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Retrospective Review of Transpulmonary Pressure Guided Positive End-Expiratory Pressure Titration for Mechanical Ventilation in Class II and III Obesity

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OBJECTIVES: Acute respiratory distress syndrome is treated by utilizing a lung protective ventilation strategy. Obesity presents with additional physiologic considerations, and optimizing ventilator settings may be limited with traditional means. Transpulmonary pressure (P_L) obtained via esophageal manometry may be more beneficial to titrating positive end-expiratory pressure (PEEP) in this population. We sought to determine the feasibility and impact of implementation of a protocol for use of esophageal balloon to set PEEP in obese patients in a community ICU.

DESIGN: Retrospective cohort study of obese (body mass index [BMI] ≥ 35 kg/m^2) patients undergoing individualized PEEP titration with esophageal manometry. Data were extracted from electronic health record, and Wilcoxon signed rank test was performed to determine whether there were differences in the ventilatory parameters over time.

SETTING: Intensive care unit in a community based hospital system in Newark, Delaware.

PATIENTS: Twenty-nine mechanically ventilated adult patients with a median BMI of 45.8 kg/m^2 with acute respiratory distress syndrome (ARDS).

INTERVENTION: Individualized titration of PEEP via esophageal catheter obtained transpulmonary pressures.

MEASUREMENTS AND MAIN RESULTS: Outcomes measured include PEEP, oxygenation, and driving pressure (DP) before and after esophageal manometry at 4 and 24 hr. Clinical outcomes including adverse events (pneumothorax and pneumomediastinum), increased vasopressor use, rescue therapies (inhaled pulmonary vasodilators, extracorporeal membrane oxygenation, and new prone position), continuous renal replacement therapy, and tracheostomy were also analyzed. Four hours after PEEP titration, median PEEP increased from 12 to 20 cm H_2O ($p < 0.0001$) with a corresponding decrease in median DP from 15 to 13 cm H_2O ($p = 0.002$). Subsequently, oxygenation improved as median F_{IO_2} decreased from 0.8 to 0.6 ($p < 0.0001$), and median oxygen saturation/F_{IO_2} (S/F) ratio improved from 120 to 165 ($p < 0.0001$). One patient developed pneumomediastinum. No pneumothoraces were identified. Improvements in oxygenation continued to be seen at 24 hr, compared with the prior 4 hr mark, F_{IO_2} (0.6–0.45; $p < 0.004$), and S/F ratio (165–211.11; $p < 0.001$). Seven patients required an increase in vasopressor support after 4 hours. Norepinephrine and epinephrine were increased by 0.05 (± 0.04) µg/kg/min and 0.02 (± 0.01) µg/kg/min on average, respectively.

CONCLUSIONS: P_L-guided PEEP titration in obese patients can be used to safely titrate PEEP and decrease DP, resulting in improved oxygenation.

KEY WORDS: acute respiratory distress syndrome; esophageal catheter; esophageal manometry; esophageal probe; mechanical ventilation; obesity; positive end-expiratory pressure; transpulmonary pressure

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The obesity epidemic in the United States continues to increase, with more than 40% of adults defined as obese (body mass index [BMI] > 30 kg/m^2) (1, 2). Underlying differences in physiology and anatomy pose a unique challenge in the management of obese patients with acute respiratory failure requiring mechanical ventilation. Treatment for patients with acute respiratory distress syndrome (ARDS) consists of a lung protective ventilation strategy (3); however, obesity has largely been an exclusion criterion in many landmark ARDS trials (3–5). There remains a paucity of evidence for ventilator optimization in obese patients with ARDS. In nonobese patients, positive end-expiratory pressure (PEEP) is titrated by established PEEP/F$_{IO_2}$ table (3). However, obese patients demonstrate decreased functional residual capacity and increased alveolar decruitment from large chest wall and abdominal pressures (2) and, thus, may benefit from higher PEEP (6). Plateau pressure (P_{PLAT}) is used as surrogate for transpulmonary pressure (P_L) to avoid barotrauma. Current lung protective guidelines recommend avoiding a P_{PLAT} greater than 30 cm H_2O, with no specific guidance for the obese (7). It has been demonstrated that forces outside of the respiratory system such as the chest wall and intra-abdominal pressure may increase P_{PLAT}, making it an unreliable surrogate for P_L (2, 6, 8, 9).

Estimating P_L, defined as (P_L = airway pressure – pleural pressure), may be more accurate in obesity than the traditional use of P_{PLAT} as a surrogate. Pleural pressure can be estimated using esophageal manometry as previously described (10, 11). Prior studies evaluating the utility of esophageal manometry for ARDS have yielded mixed results, with the most recent large randomized controlled trial, Esophageal-Pressure Guided Mechanical Ventilation 2 (EPVent-2), demonstrating no benefit for their primary outcome (11–13). Many studies using esophageal manometry to individualize ventilator settings have not focused on an obese population (9, 11, 14). Although recent studies have begun to evaluate the optimal PEEP in obese individuals (15–18), the clinical benefit of using P_L to optimize PEEP in the obese population remains unclear. Furthermore, the ease of adoption of esophageal manometry in the community ICU has not been previously described.

We sought to determine the feasibility of implementing protocol for titration of PEEP in obese mechanically ventilated patients in a community teaching hospital as well as describing outcomes in terms of respiratory mechanics and oxygenation.

MATERIALS AND METHODS

A clinical protocol for ventilator management guided by esophageal manometry was implemented for patient care at Christiana Care (**Appendix 1**, http://links.lww.com/CCX/A981). We performed a single-center, retrospective, cohort study of all patients undergoing esophageal balloon placement from December 09, 2019, to January 31, 2021, at Christiana Care in Newark, DE. Ventilator management-based esophageal balloon measurements were done in accordance with the protocol described in Appendix 1 (http://links.lww.com/CCX/A981). This study was reviewed and approved by the Christiana Care Institutional Review Board.

All adult patients 18 years old or older requiring mechanical ventilation with class II and III obesity (BMI ≥ 35 kg/m^2) with ARDS were eligible. Severity of ARDS was defined using the Berlin classification when an arterial blood gas was available (19). Blood gas results were not always available; therefore, severity of ARDS and clinical change was also classified by oxygen saturation/F$_{IO_2}$ (S/F) ratio in all 29 patients as supported by recent literature (20, 21). All patients were managed by a multidisciplinary team lead by a board-certified intensivist.

The esophageal catheter used was the CooperSurgical 5F catheter, 47-9005. The catheter was inserted into the appropriate position by a trained respiratory therapist (Appendix 1, http://links.lww.com/CCX/A981, for insertion protocol). Institutional protocol advises against placing esophageal balloon in patients with known esophageal varices, tumors, ulcers, or platelets less than $10{,}000 \times 10^9$/L. After being adequately sedated, esophageal catheter pressure was obtained at end expiratory (via the expiratory hold maneuver on the ventilator) and end inspiration (via an end inspiratory hold maneuver or P_{PLAT}). PEEP was titrated based on P_L at end expiration (End Exp P_L) until it approached 0 (±2) cm H_2O to minimize atelectasis. The upper limit for safety to prevent overdistension and barotrauma was met if P_L is greater than 20 cm H_2O at end inspiration (End Insp P_L) via an inspiratory hold maneuver. If this occurred, PEEP or tidal volume would be subsequently decreased until End Insp P_L was less than 20 cm H_2O

(11, 22, 23). Tidal volume was kept less than 8-mL/kg predicted body weight in accordance with lung protective settings.

All data were collected from the electronic medical record. Demographics, vitals, ARDS severity (based on the Berlin classification), Sequential Organ Failure Assessment (SOFA) score, and interventions (neuromuscular blockade, proning, and inhaled pulmonary vasodilators) prior to esophageal balloon placement were recorded. Ventilator settings, ventilator pressures, and hemodynamic vasopressor support were obtained before esophageal balloon placement and after optimization at 4 and 24 hours. PEEP titration occurred at time 0 hours. Our primary end points reviewed changes in ventilatory support and oxygenation. Additionally, we compared the set individualized PEEP to previously established high PEEP tables. Secondary clinical outcomes including continuous renal replacement therapy, tracheostomy, and use of extracorporeal membrane oxygenation (ECMO) were also collected. Adverse events were defined as pneumothorax, pneumomediastinum, and increasing vasopressor support any time after esophageal balloon optimization had occurred. Initiating adjunct therapies (proning, neuromuscular blockade, and inhaled pulmonary vasodilators) were left up to the treating practitioner.

Data were extracted directly from the electronic medical records by investigators. Categorical variables are presented as frequencies with percentages and continuous variables as median with interquartile range (IQR). A Wilcoxon signed rank test was used to assess the difference in the PEEP, S/F ratios, F_{IO_2}, and driving pressure (DP) pre- and postesophageal balloon placements at 4 and 24 hours. All statistical tests were two-tailed; $p < 0.05$ was considered statistically significant. Statistical analyses were conducted using the Statistical Analysis Software (SAA) software, Version 9.4 (SAS Institute, Cary, NC).

RESULTS

There were 48 total esophageal balloons placed at Christiana Care during the study time, 29 of which met the inclusion criteria of at least class II obesity (BMI ≥ 35 kg/m^2) and ARDS. Baseline characteristics of subjects are listed in **Table 1**. Median and IQR for age were 56 years (40–66 yr) and BMI 45.8 kg/m^2 (41.1–52.1 kg/m^2). Pneumonia was the most common etiology of ARDS (59%). Only 26 patients (90%) had arterial blood gases available that allowed classification of ARDS severity. Of those, 15 patients (52%) had severe ARDS, seven patients (24%) had moderate ARDS, and four patients (14%) had mild ARDS. Baseline ARDS severity classified by S/F can be found in Table 1. Median and IQR for SOFA scores were 8 (5–12). Most of the patients were admitted to the medical ICU (n = 21, 73%). Median days of mechanical ventilation prior to balloon insert were 1 day. Sixteen underwent balloon insertion within the first

TABLE 1.
Patient Characteristics

Characteristic	All Patients
Age, yr, median (IQR)	56 (40–66)
Gender, *n* (%)	29 (100)
Male	16 (55)
Female	13 (45)
Body mass index, kg/m^2, median (IQR)	45.8 (41.1–52.1)
Race, *n* (%)	
Caucasian	19 (65)
Other	10 (35)
Etiology of ARDS, *n* (%)	
Pneumonia	17 (59)
Trauma	1 (3)
Other	11 (38)
Hypoxemia–ARDS classification,[a] *n* (%)	26 (90)
Mild (P/F < 300)	4 (14)
Moderate (P/F < 200)	7 (24)
Severe (P/F < 100)	15 (52)
Hypoxemia–S/F, *n* (%)	29 (100)
Mild (S/F < 315)	1 (3)
Moderate (S/F < 235)	7 (24)
Severe (S/F < 150)	21 (73)
Sequential Organ Failure Assessment score, median (IQR)	8 (5–12)
Unit, *n* (%)	
Medical ICU	21 (73)
Surgical ICU	4 (14)
Neurologic ICU	3 (10)
Cardiac ICU	1 (3)

ARDS = acute respiratory distress syndrome, IQR = interquartile range, P/F = Pa_{O_2}/F_{IO_2} ratio, S/F = median oxygen saturation/F_{IO_2}.
[a]Arterial blood gas was not obtained on three patients.

day, seven between days 1 and 10, and four patients had a balloon insertion after 10 days on mechanical ventilation.

Within our cohort, 25 (86%) had an increase in PEEP after P_L was determined postesophageal balloon insertion. The average End Insp P_L was 8.32 cm H_2O. No patients had an End Insp P_L greater than 14 cm H_2O. The average End Exp P_L was –2.72 cm H_2O. Comparison of ventilator settings between baseline, 4 hours, and 24 hours are shown in **Table 2**. Median P_{PLAT} was 33 cm H_2O after 4 hours and 31 cm H_2O after 24 hours. Comparison of P_{PLAT} and PEEP is shown in **Figure 1**. After 4 hours, median PEEP increased from 12 to 20 cm H_2O ($p < 0.0001$), with a corresponding decrease in median DP from 15 to 13 cm H_2O ($p = 0.002$). Additionally, at 4 hours, oxygenation improved as median F_{IO_2} decreased from 0.8 to 0.6 ($p < 0.0001$) and median S/F improved from 120 to 165 ($p < 0.0001$). Furthermore, improvements in oxygenation continued at 24 hours. After 24 hours, median PEEP decreased from 20 cm H_2O at 4 hours to 16 cm H_2O ($p = 0.02$), median F_{IO_2} decreased even further from 0.6 at 4 hours to 0.45 ($p = 0.004$), and median S/F improved from 165 at 4 hours to 211 ($p = 0.001$).

Additionally, we compared PEEP set based on P_L PEEP titration with the PEEP that would have been set based on empirical high PEEP/F_{IO_2} table. The set PEEP based on our P_L-guided titration did not match the PEEP recommended by the table in 18 patients (62%), with eight patients having a higher set PEEP and 10 patients with a lower set PEEP (**Fig. 2**).

Clinical outcomes are shown in **Table 3**. No patients developed pneumothoraces, and only one patient (3%) developed pneumomediastinum. Two patients (7%) required renal replacement therapy. Increase vasopressor use (norepinephrine, vasopressin, or epinephrine) was seen in seven patients (24%) after 4 hours and seven patients (24%) after 24 hours compared with baseline. Baseline average norepinephrine was 0.07 (± 0.14) μg/kg/min, and average epinephrine was 0.01 (±0.02) μg/kg/min. At 4 hours, average increase for norepinephrine was 0.05 (± 0.04) μg/kg/min, and epinephrine was 0.02 (±0.01) μg/kg/min. At 24 hours, average increase for norepinephrine was 0.10 (± 0.09) μg/kg/min, and epinephrine was 0.01 μg/kg/min (± 0.01). Vasopressin did not increase at 4 hours, whereas one patient had an increase at 24 hours. Inhaled pulmonary vasodilators (inhaled nitric oxide) were started on two patients (7%), and no patients received ECMO. Prior to esophageal balloon placement, five patients (17%) had been in prone position. A new prone position session (within 24 hr of balloon insertion) was performed in five patients (17%). Out of all 29 patients, there were 21 patients with Pao_2/F_{IO_2} less than 150, with a total of seven patients (33%) proned, and five (24%) of which were after balloon placement. Within the patient's hospital stay, five (17%) required tracheostomy.

DISCUSSION

The use of P_L to titrate PEEP in obese patients demonstrated rapid improvement in oxygenation without a signal for clinically significant harm. Our experience demonstrates the feasibility of implementation in a community ICU. This analysis adds to current ARDS literature with its focus on a population that is often excluded.

Prior evidence from Amato et al (24) demonstrated the primary contributor to improved mortality in ARDS comes from limiting DPs. In our cohort, we

TABLE 2.
Respiratory Mechanics Before and After Esophageal Manometry at 4 and 24 hr

Respiratory Mechanic	Before	After 4 hr	*p* (Before vs 4 hr)	After 24 hr	*p* (4 vs 24 hr)
Positive end-expiratory pressure (cm H_2O)	12 (10–16)	20 (16–20)	< 0.0001	16 (14–20)	0.023
F_{IO_2}	0.8 (0.65–1)	0.6 (0.5–0.7)	< 0.0001	0.45 (0.4–0.6)	0.004
Median oxygen saturation/F_{IO_2} ratio	120 (96–150.77)	165 (141.43–196)	< 0.0001	211.11 (156.7–247.5)	0.001
Driving pressure (cm H_2O)	15 (12–18)	13 (12–16)	0.002	14 (11–15)	0.379

Comparison of positive end-expiratory pressure, F_{IO_2}, median oxygen saturation/F_{IO_2} ratio, and driving pressure, between baseline vs 4 and 4 vs 24 hr.

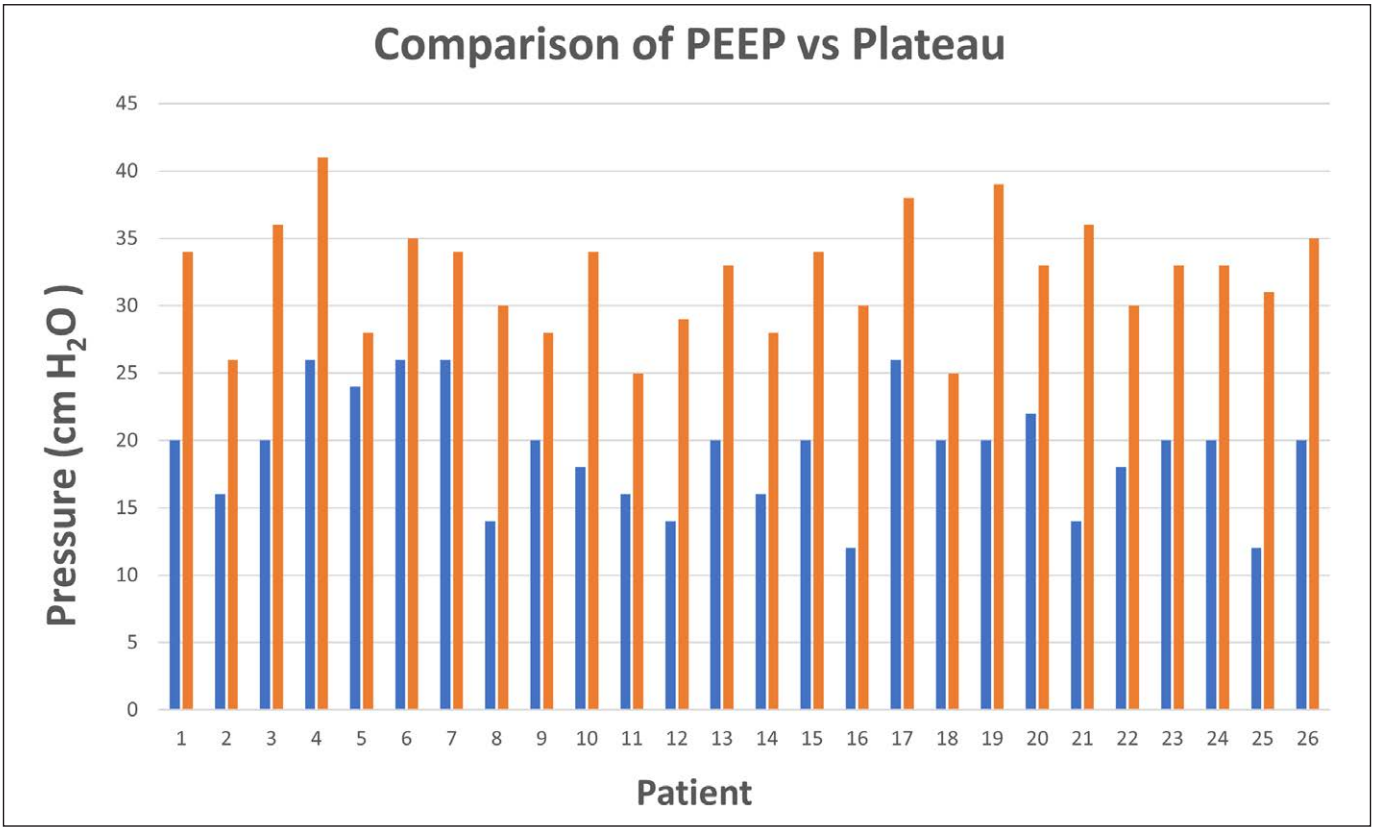

Figure 1. Comparison of positive end-expiratory pressure (PEEP) versus plateau pressures at 4-hr postballoon insertion. *Blue*: PEEP (cm H_2O). *Orange*: plateau pressure (cm H_2O). Note: plateau pressure was not obtained in three patients.

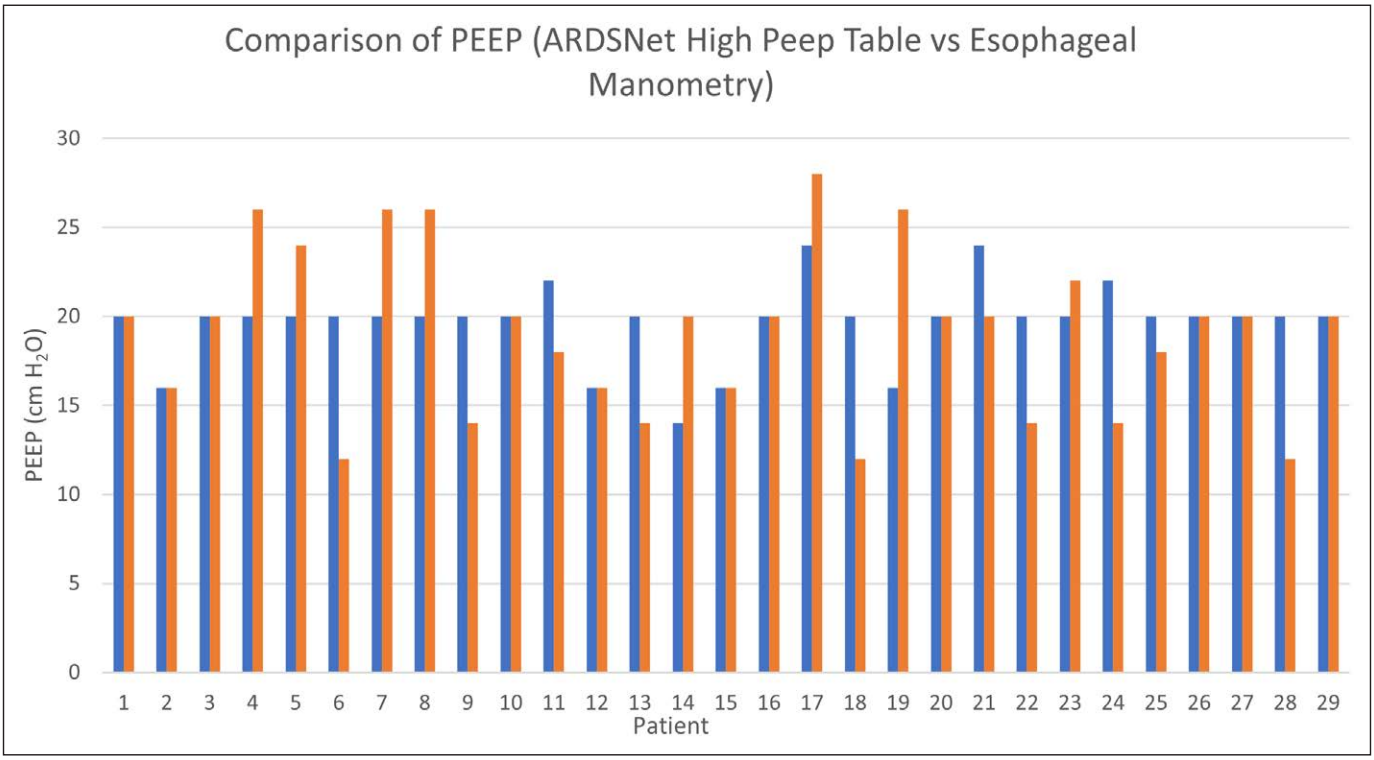

Figure 2. Comparison of positive end-expiratory pressure (PEEP) (Acute Respiratory Distress Syndrome Network [ARDSNet] high PEEP table versus esophageal manometry) at 4-hr postballoon insertion. *Blue*: PEEP (cm H_2O) set by ARDSNet high PEEP table. *Orange*: PEEP (cm H_2O) titrated via esophageal manometry.

TABLE 3.
Clinical Outcomes

Outcome	Patients, *n* (%)
Adverse events	
Pneumothorax	0 (0)
Pneumomediastinum	1 (3)
Increased vasopressor	
After 4 hr	7 (24)
After 24 hr	7 (24)
Rescue therapies	
Inhaled pulmonary vasodilators	2 (7)
Extracorporeal membrane oxygenation	0 (0)
New prone position[a]	5 (17)
Continuous renal replacement therapy	2 (7)
Tracheostomy	5 (17)

[a]Within first 24 hr of balloon insertion.

demonstrated a statistically significant decrease in DPs through increased PEEP and an associated improvement in oxygenation. In addition, atelectotrauma was reduced by keeping End Exp P_L near zero, as previously demonstrated by Fumagalli et al (15).

Despite an elevated P_{PLAT} greater than 30 cm H_2O in 16 patients, the End Insp P_L was never greater than 14 cm H_2O, well within a safe range. Additionally, there were no adverse effects from the elevated P_{PLAT}. Prior trials have demonstrated higher PEEP is effective and safe, and the commonly used low PEEP/F_{IO_2} table may be deleterious in the critically ill obese population (6). The first EPVent trial was criticized for the use of a low PEEP table (11). The second EPVent trial, a large multicentered randomized controlled trial, by Beitler et al (14) compared P_L-guided PEEP with an empiric high PEEP table. They demonstrated no difference in mortality or PEEP (14). The EPVent trials did not address the role of P_L in the very obese population. Furthermore, use of an empiric high PEEP table is not usual care at most institutions. When we compared the P_L set PEEP with the corresponding PEEP based on an empiric high PEEP table, we found that P_L-guided PEEP was different from PEEP based on an empiric high PEEP table in most patients. Without the use of esophageal manometry, the P_{PLAT} would have been considered unsafe, and such a high PEEP would have been abandoned based on current practice guidelines.

Although our study did not evaluate mortality, prior publications have described lower mortality with use of PEEP titrate based on esophageal manometry. Sarge et al (13) conducted a post hoc reanalysis of EPVent-2 data and found lower mortality with P_L-guided PEEP in patients with lower Acute Physiology And Chronic Health Evaluation II (APACHE-II) score less than 27.5. They attributed this to the deleterious hemodynamic effects of higher PEEP and alveolar overdistention in patients with extrapulmonary organ failure. Patients with lower APACHE-II scores had primary pulmonary disease and benefited more from precise PEEP titration. In addition, they described lower mortality in patients with End Exp P_L set closest to 0 cm H_2O (mitigating the effect of both atelectasis and hyperinflation), independent of baseline organ dysfunction (13).

Additionally, Florio et al (16) individualized care with P_L in critically ill obese patients through "lung rescue teams" and notably demonstrated significantly decreased mortality at 28 days, 3 months, and 1 year. Finally, our findings closely mirror and support previous findings by Rowley et al (17) and continue to build on individualized care approach with a slightly larger cohort without a signal for clinically significant adverse events.

Adverse events were limited in our study as only one patient developed pneumomediastinum, and no pneumothoraces were seen. Seven patients required an increase in vasopressor support after 4 hours. The average increase in norepinephrine and epinephrine was 0.05 (± 0.04) and 0.02 (± 0.01) μg/kg/min, respectively. These initial small increases are unlikely to be clinically significant. However, at 24 hours, average increase in norepinephrine and epinephrine was 0.10 (± 0.09) and 0.01 (± 0.01) μg/kg/min, respectively. Although it cannot be determined whether this further increase was due to PEEP change or organ dysfunction, we favor the latter as the initial increase in vasopressor was minimal. This is supported by physiologic data by Florio et al (25) who found that increasing PEEP decreased work of breathing without compromising right heart function. Our findings are consistent with prior literature where high levels of PEEP did not substantially increase vasopressor requirements (6).

Although proning has become a standard of care in severe ARDS (26), a very high BMI can raise safety concerns. There are limited systematic data in this population; however, prior data have shown

improvement in oxygenation when performed by an ICU team that has extensive familiarity with the modality (27). Nonetheless, proning in the obese has been associated with complications including endotracheal tube dislodgement, facial edema, pressure injuries, and worsening multiple organ failure (28, 29). Ventilator optimization with P_L may represent a safe and effective strategy in addition to prone positioning in the obese.

Limitations of this study include being a retrospective chart review without randomization or a control group. As such, data including arterial blood gas were unable to be obtained on all patients, and an S/F ratio was used as a surrogate (20, 21). Proning occurred in a limited number of patients, revealing an area for improvement but also highlighting the importance of concurrent ventilator optimization. Furthermore, as a single-center study in a community setting, we were limited in sample size and may not be generalizable to all ICU settings.

Esophageal manometry is a minimally invasive tool to individualize care. Titrating PEEP to End Exp P_L target with the aid of esophageal manometry in obese patients can be done by respiratory therapists following protocol, as we have demonstrated. However, rather than a one-size-fits-all approach, this protocol results in individualized PEEP setting based on each patient's physiology. This raises the possibility of achieving the best of both protocolized and individualized care for our patients. Future studies assessing benefit of specific protocols on patient center outcomes would be welcomed.

CONCLUSIONS

Obesity complicates optimal ventilator management by increasing transmitted intrathoracic pressures onto the lungs leading to atelectasis. Optimizing ventilator settings with esophageal manometry and P_L is minimally invasive and feasible in a community hospital. A protocol of PEEP titration aided by esophageal manometry led to substantial variation from protocolized empiric PEEP tables. Our findings show that P_L-guided PEEP titration in obese patients can be used to safely increase PEEP and decrease DP, and results in improved oxygenation.

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All authors all contributed substantially to the study design, data acquisition, data analysis and interpretation, and the writing of the article. All parties had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis and, especially, any adverse effects. All parties have revised and had final approval of the version published.

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