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Higher Class of Obesity Is Associated With Delivery of Higher Tidal Volumes in Subjects With ARDS

Saminder S Kalra, Matthew Siuba, Anupol Panitchote, Eduardo Mireles-Cabodevila, Robert L Chatburn, Sudhir Krishnan, and Abhijit Duggal

BACKGROUND: Obese subjects are at higher risk of development and progression of ARDS. There are limited data regarding mechanical ventilation practices and use of adjunctive therapies in subjects with ARDS across different obesity classes. We hypothesized that the adherence to lung-protective ventilation would be worse with rising body mass index class in patients with ARDS. METHODS: We conducted a retrospective observational study of subjects with ARDS. We evaluated the differences in ventilator settings, airway pressures, gas exchange, use of rescue therapies, length of hospital stay, and mortality among subjects based on the obesity classes of the WHO. RESULTS: The study included 613 subjects with ARDS: 21.4% were normal weight, 25% were overweight, and 53.7% were obese; 33.3% of the obese subjects met criteria for class I–II obesity, while 20.4% were class III obese (morbid obesity). On day 1, 53% of subjects with class III obesity had tidal volumes > 8 mL/kg, compared to 26% of the subjects with normal weight. In addition, 48% of the morbidly obese subjects received at least one rescue therapy as compared to 37% of normal weight subjects and 36% of overweight subjects. There were significant differences in the use of rescue therapies among the groups. In a multivariable model, subjects with class III obesity were significantly more likely to receive tidal volume > 8 mL/kg predicted body weight on day 1 when compared with subjects with normal weight (odds ratio 3.14, 95% CI 1.78–5.57). There was no difference in length of stay in ICU or hospital, duration of mechanical ventilation, or adjusted ICU or hospital mortality among the 4 groups. CONCLUSIONS: In this study, the risk of exposure to higher tidal volumes and the need for specific rescue therapies rose with higher classes of obesity in subjects with ARDS. More research is needed to identify how to better implement lung-protective ventilation in patients with obesity. *Key words: ARDS; mechanical ventilation; obesity; morbid obesity; class III obesity; mortality*. [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Nearly 40% of critically ill patients are classified as obese, which poses unique challenges with mechanical ventilation.[1] Obesity alters the structural mechanics of the chest wall and the lung parenchyma. These changes manifest physiologically with decreases in total lung capacity, functional residual capacity, and vital capacity. High pleural pressures also occur as a result of decreased chest wall compliance.[2-4] Obese subjects are at a higher risk of

Dr Kalra is affiliated with the Division of Pulmonary and Critical Care, Department of Medicine, University of Florida, Gainesville, Florida. Mr Chatburn and Drs Siuba, Mireles-Cabodevila, Krishnan, and Duggal are affiliated with the Department of Critical Care, Respiratory Institute, Cleveland Clinic Foundation, Cleveland, Ohio. Dr Panitchote is affiliated with the Division of Critical Care Medicine, Department of Medicine, Khon Kaen University, Khon Kaen, Thailand.

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Mr Chatburn has disclosed relationships with IngMar Medical, Drive/DeVilbiss, and imtmedical. The remaining authors have disclosed no conflicts of interest.

Correspondence: Abhijit Duggal MD MPH MSc, Department of Critical Care Medicine, Respiratory Institute, Cleveland Clinic Foundation, Cleveland, Ohio. E-mail: duggala2@ccf.org.

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exaggerated differences in regional air flow, have a higher incidence of dorsocaudal parenchymal atelectasis, and can have significant differences in plateau pressures (P_{plat}) calculated with transrespiratory pressure compared to transpulmonary pressure.[5] These physiologic changes may have a significant impact on the development and progression of ARDS.[6]

Lung-protective ventilation remains the cornerstone of care for patients with ARDS.[7] Important aspects in the management of ARDS include the use of high-PEEP strategies,[8,9] a fluid-restrictive strategy,[10] early use of neuromuscular blocking agents,[11] and prone position ventilation.[12] Previous studies have reported that ventilator strategies in obese subjects are suboptimal because they are more likely to receive tidal volumes based on actual body weight instead of predicted body weight,[13] have higher P_{plat},[14] and receive inadequate PEEP.[15] Use of prone position ventilation is also inconsistent in this population.[16]

The purpose of this study was to describe the practice regarding mechanical ventilation and use of adjunctive therapies in subjects with ARDS across different obesity levels at a tertiary-care academic medical center. We hypothesized that the adherence to lung-protective ventilation worsens with rising body mass index class in subjects with ARDS, with the results including a potentially increased need for rescue therapies and increased mortality.

QUICK LOOK

Current knowledge

Studies have indicated that ventilator strategies in obese patients are suboptimal. Obese patients are more likely to receive tidal volumes based on actual body weight instead of predicted body weight, are exposed to higher plateau pressures, and receive inadequate PEEP. The existing literature has not explored whether this risk is higher with increasing class of obesity.

What this paper contributes to our knowledge

Our study indicates that subjects with ARDS with higher obesity class were more likely to receive higher tidal volumes than normal weight subjects, and the risk increased with increasing class of obesity. With higher classes of obesity, subjects were more likely to need rescue therapies such as neuromuscular blocking agents and inhaled vasodilators.

Methods

This retrospective cohort study was approved by the Cleveland Clinic Institutional Review board. We included all subjects admitted to the medical ICU with a diagnosis of ARDS based on the Berlin definition[17] from January 2010 to May 2017. We excluded patients $\leq$ 18 y old, pregnant patients, and those with body mass index < 18.5 kg/m^2 due to high risk of confounding given strong association with chronic disease. Subjects who underwent mechanical ventilation for < 48 h or had missing data about body mass index were also excluded. The cohort was divided into 4 subgroups based on the World Health Organization (WHO) obesity classes:[18] normal weight (body mass index 18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), obese (class I, 30–34.9 kg/m^2; class II, 35–39.9 kg/m^2), and morbidly obese (class III, $\geq$ 40 kg/m^2). We collected baseline demographics, cause of ARDS, comorbidities, and oxygenation index ($F_{IO_2} \times$ mean airway pressure/P_{aO_2}).

Mechanical ventilation parameters were recorded on days 1, 2, and 3 of mechanical ventilation. Adherence to PEEP guidelines was defined as observed PEEP greater than or equal to that recommended by the ARDSnet PEEP/F_{IO_2} table.[8] Severity of illness was measured with the Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE III), using scores from the first 24 h after the diagnosis of ARDS was made. We also collected data on the ICU-specific outcomes and therapies used, including percentage fluid overload, acute kidney injury, renal replacement therapy, septic shock, and use of sedatives, analgesics, and neuromuscular blocking agents during the first 72 h after ICU admission. Percentage of fluid overload was calculated using the following formula: (fluid intake – total output)/body weight at day 1 of ARDS $\times$ 100.[19] Acute kidney injury and severity of acute kidney injury were defined according to the Kidney Disease Improving Global Outcomes 2012 guidelines, using serum creatinine and urine output criteria. Septic shock was defined according to the Sepsis-3 consensus definition.[20] Adjunctive/rescue therapies were defined as the use of neuromuscular blocking agents, positive-pressure ventilation, inhaled vasodilators (prostacyclin or nitric oxide), high-frequency oscillatory ventilation, or extracorporeal membrane oxygenation.

The primary outcome of interest was the difference in ventilator settings among the 4 subgroups. Secondary outcomes included the use of rescue therapies, ICU and hospital mortality, 28-d mortality, 90-d mortality, duration of mechanical ventilation, and length ICU and hospital stay.

Statistical Analysis

Descriptive statistics are reported as *n* (%) for categorical variables; continuous variables are reported as either mean (SD) or median (interquartile range). We used the Student *t* test, analysis of variance, Wilcoxon rank-sum test, or Kruskal-Wallis test as appropriate for continuous variables,

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Table 1. Baseline Characteristics by Body Mass Index Categories

Variable	Normal Weight	Overweight	Class I–II Obesity	Class III Obesity	*P*	Missing
Age, y	56 (44–67)	60 (47–70)	56.5 (44–66)	54 (41–63)†	.001	0 (0)
Height, in	66 (64–70)	67 (64–70)	67 (64–71)	67 (63–69)	.61	0 (0)
Male sex	76 (58)	93 (6.8)	105 (51.5)	59 (47.2)	.09	0 (0)
Diabetes mellitus	35 (26.7)	34 (22.2)	63 (3.9)	51 (4.8)†	.01	0 (0)
Congestive heart failure	5 (3.8)	15 (9.8)	31 (15.2)*	18 (14.4)*	.01	0 (0)
Chronic kidney disease	20 (15.3)	22 (14.4)	33 (16.2)	14 (11.2)	.65	0 (0)
Chronic liver disease	21 (16)	25 (16.3)	34 (16.7)	14 (11.2)	.55	0 (0)
Malignancy	38 (29)	37 (24.2)	42 (2.6)	14 (11.2)*	.01	0 (0)
SOFA	12 (9–15)	13 (10–15.8)	12.5 (9–16)	12 (9–15)	.38	11 (7.8)
APACHE III	113 (95–139)	117 (98–146)	119 (92–142)	113 (85–139)	.24	23 (3.8)
Cause of ARDS						
Pneumonia	103 (78.6)	122 (79.7)	141 (69.1)	97 (77.6)	.074	0 (0)
Aspiration pneumonia	28 (21.4)	24 (15.7)	29 (14.2)	18 (14.4)	.32	0 (0)
Extrapulmonary sepsis	16 (18.2)	20 (13.1)	23 (11.3)	8 (6.4)	.31	0 (0)
Acute pancreatitis	2 (1.5)	6 (3.9)	14 (6.9)	6 (4.8)	.14	0 (0)
TRALI	1 (0.8)	1 (0.7)	5 (2.5)	2 (1.6)	.53	0 (0)
ABG analysis on day 1						
F_{IO_2}	0.85 (0.55–1)	0.85 (0.6–1)	1 (0.6–1)	0.9 (0.63–1)	.27	88 (14.4)
P_{aO_2}	90 (71–114)	89 (74–12.8)	86 (68–118.8)	79.8 (68–101.5)	.10	77 (12.6)
P_{aO_2}/F_{IO_2}	120 (85–186.7)	126 (89–178.4)	114 (78–161.3)	102 (76–157.1)	.078	82 (13.4)
Oxygenation index	12.7 (8–2.3)	12.1 (8.3–21.5)	15.1 (8.9–25.9)	17.5 (10–27.3)	.054	187 (30.5)
P_{aCO_2}	41 (35–5.2)	40 (35–52)	43 (35–48)	44 (40–52)	.046	77 (12.6)
Lactate	2.7 (1.5–3.8)	2.4 (1.7–4.9)	2.2 (1.4–4.8)	1.9 (1.5–4.3)	.47	144 (23.5)

Data are presented as median (interquartile range) or *n* (%). Normal Weight: $n = 131$ subjects; Overweight: $n = 153$ subjects; Class I–II Obesity: $n = 204$ subjects; Class III Obesity: $n = 125$ subjects.
* $P < .05$ when compared with normal group.
† $P < .05$ when compared with the overweight group.
APACHE = Acute Physiology and Chronic Health Evaluation score
SOFA = Sequential Organ Failure Assessment score
TRALI = transfusion-related acute lung injury
ABG = arterial blood gas

and we used the chi-square test or Fisher exact test for discrete variables. Confidence intervals (CI) and *P* values reflect a 2-tailed alpha level of 0.05.

The missing data were handled by creating and analyzing 50 imputed data sets.[21] The imputation processes included variables that were included in logistic regression models.[22] After creating the complete data sets, we estimated the multiple regression models for each filled-in data set separately. The model estimates and standard errors were combined into a single set of results using Rubin's rules.[23] Multivariable logistic regression was carried out to determine the factors associated with an elevated tidal volume (> 8 mL/kg predicted body weight) on days 1–3. Correlation analysis of the predictors was conducted to avoid the multi-collinearity in regression models. The variables significant at $P < .1$ on univariable analysis were identified as potential predictor variables and entered into a multivariable regression model. Forward and backward stepwise methods were used for model selection in each data set. All the statistical analyses were performed by using R software version 3.5.1 using the automatic predictor selection tool of the MICE 3.0.0 package.

Results

Demographics

A total of 613 subjects were included in our analysis (Table 1), distributed among the different WHO weight classes as follows: 21.4% (131 of 613) were normal weight, 25.0% (153 of 613) were overweight, and 53.7% (329 of 613) were obese. Of the obese subjects, one third (204 of 613) were class I–II, and 20.4% (125 of 613) were class III. There was a greater percentage of diabetic subjects with class III obesity compared to the overweight group. Obese and morbidly obese subjects had a higher occurrence of congestive heart failure compared to the normal weight group. Subjects in obesity class III were younger on average and carried a lower burden of active malignancy compared to the normal weight group. P_{aO_2}/F_{IO_2} and the SOFA and APACHE III scores were relatively similar in all

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4 groups. Oxygenation index increased as the level of obesity increased.

Primary Outcome

Results for mechanical ventilation parameters are shown in Table 2. Subjects with class III obesity were exposed to significantly higher tidal volumes compared to other groups for the first 3 d of their ICU stay. On day 1, 52.5% (52 of 99) of subjects with class III obesity had recorded tidal volumes > 8 mL/kg, decreasing to 44% (48 of 109) by day 2. In comparison, only 26% (30 of 114) and 28% (34 of 119) of the subjects with normal weight had tidal volumes > 8 mL/kg on days 1 and 2, respectively (Table 3).

Subjects with class I–III obesity had statistically significantly higher PEEP for the first 72 h after diagnosis of ARDS compared to normal or overweight subjects. However, adherence to the PEEP/F_{IO_2} table was not significantly different among the groups. There was no significant difference in the P_{plat} and driving pressure among the different obesity categories on day 1 compared to day 3 after diagnosis of ARDS. P_{plat} was > 30 cm H_2O for 41.7% (15 of 36) of class III obesity subjects on day 1, and 33.9% of these subjects continued to be exposed to high P_{plat} on day 2.

Secondary Outcomes

The obese and morbidly obese subjects had a lower percentage of septic shock compared to the normal weight group ($P = .002$). Although diuretic use was not different among the groups, subjects with morbid obesity had a significantly lower percent of fluid overload on day[1] to day [3] compared to the other groups ($P < .001$). There was no difference in prevalence of acute kidney injury, but the class III obesity group underwent renal replacement therapy more than the other groups ($P = .046$).

Approximately 48% (60 of 125) of the morbidly obese subjects received at least one rescue therapy as compared to 36.6% (48 of 131) of normal weight subjects and 35.9% (55 of 153) of overweight subjects. Overall, the use of most rescue therapies was higher in the class III obesity group compared to the normal weight group, including neuromuscular blocking agents, prone positioning, and inhaled vasodilators. The use of sedation for > 48 h was also higher in obese subjects ($P = .01$) (Table 4).

Effect of Body Mass Index Categories on Tidal Volume. After a multivariable adjustment for P_{aCO_2}, lactate, and driving pressure on day 1 (model on day 1) and P_{aCO_2}, P_{aO_2}/F_{IO_2}, and lactate on day 2 (model on day 2), subjects with class III obesity received tidal volumes > 8 mL/kg predicted body weight on day 1–2 when compared with subjects with normal weight. Adjusted odds ratios for class III obesity on day 1 and day 2 were 3.61 (95% CI 2.00–6.53) and 2.35 (95% CI 1.31–4.22), respectively (Table 5).

Effect of Body Mass Index Categories on Stay and Mortality. There was no difference in duration of mechanical ventilation or length of ICU or hospital stay among the groups. Subjects with class III obesity had a lower unadjusted 28-d mortality compared to the overweight group ($P = .01$) and had a lower unadjusted 90-d mortality compared to normal weight and overweight group ($P = .002$) (Table 6).

After adjustment for confounding factors including age, APACHE III score, history of liver disease and malignancy, and septic shock, we did not find any association between 28-d survival and 90-d survival among overweight, obese, and morbidly obese subjects compared to normal weight subjects. Adjusted hazard ratios for mortality of overweight, obese, and morbidly obese subjects at day 28 were 1.22 (95% CI 0.88–1.7), 1.21 (95% CI 0.87–1.68), and 1.02 (95% CI 0.69–1.50) respectively; at day 90, 1.01 (95% CI 0.75–1.37), 0.99 (95% CI 0.73–1.33), and 0.86 (95% CI 0.61–1.22).

Discussion

Subjects with ARDS in the higher obesity class were more likely to receive higher tidal volumes than normal weight subjects, and risk increases with increasing class of obesity. Roughly half of those with class III obesity had tidal volumes > 8 mL/kg predicted body weight throughout the first 72 h of ARDS diagnosis, compared with < 30% of those with normal body mass index. Subjects with class III obesity were also more likely to receive rescue therapy with neuromuscular blockade or pulmonary vasodilators, despite no significant difference in severity of ARDS or critical illness. Obese subjects were more likely to be treated with higher PEEP, although the difference was only 2 cm H_2O on average. Compliance with recommended PEEP strategies based on the ARDSNet PEEP/F_{IO_2} tables was suboptimal through all weight classes. The majority of these subjects were treated at this facility prior to the creation of an institutional ARDS protocol emphasizing PEEP:F_{IO_2} table adherence, which may explain the low overall compliance.

Additionally, the increased use of neuromuscular blockade and pulmonary vasodilators may have been necessary as a result of higher airway pressures attributable to nonprotective tidal volumes delivered. Delivering higher-than-ideal tidal volumes raises P_{plat}, which can be injurious itself[7]; obese patients are already more likely to have elevated P_{plat} compared to the general population.[14] Furthermore, an elevated (or borderline elevated) P_{plat} may make treating clinicians hesitant to increase PEEP to improve oxygenation, despite the fact that obese patients have a

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Table 2. Mechanical Ventilation Parameters by Body Mass Index Categories

Variable	Normal Weight	Overweight	Class I–II Obesity	Class III Obesity	*P*	Missing
Mode on day 1						
VCV	54 (49.1)	69 (58.5)	81 (51.3)	55 (56.1)	.58	129 (21.0)
PCV	42 (38.2)	44 (37.3)	59 (37.3)	31 (31.6)		
PRVC	11 (10)	4 (3.4)	14 (8.9)	9 (9.2)		
Others	3 (2.7)	1 (0.8)	4 (2.5)	3 (3.1)		
Mode on day 2						
VCV	53 (45.3)	68 (51.5)	82 (47.4)	60 (56.6)	.80	85 (13.9)
PCV	43 (36.8)	46 (34.8)	65 (37.6)	35 (33)		
PRVC	15 (12.8)	12 (9.1)	20 (11.6)	7 (6.6)		
Others	6 (5.1)	6 (4.5)	6 (3.5)	4 (3.8)		
Mode on day 3						
VCV	49 (41.5)	65 (47.8)	87 (5.3)	57 (51.8)	.79	76 (12.4)
PCV	48 (4.7)	51 (37.5)	62 (35.8)	37 (33.6)		
PRVC	14 (11.9)	11 (8.1)	18 (1.4)	9 (8.2)		
Others	7 (5.9)	9 (6.6)	6 (3.5)	7 (6.4)		
Tidal volume, mL/kg PBW						
Day 1	7.1 (6.6–8.2)	7.4 (6.7–8.4)	7.5 (6.6–8.8)	8.2 (7.3–9.4)*†‡	< .001	108 (17.6)
Day 2	7.2 (6.6–8.3)	7.1 (6.4–8.1)	7.5 (6.6, 8.4)	7.8 (7–9.6)*†‡	< .001	75 (12.2)
Day 3	7.3 (6.5–8.2)	7.4 (6.6–8.1)	7.3 (6.4, 8.5)	7.8 (7–9.2)*†‡	.01	75 (0.012)
PEEP, cm H_2O						
Day 1	8 (5–12)	10 (8–12)	10 (8–14)*	10 (8, 14.3)*	.003	97 (15.8)
Day 2	10 (7.5–12)	10 (8–12)	10 (8–14)*	12 (10–15)*†	< .001	65 (1.6)
Day 3	8 (5–12)	10 (8–12)	10 (8–14)*†	12 (8–16)*†	< .001	66 (1.8)
PEEP adherence§						
Day 1	14 (12.4)	9 (7.2)	15 (8.9)	16 (16.7)	.11	110 (17.9)
Day 2	25 (25.5)	16 (16.7)	35 (23.2)	18 (19.6)	.44	176 (28.7)
Day 3	23 (28.7)	21 (23.6)	36 (25.9)	20 (26)	.90	228 (37.2)
P_{plat}, cm H_2O						
Day 1	28 (22–33)	26 (22–30)	29 (22–31)	28.5 (23–32.5)	.47	436 (71.1)
Day 2	26 (22.8–31)	25 (21–28)	27 (22–32)	28 (23–32.3)	.06	368 (0.061)
Day 3	26.5 (21–3.3)	25 (21–29)	26 (22–30.5)	28.5 (23–33)	.19	371 (60.5)
$P_{plat} > 30$ cm H_2O						
Day 1	11 (35.5)	11 (24.4)	20 (3.8)	15 (41.7)	.40	436 (71.1)
Day 2	14 (29.2)	10 (16.9)	25 (30.5)	19 (33.9)	.18	368 (6.0)
Day 3	11 (25)	12 (22.6)	22 (25.3)	22 (37.9)	.25	371 (60.5)
Driving pressure, cm H_2O						
Day 1	16 (10.5–20.5)	14 (12–17)	14 (11–20)	15.5 (12–19.5)	.92	436 (71.1)
Day 2	15 (12–18)	14 (10.5–17)	13 (11–19)	14 (11–18)	.69	368 (6.0)
Day 3	16 (12–21)	14 (11–17.3)	13 (11–18)	14 (11.3–18)	.44	372 (6.7)

Data are presented as median (interquartile range) or *n* (%). Normal Weight: $n = 131$ subjects; Overweight: $n = 153$ subjects; Class I–II Obesity: $n = 204$ subjects; Class III Obesity: $n = 125$ subjects.
* $P < .05$ when compared with the normal group.
† $P < .05$ when compare with the overweight group.
‡ $P < .05$ when compared with the class I and II obese group.
§ PEEP adherence is PEEP that was set ≥ PEEP/F_{IO_2} table.
PBW = predicted body weight
VCV = volume control ventilation
PCV = pressure control ventilation
PRVC = pressure regulated volume control
P_{plat} = plateau pressure

disproportionately positive response to increased PEEP in terms of ventilator-free days and mortality.[24] One rescue therapy potentially underused in this cohort of obese subjects was prone position ventilation, especially given the physiologically plausible benefit (ie, offloading the contribution of decreased abdominal and chest wall compliance from the lung). Prone positioning has been reported not only to decrease mortality in moderate to severe ARDS but also to be feasible and safe in the morbidly obese.[12,16]

Despite the higher tidal volumes in subjects with class III obesity, this group had a lower unadjusted mortality rate

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Table 3. Tidal Volume by Body Mass Index Categories

Tidal Volume, mL/kg PBW	Normal Weight	Overweight	Class I–II Obesity	Class III Obesity	*P*
Day 1					
< 6	10 (8.8)	6 (4.8)	12 (7.2)	3 (3)	.01
6–8	74 (64.9)	77 (61.6)	97 (58.1)	44 (44.4)	
> 8	30 (26.3)	42 (33.6)	58 (34.7)	52 (52.5)	
Day 2					
< 6	14 (11.8)	13 (9.8)	14 (7.9)	8 (7.3)	.12
6–8	71 (59.7)	84 (63.2)	104 (58.8)	53 (48.6)	
> 8	34 (28.6)	36 (27.1)	59 (33.3)	48 (44)	
Day 3					
< 6	14 (12)	12 (9)	20 (11.2)	6 (5.5)	.12
6–8	71 (6.7)	85 (63.9)	98 (55.1)	58 (52.7)	
> 8	32 (27.4)	36 (27.1)	60 (33.7)	46 (41.8)	

Data are presented as *n* (%). Normal Weight: *n* = 131 subjects; Overweight: *n* = 153 subjects; Class I–II Obesity: *n* = 204 subjects; Class III Obesity: *n* = 125 subjects.
PBW = predicted body weight

Table 4. Subject Course in the ICU by Body Mass Index Categories

Variable	Normal Weight	Overweight	Class I–II Obesity	Class III Obesity	*P*
Fluid overload, %					
Day 1	2.3 (−0.1 to 5.1)	1.8 (0.1–3.7)	1.4 (−0.2 to 3)	0.4 (−0.3 to 1.5)*†‡	< .001
Day 2	4.6 (2.1–9.9)	3.6 (1.3–6.7)	3 (0.7–5.2)*	1.8 (0.1–3.1)*†‡	< .001
Day 3	6.5 (2.4–14)	4.1 (1.9–9)*	4.6 (1.1–6.7)*	2.6 (−0.1 to 4.1)*†‡	< .001
Septic shock	91 (69.5)	89 (58.2)	106 (52.2)*	59 (47.2)*	.002
Diuretic use on day 2–7	60 (45.8)	70 (46.1)	91 (44.6)	72 (57.6)	.11
Renal replacement therapy	46 (35.1)	59 (38.6)	90 (44.1)	64 (51.2)	.043
Acute kidney injury	93 (71)	117 (76.5)	162 (79.4)	98 (78.4)	.33
Analgesia > 48 h	93 (71)	110 (71.9)	150 (73.5)	83 (66.4)	.58
Sedation > 48 h	91 (69.5)	104 (68)	160 (78.4)	103 (82.4)	.01
Antipsychotics	51 (38.9)	69 (45.1)	88 (43.1)	55 (44)	.75
Rescue therapies	48 (36.6)	55 (35.9)	90 (44.1)	60 (48)	.11
Neuromuscular blockade	34 (26)	47 (3.7)	73 (35.8)	52 (41.6)	.045
Prone positioning	10 (7.6)	10 (6.5)	30 (14.7)	17 (13.6)	.041
HFOV	9 (6.9)	2 (1.3)	3 (1.5)	3 (2.4)	.036
Inhaled vasodilators	21 (16)	25 (16.3)	47 (23)	39 (31.2)*†	.01
ECMO	2 (1.5)	6 (3.9)	4 (2)	3 (2.4)	.60

Data are presented as median (interquartile range) or *n* (%). Normal Weight: *n* = 131 subjects; Overweight: *n* = 153 subjects; Class I–II Obesity: *n* = 204 subjects; Class III Obesity: *n* = 125 subjects.
* *P* < .05 when compared with the normal group.
† *P* < .05 when compare with the overweight group.
‡ *P* < .05 when compared with the class I and II obese group.
HFOV = high-frequency oscillation ventilation
ECMO = extracorporeal membrane oxygenation

compared to the rest of the cohort. An obesity paradox regarding ARDS has been described previously,[2,25-27] suggesting that patients with higher body mass index have a lower mortality rate compared to normal weight patients. This may be a result of more frequent but less severe episodes of critical illness compared to populations at lower weight classes. Importantly though, in multivariable analysis adjusting for comorbidities and severity of illness, there were no significant differences in mortality.

Unlike previous studies, we have looked at multiple classes of obesity rather than using a dichotomous cutoff. Use of the WHO obesity classes provides a better understanding of the distribution of tidal volumes across the spectrum of obesity. Our study not only confirms findings from previous studies where obesity has been identified as a risk factor for exposure to higher tidal volumes,[28] but further shows that subjects with higher classes of obesity are more likely to receive higher tidal volumes. Clinicians

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Table 5. Multivariable Analysis of Covariates Associated With Higher Tidal Volume Ventilation (> 8 mL per kg PBW)*

Variable	Odds Ratio (95% CI)	*P*	Area Under ROC (95% CI)
Day 1			
Body mass index			
Normal weight	Reference		
Overweight	1.41 (0.79–2.50)	.24	
Class I and II obesity	1.69 (0.97–2.92)	.061	0.67 (0.62–0.72)
Class III obesity	3.61 (2.00–6.53)	< .001	
P_{aCO_2} on day 1†	0.97 (0.95–0.98)	< .001	
Driving pressure on day 1†	1.05 (1.01–1.09)	.02	
Day 2			
Body mass index			
Normal weight	Reference		
Overweight	1.01 (0.57–1.77)	.98	
Class I and II obesity	1.25 (0.74–2.11)	.41	0.67 (0.62–0.72)
Class III obesity	2.35 (1.31–4.22)	.004	
P_{aCO_2} on day 2†	0.96 (0.94–0.98)	<.001	
Lactate on day 2†	1.08 (1.00–1.16)	.042	
P_{aO_2}:F_{IO_2} on day 2 (per 10 units increase)	0.96 (0.94–0.99)	.01	

* Analysis using multivariable logistic regression from 50 imputed dataset.
† per 1 unit increase.
ROC = receiver operating curve
PBW = predicted body weight

Table 6. Differences in Outcomes Among Body Mass Index Categories

Variable	Normal Weight	Overweight	Class I–II Obesity	Class III Obesity	*P*
Length of stay in ICU, d	13 (8–22)	12 (8–20)	12 (7–18)	13 (7–23)	.51
Length of stay in hospital, d	18 (12.5–27)	18 (10–28)	18 (10–25)	19 (12–30)	.50
Duration of mechanical ventilation, d	11 (6–20)	11 (6–19)	11 (6.8–18.3)	13 (7–21)	.38
Hospital mortality	71 (54.2)	85 (55.6)	97 (47.5)	52 (41.6)	.08
ICU mortality	70 (53.4)	81 (52.9)	94 (46.1)	51 (4.8)	.12
Mortality at day 28 (%)	62/122 (50.8)	84/147 (57.1)	92/190 (48.4)	45/121 (37.2)*	.01
Mortality at day 90 (%)	82/117 (70.1)	92/138 (66.7)	101/178 (56.7)	54/113 (47.8)*†	.002

Data are presented as median (interquartile range) or *n* (%). Normal Weight: *n* = 131 subjects; Overweight: *n* = 153 subjects; Class I–II Obesity: *n* = 204 subjects; Class III Obesity: *n* = 125 subjects.
* $P < .05$ when compare with the overweight group.
† $P < .05$ when compared with the normal group.

may be overestimating predicted body weight or height in obese subjects despite the fact that functional residual capacity decreases as body mass index increases.[4]

Given the retrospective and single-center nature of the study, some results may be difficult to generalize. There are, however, a number of strengths to our study. Our study used the consensus WHO definition and classes of obesity. Patients with very low body mass index were excluded because they tend to have a high burden of disease, and their underlying comorbidities can affect the outcomes of interest. We developed exhaustive models to account for any potential confounding from underlying comorbidities and ICU-specific therapies, and we reported this for both our primary and secondary outcomes of interest.

Globally, compliance with lung-protective ventilation strategies is poor, whether in obese patients or normal weight patients.[29] Collaboration of physicians with respiratory therapists to ensure safe tidal volume ranges are chosen in a protocolized fashion may be a way forward in this area. Evidence suggests initial tidal volumes tend to persist, so engagement of the multiprofessional care team is crucial.[30] Future research should target lung-protective ventilation implementation in this particularly high-risk patient population.

Conclusions

Subjects with ARDS who have class III obesity were exposed to high tidal volumes at a much higher rate than were nonobese subjects, and they also received neuromuscular blockade and pulmonary vasodilators more frequently. Prone position ventilation was likely underused given the putative physiologic benefits. The proportion of subjects in this ARDS cohort with class III obesity was very high, although adjusted mortality was not different compared to the other weight classes, which may reflect a component of the obesity paradox in the critically ill. Given the high incidence of disease in this population, it is especially important to provide vigilant lung-protective ventilation.

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