Ventilation in critically ill obese patients—Why it should be done differently?
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Abstract
Considering the increasing prevalence of obesity among the critically ill patient, mechanical ventilation of this type of patients has almost become a daily practice. However, no consensus regarding mechanical ventilation for obese patients has recently been published. Considering the particular pathophysiological features of respiratory system in obese patients, the risk of ventilator induced lung injury (VILI) is highly elevated. This narrative review aims to present the constrains related to mechanical ventilation in obese patients, as well as the features that predispose them to VILI. Moreover, the effects every determinant incriminated in VILI were described with application on the pathophysiological features of obese patients. Increased emphasis was placed on the newly concept of ergotrauma as one of the main determinants of VILI. This is one of the first reviews dedicated to the effects of mechanical power and ergotrauma on mechanically ventilated patients with obesity. Moreover, increased attention was given to the impact of biotrauma related to VILI, considering that the new concept of “pre-conditioning cloud” related to obesity has recently emerged.

Keywords
Obesity; Mechanical ventilation; Ventilator induced lung injury; VILI; Biotrauma; Ergotrauma; Volotrauma; Atelectrauma; Barotrauma

1. Introduction
Since the early 90’s, the prevalence of obesity has continuously increased both in Europe and United States. According to the latest World Health Organization (WHO) report obesity affects more than 650 millions of people all over the world becoming a more important cause of morbidity and mortality than starvation [1].

As expected, a higher prevalence of obesity has also been observed among admitted patients in intensive care units (ICU). Although overweight and obese patients admitted to the ICU registered a lower mortality compared to underweight patients, it has been demonstrated that they are more prone to a longer ICU and hospital stay [2–4]. Despite the so-called “obesity paradox of ICU patients” translated by a better prognosis and a higher survival rate of the critically ill obese patients, higher rates of mechanical ventilation on ICU admission were reported along with a greater dependence on mechanical ventilation and an increased risk for infections [2, 4–6]. Moreover, it was reported that obese patients are more likely to develop hypoxemic respiratory disfunction and are more susceptible to undergoing an acute respiratory distress syndrome (ARDS) [6]. Even if there is still insufficient data regarding ICU mortality in obese patients requiring mechanical ventilation, the obesity-related pathophysiological changes make the ventilation very challenging and put these patients at risk for ventilator-induced lung injury (VILI) [5, 7].

Increased lung stress and strain during mechanical ventilation promote the whole set-up for all four mechanisms (barotrauma, volotrauma, atelectrauma and biotrauma) responsible for producing VILI [8].

Despite the increased number of mechanically ventilated obese patients, there is no consensus on recommendations regarding mechanical ventilation in obese patients admitted in the ICU. In this narrative review based on extensive literature search, we summarized the latest data regarding the impact of VILI in critically ill obese patients.

2. Constrains in ventilating obese patients
It has already been demonstrated that obese patients are characterized by a decreased respiratory compliance [9–11]. Specific fat tissue deposition in the mediastinum, abdominal cavities, around the diaphragm and the ribs decrease chest wall compliance [11–13]. According to Lazarus et al. [13] chest compliance is mostly affected by central (upper body) distribution of the fat tissue and may be normal in peripheral (lower body) distribution.
Although it may be anticipated that low respiratory compliance is only related to the increased adiposity in the chest wall, numerous studies indicated that this tends to be linked to increased pulmonary blood volume and closure of dependent airways [10, 11]. In other words, low lung compliance results in early closure of the airways at low volumes and atelectasis [14].

Numerous studies indicate that the spirometry and plethysmography measurements in obese patients showed decreased expiratory reserve volume (ERV) and functional residual capacity (FRC) even in initial stages of obesity [11, 12, 15]. Moderate effects or the lack thereof were reported on total lung capacity (TLC) and vital capacity (VC) [14]. Pelosi et al. [16] reported since early 90’s that these changes make the lungs of obese patients more prone to atelectasis. Decreased ERV and FRC may also be translated into the tendency of obese patients to breathe on a flatter and less efficient part of pressure-volume curve causing an increased work of breathing [17, 18]. Moreover, according to Mafort et al. [15] the decreased ERV is further associated with abnormalities in ventilation distribution and alteration of ventilation-perfusion ratio (V/Q). An increased body fat distribution, more than body mass index (BMI), is associated with a slightly decreased forced expiratory volume (FEV₁) and a normal FEV₁/FVC (forced vital capacity) ratio, suggesting an impractical use of these dynamic parameters [11, 12, 19].

Obesity is associated with an increased airway resistance caused by airway narrowing and premature closure, changes that promote bronchial hyperresponsiveness in non-asthmatic patients [15]. Nevertheless, airway narrowing and premature closure are associated with gas trapping which generates intrinsic positive end-expiratory pressure (PEEPi). This in turn contributes to the V/Q mismatch, atelectasis development and impaired oxygenation [12, 14, 20]. PEEPi favours a supplementary load on inspiratory muscles and thus intensifies breathing work [18].

3. Background of ventilator-induced lung injury in obese patients

Apart from the difficulty of managing mechanical ventilation in critically ill patients, often with inhomogeneous lung injuries, the additional obesity-related pathophysiological changes impede the management of this type of patients. In other words, as already mentioned, the respiratory profile of the obese patients renders the lung susceptible to VILI. Considered one of the most serious complication of mechanical ventilation, VILI includes different pathophysiological mechanisms which in the long run worsen lung injuries [21]:

3.1 Barotrauma and volotrauma

Since publication of the extended research of Dreyfuss et al. [22], the main mechanism of VILI was considered to be pressure-related and resulted in pneumothorax, pneumomediastinum or gas embolism [22, 23]. Subsequently, experimental data indicated that excessive lung strain caused by inappropriate tidal volumes (volotrauma) is the hallmark of pathophysiological mechanism of VILI [22–24]. Nowadays it is clear that both mechanisms are in close interaction, considering the fact that stress and strain are related through a proportionality constant represented by the tissue elastance of the lung [21, 23, 25]. In other words, the fundamental pathological mechanism of VILI is considered to be explained through the damage caused by pressure applied directly to the lung tissue (stress) connected to volume change beside the resting volume (strain) [26].

Since the early 2000 experimental evidence was confirmed by large clinical trials, such as the Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome—ARMA trial which proved that the use of low tidal volumes and avoidance of excessive lung stress are associated with an increased survival rate [27]. Another more recent trial (A Trial of intraoperative low-tidal-volume ventilation in abdominal surgery—IMPROVE trial) which included 400 patients also demonstrated a higher incidence of pulmonary and extrapulmonary complications in patients ventilated with higher tidal volumes [28].

Guivarç et al. [8] demonstrated in his experimental study on obese mechanical ventilated mice with tidal volumes calculated on actual body weight, that inflammation and interstitial oedema may occur after only two hours.

In the face of already proven deleterious effects of volotrauma and despite general recommendations regarding the use of proper tidal volumes according to ideal body weight (IBW), recent data suggest that obese patients are still at high risk for volotrauma occurrence [8]. A secondary analysis of the data resulted from the Intraoperative ventilation settings and their associations with postoperative pulmonary complications in obese patients—LAS VEGAS trial. The latter revealed that obese patients received ventilation with higher tidal volumes than predicted body weight [29]. Jaber et al. [30] also reported in his research which included almost 3000 patients that obese patients were ventilated with higher tidal volumes than patients with normal BMI.

3.2 Atelectrauma

Repeated alveolar recruitment and derecruitment is one of the most prominent factor contributing to atelectrauma [31]. The lack of lung homogeneity and the presence of regions with different elasticity amplify stress and strain [21, 32, 33]. As a result, increased shearing forces between aerated and atelectatic areas of the lung may occur, thereby causing atelectrauma [21, 34].

As previously mentioned, respiratory pathophysiological changes like airway narrowing and premature closure, typically identified in obese patients, expand the atelectatic areas promoting the lack of uniformity in the lung [14, 35]. Increased intraabdominal pressure, also present in obese patients, is further associated with lung collapse, atelectasis and increased transpulmonary pressure [36]. It was observed that collapsed lung areas affect neighbouring aerated areas causing deformation and increased stretch [37]. These structural changes eventually promote shear forces exacerbation [37]. So, beside the already existing atelectatic areas, mechanically ventilated patients with obesity are particularly prone to developing at-
electrauma, especially in the absence of adequate ventilation parameters.

In order to prevent lung atelectasis and to minimize the risk of atelectrauma, researchers of the Effect of intraoperative high positive end-expiratory pressure (PEEP) with recruitment manoeuvres vs. low PEEP on postoperative pulmonary complications in obese patients—PROBESE trial evaluated the effects of protective intraoperative ventilation using different levels of PEEP [38]. Despite expectations, no benefit was obtained in the group ventilated with increased PEEP [38]. Nestler et al. [39] demonstrated that an increased PEEP together with recruitment manoeuvres may be beneficial for intraoperative mechanical ventilation of obese patients, but these positive effects were not sustained during the postoperative period. Given these findings, Ball and Pelosi recommend using an increased fraction of inspired oxygen (FiO2) over PEEP in order to prevent driving pressure increase and hyperinflation [40]. Moreover, these authors suggest that recruitment manoeuvres should only be used as a rescue method in severe hypoxic dysfunctions [40].

3.3 Mechanical power or "ergotrauma"

Beyond the already incriminated mechanical factors implicated in producing VILI, a recent concept has been advanced through which the mechanical power delivered during mechanical ventilation may be an independent factor for VILI development [41]. If until recently all the physical parameters implicated in mechanical ventilation (pressure, flow, resistance and frequency) were studied as individual data, it is assumed that the combined effects of these parameters should be considered [42]. Gattinoni et al. [42] proposed that mechanical power and its determinant factors may be appreciated through a complex equation derived from the equation of motion. Through this mathematical expression the authors could easily determine mechanical power as the result of the product between respiratory frequency and energy, the latter being the sum of the forces which open the lung, push the air into the lung and keep the lung open [25, 42, 43]. The importance of evaluating mechanical power may be useful in the pathogenic process of VILI because repeated tidal energy cycles above the lung tissue tolerance is associated with local structural disruption [43, 44]. Although this concept has recently aroused much interest, there is a lack of practical measurement tools for mechanical power in daily practice [41]. Nevertheless, Marini et al. [44] suggest a special consideration when it comes to setting a plateau pressure, or driving pressure and PEEP, underlining therefore that neither is reliable enough to measure the exact amount of energy delivered to the tissue with every cycle.

Considering the novelty of the concept and the lack of studies, both experimental and clinical, specifically targeting the evaluation of the impact of ergotrauma on mechanically ventilated obese patients, its effects are estimated based on the well-known patient-dependent factors.

According to Marini et al. [43] one conditional factor that may potentiate the deleterious effects of ergotrauma is represented by chest wall elasticity. Notwithstanding, this means that the energy transferred to the lung may be lower than anticipated due to the spent energy used to overcome the de-

3.4 Biotrauma and the pre-conditioning mechanism

The effects of every injurious ventilator-related stimuli are considered to be biologically translated into an increased inflammatory mediator release and leucocyte recruitment [23, 34]. Beyond the local lung injuries, the systemic release of these inflammatory mediators may be associated with multiple organ failure and even death [37, 46].

The “biotrauma hypothesis” as part of VILI was initially outlined through the results obtained in experimental studies on subjects with ARDS ventilated in a protective manner. A lower level of proinflammatory mediators was also detected in the bronchoalveolar lavage after changing the ventilation strategy and increasing the tidal volume [23, 47]. However, the experimental data of Ricard et al. [47] concluded that solely large tidal volumes are not deleterious enough to induce ARDS and a previous lung damage may be mandatory.

The molecular mechanisms underlying biotrauma were mostly highlighted through experimental studies and are summarized in Table 1 [48–50]. The impact of biotrauma in obese patients lacks reliable studies. However, some assumptions may be made considering the data regarding obesity-related immune status.

On the one hand, obesity is associated with a chronic inflammatory state induced by augmented proinflammatory adipocytokines release, decreased anti-inflammatory cytokines and macrophage activation [52]. On the other hand, recent reports indicate that this continuous inflammatory state may offer some protection against further lung injuries, calling this effect as “pre-conditioning cloud” [53]. The concept of preconditioning evolved from the pharmacological process called hormesis and was recently applied in many medical fields including ischemic preconditioning [54]. The “pre-conditioning cloud” in obese patients proposed by Fernandez-Bustamante et al. [7] has evolved from the obesity-paradox according to which critically ill obese patients have a decreased rate of mortality [2–4, 53]. Considering that all these hypotheses are based on observations, further research studies are required.
4. Some practical aspects

The reported findings suggest that the available recommendation regarding mechanical ventilation for ARDS patients may not fit all groups of patients, such as obese patients [24]. However, there is limited data regarding current practice of mechanical ventilation in critically ill obese patients and most information comes from intraoperative clinical trials [29, 33]. Although ARDS net trial excluded obese patients, this protocol is extensively used for this group of patients [40, 55]. Taking into account that very few studies dedicated to the evaluation of different ventilatory strategies are currently available, an individualized approach should be adopted in obese patients with ARDS [45].

Experts recommend initiation of mechanical ventilation for adopting a protective strategy [40]. Ventilation with low tidal volume (6 mL/kg), titrated according to ideal body weight, may be associated with a more homogenous ventilation of aerated lung [40, 56, 57]. However, if tidal volume is too low in order to avoid overdistension, high PEEP use is recommended in order to avoid atelectasis [32]. Recruitment manoeuvre and PEEP titration are often reported, but their clinical impact is usually lacking [45]. Using electric impedance tomography may offer the possibility for PEEP optimization in obese patients [58].

Jong et al. [45] reported that driving pressure may not have an impact on obese patients mortality. Taking into account the elevated chest wall elastance, routinely monitoring oesophageal pressure as a surrogate for transpulmonary pressure should be considered [24, 45]. Since this type of monitoring is not widely available, Ball et al. [40] suggest that driving pressure of 17 cmH₂O should be targeted.

5. Conclusions

This review synthetises the latest data available regarding the challenges that we face in managing critically ill obese patients with ARDS. In the absence of clear available guidelines, practical decisions may have to be made based on experts’ opinion and on a better understanding of underlying pathophysiology processes.

Although it was observed that obese patients admitted in ICU have a lower mortality rate, a higher risk of prolonged mechanical ventilation should not be neglected together with its associated adverse effects.

This paper review proves that obese patients may have an increased susceptibility to the injuries induced by mechanical ventilation. Considering their high BMI there is a general tendency to use increased tidal volumes predisposing to increased risk of volotrauma and barotrauma. Taking into account the obesity-related pathophysiological changes of the respiratory system, a raised exposure level to the effects of atelectrauma is to be expected. Notwithstanding, considering the difficulties usually met during mechanical ventilation, obese patients may be a perfect target for the effects of the newly described ergotrauma. As obese patients may be the target of all types of ventilator-induced injuries, it should also be expected that they carry an exacerbated inflammatory burden. Since a “pre-conditioning effect” caused by the chronic inflammatory status is usually seen in obese patients, the impact of biotrauma still remains to be debated.

AUTHOR CONTRIBUTIONS

CC, RU—designed the research study. CC—performed the research. AMC, RT and IMG—analyzed the data. CC and LM—wrote the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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