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REVIEW

The optimum timing to wean invasive ventilation for patients with AECOPD or COPD with pulmonary infection

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Abstract: COPD is characterized by a progressive decline in lung function and mental and physical comorbidities. It is a significant burden worldwide due to its growing prevalence, comorbidities, and mortality. Complication by bronchial-pulmonary infection causes 50%–90% of acute exacerbations of COPD (AECOPD), which may lead to the aggregation of COPD symptoms and the development of acute respiratory failure. Non-invasive or invasive ventilation (IV) is usually implemented to treat acute respiratory failure. However, ventilatory support (mainly IV) should be discarded as soon as possible to prevent the onset of time-dependent complications. To withdraw IV, an optimum timing has to be selected based on weaning assessment and spontaneous breathing trial or replacement of IV by non-IV at pulmonary infection control window. The former method is more suitable for patients with AECOPD without significant bronchial-pulmonary infection while the latter method is more suitable for patients with AECOPD with acute significant bronchial-pulmonary infection.

Keywords: mechanical ventilation, weaning, spontaneous breathing trial, pulmonary control window, chronic obstructive pulmonary disease

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Introduction

COPD is characterized by a progressive decline in lung function and mental and physical comorbidities (eg, depression, dystrophy, and heart failure).[1] An exacerbation of COPD is an acute event caused by several factors. To those patients who need ventilator support because of lung infection, weaning mechanical ventilation may be particularly difficult. The clinician's concern is the optimum timing regarding the condition of the patient to wean mechanical ventilation. Unfortunately, there is no consensus or guideline that can give us a distinct conclusion. The aim of this paper is to summarize the evidence-based optimum timing to wean invasive ventilation (IV) in patients with acute exacerbations of COPD (AECOPD) or COPD with pulmonary infection.

COPD and its AECOPD and lung infection in COPD

COPD is currently a significant burden in the People's Republic of China because of greater risk exposure and uneven medical resource allocation between urban and remote areas. A population-based, cross-sectional survey conducted between 2002 and 2004 suggested a COPD prevalence of 8.2% among Chinese population over 40 years old.[2] Other studies reported varied prevalence ranging from 5% to 13%.[3–6] According to the 2004 Global Burden of Disease study, an annual sum of 3 million people die of COPD worldwide. In the People's Republic of China alone, COPD-related mortality was 27.3 in males and 21.3 in females per 100,000 heads according to a national,

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prospective cohort study conducted between 1990 and 2000. Acute chronic respiratory failure, heart failure, pulmonary infection, pulmonary embolism, cardiac arrhythmia, and lung cancer are the major causes of death in patients with COPD according to a cross-sectional study involving ten European centers.[7]

AECOPD are a common cause of comorbidities and COPD-related mortality.[8–11] They are characterized by an increase in the symptoms of dyspnea, sputum volume, and sputum purulence with or without symptoms of upper respiratory infection.[12] They may also involve worsening of existing symptoms, which require alterations in treatment ranging from antibiotic administration, short courses of oral corticosteroids, and increased bronchodilator usage.[13–14] Reported AECOPD incidence varied between 2.5 and 3 episodes per patient and year.[15] Being its major cause, infection accounted for 50%–70% AECOPD occurrences worldwide and 80%–90% AECOPD occurrences in the People's Republic of China alone.[16,17] Other predisposing factors include environmental pollution, low temperatures, and concomitant heart failure.[18,19] Subsequent onset of acute respiratory failure (ARF) may result if AECOPD are accompanied by bronchial infections, bronchospasm, left ventricular failure, pneumonia, pneumothorax, or thromboembolism. Once ARF occurs, in-patient mortality (4%–30%) substantially rise up to 50% among elderly patients and 11%–26% among intensive care unit (ICU) patients.[10,20–23]

Lung infection other than acute exacerbation is quite common in patients with COPD. The most prevalent form is community-acquired pneumonia. Bronchoscopic studies have shown that at least 50% of patients have bacteria existence in their lower airway during exacerbations of COPD.[1] Viruses are also the common etiology of COPD exacerbation next to bacteria. Many patients with COPD who have comorbidities such as hypertension, diabetes, cardiovascular disease are susceptible to lung infection. As stated earlier, lung infection usually accounts for 50%–70% of AECOPD. Not all lung infections in COPD need intensive care. Only the patients who meet the criteria for hospital admission or ICU admission need to be treated in a timely manner.

Treatment for AECOPD/COPD with lung infection patients

Hospital admission is warranted in an increasing number of patients with AECOPD to prevent ARF onset.[24] An "ABC approach" involving antibiotics, bronchodilators, and corticosteroids is generally extended to maximize lung function and to reverse the predisposing causes of exacerbations.[25] Mechanical ventilation is also suggested in 26%–74% of patients with COPD so that the respiratory muscle load may be alleviated to reduce dyspnea and respiratory rate and improve arterial oxygenation, partial pressure of carbon dioxide in arterial blood ($PaCO_2$), and pH.[26–28] The criteria to start ventilatory support vary but commonly involve the following: 1) moderate to severe dyspnea where accessory muscles are recruited and abdominal breathing prevails; 2) hypercapnic acidosis (pH $<$7.35); 3) tachypnea ($>$25 rpm).[29]

Non-invasive ventilation (NIV) is validated in patients with early AECOPD because their tolerable coughing ability suggests a stronger need for respiratory muscle fatigue relief rather than airway clearance. It is thus initially provided for patients with severe AECOPD with respiratory acidosis to reduce intubation rate, shorten ICU stay, and decrease patient mortality. Nonetheless, IV is indicated if NIV measures fail to improve clinical manifestation and blood gas parameters 1 hour after implementation.[29] Any patient with ineffective airway clearance (eg, post-surgical patients or patients with COPD with hypercapnic ARF and pneumonia) needs IV

Table 1 Indications for non-invasive ventilation (NIV) and invasive ventilation (IV)

NIV indications	IV indications
Clinical manifestations	Cardiac/respiratory arrest
Moderate to severe dyspnea	Non-respiratory organ failure
Respiratory rate over 25 breaths/min	Severe upper gastrointestinal bleeding
Obvious use of accessory muscles	Hemodynamic instability
Paradoxical breathing	Unstable cardiac arrhythmia
Gas-exchange abnormalities	Facial surgery
$PaCO_2$ exceeding 45 mmHg	Facial trauma or deformity
pH below 7.35	Upper airway obstruction
PaO_2/FiO_2 below 250 mmHg	Inability to cooperate
	Airway protection
	Clear of secretions and saliva
	A high risk of aspiration

Abbreviations: FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood.

support to improve sputum discharge and ventilation. Table 1 summarizes the indications for both ventilation types.[30]

In spite of its importance, IV should be discarded whenever appropriate to avoid time-dependent complications associated with intubation, tracheotomy, or ventilation (Table 2).[31–33] To derive optimum advantages from mechanical ventilation, one should identify the optimum timing for withdrawal so that complications may be prevented while respiratory function is restored. NIV has been suggested to serve the purpose because it was identically capable in unloading respiratory muscles.[34] Its application after IV also significantly reduced weaning time, alleviated ventilator-associated complications, and improved survival.[35–37] However, no consensus has yet been reached regarding the optimal time when NIV should replace IV. According to the Chinese *Guideline for Mechanical Ventilation in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease 2007*, weaning with T-tube is advised in COPD patients without obvious bronchial-pulmonary infection while replacement by NIV at pulmonary infection control (PIC) window is advised in COPD patients with obvious bronchial-pulmonary infection.

Table 2 Complications associated with intubation, tracheotomy, or ventilation

Common complications of intubation and tracheotomy
Airway complications
Laryngeal edema
Tracheal mucosal trauma
Contamination of the lower respiratory tract
Loss of humidifying function of the upper airway
Common complications of mechanical ventilation
Mechanical complications
Accidental disconnection
Leaks in the ventilator circuit
Loss of electrical power
Loss of gas pressure
Pulmonary complications
Ventilator-induced lung injury
Barotrauma
Oxygen toxicity
Atelectasis
Nosocomial pneumonia
Inflammation
Auto-PEEP
Asynchrony
Acid–base complications
Respiratory acidosis
Respiratory alkalosis
Cardiovascular complications
Reduced venous return
Reduced cardiac output
Hypotension
Gastrointestinal and nutritional complications
Gastrointestinal bleeding
Malnutrition
Renal complications
Reduced urine output
Increase in antidiuretic hormone (ADH) and decrease in atrial natriuretic peptide (ANP)
Neuromuscular complications
Sleep deprivation
Increased intracranial pressure
Critical illness weakness

Abbreviation: PEEP, positive end-expiratory pressure.

Weaning in COPD patients without obvious bronchial-pulmonary infection

Tobin summarized six stages in mechanical ventilatory support: 1) treatment of ARF; 2) suspicion that weaning may be possible; 3) assessment of readiness to wean; 4) spontaneous breathing trial (SBT); 5) extubation; and 6) reintubation when required. One is only liberated from IV when he successfully passes the first five steps and avoids the last.

Weaning accounts for almost half of the time in mechanical ventilation and allows resumption of spontaneous breathing after gradual reduction of mechanical support.[38–42] Randomized and non-randomized historical cohort studies verified a more significant reduction in the duration of mechanical ventilation when a weaning protocol, involving weaning parameter evaluation and subsequent breathing trials, was used instead of mere clinical judgment.[43–46] In view of general delays in weaning and the associated increase in mortality,[41,47,48] assessment should be performed every day to allow prompt initiation of weaning.

Variations exist between protocols but weaning parameters essentially stem from observations in respiratory mechanics, gas exchange, and breathing patterns. Table 3 is a list of parameters to be considered before weaning.[47] Daily screen of weaning parameters was found to have predicted a successful extubation with 82% accuracy, nearly 90% sensitivity and positive predictive values. Significance of passing the screen could also be extended to hospital survival prediction during the 1st week and a half of mechanical ventilation. Its prognostic significance seemed to be limited though, since up to 29% of the patients failed the screen but withstood extubation.[49] Thus, a successful weaning attempt does not necessarily require fulfillment of all the mentioned criteria.

SBT is usually granted to a patient who has passed the weaning assessment. SBT failure is defined by 1) objective indices such as tachypnea, tachycardia, hypertension, hypotension, hypoxemia or acidosis, and arrhythmia; 2) subjective indices such as agitation or distress, depressed mental status, diaphoresis, and evidence of increasing effort.[47] Subsequently, weaning failure refers to SBT failure or the need for

Table 3 Assessment of weaning parameters

Clinical assessment	1. Adequate cough
	2. Absence of excessive tracheobronchial secretion
	3. Resolution of disease acute phase for which the patient was intubated
Objective measurement	4. Clinical stability
	Stable cardiovascular status (ie, fc ≤140 beats/min), systolic BP 90–160 mmHg, no or minimal vasopressors
	Stable metabolic status
	5. Adequate oxygenation
	SaO_2 >90% on FiO_2 0.4 (or PaO_2/FiO_2 ≥150 mmHg)
	PEEP ≤8 cm H_2O
	6. Adequate pulmonary function
	f_R ≤35 breaths/min
	MIP ≤–20 to –25 cm H_2O
	V_T >5 mL/kg
	f_R/V_T <105 breaths/min/L
	No significant respiratory acidosis
	7. Adequate mentation
	8. No sedation or adequate mentation on sedation (or stable neurologic patient)

Abbreviations: BP, blood pressure; fc, frequency of cardiotach; FiO_2, fraction of inspired oxygen; f_R, frequency of respiration; MIP, maximal inspiratory pressure; PaO_2, partial pressure of oxygen in arterial blood; PEEP, positive end-expiratory pressure; SaO_2, arterial oxygen saturation; V_T, tidal volume.

reintubation within 48 hours of extubation.[50,51] According to the number of attempts or days prior to successful weaning, patients may be classified into three groups:[47] 1) simple weaning (patients who proceeded from initiation of weaning to extubation on the first attempt without difficulty); 2) difficult weaning (patients failing the first attempt who took up to three attempts or as long as 7 days from the first SBT to achieve successful weaning); and 3) prolonged weaning (patients who failed at least three weaning attempts or required >7 days of weaning after the first SBT). Independent factors suggestive of prolonged weaning include COPD occurrence,[47] higher $PaCO_2$ and heart rate during the first SBT.[52] Sellares et al also found a higher $PaCO_2$ and heart rate among prolonged weaning patients before their first SBT, implying their worse condition when subjected to the initial trial.[52]

SBT is commonly delivered via pressure support ventilation (PSV) at 7 cm H_2O, continuous positive airway pressure, or T-piece. A conventional protocol-directed SBT takes 120 minutes but a 30 minutes trial performed via either T-tubes or PSV was found to be equally effective in identifying successful extubations.[44,53] Comparing the delivery frequency, once-daily and multiple-daily T-piece trials were found to be equally effective.[50] Consensus has also been established over the identical validity of pressure support and T-tube in SBT.[54] A similar conclusion was valid among infants and children when pressure support was 10 cm H_2O.[55] Further to these findings, pressure support was found to overrun T-tube in difficult-to-wean patients since success of the former and failure of the latter regardlessly indicated successful extubation with unchanged reintubation rate.[56] Indeed, pressure support might have surpassed T-tube because it compensated for the extra breathing workload caused by an endotracheal tube.[57–61] In addition, Cabello et al observed more successful pressure support trials in difficult-to-wean patients when positive end-expiratory pressure (PEEP; 5 cm H_2O) was incorporated to PSV.[62] This could be explained by the abilities of PEEP to 1) reduce respiratory muscle energy expenditure;[63] 2) attenuate intrinsic PEEP so that the work of breathing required to trigger the ventilator reduces;[64,65] and 3) decrease pulmonary artery occlusion pressure.[62] For the past few years, computer-driven automated weaning was introduced to perform SBT automatically in intubated patients but its value remained questionable from results of different studies.[66] Generally, the technology failed to facilitate weaning in surgical patients but prevailed in difficult-to-wean patients,[67] such as those with COPD, ischemic heart disease, and immunosuppresion.[68,69]

NIV has been proposed as an alternative weaning tool in COPD patients who failed SBT. According to a number of randomized controlled studies and meta-analysis, such application was associated with reduced mechanical ventilation, shortened ICU and hospital stay, decreased incidence of septic shock, and pneumonia and improved survival.[35,37,70] Theoretically speaking, extubated patients administered with NIV should not be declared as weaning success unless they ultimately get rid of the ventilatory support. Increased use of NIV as a weaning tool thus leads to a new weaning category called "weaning in progress" wherein extubated patients continue to be supported by NIV. In spite of its benefits among COPD patients, NIV should not be indicated in all patients

Table 4 Standard of the PIC window

Indexes	Evaluation
Imaging change	Significantly decreased radiographic infiltrations
Ventilator settings	10–12 beats/min for SIMV 10–12 cm H_2O for PSV
Body temperature	≤38°C
Leukocyte count	<10,000/mm^3 or 2,000/mm^3 less than before
Sputum quantity	Significantly reduced
Lightening of sputum color	Changed to white
Decreased density of sputum	<II (second level)

Abbreviations: PIC, pulmonary infection control; PSV, pressure support ventilation; SIMV, synchronized intermittent mandatory ventilation.

failing SBT because they may be exposed to extubation failure due to substantial comorbidities.[47]

To summarize, the amount of time needed for IV liberation depends on a sequence of events including suspicion for weaning possibility, performance of weaning assessment, and weaning itself. In order to promptly discard ventilatory support, weaning assessment is daily performed in ventilated patients. When SBT fails in selected COPD patients, NIV may be recruited to shorten the duration of IV.

Replacement of invasive ventilation by non-invasive ventilation at PIC window

In the People's Republic of China, 80%–90% AECOPD cases occur as a result of bronchial-pulmonary infection. A significant proportion of them further develop into hypercapnic respiratory failure which requires invasive ventilatory support. In order to restore respiratory function and avoid time-dependent complications, studies are being conducted to search for an optimum timing to discard IV.

PIC window has been defined as a prompt stage of controlled pulmonary infection following artificial airway establishment, sputum drainage, and antibiotic administration. It was marked by thinning and decrease of sputum; clearing of sputum cloudiness; decreases in body temperature, radiographic infiltrations, and leukocytes (Table 4).[17] At this stage, COPD patients with severe hypercapnic respiratory failure tend to be more stable and respiratory muscle fatigue becomes relatively more significant in the development of respiratory failure.[17] Wang et al[17] proposed this stage as an optimum timing to replace IV with NIV so that ventilatory insufficiency and respiratory muscle fatigue may be resolved while lower airway infection and ventilator-associated pneumonia can be avoided. Such a hypothesis was verified through a prospective cohort study and a prospective, multi-centered, randomized controlled trial among COPD patients with severe hypercapnic respiratory failure.[71–73] In both research plans, the study groups were liberated from IV in exchange for NIV at PIC window while the control groups proceeded with IV throughout. By the end of the trials, the study groups were found to possess lower ventilator-associated pneumonia risks and mortality rate while requiring shorter durations of IV, ventilatory support, and ICU stay.[17,74] Another study with nine patients yielded similar results except in two patients who presented with unstable hemodynamic condition and consciousness disturbance correspondingly.[75]

While the significance of PIC window has been verified, one should be reminded of how proper training, skills, and observation ascertain the identification of such a stage. Zhang failed to recognize PIC window in several clinical cases thus led to delay in response and subsequently compromised prognosis and increased medical costs.[75] An increased intubation rate has also been associated previously with inexperienced labor among hypercapnic ARF patients.[76,77] Such results suggested how proper caring and observation hold the key to the betterment of all ventilated patients above other clinical advancements.

Conclusion

Ventilatory support is essential among AECOPD patients to prevent and treat ARF. While NIV is increasingly suggested as a primary option, IV may not be avoided under certain conditions. In such cases, strategies should be implemented to discard IV as soon as possible so that time-dependent complications may not arise as a result of prolonged IV. In AECOPD patients, weaning by SBT (assisted with NIV) is suggested under insignificant bronchial-pulmonary infection while replacement by NIV at PIC window is encouraged under significant bronchial-pulmonary infection.

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Disclosure

The authors report no conflicts of interest in this work.

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