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Rheological Theory Applied to Mechanical Ventilation in Acute Respiratory Distress Syndrome: A New Paradigm for Understanding and Preventing Ventilator-Induced Lung Injury

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Abstract

The concept of mechanical power (MP) has emerged as a comprehensive indicator of ventilator-induced lung injury (VILI), integrating the effects of tidal volume, airway pressures, respiratory rate, and flow. However, applying MP as an absolute threshold (e.g., 12 J/min) across heterogeneous patients with acute respiratory distress syndrome (ARDS) may be inadequate. This article explores a rheological model for the respiratory system that reconceptualizes the lung as a viscoelastic body and advocates for individualized MP thresholds. We propose adjusting MP based on ideal body weight (J/min/kg) and, more accurately, on static compliance (J/min/L), which better reflects functional lung size ("baby lung") and mechanical vulnerability. This normalization offers a more precise risk stratification and easier setting of ventilation targets, particularly in patients with low compliance or abnormal body composition. Emerging evidence suggests that normalized MP correlates more closely with mortality than absolute MP values and aligns with the physiological stress-strain behavior of pulmonary tissue. Adopting MP normalization within lung-protective strategies could enhance the safety and efficacy of mechanical ventilation, however clinical validation is still required. This review summarizes the theoretical foundations, supporting evidence, and clinical implications of this approach within the broader context of rheological modeling in ARDS.

Keywords: acute respiratory distress syndrome; ventilator-induced lung injury; rheology; mechanical ventilation; driving pressure; mechanical power; strain; stress; lung protective ventilation; materials science

1. Introduction

Rheology is the branch of physics that studies the deformation and flow of matter. It is a part of continuum mechanics that studies the data obtained when a force (load) is applied to a specific material in an experimental setting. Its primary objective is to find the "constitutive equations" of each material: mathematical models (generally differential equations of tensorial character) that describe the relationship between the stress suffered by the material and the strain induced by the applied force [1].

Acute respiratory distress syndrome (ARDS) represents one of the greatest challenges in the management of critically ill patients. For decades, ventilatory strategies have evolved based on concepts such as barotrauma, volutrauma, atelectrauma, and biotrauma. However, these models

have shown limitations in fully understanding the pathophysiological mechanisms of ventilator-induced lung injury (VILI) [2,3].

The application of concepts derived from rheology and materials science, based on experimental evidence in laboratory animals and recent human research, has enabled the development of a new paradigm that explains the mechanisms of lung damage during mechanical ventilation more precisely than theories used in the past [4]. This rheological approach considers the lung as a viscoelastic body subject to deforming forces whose magnitude, frequency, and velocity determine the development of structural lesions (Table 1) [2,3].

Key concepts of rheological theory applied to the lung include the following:

Stress. Stress is the value of the maximum limit of force per unit area [1]. It corresponds to the transpulmonary pressure (PTP) difference between inspiration and expiration. PTP is the difference between alveolar pressure (Palv) and pressure within the pleural space (Ppl) [2]. It is assumed that clinically, pleural space pressure (mediastinal pressure) can be estimated by measuring esophageal pressure (Pes).

Strain, deformation, or relative displacement. This is the multidimensional deformation suffered by the body, i.e., the change in shape relative to the original state [1]. In classical respiratory physiology, the concept of strain does not exist, but its equivalent could be considered the quotient between tidal volume (V_T) and functional residual capacity (FRC).

Young's Modulus (Figure 1). To generate knowledge about the physical behavior of each body, rheology performs what we call tensional experiments. Different solid materials are subject to increasing axial tension until fracture or rupture occurs. Each material's behaviour is described by what is called the stress-strain curve. In all stress-strain curves, an initial zone that is linear can be identified, defining its elastic behavior [4,5]. The equation of this linear part is called the constitutive equation of an elastic solid (Hooke's Law). The proportionality constant (the slope of this line) E_Y (cmH_2O) is called the Young's modulus of elasticity of the solid. The Young's modulus of the respiratory system is called specific lung elastance (ESL).

Strain rate or deformation velocity. The velocity at which relative deformation occurs with respect to its original position [1]. In classical respiratory physiology, this would correspond to flow divided by FRC.

Driving pressure (DP). DP corelates the classic model with the rheological model. DP = plateau pressure – total positive end-expiratory pressure (total PEEP). Marini et al. [6] found a good correlation between stress (PTP) and DP. Chiumello et al. [7] corroborated this point and additionally determined a threshold DP value of 15 cmH_2O that would have very good diagnostic accuracy for detecting that the lung is being subjected to stress equal to or greater than 12 (strain of 1), the point from which VILI would begin.

Mechanical power (MP). In 2016, Gattinoni et al. [8] developed the concept of MP. To date, this is the model that has most successfully approximated rheological theory and classical respiratory physiology. It attempts to combine all parameters, both static and dynamic, that would play a role in generating the energy that the ventilator delivers to the lung and airways per unit time.

Resilience. This is the deformation per unit volume (J/m^3) produced within a material when stress is applied from a base state to the yield point [1,4]. It constitutes the maximum capacity of a material to absorb energy when elastically deformed and then, upon unloading, completely recover this energy without losses (Figure 2).

Is it worth mentioning/providing a definition the Elastic Region? Haven't seen anything specifically about it in other articles/talks

Table 1. Fundamental concepts of rheology applied to the respiratory system.

Concept	Physical Definition	Pulmonary Application	Units
Stress	Force per unit area (f/A)	Transpulmonary pressure (PTP)	cmH_2O

Strain	Relative deformation (dX-dX$_0$)/dX$_0$	Tidal volume/Functional residual capacity (V$_T$/FRC)	Dimensionless
Strain rate	Deformation velocity	Flow/FRC	s^{-1}
Young's Modulus (E$_Y$)	Proportionality constant between stress and strain	Specific lung elastance (ESL)	cmH$_2$O
Driving pressure (DP)	Difference between plateau pressure and PEEP	Clinical approximation to pulmonary stress	cmH$_2$O
Mechanical power (MP)	Energy per unit time	Energy delivered to respiratory system per minute	J/min
Resilience	Maximum energy storable without permanent deformation	Energy threshold to prevent VILI	J/m³

F: force; A: area; PTP: transpulmonary pressure; cmH$_2$O: centimeters of water; V$_T$: tidal volume; FRC: functional residual capacity; E$_Y$: Young's modulus; DP: driving pressure; ESL: specific lung elastance; MP: mechanical power; VILI: ventilator-induced lung injury.
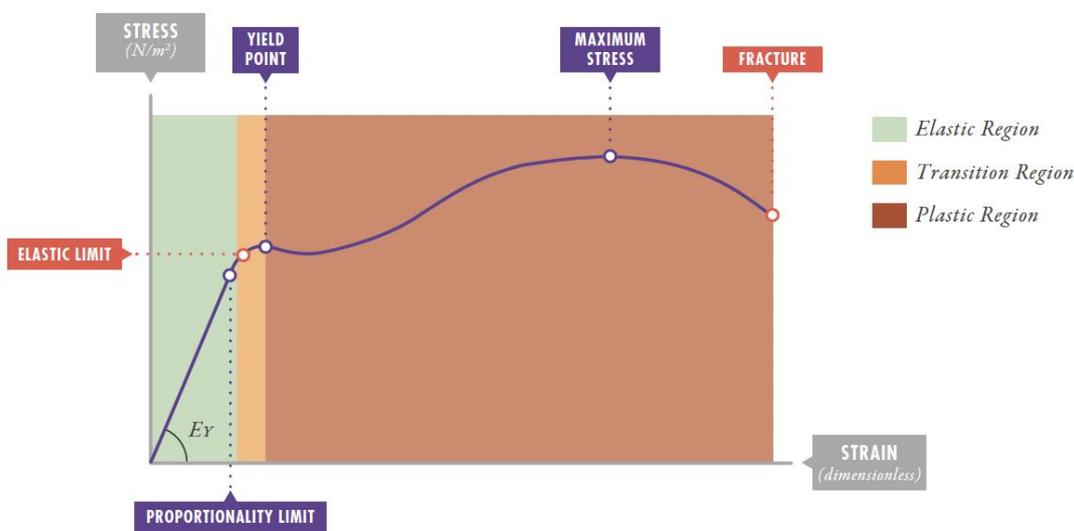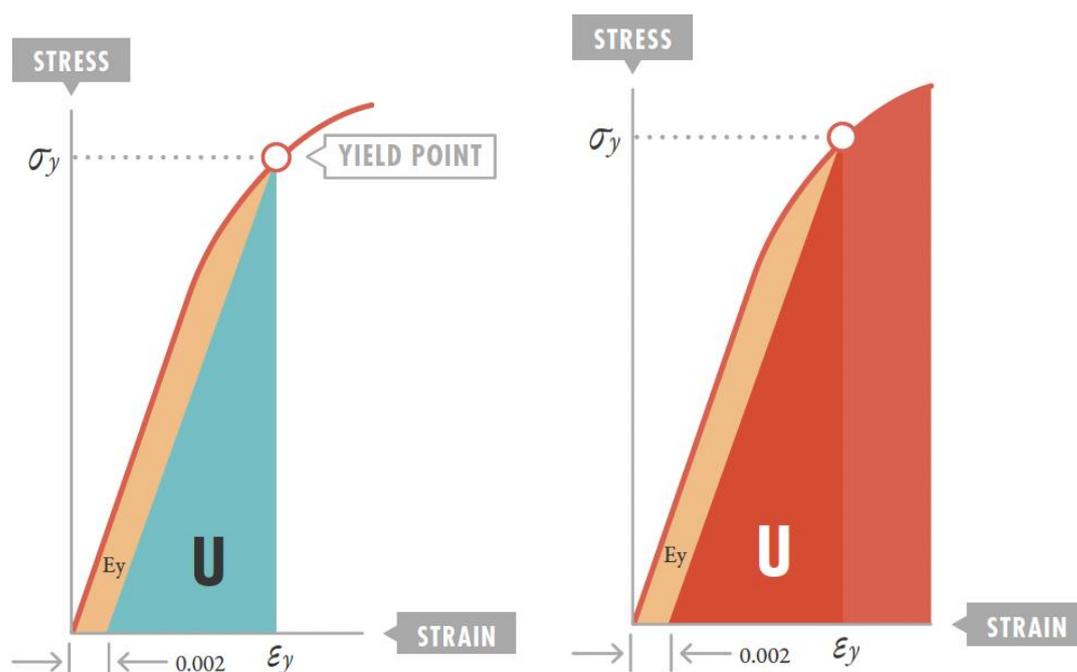

Figure 1. Stress-strain curve. E$_Y$: Young's modulus of elasticity.

Figure 2. Resilience: maximum energy that can be stored in an elastic body and subsequently recovered without any loss (left). Pathogenesis of ventilator-induced lung injury: deformation energy exceeds resilience (right). **σy: stress at maximum elasticity point; εy: strain at maximum elasticity point; U: resilience.**

2. Refutation of Classical VILI Theories. New VILI Concepts

Since the 1970s, two static variables have been fundamentally studied as VILI inducers: pressure and volume.

Initially, the concept of barotrauma emerged, relating excessive peak airway pressure (greater than 36 cmH$_2$O). A decade later, experimental studies demonstrated that when generated volumes were relatively low, pressures up to 45 cmH$_2$O did not induce lung injury, and high volumes did cause injury despite using low pressures [9].

Volume then became considered the main determinant of VILI. This concept continued developing, and in 2000, the ARDS Network trial was published in The New England Journal of Medicine, [10] proving that ventilating ARDS patients with volumes of 6 mL/kg ideal body weight versus 12 mL/kg reduced mortality.

Simultaneously with volutrauma studies, several works began investigating the modulating role that PEEP could have. In the 1990s, this idea gave rise to the concept of atelectrauma, which considers that periodic opening and closing of collapsed alveolar units also generates tissue damage. Marcelo Amato et al. [11] published in 1995 one of the first clinical studies in ARDS patients comparing this new ventilatory strategy, called "open-lung," with the classical strategy, giving weight to using PEEP above the lower inflection point of the pressure-volume curve.

In the late 1990s, Slutsky et al. [12] developed the concept of biotrauma, which attributes part of both local and systemic lesions to the inflammatory reaction triggered in damaged lung tissue.

In summary, the classical theories explaining VILI development have been:

1.Barotrauma: lung injury caused by excessive airway pressures [9,13].

2.Volutrauma: damage due to elevated tidal volumes [9,13].

3.Atelectrauma: injury from cyclic opening and closing of alveolar units [9,13].

4.Biotrauma: inflammatory response secondary to mechanical damage [12].

However, these theories present important limitations:

González-López et al. [14] demonstrated in 2012 that patients ventilated with lower driving pressures (22.6 ± 6 cmH$_2$O) but with lower PEEP experienced greater pulmonary inflammation despite receiving protective tidal volumes of 7 mL/kg. This finding directly contradicts barotrauma theory, suggesting that pressure alone does not explain lung damage.

Rahaman [15] provided mathematical proof that ventilation of healthy lungs with tidal volumes of 6-10 mL/kg should not cause VILI, since the generated strain (0.17-0.29) produces stress (2.31-3.86 cmH_2O) well below the harmful threshold. However, upon reaching total lung volume (strain of 1.5), the resulting stress (17 cmH_2O) exceeded the safety threshold, explaining why conventional ventilatory strategies do not cause damage in healthy lungs but can be injurious in ARDS.

The LUNG SAFE study [16] and Amato et al.'s meta-analysis [17] in 2015 revealed that DP was the factor most consistently associated with mortality, regardless of tidal volume, plateau pressure, or PEEP values used, thus questioning classical theories.

These findings suggest that traditional theories are incomplete and that a model based on rheological principles offers a more coherent explanation of VILI mechanisms.

Rheological theory considers the lung as a viscoelastic body whose behaviour can be described by Voigt's constitutive equation [18]:

Stress = E_Y × Strain + η × Strain rate

E_Y: Young's modulus (specific elastance); η: viscosity coefficient

Thus, from a physical standpoint, it is reasonable to assume that the respiratory system behaves as a viscoelastic body. In fact, in the context of mechanical ventilation, at least three phenomena related to the viscoelastic properties of the respiratory system have been identified:

Dynamic hysteresis (in the dynamic pressure-volume loop).

Relaxation index or stress relaxation (P1-P2 difference after a 5-second inspiratory pause).

Stress index.

3. New VILI Concepts Related to Rheological Theory

3.1. The Lung as an Elastic Solid

Gattinoni et al. [19] demonstrated in 2008 and Protti et al. [20] in 2011 that the lung behaves as an elastic solid, with a linear relationship between stress and strain, fulfilling Hooke's law:

$\Delta PTP = ESL \times (V_T / FRC)$

ΔPTP: transpulmonary pressure increment; ESL: specific lung elastance; V_T: tidal volume; FRC: functional residual capacity

Specific lung elastance (ESL) in adults with ARDS is remarkably constant: 13.5 ± 4.1 cmH_2O (95% CI: 11.8-15.2), regardless of ARDS cause, V_T, or PEEP used [21]. In children with ARDS, this value is similar: 13.5 cmH_2O (95% CI: 10-15.3) [22]. This value does not change with age.

3.2. Strain Threshold and VILI Development

The lung's stress-strain curve shows a linear relationship up to strain values near 1, losing linearity between 1.5 and 2. This point marks the elastic limit beyond which irreversible microfractures begin to occur in lung parenchyma [20].

In animal experiments, Protti et al. [20] demonstrated that VILI risk increased exponentially with strain value. Animals without VILI presented strain values of 1.29 ± 0.57, while those with VILI had values of 2.16 ± 0.58 ($p < 0.001$), with associated mortality of 86% after only 60 hours of mechanical ventilation.

3.3. Stress and Strain Estimation with the Ventilator

The rheological model and classical elastic-resistive model represent distinct and, in principle, incommensurable (mutually exclusive?) paradigms. The main limitation for applying the rheological model in clinical practice is the difficulty of estimating FRC at the bedside using a conventional ventilator. However, recent studies have established functional equivalence between both approaches [23].

Cortés-Puentes et al. [6] demonstrated a consistent relationship between rheological stress (ΔPTP) and driving pressure (DP), a parameter easily measurable clinically as the difference between plateau pressure (Pplat) and total PEEP, both measured under static conditions. The ΔPTP/DP ratio oscillates between 0.46 and 0.79, being approximately 0.75 in ARDS patients, and remains stable with PEEP changes, although it decreases with elevated intra-abdominal pressure (except in ARDS).

Chiumello et al. [23] replicated these findings and confirmed significant correlation between stress and DP ($R^2 = 0.7$; $p < 0.001$). In ARDS patients, stress represents between 73 and 85% of DP. Considering that lung Young's modulus (specific elastance) in human ARDS is 13 cmH_2O, it follows that pulmonary stress equal to or greater than this value can induce VILI.

Chiumello et al. [23] validated DP use as a marker of injurious stress, establishing a clinical threshold of 15 cmH_2O with high diagnostic capacity (AUC = 0.864; 95% CI: 0.80-0.93; sensitivity = 0.90; specificity = 0.78). This threshold identifies the presence of pulmonary stress ≥ 12 cmH_2O, associated with VILI risk.

In conclusion, DP represents the key parameter that allows establishing a connection between the classical elastic-resistive model and the rheological model, thus providing functional equivalence between both paradigms. A DP threshold value of 15 cmH_2O, which in humans is associated with an approximate strain of 1.5, appears to mark the elastic limit beyond which VILI is induced.

Along these lines, Rahaman et al. [15], applying rheological theory, offer a coherent explanation for a widely observed fact in clinical practice: conventional mechanical ventilation does not induce VILI in healthy lungs. Under physiological conditions, healthy lung FRC is approximately 35 mL/kg, while total lung capacity (TLC) reaches 85 mL/kg [24]. If a ventilatory strategy were applied that brought end-inspiratory volume to TLC and end-expiratory volume to FRC, the resulting strain would be 1.5. This deformation level translates, according to specific elastance modulus (ESL), into stress (ΔPTP) equivalent to a driving pressure clearly superior to the 15 cmH_2O threshold, thus positioning in a range capable of generating VILI even in a previously healthy lung.

Conversely, in the same lung, using tidal volumes of 6 mL/kg (strain = 0.17; stress = 2.31 cmH_2O; DP = 2.89 cmH_2O) or even 10 mL/kg (strain = 0.29; stress = 3.86 cmH_2O; DP = 4.82 cmH_2O) is considered safe, as it remains well below the injurious threshold. This practice is same as the ventilatory strategy traditionally employed in patients without lung disease, supporting its safety from a rheological perspective.

3.4. Mechanical Power and Injury Threshold

MP integrates all factors capable of producing VILI (V_T, pressures, frequency, and flow) into a single physical magnitude representing energy transmitted to the respiratory system per unit time [25].

The simplified formula for its calculation is:

MP (J/min) = $0.098 \times RR \times V_T \times (PIP - DP/2)$

MP: mechanical power; RR: respiratory rate; V_T: tidal volume; PIP: peak inspiratory pressure; DP: driving pressure.

Gattinoni et al. [26] experimentally demonstrated the existence of an MP threshold (approximately 12 J/min) above which VILI occurs, regardless of the combination of ventilatory parameters used.

4. Ventilatory Strategy in ARDS from Rheological Perspective

4.1. Mechanical Power Adjustment by Ideal Weight or Compliance

MP adjustment by ideal body weight (IBW) or compliance (C) is a crucial aspect of the rheological model that deserves greater attention since MP as an absolute value (12 J/min) presents important limitations by not considering individual patient characteristics [25-31]:

1. It was derived primarily from studies in animal models with homogeneous anatomy/structural features.

2. Body size differences between patients were not accounted for.

3. Differences in the proportion of functional "baby lung" available in each ARDS case were not adjusted.

4. Differences in lung compliance between patients were not factored in.

Thus, MP could be normalized by patient's ideal weight [27-31], providing a more individualized value:

- **Normalized MP (J/min/kg) = Total MP (J/min)/Ideal weight (kg).**

Preliminary studies suggest that a threshold of approximately 0.25-0.3 J/min/kg might be more appropriate.

This approach is similar to V_T normalization by ideal weight already routinely used.

Or it could be normalized by compliance [27-31], potentially more precise than ideal weight adjustment, as it directly reflects functional lung tissue:

- **Specific MP (J/min/L) = Total MP (J/min)/Static compliance (L/cmH$_2$O)**

The advantage of this approach is that it considers the severity of lung involvement in each individual patient, adjusting the "dose" of mechanical energy according to available functional tissue. This adjustment attempts to represent the theory of ARDS lung as a "baby lung" [33].

Some recent studies have begun exploring these normalizations (IBW and compliance):

Serpa Neto et al. [34] found that compliance-normalized MP showed better correlation with mortality than absolute MP.

Gattinoni et al. [33] subsequently proposed the concept of "specific mechanical power" that considers the baby lung.

Cressoni et al. [25] suggested that the injury threshold might be between 0.12-0.15 J/min per mL of functional lung tissue.

Ito et al.[29] have shown that weight adjustment underestimates MP compared to compliance-adjusted MP in pediatrics.

MP normalization would have important practical implications [30-32, 35-38]:

1.Patients with severe ARDS (lower compliance) would require lower absolute MP thresholds.

2.Patients with preserved compliance could tolerate higher absolute MP values.

3.Ventilatory strategy could be dynamically adjusted according to compliance evolution.

4.It would allow more precise comparisons between patients with different characteristics.

However, to implement this approach requires:

1.Clinical studies validating specific normalized MP thresholds.

2.Practical methods to estimate baby lung volume at bedside.

3.Algorithm development to automatically adjust ventilatory parameters according to normalized MP.

4.Validation in specific populations (pediatric, obese, etc.).

In summary, this perspective of MP adjustment by ideal weight or compliance represents an important advance in individualized protective ventilation and is aligned with fundamental principles of the rheological model. However, it is important to note that research in this field continues evolving and more studies are needed to establish definitive normalized MP thresholds.

4.2. VILI Development Dynamics and Recruitment. Optimal PEEP

VILI is a time-dependent phenomenon. Gattinoni et al. [39] demonstrated in 2013 that VILI development follows a temporal relationship with applied strain:

With strain of 2.5: detectable VILI occurs at 6 hours with 100% mortality at 48 hours.

With strain of 1.154 and 0.556: VILI was detectable at 24 and 36 hours respectively.

With strain of 0.217: absence of VILI after 60 hours of ventilation despite using end-inspiratory volumes equal to TLC (with initial inspiratory Pplat values of 36 ± 3 cmH$_2$O), not only does VILI not appear, but Pplat values at experiment end were the lowest among the four cohorts.

It is important to highlight that none of the theories proposed to date to explain the etiopathogenic mechanism of VILI (barotrauma, volutrauma, atelectrauma, biotrauma) have explicitly considered a mechanism that included ventilation application time as an important responsible factor.

Therefore, VILI development occurs exponentially, initiating in interface zones of naturally non-homogeneous structures (subpleural microatelectasiae, peribronchial and intraparenchymal areas). These zones act as "stress multipliers" (stress raisers), similar to material fatigue mechanisms [2].

A crucial finding was that these initial VILI densities only appear in computed tomography images performed during expiration, indicating they are highly recruitable areas. This suggests that

adequate PEEP use could prevent their appearance by maintaining more homogeneous parenchyma [40].

Protti et al. [18] observed that both low and high strain rate groups showed lower stress relaxation (P1-P2 difference) when ventilated with 10 cmH$_2$O PEEP compared to 0 cmH$_2$O PEEP (ZEEP). This effect was independent of strain rate, suggesting that PEEP reduces viscous behaviour of lung parenchyma during ventilation.

The use of sufficiently elevated PEEP level (so-called optimal PEEP) is the most relevant measure amongst those constituting lung protection strategy. It has been proved to have a very important effect (NNT = 5 patients; 95% CI = 3 to 10) in reducing mortality in severe ARDS patients [41]. Maintaining permanent opening of the highest possible percentage of recruitable alveoli through high continuous distending pressure prevents VILI because it prevents atelectrauma caused by cyclic collapse of these alveoli during expiratory phase [42]. To correctly apply open-lung strategy [11, 43-45], high PEEP use must be optimized according to each patient's lung mechanics. For this, it is necessary that all patients have their static compliance curve analysed in its inspiratory ramp (for example, through "super-syringe" technique), prescribing a PEEP level 2 cmH$_2$O above the lower inflection point (LIP) of this curve. This is the transpulmonary pressure point corresponding to that patient's "functional residual capacity (FRC)." With this PEEP level, the entire respiratory cycle is performed above FRC, just as it happens in healthy lungs, atelectrauma is avoided, and intrapulmonary shunt is minimized (therefore, FiO$_2$ requirements are reduced).

Data from open lung strategy clinical trials, makes it possible to infere that this LIP is situated in 95% of cases between 12.35 and 13.43 cmH$_2$O. Therefore, to be 97.5% certain that the patient receives optimal PEEP, approximately 15 cmH$_2$O PEEP should be prescribed. This achieves a partial arterial oxygen pressure/inspired oxygen fraction (P/F) ratio between 170 and 200, indicating that shunt will have been reduced to 30-40%. High PEEP levels may be necessary, even using Pplat values above 32 cmH$_2$O, provided the 15 cmH$_2$O limit in DP is not exceeded.

Clinically, performing static compliance curve is usually not feasible, and therefore "optimal" PEEP level must be determined indirectly. Kacmarek, Amato, and other investigators [46] have verified that determining PEEP level based on static compliance curve LIP and doing so by measuring shunt degree produces results without statistically significant differences.

Therefore, in the clinical setting, it seems reasonable to determine "optimal" PEEP level based on the P/F ratio value obtained with it [47]. A P/F ratio > 150-175 seems a reasonable objective. Clinical trials using higher PEEP levels (super PEEP trials) have only managed to demonstrate very marginal survival improvement [48-50], particularly in the most severe patients [51, 52]. Any further PEEP increase will result in a merely "cosmetic" effect and subject the patient to unnecessary hemodynamic compromise. Recently, it has been demonstrated that daily lung mechanics trends can be assessed based on real-time responses of respiratory system compliance, end-expiratory lung volume, and stress and strain with respect to PEEP changes using a non-invasive nitrogen washout technique [31]. It has also been demonstrated that, although PEEP increase up to 10 cmH$_2$O increases tension and stress, their levels remain below known harmful values in pediatric ARDS [32].

In summary, the hypothesis is that PEEP effect on VILI incidence, from rheological perspective, relates to its capacity to:

Increase FRC: by increasing the denominator in the strain equation (V$_T$/FRC), it reduces strain for the same V$_T$.

Homogenize lung parenchyma: prevents "stress multiplier" formation by maintaining recruited unstable alveolar units.

However, it is important to highlight that PEEP does not always increase FRC in ARDS patients, and its effect on lung recruitment is difficult to predict at bedside.

Furthermore, for now, PEEP effect on VILI production has not yet been perfectly established experimentally within the new rheological theory framework.

4.3. Importance of Respiratory Rate

Respiratory rate (RR) plays a fundamental role in VILI development. Marini et al. [53] first described in 2000 that elevated RR worsened VILI in an animal model.

Karolinska Institute researchers [54] demonstrated, using a "double hit" model (alveolar lavage followed by aggressive ventilation), that animals ventilated with 40 bpm RR presented worse P/F ratio and higher biochemical and anatomopathological VILI markers compared to those ventilated at 20 bpm, despite using protective strategies (6 mL/kg V_T, 10 cmH$_2$O PEEP).

This effect is explained by RR contribution to total mechanical power:

MP = RR × V_T × Pressures

MP: mechanical power; RR: respiratory rate; V_T: tidal volume

Elevated RR linearly increases MP delivered to the respiratory system, potentially exceeding the safety threshold even with protective tidal volumes.

4.4. Importance of Flow

Gattinoni's group [55] demonstrated that not only strain magnitude is important, but also the velocity at which it occurs (strain rate). In experiments with pigs ventilated with similar strain (2.1 ± 0.9) but different flow velocities:

The high strain rate group (I:E ratios of 1:5 to 1:9) presented:

Worse compliance and P/F.

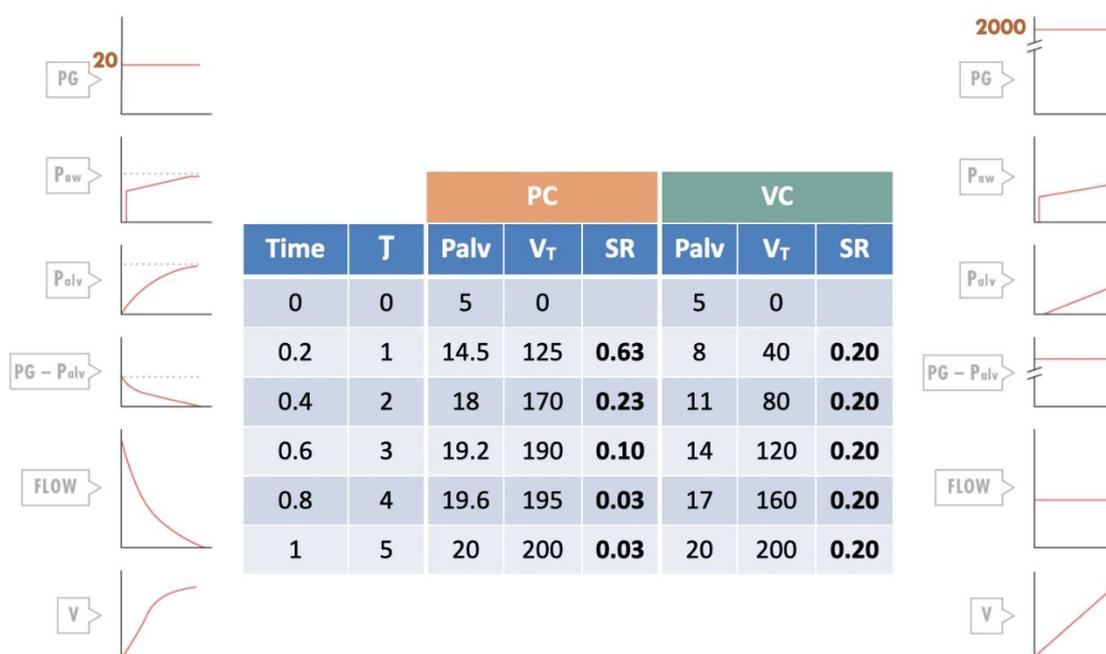Higher inflammatory markers and anatomopathological signs of pulmonary oedema.

Higher VILI prevalence (73% vs 20%, p = 0.01).

Higher mortality at 54 hours (47% vs 13%).

These findings suggest that high inspiratory flows increase VILI risk by increasing strain rate, even maintaining other ventilatory parameters constant.

Additionally, the group with greater VILI presented higher values in dynamic pulmonary hysteresis index (Joules) and stress relaxation index (P1-P2, cmH$_2$O), parameters that can be monitored in clinical practice.

To illustrate the gas delivery problem, an example can be posed comparing VC and PC (Figure 3) in which we can see that, despite strain being the same, strain rate will be 3 times higher in PC in the first time constant.

Time	τ	PC			VC		
		Palv	V_T	SR	Palv	V_T	SR
0	0	5	0		5	0	
0.2	1	14.5	125	0.63	8	40	0.20
0.4	2	18	170	0.23	11	80	0.20
0.6	3	19.2	190	0.10	14	120	0.20
0.8	4	19.6	195	0.03	17	160	0.20
1	5	20	200	0.03	20	200	0.20

Figure 3. Comparative example of gas delivery in pressure control (PC) and volume control (VC). Time constant (τ) is considered to be 0.2 seconds (5 time constants are completed in 1 second). Ideal weight is 30 kg and age 8 years. Estimated functional residual capacity is 1000 mL. Tidal volume (V_T) to be delivered is 200 mL and plateau pressure (Pplat) or alveolar pressure (Palv) to be reached when gas delivery is completed is 20 cmH$_2$O. **τ: time constant; Ti: inspiratory time; PG: generator pressure (working pressure); Paw: airway pressure; Palv: alveolar pressure; V: volume; SR: strain rate.**

4.5. Importance of Ventilatory Mode

Ventilatory mode choice significantly influences VILI development, mainly through its effect on flow pattern.

In a series of experiments [56-58] comparing continuous mandatory pressure-controlled modes with adaptive control scheme (PC-CMVa) versus continuous mandatory volume-controlled modes with fixed control scheme (VC-CMVs), clear superiority of VC-CMV modes was observed in both oxygenation parameters and anatomopathological findings. That is, PC-CMVa modes produced more VILI.

This finding is surprising but may be related to the higher peak flow necessary in PC-CMVa to introduce the same volume (same strain) inducing higher strain rate and, as Gattinoni's team has demonstrated [55].

Schmidt et al. [59] have also demonstrated that ventilation with expiratory flow control attenuates lung injury in a porcine ARDS model. This finding suggests that not only inspiratory flow is important, but also deformation velocity during expiration (expiratory strain rate).

High-frequency oscillatory ventilation (HFOV) use could be a typical example of daily practice. According to volu/barotrauma theories, HFOV use should be safer and cause less damage than conventional MV, since administered V_T is below dead space with moderate continuous distending pressure. Contrary to this theory, currently available literature has not demonstrated superiority and has even shown worse results when using HFOV versus conventional mechanical ventilation, a paradox that can be explained by energy transmission in HFOV. Since the modality uses simple harmonic motion to provide ventilation, energy transmitted by this wave can exceed the MP threshold for VILI formation.

4.6. Tidal Volume and Driving Pressure

In all mammalian species, [60] from bat to whale, physiological V_T is 6.3 mL/kg. V_T limitation to 6 mL/kg constitutes one of the fundamental aspects of lung protective ventilation strategy. Lung involvement in ARDS is very heterogeneous, with collapsed and non-recruitable zones coexisting with healthy or recruitable zones that remain open throughout the respiratory cycle. If very high V_T are used, these ventilatable zones receive all inspired air (the volume that should come to them plus the remaining that should go to collapsed zones). V_T limitation aims to avoid overdistension of these open zones and is a therapeutic measure that, although not proven to decrease barotrauma, has managed to moderately decrease ARDS patient mortality [10] (number needed to treat [NNT] = 12 patients; 95% CI: 8 to 36). But it is fundamental that this V_T limitation be accompanied by adequate PEEP to maximize recruitment and decrease overdistension by distributing inspired air among the highest possible number of alveoli.

Since the beginnings of lung protective ventilation [61], in pressure control modes, V_T limitation was established indirectly by limiting maximum Pplat (35 cmH$_2$O). This maximum Pplat correlates with PTP needed to insufflate lungs of a paralyzed and ventilated adult to obtain TLC [62]. However, experimental animal models have demonstrated that the main cause of overdistension is applied V_T rather than maximum Pplat [9]. This implies that absence of V_T limitation can cause VILI despite Pplat < 30 cmH$_2$O and, conversely, lower V_T (6 mL/kg) using sufficient PEEP and recruitment maneuvers could make it possible for the patient to tolerate higher Pplat (40 cmH$_2$O) [49]. Although this topic is still controversial, in subsequent consensus guidelines for ARDS ventilatory management, for both adults and children, a maximum Pplat limit around 30 cmH$_2$O was established [63-65].

In relation to this, DP has been independently associated with mortality. Amato's study [66] reflects that Pplat increase is not always deleterious nor PEEP increase always protective, but rather the pressure difference between both that causes lung injury. A differential pressure below 15 cmH$_2$O has been established as a safety point [66].

On the other hand, it is not proven that using less than 6 mL/kg V_T is positive for ARDS. In fact, since recruitment occurs through insufflation pressure (and is maintained by PEEP), using lower V_T could be renouncing recruiting potentially recruitable zones and thereby worsening atelectrauma. In neonates with hyaline membrane disease, it has been seen that using 3 mL/kg V_T versus 5 mL/kg

produces greater pulmonary inflammation [67]. Consistent with this, Eichacker [68] published meta-analysis data indicating that $V_T < 5$ mL/kg should not be used routinely since both high and low V_T use can increase mortality. With Pplat of 28-32 cmH$_2$O being what most decreases mortality. This point has also been highlighted in the Cochrane meta-analysis published in 2013, which emphasizes that mortality does not increase until Pplat is greater than 32 cmH$_2$O [69].

Based on all the above and supported by Costa et al.'s 2021 meta-analysis [28], from a practical standpoint, initial V_T should be 6 mL/kg ideal weight. If, having programmed adequate initial PEEP (15 cmH$_2$O), Pplat is equal to or greater than 32 cmH$_2$O, then V_T should be decreased, with 4.5 mL/kg ideal weight recommended as lower limit.

Classically, in cases where V_T is decreased below 6 mL/kg, minute volume loss was compensated with RR increase. However, it has been seen that resulting acidosis from permissive hypercapnia-based strategy is less injurious than V_T increase necessary to correct it. And if accompanied by other lung protection measures (especially adequate PEEP level [70], it has demonstrated improving hemodynamics of adult patients ventilated for ARDS [71].

This supposed protective effect of permissive hypercapnia cannot be explained with classical VILI theories but may fit with the new vision provided by rheological theory. Considering that RR has a direct effect on MP increase, this can explain the beneficial effect of hypercapnia.

4.7. Resilience Implication in ARDS Ventilatory Strategy

Material resilience is deformation per unit volume (J/m³) produced within a material by deformation when stress is applied from a base state to the yield point. It constitutes the maximum capacity of a material to absorb energy when elastically deformed and then, upon unloading, completely recover this energy without losses. Since the first part of the stress-strain curve is linear, resilience is calculated as the geometric area of the triangle below the initial linear elastic region of that curve, up to the yield point (Figure 2). Therefore, it is half the product of stress and strain within that first segment [4, 14, 39].

When deformation energy remains within this elastic "comfort" zone, there is no energy loss. Then, there is no excess energy that leaks into the material producing microfractures and deformations, ending with material rupture (yield limit) (Figure 2) [25, 26, 72].

This threshold effect is a prediction of materials science. It requires staying in the deformation "comfort" zone to avoid creating microfractures. Therefore, to minimize VILI, it is important to adjust ventilator settings (in non-invasive and invasive ventilation) to maintain the energy level involved so that it is less than human lung resilience (J/m³), diseased or not. If deformation energy exceeds the safe zone, VILI appears [4].

4.8. Self-Inflicted Lung Injury (SILI)

Classically, preserving patient's spontaneous breaths was recommended; in fact, this is the basis for justifying Airway Pressure Release Ventilation (APRV) use. However, it has been demonstrated that muscle relaxant use in the most acute phase after intubation decreases mortality. [73] This data has been confirmed in a meta-analysis [74].

In recent years, the concept of self-inflicted lung injury (SILI) has been developed, extending the rheological model to patients with spontaneous breathing [30, 75]. During respiratory effort, especially in ARDS, elevated negative pleural pressures are generated that can produce:

Increased regional strain. Especially in dependent zones, where negative pleural pressure can cause excessive local deformations.

Pendelluft. Air movement between lung regions with different time constants, increasing regional strain without changes in total V_T.

Increased strain rate. Vigorous inspiratory efforts generate high flows that increase deformation velocity.

Increased mechanical power. The sum of patient's respiratory work and energy delivered by ventilator can exceed lung resilience threshold.

From rheological perspective, SILI can be prevented through:

Adequate sedation in initial phases of severe ARDS.

Ventilatory modes that limit inspiratory effort.

Trigger and cycling adjustment to avoid mismatches/asynchronies?.

Oesophageal pressure monitoring to estimate real stress.

Neuromuscular blockade consideration in selected cases.

5. Rheological Model Limitations

Some limitations of the new rheological theory are shown below:

5.1. Regional Lung Variability Not Captured by the Model

Current mathematical models of lung mechanics present important limitations for capturing regional lung heterogeneity, especially in pathological states like ARDS. This marked heterogeneity (areas of alveolar collapse, consolidation, and relatively preserved zones coexisting in the same lung) generates regional mechanical behaviours that cannot be adequately represented by global parameters. Current models, by assuming homogeneous properties, can lead to erroneous interpretations of global lung mechanics.

5.2. Interaction Between Mechanical Ventilation and Inflammation Not Completely Explained

Current models focus primarily on mechanical parameters, without adequately incorporating biological aspects of ventilator-lung interaction. Mechanical ventilation can induce or exacerbate pulmonary and systemic inflammatory response through mechanisms like biotrauma and mechanotransduction, processes that are not adequately integrated into conventional mechanical models.

Experimental studies by Chiumello et al. [76] have demonstrated that specific ventilation patterns can modulate gene expression and inflammatory mediator release, even in the absence of evident changes in mechanical parameters. This bidirectional interaction between mechanics and inflammation represents a significant challenge for current models.

5.3. Challenges for Determining the "Baby Lung" Precisely at Patient Bedside

The "baby lung" concept, introduced by Gattinoni, [33] has been essential to the understanding of ARDS pathophysiology and the adaptation of ventilatory strategies. However, precise quantification of functional lung tissue at bedside remains a significant challenge.

Currently, "baby lung" volume estimation requires advanced imaging techniques like quantitative computed tomography, which is not routinely available in intensive care units. Indirect methods, such as compliance-based or physiological dead space estimation, present important limitations and may not accurately reflect lung tissue truly available for ventilation.

In relation to these limitations, several solutions are proposed:

Implementation of multicompartmental models incorporating different time constants for different lung regions.

Integration of real-time functional imaging data to adjust regional model parameters.

Development of finite element-based computational simulations considering patient-specific geometry.

Development of integrated models incorporating real-time biological VILI parameters along with mechanical variables to adjust model parameters.

Creation of experimental models allowing characterization of the relationship between mechanical parameters and their specific biological response.

Validation of simplified methods to estimate "baby lung" based on lung mechanics parameters accessible at bedside.

6. Conclusions

In summary, the rheological described above explains how the lung, as a viscoelastic body, behaves more like a viscous liquid than an elastic solid when subject to rapid deformations, increasing energy dissipation as heat and structural damage.

Therefore, the rheological model provides a solid theoretical framework to understand VILI mechanisms in ARDS, integrating materials science and thermodynamics concepts. This approach explains why apparently safe ventilatory strategies can cause lung damage, and why interventions like limiting DP, reducing RR, or controlling flow are protective (Table 2).

Clinical application of these concepts suggests that:

1.DP should be maintained below 15 cmH$_2$O to avoid exceeding lung elastic limit.

2.Total MP should be limited to less than 12 J/min, adjusting tidal volume, respiratory rate, and flow.

3.PEEP should be optimized to homogenize parenchyma and prevent stress multiplier formation.

4.Inspiratory and expiratory flow control can reduce strain rate and minimize viscous component of lung damage.

5.In patients with spontaneous breathing, the additional effect of respiratory effort on total mechanical power should be considered, justifying muscle relaxant use in the most severe phases of disease.

Table 2. Ventilatory strategy based on rheological model to prevent ventilator-induced lung injury (VILI) in acute respiratory distress syndrome (ARDS).

FRC: functional residual capacity; Pplat: plateau pressure; PEEP: positive end-espiratory pressure; J: Joules.

Parameter	Recommendation	Rheological Justification
Driving pressure (DP)	< 15 cmH$_2$O	Maintains strain < 1 (elastic limit)
Tidal volume	Adjusted for DP < 15 cmH$_2$O Adjusted for Pplat = 28-32 cmH$_2$O	Limits stress and strain
PEEP	PEEP titration to maximize homogeneity and recover pulmonary FRC	Reduces stress multipliers Reduces strain Reduces strain rate
Respiratory rate	Lowest possible allowing adequate ventilation	Limits mechanical power
Inspiratory flow	Moderate, avoiding high peaks	Reduces strain rate
Mechanical power	< 12 J/min	Below injury threshold
Inspiratory time	Prolonged (lower flow)	Reduces strain rate
Flow pattern	Constant and square	Optimizes stress distribution Decreases strain rate
Expiratory flow control	Consider if available	Reduces expiratory strain rate

Finally, this model offers a more solid scientific basis for developing personalized ventilatory strategies and could guide future research on ARDS prevention and treatment.

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