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Time to generate ventilator-induced lung injury among mammals with healthy lungs: a unifying hypothesis

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Abstract Purpose: To investigate ventilator-induced lung injury (VILI), several experimental models were designed including different mammalian species and ventilator settings, leading to a large variability in the observed time-course and injury severity. We hypothesized that the time-course of VILI may be fully explained from a single perspective when considering the insult actually applied, i.e. lung stress and strain. **Methods:** Studies in which healthy animals were aggressively ventilated until preterminal VILI were selected via a Medline search. Data on morphology, ventilator settings, respiratory function and duration of ventilation were derived. For each animal group, lung stress (transpulmonary pressure) and strain (end-inspiratory lung inflation/lung resting volume ratio) were estimated. **Results:** From the Medline search 20 studies including five mammalian species (sheep, pigs, rabbits, rats,

mice) were selected. Time to achieve preterminal VILI varied widely (18–2,784 min), did not correlate with either tidal volume (expressed in relation to body weight) or airway pressure applied, but was weakly associated with lung stress ($r^2 = 0.25$, $p = 0.008$). In contrast, the duration of mechanical ventilation was closely correlated with both lung strain ($r^2 = 0.85$, $p < 0.0001$) and lung strain weighted for the actual time of application during each breath ($r^2 = 0.83$, $p < 0.0001$), according to exponential decay functions. When it was normalized for the lung strain applied, larger species showed a greater resistance to VILI than smaller species (medians, 25th–75th percentiles: 690, 460–2,001 min vs. 16, 4–59 min, respectively; $p < 0.001$). **Conclusion:** Lung strain may play a critical role as a unifying rule describing the development of VILI among mammals with healthy lungs.

Keywords Ventilator-induced lung injury · Mechanical ventilation · Lung stress · Lung strain · Comparative physiology

Introduction

Although during respiratory failure mechanical ventilation is essential for the maintenance of respiratory

function, it has been unequivocally observed to be associated with deterioration of the underlying lung injury [1]. Hence, the existence of a lung injury directly caused by aggressive ventilation, i.e. ventilator-induced lung injury

(VILI), has constantly accompanied the development of ventilation over the past 30 years [1–3]. Although most of the information available has been obtained in experimental settings, the clinical relevance of VILI has been clearly demonstrated in patients affected by acute respiratory distress syndrome (ARDS), in which a more “gentle” ventilation has been shown to improve survival [4]. Nonetheless, when looking at the bulk of data available on VILI, a large variability in the findings observed and in the experimental models employed (mammalian species, ventilatory setting, severity of VILI) appears to hinder direct comparison between different studies, thereby weakening the solidity of the information obtained. Apparently, no unique rule has been proposed so far to potentially unify all the information obtained from a single and comprehensive perspective.

Traditionally VILI has been considered to be strictly related, among other mechanisms [5–8], to the application of excessive airway pressure (barotrauma) [2, 9, 10] and excessive tidal volume (V_T , volutrauma) [11]. More recently, two different parameters describing the mechanical insult associated with ventilation have been proposed as actual determinants of VILI: lung stress, defined as the pressure developing within the lung fibrous skeleton, which equals the applied transpulmonary pressure [12], and lung strain, defined as the ratio between the lung volume variation (due to both V_T and positive end-expiratory pressure, PEEP) and the lung resting volume [13]. In ARDS, we have recently shown that both V_T expressed in relation to body weight and the airway pressure applied are “inadequate surrogates” for the evaluation of the actual lung stress and strain applied, due to a large variability in lung resting volume (functional residual capacity, FRC) and in chest wall mechanics [14]. Moreover, we have recently reported [15] that different mechanisms, such as the intratidal lung opening and closing, may be responsible for the lung injury associated with ventilation in ALI/ARDS, therefore questioning direct translation to humans of findings obtained from experimental settings regarding the role of an excessive V_T and airway pressure.

We hypothesized that only the extent of the maximal stress and strain actually applied may fully explain the time-course of the development of VILI among different species, providing a unique rule describing this phenomenon. To test this hypothesis, by retrospectively analysing data available in the literature, and keeping constant the type of injury considered (end-stage respiratory insufficiency), we investigated the possible relationship between the time to achieve preterminal VILI and the degree (and type) of the insult applied in *in vivo* models of healthy animals of different mammalian species.

Materials and methods

Data selection

From a Medline search, updated until November 2009, articles on healthy animals ventilated until the achievement of

preterminal lung injury were selected. Such injury, denoting a degree of VILI incompatible with survival, was defined as the occurrence of at least one death explicitly related to ventilation, or the development of at least one of the following pathological conditions, as constantly associated with imminent death: a decrease in the ratio between arterial partial pressure of oxygen (P_aO_2) and inspiratory oxygen fraction (F_iO_2) below 200, an increase in respiratory system elastance greater than 150%, and the presence of lung oedema as shown by an increase in either wet-to-dry ratio or extravascular lung water greater than 150%. As the application of a relatively high degree of PEEP is commonly considered protective against VILI [2, 3, 16], we arbitrarily excluded articles in which a PEEP value greater than 7 cmH₂O was applied, or articles (or groups of animals) in which the role of PEEP was specifically investigated. We defined as “VILI groups” animals ventilated until the achievement of pre-terminal lung injury, and as “control groups” animals ventilated without the achievement of such injury.

Morphometric, ventilatory setting and respiratory function data

From the selected articles, morphometric data from the different animal species employed were obtained. Similarly, data on the type of ventilation, as well as data on V_T , airway pressure, PEEP, respiratory rate, inspiratory to expiratory ratio, P_aO_2 , F_iO_2 , and respiratory system compliance were obtained from the selected articles. Duration of mechanical ventilation was defined as the average time until the achievement of preterminal lung injury for animals included in the VILI groups, while it equalled the time of exposure to mechanical ventilation for animals included in the control groups.

Calculation of maximal lung stress and strain

Maximal pulmonary stress, i.e. the maximal transpulmonary pressure applied at end-inspiration, was estimated based upon data on the airway pressure recorded and measurements of partitioned respiratory mechanics for each species, as direct data on pleural pressures were not available [13]:

$$\text{Lung stress} = \text{Airway pressure} \times \left(\frac{\text{Elastance}_{\text{Lung}}}{\text{Elastance}_{\text{Total}}} \right)_{[\text{species}]} \quad (1.1)$$

where “Airway pressure” denotes peak airway pressure (or plateau airway pressure), and “ $\left(\frac{\text{Elastance}_{\text{Lung}}}{\text{Elastance}_{\text{Total}}} \right)_{[\text{species}]}$ ” denotes the ratio between the lung elastance and total elastance of the respiratory system characterizing each species.

Maximal lung strain, i.e. the lung strain resulting at end-inspiration, was estimated as previously reported

[13], assuming a monoalveolar lung model, thereby not taking into account possible dishomogeneities developing during inflation:

$$\text{Lung strain} = (V_T + \text{PEEP volume})/\text{FRC} \quad (1.2)$$

where V_T denotes the V_T applied, and “PEEP volume” the inflated lung volume due to the PEEP applied.

Finally, the average strain applied to the lung during each breath was calculated according to the inspiratory–expiratory time ratio:

$$\text{Weighted lung strain} = [(V_T + \text{PEEP volume})/\text{FRC} \\ \times T_{\text{insp}} + (\text{PEEP volume}/\text{FRC}) \times T_{\text{exp}}]/(T_{\text{insp}} + T_{\text{exp}})$$

where V_T denotes the V_T applied, PEEP volume the inflated lung volume due to the applied PEEP, T_{insp} the inspiratory time of each tidal breath, and T_{exp} denotes the expiratory time of each tidal breath.

Statistical analysis

The relationships between the duration of mechanical ventilation and different ventilatory parameters were analysed by applying the following exponential equation: $y = a \times \exp(-b \times x)$, where y equals the duration of mechanical ventilation, and x the ventilator parameter tested. Statistical significance was defined as $p < 0.05$. All data are expressed as means \pm SD, unless otherwise indicated.

Additional details on the methods employed and the analyses performed are provided in the Electronic supplementary material.

Results

Paper selection and study population

From the Medline search 20 original papers were selected for analysis (see Table 1, as well as Tables 2 and 3 in the Electronic supplementary material). From this selection we were able to include five different mammalian species (sheep, pigs, rabbits, rats and mice). As expected, body weight varied widely across the species considered, ranging from 0.023 kg (mice) to 29.9 kg (sheep). Of note, time to achieve preterminal lung injury during mechanical ventilation was markedly variable among the different studies, ranging from 18 to 2,784 min.

Classical predictors of VILI: tidal volume and airway pressure

As shown in Fig. 1a, in animals included in VILI groups, no relationship was observed between the V_T applied and the duration of mechanical ventilation recorded ($p = 0.73$).

Moreover, the V_T applied in animals of control groups appeared to markedly overlap that applied in VILI groups. Similarly, no association was observed between the airway pressure applied and the duration of mechanical ventilation in the overall population of mammalian species ($p = 0.21$, Fig. 1b).

Novel predictors of VILI: maximal lung stress and lung strain

Among animals included in the VILI groups, maximal lung stress was inversely correlated with the duration of mechanical ventilation (see Fig. 1 in the Electronic supplementary material) according to an exponential decay function, although the relationship did not appear to be highly accurate ($r^2 = 0.25$, $p = 0.008$). In contrast, the duration of mechanical ventilation appeared to be closely and inversely correlated with the maximal lung strain applied ($r^2 = 0.85$, $p < 0.0001$; Fig. 2). Of note, data from animals included in the control groups appeared to be shifted mostly leftward and downward as compared to the relationship observed in the VILI groups, suggesting the importance of a threshold limit of time and strain for the development of preterminal VILI. Moreover, when considering lung strain weighted for the actual time of application during each tidal breath (see Table 4 in the Electronic supplementary material), a similar relationship was observed ($r^2 = 0.83$, $p < 0.0001$; Fig. 3), although there was a greater separation between animals ventilated with a lung strain greater than 2.0, in which the development of preterminal injury appeared to be almost immediate, and animals ventilated with a lung strain below 1.5, in which the time to achieve VILI exponentially increased with the decrease of lung strain. Finally, when the duration of mechanical ventilation was normalized for either the maximal lung stress or lung strain applied, larger animals showed a greater resistance to the development of VILI than smaller species (medians, 25th–75th percentiles:: 46, 36–135 vs. 2, 1–9 min/cmH₂O, for lung stress, respectively; $p < 0.001$; see Fig. 3 in the Electronic supplementary material; and 690, 460–2,001 vs. 16, 4–59 min for lung strain, respectively; $p < 0.0001$; Fig. 4).

Discussion

When a mechanical force is applied to a material, two phenomena occur as a reaction to the insult applied: generation of a pressure with equal intensity and opposite sign to the one actually applied, defined as “stress”, and, if the material is deformable enough, modification of its resting shape, defined as “strain” [13]. If we consider the pulmonary fibrous skeleton as the material stressed during

Table 1 Study population (VILI group)

First author [Reference]	Species	Group name ^a	Sample size (no. of animals)	Body weight (kg)	V_T /kg body weight (ml/kg)	FRC (ml)	Paw (cmH ₂ O) ^b	Lung stress (cmH ₂ O)	Lung strain	Time to preterminal lung injury (min)
Kolobow [10]	Sheep ^c	B	7	26.00	58.9	643 ^e	50.0	31.5	2.73	1,440
Tsuno [27]	Sheep ^c	B	8	29.90	22.0	833 ^e	30.0	18.9	1.16	2,784
Tsuno [27]	Sheep ^c	C	11	29.90	30.8	703 ^e	30.0	18.9	1.32	2,472
Mandava [20]	Sheep ^c	–	11	23.00	49.9	640 ^e	50.0	31.5	2.76	720
Tsuno [28]	Pigs ^c	B	11	3.72	52.0	114 ^f	40.0	32.6	1.91	1,320
Sinclair [29]	Rabbits ^d	Eucapnia	6	3.30	25.0	25.8 ^f	30	18.3	3.20	240
Webb [2]	Rats ^d	HIPPB _{45/0}	6	0.230	43.9	1.73 ^f	45.0	35.6	5.83	25
Dreyfuss [9]	Rats ^c	g4	8	0.323	40.0	2.43 ^f	45.0	35.6	5.31	20
Dreyfuss [11]	Rats ^c	HiP-HiV	6	0.300	40.0	2.26 ^f	45.0	35.6	5.31	20
Dreyfuss [11]	Rats ^c	LoP-HiV	7	0.300	44.0	2.26 ^f	Negative	–	5.85	20
Sibilla [30]	Rats ^d	g1	9	0.257	34.6	1.93 ^f	56.2	44.4	5.52	39
Sibilla [30]	Rats ^d	g2	9	0.257	32.5	1.93 ^f	43.1	34.1	4.96	79
Sibilla [30]	Rats ^d	g3	6	0.257	18.8	1.93 ^f	34.7	27.4	4.01	253
Casetti [31]	Rats ^c	iT = 1.0	10	0.350	51.5	2.63 ^f	45.0	35.6	6.84	30
Casetti [31]	Rats ^c	iT = 1.5	10	0.350	49.0	2.63 ^f	45.0	35.6	6.51	30
Valenza [32]	Rats ^d	ZEEP	5	0.235	42.0	1.77 ^f	42.8	33.8	5.58	18
Valenza [32]	Rats ^d	PEEP 3	5	0.235	34.0	1.77 ^f	43.5	34.4	5.27	55
Valenza [32]	Rats ^d	PEEP 6	5	0.235	25.0	1.77 ^f	46.2	36.5	5.07	60
Walder [33]	Rats ^d	g4	8	0.300	36.0	2.26 ^f	29.7	23.5	5.32	338
Walder [33]	Rats ^d	g5	6	0.300	45.0	2.26 ^f	35.7	28.2	6.51	290
Valenza [34]	Rats ^d	Supine	15	0.262	34.3	1.97 ^f	28.8	22.8	4.56	73
DiRocco [35]	Rats ^d	VILI	6	0.425	28.2	3.20 ^f	40.0	31.6	3.75	78
Moriondo [36]	Rats ^d	MV-4	5	0.345	32.0	2.60 ^f	60.3	47.7	4.58	105
Villar [37]	Rats ^d	HTV	20	0.325	20.0	2.66 ^f	25.0	19.8	2.66	240
Wilson [38]	Mice ^d	g1	12	0.0270	34.5	0.36 ^f	39.0	34.0	2.57	156
Caironi [21]	Mice ^d	HVt WT	15	0.0234	30.0	0.31 ^f	21.9	19.1	2.38	540
Wilson [39]	Mice ^d	WT	11	0.0292	38.5	0.39 ^f	45.5	39.6	2.87	105
Pedreira [40]	Mice ^d	Vehicle _{PIP25}	8	0.0350	30.5	0.47 ^f	25.0	21.8	2.27	120

^a Name of the animal group included in the current analysis as reported in the original publication

^b Airway pressure applied (either peak or plateau airway pressure, if during pressure-controlled ventilation)

^c Ventilated in pressure-controlled mechanical ventilation

^d Ventilated in volume-controlled mechanical ventilation

^e Values directly measured by the investigators and explicitly reported in the original publication

^f Values estimated from physiological studies in healthy animals of the same species, as described in the “Materials and methods”

ventilation and the lung parenchyma as homogeneously inflating during inspiration, lung stress equals the pressure actually applied to the lung parenchyma, i.e. the trans-pulmonary pressure, and lung strain equals the ratio between the end-inspiratory inflated volume and the lung resting volume, i.e. FRC [13]. Both lung stress and strain have been recently investigated as possible parameters to quantify the mechanical insult commencing the entire cascade of VILI, whether is deemed to be either an inflammatory or a pure mechanical process (or a combination of the two) [14, 17]. Considering V_T as the most commonly employed parameter in experimental VILI, we did not observe any correlation between the time to achieve preterminal lung injury and the V_T /kg body weight applied, while a strict and exponential correlation was observed between the duration of mechanical ventilation and lung strain. It is, however, worth noting that the use of V_T /kg body weight as a surrogate for lung strain holds true only if FRC is linearly correlated with body mass among different mammals. Unfortunately, although

preliminary studies have indicated such a correlation [18], FRC appears to be correlated rather with body weight to the power 1.13 [19]. This indicates that in smaller animals, lung resting volume is smaller than in larger animals, in proportion to their body mass, as also confirmed by our data (power 1.25 by allometric analysis, $r^2 = 0.99$, $p = 0.0001$, see Fig. 4a in the Electronic supplementary material). It is therefore likely that the poor value of V_T /kg body weight and the firm validity of lung strain in predicting the time to achieve preterminal lung injury relies on the nonlinear correlation between the lung resting volume receiving V_T and body mass throughout the species considered. Of note, no association was observed between the V_T /kg body weight applied and the resulting lung strain (see Fig. 5 in the Electronic supplementary material).

When lung strain reached a value around 2–3, the mechanical ventilation time to achieve preterminal lung injury exponentially decreased even down to relatively few minutes. Several factors may provide a rationale for

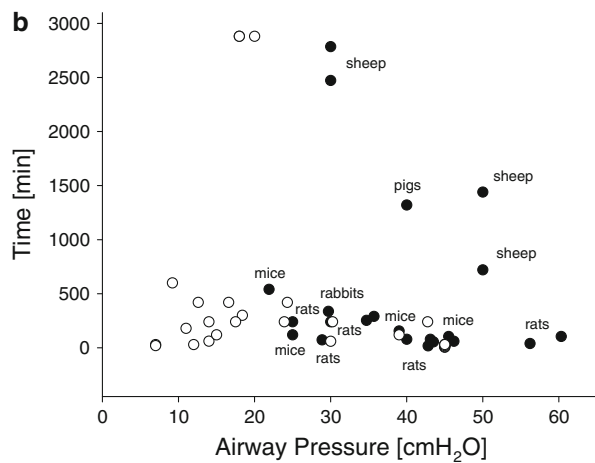
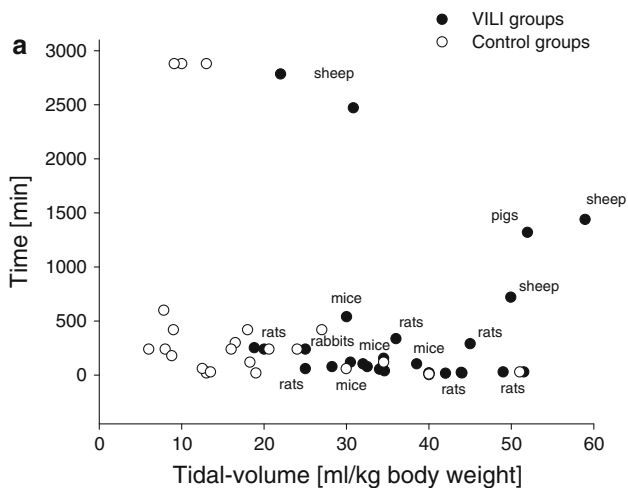


Fig. 1 Relationship between the duration of mechanical ventilation and the tidal volume (a) and the airway pressure applied (b), for both animals included in the VILI groups (*solid circles*) and animals included in the control groups (*open circles*). The duration of mechanical ventilation was the time to achieve preterminal lung injury in the VILI groups, and the time of application of mechanical ventilation as experimentally set for animals included in the control groups. Each point represents data obtained in a group of animals, as reported in the studies included in the current analysis. For detailed information regarding the cited articles, see Tables 1 and 3 in the Electronic supplementary material. For clarity, the species studied is indicated only for animals included in the VILI groups. In animals included in the VILI groups, no relationship was observed between the tidal volume applied and the duration of mechanical ventilation. Similarly, the time to achieve preterminal lung injury did not appear to be related to the airway pressure applied. Of note, data derived from the control groups appeared to markedly overlap the data obtained from the VILI groups, both for the tidal volume and the airway pressure applied

the exponential shape of this relationship. Firstly, the decrease in FRC with a reduction in body mass to a power greater than 1 may provide per se a simple explanation for this exponential association, suggesting that smaller species may be positioned (as observed) in the flatter and

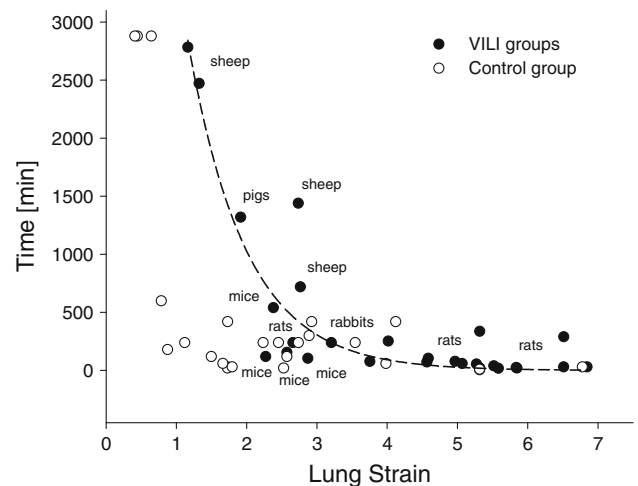


Fig. 2 Time to achieve preterminal lung injury as a function of the lung strain applied in animals included in the VILI groups (*solid circles*). To describe the relationship (*dashed line*) an exponential decay function was employed [$y = a \times \exp(-b \times x)$]. Data from animals in the control groups are also shown (*open circles*). Each point represents data obtained in a group of animals, as reported in the studies included in the current analysis. For clarity, the mammalian species studied is indicated only for animals included in the VILI groups. The duration of mechanical ventilation appears to be highly and inversely correlated with the value of lung strain applied throughout the species studied ($r^2 = 0.85, p < 0.0001$). Of note, data from the control groups are shifted mostly leftward and downward as compared to the relationship observed in the VILI groups

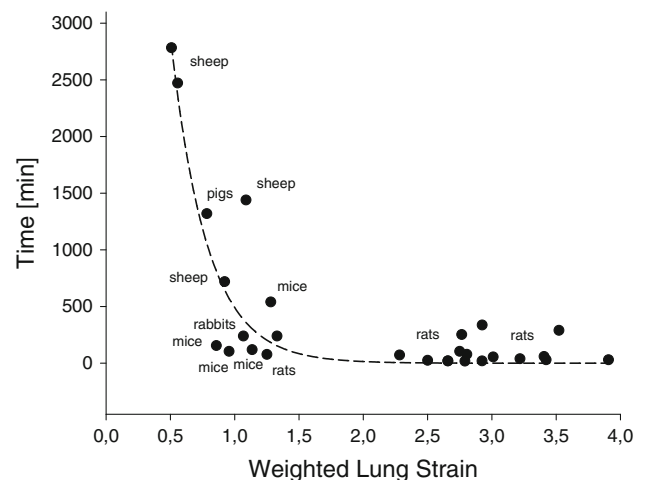


Fig. 3 Relationship between the time to achieve preterminal lung injury and the lung strain applied as weighted for the actual time of exposure during each tidal breath. To describe the relationship, an exponential decay function (*dashed line*) was employed [$y = a \times \exp(-b \times x)$]. Each point represents data obtained in a group of animals, as reported in the studies included in the current analysis. The duration of mechanical ventilation appears to be closely and inversely correlated with the weighted lung strain applied ($r^2 = 0.83, p < 0.0001$). Of note, this relationship indicates a critical threshold (around 1.5–2.0) of weighted lung strain separating two different types of injury (see “[Discussion](#)” for more details). For clarity, data from the control groups are not shown

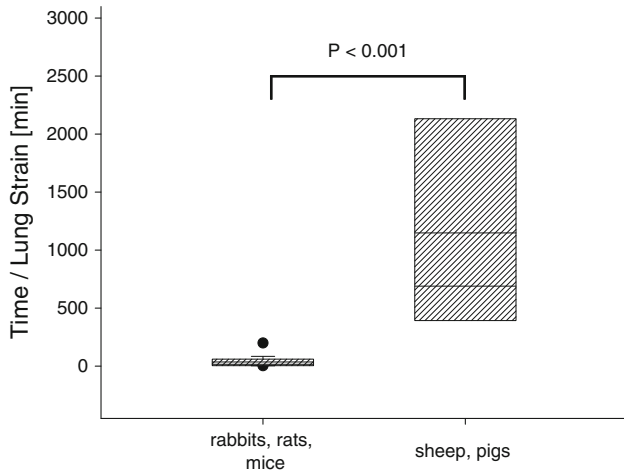


Fig. 4 Time to achieve preterminal lung injury per unit of lung strain applied in smaller (rabbits, rats and mice) and larger (sheep and pigs) mammalian species included in the VILI groups. Data are presented as medians and means (solid lines within the boxes), as well as 25th and 75th percentiles and 95% confidence interval. Smaller species showed a shorter duration of mechanical ventilation per unit of lung strain applied than larger species ($p < 0.001$)

rightward part of the relationship, in contrast to larger species, as such species are always subjected to a greater lung strain for a similar V_T /kg body weight applied. Secondly, it has been observed that the compliance of the chest wall is higher in smaller animals, as shown by the power laws reported among several mammal species ($b = 0.73$ [19]), as well as the power law observed in the species included in our study ($b = 0.61$, $r^2 = 0.92$, $p = 0.009$, see Fig. 4b in the Electronic supplementary material). Consequently, the same lung stress applied at the end of inflation may result, in smaller species, in a higher lung strain, thereby inducing more severe and rapid lung injury. Thirdly, based upon the pathological alteration of the lung during the development of VILI, it is likely that the initial lung strain applied does not remain constant throughout the period in which mechanical ventilation is applied, but it rather progressively increases. In fact, as the interstitial oedema begins to develop as a consequence of the altered permeability of the alveolar capillary membrane, FRC will progressively shrink, leading to a further increase in the lung strain actually applied and therefore to the “avalanche” process often characterizing the manifestation of VILI [9, 20, 21].

In contrast to what we expected, the estimated maximal lung stress appeared to be poorly correlated with the duration of mechanical ventilation before the development of preterminal lung injury (see Fig. 1 in the Electronic supplementary material). Although we cannot exclude some errors in estimating the transpulmonary pressure applied (especially in larger animals), this finding may suggest that the overall cascade of phenomena leading to the manifestation of VILI is more associated

with the degree of the alveolar deformation rather than with the resulting actual maximal stress. Moreover, these findings may also indicate that for the same maximal stress applied, the resulting alveolar deformation across different species may be different, probably due to a different composition of the force-bearing structure of the lung. In support of this hypothesis, Mercer et al. [22] observed that smaller species have a relatively lower proportion of stress-bearing elements (collagen and elastin fibres) within the lung than larger species.

The differential composition of the lung fibrous skeleton observed across mammalian species may also provide a rationale for the difference in susceptibility to VILI observed between smaller and larger animals, as previously observed [23]. In fact, when we compared the time to achieve preterminal lung injury per unit of lung strain applied, smaller species showed a more rapid development of VILI than larger species. Of note, a similar distinction between these mammalian species has been also observed when considering the relationship between body mass and chest wall compliance [24], and indirectly when looking at the variation in the proportional amounts of collagen and elastin fibres within alveolar septa with the increase in body mass [22].

Although our analysis was limited by its retrospective nature and the small range of species considered, we think it may provide some insights for clinical purposes. In fact, the strict and exponential correlation between the time to achieve preterminal lung injury and the lung strain or the weighted lung strain applied may also indicate a critical threshold suggesting two possible different mechanisms for the development of VILI: (1) development of VILI directly related to the excessive global stress and strain applied (above a value of weighted lung strain of 2.0), and (2) a less rapid time-course probably associated with different mechanisms other than the pure application of an excessive global stress and strain (below a value of weighted lung strain of 1.5), such as a regional dishomogeneity in the stress/strain distribution [17], intratidal alveolar opening and closing [5, 6], regional hypocapnia [25] and regional areas of stress/strain amplification [26]. Such observations may have important consequences. In fact, when adapting the relationship between the duration of mechanical ventilation and the lung strain applied to patients affected by ARDS, it is surprising that even a V_T equal to 12 ml/kg body weight leads to a lung strain largely below the threshold of 1.5. In fact, if we consider a man of 70 kg predicted body weight with an FRC of about 900 ml [15], the application of a V_T of 12 ml/kg body weight and a PEEP level of 10 cmH₂O will result in a lung strain of about 1.3, which will even be reduced to 0.70 when corrected for the actual time of application. Although representing a rough estimate, these data may suggest that the mechanisms by which a low V_T ventilation improves survival in ARDS may hardly be explained only by the reduction in an

excessive global lung stress and strain. On the contrary, it is more likely that the reduction in the effects of other mechanisms potentially related to VILI may play a critical role in such improvement, such as a reduction in intratidal lung oscillation (or cycling lung opening and closing) related to the driving pressure applied. Indeed, in a relatively large population of ARDS patients, we recently observed that lung strain was not associated with mortality, in contrast to what we observed for the amount of lung opening and closing, which appeared to be an independent predictor of in-hospital mortality [15].

In conclusion, although some limitations of the analysis reported should be acknowledged (mainly its

retrospective nature, the necessity to estimate some respiratory parameters not directly reported or measured, and the assumption of an homogeneous alveolar inflation during inspiration), we think that the data provided may suggest the uniqueness of lung strain, and of lung strain as weighted for the inspiratory/expiratory time, as a unifying rule describing the development of VILI among mammals with healthy lungs. Further studies would be greatly welcomed to prospectively verify this hypothesis.

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