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Lung Mechanotransduction, the minuet of Biophysics (Part 1)

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Abstract

The dynamic processes associated with lung pathophysiology have always been explored from a traditionalist perspective. This review conceptualizes an amalgam of biological and biophysical concepts that aim to optimize the understanding of the pathophysiology associated with lung injury from a broader, more complex, and at the same time more complete perspective using arguments from the exact sciences. We hypothesize that the Anti-Zener model could be a more accurate potential explanatory model to support mechanotransduction.

In this part we will discuss the concepts of mechantransduction, mechanobiology, stress, strain, strain rate, resilience, alveolar anisotropy, and the role of surfactant.

Keywords: Mechanotransduction, Young´s modulus, Zener model, Stress, Strain

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Introduction

The lung, as a dynamic and highly adaptive structure, responds to mechanical and energetic stimuli through a complex process called mechanotransduction, whereby epithelial, endothelial and extracellular matrix cells convert mechanical signals into biochemical responses. This interaction is regulated by key factors such as stress and strain, which are involved in tissue deformation and force distribution within the lung parenchyma.

Due to the viscoelastic nature of lung tissue, its mechanical behavior does not follow purely elastic or viscous models but exhibits a time-dependent response (among other factors), characterized by phenomena such as hysteresis and progressive adaptation to mechanical loads. Lung resilience, understood as its capacity to recover its structure after deformation, is intrinsically dependent on its fibrillar architecture and its interaction with the extracellular matrix. Moreover, lung tissue is anisotropic due to the heterogeneous arrangement of collagen and elastin fibers. As a result, its mechanical response varies depending on the direction of the applied force, adding complexity to its mechanical characterization. In this context, lung microrheology emerges as a fundamental approach to study the local mechanical properties of the tissue at microscopic scales, allowing a better understanding of the distribution of forces and deformation within the cellular environment. While classical models such as Young's modulus, Kelvin-Voigt model, or Zener model have been employed to describe the mechanical response of the lung, we propose the Anti-Zener models as a more complete, but more complex, representation, as it incorporates additional elements that better capture the nonlinear dynamics and structural heterogeneity of the tissue.

Thus, the study of lung mechanotransduction is not only essential for understanding respiratory physiology, but also for the development of therapeutic strategies in the pathologies where lung mechanics are altered, such as acute respiratory distress syndrome (ARDS).

Mechanotransduction

This is the process by which cells assimilate or translate mechanical forces into signaling or phenotypic changes. In an interacting three-dimensional environment, tensile forces (stress), shear force, and compressive stimuli influence cell phenotype, viability, programmed death, morphology, differentiation, and even evolution. In an undamaged ventilatory environment, the transmural pressure of the lung parenchyma is responsible for keeping the alveoli open and preventing their collapse. During inspiration, the alveolar-capillary barrier undergoes strain, generating internal tension that affects epithelial and endothelial cells. Conversely, during expiration, the elastic recoil of the lung contracts the parenchyma and alveoli, increasing intra-alveolar pressure and inducing a transient compressive force on the epithelial lining. These shear forces on the alveolar surface generate a vectorial shear force on the epithelial surface that is time-dependent in the context of the assimilation or dissipation of the applied energy. [1]

Under normal conditions, there is an equilibrium between these forces; however, during mechanical ventilation or lung injury, these forces are altered in magnitude and distribution and exhibit abnormal and heterogeneous behavior. At the epithelial level, airway and alveolar cells are exposed to cyclic stress mainly due to lung expansion, low levels of airflow shear stress in the upper airway and basement membrane stiffness. In the face of lung injury, epithelial cells are under increased shear stress, increased traction, increased stiffness, and even aberrant flow (air-liquid interface) in deep lung areas. Moreover, in those collapsed zones, epithelial cells could be subjected to complex hydrodynamic stress during the reopening process. [2] The air-liquid interface and its interaction with altered surfactant properties may influence the absolute mechanics of the lung. [2] Experimental studies suggest that mechanotransduction and focal adhesion kinase (FAK) respond to heterogeneous strain [3] when the lung exceeds 20% of its maximum tolerated distension capacity. [4] In vitro studies have standardized strain levels higher than 20% [5] to be categorized as overdistension, generating epithelial injury. Similar experimental studies in mice lungs conclude that heterogeneous and cyclic deformation can reach a strain between 80% and 100% at the regional level, and over 150% at the local intra-alveolar level. [6] Likewise, ex vivo studies in mice and pigs lungs using digital imaging technology describe heterogeneous and anisotropic strain in the injured lung parenchyma. [7]

Mechanobiology

Most experimental work has shown that cellular injury is directly proportional to the magnitude of strain(5). The cellular response to strain occurs rapidly with as little as 20% of the stretch, resulting in an induction of oxygen free radical (ROS) production within 15 minutes of the stimulus. [4,8-10] Overstretching by as little as 10% - 20% over-stretch results in amplified IL-8 production via the mitogen-activated protein kinase and p38 pathway. [10-12] In addition, the pro-inflammatory response due to lipopolysaccharide stimulation is reduced when the strain does not exceed its maximum tolerance limits. [12] Elevated Na^+/K^+-ATPase activity and increased expression of intercellular adhesion molecule

(ICAM-1) [10] are observed under conditions of epithelial mechanical overload. These changes are attributed to the cyclic mechanical forces to which the cells are subjected.

At low shear stress levels (0.69×10^{-3} to 2.8×10^{-3} dyn/cm²), alveolar epithelial cells exhibit reduced proliferation rates. [13] Conversely, when exposed to shear stress >8 dyn/cm², these cells demonstrate increased surfactant secretion([14]). Experimental data suggest that under certain conditions, alveolar shear stress may exceed 15 dyn/cm², [15] and exposure to 30 dyn/cm² alters cytoskeletal integrity via disruption of keratin intermediate filaments (KIFs). [16,17]

The importance of surfactant lies in its ability to balance the complex interfacial forces during cyclic closure and reopening at the alveolar level. The balance is disrupted when there is intrapulmonary plasma infiltration, which directly impairs the ability of surfactant to maintain near-zero surface tension in the alveolus. This combination of tangential stress and normal transmural pressures varies over time and space during shear, leading to cellular injury and disruption of the epithelial barrier. [2] The increase in spatial pressure gradients would account for epithelial cell damage, reduced cell confluence, and shearing-induced detachment and cell death due to the "fluidization" of the cytoskeleton (decreased rigidity with increased viscosity). [18] Both cyclic and static compression have been shown to activate extracellular signal-regulated kinase (ERK) phosphorylation and heparin-binding epidermal growth factor (HB-EGF) expression in bronchial epithelial cells. [19] These effects are observed after 1–2 hours of sustained pressure at 30 cmH_2O. [20]

Physiological strains (~5% cyclic strain) do not induce a proinflammatory response. [21,22] However, they may reduce epithelial barrier function and decrease fibronectin production. [23] 20-30% increase in strain results in activation of cytoskeletal actin and calcium influx. [24] 15% increase in strain, cell migration is reduced, and although capillary formation is also reduced, the expression of proteoglycans, adhesive proteins, and growth factors involved in extracellular matrix remodeling and cell-matrix interaction increases. [25] 20% increase in strain, production of IL-8, IL-6, monocyte chemoattractant protein and actin polymerization are induced. [24] In the same way, at higher stiffness (~50 kPa), endothelial cells increase their capacity for proliferation and migration through mechanotransduction pathways, activating TGF-B, Toll-like receptors, necrosis factor, and other pathways. Similarly, barrier signals that activate the coagulation cascade. A stiffness at 40 kPa, induces an inflammatory response characterized by increased production of ICAM-1, cellular adhesion molecules, fibronectin, guanine nucleotide factor and Rho-activating factor, compared to mild stiffness (1.5 to 2.8 kPa).

Despite its biophysical importance, surfactant is often overlooked in models of energy transfer. Experimental data show that in healthy lungs, surfactant reduces surface tension to ~20 mN/m during inspiration and close to 0 mN/m during expiration. In contrast, ARDS is characterized by elevated surface tension levels >20 mN/m, impairing alveolar mechanics and contributing to ventilator-induced injury. [15]

Stress

Stress is defined as the force per unit area acting on a given surface. From a pathophysiological perspective, and considering the current definitions of the vectorial forces acting on the pulmonary parenchyma, stress can be defined as the difference between alveolar pressure (Palv) and pleural pressure (Ppl), both during inspiration and expiration:

$$\text{Stress} = [\text{Palv} - \text{Ppl}](\text{inspiration}) - [\text{Palv} - \text{Ppl}](\text{expiration})$$

However, for now, the only surrogate of Ppl is esophageal pressure, which is obtained invasively through measurements from an esophageal catheter. [26]

Strain

Strain is defined as the modification capacity of a given tissue, from its basal conformation (T0 moment) to its maximum stretch-recoil, without exceeding its tolerance limits prior to injury. [27] In this sense, incorporating this concept from materials engineering into respiratory pathophysiology can be very complex and is subject to many errors of interpretation. Some authors state that this concept will depend on the control variable in mechanical ventilation. Gonzalez et al, [28] state that the strain in control volume is equal to the tidal volume (VT) over the residual functional capacity (RFC); while in pressure control, strain is equal to the exhaled tidal volume (VTe) divided by the PEEP.

The marked heterogeneity of strain in different lung regions could be due to unbalanced ventilation, [29] physical properties of the parenchyma, [30] airway geometry, [31] flow resistance, and the poorly understood behavior of the air-surfactant interface. [32] Experimental work in ex-vivo murine and porcine lungs found that the lower and central regions exhibited greater strain than the rest of the parenchyma, [7] in contrast to the human lung, where the greatest strain is found in the apices. Even minimal increases in strain above its maximum limit could deform lung tissue and alter its correlation coefficient

due to its non-linear behavior. After 6 hours of repeated exposure to this cyclic stress, lung compliance begins to fall inescapably(6).

Strain rate

For the exact sciences, the temporal quantification of variables is a fundamental parameter for measuring the behavior of fluids. Cyclicity is probably the key to understanding the resilience and anisotropy of materials when subjected to repetitive stress([33]). Applying these concepts from materials engineering to respiratory pathophysiology could be very complex. In any case, it is estimated that the flow divided by the functional residual capacity (FRC) could be the closest to this concept (1/second)([28]).

Resilience

Viscoelastic materials exhibit characteristics of elastic materials, as they have the ability to store energy when deformed by loads (stress) and to return all that energy once the load has ceased. They also exhibit characteristics of a viscous materials since mechanical energy is continuously dissipated in the form of heat. Therefore, viscoelastic materials simultaneously store and dissipate mechanical energy when subjected to stress. On this basis, mechanical stress is not only related to deformation (strain), but also to the rate of change over time.

Alveolar Anisotropy

Anisotropic strain is defined as the radius between the minor strain and the major strain, where unity defines isotropy. Its variability differs throughout the lung tissue, with areas exhibiting varying degrees of less isotropy. The degree of anisotropy changes according to the geographic location of the lung and may also be influenced by variations in flow. Strain divergence also leads to increased anisotropy with higher inflation volumes. Likewise, the anisotropy resulting from cyclic deformation may stem from a combination of non-uniform stress along the airway due to the underlying complex bronchial network, [34] the geometry of the pulmonary lobes parenchyma, [35] and the anisotropic properties of the airway. [36] Airway components such as elastin and collagen exhibit directionally dependent mechanical properties, being more rigid in the longitudinal direction than in the circumferential direction. [7] The higher the cycling speed, the higher the peak pressure, which translates into a higher pulmonary viscoelastic rate, [37] resulting in a decreased slope of the strain-volume or strain-pressure curve, depending on the anatomical location within the pulmonary parenchyma. [38] Some studies propose the use of anisotropy as an early detection biomarker for lung injury. [39]

The concept of anisotropy is broadly applied at different structural levels and provides a wide explanatory framework for the architectural design of different materials in order to obtain the desired mechanical performance. Since the stress-strain condition is rarely equiaxial, an advantage of anisotropy lies in reinforcing the mechanical properties of materials for certain directions. For example, the vertical alignment of nanoscale hydroxyapatite crystals in mammalian tooth enamel maximizes tooth stiffness against substantial masticatory loads. [40,41] Anisotropic structuring allows for unique biological functions, such as solid adhesion, combined with easy release, enabling quick and spontaneous adaptation to stress. [42] Although the differences between biological and non-biological interfaces are of high relevance, biological systems are generally hygroscopic, more flexible, and prone to strain, while also exhibiting high shear capacity to withstand viscoelastic and plastic strain (the irreversible part of the total strain). However, they are also weaker and less resistant to microcracks, which makes them particularly prone to easy propagation of microcracks. [43] The anisotropic nature of materials is based on the alignment of their components relative to the imposed stress, i.e., the angle between the load axis and the rigid direction of the material or the longitudinal axis of its components. [44]

The resistance of a material to elastic deformation is represented by its stiffness, and hence by Young's modulus. [45] In the case of an orthotropic material, defined as having different mechanical properties in three mutually perpendicular directions but which are symmetrical regarding these three axes, the off-axis stress tends to generate a shear strain, which also leads to axial deformation. [46] However, the variation in Young's modulus shows certain orthogonal orientation, where the stress is perpendicular to the longitudinal axis of its components.

There are several theories that could explain the resistance of materials to deformation and damage. The Tsai-Wu error criterion [47] considers the total strain energy (distortion energy and expansion energy) to predict failure and distinguish between compressive and tensile error forces. In contrast, the Tsai-Hill [45] error criterion accounts for distortion energy, which represents the part of the deformation energy that causes changes in the shape of the body. However, these models cannot predict other types of failure, such as fiber error, matrix error and fiber-matrix connection error.

It is also assumed that the theoretical shape of sockets is a rather elliptical three-dimensional representation. In this context, based on materials engineering, a honeycomb could correspond to a special group of materials known as "amorphous", which exhibit unique mechanical properties and failures in their viscoelastic behavior are usually due to morphological fractures strongly influenced by normal stress. [48] From these data, new theories derived from multiaxial atomic simulation have emerged, of which, the Mohr-Coulomb criterion [49] could capture the multiaxial deformation during shear and normal stress. However, plastic behavior might be better described by means of the extended von Mises criteria. [50] By unifying these and other criteria, a new extended model called the Ellipse criterion is described:

$$\frac{\sigma^2}{{\sigma_0}^2} + \frac{\tau^2}{{\tau_0}^2} = 1$$ [51]

Where σ_0 is the normal critical stress, and τ_0 is the shear failure stress.

Experimental studies suggest that the ratio τ_0/σ_0would be a critical parameter in controlling the fracture of the material. The same criterion (Ellipse) also involves the tensile fracture angle; that is, the angle of inclination between the shear plane and the tensile stress whose values would be between 45° to 90°. [48]

In a practical sense, the anisotropy of biological tissues can be evaluated by the use of optical microscopy, computed microtomography, [52] scanning electron microscopy and transmission electron microscopy, as well as by the benefit of using 3D reconstruction for the evaluation of microcracks. [53]

Micro-Rheology

Rheology is the science that studies the deformation and flow of materials when subjected to mechanical forces (stress). Depending on the characteristics of the material and its mechanical events, different rheological properties will be obtained. These properties will be determined by studying the deformation of the material during the application of stress (σ). Stress consists of the application of a force (F) on a certain surface area of the material (A). Stress can be classified into "normal" (uniaxial compression or extension, when F is applied perpendicular to the material cross-section) or shear stress (when F is applied parallel to the material cross-section).

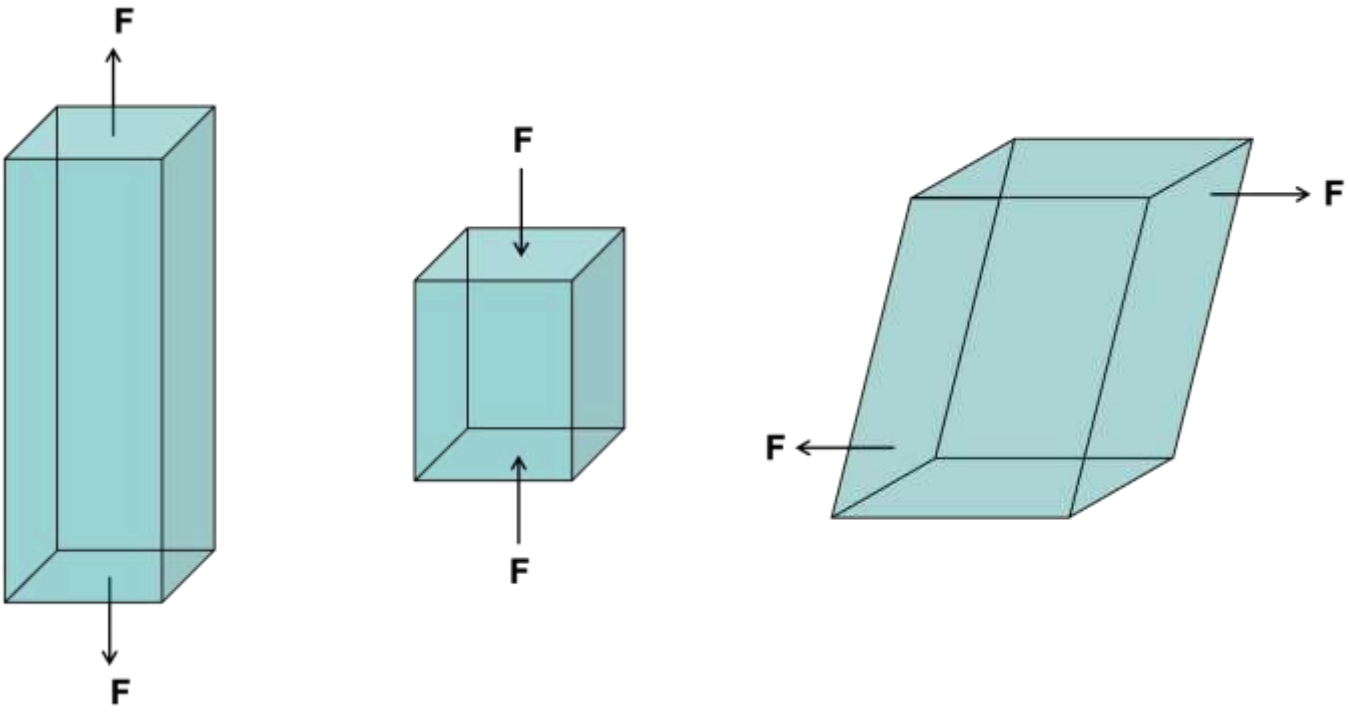

Figure 1: Types of stress applied to specific areas of the surface of a material

Fluids can be classified rheologically according to their flow behavior. A perfect fluid is one whose shear rate is linearly proportional to the shear stress, and where the constant of proportionality is the viscosity (η), which represents the resistance to flow. These fluids follow Newton's Law (Newtonian fluids), and air is within this classification. On

the other hand, those fluids that do not follow this law are called non-Newtonian, which in turn can be subclassified into time-dependent (the structure of the fluid changes as the flow time increases) or time-independent. In the latter, the "viscosity" is not a constant property in relation to the shear rate, and this property is called apparent viscosity since its value is a function of the shear rate.

The viscoelastic cell behavior is mainly coordinated by the cytoskeleton and by the level of pre-stress imposed by the active contractile stress. Lung epithelial cells are very soft (G'~0.5 kPa) and over a wide range of frequencies exhibit predominantly solid behavior. [54] Repetitive strain increases the stiffness of lung epithelial cells. An increase of about 60% [55] of the storage modulus is described, and consequently, a more solid body-like behavior. This stiffness is due to the disruption of the actin cytoskeleton. [56] The increased stress exerted on intercellular junctions during strain could overcome the resistance provided by adhesion forces, which will cause injury to the epithelial monolayer. Experimentally, [57] when primary alveolar cells were subjected to biaxial cyclic strain (15 cycles/min) (6% - 17%) for 1 hour, only the highest stress (17%) produced a significant increase in transepithelial permeability, suggesting a possible threshold limit. This finding is repeated at high inflation volumes in ex vivo lung experiments. [57]

During ARDS, changes in mechanical stress on lung tissue occur and often these changes will result in irregular repair of the epithelium. This will generate apoptosis and unregulated cell death. Therefore, it is important to maintain the restoration capacity of the epithelial barrier, mediating an adequate control of the physical forces involved in the regulation of the reparative process, although the latter is not well known.

Direct measurements of alveolar epithelial cells revealed a Young's modulus of about ~0.5kPa, [54] while measurement of internal tensile stress reveals average stress values of ~0.1 kPa for the alveolar epithelium. [58] Pulmonary pressure (PL) is transmitted from the pleural surface to the internal structures; that is, any stress will be transmitted through a three-dimensional mesh that will concentrate such stress in the parenchyma. This stress concentration is particularly relevant in the interalveolar septa. Since the apical surface of the alveolar cells is part of the air-liquid interface, and the radius of curvature of the interface is very small, alveolar surface tension supports most of the PL. [59,60] However, the relative contribution of epithelial cells to the tensile stress in the interalveolar septum remains poorly defined. Regional differences in applied stress, whether due to the structure or composition of the interalveolar septa, cause non-uniform stretching of epithelial cells. Thus, the tension experienced by alveolar epithelial cells is determined both by cellular stiffness and the mechanical properties of the cellular microenvironment. Consequently, type II alveolar cells, which are usually located in the corners, might show less stretching under inflation pressure than type I cells located in the alveolar septa. [61] Therefore, in the presence of heterogeneity in alveolar septal deformation, type I cells experience greater mechanical strain than type II cells. [61] Increased stress occurs only if the cells undergo large deformations, with a significantly higher level of stress levels being observed in lungs ventilated with a high tidal volumes. [62]

Because the rheological behavior of viscoelastic materials is complex to visualize, mechanical models are often used to represent this characteristic. The behavior of a Newtonian fluid is represented by a piston working in a cylinder, while the elastic behavior of a Hookean solid is represented by a spring. The dashpot represents the dissipation of energy in the form of heat, while the spring represents the energy stored in a given body. With the dashpot, the applied stress is independent of the applied strain, while in the spring the constant of proportionality between stress and strain applies. Under this perspective, certain combinations of these elements (springs and dashpots) could adequately represent viscoelastic behavior. However, despite the large number of models obtained by different combinations, practically all of them are based on the Maxwell (spring-dashpots in series) and Kelvin (spring-dashpots in parallel) models. Despite this, many of the experimental models do not correlate adequately with what is being measured. Generalized models are obtained by superimposing a sufficient number of Maxwell or Kelvin models, which would improve accuracy, although making them more complex to understand.

Rheological properties can be modified by temperature, reaction and even time changes. Considering the equivalence principle (time <-> frequency <-> temperature), the behavior of a material over long periods is equivalent to that obtained at high temperatures and low oscillation frequencies. Regarding frequency sweeps (constant temperature), at very high frequencies (equivalent to low temperatures) the elastic modulus is higher than the viscous one and therefore the material will behave as a solid body. On the contrary, at lower frequencies (or higher temperatures) the material will start to flow, and the elastic modulus will decrease towards values close to viscous behavior. However, for a correct interpretation of the temperature-time superposition principle, it is necessary to consider that this relaxation time

corresponds to the time that a material needs to reorganize its structure (cytoskeleton) and reach a new state of equilibrium after having been subjected to an external stress. This is why an increase in temperature reduces the relaxation times since, due to its entropy, less time will be needed to readapt.

Rouse's theory is a model that rigorously studies viscoelasticity and is represented by a polymer through a series of beads linked by a series of springs. Thus, when an effort (energy, stress) is applied to a material, it can dissipate it (viscous component) generating changes in its configuration, or store energy in the links or springs (elastic component).

The moduli gradually decrease with increasing oscillation frequency, while the complex viscosity tends to increase as the oscillation frequency decreases. This is related to the fact that as the applied stress increases, the moduli increase, while the resistance to deformation tends to decrease.

Young's modulus

The mechanical properties of a body are characterized by the relationship between force (F) and strain. When in a pure elastic solid, the length (L) and area (A) are constant, the linear strain ($\varepsilon = \Delta L/L$) is related to a normal stress ($\sigma = F/A$), according to the constitutive equation $\sigma = E\ \varepsilon$, where E is Young's modulus. On the other hand, the application of a tangential force on A will result in an angular deformation (θ) relative to the shear stress ($\tau = F/A$) as $\tau = G\theta$, where G is the shear modulus. For an isotropic homogeneous elastic body, $G = E/2\ (1 + \nu)$, where $\nu = 0.5$ and $G = E/3$.

Elastic solids are able to store energy during their deformation and give it back during the process of recovery of their initial shape. On the other hand, a purely viscous body dissipates energy. When a viscous Newtonian fluid is subjected to shear stress, the velocity of the fluid layers increases with the normal shear velocity ($d\nu/d\chi$) according to the constitutive equation:

$$\tau = \mu\ d\nu/d\chi$$

where μ corresponds to the coefficient of viscosity.

It is inferred that cells in general exhibit viscoelastic behavior, and as such, would be able to store and dissipate energy. A simplistic way to characterize a viscoelastic body is to measure the shear modulus (G*), which is defined as the ratio between the applied stress and the resulting strain. This modulus could be further divided into real and imaginary parts:

$$G^* = G' + iG''$$

where G' is the elastic (storage) modulus and represents the energy and elastic resistance to deformation. The component G", is the viscous (or loss) modulus and represents the energy dissipation and frictional resistance to strain.
The ratio of the two moduli G"/G' is known as the tangent ratio and provides an index of the degree of liquid or solid behavior. For a pure elastic solid G" = 0 and the tangent ratio is 0. Conversely, the tangent ratio is infinite for a pure viscous body (G' = 0).

Now, for a pyramid with four identical sides, in a linear elastic half-space of Young's modulus E, the force-indentation relationship (F-δ) is defined by the Hertz pyramidal model:

$$F = \frac{3\ E \tan\theta\ \delta^2}{4\left(1 - \nu^{\frac{1}{2}}\right)}$$

where θ is the half-included angle of the pyramid and δ is the Poisson's radius. If it is assumed that the cell is incompressible, ν is usually taken as 0.5. [54] This model allows for an accurate estimate of the mechanical interaction at the cell surface, approximately 0.2 μm^2. The Hertz model assumes infinite thickness. However, the thickness of epithelial cells ranges from 5 to 10 μm in the nuclear region and decreases markedly at the periphery. [63]

The Hertz model also assumes that the sample behaves as a pure elastic body. However, if it is inferred that the cells exhibit viscoelastic characteristics, then the estimated and fitted Young's modulus would increase linearly regarding velocity(64) over a wide range of frequencies.

The clinical application of the use of Young's modulus is limited to experimental animal models, [65] where individualization of driving pressure (DP) according to lung elastance would decrease the inflammatory response and structural lung damage, without a significant impact on oxygenation.

The surfactant

The cellular response to deformation and tolerance mechanisms will depend on factors such as linear strain, stretching frequency and measurement in cycles/minute. In this context, surfactant release, inflammatory response, remodeling, fibrosis, cell death and injury per se have been evaluated by in vitro studies.

Surface tension is the energy required to increase the surface area by 1 square meter. The designation of surfactant material implies having the ability to modify the surface tension existing between two phases, which leads to a change in its elastic and mechanical properties. Pulmonary surfactant can reduce the surface tension at the water-air interface to as low as 2 mN/m, when the water is at 25°C. According to the Laplace equation ($\Delta P = 2\ \gamma/R$, where γ is the surface tension and R is the radius), the intraalveolar pressure increases as R decreases, due to higher surfactant concentration.

Some in vivo studies affirm that after facing 15 minutes of static strain (ε=11.8%), type I alveolar cells respond with an increase in surfactant release. [66] When these same cells are subjected to low strain levels (ε=5%) but at high frequencies (50 cycles/min), there is also an increase in surfactant synthesis. [67] With this evidence, there is a linear relationship between strain and surfactant release; however, its pathological threshold is still debatable.

Taskar et al [68] demonstrated that if surfactant is deficient, the lung is more vulnerable to damage during repetitive shear.

The conceptualization of the air-fluid interface phenomenon could be statistically represented by the Young-Laplace equation:

$$p_L - p_g = \gamma\kappa$$

where p_L is the liquid pressure, p_g is the gas pressure and K is the curvature of the interface.

Then:

$$\kappa = \pm\ 1/R_1\ \pm 1/R_2$$

where R_1 and R_2 are the radius of curvature of the orthogonal planes.

When surfactant adsorbs to an air-fluid interface, the intermolecular forces are modified due to its hydrophilic properties. This reduces the intermolecular forces acting perpendicular to the interface, decreasing γ as a function of surfactant concentration(⌈). γ is generally a decreasing function of ⌈, i.e., γ = F(⌈), where dF/d ⌈ ≤ 0. A surface element located at the air-fluid interface where there is a variation of ⌈ will experience a larger γ on the side where ⌈ is smaller, and vice versa. The surface tension difference across the element exerts a stress called Marangoni stress, (τM), which is tangential to the interface, directed towards the region of higher γ / and lower ⌈). Then, this stress imbalance generates a drag of the viscous fluid located under the surface element through a friction effect, a result known as Marangoni flow. This flow generates an equilibrium between the surface tension gradients, causing the transport of fluid and surfactant adsorbed on its surface. These flow mechanisms influence the distribution of fluids in the alveoli.

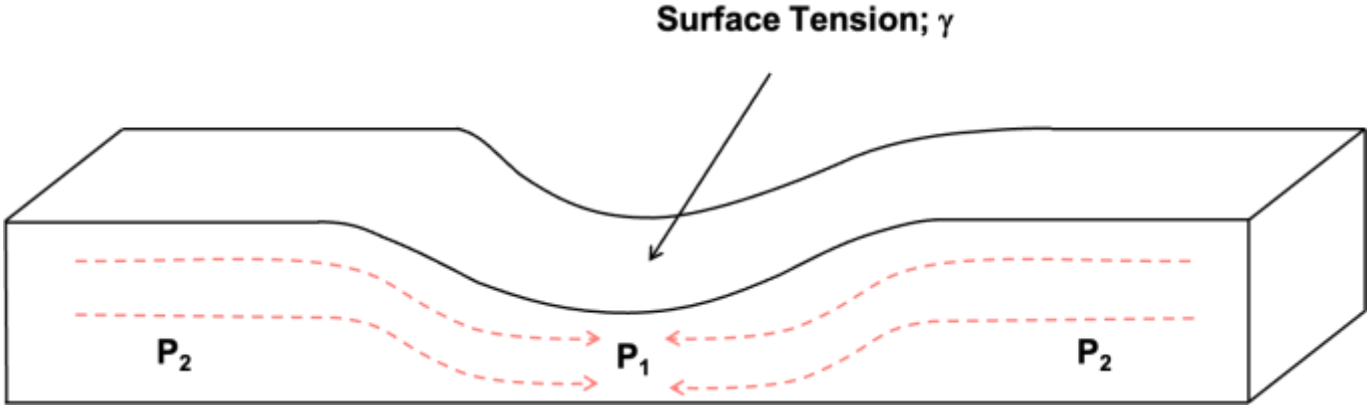

Figure 2: Flow induced by local curvature variation. P1 < P2, which drives a filling flow (adapted from the above text).

Because surfactant tends to favor wetting, it is reasonable to assume that lung fluids have virtually zero contact angles in the airway and form macroscopic structures that equilibrate with neighboring layers of adsorbed fluid. The regulation of fluid thickness across the airway epithelium is controlled by osmotic (passive) and ion channel-mediated (active) mechanisms. Surface tension behavior, like that of a valve, limits the rate at which an air bubble advances to make its way through a collapsed airway. For these purposes, the dimensionless Reynolds number is generally small in peripheral airway flows, implying that there is greater dominance of viscous forces over fluid inertia forces. Likewise, the force of gravity competes against surface tension in the context of controlling fluid distribution in the airway. The two forces are of comparable magnitude in airways with radii similar to capillary length:

$$L= (\gamma/\rho g)1/2$$

Where p is the difference in density between the fluid and the air, g is the acceleration due to gravity, L is the order of 1mm for water in air.

Airway geometry plays an important role in fluid readjustment through a coupling in its distribution of compressive stresses derived from low fluid pressures and the shape of the airway wall. This theory has been termed elastic-capillary airway instability. Hill et al [69] calculated the static distributions of wall and fluid in a single lobe of an axially and uniformly collapsed tube, showing how movement of the air-fluid interface through the lobe leads to multiple stationary configurations for the same parameters, and consequently to hysteresis of the tube pressure-volume relationship. By readjusting the airway wall and the fluid inside, this estimate could contribute to the calculation of such hysteresis in the airway and consequently of the whole lung. These authors identified a dimensionless deformation parameter:

$$W= \gamma R2/D$$

That characterizes the relative importance of surface tension γ regarding the bending stiffness of the airway wall D and radius R. However, there is uncertainty as to what the actual values of W should be. Other recent models [70,71] have shown that if the fluid volume or W is sufficient, an axially uniform fluid-coated elastic tube can exhibit hysteresis and compliance.

Final message

In this first part, the fundamental concepts for a correct interpretation of biology and exact sciences were explored. The complexity of the content is absolutely necessary as an introductory gateway to the explanatory context that we put forward as a potential hypothesis for a better explanation of energy transfer in the respiratory system, providing a fundamental relevance to the role of surfactant in mechanotransduction.

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