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Critical Care [ALERT]

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ABSTRACT & COMMENTARY

Use Push-Dose Phenylephrine with Caution in Septic Patients

By Samuel Nadler, MD, PhD

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SYNOPSIS: Phenylephrine pushes in septic patients were associated with early hemodynamic stability, but higher intensive care unit mortality.

SOURCE: Hawn JM, Bauer SR, Yerke J, et al. Effect of phenylephrine push before continuous infusion norepinephrine in patients with septic shock. *Chest* 2021;159:1875-1883.

Patients with septic shock frequently are treated with vasopressor infusions to maintain mean arterial pressure (MAP). However, emergent or transient drops in MAP can be treated with "push-dose" vasopressors. In this study, the authors examined the effects of push-dose phenylephrine (PE) on patients with septic shock who also received vasopressor infusions.

A total of 1,317 patients were included who were 18 years of age or older, admitted to an intensive care unit (ICU) requiring continuous norepinephrine (NE) infusion, and met definitions for sepsis. Of these, 181 patients received a push dose of PE between 60 minutes prior and 120 minutes after the initiation of NE infusion. Patients were excluded if they received PE pushes outside this window. A propensity score was used to match patients receiving PE with a control group that did not receive push-dose PE. The primary outcome was hemodynamic stability at three and 12 hours defined as MAP ≥ 65 mmHg for six hours without further increases in vasopressor infusions. Secondary outcomes included mortality, length of stay (LOS), duration of mechanical ventilation, and vasopressor need, among other variables.

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Primary and secondary outcomes were reported for both propensity score matched and unmatched samples. Other than a higher incidence of chronic obstructive pulmonary disease (COPD) in the PE push group vs. non-PE push group (29.1% vs. 17.4%, respectively), the propensity score matched groups were similar.

In the matched groups, patients receiving push-dose PE had statistically greater hemodynamic stability at three hours (28.4% vs. 18.8%), but not at 12 hours (58.2% vs. 50.0%). Compared with patients not receiving push-dose PE, those patients who did had higher ICU mortality (22.0% vs. 31.2%), hospital mortality (22.5% vs. 39.0%), ICU LOS (9.3 vs. 12.4 days), and vasoactive infusion duration (2.0 vs. 2.6 days), but not hospital LOS, duration of mechanical ventilation, or maximum NE infusion dose. Multivariate-adjusted models demonstrated that PE push dosing was independently associated with higher three-hour hemodynamic stability (odds ratio [OR], 1.8; 95% confidence interval [CI], 1.09-2.97; $P = 0.02$). However, PE pushes were associated with higher ICU mortality (OR, 1.88; 95% CI, 1.10-3.21; $P = 0.02$).

■ COMMENTARY

This study examined the effect of push-dose PE on patients with septic shock and hemodynamic instability. As with any retrospective cohort study, there is a risk of unknown, confounding variables that explain the observed differences in the two experimental groups. The need for PE pushes might simply be a marker for greater severity of illness. However, the authors used a propensity score to adjust for known variables, and the two groups appeared to be well-matched.

Notably, Sequential Organ Failure Assessment (SOFA) scores in both unmatched and propensity matched cohorts were similar, and the changes in SOFA score over 72 hours were nearly identical, supporting similar severity of illness between the groups. Furthermore, in the propensity matched groups, lactate levels, total fluid administration, and corticosteroid use also were similar.

The primary outcome in this study was hemodynamic stability at three and 12 hours. Push-dose PE was associated with greater hemodynamic stability at three hours, but not at 12 hours. Although not statistically significant, PE dosing tended to decrease the time to hemodynamic stability within three hours ($P = 0.06$).

This raises the question: What is the most appropriate outcome? Phenylephrine rapidly supports MAP by increasing cardiac afterload. However, this increase in MAP may not correlate with greater cardiac output and improved perfusion in septic patients with myocardial dysfunction. Indeed, when PE infusions were substituted for NE infusions for the treatment of sepsis during a shortage of NE, mortality worsened.[1] Thus, the increase in mortality observed in patients with PE pushes despite improved hemodynamic stability implies PE may be the wrong agent to counteract transient hypotension.

Although push-dose phenylephrine improved hemodynamic numbers, the number of patients who survived the ICU seemed to be less. Caution should be undertaken when considering push-dose PE for transient hypotension in patients with septic shock. ■

REFERENCE

1. Vail E, Gershengorn HB, Hua M, et al. Association between US norepinephrine shortage and mortality among patients with septic shock. *JAMA* 2017;317:1433-1442.

ABSTRACT & COMMENTARY

High Pleural Pressure Prevents Overdistension in ARDS Patients with High Body Mass Index

By Vibhu Sharma, MD, MS

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SYNOPSIS: High airway pressure is required to recruit lung atelectasis in patients with acute respiratory distress syndrome and body mass index ≥ 35 kg/m^2.

SOURCE: De Santis Santiago R, Droghi MT, Fumagalli J, et al. High pleural pressure prevents alveolar overdistension and hemodynamic collapse in ARDS with class III obesity. *Am J Respir Crit Care Med* 2020;203:575-584.

This was an interventional crossover trial in obese adults with acute respiratory distress syndrome (ARDS). The authors also studied a swine model of ARDS to assess the impact of recruitment maneuvers and high plateau pressures. For the clinical part of the study, the obese adults with ARDS enrolled in the trial underwent esophageal manometry to estimate pleural pressures; all were paralyzed and sedated. Esophageal pressures (Pes) were used as a surrogate for plateau pressures (Pplat). Electrical impedance tomography (EIT) was used to determine whether lungs were collapsed or overdistended.

Electrical conductance in lung tissue varies with the amount of blood and air in the lung at any given time. These changes can be measured and plotted over time and converted into two-dimensional images that generate the distribution of conductance (or impedance) in lung tissue. Transthoracic echocardiography was used to assess the tricuspid annular plane systolic excursion (TAPSE) and the tricuspid systolic excursion velocity (S') to assess right ventricle (RV) function in the standard apical four-chamber view at baseline and in response to the recruitment maneuver. RV failure is associated with a TAPSE < 17 cm and an S' < 10 cm/s.

A cohort of 19 obese ARDS patients were recruited. The EIT data from this group were compared to five non-obese patients from the Alveolar Recruitment Trial (ART).[1] The obese patients received initial ventilation with ARDS Network (LungARDSnet) criteria for 30 minutes using the positive end-expiratory pressure/fraction of inhaled oxygen (PEEP/FiO_2) table and then were crossed over to a standardized sequence of procedures including recruitment maneuvers to determine optimal PEEP (LungRECRUITED). The Pressure-Volume (PV) tool was used to determine optimal PEEP by first applying a lung recruitment maneuver. Pressure-controlled ventilation (PCV) with a delta pressure of 10 cm H_2O was used for recruitment at a set respiratory rate of 20 breaths/minute. PEEP was increased until a Pplat of 50 cm H_2O was reached, which was maintained for one minute. Thereafter, volume-controlled ventilation (VCV) was reinstituted, and PEEP was reduced by 2 cm H_2O every 30 seconds. The optimal PEEP was set at the PEEP value with the best static compliance of the respiratory system (Crs) plus 2 cm H_2O. A second recruitment maneuver was performed, and VCV with optimal PEEP instituted.

The experimental part of the study compared similar maneuvers in sedated and paralyzed swine with simulated abdominal obesity and ARDS and swine with normal lungs. Abdominal obesity was simulated in swine by application of external abdominal weights, which induced an increase in Pplat. The swine underwent left and right heart catheterization as well to assess hemodynamic response to recruitment maneuvers. Mean arterial pressure (MAP), mean pulmonary artery pressure (mPAP), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) were calculated. Cardiac transmural pressures were computed in systole and diastole by subtracting Pes during inspiratory and expiratory pauses from the relevant chamber pressure.

The primary aim was to determine the cardiovascular response to a recruitment maneuver in the setting of obesity. An additional aim was a descriptive comparison of recruitment maneuvers on lung mechanics in obese vs. non-obese patients.

The results for the clinical study demonstrated improved Crs and more homogenous ventilation in response to recruitment maneuvers among the obese

patients studied. Driving pressure decreased, and the partial pressure of arterial oxygen/fraction of inspired oxygen (P/F) ratio improved by 129 mmHg in the LungRECRUITED approach. Right heart function parameters (TAPSE and S') remained unchanged with higher airway pressures. MAP was unchanged, and no patient required either a fluid bolus or changes in vasopressor doses during or after the recruitment maneuver. Lung collapse was higher and overdistension was lower for the obese patients with ARDS compared to the non-obese ART cohort at similar PEEP levels.

PV curves plotted by lung region (dependent and non-dependent) showed absence of overdistension for a pressure up to 25 cm H_2O in the non-dependent region for obese patients. However, overdistension was seen in the non-dependent region among non-obese patients with ARDS in the historical comparator ART cohort. For dependent regions, the PV tool showed poorly compliant lung in obese ARDS patients with "exponential positive growth," implying successful lung recruitment with recruitment maneuvers in this group. In contrast, overdistension was seen in the historical non-obese ART cohort with ARDS.

The results for the experimental part of the study were nearly identical to results in the obese patients studied in that, among swine with modeled obesity (high Pes) and ARDS, the LungRECRUITED strategy was associated with a reduction in shunt fraction, increase in the P/F ratio by 125 mmHg, improved Crs, and improved driving pressure. While PVR was high at the onset, it decreased after the LungRECRUITED strategy. MAP and SVR were unchanged. Transmural cardiac pressures and left ventricular function also were unchanged. The LungRECRUITED strategy resulted in increased homogeneity of ventilation.

■ COMMENTARY

The original ARDSNet trial (and others) typically has excluded patients with morbid obesity (defined as > 1 kg/cm body weight). The study reported here is a valuable clinical and experimental endeavor to inform management of ARDS in the obese patient. A single-center study that assessed use of the esophageal balloon to adjust PEEP showed that compliance and oxygenation improved relative to the standard of care.[2] A subsequent multicenter randomized trial of patients with moderate to severe ARDS (EPVent2) found that PEEP titration guided by Pes did not result in a significant difference in death or days free from mechanical ventilation compared with a standard high PEEP-FiO_2 strategy.[3] There were no differences between groups with respect to barotrauma or pneumothoraces requiring drainage. However, this trial was underpowered for the stated secondary endpoints (e.g., 28-day mortality). Although obese patients were not explicitly excluded, the mean actual body weight in the EPVent2 study was 80 kg; body mass index (BMI) was not reported. The mean BMI in the study reviewed here was 57 kg/m^2.

In the study reviewed here, mean Pplat in the LungRECRUITED strategy was higher (30.4 cm H_2O) compared with the LungARDSnet strategy (25.6 cm H_2O); however, the transpulmonary pressure was -4.3 cm H_2O in the LungARDSnet strategy compared with +1.4 cm H_2O in the LungRECRUITED strategy, suggesting optimal PEEP-sustained lung recruitment with the LungRECRUITED strategy.

What should the clinician at the bedside take away from this study? A lung recruitment strategy may be useful in morbidly obese patients with ARDS with no adverse effects in the setting of a properly performed recruitment maneuver. A reduction in driving pressure, an improvement in P/F ratio, and more homogenous ventilation/perfusion (VQ) matching can be expected. Clinicians ought to be careful to include only those patients with a BMI ≥ 35, with expected benefits possibly higher for more obese patients. It is imperative to ensure that a properly trained respiratory therapist with experience in the placement of an esophageal balloon is present continuously at the bedside while recruitment maneuvers are being performed.

The ARDSNet trial demonstrated the mortality benefit of a lower Pplat. The Pplat in the LungRECRUITED group was higher than in the LungARDSnet group but was likely necessary to maintain VQ matching as evidenced by the positive transpulmonary pressure in the former. The driving pressure was lower, however, and this bodes well from a mortality perspective given the association of a lower driving pressure with lower mortality.[4] Oxygenation was better, as evidenced by the improved P/F in the LungRECRUITED group; however, the P/F ratio does not predict mortality in the setting of ARDS.

A few caveats apply. Previous studies have suggested that recruitment maneuvers may delay other interventions shown to affect mortality (e.g., proning). Further, paralysis and deep sedation required for these maneuvers are not the standard of care in ARDS management and may be harmful. There are associated risks to placement of the esophageal balloon and the need for trained respiratory therapists to perform and interpret the study.

In summary, this study shows that a LungRECRUITED strategy is safe and results in improved driving pressure as well as sustained improvements in VQ matching in morbidly obese adults with ARDS. All maneuvers can be safely performed with careful monitoring by trained staff. Translation of a LungRECRUITED strategy into a mortality benefit remains to be demonstrated with a randomized trial exclusively recruiting morbidly obese patients randomized to a LungARDSnet vs. a LungRECRUITED strategy. ■

REFERENCES

1. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators, Cavalcanti AB, Suzumura É, Laranjeira LN, et al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: A randomized clinical trial. *JAMA* 2017;318:1335-1345.
2. Talmor D, Sarge T, Malhotra A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med* 2008;359:2095-2104.
3. Beitler JR, Sarge T, Banner-Goodspeed VM, et al. Effect of titrating positive end-expiratory pressure (PEEP) with an esophageal pressure-guided strategy vs an empirical high PEEP-Fio2 strategy on death and days free from mechanical ventilation among patients with acute respiratory distress syndrome: A randomized clinical trial. *JAMA* 2019;321:846-857.
4. Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015;372:747-755.

ABSTRACT & COMMENTARY

Elucidating the Long-Term Effects of COVID-19

By Betty Tran, MD, MSc

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SYNOPSIS: In this prospective uncontrolled cohort study of COVID-19 survivors performed four months after their hospitalization, many patients reported at least one symptom not previously present, and abnormalities on lung computed tomography scan were common.

SOURCE: Writing Committee for the COMEBAC Study Group; Morin L, Savale L, Pham T, et al. Four-month clinical status of a cohort of patients after hospitalization for COVID-19. *JAMA* 2021;325:1525-1534.

The COMEBAC (Consultation Multi-Expertise de Bicêtre Après COVID-19) was a prospective uncontrolled cohort study of adult patients admitted to a university hospital near Paris for COVID-19 (diagnosed via reverse transcriptase-polymerase chain reaction [RT-PCR], typical computed tomography [CT] lung scan, or both) from March 1 to May 20, 2020. Inclusion criteria were survival to four months post-hospital/intensive care unit (ICU) discharge and hospitalization for at least 24 hours primarily for COVID-19.

At three to four months post-hospital or ICU discharge, telephone assessments asked patients about respiratory, cognitive, and neurologic symptoms. All ICU patients and those who were symptomatic were further evaluated in the ambulatory setting with a general physical exam, bloodwork, and several tests assessing quality of life (36-Item Short-Form Health survey questionnaire), fatigue (Multidimensional Fatigue Inventory scale), and dyspnea (modified Medical Research Council scale, 6-minute walk test, pulmonary function tests, Nijmegen questionnaire, and hyperventilation provocation test). All patients had a high-resolution lung CT and a transthoracic echocardiogram performed if they were an ICU patient or had a pulmonary embolism or cardiac symptoms. In addition, all patients underwent psychometric testing (Montreal Cognitive Assessment, McNair self-questionnaire, and d2-R test) and were evaluated for anxiety, depression, and insomnia symptoms (Hospital Anxiety and Depression Scale, 13-item Beck Depression Inventory score, Insomnia Severity Index, and Posttraumatic Stress Disorder Checklist).

Among the 1,151 patients admitted because of COVID-19, 834 were eligible for telephone consultation, and 478 (57%; 142 ICU patients and 336 non-ICU patients) consented to be part of the study. Of 294 patients eligible for ambulatory assessment, 177 consented (97 ICU patients, 80 non-ICU patients). Median time to telephone assessment was 113 days (interquartile range [IQR] 94-128 days) post-discharge, and median time to ambulatory assessment was 125 days (IQR 107-144 days).

Of the 478 patients assessed via telephone, 244 (51%) reported at least one symptom that was not present pre-COVID-19 infection, most commonly

fatigue (31.1%), memory difficulties (17.5%), dyspnea (16.3%), and persistent paresthesia (12.1%). During the ambulatory assessment, cognitive impairment was confirmed in 38.4% of patients, more commonly in patients ≥ 75 years of age. In ICU patients, symptoms of anxiety (23.4%), depression (18.1%), and significant posttraumatic stress (7.4%) were notable. ICU neuromyopathy was identified in 27.5% of previously intubated patients. Lung abnormalities were noted in a majority of both previously intubated patients (75.5%) and nonintubated ones (58.2%), most commonly persistent ground glass opacities (42.4%) and fibrotic lesions (19.4%), particularly in patients who had acute respiratory distress syndrome. Among the 78 patients assessed in the ambulatory setting with reports of new-onset dyspnea, the dyspnea was attributed to lung CT abnormalities in 56.4% and to hyperventilation provocation test-confirmed dysfunctional breathing in 17.9%. Of the patients who had echocardiograms performed, 9.6% had an ejection fraction of less than 50%; all had been ICU patients. Among the 95 of 478 patients who had acute kidney injury, two displayed persistent kidney dysfunction at four months.

■ COMMENTARY

There have been few systematic comprehensive evaluations of the long-term clinical consequences of COVID-19 infection thus far. Anecdotally, many patients have presented to our outpatient clinics with reports of persistent symptoms post-COVID-19 infection. This cohort study reports that at least half of patients who were hospitalized for COVID-19 infection had at least one persistent symptom that was not present pre-infection. Although persistent cardiac and renal dysfunction was uncommon, lung CTs frequently revealed persistent abnormalities, although fibrosis was less common (19%). Interestingly, many patients exhibited dysfunctional breathing not attributable to parenchymal lung findings as confirmed on hyperventilation provocation testing. Not surprisingly, psychological sequelae were common, as they have been described previously in ICU survivors.[1]

However, it is important to note that the findings of this study cannot confirm that COVID-19 was the direct causative agent, since there was no non-COVID-19 control group or pre-COVID-19 assessments done on the same patients. Furthermore, this study was conducted prior to more widespread use of corticosteroids, higher doses of anticoagulation, and many immunomodulator therapies, all of which may (or may not) have an impact with regard to the persistence of symptoms.

Despite its limitations, this study, in addition to our anecdotal experience, highlights the need for comprehensive COVID-19 clinics to address persistent symptoms post-infection. Given the wide range of symptoms, engaging multiple subspecialties in treating these patients is key. In the May 2021 issue of *Critical Care Alert*, Dr. Radigan nicely summarized a diagnostic approach to evaluating post-COVID-19 patients in follow-up clinics.[2] These clinics also will be valuable in collecting further data on the longer-term outcomes of these patients and how those outcomes are associated with COVID-19 disease. ■

REFERENCES

1. Jackson JC, Pandharipande PP, Girard TD, et al. Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: A longitudinal cohort study. *Lancet Respir Med* 2014;2:369-379.
2. Radigan K. Post-COVID-19: The crisis after the crisis. *Critical Care Alert* 2021;29:9-13.

ABSTRACT & COMMENTARY

Driving Pressures More Strongly Predicted Survival than P/F Ratios in Patients with ARDS

By Samuel Nadler, MD, PhD

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SYNOPSIS: Optimizing positive end-expiratory pressure to minimize driving pressure may be a better strategy for ventilator adjustment than maximizing partial pressure of arterial oxygen/fraction of inspired oxygen (P/F) ratios to improve outcomes in patients with acute respiratory distress syndrome.

SOURCE: Yehya N, Hodgson CL, Amato MBP, et al. Response to ventilator adjustments for predicting acute respiratory distress syndrome mortality. Driving pressure versus oxygenation. *Ann Am Thorac Soc* 2021;18:857-864.

Lung protective ventilation has become the standard of care for patients with the acute respiratory distress syndrome (ARDS). Beyond this, the ventilator adjustments most closely associated with mortality remain unclear. Yehya et al re-evaluated the ALVEOLI and ExPress trials, two previous studies of higher vs. lower positive end-expiratory pressure (PEEP) in patients with ARDS.[1,2] The relationships between changes in PaO_2/FiO_2 ($\Delta P/F$) or changes in driving pressure ($\Delta\Delta P$) on mortality were examined. Multiple sensitivity analyses further stratified patients by the presence of passive ventilation, level of pre-randomization PEEP, changes in tidal volumes (ΔVt) and changes in driving pressure attributable only to changes in Vt.

Within the ALVEOLI trial, positive $\Delta\Delta P$ (hazard ratio [HR], 1.50; 95% confidence interval [CI], 1.21-1.85; $P < 0.001$) but not negative $\Delta P/F$ (HR, 0.95; 95% CI, 0.86-1.04; $P = 0.232$) was associated with higher mortality among the 372 patients with complete data prior to randomization. This relationship remained when the analysis was restricted to patients with passive ventilation, baseline $P/F \leq 200$, those in the high PEEP arm, and when adjusted for pre-randomization PEEP or changes in Vt. Neither $\Delta\Delta P$ nor $\Delta P/F$ correlated with mortality in the low PEEP arm.

A similar analysis of 596 patients from the ExPress trial showed a stronger association between mortality and positive $\Delta\Delta P$ (HR, 1.42; 95% CI, 1.14-1.79; $P = 0.002$) than with Δ P/F (HR, 0.95; 95% CI, 0.9-1.00; $P = 0.040$). This held true in patients with passive ventilation, those in the higher PEEP arm, and when adjusted for pre-randomization PEEP, but not in the low PEEP arm. When both data sets were combined into one complete model, $\Delta\Delta P$ was more strongly associated with mortality than $\Delta P/F$ (HR 1.48 vs. 0.95, respectively).

■ COMMENTARY

This study represents a complicated re-analysis of two previously published data sets that were developed to determine if higher or lower PEEP strategies affected mortality in patients with ARDS. Neither of these trials showed a significant benefit from higher PEEP strategies. Thus, the conclusions drawn from this re-analysis must be viewed in the context of the failure of these previous studies to show a benefit from protocols to adjust PEEP to optimize outcomes. However, within the data, there may be correlations that can be used to drive future studies. Although correlation does not mean causation, the improvements in mortality with lower driving pressure (ΔP) after changes in PEEP imply a more physiologic protocol of PEEP titration that minimizes ΔP, rather than adjusting to a fixed PEEP level, might improve outcomes.

Does the observed correlation make physiologic sense? Injury to the lung in ARDS can be quite heterogeneous. The effect of PEEP throughout the lung will vary as well. Increases in PEEP that cause decreases in ΔP imply improved overall compliance of the respiratory system or a more "open lung," while increased PEEP associated with increased ΔP suggests worsening compliance or over-distention. If maximizing lung compliance as the parameter most closely associated with mortality is the goal, a driving pressure-based approach may be appropriate. Interestingly, neither $\Delta\Delta P$ nor $\Delta P/F$ was correlated with mortality in the low PEEP arms. This suggests these lower levels of PEEP do not commonly lead to over-distention but may not fully recruit lung tissue.

Other studies support the notion that decreased driving pressures are associated with improved outcomes. Amato et al similarly found that ΔP was more closely associated with mortality than PEEP or plateau pressure.[3] More recently, Barrot et al found no difference in 28-day mortality in patients with ARDS randomized to a conservative vs. liberal oxygenation strategy.[4] Thus, higher PaO_2 or P/F ratios may not be good surrogates for ventilator titration, and changes in ΔP might be better.

More definitive studies of driving pressure-driven protocols for ventilator adjustment likely will be published. Until that time, paying attention to the $\Delta\Delta P$ as you adjust PEEP in patients with ARDS on the ventilator could improve their outcomes. ■

REFERENCES

1. Brower RG, Lanken PN, MacIntyre N, et al; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004:351:327-336.
2. Mercat A, Richard JCM, Vielle B, et al. Positive end-expiratory pressure settings in adults with acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2008;299:646-655.
3. Amato MBP, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015;372:747-755.
4. Barrot L, Asfar P, Mauny F, et al. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. *N Engl J Med* 2020;382:999-1008.

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CME/CE QUESTIONS

1. **In the article by Hawn et al, push-dose phenylephrine in patients with sepsis was associated with which of the following?**
   a. Increased survival
   b. Decreased survival
   c. No change in survival
   d. Improved Sequential Organ Failure Assessment (SOFA) score

2. **Which of the following accurately reflects the lung recruitment maneuver in the obese acute respiratory distress syndrome (ARDS) patient in the study by De Santis Santiago et al?**
   a. Pressure-controlled ventilation (PVC) and serial inflation to plateau pressure (Pplat) 50 cm H_2O
   b. PCV and serial inflation to Pplat 25 cm H_2O
   c. Volume-controlled ventilation (VCV) and positive end-expiratory pressure (PEEP) increased to 25 cm H_2O
   d. VCV and PEEP titrated to 50 cm H_2O

3. **Compared with a LungARDSnet strategy, which of the following accurately reflects lung mechanics with a LungRECRUITED strategy in the obese patient with ARDS?**
   a. Higher compliance of the respiratory system (Crs)
   b. Lower partial pressure of oxygen/fraction of inspired oxygen (P/F) ratio
   c. Lower Pplat
   d. More negative transpulmonary pressures

4. **In the COMEBAC study, which of the following statements is true?**
   a. A minority of patients reported at least one symptom that was not present pre-COVID-19 infection.
   b. The most common persistent computed tomography lung abnormality was fibrosis.
   c. The most common persistent symptom was fatigue.
   d. The majority of COVID-19 intensive care unit survivors had chronic kidney disease at four-month follow-up.

5. **In the study by Yehya et al, re-analysis of the ALVEOLI and ExPress trials showed that changes in driving pressure were better correlated with mortality in which population?**
   a. Every patient
   b. Spontaneously breathing patients
   c. Patients in the high PEEP arms
   d. Patients with high tidal volumes

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- identify relevant topics in the practice of critical care medicine;
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