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The pleural gradient does not reflect the superimposed pressure in patients with class III obesity

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Abstract

Background The superimposed pressure is the primary determinant of the pleural pressure gradient. Obesity is associated with elevated end-expiratory esophageal pressure, regardless of lung disease severity, and the superimposed pressure might not be the only determinant of the pleural pressure gradient. The study aims to measure partitioned respiratory mechanics and superimposed pressure in a cohort of patients admitted to the ICU with and without class III obesity (BMI ≥ 40 kg/m^2), and to quantify the amount of thoracic adipose tissue and muscle through advanced imaging techniques.

Methods This is a single-center observational study including ICU-admitted patients with acute respiratory failure who underwent a chest computed tomography scan within three days before/after esophageal manometry. The superimposed pressure was calculated from lung density and height of the largest axial lung slice. Automated deep-learning pipelines segmented lung parenchyma and quantified thoracic adipose tissue and skeletal muscle.

Results N = 18 participants (50% female, age 60 [30–66] years), with 9 having BMI < 30 and 9 ≥ 40 kg/m^2. Groups showed no significant differences in age, sex, clinical severity scores, or mortality. Patients with BMI ≥ 40 exhibited higher esophageal pressure (15.8 ± 2.6 vs. 8.3 ± 4.9 cmH_2O, $p = 0.001$), higher pleural pressure gradient (11.1 ± 4.5 vs. 6.3 ± 4.9 cmH_2O, $p = 0.04$), while superimposed pressure did not differ (6.8 ± 1.1 vs. 6.5 ± 1.5 cmH_2O, $p = 0.59$). Subcutaneous and intrathoracic adipose tissue were significantly higher in subjects with BMI ≥ 40 and correlated positively with esophageal pressure and pleural pressure gradient ($p < 0.05$). Muscle areas did not differ between groups.

Conclusions In patients with class III obesity, the superimposed pressure does not approximate the pleural pressure gradient, which is higher than in patients with lower BMI. The quantity and distribution of subcutaneous and intrathoracic adiposity also contribute to increased pleural pressure gradients in individuals with BMI ≥ 40. This study introduces a novel physiological concept that provides a solid rationale for tailoring mechanical ventilation in patients with high BMI, where specific guidelines recommendations are lacking.

Keywords Mechanical ventilation, Obesity, Respiratory insufficiency, Critical care

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Background

The global prevalence of obesity is expected to rise significantly, leading to its classification as an ongoing pandemic. Individuals with class III obesity (BMI ≥ 40 kg/m^2), also known as severe obesity, present a significant burden for healthcare systems due to increased morbidity, mortality, and associated costs [1, 2]. Patients with a BMI ≥ 40 kg/m^2 also face a heightened risk of developing severe acute respiratory failure, representing a clinical challenge for intensivists [3, 4].

Subjects with severe obesity are often excluded by most clinical trials that investigate strategies for ventilatory management [5–10]. As a result, the most recent guidelines on acute respiratory distress syndrome (ARDS), one of the most severe forms of hypoxemic respiratory failure, do not provide specific recommendations for patients with obesity, where the standard ventilatory management might not be as effective as for patients with lower BMI [11, 12]. Although current guidelines discourage routine recruitment maneuvers and high positive end-expiratory pressure (PEEP), maintaining higher airway pressure might be beneficial in patients with severe obesity. In fact, the adipose load directly affects respiratory mechanics, leading to lung and airways collapse [13]. However, the physiological targets for ventilatory adjustments in obesity are poorly defined.

In subjects with normal weight, the pleural pressure (Ppl) has a positive gradient along the vertical axis (i.e., lower in non-dependent, higher in dependent lung regions), with this gradient being greater in the presence of ARDS [14]. The superimposed pressure, the hydrostatic pressure exerted by the lungs at a given level, is considered the driving force of the Ppl gradient and possibly a target for the treatment of lung collapse. In a landmark study, Yoshida et al. demonstrated that the superimposed pressure highly approximates the vertical Ppl gradient in both normal and injured lungs [15]. However, in subjects with obesity, the end-expiratory esophageal pressure (Pes), a surrogate for Ppl in dependent pleural regions, is higher regardless of the presence of lung disease [16, 17].

The superimposed pressure might not be the primary Ppl determinant in patients with obesity, as believed for non-obese patients. We hypothesized that in patients with class III obesity, the vertical Ppl gradient does not approximate the superimposed pressure. We also hypothesized that other factors, such as adipose tissue and muscle distribution in the chest contribute to the increased Ppl gradient in these subjects. If true, non-pulmonary factors may dictate the severity of lung collapse and responses to PEEP in severe obesity.

In the present study, we partitioned respiratory mechanics and measured superimposed pressure in a cohort of patients admitted to the ICU, and we quantified the amount of thoracic adipose tissue and muscle on routine chest computed tomography (CT) scan using a validated deep-learning image analysis pipeline [18, 19].

Methods

Study design and study population

This is a single-center study approved by Mass General Brigham Institutional Review Board (protocol #2020P003196) and conducted at Massachusetts General Hospital (Boston, USA). Data were prospectively collected from 2016 to 2022 and retrospectively analyzed for the present study. The need for informed consent was waived, given the retrospective nature of the study. All the subjects enrolled in the study were evaluated by the lung rescue team (LRT), a consult team involved in the ventilatory management of patients with acute respiratory failure where conventional treatments had failed [20].

The literature shows that a BMI ≥ 40 kg/m^2 marks an inflection point where respiratory physiology undergoes the most pronounced changes compared to lower BMI [21, 22]. To better characterize the respiratory mechanics abnormalities associated with severe obesity, we categorized the study population into two distinct groups based on their BMI: non-obese individuals (BMI < 30 kg/m^2) and individuals with class III obesity (BMI ≥ 40 kg/m^2).

Patients included in the present study had acute respiratory failure and were intubated and paralyzed, for whom the LRT performed an advanced respiratory mechanics assessment with esophageal manometry. Inclusion also required that patients underwent a CT scan of the chest within three days before or after LRT evaluation. Patients were excluded from the present study if: they were younger than 18 years old; they had class I or class II obesity (BMI between 30 and 39.9 kg/m^2); the difference of PEEP at the time of the CT scan and esophageal manometry was greater than four cmH_2O.

Study procedures

The LRT assessment has been previously described [20]. Briefly, sedation and paralysis were optimized before each assessment, with patients being ventilated in volume-control mode. Vital signs, mechanical ventilation settings, and arterial blood gas variables were recorded. Demographic data, ICU admission diagnosis, cause of respiratory failure, length of mechanical ventilation, and mortality scores, such as Simplified Acute Physiology Score (SAPS II) and the Acute Physiology and Chronic Health Evaluation

(APACHE II), were also retrieved. Complete calculations for partitioned respiratory mechanics and Ppl gradient are reported in the supplementary material. We also reported in Figure E1 (supplementary material) an illustrative tracing of parameters recorded during each LRT assessment, i.e., flow, tidal volume, airway pressure, and esophageal pressure.

CT image analysis

A detailed description of all image analyses is provided in the supplementary material. Briefly:

- *Lung segmentation*. All CT chest images underwent a segmentation process using a previously validated automated deep-learning image analysis pipeline [19, 23, 24]. Briefly, this is a multi-resolution, unsupervised convolutional neural network, that provides accurate and consistent segmentation across all the images.
- *Superimposed pressure measurement.* The superimposed pressure (SP) was assessed from lung density analysis using two different approaches. The first measurement was performed at the highest anteroposterior section of the lungs (SP_{global}). In the second approach, the superimposed pressure was also measured at a regional level to analyze its distribution along the entire length of the lungs. This was done by dividing the lung into ten equal vertical sections craniocaudally ($SP_{regional}$). Figure E2 (supplementary material) illustrates SP_{global} and $SP_{regional}$ measurements in two subjects with BMI < 30 and ≥ 40 kg/m^2, respectively.
- *Quantification of subcutaneous adipose tissue and muscle on axial images*. Body composition analysis was performed at the level of the T5, T8, and T10 thoracic vertebral level using a fully automated deep learning image analysis pipeline. Figure E3 (supplementary material) illustrates the segmentation of cross sectional areas of skeletal muscle tissue and subcutaneous adipose tissue in two subjects with BMI < 30 and ≥ 40 kg/m^2, respectively.
- *Intrathoracic adipose tissue volume.* The adipose tissue within the endothoracic fascia from the top of the sternal manubrium to the caudal border of the diaphragm. Figure E3 (supplementary material) illustrates the three-dimensional distribution of intrathoracic adipose tissue volume in two subjects with BMI < 30 and ≥ 40 kg/m^2, respectively.

Figure 1 provides a schematic representation of the above-described analyses performed on CT scans.

Statistical analysis

The study sample size was calculated based on Pes values recorded in our prior studies, which suggest the end-expiratory Pes to be on average 8 ± 4 standard deviation (SD) cmH_2O higher in subjects with BMI ≥ 40 kg/m^2 compared to subjects without obesity [16, 17, 21]. Therefore, a sample size of at least n = 16 (with 8 participants in each group) was required to achieve a statistical power of 95% for detecting a difference with an effect size (d) of 2 at a significance level (α) of 0.05.

Continuous variables are expressed as mean ± standard deviation (SD) or median [interquartile range] according to their distribution. Categorical variables are expressed as count (n) and percentage (%). Continuous variables were compared between two groups by Student T-test or Wilcoxon test, while two-way ANOVA for repeated measures compared continuous variables between more than two groups. In case of a between-group difference, pairwise comparisons were performed with paired Student's t-tests after post hoc Bonferroni correction. Categorical variables were compared through the Fisher's Exact test. Intraclass correlation coefficients were computed on a random sample of five subjects to characterize inter- and intrareader reliability for intrathoracic adipose tissue segmentation.

We correlated two continuous variables, computing Pearson or Spearman r coefficients, according to the normality of the variables. Linear regressions and the relative 95% Confidence intervals (CI) were reported in each correlation graph. We tested the associations of variables that quantify intrathoracic and subcutaneous adipose tissue and muscle (independent variable) with end-expiratory Pes (dependent variable) in multivariate analysis models, controlling for age, sex, and clinical severity (SAPS II).

A $p < 0.05$ was deemed statistically significant. Statistical analysis was performed using GraphPad Prism (version 9, GraphPad Software, San Diego, California, USA) and STATA (version 18.0, StataCorp, Texas, USA).

Results

Patient characteristics

Eighteen participants were included, among whom 9 (50%) were female, with a median age of 60 [30–66] years and a BMI of 35 [25–48] kg/m^2. All patients suffered from acute respiratory failure with a PaO_2/FiO_2 of 171 ± 67 mmHg at the time of LRT procedures. Respiratory failure was due to a medical or surgical condition in 67% and 33% of cases, respectively, with SAPS II and APACHE II scores on study day of 40.9 ± 9.4 and 18.9 ± 8.9, respectively. Table E1 and Table E2 in

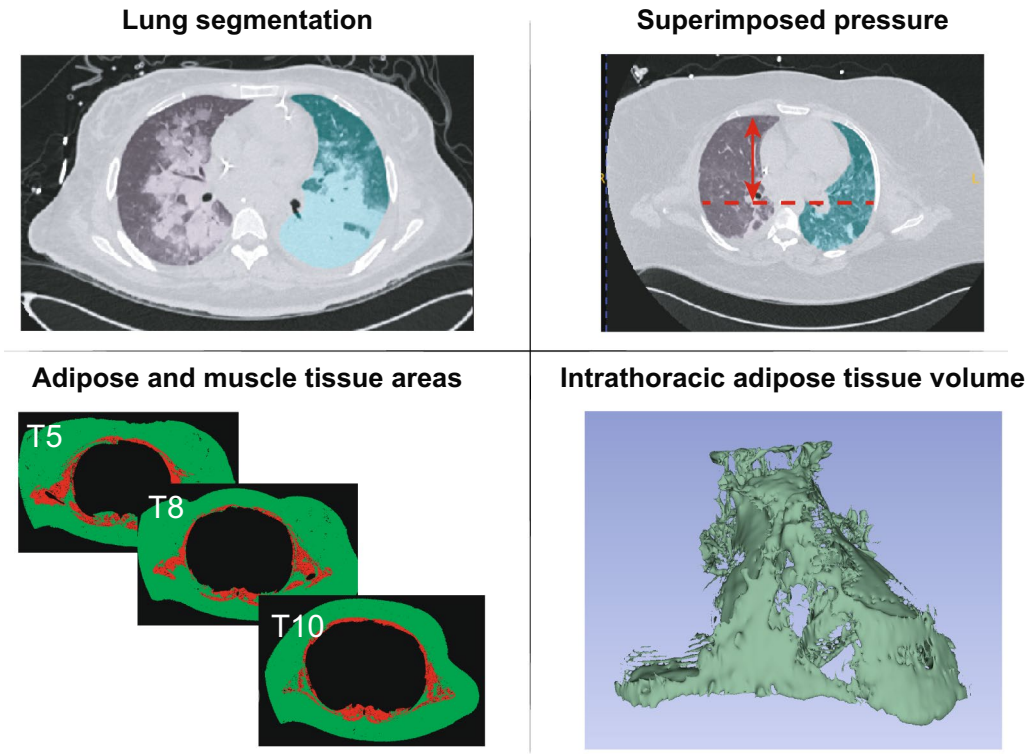

Fig. 1 Schematic representation of analyses performed on computed tomography (CT) scans. *Top left*: segmentations of lung performed through a multi-resolution, unsupervised convolutional neural network model. This process allows for precise individualization of lung tissue and for differentiating it from surrounding tissues. *Top right*: superimposed pressure measurement at the highest anteroposterior section of the lungs, calculated using lung density (derived from CT numbers in Hounsfield units, HU) and lung height (distance between the ventral border and the esophageal level, red arrows). *Bottom left*: segmentation images for muscle and adipose tissue at T5, T8, and T10 thoracic vertebral levels, with skeletal muscle tissue cross sectional area depicted in red and subcutaneous adipose tissue cross sectional area in green. *Bottom right*: three-dimensional distribution of adipose tissue volume within the thoracic cavity

supplementary material report complete demographics and clinical characteristics of the overall population.

The study population was divided into patients with BMI < 30 or ≥ 40 kg/m^2, with 9 subjects in each group (BMI of 25 [23–28] and 48 [42–54] kg/m^2, respectively, $p < 0.001$). No statistically significant difference was detected between groups regarding age, sex, clinical scores severity, ICU, and intra-hospital mortality. Complete demographics and clinical characteristics for each group are summarized in Table 1. Table E3 in the supplementary material provides the PEEP values applied during both imaging and esophageal manometry, and the time between the latter and the CT scan for each subject. Figure E4 in the supplementary material shows chest CT images in the coronal and axial planes demonstrating lung morphology and degree of injury in all subjects included in the study.

Respiratory mechanics

Patients with a BMI < 30 kg/m^2 had an FiO_2 of 0.7 ± 0.2 and a PaO_2/FiO_2 of 163 ± 56 mmHg. When esophageal manometry was performed, these patients had a total PEEP of 9 ± 4 cmH_2O, a driving pressure of 14.8 ± 4.9 cmH_2O, and an end-expiratory Pes of 8.3 ± 4.9 cmH_2O. The overall respiratory system elastance was 49.7 ± 21 cmH_2O/l, which was mainly attributable to high lung elastance. The elastance ratio (E_{lung}/E_{rs}) was 0.8 ± 0.1.

In patients with a BMI ≥ 40 kg/m^2, the FiO_2 was 0.8 ± 0.3, and PaO_2/FiO_2 was 179 ± 79 mmHg, none of which was significantly different than the other study group. Also, the driving pressure was not different (11.2 ± 3.8 cmH_2O). However, these patients had a significantly higher total PEEP of 15 ± 3 cmH_2O ($p = 0.04$) compared to the group with BMI < 30 kg/m^2, and the end-expiratory Pes was significantly increased to 15.8 ± 2.6 cmH_2O ($p = 0.001$). The overall respiratory system elastance was 30.9 ± 12 cmH_2O /l, significantly lower than in the BMI < 30 kg/m^2 group ($p = 0.03$). The chest wall elastance did not differ significantly between the groups ($p = 0.77$), and the elastance ratio (E_{lung}/E_{rs}) was similar at 0.7 ± 0.1.

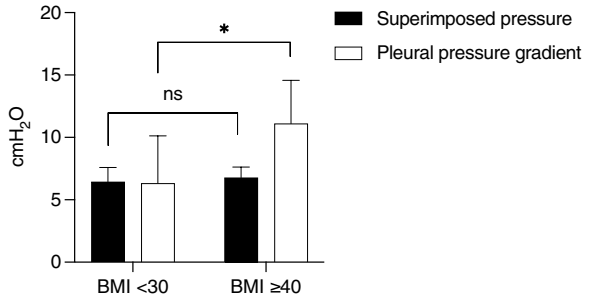

Fig. 2 Superimposed pressure (black) and pleural pressure gradient (white) reported as mean ± 95%CI. P = ns (non-significant) for superimposed pressure and *$p = 0.04$ for pleural pressure gradient between patients with BMI < 30 and ≥ 40 kg/m^2. BMI = body mass index

Table 1 Demographics and clinical characteristics of the study cohorts

	BMI < 30 n = 9	BMI ≥ 40 n = 9	*p*-value
Age, years	60 [23–68]	58 [53–62]	0.96
Male, n (%)	5 (55)	4 (45)	1.0
Race, n (%)			0.12
White	3 (33)	7 (78)	
Black or African American	4 (45)	1 (11)	
Asian	1 (11)	0 (0)	
Not reported	1 (11)	1 (11)	
Ethnicity, n (%)			1.0
Not hispanic or latino	8 (89)	7 (78)	
Hispanic	0 (0)	1 (11)	
Not reported	1 (11)	1 (11)	
Actual body weight, kg	71.3 ± 13.9	140.3 ± 18.7	< 0.001
Ideal body weight, kg	63.3 ± 10.9	64.3 ± 12.4	0.87
BMI, kg/m^2	25 [23–28]	48 [42–54]	< 0.001
Reason for ICU admission, n (%)			0.62
Medical	7 (77)	5 (55)	
Surgical	2 (23)	4 (45)	
ICU LOS, days	25 [22–34]	19 [13–40]	0.33
Hospital LOS, days	41 [28–48]	29 [17–41]	0.15
Ventilation days	24 [13–35]	18 [13–38]	0.93
Ventilator free days	0 [0–15]	0 [0–10]	0.96
ICU mortality, n (%)	4 (45)	6 (67)	0.64
Alive at hospital discharge, n (%)	5 (55)	3 (33)	0.64
Tracheostomy, n (%)	2 (22)	1 (11)	1.0
SAPS II	40.2 ± 5.1	41.6 ± 12.7	0.77
APACHE II	19.1 ± 7.3	18.8 ± 10.8	0.94
Days between chest CT scan and study	1 [0–1]	−2 [−1 to 2]	0.31
PEEP during chest CT scan, cmH$_2$O	8 ± 5	14 ± 4	0.02

Data reported as mean (± SD) (standard deviation) or median [IQR] (interquartile range)

BMI body mass index, *ICU* intensive care unit, *LOS* length of stay, *SAPS* Simplified Acute Physiology Score, *APACHE* Acute Physiology and Chronic Health Evaluation, *CT* computed tomography, *PEEP* positive end-expiratory pressure

Complete respiratory and hemodynamic variables recorded on the study day are summarized for each group in Table 2.

Superimposed pressure

We compared the *global* superimposed pressure (i.e., measured at the highest anteroposterior section of the lungs) and the Ppl gradient between patients with BMI < 30 and those with BMI ≥ 40 (Fig. 2). While the superimposed pressure was not different between the two groups, 6.5 ± 1.5 (BMI < 30 kg/m^2) vs. 6.8 ± 1.1 cmH$_2$O (BMI ≥ 40 kg/m^2), $p = 0.59$, patients with severe obesity had a Ppl gradient significantly higher than patients with lower BMI (6.3 ± 4.9 vs. 11.1 ± 4.5 cmH$_2$O, $p = 0.04$).

We also calculated the *regional* superimposed pressure (i.e., measured for each thoracic section after dividing the lungs into ten equal-thickness vertical sections craniocaudally). The superimposed pressure distribution in the overall population is shown in Fig. 3 (A), which suggests a progressively higher pressure in the craniocaudal axis until section eight (corresponding on average to 16–17 cm of the entire craniocaudal length of the lungs). The morphology of regional superimposed pressure distribution in patients with BMI < 30 and those with BMI ≥ 40 is illustrated in Fig. 3, B.

Quantification of thoracic adipose tissue and muscle

We quantified subcutaneous adipose tissue and muscle at three thoracic spinal levels: T5, T8, and T10. The cross-sectional area of the subcutaneous adipose tissue was significantly higher at each thoracic level in patients with BMI ≥ 40 kg/m^2, $p < 0.05$, after multiple comparison tests between the two study groups (Fig. 4, A). At T10, the subcutaneous adipose tissue correlated positively with BMI ($r = 0.92$, $p < 0.0001$) (Fig. 4, B) and with the end-expiratory Pes ($r = 0.76$, $p = 0.001$) (Fig. 4, C). In contrast, muscle cross-sectional area did not differ between subjects with BMI < 30 vs ≥ 40 kg/m^2 at T5, T8, and T10 ($p > 0.0.5$ between groups) (Fig. 4, D). We also found no significant correlation of muscle cross-sectional area with BMI ($r = 0.01$, $p = 0.96$) (Fig. 4, E) and with the end-expiratory Pes ($r = 0.18$, $p = 0.46$) (Fig. 4, F).

We also quantified intrathoracic adipose tissue volume. Patients with BMI ≥ 40 kg/m^2 had on average, 666.2 ± 285.4 cm^3 of adipose tissue, as compared to patients with BMI < 30 kg/m^2, who had a volume of 298.5 ± 194.7 cm^3, $p = 0.05$ (Fig. 5, A). The intrathoracic adipose tissue volume positively correlated with the end-expiratory Pes ($r = 0.55$, $p = 0.02$) (Fig. 5, B). The intraclass correlation coefficients for the intra- and inter-reader reliability analyses were 0.99 (95% CI 0.97, 1.00) and 0.98 (95% CI: 0.83, 1.00), respectively.

Table 2 Respiratory and hemodynamics variables on study day for each study group

	BMI < 30 n = 9	BMI ≥ 40 n = 9	*p*-value
Vitals			
SpO_2, %	97 ± 1	96 ± 3	0.39
Heart rate, beats/min	91 ± 21	80 ± 25	0.34
Systolic arterial blood pressure, mmHg	108 ± 14	123 ± 22	0.13
Diastolic arterial blood pressure, mmHg	51 ± 5	52 ± 11	0.65
Mean arterial blood pressure, mmHg	70 ± 6	76 ± 13	0.24
Arterial blood gas			
pH	7.33 ± 0.09	7.35 ± 0.09	0.75
PaO_2, mmHg	99 [89–107]	106 [76–178]	0.96
$PaCO_2$, mmHg	49 ± 9	45 ± 8	0.28
Base Excess, mEq/l	0.3 ± 5.1	0.9 ± 6.5	0.83
Respiratory variables			
FiO_2	0.7 ± 0.2	0.8 ± 0.3	0.56
PaO_2/FiO_2, mmHg	163 ± 56	179 ± 79	0.64
Tidal volume, ml	315 ± 69	368 ± 38	0.06
Tidal volume/Ideal body weight, ml/kg	5.1 ± 1.1	5.9 ± 0.9	0.13
Respiratory rate, breaths/min	27 ± 6	25 ± 6	0.58
Minute volume, l/min	8.3 ± 2.1	9.2 ± 2.1	0.36
Ventilatory ratio	1.8 ± 0.6	1.8 ± 0.6	0.94
External PEEP, cmH_2O	8 ± 4	14 ± 3	0.03
Total PEEP, cmH_2O	9 ± 4	15 ± 3	0.04
End-expiratory Pes, cmH_2O	8.3 ± 4.9	15.8 ± 2.6	0.001
End-inspiratory Pes, cmH_2O	11.1 ± 5.5	18.9 ± 2.9	0.002
Driving pressure, cmH_2O	14.8 ± 4.9	11.2 ± 3.8	0.11
Inspiratory transpulmonary pressure, cmH_2O	12.6 ± 5.3	7.4 ± 2.6	0.02
Expiratory transpulmonary pressure, cmH_2O	0.7 ± 5.5	-0.6 ± 4.1	0.59
Driving transpulmonary pressure, cmH_2O	12 ± 4.7	8 ± 3.4	0.06
Elastance, cmH_2O/l			
Respiratory system	49.7 ± 21	30.9 ± 12	0.03
Lung	40.4 ± 19.9	22.3 ± 11.2	0.03
Chest wall	9.2 ± 5.3	8.6 ± 3.5	0.77
Elastance lung/elastance respiratory system	0.8 ± 0.1	0.7 ± 0.1	0.12

Data reported as mean ± SD (standard deviation) or median [IQR] (interquartile range)

BMI body mass index, *SpO_2* peripheral oxygen saturation, *PaO_2* partial pressure of oxygen in the arterial blood, *$PaCO_2$* partial pressure of carbon dioxide in the arterial blood, *FiO_2* fraction of inspired oxygen, *PEEP* positive end-expiratory pressure, *Pes* esophageal pressure

We examined the association between variables that quantify adipose tissue and the Ppl gradient. While the Ppl gradient was positively correlated with the subcutaneous adipose tissue at T10 (r = 0.54, $p = 0.03$), no significant association was recorded with the intrathoracic adipose tissue volume (r = 0.31, $p = 0.22$) (Fig. 5, C and D). Also, we did not find any other significant association between either adipose or muscle tissue with chest wall elastance. Correlations between chest wall elastance and adipose tissue volume, subcutaneous adipose tissue, and muscle tissue at T10 are reported in Figure E5 of the supplementary material.

Finally, we examined the relationship between adipose tissue and muscle and end-expiratory Pes in a multivariate model that controlled for other possible confounding factors, such as age, sex, and clinical severity of illness. Both subcutaneous adipose tissue cross-sectional area at T10 and intrathoracic adipose tissue volume showed a positive and significant association with end-expiratory Pes, while no association was found with muscle cross-sectional area

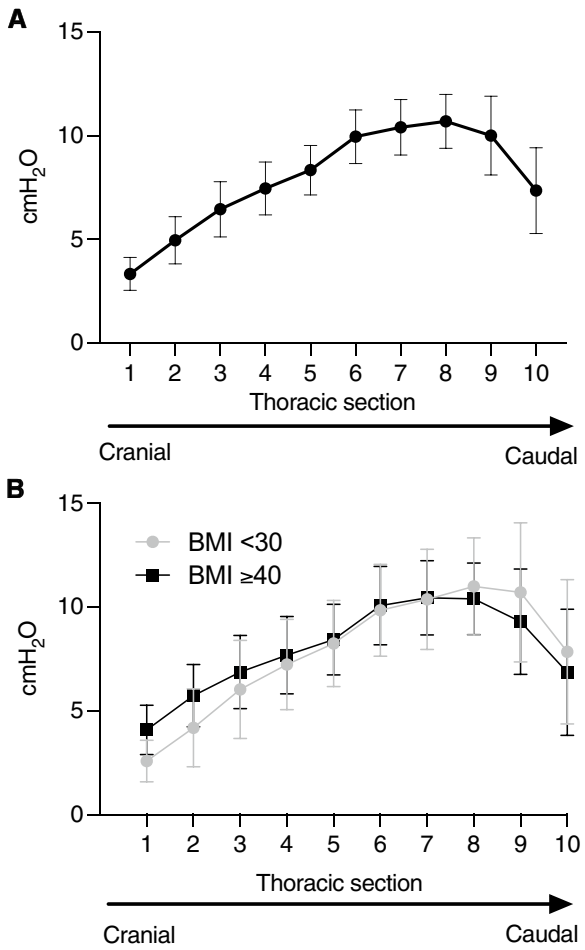

Fig. 3 **A** Regional superimposed pressure measured for the overall population at each thoracic section with 1 being the most cranial and 10 the most caudal, reported as mean and 95%CI. **B** Regional superimposed pressure for patients with body mass index (BMI) < 30 or ≥ 40 kg/m^2 measured at each thoracic section, with 1 being the most cranial and 10 the most caudal, reported as mean and 95%CI. *$p < 0.001$ between thoracic sections, repeated measures two-way ANOVA

at T10. Complete results of the models are provided in Tables E4, E5, and E6 in the supplementary material.

Discussion

This study demonstrated that in patients with class III obesity suffering from acute respiratory failure: (I) the Ppl gradient was significantly higher than the superimposed pressure; (II) the subcutaneous and intrathoracic adipose tissue was a primary determinant in generating high levels of pleural pressure; and (III) the chest wall elastance was not different compared to non-obese subjects and was not influenced by either adipose tissue or muscle.

This is the first study to investigate the superimposed pressure resulting from class III obesity and its relationship with Ppl gradients. We found that the extent of these two variables does not coincide in this subpopulation of patients. This result is at variance with our findings in lower-weight patients and challenges previous studies where Ppl gradient matched superimposed pressure measured on CT scan imaging [15]. Furthermore, our CT data suggest that the quantity of adipose tissue, either cross sectional area of subcutaneous adipose tissue or intrathoracic adipose tissue volume, might be the dominant factor generating high intrapleural pressures in severe obesity. In addition to providing novel information on the mechanisms leading to the known pleural pressure abnormalities in patients with severe obesity, the current study may help explain differences in physiological responses to standardized respiratory treatment between patients with class III obesity and the population with lower weight.

Pleural pressure distributions result from the interaction between the mechanical and geometric characteristics of the lungs and chest wall, resulting in a vertical Ppl gradient [25]. The gradient is increased in lung diseases such as ARDS, where the lungs are edematous, and their weight is abnormally high [14]. In fact, studies showed the correlation between lung weight and Ppl gradients, which are augmented when the lungs are injured [26]. However, the effects of severe obesity and thoracic adipose tissue on Ppl gradients and their interaction with lung characteristics are less understood. The weight of the lungs might not be the only determinant of the Ppl gradient in subjects with severe obesity, where increased adipose tissue in the chest and abdomen compresses the lungs. This study investigated the mechanisms that generate high Pes in patients with class III obesity. We used chest CT scan to quantify the pressure exerted by the lungs and to quantify thoracic adipose tissue and muscle.

The weight of the lungs can be estimated in terms of superimposed pressure, which we compared to the extent of the Ppl gradient. This gradient has been extensively investigated in animal models [15, 27, 28] and experimental settings [29]. However, it cannot be *directly* measured in the clinical setting. The Pes has been shown to reflect the Ppl at the esophagus level (i.e., dependent lung regions). We *indirectly* estimated the Ppl also according to the elastance-ratio method [$P_{plat} \times (E_{lung}/E_{rs})$], which is considered a reliable approximation of the Ppl in the non-dependent lung regions [15, 30]. Therefore, we calculated the Ppl gradient and confirmed that in patients with BMI < 30 kg/m^2, the extent of the superimposed pressure and the Ppl gradient are

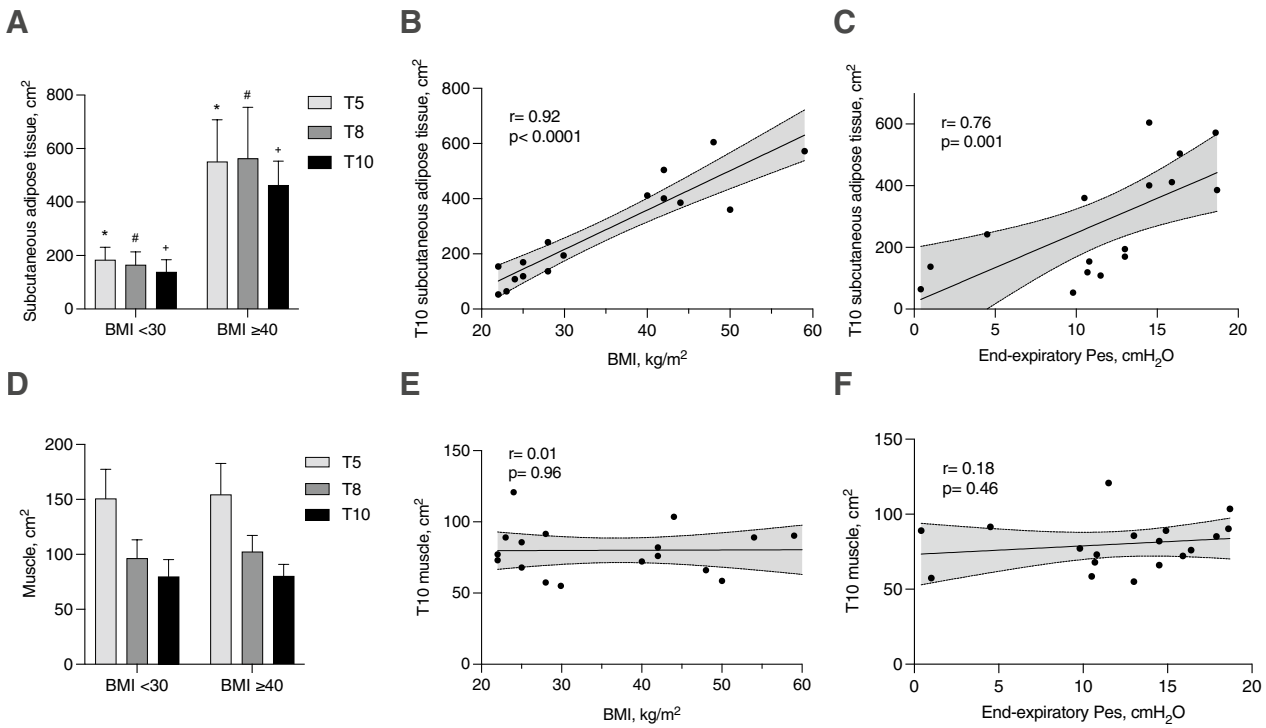

Fig. 4 Subcutaneous adipose tissue (**A**–**C**) and muscle (**D**–**F**) areas at different thoracic vertebral levels. **A** Subcutaneous adipose tissue cross sectional area at T5, T8, and T10 in patients with body mass index (BMI) < 30 or ≥ 40 kg/m^2. Two-way ANOVA, pairwise comparisons between groups: $^{*,\#,+}p < 0.0001$ **B** Correlation between subcutaneous adipose tissue cross sectional area at T10 and BMI. **C** Correlation between subcutaneous adipose tissue cross sectional area at T10 and end-expiratory esophageal pressure (Pes). **D** Muscle cross sectional area at T5, T8, and T10 in patients with BMI < 30 or ≥ 40 kg/m^2. Two-way ANOVA, pairwise comparisons between groups: $p > 0.05$. **E** Correlation between muscle cross sectional area at T10 and BMI. **F** Correlation between muscle cross sectional area at T10 and end-expiratory Pes. For each correlation, r and *p* values are reported in the graphs, along with linear regression line and 95% confidence intervals

comparable. However, in individuals with a BMI ≥ 40 kg/m^2, the Ppl gradient was significantly higher than the superimposed pressure. This finding prompted us to investigate other mechanisms associated with such a higher Ppl gradient in subjects with severe obesity.

We focused on the *quantity* of adipose and muscle tissues at the chest level, which have been less investigated in prior studies than the abdominal adipose tissue [31, 32]. We utilized a method based on imaging deep-learning analysis that has been previously validated and shown to be accurate and reliable [18]. We found that muscle does not increase in subjects with high BMI or correlate with any respiratory mechanics variables. On the other hand, subcutaneous and intrathoracic adipose tissue were significantly higher in subjects with class III obesity. Both subcutaneous adipose tissue cross-sectional area and intrathoracic adipose tissue volume positively correlated with the absolute values of end-expiratory Pes. Moreover, the subcutaneous adipose tissue area at T10 also correlated with the Ppl gradient, suggesting that a compressive effect by adipose tissue may contribute to the increased esophageal pressure values recorded in subjects with severe obesity. This explanation is also compatible with the observation that chest wall elastance was not increased in individuals with higher BMI, contradicting previous findings that subjects with obesity had stiffer chest walls. However, our data are aligned with results by others [16, 17, 21, 33, 34] and can be explained by a prevalent mechanism of mass loading exerted by thoracic adiposity on intrathoracic structures [35].

The present study has important clinical and research implications that should be considered when caring for critically ill patients with an elevated BMI. First, the study provides evidence that thoracic adiposity and not only the pulmonary characteristics themselves heavily influence pleural mechanics. We might speculate that the adipose tissue distribution (thoracic vs. abdominal) and its quantity might correlate with the extent of the Ppl gradient. We envision that imaging might predict the extent of such gradient, based on adipose tissue quantity and its specific distribution in the body, and therefore help clinicians setting mechanical ventilation, even in the absence of advanced tools such as esophageal pressure monitoring and electric impedance

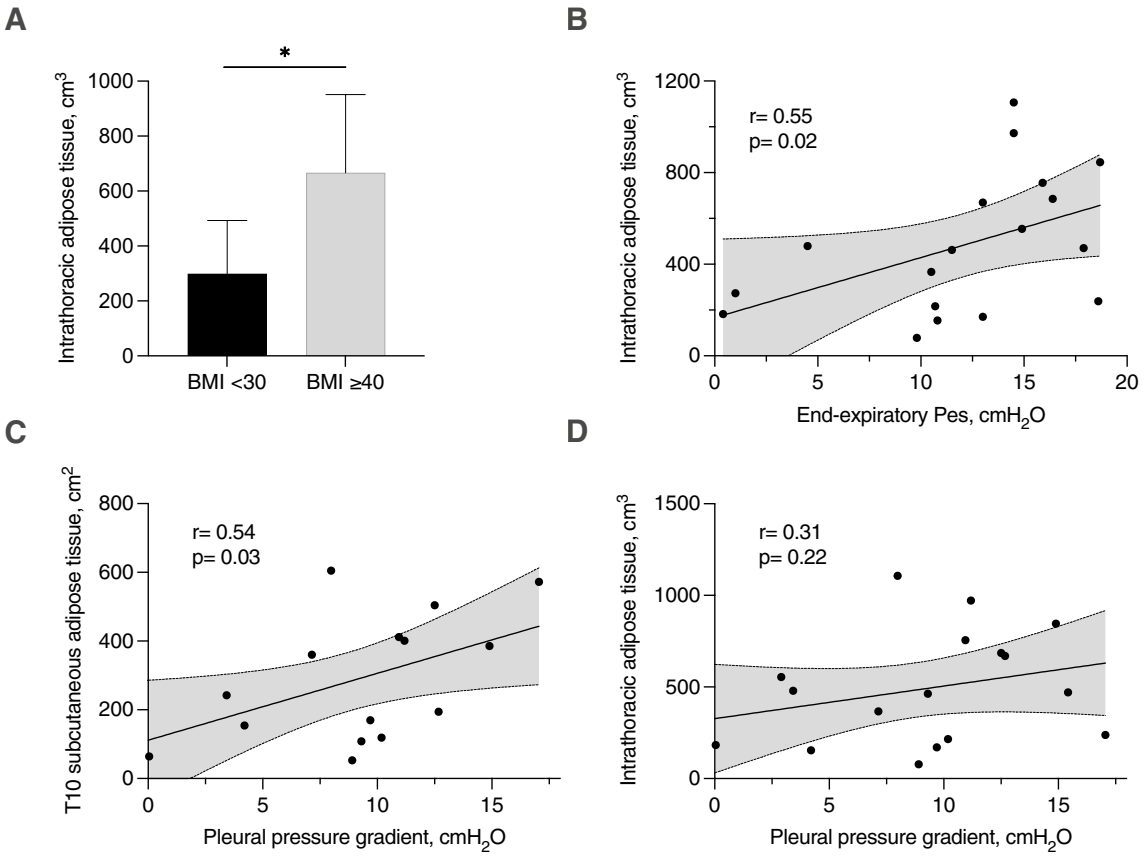

Fig. 5 **A** Intrathoracic adipose tissue volume in patients with body mass index (BMI) < 30 or ≥ 40 kg/m^2. *$p = 0.05$. **B** Correlation between intrathoracic adipose tissue volume and end-expiratory esophageal pressure (Pes). **C** Correlation between subcutaneous adipose tissue cross sectional area at T10 and the pleural pressure gradient. **D** Correlation between intrathoracic adipose tissue volume and the pleural pressure gradient. For each correlation, r and *p* values are reported in the graphs, along with linear regression line and 95% confidence intervals

tomography. Second, increased intrathoracic/pleural pressure causes airway and alveolar collapse and requires specific therapeutic responses. Efforts aimed at counteracting the increased intrathoracic pressure, such as keeping high PEEP levels and performing recruitment maneuvers, have a strong rationale with respect to our findings [22, 36, 37]. We further provide evidence supporting the need for randomized prospective trials on ventilatory management specifically targeting patients with severe obesity. Third, our results may help explain why patients with severe obesity tend to have more severe hypoxemia than expected based on the mere extent of lung disease. In fact, patients with BMI ≥ 40 kg/m^2 had comparable arterial oxygenation but received higher PEEP than non-obese subjects in our study. However, lung elastance was lower in the subjects with severe obesity, while the superimposed pressure (an index associated with interstitial edema) was comparable between the two groups. The fact that subjects with higher BMI are more hypoxic than expected based on lung conditions might contribute to the equivocal effects of obesity on ARDS mortality [38, 39].

A few recent studies investigated mechanical ventilation settings in patients with obesity. Li et al. tested the benefits of recruitment maneuvers and PEEP titration based on respiratory system compliance in patients undergoing laparoscopic bariatric surgery [40]. The authors reported a lower incidence of atelectasis in the intervention study group, where PEEP was, on average, 15 cmH_2O, as compared to 8 cmH_2O in controls [40]. The benefits of providing higher respiratory pressures were also tested in the post-extubation period by means of non-invasive ventilation (NIV). De Jong et al. conducted the EXTUB-OBESE multicenter randomized controlled trial, where patients with obesity were assigned to NIV or standard oxygen therapy after extubation in the ICU [41]. The study demonstrated that subjects with obesity had fewer treatment failures (a composite outcome) as compared to control subjects. Other recent observational studies focused on the impact of obesity on respiratory mechanics. For instance, Beloncle et al. measured

esophageal pressure and the presence of airway closure in a cohort of patients admitted to the ICU, with or without obesity, and with or without ARDS [42]. The authors found that patients with obesity and ARDS had a higher degree of complete airway closure than non-obese. Moreover, the study also reported higher end-expiratory Pes, regardless of the presence of ARDS, and no difference in chest wall elastance between groups, which aligns with our findings. The presence of complete airway closure has also been confirmed by Coudroy et al., who found its presence up to 65% in subjects with ARDS and BMI $\geq$ 40 kg/m^2 [43]. The study also found a positive and significant correlation between BMI and end-expiratory Pes, confirming our results shown in Table 2. The importance of considering the unique physiologic features of obesity has been recently highlighted by Chen et al. in a prospective observational multicenter study [44]. The authors reported that individuals with obesity and ARDS had higher survival rates when mechanical ventilation was set to keep end-expiratory transpulmonary pressure equal to or higher than 0 cmH_2O. Taken together, these studies suggest that standard ventilatory strategies might fail when caring for patients with obesity, especially with extreme BMI. The abdominal adipose tissue load has been advocated by most investigators as the key factor for increased esophageal pressure [45]. The role of thoracic adiposity has been less investigated, and our study suggests that its quantity and distribution might have a relevant impact on respiratory mechanics.

The study has some strengths. It introduces a novel physiologic concept; as shown, the Ppl gradient does not approximate the superimposed pressure in patients with class III obesity. The study utilized advanced imaging techniques that allowed us to precisely quantify the amount of thoracic adipose tissue. Finally, the study provides Pes measurements that were carefully recorded and analyzed offline, according to the experience proved by our research group on this subject.

The study also has some limitations. Its design is retrospective, although all respiratory mechanics data are prospectively collected and analyzed by a dedicated team at our institution. The sample size is relatively small, and the risk for increased type II error (i.e., if no differences between study groups are recorded when instead there are) should be acknowledged. However, we calculated the sample size to achieve a statistical power of 95% relative to the primary endpoint (end-expiratory Pes), which is higher than the conventional minimum (80%) and decreases the likelihood of type II error by providing more solid and credible results. We also hope that the present study might foster future studies with larger sample sizes in order to corroborate our findings. The chest CT scan was performed on a day different from esophageal manometry for some patients. However, we limited this timeframe to a maximum of three days. It should also be acknowledged that performing a CT scan in patients with very high BMI is technically challenging and sometimes unsafe for critically ill patients. Also, the PEEP level during imaging differed from the PEEP level during esophageal manometry for some subjects. For this reason, we allowed a maximum PEEP difference of four cmH_2O. We reported a table with differences in both days and PEEP levels for each subject to provide the highest transparency to the study. Another possible limitation is the estimation of the pleural pressure in the non-dependent regions of the lungs through the elastance ratio method. We know this approach has not been thoroughly investigated in subjects with obesity; however, to date, it is the only way to estimate the Ppl gradient at the bedside. Our study further encourages new studies that can confirm the validity of the elastance ratio method also in the obese population.

We acknowledge another important limitation of the study. Subjects with BMI $\geq$ 40 kg/m^2 had higher PEEP levels than the other study group, which might represent a selection bias of the study that could limit the generalizability of our findings. This reflects the management of patients with morbid obesity at our Institution, where a dedicated LRT often utilizes non-standard mechanical ventilation parameters, such as higher PEEP and recruitment maneuvers in patients with very high BMI, with the goal of optimizing lung recruitment and improving clinical outcomes [36]. However, we believe that the influence of PEEP on Pes and Ppl gradient might have been limited, given prior findings on large animals and human cadavers with lung injury that showed constant Ppl gradient at increasing levels of PEEP [15]. Furthermore, only 20–30% of higher PEEP was likely transmitted to the pleural cavity, given the E_{lung}/E_{rs} of about 0.7–0.8 in both groups. Based on the E_{lung}/E_{rs} one could estimate the expected influence of different PEEP levels on Pes and Ppl gradient, which we found to be relatively minor. Moreover, previous studies demonstrated that absolute values of Pes are significantly elevated in spontaneously breathing subjects with class III obesity before and after starting CPAP, suggesting a minimal effect of applied external PEEP [21]. Finally, we acknowledge that electric impedance tomography might have provided further information about ventilation distribution. This could have detected overdistension of the non-dependent lung regions, especially when high PEEP levels were used in patients with high BMI.

Conclusions

In patients with class III obesity (i.e., BMI ≥ 40 kg/m^2), the superimposed pressure does not approximate the Ppl gradient, which we found to be higher than in patients with lower BMI. The elevated Ppl gradient indicates that mechanisms beyond superimposed pressure, such as the quantity and distribution of subcutaneous and intrathoracic adipose tissue, contribute to increased Ppl gradients in individuals with severe obesity. These findings underscore the necessity for tailored ventilatory strategies in patients with class III obesity to mitigate the elevated intrathoracic pressure and its adverse effects on lung volumes and airway closure. Implementing these customized approaches can enhance respiratory outcomes and overall clinical management for patients with severe obesity.

Abbreviations

BMI	Body Mass Index
ARDS	Acute respiratory distress syndrome
PEEP	Positive end-expiratory pressure
Ppl	Pleural pressure
Pes	Esophageal pressure
CT	Computed tomography
ICU	Intensive care unit
SAPS II	Simplified acute physiology score II
APACHE II	Acute physiology and chronic health evaluation II
LRT	Lung rescue team
SP	Superimposed pressure
SPglobal	Global superimposed pressure
SPregional	Regional superimposed pressure
PaO_2/FiO_2	Partial pressure of oxygen to fraction of inspired oxygen ratio
E_{lung}/E_{rs}	Elastance of the lung to elastance of the respiratory system ratio
T5, T8, T10	Thoracic vertebral levels 5, 8, and 10
CI	Confidence Interval

Supplementary Information

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Supplementary file 1

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Author contributions

MC, LB, RRS, LG, and SS conceived the study. SS, LM, DM, YX, AN and SG performed data analysis. SS, MC and LB prepared the first draft of the manuscript. All authors were responsible for data acquisition and interpretation. All authors reviewed the manuscript and approved the final submitted version.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Competing interests

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Ethics approval and consent to participate

This study was approved by Mass General Brigham Institutional Review Board (protocol #2020P003196). The need for informed consent was waived, given the retrospective nature of the study.

Consent for publication

Not applicable.

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References

1. WHO. Obesity and overweight . Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
2. CDC. Adult Obesity Facts. Obesity. 2024. Available from: https://www.cdc.gov/obesity/php/data-research/adult-obesity-facts.html
3. Hibbert K, Rice M, Malhotra A. Obesity and ARDS. Chest. 2012;142:785–90.
4. De Jong A, Verzilli D, Jaber S. ARDS in obese patients: specificities and management. Crit Care. 2019;23:74.
5. Gaulton TG, Berra L, Ferreyro BL, Cereda M. Reporting and representation of obesity in randomized controlled trials of noninvasive oxygenation strategies in hypoxemic respiratory failure. Intern Emerg Med. 2022;17:2437–9.
6. Guérin C, Reignier J, Richard J-C, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368:2159–68.
7. The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network. Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome. N Engl J Med. 2019;380:1997–2008.
8. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA. 2008;299:637–45.
9. Mercat A, Richard J-CM, Vielle B, Jaber S, Osman D, Diehl J-L, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA. 2008;299:646–55.

10. Higher versus Lower Positive End-Expiratory Pressures in Patients with the Acute Respiratory Distress Syndrome. N Engl J Med. 2004;351:327–36.
11. Grasselli G, Calfee CS, Camporota L, Poole D, Amato MBP, Antonelli M, et al. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. Intensive Care Med. 2023;49:727–59.
12. Qadir N, Sahetya S, Munshi L, Summers C, Abrams D, Beitler J, et al. An update on management of adult patients with acute respiratory distress syndrome: an official American thoracic society clinical practice guideline. Am J Respir Crit Care Med. 2024;209:24–36.
13. Grassi L, Kacmarek R, Berra L. Ventilatory mechanics in the patient with obesity. Anesthesiology. 2020;132:1246–56.
14. Pelosi P, D'Andrea L, Vitale G, Pesenti A, Gattinoni L. Vertical gradient of regional lung inflation in adult respiratory distress syndrome. Am J Respir Crit Care Med. 1994;149:8–13.
15. Yoshida T, Amato MBP, Grieco DL, Chen L, Lima CAS, Roldan R, et al. Esophageal manometry and regional transpulmonary pressure in lung injury. Am J Respir Crit Care Med. 2018;197:1018–26.
16. Pirrone M, Fisher D, Chipman D, Imber DAE, Corona J, Mietto C, et al. Recruitment maneuvers and positive end-expiratory pressure titration in morbidly obese ICU patients. Crit Care Med. 2016;44:300–7.
17. Fumagalli J, Berra L, Zhang C, Pirrone M, Santiago RRDS, Gomes S, et al. Transpulmonary Pressure describes lung morphology during decremental positive end-expiratory pressure trials in obesity*. Crit Care Med. 2017;45:1374–81.
18. Bridge CP, Best TD, Wrobel MM, Marquardt JP, Magudia K, Javidan C, et al. A fully automated deep learning pipeline for multi-vertebral level quantification and characterization of muscle and adipose tissue on chest CT scans. Radiol Artif Intell. 2022;4:e210080.
19. Gerard SE, Herrmann J, Kaczka DW, Musch G, Fernandez-Bustamante A, Reinhardt JM. Multi-resolution convolutional neural networks for fully automated segmentation of acutely injured lungs in multiple species. Med Image Anal. 2020;60:101592.
20. Spina S, Capriles M, De Santis SR, Florio G, Teggia-Droghi M, Grassi L, et al. Development of a lung rescue team to improve care of subjects with refractory acute respiratory failure. Respir Care. 2020;65:420–6.
21. Florio G, De Santis Santiago RR, Fumagalli J, Imber DA, Marrazzo F, Sonny A, et al. Pleural pressure targeted positive airway pressure improves cardiopulmonary function in spontaneously breathing patients with obesity. Chest. 2021;159:2373–83.
22. De Santis Santiago R, Teggia Droghi M, Fumagalli J, Marrazzo F, Florio G, Grassi LG, et al. High pleural pressure prevents alveolar overdistension and hemodynamic collapse in acute respiratory distress syndrome with class III obesity. A clinical trial. Am J Respir Crit Care Med. 2021;203:575–84.
23. Gerard SE, Patton TJ, Christensen GE, Bayouth JE, Reinhardt JM. FissureNet: a deep learning approach for pulmonary fissure detection in CT images. IEEE Trans Med Imaging. 2019;38:156–66.
24. Gerard SE, Herrmann J, Xin Y, Martin KT, Rezoagli E, Ippolito D, et al. CT image segmentation for inflamed and fibrotic lungs using a multi-resolution convolutional neural network. Sci Rep. 2021;11:1455.
25. Plataki M, Hubmayr RD. Should mechanical ventilation be guided by esophageal pressure measurements? Curr Opin Crit Care. 2011;17:275–80.
26. Gattinoni L, Caironi P, Pelosi P, Goodman LR. What has computed tomography taught us about the acute respiratory distress syndrome? Am J Respir Crit Care Med. 2001;164:1701–11.
27. D'Angelo E, Bonanni MV, Michelini S, Agostoni E. Topography of the pleural surface pressure in rabbits and dogs. Respir Physiol. 1970;8:204–29.
28. Agostoni E. Mechanics of the pleural space. Physiol Rev. 1972;52(1):57–128.
29. Daly WJ, Bondurant S. Direct measurement of respiratory pleural pressure changes in normal man. J Appl Physiol. 1963;18:513–8.
30. Gattinoni L, Chiumello D, Carlesso E, Valenza F. Bench-to-bedside review: chest wall elastance in acute lung injury/acute respiratory distress syndrome patients. Crit Care. 2004;8:350.
31. Mahabadi AA, Massaro JM, Rosito GA, Levy D, Murabito JM, Wolf PA, et al. Association of pericardial fat, intrathoracic fat, and visceral abdominal fat with cardiovascular disease burden: the Framingham Heart Study. Eur Heart J. 2008;30:850–6.
32. Fumagalli IA, Le ST, Peng PD, Kipnis P, Liu VX, Caan B, et al. Automated CT analysis of body composition as a frailty biomarker in abdominal surgery. JAMA Surg. 2024. https://doi.org/10.1001/jamasurg.2024.0628.
33. Hedenstierna G, Santesson J. Breathing mechanics, dead space and gas exchange in the extremely obese, breathing spontaneously and during anaesthesia with intermittent positive pressure ventilation. Acta Anaesthesiol Scand. 1976;20:248–54.
34. Behazin N, Jones SB, Cohen RI, Loring SH. Respiratory restriction and elevated pleural and esophageal pressures in morbid obesity. J Appl Physiol. 2010;108:212–8.
35. Sharp JT, Henry JP, Sweany SK, Meadows WR, Pietras RJ. Effects of mass loading the respiratory system in man. J Appl Physiol. 1964;19:959–66.
36. For the investigators of the lung rescue team, Florio G, Ferrari M, Bittner EA, De Santis Santiago R, Pirrone M, et al. A lung rescue team improves survival in obesity with acute respiratory distress syndrome. Crit Care. 2020;24:4.
37. De Jong A, Wrigge H, Hedenstierna G, Gattinoni L, Chiumello D, Frat J-P, et al. How to ventilate obese patients in the ICU. Intensive Care Med. 2020;46:2423–35.
38. Zhi G, Xin W, Ying W, Guohong X, Shuying L. "Obesity Paradox" in acute respiratory distress syndrome: asystematic review and meta-analysis. PLoS ONE. 2016;11:e0163677.
39. Ball L, Serpa Neto A, Pelosi P. Obesity and survival in critically ill patients with acute respiratory distress syndrome: a paradox within the paradox. Crit Care. 2017;21:114.
40. Li X, Liu H, Wang J, Ni Z-L, Liu Z-X, Jiao J-L, et al. Individualized positive end-expiratory pressure on postoperative atelectasis in patients with obesity: a randomized controlled clinical trial. Anesthesiology. 2023;139:262–73.
41. De Jong A, Bignon A, Stephan F, Godet T, Constantin J-M, Asehnoune K, et al. Effect of non-invasive ventilation after extubation in critically ill patients with obesity in France: a multicentre, unblinded, pragmatic randomised clinical trial. Lancet Respir Med. 2023;11:530–9.
42. Beloncle FM, Richard J-C, Merdji H, Desprez C, Pavlovsky B, Yvin E, et al. Advanced respiratory mechanics assessment in mechanically ventilated obese and non-obese patients with or without acute respiratory distress syndrome. Crit Care. 2023;27:343.
43. Coudroy R, Vimpere D, Aissaoui N, Younan R, Bailleul C, Couteau-Chardon A, et al. Prevalence of complete airway closure according to body mass index in acute respiratory distress syndrome: pooled cohort analysis. Anesthesiology. 2020;133:867–78.
44. Chen L, Grieco DL, Beloncle F, Chen G-Q, Tiribelli N, Madotto F, et al. Partition of respiratory mechanics in patients with acute respiratory distress syndrome and association with outcome: a multicentre clinical study. Intensive Care Med. 2022;48:888–98.
45. Esquinas AM, Lemyze M, editors. Mechanical ventilation in the critically Ill obese patient. Cham: Springer; 2018. https://doi.org/10.1007/978-3-319-49253-7.

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