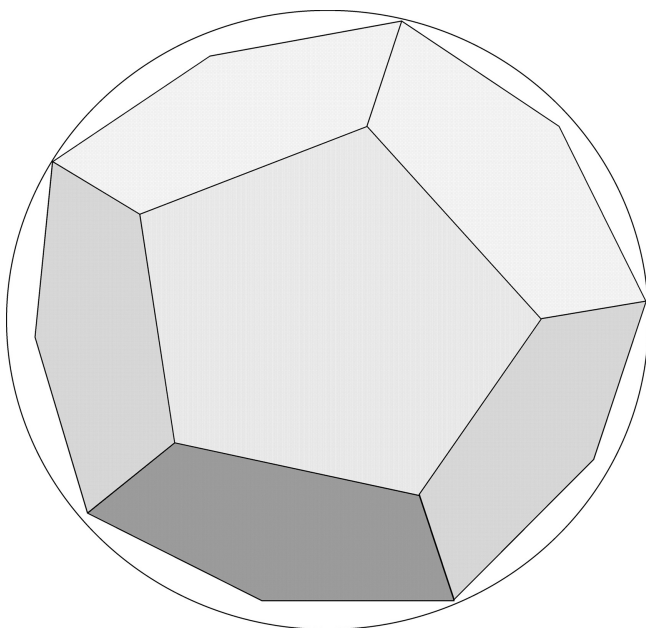


Fig. 4. Model of alveolus with regular dodecahedron shape. When the lung is inflated, the dodecahedron shape becomes spherical.

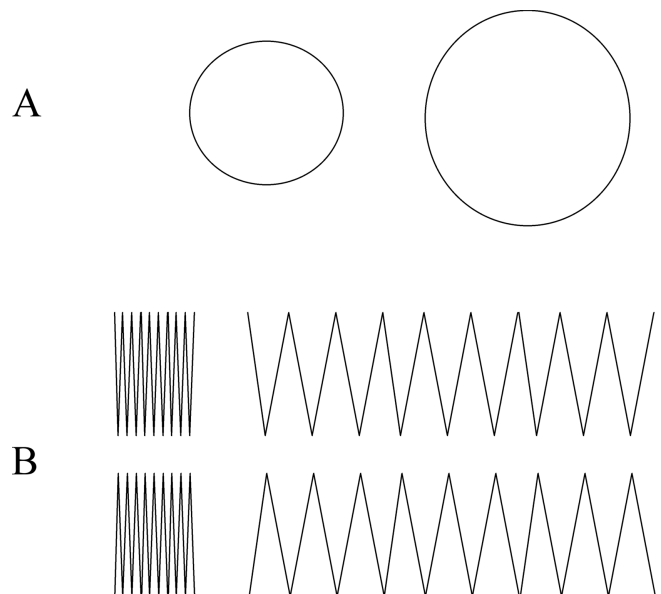


Fig. 5. Two of the four possible shapes proposed by Gil et al. (1979) by means of which the architecture of the alveolus can be modified with respiratory movements. **A:** balloonlike increase/decrease in alveolar size. **B:** crumpling of the alveolar surface, similar to the folding of an accordion.

and Smith, 1986). According to Wilson and Bachofen's proposal (1982) lung tissue has two kinds of force-bearing networks: the first comprises the connective tissue that begins in the pleura and extends as far as the interlobar and interlobular fissures. The second network begins around the bronchi and vessels and stretches as far as the linear elements that surround the mouth of the alveoli (Fig. 7). This second network may interact with surface tension forces. When the lung expands, this network tenses and as a result the alveolar mouths open. The surface tension acts in terms of the curvature of the wall: in small alveoli, surface tension will be greater than in large alveoli. If the surface tension of the PAS is suppressed, their walls become flaccid (Fig. 7) (Wilson and Bachofen, 1982). In this sense, Schürch et al. (1992) and Butler et al. (2002) suggest that the alveolar surface decreases when the surface tension is high. For Wilson (1981) surface tension can act in two ways: either directly, by providing an additional contractile force, or indirectly, by distorting the alveolar geometry and increasing the force in the tissue elements. Interstitial cells may participate in the changes in dynamic mechanical behavior (Dolhnikoff et al., 1995, 1998). The alignment of cytoskeletal actin filaments perpendicular to the force vector in mechanically strained pulmonary fibroblasts (Breen, 2000) (Fig. 8) has been described. There exists therefore a set of recoil forces that interact among themselves according to the mechanical requirements of the lung parenchyma. The interstitial cells are connected in series with the fiber network system (Yuan et al., 1997), while the surface tension forces are connected in parallel with the tissue.

Dissipative energy

There is no consensus regarding which of the forces that oppose lung distension are responsible for lung hysteresis. It has been proposed that conservative energy is related to tissue, while it is surface tension that dissipates energy (Wilson, 1981). After insufflating lungs of different animal species with gas or liquid, it was observed that liquid-filled lungs displayed a smaller hysteresis surface on the p-v curve (Mead et al., 1957; Bachofen et al., 1970; Bachofen and Hildebrandt, 1971;

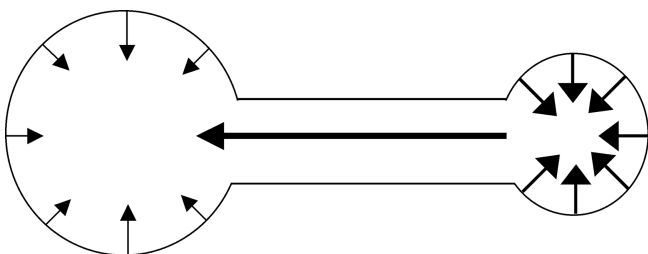


Fig. 6. Schematic representation of the consequence of Laplace's Law. When two bubbles of different sizes are connected, the bubble with the greatest surface tension, the small bubble, deflates to the benefit of the large bubble.

Jones et al., 1996). This suggests that, as the air-liquid surface is removed from the lungs, there is no surface tension to oppose distension, so that these lungs reach TLC with lower T_{pp} . According to Laplace's Law, surface tension is inversely related to the curvature of the PAS wall (Fig. 6) (Bachofen et al., 1970, 1987). The curvature of the PAS wall has been measured at different points in the respiratory cycle and it has been found that it is inversely proportional to lung volume, and that at 40% of the TLC alveolar curvature is smaller in inflation than in deflation (Bachofen et al., 1970, 1987; Gil and Weibel, 1972; Gil et al., 1979). From this it has been deduced, in the first place that surface tension is greater in inflation than in deflation, which is related to the p-v curve; to maintain a given pulmonary volume, greater T_{pp} is required in inflation than in deflation. In the second place, at low T_{pp} surface tension forces are at work, while at high pressures tissue forces predominate (Bachofen et al., 1970, 1987). However, Lum and Mitzner (1987) suggest that surface tension does not correlate with alveolar size in all lung volumes.

According to Wilson (1985) tissue forces are not dissipated. However, evidence of the existence of hysteresis is observed on the p-v curve above the lower inflection point, where tissue forces predominate. For Fredberg and Stmentanic (1989) tissue hysteresis exists and is directly related to lung elastance and the volume increase, but inversely related to pressure increase. This proposal differs from that made by Bachofen and Hildebrandt (1971) in relation to hysteresis on the p-v

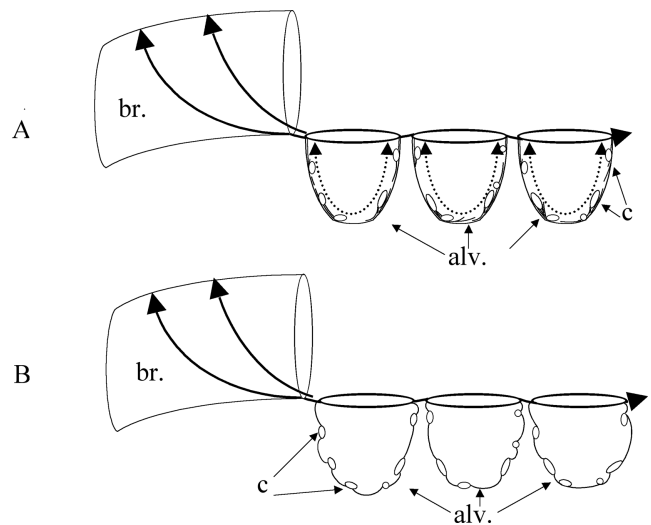


Fig. 7. Schematic representation of the network that spreads around the bronchi (br) and vessels and surrounds the mouths of the alveoli (arrows with continuous line). **A:** When the lung slackens, the tension of this network opens the mouths of the alveoli; the surface tension (arrows with dotted lines inside the alveoli) tenses the alveolar wall and folds appear in it. **B:** When the alveolus does not have surface tension, the network tenses the mouths, opening the alveoli. The lack of surface tension makes the alveolar walls flaccid. Wilson and Bachofen (1982). c: capillaries.

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curve.

An alternative hypothesis suggests that recruitment/derecruitment is responsible for dissipating energy (Frazer and Franz, 1981; Smaldone et al., 1983; Frazer et al., 1985). According to Bachofen et al. (1987) the alveolar wall membranes unfold during the recruitment process, implying that the energy used to combat the adhesive forces of the membranes is dissipative, rather like what occurs with velcro (Fig. 9),

Cytoskeletal actin filaments which are aligned as a result of tension forming in the lung tissue, may also be involved in hysteresis (Fig. 8) (Breen, 2000) and it is suggested that cross-bridge rate processes also participate in this spending of energy (Kikuchi et al., 1994; Dolhnikoff et al., 1995, 1998; Yuan et al., 1997; Adamicza et al., 1999). Some authors support the participation of the bronchial musculature in lung parenchyma hysteresis (Kimmel et al., 1995; Kaminsky et al., 1997), while others oppose it (Dolhnikoff et al., 1995). Other factors, such as the opening and closing of the small airways (Cormier et al., 1993; Rodarte et al., 1999;) and hyperapnea (Kaminsky et al., 1997) etc. have been associated with hysteresis. In our opinion, all the airway-related processes ought to be dealt with within the concept of bronchial hysteresis.

The nature of the forces related to lung hysteresis is quite varied. Fredberg and Stmenovic (1989) relate dissipative energy with four processes: 1) the kinetics of surface-active molecule absorption-desorption to the surface film; 2) the kinetics of recruitment-recruitment; 3) the kinetics of fiber-fiber network within the connective matrix; and 4) the kinetics of cross-bridge attachment-detachment within the contractile elements.

Clinical application of parenchymal hysteresis

Positive end-expiratory pressure (PEEP) is the most widely used recruitment technique in the treatment of adult respiratory distress syndrome (Van der Kloot et al., 2000; Villagr a et al., 2002). This technique consists in applying a positive pressure during expiration, with the aim of maintaining the greatest possible number of alveoli open and reducing the atelectasia area. Two working pressures are normally involved: the pressure that marks the end of expiration, which may reach up to 40 cm of H₂O, and PEEP, which usually applies to the

lower inflection point on the p-v curve. This therapeutic procedure can be very traumatic and for this reason the concept of biotrauma, in which overventilation is related to chemokine release, is currently proposed (Heinz et al., 2001). Another ventilation technique is that which is known as liquid respiration (Hirschl et al., 2002). This consists of filling the lungs with a liquid through which the gases are well diffused. The liquid suppresses the air-liquid interface from the alveolar membrane, making the lung more distensible as there is no surface distension decreasing the atelectasia areas.

Bronchial hysteresis

What has been described above receives the name of parenchymal hysteresis, as it is related to lung parenchyma structures. Hysteresis also exists at bronchial level and, coupled with parenchymal hysteresis, is known as lung hysteresis. The origin of the proposal of bronchial hysteresis lies in a group of functional studies in which it was demonstrated that the dead space is greater in inspiration than in expiration (Martin and Proctor, 1958; Froeb and Mead, 1968). It was later proposed, following studies on histological sections, that bronchial luminal diameter decreases when T_{pp} is drops (Fig. 10) and that bronchi whose diameter is smaller than 0.6 mm may even fully close (Hughes et al., 1970). These studies were complemented by radiological studies in which it was demonstrated that bronchial luminal diameter and the length of the bronchus are shorter in inflation than in deflation (Hughes et al., 1972) (Fig. 10). After measuring the bronchial lumen surface at different points during the respiratory cycle, it was proposed that it is related to T_{pp} (Escolar et al., 2003a) (Fig. 10).

The existence of hysteresis of the bronchial wall has been proposed through morphological studies. After measuring the bronchial wall during a respiratory cycle, it was possible to conclude that it is greater during expiration (Escolar et al., 2003a) (Fig. 10). On studying the behavior of the bronchial wall in relation to its size, it was observed that hysteresis was more marked in larger bronchi (Escolar et al., 2003b), which led to the proposal that bronchial wall hysteresis is related to the amount of tissue contained in the wall. A similar proposal was made by Burns and Gibson (2002)

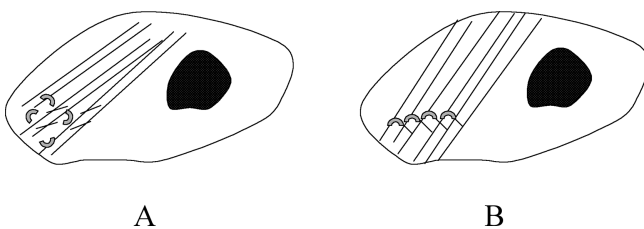


Fig. 8. Schematic representation of the cytoskeleton actin filaments. **A:** non-organized filaments. **B:** filaments aligned by the application of forces. The alignment of actin filaments consumes energy.

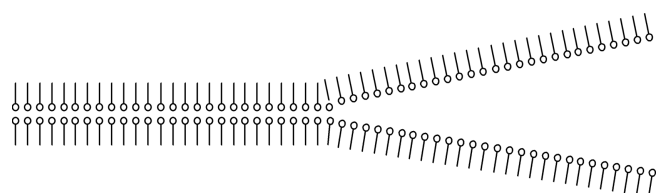


Fig. 9. Schematic representation of two adhered membranes that become unstuck at the right end. This mechanism is similar to what occurs with velcro: the energy that is used to unstuck the two velcro surfaces is not recovered when they are restuck.

following a functional study on asthmatic individuals. Coupled with this is the fact that the wall of large bronchi increases in deflation (Escolar et al., 2003b). James et al. (1988) measured the bronchial wall in expiration and concluded that it increased between 100% and 25% of the TLC, and decreased between 25% and 0% of the TLC (Fig. 10). We consider that this apparently paradoxical behavior of the bronchus may be explained by the concept of hysteresis. It has been proposed that, as a result of the negative pressure that is exerted within the thorax during expiration, the epithelial microcirculation of the bronchial wall may be ingurgitated, thus thickening the airway wall (Burns and Gibson, 2002). The bronchial wall is a viscoelastic body, which implies that the response to intrathoracic pressure changes might be delayed; epithelial microcirculation would be ingurgitated between 100% and 25% of the TLC, and emptied between 25% and 0% of the TLC (James et al., 1988; Escolar et al., 2003a) (Fig. 10).

Clinical application of bronchial hysteresis

Several studies have shown that the functional response to deep inspiration is different in asthmatic and healthy subjects. Most studies report that it has a bronchodilatory effect in healthy subjects, while severe asthmatics display bronchoconstriction after deep inspiration (Burns and Gibson, 2002). Pellegrino et al. (1998) suggest that measuring the effects of deep

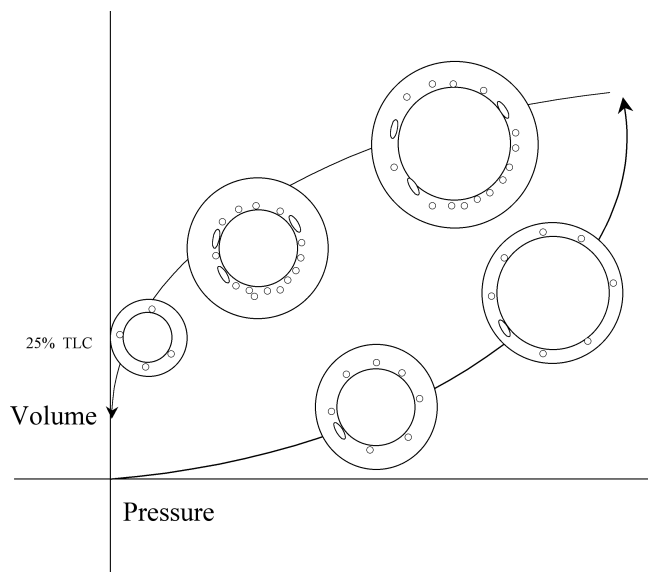


Fig. 10. Schematic representation of bronchial hysteresis. In inspiration, the bronchial lumen increases and decreases when the transpulmonary pressure is raised and dropped. The bronchial lumen is always greater in expiration than in inspiration. In expiration, the bronchial wall increases when the transpulmonary pressure is dropped to 25% of the TLC; from this point on, the bronchial wall decreases. The small circles, which represent epithelial microcirculation, proliferate during expiration, causing the bronchial wall to increase in size.

inhalation on lung function is an easy and simple test to monitor the effectiveness of therapy.

The future of lung hysteresis

Lung morphology varies throughout the respiratory cycle. Knowledge about the structural changes that take place in the lung may be of assistance in the diagnosis and treatment of different parenchymal and airway diseases. However, the question raised by Lichtwarck-Aschoff et al. (2000), "Does the change in lung volume as manifested in the p-v curve reflect what occurs at the level of 300 million alveoli?" reveals the lack of knowledge currently available about the morphology of the lung parenchyma in relation to hysteresis. We believe that further morphological descriptions are needed if we are to attempt to demonstrate the hypotheses proposed in the functional studies.

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