Ventilator Strategies for Chronic Obstructive Pulmonary Disease and Acute Respiratory Distress Syndrome

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KEYWORDS

• Respiratory failure • Hypoxia • ARDS • COPD • APRV
• Airway pressure release ventilation • ALI • PEEP

KEY POINTS

- Identification of high-risk patients for pulmonary complications is an important part of determining outcomes.
- Low tidal volume ventilation is the only ventilator strategy that has been shown in prospective randomized trials to improve mortality in ARDS and COPD.
- Once COPD patients are intubated the minute ventilation should be titrated to Ph and not to the $Paco_2$.
- A restrictive fluid schedule that maintains perfusion but aims at keeping patients fluid neutral has been associated with shorter ICU and ventilator days in ARDS.
- In ARDS several studies show APRV to have physiologic benefits and to improve some measures of clinical outcome, such as oxygenation, use of sedation, hemodynamics, and respiratory mechanics. None have shown a survival benefit when compared with conventional lung protective ventilation.

INTRODUCTION

Worldwide 52 million people have been diagnosed with COPD. The incidence and the complications that it has caused are increasing.[1] In 1990 it was the 6th most common cause of death worldwide but is expected to be the third most common by the year 2020.[2] Patients with COPD often require respiratory support for a variety of reasons including exacerbations of the disease, complications related to other medical conditions and elective and emergent surgical interventions. In these surgical situations if the clinical situations allows the best time to optimize the patient to prevent complication is pre-operatively. When mechanical ventilation becomes necessary in this challenging population morbidity can be minimized with the application of evidence-based approaches.

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Acute respiratory distress syndrome (ARDS) is defined by the acute onset of hypoxemia and bilateral infiltrates after a trigger. The definition has changed over time to its current status. Although it only effects about 5% of mechanically ventilated patients, 75% of those present with a moderate or severe form.[3] Unlike COPD, the incidence of ARDS is decreasing secondary to the decrease in the numbers of triggers secondary to the institution of such interventions, such as limited resuscitations, early source control, restrictive transfusion strategies, ventilator care bundles, and lung-protective ventilation.[4]

This article discusses the basic concepts of mechanical ventilation in patients with COPD and ARDS, reviews predisposing factors to the development of complications, and discusses current strategies for the recognition and prevention of these adverse effects in the application of mechanical ventilation in this population.

PREDICTING PULMONARY COMPLICATIONS

Ventilator strategies can play a pivotal role in the deciding the outcome of patient once pulmonary complications have developed. The issue is that by far the best means to improve pulmonary-related morbidity is to prevent it from happening. A large part of that preventive piece is to recognize high-risk groups so that at the very least preparations can be made. Virtually all of the interventions described herein have been shown to be at least partially protective if instituted before pulmonary complications have developed. For example, low tidal volume ventilation is a proven ventilator strategy for the treatment of both COPD and ARDS, and has also been shown to minimize the risk of the development of ARDS. In high-risk patient populations, it would only stand to reason that strict adherence to low tidal volume protocols be observed.

The risk of postoperative pulmonary complications (PPCs) increases nearly up to 3-fold for patients with a moderate or severe systemic disease (American Society of Anesthesiology class III) and up to 5-fold in moribund patients (American Society of Anesthesiology class IV).[5] The individual risk does not only relate to a patient's comorbidities, but is also influenced by the type and/or duration of surgery, and it may also be modified by the corresponding type of anesthesia.[6] Therefore, an American Society of Anesthesiology class IV patient undergoing a short, low-risk procedure under regional anesthesia might have a lower risk of PPCs than a patient without comorbidities planned to undergo a long-lasting, high-risk surgical procedure under general anesthesia. Tailoring the type of anesthesia to the patient is an important step in avoiding PCC.

Active smokers have an increase in tracheobronchial secretions and a decrease in mucociliary clearance. They depend on coughing for the removal of secretions, and they may need longer weaning from mechanical ventilation on the intensive care unit (ICU).[7] Smoking is also associated with pulmonary and cardiac diseases. Smokers have been included in all studies on intraoperative lung-protective ventilation strategies. Whether smokers benefit more than nonsmokers from any specific ventilator settings remains unclear.[8,9]

Advanced age, specifically an age of greater than 65 years, approximately doubles the risk of PPC not only owing to "accumulating comorbid conditions,"[10] but as an independent predictor of outcome based on age-related changes in the lungs, which are summarized in **Table 1**.[2,11,12]

In an animal model of mechanical ventilation with high tidal volumes, older lungs developed more severe pulmonary injury than younger ones.[13] It seems that elderly patients are more vulnerable to high tidal volumes, and that, in turn, they may benefit more from lung-protective mechanical ventilation than younger ones.[14]

The development of PCC starts early in the patient's hospital course and the intraoperative ventilator settings have been shown to impact outcome in the elderly. Two trials so far specifically addressed this patient population and found at low tidal volume strategies intraoperatively lead to higher intraoperative pulmonary compliance, lower airway resistance, higher Pa_{O_2}/Fi_{O_2} ratio, and higher Pa_{CO_2} levels in the intervention group.[8,15]

MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Patients with COPD suffer from chronic inflammation of small airways and lung parenchyma, resulting in obstructive bronchiolitis, parenchymal destruction, and emphysema. Increased airway resistance and decreased elastic recoil lead to limited airflow and an impaired ability of the airways to remain open at the end of expiration. In turn, the collapse of airways at the end of expiration results in incomplete expiration, higher residual end-expiratory volume, hyperinflation, and auto–positive end-expiratory pressure (auto-PEEP). Progression of chronic inflammation and parenchymal destruction result in impaired gas exchange with hypoxemia and hypercapnia. In case of the need for ventilatory support for acute exacerbations, the use of noninvasive mechanical ventilation reduces mortality in patients with COPD.[9,10]

Patients with COPD planning to undergo elective surgery should be in a stable disease condition, and they should receive optimal individual medical treatment. In case of acute exacerbations, surgery should be postponed. However, even stable patients with COPD have an up to a 4-fold increased risk of PPC,[16,17] which is higher the worse the disease is. Absolute cutoff levels as contraindications for surgery[18] or predictors of the perioperative risk of patients with COPD are missing. Nevertheless, patients with an FEV_1 of greater than 60% are typically considered to be at low risk of PPC, even if they had planned to undergo lung resection.[19]

Physiologic Changes in Chronic Obstructive Pulmonary Disease Relevant to Mechanical Ventilation

Expiratory flow limitation is the principal physiologic alteration in COPD and is overcome by increasing the inspiratory flow and lung volume. Although the issue is expiratory, the compensation is inspiratory, and this, combined with high respiratory drive, leads to the development of inspiratory muscle fatigue, which is of central pathophysiologic importance in the development of acute respiratory failure in these patients.

The airflow obstruction, low elastic recoil, high ventilatory demand, and short expiratory time result in air trapping and consequent DH. In patients with COPD with acute respiratory failure, DH is the main factor explaining the increased intrathoracic pressure, increased work of breathing (WOB), ventilator dependency and weaning failure.[11,12]

Role of Noninvasive Positive-Pressure Ventilation in Treating Obstructive Pulmonary Disease Patients

Noninvasive positive-pressure ventilation (NPPV) has been accepted widely as the first choice in treating obstructive airway disease patients with respiratory failure. It provides a significant reduction in endotracheal intubation and thereby its complications (eg, ventilator-associated pneumonia, tracheal and laryngeal complications) if considered early in the course of the disease.[10,13,14]

Expiratory positive airway pressure applied offsets intrinsic PEEP resulting from expiratory airflow obstruction. Inspiratory positive airway pressure augments tidal volume for any given respiratory effort leading to less mechanical disadvantage,

decreased respiratory rate, decreased WOB, and improvements in ventilation (generally reduced $Paco_2$).[20]

Indications for Invasive Mechanical Ventilation

Although NPPV is now considered the first choice for the treatment of selected patients experiencing COPD exacerbations, there are some patients for whom NPPV may not be suitable owing to the severity of their conditions.[9] Another requirement for continuing with NPPV is the patient maintains a level of alertness to protect their airway. Having a patient vomit with a tight-fitting NPPV mask in place can be a recipe for a poor outcome. The main goals of mechanical ventilation are to improve pulmonary gas exchange and to rest compromised respiratory muscles sufficiently to recover from the fatigued state.

Major criteria (any one of the following)[9,21]

- Respiratory arrest
- Loss of consciousness
- Psychomotor agitation requiring sedation
- Hemodynamic instability with a systolic blood pressure less than 70 or greater than 180 mm Hg
- Heart rate less than 50 beats/min with loss of alertness
- Gasping for air

Minor criteria (any two of the following)

- Respiratory rate >35 breath/min
- Worsening acidemia or pH <7.25
- Pao_2 less than 40 mm Hg or Pao_2/Fio_2 less than 200 mm Hg despite oxygen
- Decreasing level of consciousness

Choice of Ventilator Mode in Chronic Obstructive Pulmonary Disease

Accomplishing gas exchange and alleviating respiratory muscle fatigue may be accomplished using any mode available on the ventilator, but the choice may vary with the status of the patient with COPD. For the obtunded or postoperative patient, pressure-support ventilation may not be the first choice until the patient respiratory drive returns. Therefore, either assist-control or synchronized intermittent mandatory ventilation, with either volume or pressure targets, should be used. High inspiratory flow rates are preferred to reduce the inspiratory–expiratory ratio, thus allowing more time for expiration. If the patient's respiratory drive is still present after intubation, the use of pressure-support ventilation or of synchronized intermittent mandatory ventilation with a low rate is preferable, because this is less likely to induce or worsen any preexisting DH and auto-PEEP.[22]

Clinicians have to be aware of the patient's baseline condition after assuming control of the pulmonary dynamics of patients with COPD. The main hazard is overventilating the patient. There may be an impulse to increase the respiratory rate and tidal volumes in an attempt to "normalize" the blood gas of the patient with COPD. The higher expiratory flows to accomplish this increased minute volume may lead to additional air trapping. This in turn would lead to worsen hypercapnia and respiratory dyssynchrony. The increased intrathoracic pressure would also lead to decreased venous return and right-sided heart failure, exacerbating the situation.

Owing to the patients baseline metabolic compensation, if the $Paco_2$ is normalized to 40 mm Hg, acute alkalemia ensues. This alkalemia is a problem, because it prolongs mechanical ventilation by depressing the respiratory center and increasing respiratory muscle weakness. Continuing mechanical ventilation in this manner for 2 to 3 days

would facilitate renal excretion of bicarbonate, thereby returning the acid–base status of the patient with COPD to normal. Unfortunately, when weaning is attempted, the patient is likely to develop acute respiratory acidosis or respiratory failure. To prevent this cycle, minute ventilation should be titrated to the pH and not to the $Paco_2$.

As we will see in the treatment of ARDS, the choice of low tidal volume ventilation is beneficial in the prevention overventilation. Low tidal volumes limit peak alveolar (plateau) pressure to less than 30 cm H_2O for patients with COPD.[23] With a lower tidal volume, the inspiratory–expiratory ratio is decreased, allowing longer expiration so that the hyperinflated COPD lung can empty. Consequently, this method is unlikely to induce alkalemia, cause or aggravate DH and auto-PEEP, or overdistend the alveolar lung units in the ventilated patient with COPD. Reducing respiratory rate and increasing inspiratory flow also increases expiratory time and facilitates emptying of the lung.

The Use of Positive End-Expiratory Pressure in Patients with Chronic Obstructive Pulmonary Disease

The balance in using PEEP in this patient population that already traps air (and causes intrinsic or auto-PEEP) is by applying to much PEEP and limiting expiratory flow (**Figs. 1** and **2**). To prevent this from occurring, external PEEP should be kept below 75% to 85% of auto-PEEP to avoid any worsening of hyperinflation or circulatory compromise.[16,24] Determination of dynamic pulmonary hyperinflation is, however, not easy to perform in an ICU. It requires insertion of an esophageal balloon and assessment of the abdominal muscles that can be recruited during expiration.[17] It has been shown, however, that changes in inspiratory capacity replicate that of hyperinflation, the greater the inspiratory capacity, the lower the end-expiratory lung volume assuming a constant total lung capacity.[18]

Diagnosis of Auto–positive End-Expiratory Pressure

Quantifying auto-PEEP is not a precise process. Auto-PEEP can vary among individual lung units owing to different degrees of obstruction; auto-PEEP is not uniformly distributed throughout the lung, but varies in direct proportion to the airway resistance present in a particular lung unit. A number of methods can be used to detect auto-PEEP in the mechanically ventilated patient. On some ventilators, a 2-second pause can be invoked after the end of expiration. This technique, however, is valid only if

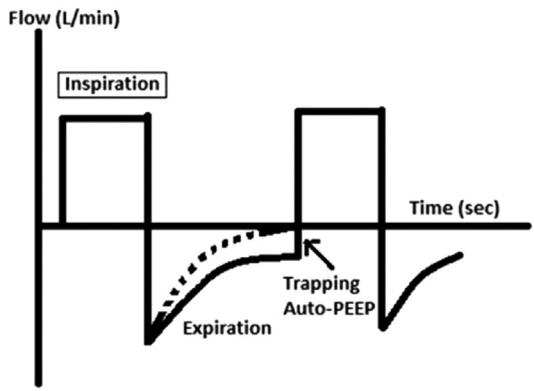

Fig. 1. Generation of auto–positive end-expiratory pressure (PEEP). (*From* Ahmed SM, Athar M. Mechanical ventilation in patients with chronic obstructive pulmonary disease and bronchial asthma. Indian J Anaesth 2015;59(9):589–98; with permission.)

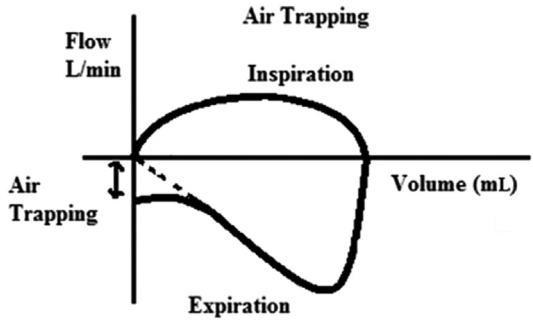

Fig. 2. Air trapping in a flow–volume loop. (*From* Ahmed SM, Athar M. Mechanical ventilation in patients with chronic obstructive pulmonary disease and bronchial asthma. Indian J Anaesth 2015;59(9):589–98; with permission.)

the patient is not breathing spontaneously. The auto-PEEP is then calculated by subtracting the external PEEP from the total PEEP.[19] This method limits the procedure's application to the heavily sedated, paralyzed, or physically exhausted patient with COPD. An esophageal balloon avoids this problem, but may not be readily available in all hospital ICUs. If the patient has a central venous pressure (CVP) line, auto-PEEP effects can be detected owing to the increased WOB reflected by greater changes in pleural pressure (which are transmitted to intrathoracic blood vessels and can be measured via CVP or pulmonary artery catheter). A large decrease in CVP during a spontaneous or assisted breath suggests that a high inspiratory threshold is needed to trigger the ventilator.

Diagnosis of Dynamic Hyperinflation

1. Slow filling of manual ventilator bag
2. Capnography trace not reaching plateau
3. Expiratory flow not reaching zero in flow-time–volume graph
4. Measure the intrinsic PEEP

Auto-PEEP can also be detected on ventilators equipped with graphic waveform monitoring. Although not readily quantifiable, auto-PEEP is easily recognized on the expiratory portion of the flow waveform. If expiratory flow does not return to zero before the next inspiration, auto-PEEP is present. For patients who are making spontaneous efforts to breathe, observing their respiratory efforts and the ventilators response is another useful technique, provided the ventilators sensitivity is set correctly (at -1 cm H_2O or on flow triggering). Because auto-PEEP increases the pressure gradient required to inhale, the patient's effort may not be able to trigger the ventilator; the result is a missed breath or cycle. Clinical signs associated with auto-PEEP (in patients making spontaneous efforts to breathe) include accessory muscle use, retractions, and increased ventilatory drive.

Management of Auto–positive End-Expiratory Pressure

The basic goal in the situation of auto-PEEP is to allowing more time for exhalation. This can be accomplished by reducing the respiratory rate or inspiratory–expiratory ratio (typically to 1:3–1:5) to allow more time for exhalation and reduce breath stacking. However, this pattern can result in low minute ventilation causing hypercapnia, hypoxia, or acidosis. This leads to increased pulmonary vascular resistance and worsened hemodynamic instability. If this is a concern, a higher inspiratory flow rate with

high peak pressures can be used, but this places the patient at increased risk of barotrauma.

Application of Positive End-Expiratory Pressure

The use of external PEEP in ventilated patients with COPD has theoretic benefits by keeping small airways open during late exhalation, so potentially reducing intrinsic PEEP or auto-PEEP. Additionally, it has been seen that if external PEEP is kept below the intrinsic PEEP, no significant increase in alveolar pressure and cardiovascular compromise occurs.[25]

There are only 3 factors that determine auto-PEEP: (1) minute ventilation, (2) inspiratory–expiratory ratio, (3) expiratory time constants. Of the 3 factors, minute ventilation is the most important factor that causes DH. Hence, when ventilating patients with COPD, a smaller tidal volume, slow respiratory rate, and high peak flow should be used with an aim to target normal pH and not $Paco_2$ (permissive hypercapnia).

Strategies to Improve Pulmonary Gas Exchange

The hypoxemia of obstructive air diseases is basically due to 1 of the 3 general causes: shunt, ventilation–perfusion abnormalities, and diffusion defects. In general, individuals with acute exacerbations of COPD have a greater degree of ventilation defect (causing hypercapnia) than chronic patients, who mainly develop perfusion defect (causing hypoxia). Nonetheless, hypoxic vasoconstriction and collateral ventilation in chronic patients decrease the expected ventilation–perfusion abnormalities. Thus, managing the cause is of prime importance in the treatment of hypoxemia of COPD. Moreover, evidence shows beneficial effects of controlled breathing techniques such as active expiration, slow and deep breathing, pursed-lips breathing, relaxation therapy, specific body positions, and inspiratory muscle training.

Strategies to Rest Compromised Respiratory Muscles and Reduce the Work of Breathing

In patients with COPD they live in a state of compromised pulmonary mechanics coupled with a high respiratory drive. This combination leaves them teetering at the edge of their physiologic reserve. Recognition of the factors that contribute to their already increased work of breathing can help the clinician minimize these factors to optimize the patient (**Table 1**). Many of the interventions done to combat COPD have the goal of decreasing respiratory work load, increasing muscular strength and if needed providing mechanical ventilatory support.

Table 1
Factors affecting respiratory work of breathing

Obstructions to Inhalation	Respiratory Muscle Inhibitors	Ventilator Circuit Factors
Resistive load (bronchospasm)	Sedation causing depressed drive	Narrow endotracheal tube
Parenchymal compliance (pulmonary edema, pneumonia, atelectasis)	Muscle weakness (electrolyte abnormalities, chronic atrophy)	External PEEP
Chest wall compliance (obesity, pleural effusion, abdominal distention)		Decreased trigger threshold of the ventilator

Abbreviation: PEEP, positive end-expiratory pressure.

OUTCOMES IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Predicting PPCs remains a challenge for most of the researchers. Although many studies have attempted to predict PPCs, they were not specifically for patients with COPD. Patients with COPD are at an increased risk for PPCs. A recent review estimated the incidence of unadjusted PPCs as 18.2% in patients with COPD undergoing surgery.[5] Increasing severity of COPD confers greater risk, from 10% with mild to moderate disease to 23% in patients with severe disease.[26]

Evidence shows that history and physical examination are poor predictors of airway obstruction and its severity. However, the presence of history of a greater than 55 pack-year smoking, wheezing on auscultation, and patient self-reported wheezing can be considered predictive of airflow obstruction, defined as postbronchodilator forced expiratory volume 1 (FEV_1) or forced vital capacity of less than 0.70.[2] Spirometry is useful to identify airflow obstruction in symptomatic patients, but its usefulness in patients without respiratory symptoms is questionable. Smokers with normal spirometry have only a 4% risk of PPC.[27] Symptomatic patients with an FEV_1 of less than 60% predicted will benefit from inhaled treatments, but evidence does not support treating asymptomatic patients, regardless of the risk factors and airflow obstruction.[2] However, unlike in pulmonary resection, there is no cutoff value of FEV_1 or any other spirometric index to consider these patients unsuitable for surgery.

Arterial blood gas analyses are not indicated unless the patient's history suggests arterial hypoxemia or severe enough COPD that one suspects CO_2 retention. Then, the arterial blood gas should be used in essentially the same manner as one might use preoperative pulmonary function tests, that is, to look for reversible disease or to define the severity of the disease at its baseline. Defining baseline Pa_{O_2} and Pa_{CO_2} is particularly important if one anticipates postoperatively ventilating a patient who has severe COPD.

Heliox

Heliox was introduced in 1934 for the treatment of airway obstruction.[28] Because airway turbulence depends on density, heliox (having a lower density) decreases the airway resistance and, therefore, the WOB, particularly in situations associated with upper airway obstruction. When used as a carrier, heliox has also been found to improve the deposition of aerosolized bronchodilators in the lung.[29] The percentage of oxygen in heliox should be at least 20% to prevent hypoxia, and no more than 40% for heliox to show a clinically significant effect.[29] It has been shown to reduce DH by 15%, which will probably place the respiratory muscles at a better mechanical advantage and decrease the WOB.[30] Indeed, a significant decline in VCO_2 was also noted, supporting a reduced WOB leading to small but significant decrease in the Pa_{CO_2}.[31] However, owing to presence of conflicting literature, heliox therapy, which is costly and cumbersome, is not warranted for stable patients with COPD at rest with moderate to severe disease, but could be effective as an adjuvant therapy to enhance the efficacy of medical treatment. Thus, further research to identify the patients with COPD potentially able to benefit from this type of therapy is required.[31]

Corticosteroids

Short courses of systemic corticosteroids may provide important benefits in patients with exacerbations of COPD a more rapid increase in FEV_1, fewer withdrawals, and a significantly shorter duration of hospital stay.[32] This has to be balanced with the infectious complications and wound healing issues in the postoperative patient.

WEANING IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Like all ventilator patients, an aggressive weaning policy is justified in patients with COPD because prolonged intubation is associated with a variety of poor outcomes. The first step is to address any offending agent that precipitated the COPD exacerbation. Marginal respiratory mechanics and continued presence of auto-PEEP make weaning difficult in patients with COPD. Hence, factors that increase resistance such as size, secretions, kinking of the tube, and the presence of elbow-shaped parts or a heat and moisture exchanger in the circuit have to be optimized to promote early weaning. Weaning can be done with a pressure support mode, along with spontaneous breathing trials. Sequential weaning (early extubation followed by NPPV) is found to be good alternative in patients showing failed spontaneous breathing trials.[33] In contrast, role of tracheostomy is uncertain, but owing to marginal respiratory mechanics, it is also expected to help in weaning.

Summary

Ventilatory support is a lifesaving procedure in acute exacerbations of COPD. The therapeutic goals are to improve gas exchange, rest fatigued respiratory muscles, and relieve respiratory distress. NPPV is regarded as the first line of treatment, whereas invasive ventilation is reserved for life-threatening respiratory failure. However, it can cause a considerable increase in morbidity and mortality if not used properly. Therefore, it is necessary to have a good understanding of pathophysiology, mechanics, and pattern of flow obstruction and DH to provide the most suitable ventilation to these patients. The ventilatory graphics (flow, pressure, and volume) of the most of the modern ventilators becomes a valuable tool in these situations and assist in early diagnosis and management of the patient's condition before it becomes clinically overt.

MANAGEMENT OF ACUTE RESPIRATORY DISTRESS SYNDROME

ARDS is a serious clinical problem with more than 200,000 cases annually[34] that is resistant to treatment once the syndrome is fully clinically established. ARDS has a mortality rate of 30% to 60% with significant costs of care and debilitating lifelong sequelae for survivors.[35] Despite decades of research only one therapeutic modality, low tidal volume ventilation has been demonstrated to modestly improve ARDS-related mortality (9%).[36] People with ARDS are by definition severely hypoxemic, and nearly all require invasive mechanical ventilation. Yet mechanical ventilation itself can further injure damaged lungs (so-called ventilator-induced lung injury); minimizing any additional damage while maintaining adequate gas exchange ("compatible with life") is the central goal of mechanical ventilation in ARDS and acute lung injury, its less severe form.

Benefits of Low Tidal Volume Ventilation in Acute Respiratory Distress Syndrome

Low tidal volume ventilation reduces the damaging, excessive stretch of lung tissue and alveoli (so-called volutrauma), and is the standard of care for people with ARDS requiring mechanical ventilation. The ARDSnet[36] is the largest clinical trial supporting this paradigm. Although it has been noted to have some design flaws (the control arm had a high 12 mL/kg volume given) and ethical concerns (informed consent issues), it has been the foundation that using low tidal volumes improves survival for people with ARDS. Taken together, the trials suggest that a strategy of low tidal volume ventilation (6–8 mL/kg ideal body weight) reduces absolute mortality by about 7% to 9%, as compared with using 12 mL/kg tidal volumes (approximately 42% mortality in control

groups vs approximately 34% in the low tidal volume ventilation groups). This translates to a "number needed to treat" of between 11 and 15 people with ARDS to prevent 1 death by using low tidal volume ventilation.

How to Use Low Tidal Volume Ventilation in Acute Respiratory Distress Syndrome

The protocol from the ARMA trial can serve as a guide to performing low tidal volume ventilation for mechanically ventilated patients with ARDS:

- Start in any ventilator mode with initial tidal volumes of 8 mL/kg predicted body weight in kg, calculated by: [2.3 $\times$ (height in inches - 60) + 45.5 for women or + 50 for men].
- Set the respiratory rate up to 35 breaths/min to deliver the expected minute ventilation requirement (generally, 7–9 L/min).
- Set PEEP to at least 5 cm H_2O, and Fio_2 to maintain an arterial oxygen saturation (SaO_2) of 88% to 95% (Pao_2 55–80 mm Hg). Titrate Fio_2 to less than 70% when feasible.
- Over a period of less than 4 hours, reduce tidal volumes to 7 mL/kg, and then to 6 mL/kg.

Ventilator adjustments are then made with the primary goal of keeping plateau pressure (measured during an inspiratory hold of 0.5 seconds) less than 30 cm H_2O, and preferably as low as possible, while keeping blood gas parameters "compatible with life." High plateau pressures vastly elevate the risk for harmful alveolar distension (ie, ventilator-associated lung injury, volutrauma). If plateau pressures remain elevated after following the this protocol, further strategies should be tried:

- *Further reduce tidal volume*, to as low as 4 mL/kg by 1 mL/kg stepwise increments.
- *Sedate the patient* to minimize ventilator–patient dyssynchrony.
- *Consider other etiologies* for the increased plateau pressure besides the stiff, noncompliant lungs of ARDS.

Permissive Hypercapnia in Acute Respiratory Distress Syndrome

This single-minded focus on reducing plateau pressures derives from the likely survival benefit from low tidal volume ventilation and low plateau pressures observed in clinical trials. Achieving these low plateau pressures usually requires tidal volumes low enough to result in hypoventilation, with resulting increases in Pco_2 and respiratory acidemia that can be severe and, to the treating physician, anxiety provoking. This approach, "permissive hypercapnia," represents a paradigm shift from previous eras, in which achieving normal blood gas values was the main goal of mechanical ventilation. Mechanically ventilated patients with ARDS seem to tolerate very low blood pH and very high Pco_2s without any adverse sequelae:

- Current consensus suggests it is safe to allow pH to fall to at least 7.20.
- The actual Pco_2 is of little importance.
- When the pH falls below 7.20, many physicians choose to administer sodium bicarbonate, Carbicarb, or THAM (tris-hydroxymethyl amino-methane) to maintain blood pH between 7.15 and 7.20.
- However, it is unknown whether such correction of acidemia is helpful, harmful, or neither (good evidence is lacking for any of these hypotheses).

Conditions in which permissive hypercapnia for ARDS could theoretically be harmful include cerebral edema, mass lesions or seizures, active coronary artery disease,

arrhythmias, hypovolemia, gastrointestinal bleeding, and possibly others. These are hypothetical harms based on pathophysiology and not outcomes data, and the harm of ventilator-induced lung injury and the benefits of a protective ventilator strategy in ARDS are real and known. The potential risks of hypercapnia in such patients must be weighed against the risks of ARDS, and therapy individualized.

Limitations in the Use of Plateau Pressure for Acute Respiratory Distress Syndrome

Patients with reduced chest wall compliance—most commonly owing to obesity—may have higher plateau pressures at baseline[37] and during ARDS than nonobese patients. It is possible that, in some obese patients, titrating tidal volumes to plateau pressures less than 30 cm H_2O may be inadequate[38] and result in worsened hypoventilation. There are no recommendations to treat obese patients with acute lung injury or ARDS differently than nonobese patients with regard to mechanical ventilation. Esophageal manometry is considered superior to plateau pressures through its measurement of transpulmonary pressure, considered a more precise measure of potentially injurious pressures in the lung. Because it is invasive and the probes are prone to migration, esophageal manometry is not widely used.

Prone Positioning in Acute Respiratory Distress Syndrome

Prone positioning improves gas exchange and has long been used as an adjunctive or salvage therapy for severe or refractory ARDS. Prone positioning is gaining credibility as a new standard of care for ARDS after a multicenter trial published in 2013, demonstrated a dramatic near 50% relative risk reduction, and a 17% absolute risk reduction for mortality. Patients were kept in prone position for 16 hours a day in that trial conducted at 27 European centers highly experienced with prone positioning for ARDS.[39] The benefits of prone positioning have not yet been replicated in a large US trial, but a metaanalysis of 6 randomized trials[40] also concluded prone positioning saves lives in ARDS when added to a lung-protective ventilatory strategy.

High Versus Low Positive End-Expiratory Pressure in Acute Respiratory Distress Syndrome

A strategy using higher PEEP along with low tidal volume ventilation should be considered for patients receiving mechanical ventilation for ARDS. This suggestion is based on a 2010 metaanalysis of 3 randomized trials (n = 2229)[41] testing higher versus lower PEEP in patients with acute lung injury or ARDS, in which ARDS patients receiving higher PEEP had a strong trend toward improved survival. High versus low PEEP was defined as a rolling definition as the hospital stay went on but a blunt cutoff would be 10 cm H_2O to define the 2 groups.

However, patients with milder acute lung injury (Pao_2/Fio_2 ratio >200) receiving higher PEEP had a strong trend toward harm in that same metaanalysis (27.2% in the higher PEEP group and 19.4% in the lower PEEP group). Higher PEEP can conceivably cause ventilator-induced lung injury by increasing plateau pressures, or cause pneumothorax or decreased cardiac output. The ARDSnet group investigated the adverse effects of high PEEP and did not find a correlation with poor outcomes. These investigator concluded that patients who received low tidal volumes and maintained plateau pressures less than 30 cm H_2O had similar outcomes whether high or low PEEP was used.[42]

Alternative and Rescue Ventilator Modes in Acute Respiratory Distress Syndrome

Some patients with severe ARDS develop severe hypoxemia or hypercarbia with acidemia despite optimal treatment with low tidal volume mechanical ventilation. In these

situations, alternative, salvage or "rescue" ventilator strategies are often used. Their common goal is to maintain high airway pressures to maximize alveolar recruitment and oxygenation, while minimizing alveolar stretch or shear stress. The most commonly used alternative ventilatory strategies are high-frequency oscillatory ventilation (HFOV) or airway pressure release ventilation (APRV or "bilevel").

HFOV is not appropriate as a first-line treatment for ARDS.[43,44] There have been 2 randomized trials on the topic and neither was able to the show an improvement in outcomes. In contrast, the North American study showed 47% in the HFOV group died in-hospital, versus 35% receiving conventional low-tidal volume ventilation (relative risk for death with HFOV of 1.33; 95% CI, 1.09-1.64; $P = .005$). The trial was stopped for harm at this point, far short of its planned 1200 patient enrollment, when statistical analyses showed a near impossibility of equivalence or benefit from HFOV.[43] Both studies showed that HFOV patients required more sedation and more neuromuscular blockade to keep the patient on HFOV.

APRV maintains a sustained airway pressure over a large proportion of the respiratory cycle. Animal and clinical studies have demonstrated that, compared with conventional ventilation, APRV has beneficial effects on lung recruitment, oxygenation, end-organ blood flow, pulmonary vasoconstriction, and sedation requirements.[45,46] APRV has shown promise in both preventing the development on ARDS in animal models.[47] Adequate studies to show a mortality benefit when compared with low tidal volume ventilation have not yet been performed.

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) has also become a more commonly used salvage therapy for ARDS, thanks to improvements in technology making it safer and more feasible to administer. The use of ECMO for the treatment of ARDS was introduced in the early 1970s with the aim of guaranteeing a protective ventilation, as an artificial lung may provide an adequate blood CO_2 removal and oxygenation, allowing to reduce mechanical ventilation. There remains 1 randomized trial (CESAR study) of patients with ARDS. In this study, patients referred to an ECMO center showed a higher 6-month survival rate (63% vs 47%) and no difference in quality of life and spirometric parameters compared with patients treated with conventional mechanical ventilation. There have been no additional studies since then validating ECMO and its use is limited to specialized centers.[48]

Pharmacologic Adjuncts to Ventilator Strategies

Treatment with inhaled nitric oxide as a rescue therapy for ARDS has shown significant improvement in oxygenation for a short period of 48 hours. However, no benefit in terms of survival has been demonstrated.[49] Because the clinical effect of inhaled nitric oxide is counterbalanced by its very high cost, other inhaled pharmacologic alternatives were explored. Specifically, inhaled prostaglandins have been increasingly used. A recently published study that compared inhaled epoprostenol versus inhaled nitric oxide in patients with refractory hypoxemia revealed similar efficacy and safety outcomes.[50] Randomized clinical studies assessing the effectiveness of inhaled prostaglandins in ARDS have rarely been performed. A Cochrane review was able to identify only 1 clinical trial, which included 14 critically ill children with ARDS. The investigators concluded there was no evidence to support or refute the use of inhaled prostoglandins.[51]

Beta-agonist infusions have been tried owing to the idea that they could decrease patients plateau pressures and pulmonary edema. A randomized trial showed they were found to be harmful to ARDS patients, likely owing to the associated

arrhythmias.[52] Similarly, aerosolized beta-agonists have not shown improvements in outcomes.[53]

Chemical paralysis

To augment patient–ventilator synchrony and to reduce the oxygen consumption related to respiratory muscle activity, many clinicians decide to abolish any spontaneous respiratory effort by using neuromuscular blocking agents. An additional effect of neuromuscular blocking agents is the reduction of the negative increase in pleural pressure seen during spontaneous breathing, with the likely consequent reduction of stress and strain applied to the lung. It has been shown how patients with severe ARDS treated with an early, short course of neuromuscular blocking agents presented with lower mortality, reduced duration of mechanical ventilation, and fewer episodes of barotrauma. Patients with ARDS who were started on 48 hours of neuromuscular blockade within the first 48 hours of their symptoms had a significant mortality reduction 1.6% (95% CI, 25.2–38.8) in the cisatracurium group and 40.7% (95% CI, 33.5–48.4)[54]

Systemic corticosteroids

The central role of the inflammatory response in the pathogenesis of ARDS is the rationale behind the idea to use corticosteroids as a therapy in ARDS patient. Based on these concepts, several trials investigated corticosteroids use,[55,56] however, with heterogeneous results. Meduri and colleagues[55] in a study conducted in the early phase of ARDS demonstrated a decrease in ICU mortality rate; however, these findings could not be replicated in other studies.[56,57]

Volume Status

Noncardiogenic pulmonary edema is an important part of the ARDS picture. Intravenous fluid management is brought into question for the ability to worsen or improve the patient's gas exchange. Intravenous fluids are critical to maintain appropriate intravascular volume to assure hemodynamic stability; however, excessive fluid administration can worsen lung edema, further impairing gas exchange. Fluid management practices are quite variable and are often guided by philosophic approaches ranging from the very liberal or "wet" approach (prioritizes maximizing perfusion) to the very conservative or "dry" approach (prioritizes reductions in lung edema). The FACTT trial (Fluids and Catheters Treatment Trial) was performed by the ARDSnet group to try to identify the optimal approach in the ARDS setting. The investigators randomized 1000 patients to wet or dry groups with an additional factor of fluid management being guided by a CVP or a Swan Ganz catheter.[58] The wet group was approximately 1 L positive for the day, which coincided with other ARDSnet trials, suggesting that a liberal fluid strategy was the "normal" approach. The restrictive group was kept fluid neutral using diuretics. There was no difference in mortality among the groups. The 60-day mortality was 25.5% in the conservative group versus 28.4% in the liberal group (P = .3005; 95% CI for the difference, −2.6 to +8.4). The restrictive group had a significant improvement in ventilator parameters such as plateau pressure, and required less PEEP leading to fewer ventilator and ICU days.[59]

PREDICTING SURVIVAL AND OUTCOMES AFTER ACUTE RESPIRATORY DISTRESS SYNDROME

In a 2012 retrospective analysis in *JAMA*[60] including data from more than 4400 patients with ARDS enrolled in randomized trials, only the severity of hypoxemia (low Pao_2/Fio_2 ratio) was predictive of mortality. Commonly used clinical parameters of

severity (static compliance, degree of PEEP, and extent of opacities on chest radiography) were not predictive of outcome. A "high-risk" patient profile with a 52% mortality was identified post hoc, composed of severe ARDS (Pao_2/Fio_2 ratio <100) with either a high corrected expired volume of 13 L/min or greater, or a low static compliance of less than 20 mL/cm H_2O. Reviews of ARDS outcomes[61] suggest that most people who survive ARDS recover pulmonary function, but may remain impaired for months or years in other domains, both physically[35] and psychologically.[62]

SUMMARY

Ventilatory support is a lifesaving procedure in acute exacerbation of COPD and ARDS. The goals of ventilator support between the 2 groups are the same, which is to maintain gas exchange and rest fatigued respiratory muscles. Titration of the ventilator setting may differ among the groups but low tidal volume ventilation has been shown to be beneficial in both groups. The use of adjunct interventions may help to improve patient outcomes in both groups.

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