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Prevalence of Complete Airway Closure According to Body Mass Index in Acute Respiratory Distress Syndrome

Pooled Cohort Analysis

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Plateau and driving pressures have been shown to correlate with mortality in adult respiratory distress syndrome (ARDS). However, these static airway pressures may not always accurately reflect alveolar pressure.
- It has recently been recognized that in ARDS, airway closure may occur while some alveoli are still inflated. This may result in a biased estimate of mean alveolar pressure.
- Complete airway closure can only be measured by the inflection point on the initial portion of a low-flow inflation pressure–volume or pressure–time curve with the absence of cardiac oscillations and very low compliance, most likely in the terminal bronchioles.
- In 25 to 33% of patients with ARDS, airway opening pressure (the inflection point value) is greater than the total positive end-expiratory pressure measured by an end-expiratory maneuver.

What This Article Tells Us That Is New

- In a *post hoc* analysis of two cohort studies of respiratory mechanics in ARDS, the authors compared the prevalence of complete airway closure stratified by body mass index and its effects on respiratory mechanics.
- Complete airway closure was present in 41% of patients, increasing with body mass index tercile (65% in the highest).
- Driving pressure and respiratory system elastances (lung, chest wall) were higher when complete airway closure was not adjusted for.

ABSTRACT

Background: Complete airway closure during expiration may underestimate alveolar pressure. It has been reported in cases of acute respiratory distress syndrome (ARDS), as well as in morbidly obese patients with healthy lungs. The authors hypothesized that complete airway closure was highly prevalent in obese ARDS and influenced the calculation of respiratory mechanics.

Methods: In a *post hoc* pooled analysis of two cohorts, ARDS patients were classified according to body mass index (BMI) terciles. Low-flow inflation pressure–volume curve and partitioned respiratory mechanics using esophageal manometry were recorded. The authors' primary aim was to compare the prevalence of complete airway closure according to BMI terciles. Secondary aims were to compare (1) respiratory system mechanics considering or not considering complete airway closure in their calculation, and (2) and partitioned respiratory mechanics according to BMI.

Results: Among the 51 patients analyzed, BMI was less than 30 kg/m^2 in 18, from 30 to less than 40 in 16, and greater than or equal to 40 in 17. Prevalence of complete airway closure was 41% overall (95% CI, 28 to 55; 21 of 51 patients), and was lower in the lowest (22% [3 to 41]; 4 of 18 patients) than in the highest BMI tercile (65% [42 to 87]; 11 of 17 patients). Driving pressure and elastances of the respiratory system and of the lung were higher when complete airway closure was not taken into account in their calculation. End-expiratory esophageal pressure ($\rho = 0.69$ [95% CI, 0.48 to 0.82]; $P < 0.001$), but not chest wall elastance, was associated with BMI, whereas elastance of the lung was negatively correlated with BMI ($\rho = -0.27$ [95% CI, −0.56 to −0.10]; $P = 0.014$).

Conclusions: Prevalence of complete airway closure was high in ARDS and should be taken into account when calculating respiratory mechanics, especially in the most morbidly obese patients.

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Obesity affects many aspects of the care delivered to the patient. Among means of treatments, mechanical ventilation may be one of the most complex and difficult to apply in critical care.[1] The impact of obesity on delivery of mechanical ventilation remains debated in the operating theater and the intensive care unit (ICU), especially in acute respiratory distress syndrome (ARDS).[2,3]

In moderate-to-severe ARDS according to the Berlin definition,[4] experts recommend the use of high positive end-expiratory pressure (PEEP) levels,[5] with the aim to prevent atelectrauma from occurring during mechanical ventilation with a cycling collapse and airway and alveoli reopening causing pulmonary damages through shear forces. High PEEP strategy has been associated with decreased mortality.[6] Usual open lung strategy is guided by airway pressure measurements, easily available for clinicians at the

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bedside.[7] However, global respiratory system mechanics may be misleading in obese ARDS. For example, driving pressure of the respiratory system, computed as the difference between end-inspiratory and end-expiratory airway pressure, is a strong predictor of mortality in an overall ARDS population.[8] Conversely, it does not predict mortality in obese ARDS.[9] The actual influence of chest wall on obese respiratory mechanics has been debated, as some experts claim that the "stiff" chest wall of obese patients could impair their respiratory mechanics,[10] while others did not find any difference with nonobese patients.[11]

Recently, complete airway closure has been suggested in ARDS.[12] In these patients, lung inflation starts when airway pressure reaches a critical level of opening pressure.[13] This phenomenon may be due to the collapse of airways at end-expiration. The actual location of this collapse is unknown, but it could occur in terminal bronchioles as suggested by animal models[14,15] and histological examination of ARDS lungs.[16] As a consequence, alveoli remain inflated at end-expiration. Therefore, airway pressure may be different from alveolar pressure, altering calculation of respiratory mechanics such as driving pressure. As complete airway closure has been reported in 22% of obese anesthetized patients with normal lungs,[17] we hypothesized that this phenomenon is frequent in obese ARDS and influences the assessment of respiratory mechanics.

Our primary aim was to compare prevalence of complete airway closure stratified by body mass index (BMI). Secondary aims were to compare respiratory mechanics (respiratory system elastance, end-expiratory transpulmonary pressure, and lung elastance) accounting or not for complete airway closure, and to compare chest wall mechanics (end-expiratory esophageal pressure and elastance of the chest wall) and lung mechanics (end-expiratory transpulmonary pressure and elastance of the lung) stratified by BMI.

Materials and Methods

Patients

This study is a *post hoc* analysis of two cohort studies on ARDS in which complete respiratory mechanics were assessed using an esophageal catheter at similar PEEP levels.

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The first cohort is a prospective Canadian study (ClinicalTrials.gov NCT02457741) including patients older than 16, with moderate-to-severe ARDS according to the Berlin definition,[4] and esophageal manometry.[18] Patients with pneumothorax and bronchopleural fistula requiring chest tube, severe hemodynamic instability (defined as more than a 30% increase in vasopressors in the last 6 h or norepinephrine more than 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$), persistent ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (Pao_2/Fio_2) less than 80 mmHg, chronic obstructive lung disease with a Global Initiative for Chronic Obstructive Lung Disease classification grade greater than or equal to 3, and known or suspected elevated intracranial pressure greater than 18 mmHg were excluded. From July 2015 to November 2017, 45 patients were enrolled in the study. One additional patient was excluded from the current analysis given that person's short height (101 cm), which would have biased BMI calculation.

The second study is a retrospective study performed in a 20-bed French medial ICU. In this unit, esophageal manometry and low-inflation pressure–volume curve at PEEP 0 or 5 cm H_2O are routinely performed in all morbidly obese patients with BMIs greater than or equal to 40 kg/m^2 and moderate-to-severe ARDS, according to the Berlin definition.[4] From July 2013 to January 2018, 10 consecutive patients were admitted corresponding to the aforementioned criteria. After reviewing all tracings, one patient with esophageal balloon misplacement and two patients without low-flow inflation pressure–volume curve recorded were excluded from the current analysis. All in all, 51 patients were included in the analysis (Supplemental Digital Content, fig. 1, http://links.lww.com/ALN/C435).

Ethics

In the prospective cohort, the study was approved by the Ethics Board (Research Ethics Board No. 15-074) and informed consent was obtained from relatives when patients were unable to provide consent by themselves. In the retrospective cohort, the study was approved by the local Institutional Review Board (Research Ethics Committee, Assistance Publique des Hôpitaux de Paris 5, Paris, Institutional Review Board registration No. 00011928), and informed consent was waived, as per French law, given the retrospective nature of the study.

Data Collection

Baseline characteristics such as age, gender, weight, height, and characteristics at enrollment such as PEEP, tidal volume (V_T), respiratory rate, and Pao_2/Fio_2 were collected. BMI was computed as weight (in kg) divided by height^2 (in m^2) and patients were classified according to the World Health Organization obesity classification for obesity: nonobese for BMI less than 30 kg/m^2, grade I and II obese patients for BMI from 30 to less than 40 kg/m^2, and grade III or morbidly obese patients for BMI greater than or equal to

40 kg/m^2.[19] There were no missing data. Acute Physiology and Chronic Health Evaluation II score at ICU admission was computed and outcomes such as ICU length of stay and ICU survival were collected.

Measurements

All patients were deeply sedated and paralyzed to ensure passive ventilation and ventilated using constant flow ventilation during maneuvers (volume-controlled mode). Measurements were performed in a semirecumbent position at low PEEP set between 5 and 8 cm H_2O according to patient's tolerance for oxygenation. Esophageal pressure was measured using a catheter with an air-filled balloon (Cooper Surgical, USA) in the prospective cohort, and using a double balloon catheter (Nutrivent catheter; Sidam, Italy) in the retrospective cohort. In both studies, esophageal catheters were calibrated according to the volume of balloon inflation providing the maximum difference between end-inspiratory and end-expiratory esophageal pressure.[20] For each patient, the esophageal balloon's position was assessed by performing gentle chest compressions during an occlusion test.[20] Adequate esophageal balloon position was defined as the ratio of esophageal to airway pressure changes during the occlusion test between 0.8 to 1.2 as recommended.[21] Signals from the aforementioned catheters, and from the ventilator (airway pressure and flow measured proximal to the endotracheal tube) were sampled and digitized using an external acquisition system (MP150; Acknowledge 4.3, Biopac System Inc, USA). All patients underwent: (1) low-flow inflation (5 l/min) pressure–volume curve from PEEP 0 or 5 cm H_2O to 40 cm H_2O after a prolonged expiratory pause (to avoid auto-PEEP) using the constant flow method on the ventilator[22]; and (2) end-inspiratory and end-expiratory occlusions to measure static airway and esophageal pressures.

Definitions and Computations

Complete Airway Closure and Airway Opening Pressure. Complete airway closure was suspected according to the low-flow inflation pressure–volume curve pattern. A low inflection point associated in the initial part of the curve with the absence of cardiac oscillations and very low compliance, close to the 1.5 to 2.5 ml/cm H_2O of an occluded breathing circuit, was suggestive of complete airway closure (fig. 1).[12,13,17] When pressure exceeded the low inflection point, cardiac oscillations appeared and compliance increased dramatically as compared to the initial part of the curve (fig. 1). This low inflection point corresponds to the pressure to overcome to start inflating the lungs and was named airway opening pressure. Airway opening pressure was considered significant when greater than 5 cm H_2O.

Respiratory System Mechanics. Total PEEP corresponded to static airway pressure measured during end-expiratory occlusion (zero flow). Auto-PEEP was considered when total PEEP exceeded PEEP set. Airway plateau pressure corresponded to static airway pressure measured during end-inspiratory occlusion (zero-flow). Resistance of the respiratory system was calculated as the difference between peak airway pressure and airway plateau pressure divided by inspiratory flow.

Calculations Not Considering Complete Airway Closure. For all patients, driving pressure of the respiratory system was calculated as airway plateau pressure – total PEEP. Elastance of the respiratory system (elastance of the respiratory system) was calculated as (airway plateau pressure – total PEEP) / V_T.[23] Time constant of the respiratory system was computed as resistance of the respiratory system divided by elastance of the respiratory system.

Calculations Corrected for Complete Airway Closure. For patients fulfilling the aforementioned criteria suggesting complete airway closure, driving pressure of the respiratory system was calculated as airway plateau pressure – airway opening pressure. Elastance of the respiratory system corrected for complete airway closure was calculated as (airway plateau pressure – airway opening pressure) / V_T. Time constant of the respiratory system corrected for complete airway closure was computed as resistance of the respiratory system divided by elastance of the respiratory system considering complete airway closure. For patients not fulfilling the criteria for complete airway closure, driving pressure of the respiratory system, elastance of the respiratory system and time constant of the respiratory system remained unchanged.

Chest Wall Mechanics. End-expiratory and end-inspiratory esophageal pressure were measured during end-expiratory occlusion (zero flow). Driving pressure of the chest wall was calculated as end-inspiratory esophageal pressure – end-expiratory esophageal pressure. Elastance of the chest wall was calculated as (end-inspiratory esophageal pressure – end-expiratory esophageal pressure) / V_T.

Lung Mechanics

Calculations Not Considering Complete Airway Closure. For all patients, absolute values of transpulmonary pressure at end-expiration and end-inspiration were calculated as airway pressure – esophageal pressure at end-expiration and end-inspiration, respectively. Additionally, end-inspiratory plateau pressure of the lung using elastance-derived method was calculated[24,25] as airway plateau pressure – [airway plateau pressure × (elastance of the chest wall / elastance of the respiratory system)]. Physiologic study reported that end-inspiratory plateau pressure of the lung using elastance-derived method reflects end-inspiratory transpulmonary pressure in the nondependent lung regions.[26] Driving pressure of the lung was calculated as end-inspiratory transpulmonary pressure – end-expiratory transpulmonary pressure. Elastance of the lung was calculated as (end-inspiratory transpulmonary pressure – end-expiratory transpulmonary pressure) / V_T.

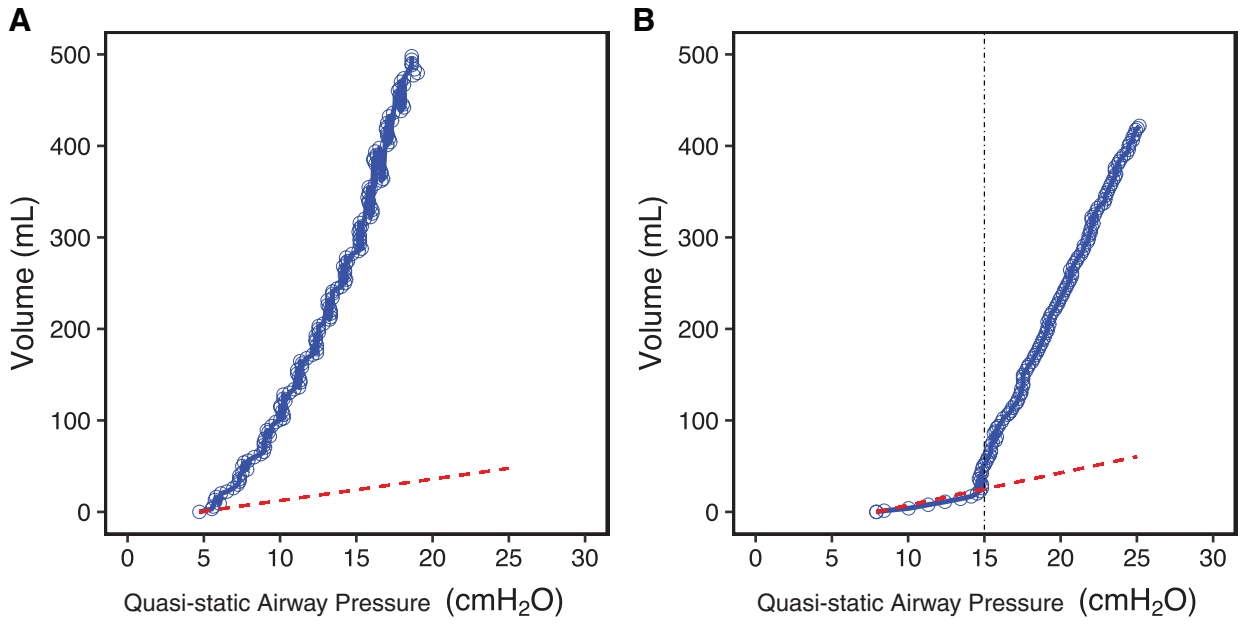

Fig. 1. Low-flow inflation pressure–volume curves from representative patients (*blue circles with blue line*) without (*A*) and with complete airway closure (*B*). *Red dashed line* represents pressure–volume curve of an occluded circuit (compliance 2.4 ml/cm H_2O). *Black dash-dotted line* marks airway opening pressure. In *A*, pressure–volume curve of the patient and the occluded circuit separate immediately and cardiac oscillations can be seen throughout the pressure–volume curve of the patient. In *B*, the initial part of the pressure–volume curve of the patient is very flat, without cardiac oscillations, and superimposed to that of the occluded circuit, suggesting that gas is compressed in the circuit and airways are closed. Above a pressure level named airway opening pressure (15 cm H_2O in the example), the two curves separate. Slope of the pressure–volume curve of the patient increases and cardiac oscillation appear, suggesting lungs are open.

Calculations Corrected for Complete Airway Closure.

Calculation of transpulmonary pressure assumes that airways are open, and airway pressure therefore reflects alveolar pressure. However, in patients with complete airway closure, airways are closed when airway pressure is lower than airway opening pressure, and airway pressure no-longer reflects alveolar pressure anymore. As a consequence, for patients fulfilling the above-mentioned criteria suggesting complete airway closure and whose total PEEP was lower than airway opening pressure, end-expiratory transpulmonary pressure was calculated as airway opening pressure – end-expiratory esophageal pressure. End-inspiratory plateau pressure of the lung using elastance-derived method, driving pressure of the lung, and elastance of the lung corrected for complete airway closure were calculated using the same formulas as calculations not considering airway closure, but values were corrected for complete airway closure. For patients not fulfilling the criteria for complete airway closure, transpulmonary pressure, driving pressure of the lung, and elastance of the lung remained unchanged.

Statistical Analysis

No statistical power calculation was conducted before this unplanned *post hoc* study. The convenience sample size was based on the available data. Continuous variables were expressed in mean ± SD or median (25th to 75th percentile) according to their distribution, and compared between the three subgroups using the Kruskal–Wallis test. Categorical variables were expressed as number (percentage and 95% CI) and compared using the Fisher exact test. Mean differences and 95% CI were calculated between paired values considering or not airway closure and were compared using paired *t* test. Additionally, Spearman ρ correlation coefficient and its 95% CI were calculated between continuous variables and BMI as a continuous variable and univariate linear regression lines were plotted. BMI as continuous or discretized variable was tested as a predictor of other variables. No variables were analyzed as effect modifiers. Two-tailed *P* value less than 0.05 was considered significant. Analyses were conducted using R software.

Results

Population Characteristics

One out of the 45 patients included in the prospective cohort was excluded for biased BMI calculation due to low height (101 cm). Out of the 10 morbidly obese ARDS consecutively admitted to ICU in the retrospective cohort, one was excluded for inadequate esophageal balloon position, and two because low-flow inflation pressure–volume curve was not performed due to technical issues. Among the 51 patients

stratified by BMI, BMI was less than 30 kg/m^2 in 18 patients (35%), from 30 to less than 40 kg/m^2 in 16 (31%), and greater than or equal to 40 kg/m^2 in 17 (33%). Their baseline characteristics and outcomes are displayed in table 1. In the pooled cohort, age was 60 yr (49 to 69), 25% of patients (11 out of 51) were female and their BMI was 36 kg/m^2 (28 to 42). Overall, patients were ventilated using V_T of 6.1 ml (5.9 to 6.3) per kg of predicted body weight, PEEP of 15 (12 to 18) cm H_2O, and respiratory rate of 26 (23 to 30) breaths/min. Pao_2/Fio_2 was 144 (104 to 163) mmHg without differences between the subgroups. Acute Physiology and Chronic Health Evaluation II score at ICU admission was 26 (19 to 30) and increased according to BMI subgroup. ICU survival was 66% (95% CI, 54 to 80) and was similar between the subgroups.

Prevalence of Complete Airway Closure

All in all, complete airway closure was suspected in 21 out of 51 patients (41% [95% CI, 28 to 55]), and was lower (22% [3 to 41]) in the BMI less than 30 kg/m^2 subgroup than in the BMI greater than or equal to 40 kg/m^2 subgroup (65% [42 to 87], table 2). Median airway opening pressure did not differ between the subgroups and ranged from 5 to 19 cm H_2O (table 2).

Respiratory Mechanics and Influence of Airway Closure Consideration in Calculations

Respiratory system mechanics are detailed in table 2. Overall, auto-PEEP occurred in 21 out of 51 patients (42% [28 to 55]). There was a significant association between airway closure and auto-PEEP ($P = 0.006$) and none of the patients without auto-PEEP had airway closure. However, only 50% of patients with auto-PEEP (21 of 42) had airway closure (Supplemental Digital Content, table 1, http://links.lww.com/ALN/C440, and Supplemental Digital Content, fig. 2, http://links.lww.com/ALN/C436). Correction for complete airway closure in calculations led to significant decrease driving pressure of the respiratory system (mean difference, −0.9 cm H_2O [−1.5 to −0.4]) and elastance of the respiratory system (mean difference, −2.7 cm H_2O/l [−4.6 to −0.9]), and to increased time constant of the respiratory system (mean difference, 0.03 s [0.01 to 0.05]).

Partitioned respiratory system mechanics are detailed in table 3. End-expiratory esophageal pressure was 14.4 cm H_2O (9.9 to 16.3) and elastance of the chest wall was 6.7 cm H_2O/l (5.2 to 10.2). Correction for complete airway closure in calculations led to significant increase end-expiratory transpulmonary pressure (mean difference, 1.0 cm H_2O [0.3 to 1.6]), end-inspiratory plateau pressure of the lung using elastance-derived method (mean difference, 0.9 [0.3 to 1.6]) and lung-to-respiratory system elastance ratio (mean difference, 0.04 [0.01 to 0.07]), and to decrease driving pressure of the lung (mean difference, −10 cm H_2O [−1.6 to −0.4]) and elastance of the lung (−2.9 cm H_2O/l [−5.1 to −0.8]).

Influence of BMI on Global and Partitioned Respiratory Mechanics

According to the BMI terciles, increasing BMI was associated with increasing prevalence of auto-PEEP, and increasing values of total PEEP, resistance of the respiratory system, time constant of the respiratory system (corrected for complete airway closure) and end-expiratory esophageal pressure (tables 2 and 3; Supplemental Digital Content, fig. 3, http://links.lww.com/ALN/C437), whereas it was associated with decreasing end-expiratory transpulmonary pressure (table 3). Considered as a continuous variable, BMI was positively associated with end-expiratory esophageal pressure (fig. 2), and negatively associated with end-expiratory transpulmonary pressure (fig. 3). BMI was associated with decreasing elastance of the respiratory system (Supplemental Digital Content, fig. 4, http://links.lww.com/ALN/C438), and of the lung (Supplemental Digital Content, fig. 5, http://links.lww.com/ALN/C439) when calculations were corrected for complete airway closure, whereas this was not the case when complete airway closure was not considered. There was no relationship between BMI and elastance of the chest wall (fig. 4).

Discussion

In this post-hoc analysis, airway closure was present in 41% of moderate-to-severe ARDS, was associated with BMI, and significantly influenced calculation of respiratory mechanics. Moreover, obesity was significantly associated with end-expiratory esophageal pressure and transpulmonary pressure, as well as elastances of the respiratory system and the lung corrected for airway closure.

Complete Airway Closure and BMI

Complete airway closure highly prevalent in our cohort. It was suggested on low-flow inflation pressure–volume curves and was based on the presence of low inflection point associated with, in the initial part of the curve, the absence of cardiac oscillations and very low compliance.[12] Although unproven yet, this might be due to collapse of the small airways, leading to gas trapping in alveoli, as recently demonstrated *in vivo* in an injured animal.[15] Cyclic opening and closure of small airways could lead to bronchial injury as reported in histological examination of ARDS lungs.[16] Complete airway closure may be due to surface tension modifications in distal airways given that type IIA secretory phospholipase A2 activity, an indirect marker of surfactant depletion, was correlated to airway opening pressure.[27] Moreover, complete airway closure has been confirmed by other groups in 34% of ARDS,[28] and in 22% of obese patients with healthy lungs undergoing laparoscopic surgery.[17] Moreover, complete airway closure pattern (presence of low inflection point associated with, in the initial part of the curve, the absence of cardiac oscillations and very low compliance) could be suspected on quasistatic

Table 1. Characteristics of Patients and Outcomes According to Body Mass Index and Airway Closure Consideration

	Pooled Cohort (n = 51)	Body Mass Index			*P* Value
		< 30 kg/m² (n = 18)	≥ 30 and < 40 kg/m² (n = 16)	≥ 40 kg/m² (n = 17)	
Baseline characteristics					
Age, yr	60 (49–69)	64 (50–75)	54 (40–64)	60 (50–66)	0.192
Gender, female, n (%)	13 (25%)	5 (28%)	3 (19%)	5 (29%)	0.752
Weight, kg	105 (82–129)	78 (63–85)	109 (100–128)	142 (119–177)	< 0.001
Height, cm	173 (168–180)	171 (163–179)	179 (168–183)	171 (168–178)	0.327
Body mass index, kg/m²	36 (28–42)	26 (24–28)	36 (33–38)	44 (42–61)	< 0.001
APACHE II score at ICU admission	24 (19–30)	20 (17–27)	24 (18–30)	29 (22–32)	0.028
Characteristics at enrollment					
Day of mechanical ventilation, days	4 (2–8)	4 (2–7)	6 (4–9)	4 (2–8)	0.528
PEEP set clinically, cm H_2O	15 (12–18)	14 (12–16)	16 (14–18)	16 (14–20)	0.122
Tidal volume, ml/kg predicted body weight	6.1 (5.9–6.3)	6.0 (5.6–6.3)	6.1 (5.8–6.2)	6.1 (6.0–6.3)	0.809
Respiratory rate, per min	26 (23–30)	25 (23–28)	24 (22–27)	28 (26–32)	0.034
PaO_2/FIO_2, mmHg	144 (104–163)	154 (108–176)	150 (108–170)	118 (95–144)	0.110
Outcomes					
ICU length of stay, days	24 (19–42)	21 (13–46)	22 (16–40)	28 (21–46)	0.603
ICU survival, n (%)	34 (67%)	11 (61%)	12 (75%)	11 (65%)	0.682

APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; PEEP, positive end-expiratory pressure.

Table 2. Respiratory System Mechanics at Low PEEP According to Body Mass Index and Respective to Airway Closure Consideration

	Pooled Cohort (n = 51)	Body Mass Index			*P* Value
		< 30 kg/m² (n = 18)	≥ 30 and < 40 kg/m² (n = 16)	≥ 40 kg/m² (n = 17)	
PEEP set, cm H_2O	5 (5–6)	5 (5–5)	5 (5–8)	5 (5–5)	0.219
Low-flow inflation pressure–volume curve					
Complete airway closure, n (%)	21 (41%)	4 (22%)	6 (38%)	11 (65%)	0.036
Airway opening pressure, cm H_2O	9.6 (8.5–13.2)	9.7 (9.2–12.2)	12.5 (7.5–16.7)	9.6 (8.8–10.7)	0.836
Respiratory system mechanics					
Auto-PEEP, n (%)	42 (82%)	11 (61%)	14 (88%)	15 (100%)	0.009
Auto-PEEP, cm H_2O	1.0 (1.0–3.0)	1.0 (0.0–2.0)	2.0 (1.0–3.0)	2.0 (1.0–4.0)	0.071
Total PEEP, cm H_2O	7.0 (6.0–9.0)	6.0 (5.3–7.0)	8.0 (6.8–9.3)	9.0 (7.0–10.0)	0.015
Plateau pressure, cm H_2O	19.9 (16.6–21.6)	18.3 (14.9–21.5)	20.0 (19.2–21.5)	18.0 (17.4–20.4)	0.260
Driving pressure, cm H_2O					
Not considering airway closure	11.4 (9.3–12.9)	11.9 (9.5–14.0)	11.6 (11.0–13.2)	10.0 (8.7–11.8)	0.115
Considering airway closure	10.9 (8.6–12.6)	11.3 (9.0–13.6)	11.3 (10.5–12.6)	8.7 (7.9–11.4)	0.080
Mean difference (95% CI)	−0.9 (−1.5 to −0.4)	−0.6 (−1.0 to −0.2)	−1.3 (−3.0 to 0.3)	−0.9 (−1.8 to −0.1)	
P Value	0.002	0.006	0.101	0.034	
Elastance, cm H_2O/l					
Not considering airway closure	27.7 (23.3–35.0)	30.3 (24.0–37.3)	27.3 (24.9–33.8)	24.1 (20.8–33.3)	0.348
Considering airway closure	26.8 (22.0–31.2)	29.2 (23.5–32.2)	26.8 (24.9–29.1)	23.1 (17.7–27.3)	0.113
Mean difference (95% CI)	−2.7 (−4.6 to −0.9)	−1.7 (−2.8 to −0.5)	−4.0 (−9.6 to 1.6)	−2.7 (−5.3 to −0.1)	
P Value	0.005	0.006	0.147	0.044	
Resistance, cm H_2O.s/l	13.1 (11.0–16.4)	11.8 (10.3–14.2)	14.5 (12.1–18.6)	14.1 (11.4–16.6)	0.046
Time constant of the respiratory system, s					
Not considering airway closure	0.47 (0.35–0.61)	0.38 (0.28–0.50)	0.51 (0.38–0.67)	0.50 (0.43–0.51)	0.078
Considering airway closure	0.50 (0.39–0.63)	0.41 (0.30–0.50)	0.55 (0.45–0.69)	0.53 (0.47–0.61)	0.039
Mean difference (95% CI)	0.03 (0.01–0.05)	0.02 (−0.01 to 0.05)	0.05 (−0.01 to 0.10)	0.02 (−0.02 to 0.06)	
P Value	0.015	0.130	0.103	0.321	

PEEP, positive end-expiratory pressure.

inflation pressure–volume curves of the five most obese anesthetized patients with healthy lungs before surgical incision in a physiologic study.[29] Although negative values of end-expiratory esophageal pressure suggest collapse of dependent lung regions,[26] as conceptualized by Dollfuss *et al.*,[30] complete airway closure may not reflect the same

Table 3. Partitioned Respiratory Mechanics According to Body Mass Index and Airway Closure Consideration

		Body Mass Index			
	Pooled Cohort (n = 51)	< 30 kg/m² (n = 18)	≥ 30 and < 40 kg/m² (n = 16)	≥ 40 kg/m² (n = 17)	*P* Value
Chest wall mechanics					
End-expiratory esophageal pressure, cm H_2O	14.4 (9.9–16.3)	9.4 (8.4–11.7)	14.4 (10.0–16.2)	15.8 (15.0–18.6)	< 0.001
End-inspiratory esophageal pressure, cm H_2O	16.6 (13.7–20.6)	12.7 (10.0–15.1)	17.2 (14.0–19.7)	20.6 (17.1–23.4)	< 0.001
Driving pressure, cm H_2O	2.8 (13.7–20.6)	2.7 (2.0–3.6)	2.9 (2.5–3.6)	2.7 (2.2–4.1)	0.686
Elastance, cm H_2O/l	6.7 (5.2–10.2)	7.2 (5.6–8.8)	7.6 (5.7–9.1)	6.2 (4.8–11.1)	0.888
Lung mechanics					
End-expiratory transpulmonary pressure cm H_2O					
Not considering airway closure	−6.6 (−9.3 to −2.1)	−2.7 (−6.6 to −1.4)	−5.4 (−7.6 to −2.0)	−9.3 (−10.3 to −6.6)	0.023
Considering airway closure	−4.8 (−6.8 to −2.0)	−2.7 (−5.6 to −1.4)	−3.5 (−5.4 to −1.5)	−6.6 (−10.3 to −6.0)	0.013
Mean difference (95% CI)	1.0 (0.3–1.6)	0.5 (0.1–0.8)	1.6 (−0.4 to 3.7)	0.9 (0.1–1.8)	
P Value	0.004	0.015	0.106	0.034	
End-inspiratory transpulmonary pressure, cm H_2O	2.9 (−0.3 to 4.8)	4.4 (2.4–7.8)	3.5 (2.2–5.7)	0.0 (−4.7 to 2.5)	0.004
Driving pressure, cm H_2O					
Not considering airway closure	7.5 (6.2–9.6)	9.1 (6.1–10.1)	8.4 (6.7–9.5)	6.5 (5.8–8.8)	0.237
Considering airway closure	6.9 (5.8–9.0)	7.7 (6.1–9.6)	7.5 (6.7–9.0)	6.1 (5.6–8.3)	0.226
Mean difference (95% CI)	−1.0 (−1.6 to −0.4)	−0.5 (−0.8 to −0.1)	−1.6 (−3.7 to 0.4)	−0.9 (−1.8 to −0.1)	
P Value	0.004	0.015	0.106	0.034	
Elastance, cm H_2O					
Not considering airway closure	19.2 (13.8–24.1)	22.8 (15.2–24.4)	18.8 (15.9–23.8)	17.9 (12.9–23.1)	0.364
Considering airway closure	18.4 (13.2–22.8)	22.2 (15.2–23.7)	18.3 (15.9–20.1)	16.9 (12.5–20.8)	0.239
Mean difference (95% CI)	−2.9 (−5.1 to −0.8)	−1.4 (−2.5 to −0.2)	−4.9 (−11.8 to 2.1)	−2.7 (−5.3 to −0.1)	
P Value	0.009	0.021	0.154	0.044	
Lung-to-respiratory system elastance ratio					
Not considering airway closure	0.69 (0.59–0.74)	0.73 (0.67–0.76)	0.69 (0.53–0.73)	0.68 (0.55–0.74)	0.356
Considering airway closure	0.71 (0.64–0.78)	0.74 (0.71–0.78)	0.71 (0.67–0.74)	0.68 (0.58–0.78)	0.370
Mean difference (95% CI)	0.04 (0.01–0.07)	0.03 (0.00–0.05)	0.06 (-0.01-0.14)	0.04 (−0.004 to 0.08)	
P Value	0.003	0.020	0.104	0.075	
End-inspiratory plateau pressure, cm H_2O					
Not considering airway closure	12.8 (10.6–14.9)	12.4 (9.9–14.5)	13.0 (11.4–14.3)	12.2 (11.3–14.9)	0.870
Considering airway closure	13.6 (11.3–15.6)	13.3 (10.1–15.3)	14.0 (11.6–15.8)	13.5 (11.3–15.2)	0.596
Mean difference (95% CI)	0.9 (0.3–1.6)	0.5 (0.1–0.9)	1.7 (−0.3 to 3.7)	0.7 (−0.1 to 1.5)	
P Value	0.005	0.024	0.092	0.083	

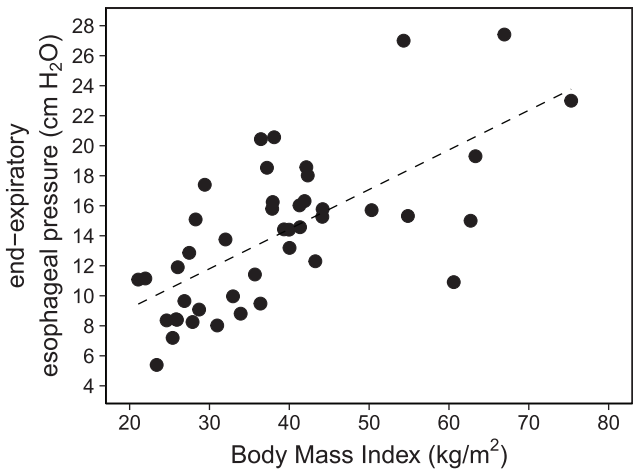

Fig. 2. Relationship between individual values of end-expiratory esophageal pressure at low positive end-expiratory pressure and body mass index (Spearman $\rho = 0.69$ [95% CI, 0.48 to 0.82]). The *dotted line* represents the regression line (end-expiratory esophageal pressure = 3.88 + 0.26 × body mass index; $R^2 = 0.45$; $P < 0.001$).

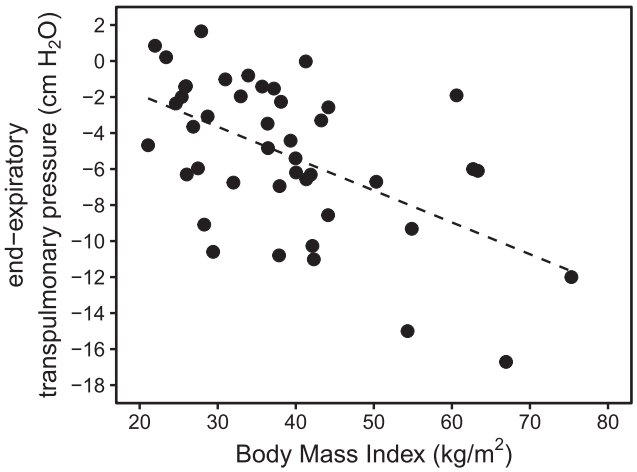

Fig. 3. Relationship between individual values of end-expiratory transpulmonary pressure considering complete airway closure at low positive end-expiratory pressure and body mass index (Spearman $\rho = -0.52$ [95% CI, −0.72 to −0.28]). The *dotted line* represents the regression line (end-expiratory transpulmonary pressure = 1.65 − 0.18 × body mass index; $R^2 = 0.28$; $P < 0.001$).

phenomenon. In the study by Dollfuss *et al.*, analysis was performed in standing subjects with healthy lungs, whereas the ARDS patients we studied were in the semirecumbent position. They reported closure of dependent lung regions when lung volume reached residual volume, whereas we reported complete airway closure at end-expiratory lung volume. In patients with complete airway closure, respiratory system compliance in the very initial part of the low-flow inflation pressure–volume curve is extremely low (around 2 ml/cm H_2O) and is similar to that of occluded circuit measured during the pretest phase of a ventilator. This suggests that gas is compressed in the circuit and does not enter the lungs, *i.e.,* that the lungs are completely closed below airway opening pressure.

The association between complete airway closure and BMI could be explained by higher superimposed pressure in obese patients than in patients with normal weight as suggested by thoracic computerized tomography studies.[11] Interestingly, median airway opening pressure in our cohort was 9.6 cm H_2O, close to that reported by Grieco *et al.*,[17]

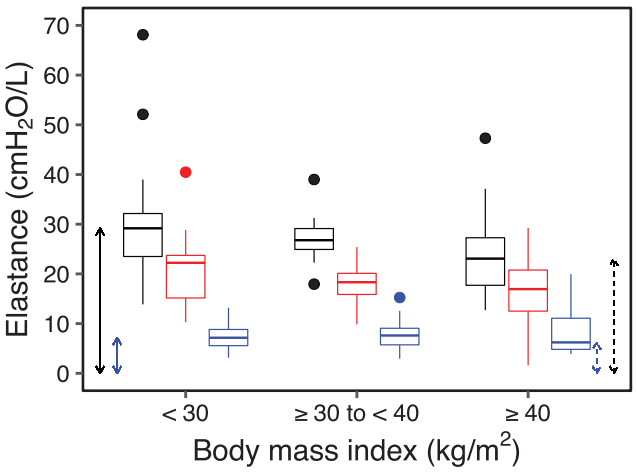

Fig. 4. Influence of body mass index on elastances. Boxplots represent median and interquartile values of elastances. Respiratory system elastance is colored in *black*, lung elastance (E_L) in *red,* and chest wall elastance (E_{CW}) in *blue*. The *plain* and *dotted arrows* represent $\frac{E_{CW}}{E_{RS}}$ ratio in low and high body mass index groups, respectively. The more the body mass index increases, the more the ratio increases, suggesting that for a given airway plateau pressure, the amount of pressure bore by the chest wall increases with body mass index.

and was not influenced by BMI. We hypothesized that airway opening pressure is related to changes in surface tension forces at the liquid–gas interface due to surfactant depletion in small airways.[12] Therefore, airway opening pressure may be more related to airways diameter than to BMI.

Complete Airway Closure and Auto-PEEP

Although there was a significant association between complete airway closure and auto-PEEP, we believe that they are not the same phenomenon. First, all of the 21 patients with complete airway closure had auto-PEEP, while only 50% of the 42 patients with auto-PEEP had complete airway closure. Therefore, auto-PEEP may be a poor predictor of airway closure. Second, auto-PEEP is a dynamic phenomenon, driven by expiratory flow limitation,[31] and favored by high respiratory rate,[32,33] whereas complete airway closure was identified after reduction of respiratory rate to eliminate auto-PEEP (Supplemental Digital Content, fig. 2, http://links.lww.com/ALN/C436). It is important to note that the 82% prevalence of auto-PEEP we reported was twice as high as that reported in a recent pooled cohort study where patients were ventilated using larger V_T and lower respiratory rate than in our study.[34] Although auto-PEEP and complete airway closure can coexist in the same patient as illustrated in Supplemental Digital Content, figure 2 (http://links.lww.com/ALN/C436) we believe they occur in different sites of the bronchial tree. Further studies are needed to better understand the relationship between these two phenomena.

Relationship between Respiratory Mechanics of the Chest Wall and BMI

We found that end-expiratory esophageal pressure was associated with BMI, which was not the case for elastance of the chest wall. Importantly, esophageal pressure, transpulmonary pressure, and elastance of the chest wall were in keeping with those reported previously in obese ICU patients with or without ARDS under invasive ventilation with similar PEEP levels, hence reinforcing the external validity of our results.[35–37]

The relationship between end-expiratory esophageal pressure and BMI is in line with the increasing superimposed pressure associated with increasing BMI.[11] However, previous studies did not find any relationship between end-expiratory esophageal pressure and BMI.[11,29] Possible explanations of this discrepancy could be pertaining to (1) the population studied (no mild ARDS in our analysis; 37% in Chiumello *et al.* study, which could have decreased the study power,[11] and anesthetized patients with healthy lungs[29]); (2) the timing of measurement (after several days of mechanical ventilation,[11] and after induction of anesthesia, in supine position and with F_{IO_2} of 100%,[29] three factors that could have favored atelectasis and subsequent changes in intrathoracic pressure); and (3) the distribution of BMI (we included patients with a large range of BMI, whereas it was narrower in the study by Chiumello *et al.*,[11] and there was no patient between 30 and 38 kg/m^2 in the study by Behazin *et al.*[29]). However, although the linear relationship between end-expiratory esophageal pressure and BMI was significant, the relatively low R^2 precluded accurate individual prediction of end-expiratory esophageal pressure based on BMI.

The influence of BMI on elastance of the chest wall is debated.[11,29,38–41] Importantly, the absence of association between BMI and elastance of the chest wall we found in the semirecumbent position may not be reproduced in the supine,[38,42] prone,[43] or Trendelenburg position.[17] Indeed, an exponential relationship between elastance of the chest wall and BMI was reported in patients ventilated in the supine position with zero PEEP,[38] which may illustrate the potentially deleterious effects of such a position in these patients. However, this difference in elastance of the chest wall between morbidly obese and patients with normal BMI at zero PEEP disappeared using PEEP.[40] Effects of obesity on the mechanics of the chest wall can be reproduced applying a load on the chest, increasing end-expiratory and end-inspiratory esophageal pressure to the same extent, shifting rightwards pressure–volume curve of the chest wall, therefore not modifying chest wall elastance.[44]

Relationship between Lung Mechanics and BMI

Elastance of the lung decreased with BMI. This surprising result contradicts previous studies which found higher elastance of the lung in obese than non-obese anesthetized patients.[38–40] The main difference with these prior studies is assessment in our analysis of complete airway closure. Better elastance of the lung in obese ARDS could be explained by the anti-inflammatory and antifibrotic effects reported in animal models with lung injury.[45] The higher prevalence of atelectasis with lower Pa_{O_2}/F_{IO_2} reported in obese anesthetized patients[46] may also have artificially worsened hypoxemia and radiologic findings, thereby increasing ARDS severity according to the Berlin definition of ARDS. This could explain why high-PEEP strategy reduced mortality of obese patients' mortality whereas it was not the case for nonobese patients.[47]

Clinical Implications

Complete airway closure was more prevalent in the most obese patients with ARDS. Driving pressure of the respiratory system was higher when complete airway closure was not considered than when its calculation was corrected for complete airway closure. This finding could help to explain the absence of relationship between driving pressure of the respiratory system and mortality in obese ARDS whereas it was the case for nonobese ARDS.[9] Likewise, end-expiratory transpulmonary pressure was lower when complete airway closure was not considered than when its calculation was

corrected for complete airway closure. As a consequence, PEEP set to obtain a positive end-expiratory transpulmonary pressure could be overestimated, and help to explain the absence of benefit of transpulmonary pressure–guided PEEP strategies.[48,49]

As it does not require additional device, it is easy to assess at the bedside and influences respiratory mechanics, we believe that complete airway closure in ARDS patients is worth assessing, especially in the obese population. Whether a ventilation strategy considering complete airway closure would improve prognosis remains to be tested.

Limitations

The main limitation of the study pertains to its design. Hemodynamic data were not collected in the retrospective part of the cohort. Moreover, bias inherent to this type of study could exist. However, information bias was limited as esophageal manometry was performed in experienced centers, and the values measured were in keeping with previous reports.[35–37] Additionally, tracings were recorded according to standard operating procedure,[21] carefully analyzed and excluded when not fulfilling quality criteria (one patient). Likewise, the risk of selection bias in the retrospective part of the cohort was limited as the recruitment rate (two patients with BMI greater than or equal to 40 kg/m^2 per year) was identical to that of another cohort study in the same country.[9] Therefore, these results deserve to be repeated prospectively and confirmed by other research teams.

Conclusions

Complete airway closure, diagnosed on a low-flow inflation pressure–volume curve, was observed in a meaningful proportion of ARDS, especially in the most obese patients. Consideration of complete airway closure significantly influenced respiratory system mechanics. Increased BMI was associated with increased end-expiratory esophageal pressure and decreased elastance of the lung corrected for complete airway closure. Conversely, elastance of the chest wall was not influenced by BMI. Therefore, complete airway closure assessment provides important information on the respiratory mechanics of ARDS, especially in obese patients.

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Competing Interests

Dr. Coudroy reports travel expenses to attend scientific meetings by MSD (Paris, France) and Fisher & Paykel Healthcare (Auckland, New Zealand). Dr. Aissaoui reports personal fees from Astra-Zeneca (Cambridge, United Kingdom), Medtronic (Dublin, Ireland), Abiomed (Danvers, Massachusets), Abott (Chicago, Illinois). Dr. Diehl reports research support from General Electric Healthcare (Chicago, Illinois). Dr. Brochard's laboratory received equipment or grants from Medtronic Covidien (Dublin, Ireland), General Electric, Air Liquide Healthcare (Paris, France), Fisher & Paykel Healthcare, Sentec (Therwil, Switzerland). The other authors declare no competing interests.

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