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Barotrauma: The statistical fallacy. A non-conventional scoping review with Bayesian meta-analysis

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Abstract

Background
Mechanical ventilator-associated damage has a high relevance in the clinical outcomes of critically ill patients. Barotrauma is a colloquial premise that has not been questioned, while other concepts such as mechanotransduction based on time-dependent viscoelastic models derived from materials engineering and physics appear as a more solid and clinically plausible postulate. This scoping review aims to provide a hypothesis that correlates lung injury associated with mechanical ventilation with dynamic ventilatory variables and inherent energy transfer.
Methods
Systematic review and Bayesian meta-analysis PubMed database was searched from inception to November 20, 2024, for studies providing ventilatory parameters collected from ICU admission. The quality of the studies was independently assessed using the RoB2 Cochrane tool.
Results
A total of 7 studies were included for a total of 4298 patients. Of the total sample, 6.6% exhibited pneumothorax, with a mean peak inspiratory pressure of 35.1 cmH_2O and 26.2 cmH_2O plateau pressure. There was no correlation with any ventilatory mode, while mechanical power presented a poor negative correlation with barotrauma. The variables that presented the highest correlation with barotrauma were respiratory rate, driving pressure and elastic static power.
Conclusions
Available data show that, dynamic variables such as respiratory rate, in combination with static variables such as driving pressure, could comprehensively explain the concept of lung injury associated with mechanical ventilation, giving rise to more complex hypotheses such as mechanotransduction and rendering barotrauma as an obsolete premises.

Keywords: barotrauma, VALI, mechanical ventilation, energy transfer

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Introduction

Barotrauma is a hypothesis that states that the damage associated with mechanical ventilator (VALI), [1] defined as acute lung injury associated with inappropriate mechanical ventilator settings, is generated when lung tissue is exposed to high airway pressures. Barotrauma includes pneumomediastinum, pneumothorax, pneumoperitoneum, pneumatocele and/or subcutaneous emphysema. In 1994, through the official announcement of the Consensus on Mechanical Ventilation, Slutsky, [2] stated that at a plateau pressure (Pplat) ≥ 35 cmH_2O the tidal volume (V_T) could be decreased even below 5 ml/kg or less. This is likely to be the onset of elevated pressure restriction. This injury, [3] could worsen morbidity and mortality outcomes in critically ill patients, and even in patients without acute pulmonary pathology.

It is possible that the first descriptions of barotrauma date back to 1974, when Webb and Tierney, [4] in an experimental model with smaller animals and by bronchoalveolar lavage showed that those animals that received airway pressures up to 45 cmH_2O presented perivascular and alveolar edema.

Considering that the lung parenchyma behaves as a viscoelastic material, if the strain rate of the deformation exceeds the limit of resilience [5] of the tissue, an anisotropic state will be generated as a consequence of repetitive stress. [6,7] This underlies the mechanical stress resulting from strain and its rate of change in relation to time. [8] The final consequence will then be the rupture of the pulmonary cytoskeleton [9] and subsequent inflammatory response, giving rise to the premise of energy transfer or mechanotransduction. [10]

It is hypothesized that barotrauma is an inadequate concept, that pulmonary injury is not due to elevated airway pressures, and instead is based on rheological principles applied to viscoelastic behavior and subsequent pulmonary microbiological response. The objective of this review is to analyze and deconstruct the evidence supporting the concept of barotrauma.

Methods

This revision was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-Scr). [11] We aimed to study barotrauma (pneumothorax) based on respiratory mechanics and ventilation settings reported in adult critically ill patients undergoing invasive mechanical ventilation in ICUs.

Search strategy and literature source

The research team developed an extensive list of possible search terms in MEDLINE. Subsequently, a search protocol was created for the aforementioned electronic database. The search combined an extensive list of titles and keywords for the concepts: critical care, critical illness, artificial respiration, mechanical ventilation, barotrauma, pneumothorax as free terms and MeSH terms delimited by study population, intervention and study type defined by strategy P (population) E (exposure) C (comparison) O (outcome) S (type of studies). The search was conducted until November 20, 2024 using the following strategy: [(“barotrauma”[MeSH Terms] or “pneumothorax”[MeSH Terms]) and “respiration, artificial”[MeSH Terms] and (“critical illness”[MeSH Terms] or “critical care”[MeSH Terms] or “critical ill*”[Title/Abstract])]

Study selection criteria

The criteria used for study inclusion were:
P: Critically ill patients hospitalized in intensive care Units.
E: Invasive mechanical ventilation: volume and pressure control.
C: Not applicable
O: Barotrauma, pneumothorax
S: Studies with high quality designs (analytical observational, randomized clinical trials, systematic reviews) were chosen.

Exclusion criteria were:
- Studies in which the sample does not meet the inclusion criteria.
- Studies in which the sample does not include the related clinical outcomes
- Studies of low methodological quality
- Incomplete studies
- Studies with subjects on invasive mechanical ventilation with ventilatory modes other than those mentioned in the inclusion criteria, or subjects on non-invasive mechanical ventilation.
- Studies in the pediatric population

Quality of the studies

Two authors (AF-C, VV) independently assessed the quality of the randomized clinical trial studies (RCT) using the RoB2 Cochrane Tool. [12] A third author (PS) resolved discrepancies at any stage.

Data extraction, synthesis and analysis

The two reviewers (AM and PS) performed an a priori table, which consists of predefined data elements for extraction that inform the state of the art on the incidence of barotrauma. One reviewer (AF-C) extracted half of the data from the original search; a second reviewer (VV) independently verified these data. The other half of the data was independently extracted by two authors (RL-L and VP-C) and reviewed by a second reviewer (AG). Discrepancies

were resolved by discussion with the third reviewer (AF-C).

Statistical analysis
STATA v.18 (StatsCorp, College Station, TX, USA) was used for data analysis.

This study does not involve human subjects, so it was not submitted to the Ethics and Scientific Committee for approval.

Comparisons were made using contingency tables derived from Bayesian linear regression, implemented with the Metropolis-Hastings (MH) adaptive algorithm. A priori informative distributions were used to calculate the covariance of a multivariate normal distribution, applying the Laplace-Metropolis approximation. Results were expressed through Bayes Factors (BF) and were obtained by comparing the Volume Control model with the Pressure Control model. For all models, we considered an acceptance rate of over 20% for the convergence of Markov Chain Monte Carlo (MCMC) iterations and an efficiency of over 10% for the MH algorithm as satisfactory.

For the main aim, by means of factor analysis of the ventilatory variables and the different power equations, we used the barotrauma variable as a construct and performed an estimation by the maximum likelihood method, assuming a representative sample given multivariate normality. Subsequently, the Kaiser-Meyer-Olkin and Bartlett test were used to ensure the adequacy of the data before exploratory factor analysis (EFA) and the number of factors was explored with parallel analysis (sedimentation). The EFA was performed using oblique rotation. Subsequently, confirmatory factor analysis (CFA) was performed using the least squares estimator. After identifying the principal components, validation was performed using structural equation modeling (unidirectional). The absolute fit indicators most frequently used in research were used because none of the independent variables, individually, provides the necessary information to evaluate a model. These indicators were Chi^2 (not significant), root mean squares error approximation index (RMSEA) < 0.080, square root mean residuals index (SRMR) < 0.080, the comparative fit index (CFI) > 0.90, which compares the estimated model with the null model indicating independence between the variables studied and the Tucker-Lewis index (TLI) > 0.90. For the reliability analysis, internal consistency was considered with Cronbach's Alpha coefficient (> 0.5).

To confirm the first point, and considering barotrauma/pneumothorax as the response variable, multiple Bayesian linear regression modeling was performed with a priori informative Beta-binomial models by adaptive algorithm (MCMC sample size = 10,000, Burn-in: 2,500, Random-walk Metropolis-Hastings's sampling) using previously published data (means and variances) of ventilatory parameters. [RR, [7] Pplat, [13] V_T, [14] DP [15]] as predictor variables in the models. The correlation between the two variables is presented using the model with the highest parsimonious convergence, and the results are presented as a posteriori means with their respective 95% credible intervals (Cred. Interval).

Multiple a priori informative Bayesian Beta-binomial linear regression models were also explored. (MCMC sample size = 10.000, Burn-in:2.500, Random-walk Metropolis-Hastings's sampling) for barotrauma as the dependent variable, and as independent variables we use the power equations [Mechanical power Gattinoni's equation ($MP_{Gattinoni}$), [16] Elastic static power (ESP) [8], Elastic dynamic power (EDP), [17] Total elastic power (TEP), Resistive power (RP) [18]] to determine their association. Likewise, the correlation between both variables is presented using the model of greatest parsimonious convergence, and the results are presented as a posteriori means with their respective 95% credible intervals (Cred. Interval).

Results

The search strategy initially identified 57 potentially relevant studies. After removing duplicate studies, the titles and abstracts of 40 studies were analyzed, of which 16 were excluded. Among the 24 studies that underwent full review, 6 were categorized as not relevant, 5 of them contained irrelevant information, and 6 of them included patients with noninvasive ventilation. After screening (Figure 1), a total of 7 studies were analyzed. [14,16,19–23]
The studies were divided into 13 subgroups according to the methodology of each study: recruitment maneuvers vs conservative PEEP, high V_T vs low V_T, volume control vs pressure control, except for the study corresponding to the systematic review (COVID-19 patients) which was not divided into subgroups. for a total of 4298 study subjects.

Of the sample, 76.9% corresponded to randomized clinical trials, while 15.4% corresponded to a cross-sectional study, and 7.7% to a systematic review with meta-analysis. Figure 2 reports the quality of the selected studies (RCT) using the Cochrane RoB2 tool.

In the descriptive analysis, 6.6% (SD 4.1%) of the total sample presented pneumothorax, while 8.1% (SD 4%) did so in volume control (VC), and 3.5% (SD 2%) did so in pressure control (PC) (BF_{10}=19.8). Likewise, a mechanical power (MP) of 32.8 J/min (SD 10.7) was found for VC, and 37.5 J/min (SD 13.6) for PC. For the total sample, a mean of 15.6 cmH_2O (SD 4) for driving pressure (DP), 24.2 bpm (SD 4.5) for respiratory rate (RR), 26.2 cmH_2O (SD 4.2) for plateau pressure (Pplat), 10.6 cmH_2O (SD 2.1) for PEEP and 512.2

ml/kg (SD 100.6) for tidal volume (V_T) were found. The rest of the variables are shown in Table 1.

In the factor analysis with the matrix including all ventilatory variables (P < 0.001; Bartlett test and KMO 0.5), we found 2 factors relevant to the construct (Factor 1: Eigenvalue 2.9, Proportion 43%; Factor 2: Eigenvalue 2.1, Proportion 72%). After rotation, we found that Factor 1 presented a variance of 2.7 (Proportion 39%) and a variance of 2.3 (Proportion 33%) for Factor 2, for a total explained variance of 72% for the model. In the confirmatory analysis, we found a variance of 1 (Proportion 50%) for both Factor 1 (Eigenvalue 1.2) and Factor 2 (Eigenvalue 0.8). This model provides a total explained variance of 1. The comparison between both models can be seen in Figure 3.

The structural equation model containing all ventilatory variables showed no significant correlation with barotrauma (P > chi^2: <0.001; RMSEA: 1.7; CFI: 0.008; TLI: -0.38; SRMR: 0.32 ; Alpha: 0.58), and on the contrary showed poor consistency with the construct.

The structural equation model based on the principal components obtained in the factor analysis (Table 2) showed adequate correlation and consistency (P > chi^2: 0.33; RMSEA: 0.00; CFI: 1; TLI: 1.04; SRMR: 0.08; Alpha: 0.84).

Bayesian linear regression modeling corroborated that the variables with the highest a posteriori probability of correlation with barotrauma (pneumothorax) were driving pressure (Mean, 2.97; 95% Credible Interval 1.04 to 6.65) and respiratory rate (Mean, 2.28; 95% Cred. Interval, 0.59 to 5.56). Among the power equations, elastic static power was the variable that showed the highest a posteriori probability of correlation with barotrauma (pneumothorax) (Mean, 2; 95% Cred. Interval, 0.5 to 4.7). The remaining variables are shown in Table 3. This model has an acceptance range of 54%, with an efficiency of 72%.

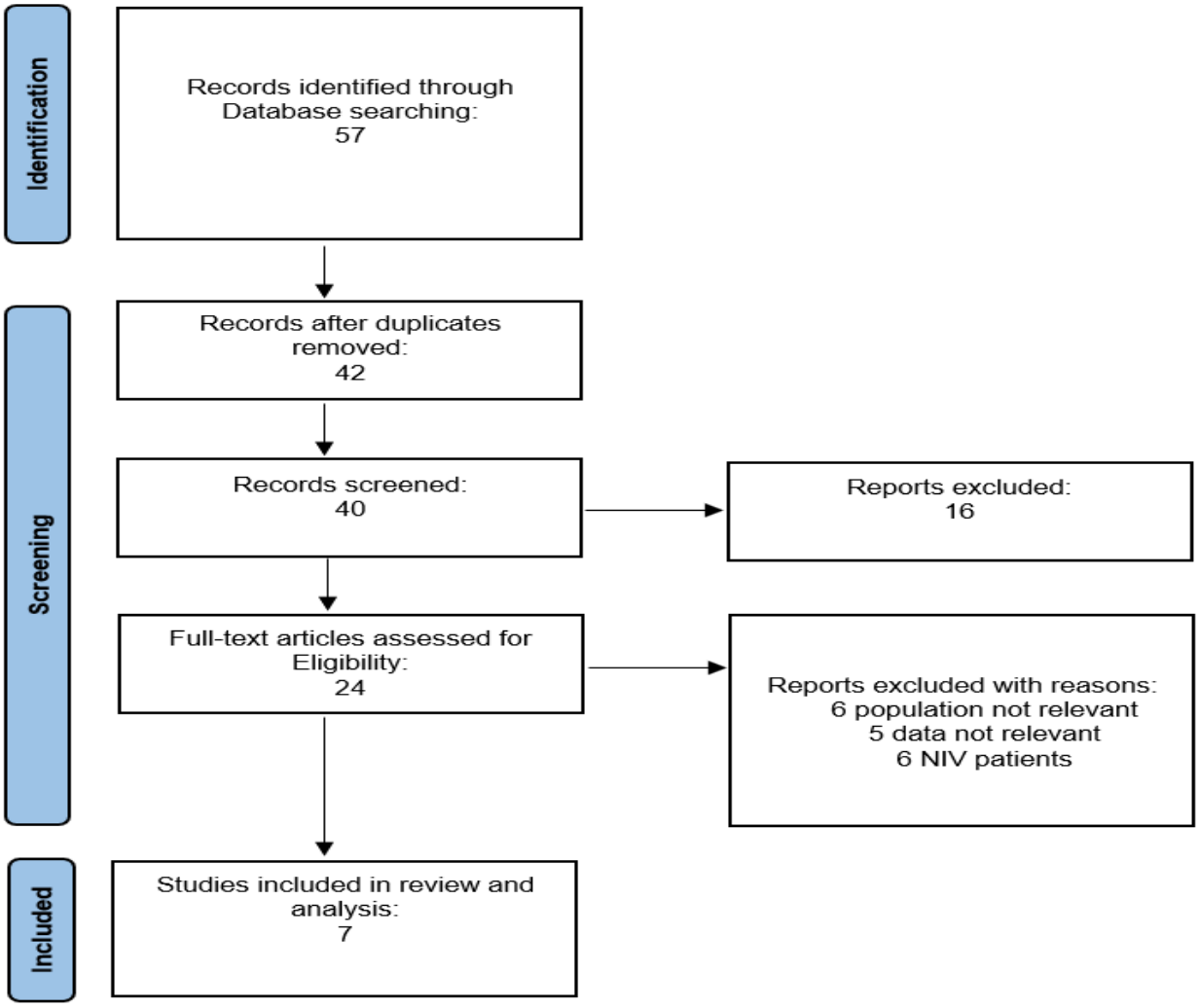

Figure 1: PRISMA Flow diagram of included studies.

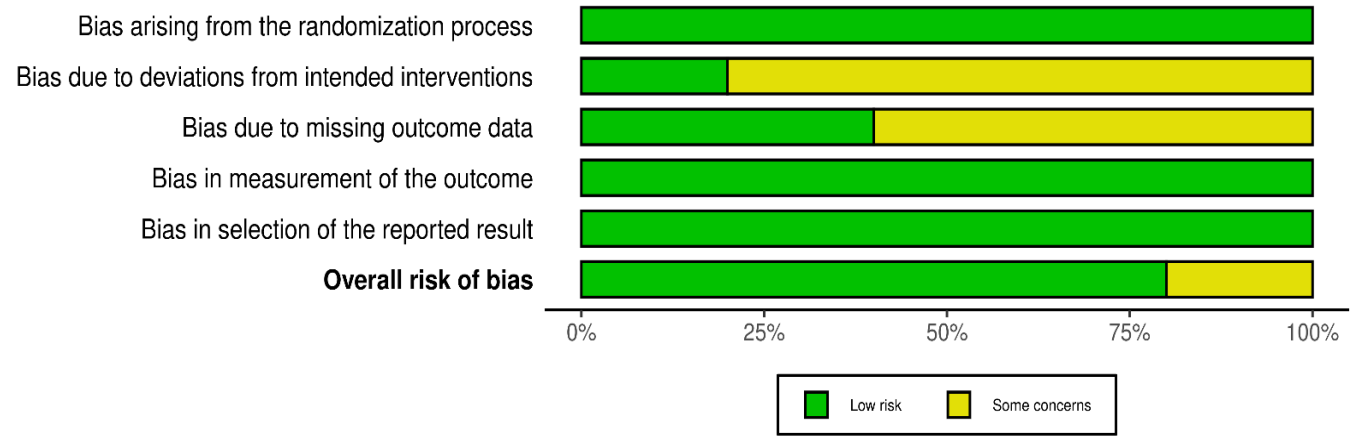

Figure 2: Graph for risk of bias (RCT).

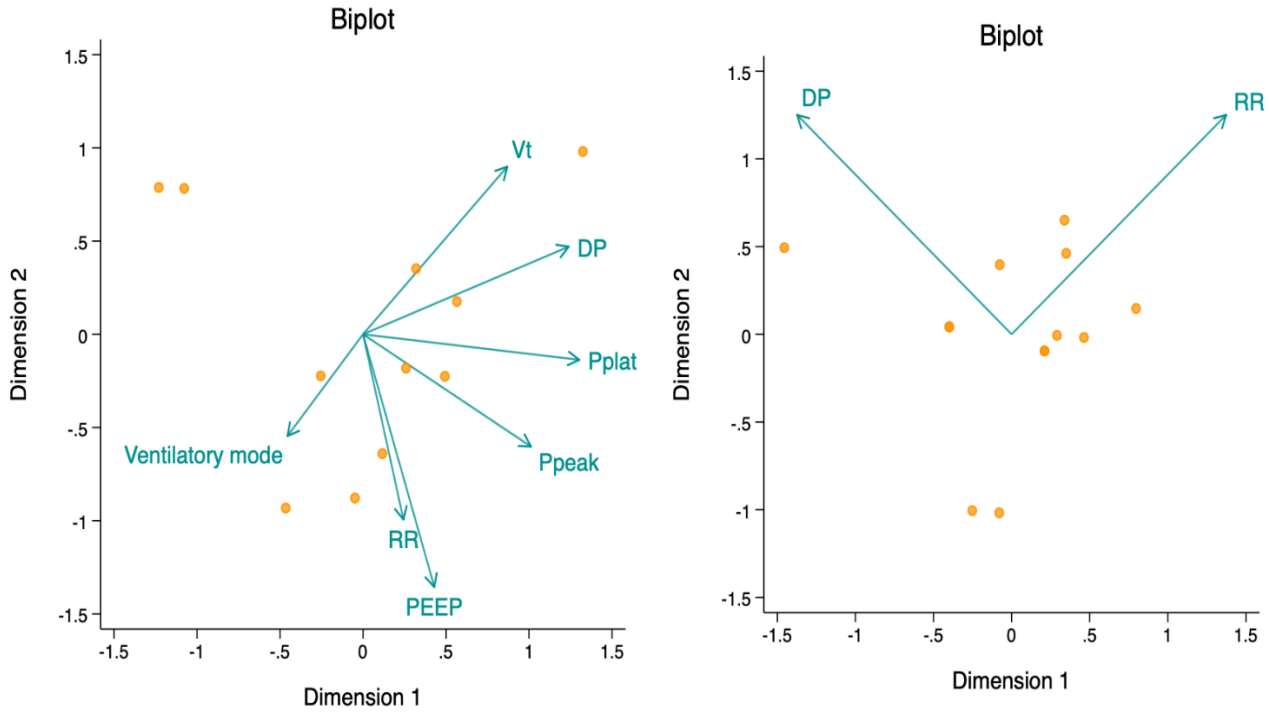

Figure 3 Comparison between the model including all ventilatory variables and the model obtained by factor analysis. RR: respiratory rate; V_T: tidal volume; DP: driving pressure; Pplat: plateau pressure; Ppeak: peak pressure; PEEP: positive end-expiratory pressure, RR: respiratory rate.

Table 1. Baseline: description of different ventilatory variables and power equations according to the ventilatory mode of the patients included in the analyzed studies. Data are presented as means and standard deviation (parenthesis).
BF_{10}: Bayes factor; VTe: expiratory tidal volume, SD: standard deviation. Data are presented as means and standard deviation (parenthesis).

Variables	**Volume** N = 3049	**Pressure** N = 1249	
	Mean (SD)	Mean (SD)	BF_{10}
Respiratory rate (bpm)	24.9 (4.7)	22.8 (4.3)	15.5
Tidal volume (ml)	535.4 (100.1)	-	-
VTe (ml)	-	458.8 (93.3)	-
Peak pressure (cmH_2O)	35.4 (7.1)	34.5 (9.7)	9.5
Plateau pressure (cmH_2O)	26.7 (4.3)	25.2 (4.6)	14.6
PEEP (cmH_2O)	10.4 (1.9)	11 (2.7)	9.5
Driving pressure(cmH_2O)	16.2 (4.4)	14.2 (2.6)	16.6
Pneumothorax (%)	8.1 (4)	3.5 (2)	19.8
Mechanical power (J/min)	32.8 (10.7)	37.5 (13.6)	10.8
Total elastic power (J/min)	24.4 (7.3)	18.8 (6.8)	17.9
Elastic static power (J/min)	13.7 (4.7)	11.4 (4.2)	15.7
Elastic dynamic power (J/min)	10.7 (4)	7.4 (2.9)	15.8
Resistive power (J/min)	10 (5.5)	9.6 (7.6)	6.8

Table 2. Structural equation model with the components obtained in the factor analysis. Ventilatory variables are expressed as coefficients, their respective p-value and 95% confidence intervals (Conf. Interval).

Model	**Barotrauma**		
	Coeff	*p*	95% Conf. Interval
Respiratory rate	0.53	< 0.01	0.16 to 0.89
Driving pressure	0.39	0.08	- 0.05 to 0.83

Table 3. Bayesian linear regression analysis of different ventilatory variables and power equations. Ventilatory variables and power equations are expressed as a posteriori means and their respective 95% credible intervals (Cred. Interval).
VCV: volume control ventilation. PEEP and Resistive power equation were omitted due to collinearity.

Variables	**Pneumothorax**	
	Mean	95% Cred. Interval
Respiratory rate	2.28	0.59 to 5.56
Plateau pressure	- 0.52	- 2.02 to 2.12
Driving pressure	2.97	1.04 to 6.65
Tidal volume	- 0.04	- 0.2 to 0.01
Peak pressure	- 0.87	- 3.39 to - 0.05
VCV	- 0.21	- 6.56 to 4.26
Mechanical power	- 0.9	- 1.9 to - 0.4
Elastic static power	2	0.5 to 4.7
Elastic dynamic power	1.1	0.4 to 2.1

Discussion

This non-conventional scoping review offers compelling Bayesian inference that challenges the concept of barotrauma as we know it today. Our complex statistical analyses offer an innovative way to evaluate the data obtained from the retrieved studies. We found no correlation between barotrauma (pneumothorax) and elevated inspiratory pressures in ventilated patients. On the contrary, factor analysis and Bayesian linear regression showed similar data: both agree that both respiratory rate and driving pressure showed high correlation with the response variable. On the other hand, peak pressure showed a very subtle negative correlation (a posteriori Mean, - 0.87; 95% Cred. Interval, -3.39 to -0.05), while ventilatory mode volume control (a posteriori Mean, - 0.21; 95% Cred. Interval, -6.56 to 4.26) showed no correlation with barotrauma.

Among the power equations, surprisingly the MP (a posteriori Mean, - 0.9; 95% Cred. Interval, -1.9 to -0.4) showed a very subtle negative correlation with barotrauma. This is probably due to the fact that in the geometrical-mathematical conception of $MP_{Gattinoni}$, both PEEP and respiratory rate are relegated to a not very important role. On the other side, viscoelastic models give the dynamic component [17] the necessary relevance that allows optimizing the current measurability regarding energy transfer.

The studies included in the analysis were published after 2000, so it is assumed that they include protective settings. This allows us to infer that although mortality in ARDS patients decreased as V_T decreased, the rate of barotrauma remained stationary, and therefore, the decrease in mortality could not be attributed to the decrease of that.

Below we detail two arguments that support the results of our study and refute the barotrauma conception.

Logical argument

A first argument against is the logic that explains that trumpet players such as Louis Armstrong or Arturo Sandoval, who during a concert of more than one hour, have never exhibited barotrauma. Bouhuys, [24] by means of an experiment with musicians of noble metal wind instruments, he designed a volumetric device adapted to a spirometer to measure the pulmonary capacities subjected to very high pressures during the use of these instruments. This author recorded by means of a diagram both the pressures and the maximum expiratory and inspiratory volumes. The three instruments tested have sufficient resistance to be overcomed to achieve effective sound. In this diagram, for the flutist an airway pressure of 50 cmH_2O was recorded, while for the trumpet player an astonishing 150 cmH_2O was recorded. None of the musicians exhibited related secondary events. Likewise, in 1994, Fiz et al [25] also performed a physiological study comparing trumpet players with healthy non-smoking subjects as a control group and found spirometric differences in favor of the trumpet player group. Maximal respiratory pressures (PImax 151.3 cmH_2O, PEmax 234.6 cmH_2O) were higher in the trumpeter group ($F = 47.49$; $P < 0.001$ for PImax; $F = 7.83$, $P < 0.01$ for PEmax). Those findings were attributed to the respiratory muscle training demanded by the practice of these musicians. Again, no related secondary events were reported.

Schorr-Lesnick et al. [26] compared spirometric values among 113 musicians including percussionists, wind players and vocalists, and found no significant differences in peak inspiratory pressures, nor did they report incidences related to barotrauma. Similar findings were found in a study by Akgün N et al. [27] which included 99 wind players members of a Turkish orchestra, who showed increased levels of FEV_1 and FEF_{50}. Again, no barotrauma-related events were reported.

Clinical argument

In 1992, Gammon et al. [28] evaluated through a longitudinal study the incidence of barotrauma in 139 patients with invasive mechanical ventilation (128 on mandatory ventilation and 11 on intermittent mandatory ventilation), of whom 35% presented with pneumothorax or pneumomediastinum and 21% had acute respiratory distress syndrome (ARDS). In the group of patients with ARDS who exhibited barotrauma, although it was associated with an increase in peak inspiratory pressure values (59 cmH_2O vs 44 cmH_2O), it was also associated with different levels of PEEP (10 cmH_2O vs 3 cmH_2O) and respiratory rate (27 bpm vs 21 bpm). Since neither Pplat values nor flow values were reported, it was not possible to calculate driving pressure or MP as a reference point for both static and dynamic safe limits.

However, to obtain a potential safe limit, we calculated the elastic static power (ESP) [8] and found that the group of those subjects in which barotrauma was reported had an ESP of 22.9 J/min, while in the group of those who did not exhibit barotrauma, as well as that group that did not have ARDS the ESP values remained within safe ranges (5.5 J/min and 4.8 J/min respectively). Due to the design of the ESP calculation ($0.098 \times V_T \times RR \times PEEP$), we can infer that probably the complications attributed to the so-called barotrauma were not necessarily generated from high airway pressures. On the contrary, they could very likely be attributed to the viscoelastic threshold of the pulmonary parenchyma having been exceeded. [29]

Anzueto et al. [30] in their analysis used an airway pressure of up to 50 cmH_2O and Pplat ≥ 35 cmH_2O as a cut-off point and reported that only 2.9% of patients on invasive mechanical ventilation (IMV) presented barotrauma. The most relevant risk factor in these patients was the presence of previous pulmonary pathologies (COPD, pulmonary fibrosis, interstitial lung diseases). This outcome occurred mainly during the first 3.4 days (SD 4.2) of ventilatory support, which corresponds to 0.52 cases per 1000 days of mechanical ventilation. Likewise, they reported a crude mortality of 51.4%, which corresponds to an absolute attributable risk of 12.2% (95% CI: 0.9 to 23.4; P = 0.04).

Regarding PEEP levels, surprisingly, those who had lower PEEP levels were those who presented a higher incidence of barotrauma (110 patients; 71.4%) while in those who used PEEP levels > 15 cmH_2O, only 2 of them (1.3%) exhibited barotrauma. In those patients in whom 9 to 12 ml/kg of V_T was used, 124 patients (80.5%) presented barotrauma.

Finally, the pathology most associated with the development of barotrauma was having had previous ARDS (RR 2.70; 95% CI: 1.55 to 4.70; P < 0.001) but also having had ARDS during ventilatory support (RR 2.53; 95% CI: 1.40 to 4.57; P = 0.002). In the multivariate analysis, the pathology least associated with barotrauma was asthma (RR 2.58; 95% CI: 1.02 to 6.51; P = 0.04). This study, which dates from 2004, does not report important data such as respiratory frequency, ventilatory mode, does not declare elastic or resistive properties of its patients, and finally, there are no important static variables such as flow or DP, nor dynamic variables such as respiratory rate.

In the ARDS Network study, [19] a similar incidence of barotrauma is mentioned for both the group receiving low V_T and those receiving “traditional” V_T (10 and 11% respectively). The authors state that in their results they found that the incidence of barotrauma was independent of the level of airway pressures, and even that its main manifestation (pneumothorax) was probably mainly due to invasive procedures (central venous catheter). In this study, the control group could reach Pplat up to 50 cmH_2O, while the intervention group up to a maximum of 30 cmH_2O. Therefore, potentially up to 67% more airway pressure could be estimated, and despite this, the incidence of pneumothorax remained constant.

In a recent systematic review with meta-analysis [31] of patients with COVID-19, only two studies reported incidence of barotrauma (OR, 3.31; 95% CI, 0.66 to 16.65, I2; 83.95%). However, 52.8% required IMV, while 42.6% developed barotrauma on noninvasive ventilation and even on oxygen therapy. From the point of view of pulmonary viscoelastic behavior, these findings are relevant to our results, since the outcome had little or nothing to do with the need for invasive ventilation or with high airway pressures, and on the contrary, there was an association with high respiratory rates and increased ventilatory work, which could be secondary to patient self-induced lung injury (P-SILI). [32]

Finally, analyzing the iconic work of Amato et al. [15] we conclude that higher plateau pressures are not necessarily associated with a higher risk of VALI, just as higher PEEP levels may not necessarily be considered protective.

Our review has important strengths. To the best of our knowledge, this is the first scoping review to analyze the correlation between ventilatory variables and power equations with the incidence of barotrauma. We used predefined inclusion and exclusion criteria and followed the PRISMA ScR checklist to ensure consistency in reviewer agreement, data extraction, and synthesis. In addition, our robust statistical analyses provide an interesting, attractive and novel postulate correlating dynamic ventilatory variables with pulmonary injury, based on physical concepts grounded in materials engineering.

This study also has important limitations. Although the risk of bias analysis was low because about 80% of the studies analyzed were randomized clinical trials, the rest of the studies used in the statistical analyses have evidence of different quality and design, which gives heterogeneity. In addition, the search was performed in a single database, and it is likely that many important studies of relevance were left out of this analysis. Among the ventilatory variables studied, flow could not be included because it was not reported in most of the studies analyzed, generating omission bias.

Conclusion

The concept of pulmonary injury associated with inadequate management of mechanical ventilator settings is much more complex than the simple association with elevated pressures. The stress (and stress raisers) that determine the heterogeneity of the mechanical vectors related to energy transfer will depend on the indemnity of the resilience of the pulmonary parenchyma at regional level, and even on the pulmonary history of each patient. The damage caused by the cyclicity of the applied stress is directly proportional to the resulting anisotropy and inversely proportional to the resilient viscoelastic capacity. With the level and quality of evidence currently available, when incorporating and applying biophysical concepts in daily practice, it does not seem to have much relevance to maintain theories such as barotrauma as an argument to support the genesis of VALI. More high-quality studies are needed for a correct contextualization of mechanotransduction.

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