Symposium 3: Asthma and allergy: From bench to bedside

Mechanical ventilation in asthma

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When the severity of asthma attack in a patient is very severe to need mechanical ventilation, a special technic - so-called 'controlled hypoventilation' - should be applied to avoid barotrauma. In such a patient, if you apply the conventional ventilation technic that is for patients without obstructive airway diseases, the mortality associated with mechanical ventilation would be reached to maximum 38%.[1] In addition, the necessity of mechanical ventilation in asthma patients is not limited to those without self respiration. We must understand the reason why they need the ventilatory support, but many Korean doctors still seem to lack such a concept and their treatment results are not very good.

Respirarion is a process of gas exchange beween O_2 and CO_2, and so there are two types of respiratory failure, i.e., oxygenation failure (type I) and hypercapnic respiratory (or ventilatory) failure (type II). Generally, the main mechanism of hypoxemia during asthma attack is V/Q imbalance which is readily correctable with O_2 therapy, and so this lecture would be concentrated to the ventilatory failure. In addition, some authors recommend a trial of NIV, especially in patients with respiratory muscle fatigue; however, invasive mechanical ventilation only would be discussed at this time.

Why severe asthma patients often require ventilatory support?

The international guidelines[2-4] express the utmost severe asthma exacerbation often requiring mechanical ventilation as respiratory arrest imminent, life-threatening, or near-fatal (Table 1). Generally, the spirometric values in the worst severity of the most guidelines are less than 25% of predicted ones. Of course, the % predicted values would be much higher in patients whose baseline values are low, such as women, children, and elderly, because their actual FEV_1 values at the time of exacerbation are very low.

Anyway, we consider for them to apply mechanical ventilation before,[5] not after, respiratory arrest develops. Therefore, the purpose of the mechanical ventilatory support in such patients is not to support the

Table 1. Asthma exacerbation (flare-up) severity

EPR3, 2007[2]	GINA 2017[3]	BTS 2016[4]
≥70% Mild	Mild	>75% Mild
69-40% Moderate	>50% Moderate	75-50% Moderate
<40% Severe	≤50% Severe	50-33% Severe
<25% Respiratory arrest imminent	Life-threatening	<33% Life-threatening CO^2 ↑ Near-fatal

LT: CO_2→ NF: <25%

patients without self respiration until their self respirations are restored. The self respiration occurs by the work of respiratory muscles and the most important respiratory muscle is diaphragm. Because the work of breathing is very high in patients with very high Raw, the diaphragm cannot work anymore at last due to muscle fatigability (ventilatory pump failure). In addition, hyperinflation causes the diaphragm to be foreshortened prior to contraction resulting in reduced contractility.[6] The typical clinical manifestation of diaphragmatic fatigability is the paradoxical thoracoabdominal movement. In this situation, they need to receive ventilatory support and we call such a treatment as 'respiratory muscle rest therapy'.[7] During the respiratory muscles rest to recover from fatigue for 1-2 days (a minimum of 12 hours)6, the asthmatic airflow limitation is resolved by anti-asthma medications and then patients can wean the ventilatory support successfully.[8] Mechanical ventilation is a treatment method to help patients temporarily as like medications.

Intubation and airway management

Endotracheal intubation is performed only in the patients with acute asthma who need a mechanical ventilatory support. Intubation without ventilatory support must aggravate diaphragmatic fatigability due to increased airway resistance and elimination of airway stenting effect of pursed-lip breathing.[9] In the same context, the tube should be removed at the same time with the ventilator weaning.

The majority of hypercapnic patients are improved with aggressive asthma medications, and so very small numbers of patients, such as those with progressive hypercapnia with acidemia, are required the intubation and mechanical ventilation.[1] The other indications for ventilator support include altered consciousness, exhaustion, respiratory arrest and hemodynamic instability. Refractory hypoxemia does not usually occur because the main mechanism of hypoxemia in asthma is V/Q mismatching.[8]

Orotracheal intubation is preferred to allow the use of a larger tube (diameter ≥8.0 mm) facilitating secretion removal.[10,11] Airway cuff pressure should be monitored to keep it lower than 20 cmH_2O to avoid tracheal dilatation and eventual tracheal rupture to innominate artery. If there is an evidence of tracheal dilatation, the position of cuff in the trachea should be changed. Even though the cuff inflation, aspiration may occur. It is necessary to check chest X-ray every day to confirm that the tube tip is located at least 2

cm above the carina. Occasionally, the tip is slipped into the right main bronchus because it is less angulated even though the tube is fixed around mouth, resulting serious complications such as barotrauma of right lung and atelectasis of left lung. When the ventilator weaning is unlikely to be done within one month, tracheostomy should be performed early to avoid tracheal stenosis.

Sedatives and paralyzing agents

For intubation and to prevent patient-ventilator dyssynchrony, sedatives are useful. Midazolam, ketamine, or propofol is recommended.[10,11] Morphin has a potential of histamine release from mast cells in asthmatics. Sedation should be often deep to the level that patients respond only with eyes opening to call, but after 1-2 days residual sedation may delay ventilator weaning. Paralytic (neuromuscular blocking) agents should not be given as possible because myopathy may occur and the ventilator weaning become difficult, particularly when used concomitantly with corticosteroids (postparalytic syndrome).

Initial ventilator settings

The main concept of the 'controlled hypoventilation' to avoid barotrauma is that increased expiratory time (T_E) allows a reduction in air-trapping (dynamic hyperinflation)(Table 2).[1] For example, V_T = 1,000 mL, RR = 15, and inspiratory flow rate = 60 L/min result in an one respiratory cycle of 4 seconds, an inspiratory time (T_I) of 1 second and a T_E of 3 seconds. If we decrease V_T to the half (500 mL), T_E is increased 0.5 second. However, decreasing RR to 12 prolongs T_E one second because the one respiratory cycle become 5 seconds. Increased inspiratory flow rate also decreases the T_I, and so a relatively higher inspiratory flow rate (70-100 L/min) is recommended in patients with obstructive lung diseases1 than the usual 40-60 L/min in the others[6].

For the respiratory muscle rest therapy, the standard mode of ventilation is A/C mode. Although the ideal mode for the controlled hypoventilation is CMV, it is not recommended due to the necessity of a paralytic agent use resulting myopathy and weaning difficulty. The actual RR is controlled by patients under the A/C mode, and so you should carefully observe the actual RR, not the back-up RR. The actual RR must be

Table 2. Initial ventilator settings for asthmatic patients

Mode	A/C
Tidal volume	6-8 mL/kg
Respiratory rate	10 breaths/min
Inspiratory flow rate	70-100 L/min
PEEP	$\leq$5 cmH_2O
FiO2	Sufficient to maintain SaO_2 >90%

close to the back-up RR. If the RR is rapid, a sedative is given as needed, and if you fail to control it, increase the V_T because the efficacy of V_T to increase V_E is much lower than that of RR. Too low V_T often stimulates the stretch receptor of the lung resulting in tachypnea. However, too long T_E is unnecessary because the expiratory flow rate and the beneficial effect on reducing dynamic hyperinflation progressively decrease throughout expiration.[12]

The application of external PEEP is not recommended in asthma except so-called 'physiologic PEEP (5 cmH_2O)'. Negative intrathoracic pressure during inspiration dilates intrathoracic airways and so air could be inspired, but increased pressure during expiration narrows airways and so air-trapping (dynamic hyperinflation, auto/intrinsic PEEP) and eventual barotrauma can occur in patients with acute severe asthma even during spontaneous breathing. Although it is well known that an external PEEP of <80% auto-PEEP could reduce the auto-PEEP due to its airway stenting effect in COPD, the mechanism of airflow limitation is quite different between asthma and COPD. The main cause of airflow limitation in patients with emphysema is a decrease in elastic recoil pressure due to alveolar wall destruction, and in turn, their increase in Raw in the collapsible airways is by the decrease in intraluminal pressure and the loss of the tethering effect of alveoli to bronchial wall associated with the decreased elastic recoil pressure.[13,14] Therefore, as the pursed-lip breathing minimizes the collapse of intrapulmonary airways during expiration,[9] the application of back-up pressure by external PEEP can prevent easily the collapse of airways[15] caused by the decreased tethering attachments (interdependence between airway wall and lung parenchyma). However, the airflow limitation in asthma is caused by increase in Raw[13] due to smooth muscle contraction, airway wall thickening and secretion, and these components are not very well reversed by external PEEP. In addition, the uneven distribution of tenacious airway secretion results in hyperinflation and barotrauma in the opened alveoli.[5] Applied PEEP helps to improve the trigger sensitivity of ventilator and attenuates the breathing workload.[8]

Because respiratory infections involving lungs frequently aggravate asthma, oxygenation failure due to shunt should be considered. To find the causative mechanism of hypoxemia in patients, arterial blood gas analyses are performed before and 15 minutes after O_2 therapy. The degree of increase in PaO_2 level per 1% increase in FiO_2 is generally $\geq$5 mmHg in patients with a predominant V/Q imbalance while <2 mmHg in those with a predominant shunt. Airway diseases have V/Q imbalance usually while lung parenchymal diseases (pneumonia or thromboembolism) have shunt. In addition, the hypoxemia score (PaO_2/FiO_2 ratio) indicating the degree of acute lung injury should be measured and monitored.

Monitoring and adjusting

All patients in ICU should be check in the order, i.e., A (airway), B (breathing: oxygenation & ventilation), C (circulation), and D (definitive disease). PaO_2 level should be maintained >60 mmHg.

Table 3. Monitoring for asthmatic patients

Plateau pressure	<30 cmH_2O
Auto-PEEP	<15 cmH_2O
End-inspiratory volume (VEI)	<1.4 L (20 mL/kg)
PaO_2	>60 mmHg
$PaCO_2$	<150 mmHg

Practically, the target of PaO_2 is 80 mmHg because airway secretion often interferes oxygenation. However, too much high FiO_2 is not desirable for the target due to oxygen toxicity. If the target is not achievable with $\leq$0.4 of FiO_2 or if CO_2 narcosis is suspected with FiO_2 increase in COPD patients, it is abandoned and blood transfusion is another method for acceptable O_2 transport to vital organs.

Because barotrauma is the main problem, the markers of air-trapping should be monitored carefully. Plateau pressure (P_{plat}) should be checked intermittently and kept <30 cmH_2O. Auto-PEEP can be measured directly by an end-expiratory occlusion (hold) maneuver and it should be kept <15 cmH_2O, although it may underestimate the severity due to the entirely obstructed airways. The end-inspiratory volume above FRC (V_{EI}) is also recommended as a marker of lung hyperinflation, but its clinical application is impractical because the patients should be paralyzed to collect exhaled volume during 20-60 seconds of apnea.[11]

As previously mentioned, the actual RR must be close to the back-up RR. When the hyperinflation marker levels are too high, disconnect the ventilator tubes from the endotracheal tube briefly or reduce RR to <2-3 supplying with 100% O_2. The increase in intrathoracic pressure by auto-PEEP leads to interfere venous return resulting in hypotension. A negative fluid balance by decreased oral intake and faster respiratory rate, and an adverse effect of medications also can cause hypotension. Therefore, a fluid bolus and a trial of hypopnea or apnea for 30-60 seconds may correct the hypotension.

For checking circulation status in addition to blood pressure, consciousness and hourly urine output ($\geq$ 50 cc) should be checked for adequate perfusion of brain and kidney. Peak pressure - P_{plat} (peak to pause pressure gradient) divided by airflow rate is the marker of airway resistance and should be monitored to evaluate the response to asthma treatment. Higher than 20 cmH_2O of the pressure gradient generally means an increased airflow limitation (bronchospasm), and $\geq$15% fall in the gradient is a significant improvement.

Other supportive measures

Hypoventilation is the almost same meaning with hypercapnia and the controlled hypoventilation is the same with 'permissive hypercapnia'. Generally, $PaCO_2$ of 60-70 mmHg is acceptable, but an increase in $PaCO_2$ is too rapid or to >90 mmHg may decrease pH. Patients with pH <7.20 may be treated with sodium bicarbonate (buffer therapy), but bicarbonate may increase CO_2 production. Although tromethamine does not generate CO_2, many patients show improvement in hypercapnia during the first 12 hours of

ventilation.[12] Hypercapnia may cause cerebral vasodilation, cerebral edema, increased ICP, and subarachnoid hemorrhage. In addition, a fall in intracellular pH reduces myocardial contractility,[12] and vasodilation with a hyperdynamic circulation and pulmonary vasoconstriction have been reported.[11] Therefore, controlled hypoventilation is avoided in such patients, especially in patients with increased ICP due to anoxic brain damage after CPR.

β-agonists and anticholinergics can be inhaled through the nebulizer attached to the ventilator or through a spacer connected to the inspiratory tube by MDI. Because the increased dead space by tubes, 2-4 times higher doses of bronchodilators are required. ICS also can be inhaled through the apparatus.

Bronchial hygiene using bronchodilator and chest physiotherapy, and controlling respiratory infections is very important. During awakening, patients should sit with stooping posture. Aminophylline is the drug that increases the contractile force of diaphragm, and so the serum theophylline level should be increased as possible. Low serum potassium level is not allowed and aminoglycosides should be withdrawn. Most importantly, hemoglobin level must be normal in patients with respiratory failure, and a supranormal level may facilitate ventilator weaning in difficult patients. Even though the PaO_2 level is acceptable (>60 mmHg), the oxygen transport index ($TO_2 = CaO_2 \times CO$) would be very low. The arterial oxygen content (CaO_2) is calculated as follows:

$$CaO_2 = 1.34\ mL \times \text{hemoglobin gram/dL} \times SaO_2 + 0.0031 \times PaO_2$$

If transfusion is required in the patients with chronic respiratory failure, packed RBC should be administered very slowly and diuretics are given to avoid volume overload.

In order to reduce CO_2 production - in other words, to decrease the respiratory exchange ratio (R) - the nutritional support using carbohydrate (R = 1.0) should be restricted, and that using lipid (R = 0.7) encouraged. To prevent pulmonary thromboembolism, stress ulcer, and decubitus ulcer, low-dose heparin, sucralfate, and frequent position change are necessary. Palpation for detecting subcutaneous emphysema may be helpful.

Ventilator weaning

After the 'respiratory muscle rest therapy' for at least 12 hours, and after the underlying disease is controled, the Raw decreased, and the $PaCO_2$ normalized, a weaning trial begins in the morning. The conventional weaning criteria are not met well to asthmatics. However, f/V_T <100 has been suggested to be predictive for successful weaning.[1]

There must be absent the remnant effects of sedatives, and patients should be kept stooping posture. At one hour interval, the time of placing to T-piece increases or the rate of SIMV decreases progressively. Five to 10 cmH_2O pressure support (CPAP) would be helpful to overcome endotracheal tube resistance. It is not desirable to discontinue pressure support completely before extubation.[15] If the patients are intolerable

to the very low partial supports, they put in the A/C mode again overnight for 'respiratory muscle rest therapy', and another weaning trial is performed next morning. After the successful ventilator weaning, extubation should be performed as soon as possible. The necessity of reintubation and ventilatory support should be observed. In patients with tracheostomy, when the tracheal foramen of tracheostomy was matured, the reinsertion of the tube would be easy. Laryngeal edema and bronchospasm should be observed for 24-48 hours.

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