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WHAT'S NEW IN INTENSIVE CARE

Intensive care medicine in 2050: ventilator-induced lung injury

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Introduction

The side effects of mechanical ventilation belong to two mainstreams: the first involves the lung, the second the hemodynamics. The former relates to the transpulmonary pressure (i.e., the always-positive force distending the lung parenchyma), the latter relates to the intrathoracic pressure (i.e., the positive or negative force hindering or favoring the venous return though a variety of mechanisms).

For sake of clarity, in this manuscript we will only refer to the ventilator-induced lung injury (VILI), i.e., the side effect of the mechanical ventilation related to unphysiological and excessive increase of transpulmonary pressure. The concept of VILI has evolved over the decades. The high volume, high pressure ventilation that was routinely used in the 1970s caused damage which was collectively referred to as "barotrauma" [1]. The recognition of the importance of the lung strain for the lung damage led to the concept of "volutrauma" [2] in the 1980s. Finally, the term "atelectrauma" has been introduced to underline the role played by the intratidal cyclic opening and closing in locally increasing stress, with subsequent inflammatory reaction [3]. The bulk of experience and scientific data accumulated over the years led progressively to more gentle ventilation. A typical ventilatory set now applied worldwide in ARDS [4] compares favorably to similar data collected 14 years before [5], as summarized in Table 1. As shown, in the years from 2002 to 2016, comparing the overall ARDS population, the tidal volume has decreased by 12.6%, peak and plateau pressures by 20.6% and 17.1% respectively, while positive end-expiratory pressure (PEEP) and the other ventilatory settings remained substantially unchanged. Interestingly, the driving pressure (estimated from the mean values of plateau and PEEP) decreased by 26%, from 20 to 14.8 cmH_2O. It is tempting to think that the decrease in mortality rate from 52% to 35.5% is associated—at least in part—with a decrease of VILI.

If so, we may wonder if further decreases of tidal volume and the other potential causes of VILI such as plateau and peak pressures would lead to a further decrease in mortality. In other words, we may ask ourselves which fraction of mortality may be attributed to the VILI when the "2016 ventilation" as described in Table 1 is applied. One may argue that the tidal volume is still 26% greater than the "indisputable" 6 ml/kg applied in the NIH trial [6]. In that study, the exposure to 12 ml/kg tidal volume compared to 6 ml/kg led to an "attributable" mortality of 8.8% (39.8 versus 31.0%). We must remind ourselves, however, that in prior randomized controlled trials, the ARDS patients exposed to 10.3, 10.7, and 10.2 ml/kg tidal volume experienced a better survival rate (although not statistically significant) compared to patients exposed to 7.1, 7.0, and 7.3 ml/kg, respectively. To be specific, the mortality rates were 37.9 versus 46.6% [7], 47 versus 50% [8], and 46 versus 50% [9], respectively. This is not to deny the merits of lower tidal volume, but simply to say its further decrease, as proposed in the "ultraprotective ventilation" associated with extracorporeal CO_2 removal, is not necessarily a good idea. Indeed it induces a severe hypoventilation with increased risk of reabsorption atelectasis and life-threatening hypoxemia [10]. This may be corrected with a further increase of PEEP; however, at the "asymptote" of this line of reasoning (minimal tidal volume and fully expanded lung), we find the high frequency oscillation ventilation (HFOV) with its disappointing results [11].

The reality is that we do not know how much mortality is presently attributable to VILI, particularly if a "gentle" ventilation, as used today, is correctly applied. Therefore, what about the future of VILI, if in the present we cannot

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Table 1 "Representative" ventilatory set applied in ARDS worldwide in 2002 and 2016

	2002	2016				
	ARDS all ($n = 231$)	ARDS all ($n = 2377$)	Mild ($n = 714$)	Moderate ($n = 1106$)	Severe ($n = 557$)	*P* value
Vt/PBW (ml/kg)	8.7 (2.0)	7.6 [7.5–7.7]	7.8 [7.6–7.9]	7.6 [7.5–7.7]	7.5 [7.3–7.6]	0.02
RR (bpm)	20 (6)	20.8 [21.5–21.2]	19.5 [19.0–19.9]	20.7 [20.3–21.1]	22.7 [21.5–23.8]	<0.001
Peak (cmH_2O)	34 (9)	27 [26.7–27.4]	24.7 [24.1–25.4]	26.9 [26.5–27.4]	30.3 [29.6–30.9]	<0.001
Plat (cmH_2O)	28 (7)	23.2 [22.6–23.7]	20.5 [19.8–21.3]	23.1 [21.6–23.7]	26.2 [25.2–27.1]	<0.001
PEEP (cmH_2O)	8 (4)	8.4 [8.3–8.6]	7.4 [7.2–7.6]	8.3 [8.1–8.5]	10.1 [9.8–10.4]	<0.001
$Power_{rs}$ estimated (J/min)[a]	31.9	23.7	21.1	23.5	29.0	–
ICU mortality (%)	52 [46–59]	35.3 [33.3–37.2]	29.7 [26.4–33.2]	35.0 [32.2–37.9]	42.9 [38.8–47.1]	<0.001

2002 data are taken from Esteban et al. [5], while 2016 data are taken from Bellani et al. [4]. Values are expressed as mean ± standard deviation (round brackets) or 95% confidence interval (square brackets)

P values refer only to the 2016 data [4]

[a] Mechanical power to the respiratory system was calculated with a simplified formula: $Power_{rs} = 0.098 \cdot RR \cdot \Delta V \cdot \left(P_{peak} - \frac{1}{2} \cdot \Delta P_{aw}\right)$ (see supplemental content of [13]) in which the tidal volume was calculated considering a body weight of 78 kg (which is the average patient weight of the cohort in the study by Bellani and colleagues [4])

really assess and measure its impact on lung damage and patient survival? In our opinion, the future of mechanical ventilation will depend on our better understanding of the interaction between the artificial ventilation and the diseased lung. Indeed, VILI is due in part to the ventilator's settings and in part to the lung's pathophysiology.

Ventilator-related causes of VILI

The ventilator's settings include tidal volume, pressure, respiratory rate, and flow. All these components have been found able to influence VILI, obviously depending on their extent [12]. We proposed to unify all these physical entities in a single variable, the mechanical power [13], although the role of some of its components (such as airway resistance and PEEP) require further investigations. In a normal 70 kg human with a normal respiratory system elastance (e.g., 12 cmH_2O/l), representative ventilatory settings in general anesthesia could be 420 ml tidal volume, 12 bpm respiratory rate, PEEP 5 cmH_2O, inspiratory to expiratory time ratio of 1:2. The associated mechanical power to the respiratory system would be approximately 4 J/min and, normalized to a normal functional residual capacity (FRC) of 1500 ml, would be approximately 2.7 mJ/min/ml. The ventilatory setting in an ARDS patient, as presented in Table 1, assuming for mild, moderate, and severe ARDS FRCs of 1000, 750, and 500 ml, respectively, would deliver mechanical power to the respiratory system of 21.1, 31.3, and 57.9 mJ/min/ml (i.e., 10–25 times greater than normal).

Lung-related causes of VILI

The same mechanical power should have completely different effects, depending on the pathophysiology of the lungs to which it is applied. In our opinion, three components must be considered: the lung size (as shown in the previous paragraph), the extent of inhomogeneity, and the recruitability. The lung size will be used to normalize the mechanical power. Even more important is the distribution of mechanical power throughout the lung parenchyma, which should parallel the distribution of stress and strain. In severe ARDS the inhomogeneity of the lung may cause, in up to 30–40% of the lung parenchyma, the appearance of stress raisers that may multiply the applied pressure by approximately 2 [14]. Therefore, the mechanical power could be locally doubled (e.g., from 50 mJ/min/ml at the airway to 100 mJ/min/ml) in that vulnerable fraction of the lung parenchyma. Finally, in patients with high recruitability, in whom PEEP is inadequately applied, the atelectrauma possibly contributes to the development of VILI. Therefore, the measurement of lung size, lung inhomogeneity, and lung recruitability would greatly increase our estimate of the VILI risk.

Conclusion: VILI in 2050

It is possible that, in the future, each ventilator will display the mechanical power applied to the respiratory system and to the lung itself, through continuous measurement of the transpulmonary pressure. The measurement of lung volume or lung tissue exposed to gas would normalize the mechanical power to the tissue at risk. As future studies relating the mechanical power to the risk of VILI will likely define a "safe" mechanical power threshold, it will be possible, after setting the ventilator, to establish whether the resulting mechanical power is associated with safe ventilation or with an unacceptable risk of VILI. Therefore we may imagine that, at entry into hospital, the lung pathophysiology will be characterized (by CT scan or alternative methods [15]), the mechanical

power measured, and their interaction assessed. If, for a given patient, the mechanical power needed to ventilate would be above a safety threshold, alternative methods will be provided, such as the artificial lung, for which hopefully by 2050, the currently remaining problems of biocompatibility and anticoagulation will be solved.

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Compliance with ethical standards

Conflicts of interest
On behalf of all authors, the corresponding author states that there is no conflicts of interest.

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