The Intensive Connection

Mechanical Ventilation

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Mechanical ventilation

Current Status 2020

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Latest Update

Second Edition

Acute Respiratory Failure

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Update Info

Intended Learning Outcomes

Mechanical ventilation Part I: Delivery of mechanical ventilation

1. List the indications of mechanical ventilation
2. Understand the aims of mechanical ventilation
3. Describe the means to delivery mechanical ventilation

Mechanical ventilation Part II: Basic Principles of Mechanical Ventilation

1. Describe the physiological basis of mechanical ventilation
2. Describe the basic functions of positive pressure ventilators
3. Describe how to apply this knowledge in clinical practice.

Mechanical ventilation Part III: Modes of mechanical ventilation: controlled modes

1. Describe the most commonly used modes of controlled mechanical ventilation
2. Discuss ventilator settings in different modes and basic waveform interpretation
3. Describe how to apply this knowledge in clinical practice.

Mechanical ventilation Part IV: Modes of mechanical ventilation: Assisted modes

1. Describe the most commonly used modes of assisted mechanical ventilation
2. Describe the proportional modes of assisted mechanical ventilation
3. Discuss ventilator settings in different assisted modes and basic waveform interpretation
4. Describe, recognize and manage patient ventilation dyssynchrony
5. Describe how to apply this knowledge in clinical practice.

Mechanical ventilation Part V: Weaning

1. To outline the different stages of the weaning process
2. To describe the pathophysiology of weaning failure
3. To be discuss the diagnostic workup and management of weaning failure

Mechanical ventilation Part VI: Complications of mechanical ventilation

1. Describe the pathophysiology and the main determinants of ventilator-Induced Lung Injury and ventilator-induced diaphragmatic dysfunction
2. Describe the strategies to prevent Ventilator-Induced Lung Injury
3. Outline the diagnostic approach, prevention, and management of Ventilator-induced diaphragmatic dysfunction
4. Discuss the clinical impact and prevention of Ventilator-Associated Pneumonia (VAP)

Relevant Competencies from CoBaTrICE

Mechanical ventilation Part I: Delivery of mechanical ventilation

- **2.9** Monitors and responds to trends in physiological variables
- **3.1** Manages the care of the critically ill patient with specific acute medical conditions

Mechanical ventilation Part II: Basic Principles of Mechanical Ventilation

- **2.9** Monitors and responds to trends in physiological variables
- **4.5** Describes the use of devices for circulatory or respiratory assist

Mechanical ventilation Part III: Modes of mechanical ventilation: controlled modes

- **3.1** Manages the care of the critically ill patient with specific acute medical conditions
- **3.8** Recognises and manages the patient with acute lung injury syndromes (ALI / ARDS)
- **2.9** Monitors and responds to trends in physiological variables
- **4.5** Describes the use of devices for circulatory or respiratory assist

Mechanical ventilation Part IV: Modes of mechanical ventilation: Assisted modes

- **3.1** Manages the care of the critically ill patient with specific acute medical conditions
- **3.8** Recognises and manages the patient with acute lung injury syndromes (ALI / ARDS)
- **2.9** Monitors and response to trends in physiological variables
- **4.5** Describes the use of devices for circulatory or respiratory assist

Mechanical ventilation Part V: Weaning

- **4.6** Initiates, manages, and weans patients from invasive and non-invasive ventilatory support.

Mechanical ventilation Part VI: Complications of mechanical ventilation

- **3.1** Manages the care of the critically ill patient with specific acute medical conditions
- **3.8** Recognises and manages the patient with acute lung injury syndromes (ALI / ARDS)
- **2.9** Monitors and responds to trends in physiological variables
- **4.5** Describes the use of devices for circulatory or respiratory assist

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1. Introduction

The mechanical ventilator is an essential part of life support in the intensive care unit (ICU). It was the need to use mechanical ventilators outside the operating theatre during the poliomyelitis epidemic in the 1950s that gave birth to the ICUs of today.
Clinicians working in ICU have to become familiar quickly, with how to handle/ use a ventilator, and fulfill the tasks of initiating, maintaining, and weaning patients from mechanical ventilation. This eCourse deals with the physiology underlying ventilatory support, and the basic principles of applying mechanical ventilation in clinical practice.

Although a mechanical ventilator is an essential, life-saving device, its use is not free of harm. Solid knowledge of the principles of mechanical ventilation and the potential harms associated with its use is of paramount importance for the successful and safe use of ventilators in the ICU.

2. Delivery of mechanical ventilation

2. 1. Indications for mechanical ventilation

Mechanical ventilation is indicated to manage the respiratory failure of any cause and to permit the pharmaceutic depression of the respiratory centre during anesthesia. As shown in Figure 1, the causes of respiratory failure can be classified into:

- Failure to maintain a patent airway
- Failure to maintain adequate ventilation
- Failure to maintain adequate oxygenation

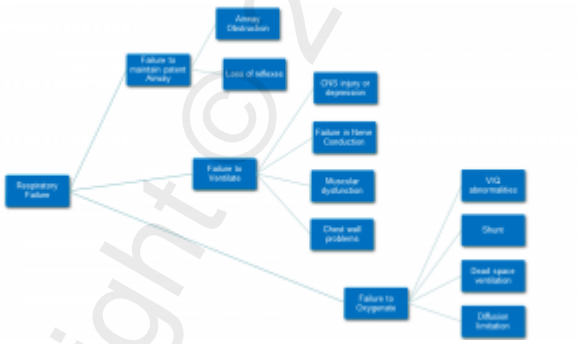

Figure 1: Causes of respiratory failure. Mechanical Ventilation module, ESICM Academy, 2018

Figure 1: The causes of respiratory failure can be classified as: failure to maintain a patent airway, due to obstruction, as in case of facial trauma or laryngeal edema, or due to loss of reflexes, as in coma or deep sedation; failure to ventilate, due to central nervous system (CNS) problems affecting the respiratory centre, such as CNS trauma or pharmaceutical depression, due to failure in nerve conduction, such as in cervical spine injury and neuromuscular blockade, due to respiratory muscle failure, such as myopathies, or due to problems of the chest wall, such as flail chest or pneumothorax; failure to oxygenate, due to V/Q mismatch, as in ARDS, due to shunt, as in congenital heart disease, due to dead space ventilation, as in exacerbation of obstructive lung diseases, or due to diffusion abnormalities, as in fibrotic lung diseases.

The choice of timing and interface to deliver mechanical ventilation depends on the underlying cause of respiratory failure.
The failure to maintain a patent airway is a common and relatively straight-forward indication for endotracheal intubation and mechanical ventilation. Common causes include:

- Decreased level of consciousness (a GCS<9 is used for trauma patients)
- Need for deep sedation
- Upper airway obstruction (trauma, hematoma, oedema)
- Inability to manage secretions

In patients with hypercapnic (failure to maintain adequate ventilation) or hypoxemic (failure to maintain adequate oxygenation) respiratory failure, the choice of timing and patient-ventilator interface to deliver mechanical ventilation is more complicated and depends on the underlying cause of respiratory failure (see ACE on COPD and Asthma).

In those patients, the main indications for mechanical ventilation are the presence of hypercapnic acidosis, hypoxemia despite administration of oxygen (PO_2< 60mmHg, with FiO_2= 50%), or dyspnea with increased work of breathing. Increased work of breathing, a common feature of acute exacerbation of obstructive lung disease, pneumonia, or ARDS, may induce muscle fatigue and is associated with a high energy expenditure of the respiratory muscles and a significant increase in regional blood flow.

Clinical signs of increased work of breathing and respiratory distress include:

- Nasal flaring
- Mouth breathing
- Recruitment of accessory and expiratory muscles
- Tracheal tug
- Intercostal recession
- Paradoxical abdominal movement
- Tachypnea
- Tachycardia
- Hypertension or hypotension
- Diaphoresis

Note

Initiating mechanical ventilation during shock in experimental setting caused a 7-fold decrease in the percentage of cardiac output received by the respiratory muscles

In text References

(Tobin and Alex. 1994; Viires et al. 1983)

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2. 2. Aims of mechanical ventilation

Overall, the goal of mechanical ventilation is to support gas exchange and sustain life until the cause of respiratory failure is resolved. As Hippocrates stated, an important goal of medical practice is to “do no harm”, and this is a crucial aspect to consider when setting the goals during mechanical ventilation.

The aims of mechanical ventilation according to the initiating indications include:

- Achieve adequate ventilation - CO_2 elimination
- Improve oxygenation
- Relieve respiratory distress – off-load respiratory muscles

Ventilatory support is now recognised as a necessary, often life-saving intervention that can be harmful. Indeed, mechanical ventilation can induce more harm than benefit to the patient by overstretching the lungs while trying to maintain normal blood gases, or by inducing respiratory muscle injury or atrophy from prolonged unloading. These complications of mechanical ventilation termed ventilator-induced lung injury (VILI), and ventilator-induced diaphragmatic dysfunction, are discussed in ACE mechanical ventilation Part VI. The choice of targets during mechanical ventilation requires a careful balance between the costs and benefits of achieving the specific target in the specific clinical situation. While targeting normal blood gases in patients with healthy lungs, as often the case is during anesthesia, is relatively safe and easy, in patients with lung injury or airflow limitation, the cost of achieving normal blood gases may be higher than the benefit.

2. 2. 1. PCO, pH targets:

A normal PCO_2 and pH are commonly targeted in patients with healthy lungs in the perioperative period, as well as in patients with any brain injury, aiming to prevent an increase in intracranial pressure. However, a normal PCO_2 is not mandatory in all patients at any cost. Permissive hypercapnia is a ventilatory management approach targeting higher than normal $PaCO_2$. This allows the application of a low tidal volume (Vt) (and lower than required minute ventilation {MV}) to prevent or minimize lung over-distention. Lung over-distention may cause either VILI, in patients with reduced FRC, or dynamic hyperinflation, in patients with flow limitation (further details are discussed ACE COPD and Asthma –Part VI). Permissive hypercapnia is, therefore, a sophisticated name for a compromise in ventilation targets, when lung pathology does not easily allow achieving normal $PaCO_2$ values (Figure 2, Figure 3).

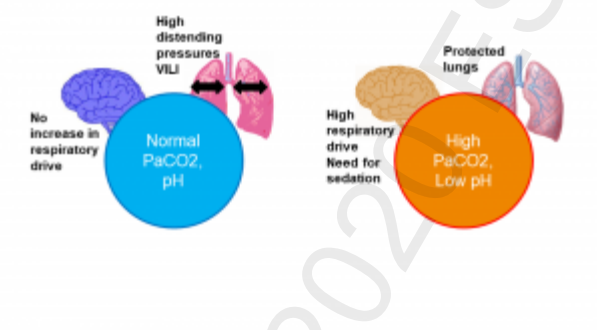

Figure 2: PaCO2 targets: costs and benefits. Mechanical Ventilation module, ESICM Academy, 2018

Figure 2: Achieving a normal $PaCO_2$ may be challenging in the presence of lung pathology. Although it prevents the increase in respiratory drive caused by hypercapnia and acidosis, if it results in high distending pressures during breathing, it may promote VILI or dynamic hyperinflation. On the other hand, limiting tidal volume and minute ventilation in such patients will protect the lungs. This is at the cost of hypercapnia and acidosis, which increase respiratory drive. Here patients often require deep sedation and/or paralysis to tolerate mechanical ventilation.

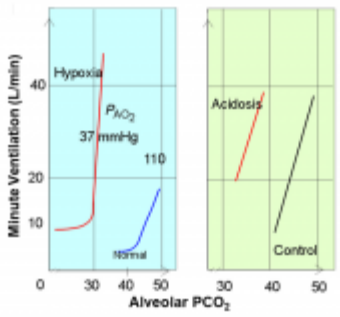

Figure 3: Correlation of respiratory drive with PaCO2. Mechanical Ventilation module, ESICM Academy, 2018

Figure 3: Changes in minute ventilation in response to changes in alveolar PCO_2, under normal conditions, and in the presence of hypoxia (left) and acidosis (right).

2. 2. 2. Oxygenation targets

In most patients targeting a SpO_2 above 90-92% is a reasonable target. Remembering the Hb dissociation curve and oxygen delivery equation (Figure 4), it becomes clear that there is no significant benefit for the patient from a supraphysiological PaO_2. Recent studies demonstrated that targeting hyperoxia had no benefit and might be associated with adverse outcomes.

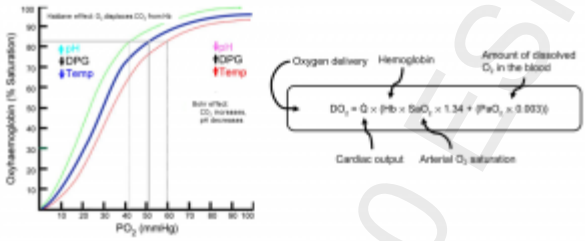

Figure 4:Hemoglobin dissociation curve and oxygen delivery equation. Mechanical Ventilation module, ESICM Academy, 2018

Figure 4: The sigmoidal shape of Hb dissociation curve indicates that increases in Hb saturation above 90% have a small effect on PaO_2. Moreover, increasing PaO_2 above 100 mmHg has minimal effects on oxygen delivery, as the amount of oxygen dissolved in blood is very small.

2. 2. 3. Off-loading the respiratory muscles

The benefits of offloading the respiratory muscles are significant. These include the relief of respiratory distress, prevention of muscle fatigue, and avoiding the increase in their blood supply (important in shock states). Moreover, avoiding rigorous breathing may prevent self-induced lung injury. Unfortunately, prolonged respiratory muscle rest may also induce structural alterations and muscle weakness (ventilator-induced diaphragmatic dysfunction, see ACE mechanical ventilation Part VI).

In text References

(Tobin and Alex. 1994; Laffey et al. 2004; Helmerhorst et al. 2015; Roussos. 1990; Dres et al. 2017; Yoshida et al. 2013)

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2. 3. Means to deliver positive pressure ventilation

The currently used positive pressure ventilators permit the delivery of oxygen mixture to the lungs by application of positive pressure at the airway opening. To effectively deliver the positive pressure, an interface that guarantees a reasonably effective pneumatic seal is required. This can be accomplished by bypassing the oropharyngeal airway (invasive), or by applying a tight-fitting facial mask (non-invasive). The two kinds of interfaces (Figure 5) used are:

- the endotracheal or tracheostomy tubes for invasive mechanical ventilation
- the non-invasive ventilation masks for non-invasive mechanical ventilation (NIMV)

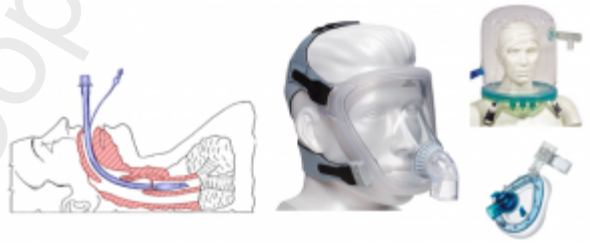

Figure 5: Interfaces to deliver positive pressure ventilation. Mechanical Ventilation module, ESICM Academy, 2018

Figure 5: From left to right: Endotracheal Tube and Non-invasive Ventilation Masks, Total face, Helmet (above), and nose-mouth mask (below).

Each interface and approach (invasive or non-invasive) has specific advantages, disadvantages and limitations which have to be carefully balanced in every patient and aligned with the goals of treatment.

Table 1: Advantages, disadvantages and limitations for Endotracheal Tube and Non-invasive Ventilation Masks

	Endotracheal Tube	**NIMV Mask**
Protection from major aspiration	YES	NO
Relief of fixed upper airway obstruction*	YES	NO
Permit suction of secretions	YES	NO
Stable, leak-proof connection with the ventilator	YES	NO
Protection from infections of lower respiratory tract by reflexes of the upper airway	NO	YES
Comfort	NO	YES
Need for sedation	YES	NO
Need for patient cooperation	NO (Sedated)	YES
Permit effective cough	NO	YES
Ability to speak	NO	YES
Ability to speak	YES	NO

- Variable airway obstruction, as occurs in obstructive sleep apnea is successfully managed with NIMV.

2. 3. 1. NIMV

The main benefit of NIMV is avoiding endotracheal intubation, and thus preventing all related complications, including all device-related ICU-acquired infections (ventilator-associated pneumonia, catheter-related bloodstream infections, urinary catheter-related

infections). Non-invasive ventilation can achieve all aims of ventilation described above. It can be used in a large number of patients with respiratory failure in the absence of contraindications. The contraindications for NIMV are

- Cardiac or respiratory arrest
- Inability to protect airway
- Inability to manage secretions
- Facial or upper airway trauma, surgery, or (potential of) obstruction
- Intractable emesis or GI bleeding
- Shock (relative contraindication, a common cause of failure of NIMV)

Note

As NIMV does not provide a stable, leak-proof connection to the ventilator, the patient must tolerate periods of disconnection. Respiratory insufficiency severe enough to require high levels of PEEP and/or FiO2 is a relative contraindication for NIMV.

The optimal location for patients receiving NIMV depends on the capacity for adequate monitoring, staff skills experience and awareness' of potential complications, and more important in recognition of the patient's needed institution of intubation and invasive mechanical ventilation. Accumulated evidence indicates that NIMV can be successfully initiated in the emergency department, in particular in patients with cardiogenic pulmonary oedema in which a benefit have shown when NIMV was started in the emergency department.

Note

Close monitoring of the patients is required the first 1-2 hours following initiation of NIMV to early recognition of signs of NIMV failure

NIMV can be delivered using either NIMV -dedicated devices or ICU ventilators. Currently two main modes of NIMV are used, the continuous positive airway pressure (CPAP) and the bilevel positive airway pressure (BIPAP). CPAP is mainly used in patients with variable airway obstruction (obstructive sleep apnea syndrome). CPAP has also been used in patients with hypoxemic respiratory failure due to cardiogenic pulmonary edema. BIPAP delivers both inspiratory positive airway pressure (termed IPAP) and expiratory positive airway pressure (termed EPAP). It is the preferred initial mode in hypercapnic respiratory failure (e.g., in COPD patients).

The Criteria for initiation and termination of NIMV are shown in table 2

Table 2: Criteria for initiation and termination of NIMV

Criteria for initiation of NIMV	Criteria for termination of NIMV
Absence of Contraindications	Hemodynamic instability
Increased dyspnoea (moderate to severe)	Decrease level of consciousness
Tachypnea (>24 breaths/min in obstructive and >30 in restrictive disease)	Worsening PH and PaCO2
Signs of increased work of breathing, use of accessory muscles, abdominal paradox	Worsening PaO2
Acute or acute on chronic respiratory failure (COPD) PaCO2 >45 mm Hg	Tachypnea >30 b/min
PH< 7.35	Intense dyspnea
Hypoxemia not corrected by oxygen therapy alone (use with caution)	Signs of increase WOB
PO2/FiO2<300	Inability to clear secretions
	Agitation or intolerance to NIV with progressive respiratory failure

The use of NIMV for acute respiratory failure has been increasing steadily over the past years, as has the success rate the prevention of intubation. Increased experience and improvements in patient-ventilator interfaces account for this success. Another important factor for the success of NIMV is appropriate patient selection.

Conditions in which NIMV has been studied and proven helpful are:

- Acute Exacerbation of COPD
- Cardiogenic Pulmonary edema
- Discontinuation of invasive mechanical ventilation
- Postoperative respiratory failure (either as a preventive or curative approach).

A meta-analysis of 17 RCT involving 1264 patients compared the efficacy of NIMV with bi-level positive airway pressure (BiPAP) in conjunction with standard care versus standard care alone, in patients with acute hypercapnic respiratory failure due to acute exacerbation of COPD, and reported that NIMV decreased the risk of mortality by 46% and decreased the risk of needing endotracheal intubation by 65%.

The efficacy of NIMV in patients with acute cardiogenic pulmonary oedema was investigated in a meta-analysis of 32 randomized trials. CPAP/BiPAP+ usual care compared to usual care alone resulted in a decrease in the mortality rate and the need for

intubation by 33% and 48%, respectively. The main concern that physicians commonly have regarding the application of NIV in patients with acute cardiogenic oedema is whether NIMV may increase the risk for acute myocardial ischemia. The meta-analysis mentioned above revealed the same incidence of MI between the usual care and NIMV plus usual care in patients with acute cardiogenic oedema. Hence, NIMV may be considered in acute cardiogenic pulmonary oedema complicating type II myocardial infarction or a non- STEMI (ST segment elevation myocardial infarction). However, it should be emphasized that patients with STEMI have not usually been included in the trials and the role of NIMV in patients with STEMI has to be elicited by further studies.

In patients with de novo acute hypoxemic respiratory failure (pneumonia) or ARDS, studies have not consistently shown benefit. NIMV failure is high in patients with moderate and severe ARDS, with some studies demonstrating an increase in mortality.

Other conditions in which NIMV has been studied, but there is currently limited evidence include:

- Chest trauma
- Asthma
- Neuromuscular diseases

Factors associated with NIMV failure include:

- Severity of disease
- Comorbidities
- Shock
- Impaired level of consciousness
- ARDS
- Severe acidosis
- Failure to improve after 1-2h of NIMV

For further details about the use of NIMV in patients with acute exacerbation of COPD, please see COPD and Asthma.

In text References

(Rochwerg et al. 2017; Scala and Pisani 2018; Osadnik et al. 2017; Vital, Ladeira and Atallah. 2013; Masip J Peacock et al. 2018)

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3. Basic Principles of Mechanical Ventilation

3. 1. Basic physiology of respiratory system related to mechanical

The main reasons for instituting mechanical ventilation are to support gas exchange and decrease the work of breathing, at the same time, allowing other interventions to reverse the cause of respiratory failure. In this ACE, we will discuss the physiologic mechanisms by which mechanical ventilation supports gas exchange and reduces the work of breathing.

3. 1. 1. Equation of motion

The respiratory control system consists of a motor arm, which executes the act of breathing, a control centre located in the brain medulla, and several pathways that convey information to the control centre. Based on the input, the control centre activates spinal motor neurons, and subsequently, peripheral nerves, to activate respiratory muscles (inspiratory and expiratory muscles), which generate pressure (Pmus). This pressure drives the inflation of lungs, which is used to overcome the elastic recoil pressure, generated as the lungs are inflated above their passive functional residual capacity (FRC),(Figure 1), and the resistance to flow, (inertia is assumed to be negligible) as described in the equation of motion (Figure 2).

According to the equation of motion (Equation 1), Pmus at time **t** is dissipated to overcome the resistive (Pres) and elastic (Pel) pressure of the respiratory system, where Rrs and Ers are resistance and elastance of respiratory system, respectively, $\Delta V(t)$ is instantaneous volume relative to passive functional residual capacity (FRC) and $V'(t)$ is instantaneous flow.

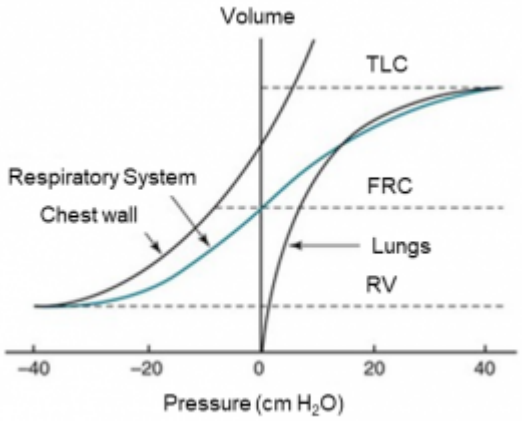

Figure 1: Pressure volume curve of the respiratory system. Mechanical Ventilation module, ESICM Academy, 2018

Figure 1: Pressure volume (PV) curves of lung, chest wall, and respiratory system. Note that FRC is defined as the point where the elastic recoil pressure is equal and opposite to the elastic recoil pressure of the chest wall, and the respiratory system PV curve crosses the X-axis at zero. Above passive FRC, the elastic recoil pressure of the respiratory system becomes positive, and thus lung inflation requires the application of external pressure. Notice also the relative flattening of the pressure-volume curve of the respiratory system near TLC, indicating that greater increases in pressure are required for a smaller increase in volume.

$$Pmus_{(t)} = Pres_{(t)} + Pel_{(t)} = Rrs \times V'_{(t)} + Ers \times \Delta V_{(t)} \quad [Eq.\ 1]$$

$$P_{TOT} = P_{AW} + P_{mus} = Rrs \times V' + Ers \times \Delta V \quad [Eq.\ 2]$$

Figure 2: Equation of motion. Mechanical Ventilation module, ESICM Academy, 2018

Figure 2: Pmus at a time(t) is dissipated to overcome the resistive (Pres) and elastic (Pel) pressure of the respiratory system, where Rrs and Ers are resistance and elastance of respiratory system, respectively, ΔV(t) is instantaneous volume relative to passive functional residual capacity (FRC) and V'(t) is instantaneous flow (Equation 1). During mechanical ventilation, the pressure provided by the ventilator (Paw or Pvent) is incorporated into the system, and the total pressure applied to the respiratory system (PTOT) is the sum of Pmus and Paw (Equation 2).

During mechanical ventilation, the pressure provided by the ventilator (Paw or Pvent) is incorporated into the system. The ventilator and the respiratory muscles can be viewed as pressure generators arranged in series. Therefore, in mechanically ventilated patients, the total pressure applied to the respiratory system (PTOT) is the sum of Pmus and Paw (Equation 2, Figure 2).

Note

The resistance and elastance of the respiratory system, particularly in the presence of lung or chest wall disease, are not constant during the breath but exhibit a considerably flow and volume dependency.

Note

the resistance and elastance of the respiratory system, particularly in the presence of lung or chest wall disease, are not constant during the breath but exhibit a considerable flow and volume dependency.

The combination of P_{TOT} , Rrs, Ers, and respiratory rate, determines minute ventilation. The partial pressures of arterial blood gases will be based on minute ventilation, and the gas exchange properties of the lungs.

3. 1. 2. PCO elimination

The levels of arterial CO_2depend on the balance between CO_2 production ($V'CO_2$) and elimination through alveolar ventilation (V'A), as described in Figure 3,Equation 3.
Total, or minute ventilation (VE), is the amount of air moved in or out of the lungs per minute. It is the product of tidal volume (VT) and respiratory rate (RR), Figure 3, Equation 4. Alveolar ventilation (V'A) represents the fraction of minute ventilation involved in gas exchange, thus excluding ventilation of airways and non-perfused alveoli, the 'dead space' ventilation (VD), as described in Figure 3, Equations 5-6. **CO_2 removal**, therefore, depends on **respiratory rate** and the **ratio of tidal volume to dead space**. These are the factors that can be manipulated during mechanical ventilation.

$$PaCO_2 = 0.86 * V'CO2/ V'A \quad Eq.\ 3$$

$$V'E = VT * RR \quad Eq.\ 4$$

$$V'A = V'E - V'D \quad Eq.\ 5$$

$$V'A = VT * RR * (1 - VD/VT) \quad Eq.6$$

Figure 3: Equations determining PaCO2.
Mechanical Ventilation module, ESICM Academy, 2018

Figure 3:

- Equation 3 $PaCO_2$ is determined by the ratio of CO_2 production ($V'CO_2$) and elimination through alveolar ventilation (V'A), where 0.86 is a constant used for unit harmonisation.

- Equation 4 Total, or minute ventilation (VE) is the amount of air moved in or out of the lungs per minute, thus the product of tidal volume (VT) times respiratory rate (RR),
- Equation 5 Alveolar ventilation (V'A) represents the fraction of minute ventilation involved in gas exchange, thus excluding ventilation of airways and non-perfused alveoli, the 'dead space' ventilation (V'D)
- Equation 6 Modifying Equation 5, to express VD as a ratio over VT, we see that alveolar ventilation depends on VT, respiratory rate, and the ratio of VT to VD.

The graphical representation of Equation 3 is known as the 'metabolic hyperbola', which expresses the $PaCO_2$ as a function of minute ventilation. Figure 4 shows the changes in the metabolic hyperbola when $V'CO_2$ or VD/VT change. Observe how minute ventilation or $PaCO_2$ differ as a result of those changes.

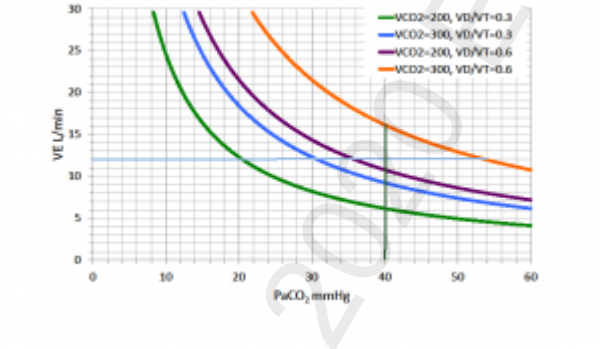

Figure 4: Graphical representation of the equation: PaCO2=0.86*V'CO2/{VE*(1-VD/VT)}. Mechanical Ventilation module, ESICM Academy, 2018

Figure 4: Graphical representation of the equation: $PaCO_2$=0.86*$V'CO_2$/{VE*(1-VD/VT)}, for two different values of $V'CO_2$ and VD/VT. The coordinates of each point in the metabolic hyperbola (x and y values) represent the value of $PaCO_2$ at this minute ventilation for a given combination of $V'CO_2$ and VD/VT. Notice that the minute ventilation required to maintain a $PaCO_2$ of 40mmHg varies from 6 to 16 L/min (vertical green line) and that the $PaCO_2$ value for minute ventilation of 12 L/min varies from 20 to 54 mmHg (horizontal blue line).

Note

Based on Equation 6, it is clear that changes in VT will have a greater impact on alveolar ventilation than changes in respiratory rate.

Challenge

Solving the equation using actual numbers: RRinitial = 10, VTinitial = 500ml, Vd = 150ml. Re-calculate V'A after a 50% increase in either RR or VT.

Note

> The Heat and Moisture Exchangers (HME) used in clinical practice have a volume of 30-50 ml, which is added to the dead space, and thus changing from a HME to a humidifier (no additional dead space volume) will increase V'A without changing minute ventilation.

3. 1. 3. Oxygenation

The mechanisms of hypoxemia are:

- Ventilation/perfusion (V/Q) mismatch
- Shunt
- Diffusion limitation
- Alveolar hypoventilation
- Low FiO2

In critically ill mechanically ventilated patients, only the first two mechanisms are clinically relevant. Significant limitations in diffusion are only observed in patients with advanced fibrosis, alveolar hypoventilation is prevented, and obviously low FiO_2 is never present. Moreover, a sixth mechanism is the decreased mixed venous oxygen content, present in patients with shock.

In mechanically ventilated patients, hypoxemia can be corrected by increasing FiO_2 and and the application of positive end-expiratory pressure (PEEP).
The increase in FiO_2 increases alveolar PAO_2 according to the equation:

$$PAO_2 = (P_{atm} - PH_2O) - \frac{PCO_2}{R}$$

Because the need for mechanical ventilation arises when supplemental oxygen administration alone is not enough to correct hypoxemia, and because hypoxemia in critically ill patients is caused by V/Q mismatch and shunt, enriching the inspired gas in oxygen is usually not enough to correct the hypoxemia.

3. 1. 4. Positive End Expiratory Pressure

PEEP improves oxygenation by permitting the reopening of alveoli closed due to atelectasis or oedema. The application of PEEP can cause a redistribution of extravascular lung water from the alveoli to the peribronchial and perivascular spaces and thus open the collapsed alveoli.

Effects of PEEP:

- Increase in FRC
    - Improved oxygenation

    - Shift of tidal breathing upward in the pressure-volume curve (more compliant)
- Decrease in intrapulmonary shunt
    - Improved oxygenation
- Reduction of alveolar opening and closing
    - Prevention of lung injury
- Increase in intrathoracic pressure
    - Decrease in venous return
    - Decrease in left ventricular transmural pressure
- Distention of normally aerated alveoli
    - Increase of dead space
    - Causing lung injury
- In the presence of airflow obstruction, there is a substitution of the pressure that must be generated by the inspiratory muscles to overcome intrinsic PEEP and generate inspiratory flow.

The hemodynamic effects of PEEP result from intrathoracic pressure increase (Figure 9). If the cardiac output is dependent on preload, then PEEP may decrease cardiac output by decreasing venous return. In cases of heart failure and volume overload, when cardiac output is less dependent on preload, PEEP can improve left ventricular function by decreasing the transmural pressure of the left ventricle. This effect is direct, due to the increase in intrathoracic pressure and indirect, by improving FRC, thus reducing work of breathing, and diminishing large inspiratory efforts which cause an increase in left ventricular afterload.

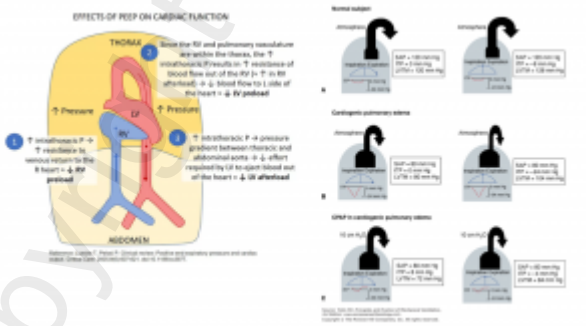

Figure 5:The hemodynamic effects of PEEP.
Mechanical Ventilation module, ESICM Academy, 2018

Figure 5: PEEP increases intrathoracic pressure, thus decreases venous return and right and left ventricular preload. Preload dependant cardiac output will be decreased by increased intrathoracic pressure. The increase in intrathoracic pressure will also decrease left ventricular afterload and the transmural pressure of the left ventricle, which may improve left ventricular (dys)function. Therefore, in cases of heart failure and volume overload, when cardiac output is less dependent on preload, PEEP can increase cardiac

output. Indirectly, by improving FRC, which may improve gas exchange and reduce work of breathing, this diminishes large inspiratory efforts and prevents the related increases in left ventricular afterload.

Overall the beneficial effects of PEEP include:

- Improved oxygenation by increasing FRC, improving V/Q match, and decreasing shunt
- Reduced work of breathing by shifting tidal breathing towards the more compliant part of the pressure-volume curve, decreasing respiratory drive by improving oxygenation, and, in the presence of intrinsic PEEP, by substituting the pressure that must be generated by the inspiratory muscles to generate inspiratory flow
- Prevent ventilator-induced lung injury (VILI) by preventing cyclic opening and closing of alveoli
- Improve left ventricular function by decreasing its transmural pressure

The detrimental effects of PEEP include:

- Overdistention of alveoli, increasing dead space thus decreasing the efficiency of CO_2 removal and promoting VILI and barotrauma
- Decrease in cardiac output

It is not possible to pre-define a specific range of PEEP for a specific patient at a specific time to ensure the beneficial effects and minimise the development of the detrimental effects of PEEP.

In text References

(Kondili, Prinianakis and Georgopoulos. 2003; Feihl and Broccard. 2009; Hess 2015; Tobin and Alex. 1994; West, Luks and 2011)

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- Tobin MJ, Alex CG. , Principles and Practice of Mechanical Ventilation., Discontinuation of mechanical ventilation. ;1177-1206., McGraw-Hill, Inc., , 1994, New York, ISBN-10: 0071736263
- Kondili E, Prinianakis G, Georgopoulos D., Patient-ventilator interaction., 2003, PMID:12821570
- Feihl F, Broccard AF., Interactions between respiration and systemic hemodynamics. Part II: practical implications in critical care., 2009, PMID:18825366
- Hess DR, Recruitment Maneuvers and PEEP Titration., 2015, PMID:26493593

- West J, Luks A,, West's Respiratory Physiology: The Essentials Tenth Edition, 2011, ISBN:9781496310118

3. 2. Basic functions of positive pressure ventilators

The mechanical ventilators currently used in Intensive Care are equipped with:

- pressurised gas source and an air/oxygen blender
- inspiratory and expiratory valves and external ventilator circuit connecting to the patient
- controllers regulating the opening and closing of inspiratory and expiratory valves, and pressurised air delivery, as well as monitoring and alarm functions

The proper function of a positive pressure ventilator requires the operator to provide the ventilator control system with information on how the breath will be initiated and terminated, and what amount of air will be delivered during inspiration. These three variables are:

- **the triggering variable**, which is the signal initiating the delivery of positive pressure
- **the control variable**, which is the algorithm that determines the delivered pressure during the mechanical inspiration
- **the cycling off variable**, which is the signal of terminating the pressure delivery.

Triggering variable: the signal initiating the delivery of positive pressure leading to the initiation of mechanical inspiratory phase.

The most commonly used triggering variables are time, pressure and flow. Other triggering variables include flow waveform, and diaphragmatic electrical activity, used in non-invasive ventilation and neurally-adjusted ventilation, respectively.
According to the set triggering mode, the delivery of positive pressure will initiate when the specified condition, as described below, is met.
Time: when a respiratory rate (RR) is set, a timed inspiration will begin at the specified interval, for example if RR is set at 20 br/min, positive pressure will be delivered every 3 sec.
Pressure: pressure triggering requires the patient to decrease the pressure in the ventilator circuit to a pre-set level (Figure 6).

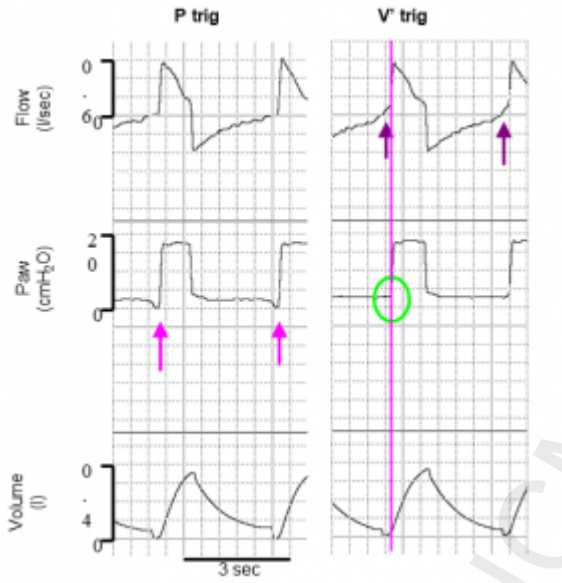

Figure 6: Pressure and Flow triggering method. From Georgopoulos D, Prinianakis G, Kondili E. Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies Intensive Care Med. 2006 Jan;32(1):34-47.

Figure 6: Triggering with pressure (left) and flow (V', right); notice the drop of pressure (pink arrows) in pressure triggering, and the absence of flow at the same time, as opposed to the change in flow without the pressure drop in flow-triggering (pink line, and purple arrows, right) (Georgopoulos, Prinianakis and Kondili. 2006).

Flow: similar to pressure triggering, the patient is required to decrease flow in the circuit to a pre-set level (Figure 6).

Note

when pressure triggering is used, the respiratory muscles are being subjected to isometric contractions during triggering, as no airflow is yet allowed in the ventilator circuit.

Variable that controls the pressure delivery

The most commonly used variables determining the delivery of positive pressure are:

- **Volume:** where the ventilator, once triggered, delivers a pre-set (tidal) volume with a pre-set flow-time profile (volume-targeted ventilation)
- **Pressure:** where the ventilator delivers a pre-set pressure (pressure targeted ventilation)

Other variables used to determine the delivery of positive pressure are:

- **Instantaneous flow and volume** (reflecting Pmus): in Proportional Assist Ventilation (PAV) where the ventilator delivers pressure which is proportional (the proportionality is pre-set) to instantaneous flow and volume (see Proportional Assist Ventilation)
- **Electrical activity of the diaphragm:** in Neurally-Adjusted Ventilation (NAVA) the ventilator delivers pressure which is proportional (the proportionality is pre-set) to diaphragmatic electrical activity, monitored by an appropriate esophageal catheter (see Neurally-Adjusted Ventilation Assist).

> **Note**
>
> Modern ventilators have the ability to combine different modes of triggering and pressure delivery control, presented in ACE Part III Modes of ventilation with combinations of triggering and pressurization variables.

Cycling off variable: the signal of terminating pressure delivery.
The most commonly used cycling off criteria, determining the end of pressure delivery and thus of the mechanical inspiratory phase, are time, pressure, and flow.

Time: tthe set inspiratory time, determined directly or indirectly by setting the respiratory rate and inspiratory to expiratory ratio, initiates the opening of the exhalation valve.
Pressure: in this case, the ventilator terminates the pressure delivery when, due to expiratory muscle activity, Paw increases above a certain threshold (usually 1.5-3 cmH_2O).
Flow: in this case, the exhalation valve opens when inspiratory flow decreases to a pre-set flow criterion, which may be either a percentage of peak inspiratory flow or a fixed value.
As a safety feature, the ventilator may terminate the pressure delivery when the duration of inspiratory flow is considerably long (i.e., above 3 sec).

In PAV mode, pressure delivery terminates when inspiratory flow decreases to zero, and in NAVA when diaphragmatic activity drops below a preset level.

> **Note**
>
> The ‘mechanical’ inspiratory time is the one chosen by the user by setting the triggering and cycling off variables. This differs from the patient’s neural inspiratory time. Ventilator settings aim to minimise this difference.

The mode of ventilation is characterised as either **‘control’** (operator-controlled) or **‘assisted’** (patient-controlled) based on the way the breath is initiated and terminated.
In other words, if the initiation and termination of the breath are controlled by the operator (triggering and cycling off being time), the mode is characterized as ‘control,’ and if the breath is initiated and terminated by the patient’s effort the mode is characterized as assisted (all other signals). Based on the variable that regulates pressure delivery, a mode is characterised as ‘volume’ or ‘pressure’ targeted.

Note

The proper function of a ventilator requires the use of the appropriate external circuit with an inspiratory and expiratory arm and filters. Additionally, air humidification should be performed with either a 'heat and moisture exchanger' (HME) mounted at the Y-piece or a heated humidifier mounted within the inspiratory tubing. Routine change of ventilator circuit as a mean to prevent ventilator-associated pneumonia is not considered necessary.

Note

Ventilators, as any other ICU equipment, require maintenance for proper function. In addition to professional maintenance, every user should be able to perform the basic calibration procedures and tests each ventilator in use.

In text References

(Branson, Hess and Chatburn 2000)

References

- Georgopoulos D, Prinianakis G, Kondili E., Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies, 2006, PMID:16283171
- Branson RD, Hess DR, Chatburn RL, Respiratory Care Equipment Second Edition, 2000, ISBN:0781712009

4. Modes of Positive Pressure Ventilation

As discussed in Part II , the parameters which define the mode of positive pressure ventilation are the triggering (and cycling off) variable and the control variable (Figure 1). When the triggering variable is time, the mode is referred to as 'control'. When a patient's effort triggers the delivery of positive pressure, the mode is referred to as 'assisted'.
The delivery of positive pressure can subsequently be regulated by a pre-set volume (volume-control, VC) or a pre-set pressure (pressure-control, PC). Modern ventilators use several combinations of trigger and control variables in the 'dual modes', as presented in Figure 2, but the basic principles of ventilation remain the same.

Set or derived Variables	Trigger	Cycling off	Respiratory Rate	Inspiratory time	Tidal Volume	Inspiratory pressure	Minute ventilation	PEEP	FiO2
Mode									
Volume Control	time	time	Set	Set	Set	Derived	set	Set	Set
Pressure Control	time	time	Set	Set	Derived	Set	Derived	Set	Set
Pressure Support	Flow or Pressure	flow	Patient's	Patient's	Derived	Set	Derived	Set	Set
Assist-volume	Flow or Pressure	volume	Patient's	Patient's	Set	Derived	Derived	Set	Set
PAV	Flow or Pressure	Flow	Patient's	Patient's	Derived	Derived	Derived	Set	Set
NAVA	EaDi	EaDi	Patient's	Patient's	Derived	Derived	Derived	Set	Set

Figure 1:Basic modes of ventilation, set and derived parameters. Mechanical Ventilation module, ESICM Academy, 2018

Figure 1: The variables set by the operator and derived from the patient's respiratory system mechanics and muscle function are presented for the most commonly used modes of ventilation.

- Blue: variables set by the operator
- Orange: variables derived based on the mechanical properties of the respiratory system and respiratory muscle function
- Pink: parameters controlled by the patient (but influenced through control-of-breathing feedback mechanisms from the set parameters).

	Control Mode				Assist Mode				Total	
Variables/ Mode	**Trigger Cycl. off**	**Resp. Rate**	**VT**	**Pinsp**	**Trigger Cycl. off**	**Resp. Rate**	**VT**	**Pinsp**	**Resp. Rate**	**Minute Volume**
Assist-VC	Time	Set	Set	Derived	V' or P	Pt's	Set	Derived	Derived	Derived
Assist-PC	Time	Set	Derived	Set	V' or P	Pt's	Derived	Set	Derived	Derived
Bi-Level (APRV)	Time*	Set*	Derived	Set	V' or P	Pt's	Derived	Set	Derived	Derived
SIMV	Time	Set	Set	Derived	V' or P	Pt's	Derived	Set	Derived	Derived
MMV	Time	Derived	Set	Derived	V' or P	Pt's	Derived	Set	Derived	Set

Figure 2:Dual modes of ventilation, set and derived parameters. Mechanical Ventilation module, ESICM Academy, 2018

Figure 2: List of common dual modes and relevant ventilator variables. In dual modes the operator defines the variables for both controlled and spontaneous (assisted) breaths. The parameters set depend on the specific mode/ventilator brand.
Abbreviations:
VC: volume control
PC: pressure control
APRV: airway pressure release ventilation
SIMV: spontaneous intermittent mandatory ventilation
MMV: mandatory minute ventilation

- In Bi-Level mode, by defining the time (duration) of P-high and P-low a mechanical respiratory rate is set.

Note

there are more than 50 different modes in the commercially available ventilators and a complete presentation is beyond the scope of this module.

In ‘control’ modes the breathing rate is set by the caregiver, and thus, the main indication to use a control mode is the lack of patient’s spontaneous breathing activity. This may be the result of brain injury or pharmacologic depression of the respiratory center (e.g. opioid overdose), or the need to provide deep sedation, and/or paralysis. The need for sedation may arise as a therapeutic intervention in brain injury or as a mean to manage dyspnoea and respiratory distress in patients with respiratory failure. In patients with acute respiratory failure, particularly in the early phase of disease, spontaneous breathing may result in injurious ventilation and ‘patient self-inflicted lung injury’. In such cases sedation and controlled modes are selected as a means to provide protective ventilation. The major complications of controlled ventilation are those associated with prolonged sedation and immobilisation, and diaphragmatic atrophy. Thus, the duration of controlled ventilation should be kept to a minimum.

4. 1. Basic controlled modes volume and pressure control

In both controlled modes, the respiratory rate, inspiratory to expiratory time ratio, presence or absence of inspiratory plateau time, as well as tidal and minute volume are selected by the operator. The tidal volume is set directly in volume control mode and indirectly in pressure control mode.

In volume control mode, the set, or independent variable is volume (tidal volume) and the dependent variable is pressure.
Based on the equation of motion:

$$Paw = V'i * Ri + Vi * Ei$$

Where Pawi is the airway pressure, V'i is the instant flow, or the set inspiratory flow, Ri is the resistance and Ei the elastance of the respiratory system, and Vi is the volume delivered, which at the end of inspiration is the set tidal volume (Vi=VT). Figure 3

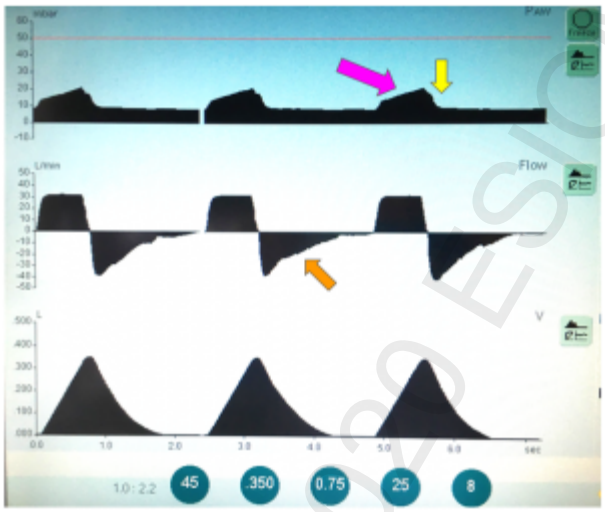

Figure 3:Waveforms in Volume Control Ventilation. Mechanical Ventilation module, ESICM Academy, 2018

Figure 3: Pressure, Flow, and Volume waveforms in volume control ventilation with constant flow. Notice the gradual increase in pressure during inflation (pink arrow), as a result of the gradual increase in elastic recoil pressure caused by the increase in lung volume above FRC. Notice the decrease to the set level of PEEP at end-inspiration (yellow arrow). Notice the shape of the passive expiratory flow-time curve - this is modified in obstructive lung diseases in the same way we see in pulmonary function tests, with an abrupt decrease of expiratory flow.

As the tidal volume is set, the pressure that will develop in the respiratory system at end-inspiration is dependent on the mechanical properties of the respiratory system. These are the resistance and elastance (assuming that the patient does not show any spontaneous breathing activity). Moreover, by setting a tidal volume and an inspiratory time, the inspiratory flow also becomes defined (set volume over set time). Most ventilators offer a choice between constant and decelerating flow shape. A constant flow allows measurement of the mechanical properties of the respiratory system. A simple visual analysis of the pressure waveform provides useful information on the mechanical properties of the respiratory system (Figure 4).

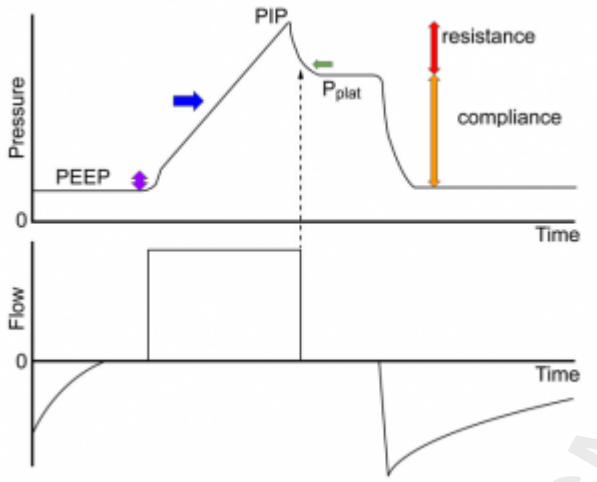

Figure 4:Waveform interpretation in Volume Control. Mechanical Ventilation module, ESICM Academy, 2018

Figure 4: In the absence of respiratory muscle activity, the instant pressure, Paw(i), at any time depends on the volume that has entered the system Vi, the set flow (V'), and the mechanical properties of the respiratory system:

$$Pawi = V' * Ri + Vi * Ei$$

The initial increase in Paw (purple arrow) is caused by the resistance of the circuit and the large airways, as only little volume has entered the system, thus the component Vi*E is small. Subsequently, both the resistance to flow and the gradually increasing elastic recoil pressure contribute to the increase in Pawi (blue arrow). The maximum pressure reached, termed Peak inspiratory pressure (PIP), is when all volume is delivered, just before the inspiratory flow terminates. When inspiratory flow becomes zero, an abrupt decrease in Paw is observed, (green arrow). If no inspiratory plateau time is chosen and expiratory valve opens, pressure drops to the set level of PEEP. If there is a set inspiratory plateau time (inspiratory flow stops, but exhalation valve does not open), we see the plateau pressure (Pplat) determined by the elastic recoil pressure:

$$Paw = (0 * Ri) + VT * E$$

A closer look at the green arrow point may reveal a gradual decrease from the point of zero flow to Ppl caused by redistribution of air in inhomogeneous lungs. As the drop of Paw from Ppeak to Ppl is caused by the elimination of flow in the system it becomes apparent that this is the amount of pressure required to overcome resistance to flow, (red arrow) thus

$$Ppeak - Ppl = V' * R$$

After measuring Ppeak and Ppl, and knowing the set, constant flow, one may calculate the resistance of the respiratory system. At the end of inspiratory time, the opening of expiratory valve results in a new, abrupt decrease in Paw, to the set level of PEEP. Following the same reasoning as above, the drop of Ppl to PEEP is caused by the elimination of volume in the system. Therefore, this is the amount of pressure required to overcome the elastic recoil caused by the tidal volume inflation (orange arrow). That is:

$$Ppl - PEEP = VT * E$$

and therefore respiratory system elastance, or compliance (C=1/E) can be measured. If there are increases in the initial pressure rise (purple arrow) we have to check for conditions causing increased circuit and large airways resistance. If we see increases in peak pressure and the difference to plateau pressure (red arrow), we have to check for conditions causing increased resistance, and if we see increased Pplat (orange arrow) we have to check for conditions resulting in decreased compliance.

During volume control ventilation respiratory system mechanics (resistance , static compliance and intrinsic PEEP) can be measured by performing the end-inspiratory and end- expiratory hold manoeuvres (Figure 5).

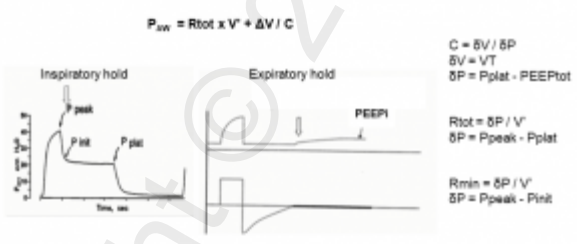

Figure 5:Measuring respiratory system resistance and compliance and driving pressure in volume control mode with constant flow. Mechanical Ventilation module, ESICM Academy, 2018

Figure 5: With airway occlusion at the end of inspiration, flow drops to zero, and the proximal airway pressure immediately decreases from a peak value (Ppeak) to a lower initial value (the pressure at zero flow Pinit), followed by a gradual decrease until a plateau (Pplat) is achieved after approx. 3 sec. **With airway occlusion at the end of expiration,** airway pressure may remains unchanged at the level of set PEEP, or increases, indicating the presence of intrinsic PEEP (PEEPi). The presence of PEEPi should be accounted for when measuring respiratory system compliance.
Static Compliance (C) of the respiratory system at end-inspiration is defined as the ratio of tidal volume and the difference between plateau pressure (Pplat) and total PEEP (set PEEP or PEEPi),

$$C = VT/P_{plat} - PEEP_{tot}$$

Driving pressure (ΔP) of the respiratory system is defined as the difference between plateau pressure (Pplat) and total PEEP (set PEEP or PEEPi) at end-inspiration (in passive conditions).

Note

Valid measurements require absence of patient's effort

Resistance of large airways determines the difference between peak inspiratory pressure (Peak) and Pinit. The difference between Pinit and Pplat (normal values 1-2 cmH_2O) is determined by time constant heterogeneity within the lungs and the viscoelastic behavior of the stress relaxation of the pulmonary tissue.

$$R_{tot} = Ppeak - PPlat/V'$$

- Rtot: total respiratory resistance
- V': preset inspiratory

$$Rmin = Ppeak - Pinit/V'$$

Rmin reflects the resistance from conducting airways and endotracheal tube

In **pressure control mode(Figure 6),** the independent variable is pressure and the dependent variables are flow and volume, as defined by the equation of motion. Thus in pressure control ventilation the instant flow depends on the mechanical properties of the respiratory system (Figure 7). Similarly when the pressure is set, the volume that will be delivered is dependent on the mechanical properties of the respiratory system and the set inspiratory time.

Note

Measuring respiratory system compliance in pressure control mode can be done similarly to volume control mode, provided that flow at end-inspiration is zero (Figure 8)

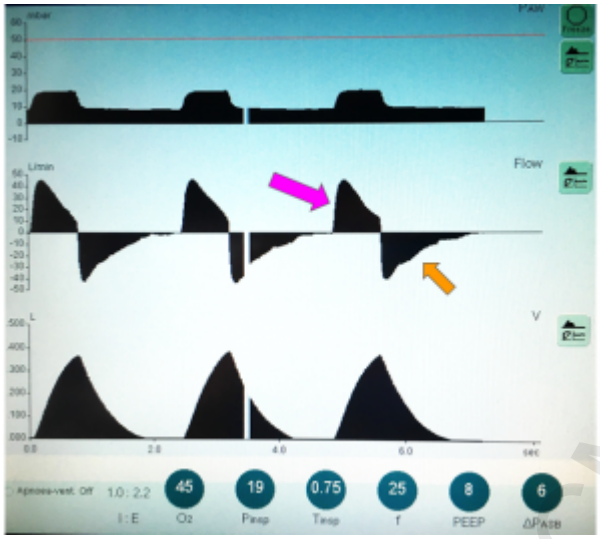

Figure 6:Waveforms in Pressure Control Ventilation. Mechanical Ventilation module, ESICM Academy, 2018

Figure 6: Pressure, Flow, and Volume waveforms in pressure control ventilation. Notice the differences with VC, the (almost) rectangular shape of the pressure waveform, which in this case is the set value. Also notice the different shape of the flow waveform (pink arrow), which in this case is the dependent variable, gradually decreasing, as the elastic recoil pressure progressively increases with lung inflation (remember the equation of motion Paw = V'(i) * Ri + Vi * Ei). Finally notice that the shape of the passive expiratory flow-time curve is the same irrespective of the mode of inspiration.

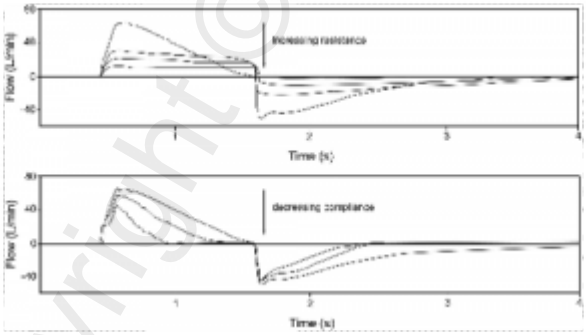

Figure 7:Waveforms in Pressure Control Ventilation -B. Dean R Hess, Respiratory Mechanics in Mechanically Ventilated Patients, RESPIRATORY CARE. NOVEMBER 2014 VOL 59 NO 11

Figure 7: In pressure control mode, the independent variable is pressure, and the dependent variables are flow and volume. Therefore, because the instant flow depends on the mechanical properties of the respiratory system, the flow waveform may provide information on these properties. Increasing resistance **(Upper panel)** will depress and flatten the inspiratory flow, while decreasing compliance **(Bottom Panel)** will decrease

peak flow and shorten the time of inspiratory flow (the lower the compliance, or higher elastance, the faster the component VT*E will reach the set value of Paw, thus make V'i become zero).

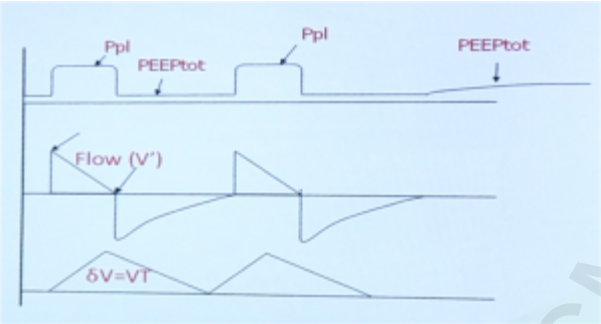

Figure 8:Waveforms in Pressure Control Ventilation - C. Mechanical Ventilation module, ESICM Academy, 2018

Figure 8: C. Measuring respiratory system compliance in pressure control mode can be done similarly to volume control mode, provided that flow at end-inspiration is zero:

$$C = VT/P_{plat} - PEEP_{tot}$$

4. 2. Setting the ventilator in control modes

When choosing ventilator settings, both oxygenation and ventilation for CO_2 elimination should be considered. Management of oxygenation relies mostly on PEEP and FiO_2, while CO_2 elimination depends on tidal volume and respiratory rate, although significant interactions should be considered. Apart from achieving arterial blood gas targets, ventilator settings should focus on preventing or minimising ventilator-induced lung injury in ARDS, and hyperinflation in obstructive lung diseases. The final choice of ventilator settings is usually a compromise between achieving blood gases targets and protecting from VILI/hyperinflation.

Ventilator parameters to set in Volume/Pressure Control Mode

- PEEP
- FiO_2
- Tidal Volume (Volume Control)
- Inspiratory pressure (Pressure Control)
- Respiratory Rate
- I:E ratio

- Inspiratory plateau (directly in VC, indirectly in PC)

4. 2. 1. PEEP

The application of PEEP aims to open and maintain patent alveoli which tend to close during tidal breathing due to the elastic recoil pressure, especially in diseased lungs. Thus, the aim of PEEP is to improve V/Q-match and oxygenation, while preventing alveolar overdistention. Even in the absence of lung injury, in the supine position, the lack of diaphragm movement and sighs, promote the collapse of alveoli in the dependent lung regions. It is also important to remember that the applied external PEEP will not only have to overcome the elastic recoil pressure of the lungs, but also that of the chest wall.

4. 2. 2. How to adjust PEEP at the bedside

The first step in PEEP titration is recognising the underlying lung pathology. Three main patterns will be examined: normal lungs, ARDS, and obstructive disease.

4. 2. 2. 1. Setting PEEP in patients with normal lungs

In patients with normal lungs and chest wall the recommended PEEP setting is 5 cmH_2O. When
chest wall elastance is high, like in the presence of abdominal hypertension, a higher PEEP will be required, even in patients with normal lungs.

4. 2. 2. 2. Setting the PEEP in patients with ARDS

Extensive literature is available on PEEP titration in patients with ARDS, yet no single method has been shown to improve clinical outcomes compared to others. It is important to remember that ARDS is characterised by inhomogeneous distribution of the pathology, suggesting that different lung regions may need different levels of PEEP. Because we provide only one level of PEEP to the whole lung, we should recognise that this should be a compromise aiming to maintain alveolar patency in the most injured regions while minimising alveolar overdistention of the healthier lung regions.

Before applying PEEP we must first assess whether the lungs are recruitable and then select the appropriate PEEP. The methods to assess lung recruitability are:

- Improvement in oxygenation and lung mechanics with PEEP. This signifies lung recruitment and shunt reduction.
- Imaging techniques (CT, helium dilution or nitrogen washout techniques, electrical impedance tomography).

It is generally accepted that lung injury leading to hypoxemic respiratory failure is best managed by PEEP higher than the 5 cmH_2O typically applied in patients with normal lungs, and that a personalised approach is preferred. There is no consensus as to what

physiologic variable should be used as an end-point for PEEP titration. The level of PEEP to be expected in patients with mild ARDS is in the range of 5-10 cmH_2O, 10-15 cmH_2O in moderate ARDS and above 15 cmH_2O in severe ARDS.
The main methods used to titrate PEEP are:

- PEEP-FiO_2 tables
- PEEP above the lower inflection point of the pressure-volume curve
- Respiratory system compliance optimisation
- Driving pressure (P_{plat} -$PEEP_{tot}$) below 14cmH_2O
- Stress index <1
- End-expiratory transpulmonary pressure P_L > 0 cmH_20
- Imaging techniques: Computerised tomographic scanning at different levels of PEEP, electrical impedance tomography, end-expiratory lung volume (EELV) increase from a lower to a higher PEEP level.

Titrating PEEP according to oxygenation is widely used and PEEP is selected based on the PEEP-FiO_2 tables proposed by the ARDS Network and other studies. This method is easily implemented in clinical practice but it lacks any personalisation and cannot be recommended as a way of PEEP titration, but rather as a starting point. Keep in mind that PaO_2 is also influenced by factors unrelated to lung recruitment, such as cardiac output.
The lower inflection point is considered to indicate the pressure at which a large number of alveoli are recruited. Selecting a PEEP level above the lower inflection point of the static respiratory system pressure-volume curve is rarely employed in clinical practice due to a number of limitations: the patient must be heavily sedated or paralysed, there are occasions where the lower inflection point cannot be identified and lung recruitment continues above the lower inflection point.

The value of PEEP that is associated with the best respiratory system compliance (Crs) can be easily applied, it is non-invasive and allows the assessment of lung recruitment. A limitation is that cyclic opening and collapse of lung units with tidal insufflations may cause an increase in measured tidal compliance not related to the PEEP-induced end-expiratory recruitment.

The concept of *driving pressure measurement to adjust PEEP*, shares the same concept with Crs optimisation. If PEEP is raised and the driving pressure decreases, leading to an increase in VT and the Crs, this suggests that the higher PEEP led to lung recruitment. In contrast, if PEEP is raised and the driving pressure increases, Crs has decreased, suggesting that higher PEEP has caused overdistention of aerated alveoli. Thus, adjusting PEEP to minimise driving pressure shares the same limitation with Crs optimisation. It also important to remember that higher distending pressures may exist locally in the in-homogeneous injured lung and are not captured by the global measurement of driving pressure.

The slope of the airway pressure-time curve (stress index) gives information about the changes in Crs during inspiration: if the slope increases during inspiration (stress index > 1), Crs is decreasing, while a decreasing slope (stress index<1) indicates increasing Crs. PEEP can be adjusted to a level at which the stress index equals 1. However, this approach requires specialised monitoring equipment to record and analyse the pressure-time relationship, limiting its adoption in clinical practice at present.

The transpulmonary pressure to guide PEEP targets a positive end-expiratory transpulmonary pressure (end expiratory P_L) of 0-10cmH_2O. This approach may be beneficial in selected patients, such as those with suspected high chest wall elastance or severe ARDS, transpulmonary pressure can be used to ensure that applied PEEP is adequate (stop end-expiratory collapse, as suggested by an end-expiratory PL above 0 cmH_2O) and not harmful (no overdistension, end-inspiratory P_L < 20-25 cmH_2O, see below in VT setting). It requires the insertion of an esophageal catheter to estimate pleural pressure.

Imaging techniques to guide PEEP include CT imaging of the lung, lung ultrasound and electrical impedance tomography. Further studies are required to incorporate these techniques as a method to adjust PEEP in clinical practice.

Summary: No single method of PEEP titration has been shown to improve clinical outcomes compared to others in ARDS patients. Lung recruitability is a critical factor determining whether the effect of PEEP is predominantly recruitment or overdistention. PEEP may be initially set using the PEEP-FiO_2 table and then individualised to optimise compliance and minimise driving pressure. In selected patients, transpulmonary pressure might be a useful guide to adjust PEEP.

4. 2. 2. 3. Setting the PEEP in patients with obstructive lung disease

In patients with obstructive lung disease and airflow limitation, intrinsic PEEP is often present (Figure 9), and the aim of the ventilatory strategy is to eliminate it. As the effects of PEEP are the same whether intrinsic or external, it is important in such patients to monitor for the presence of PEEPi and add external PEEP cautiously by monitoring the resulting total PEEP and titrating to the desired level (read more in Module on COPD). Intrinsic PEEP improves with the resolution of airway obstruction and then application of external PEEP becomes necessary. Therefore, frequent manual measurement of PEEPi is essential to identify this in time.

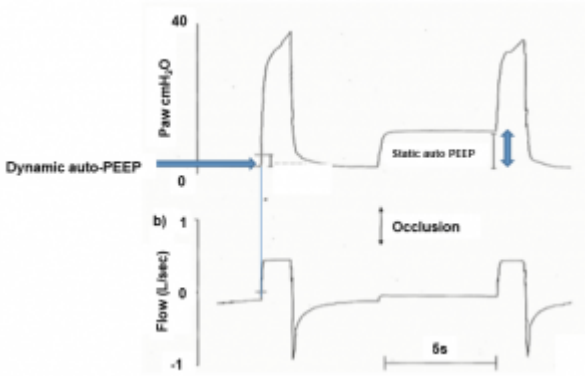

Figure 9:Intrinsic or auto-PEEP. Mechanical Ventilation module, ESICM Academy, 2018

Figure 9: In the presence of airflow limitation lung emptying may be incomplete at the end of the mechanical expiratory time. The volume remaining trapped increases pressure and can be revealed with an end-expiratory hold manoeuvre.

4. 2. 3. FiO

Once the appropriate level of PEEP is chosen the minimum FiO_2 is set to achieve the set target of SpO_2. The detrimental effects of hypoxemia are well established, but recent studies indicate that hyperoxemia may also be associated with adverse patient outcomes and should be avoided. While more studies are needed it is reasonable to avoid supra-normal PaO_2 and target an SpO_2 of 94-98% when choosing the FiO_2.

4. 2. 4. Tidal Volume

The tidal volume is one of the main components determining CO_2 elimination and $PaCO_2$, as shown in (Figure 10):

$$PaCO_2 = \frac{0.86 * V'CO_2}{VE * (1 - \frac{VD}{VT})}$$

Tidal volume is not only the main determinant of $PaCO_2$ but also of tidal lung inflation and the potential associated lung injury. Therefore, when choosing tidal volume in patients ventilated in controlled modes we need to compromise between the target PaCO2, and the prevention of lung injury.

In healthy subjects normal tidal volume has been measured in the range of 4-12 ml/kg ideal body weight (IBW). In mechanically ventilated patients in controlled modes, VT should be set initially to 6-8 ml/kg. Subsequently, optimisation of VT will depend on the resulting $PaCO_2$, and evaluation of the potential risks for lung injury.

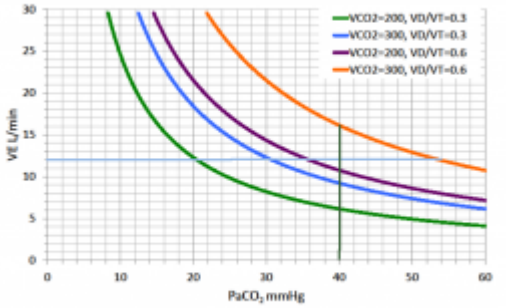

Figure 10: Graphical representation of the equation: PaCO2=0.86*V'CO2/{VE*(1-VD/VT)}.Mechanical Ventilation module, ESICM Academy, 2018.

Figure 10: Graphical representation of the equation: $PaCO_2$=0.86*V'CO_2/{VE*(1-VD/VT)}, for two different values of V'CO_2 and VD/VT. The coordinates of each point in the metabolic hyperbola (x and y values) represent the value of $PaCO_2$ at this minute ventilation for a given combination of V'CO_2 and VD/VT. Notice that the minute ventilation required to maintain a $PaCO_2$ of 40mmHg varies from 6 to 16 L/min (vertical green line) and that the $PaCO_2$ value for minute ventilation of 12 L/min varies from 20 to 54 mmHg (horizontal blue line).

In patients with healthy lungs, and even more so in patients with pulmonary edema or ARDS, the main aim when optimizing the tidal volume is to minimise end-inspiratory distending pressures which cause VILI. Several ways have been reported to evaluate end-inspiratory inflation and corresponding safety limits.
Indices of high distending pressures at end-inspiration and thresholds associated with increased risk of VILI and mortality are:

1. Inspiratory plateau pressure equal or above 30cmH_2O or above: inspiratory plateau pressure, measured after an end-inspiratory hold, is an indicator of end-inspiratory inflation. A threshold of 30cmH_2O has been shown in several studies to be associated with VILI and increased mortality
2. Transpulmonary end-inspiratory pressure of = or >24cmH_2O: measurement of the transpulmonary pressure requires using an esophageal catheter. The $P_{Lend\text{-}insp}$ can be calculated as:

$$P_Lend - insp = Ppl - P_ESend - insp$$

or

$$P_Lend - insp = Ppl * (EL/ERS)$$

where EL and ERS represent the elastance of the lung and the respiratory system respectively.

The E_L can be measured as:

$$E_L = \frac{(Ppl - P_E Send - insp) - (PEEP_t ot - P_E Send - exp)}{VT}$$

This 'elastance-derived' transpulmonary pressure is a good surrogate of the distending pressures of the non-dependent lung regions which are often at higher risk of overdistention injury.

1. Driving pressure = or >14cmH_2O: the driving pressure 'adjusts' the delivered VT to the respiratory system compliance (ΔP = VT/Crs), and thus better represents tidal inflation in relation to the aerated lung volume. A recent meta-analysis found that ΔP was the strongest predictor of outcome among the various ventilator variables and proposed a safe threshold of ≤14cmH_2O.

Other indices of high distending pressures at end-inspiration include the stress index calculated from the slope of inspiratory pressure waveform (Figure 11) and the inspiratory mechanical power (Figure 12). This remains to be validated in large clinical trials. Similarly, the choice of tidal volume is a compromise between achieving blood gas targets and protecting the lung from VILI.

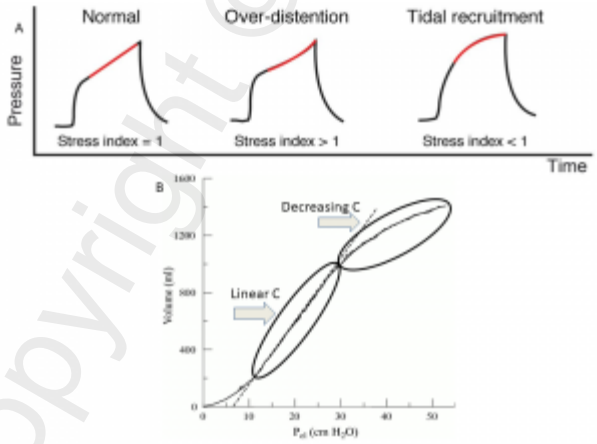

Figure 11:The stress index. Respiratory Mechanics in Mechanically Ventilated Patients RESPIRATORY CARE • NOVEMBER 2014 VOL 59 NO 11

Figure 11: The stress index mathematically describes the slope of the pressure-time curve during volume control (VC) ventilation with constant flow. If, during tidal inflation, compliance remains constant (linear part of P-V curve, B,) an upward concavity will be observed, which corresponds to a stress index >1. If compliance progressively increases, suggesting recruitment during tidal inflation, a downward concavity will appear,

corresponding to a stress index <1. When an upward concavity is observed in the pressure waveform of a patient ventilated in VC, hyperinflation should be suspected, and tidal volume and/or PEEP adjusted to limit it.

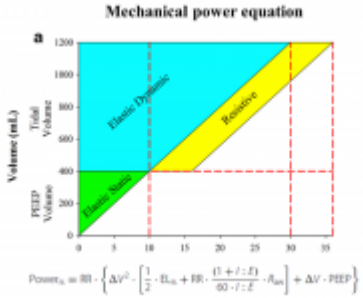

Figure 12:Ventilator-related causes of lung injury. Intensive Care Medicine, October 2016, Volume 42, Issue 10, pp 1567-1575

Figure 12: This graph is composed of a large triangle (green plus blue), to which a parallelogram (Resistive, yellow) is added on the right. The left side of the big triangle represents the total volume (i.e. TV + PEEP volume), while the upper side represents the plateau pressure. The slope of the hypotenuse represents the compliance of the system. The area of this large triangle is the total elastic energy present at plateau pressure. This total elastic energy has two components: the smaller triangle (Elastic Static, green), which represents the energy delivered just once when PEEP is applied, and the larger rectangle trapezoid (Elastic Dynamic, blue), whose area represent the elastic energy delivered at each tidal breath. Note that the rectangle trapezoid results from the sum of two components (both blue): a rectangle, whose area is TV × PEEP (third component of the power equation) and a triangle, whose area is TV × ΔPaw × 1/2, equal to ELrs × TV × 1/2 (first component of the power equation). The third component of the power equation is the area described by the Resistive parallelogram (yellow), whose area is equal to (Ppeak − Pplat) × TV. From Gattinoni et al Intensive care medicine 2016;10:1567-1575

In patients with obstructive lung disease, tidal volume is limited by the volume that can be exhaled in every breath, so the main aim when optimising the tidal volume is to minimise dynamic hyperinflation. Thus, the optimisation of VT relies on the measurement of PEEPi and the ventilatory strategy relies on limiting VT and increasing expiratory time (see Figure 9, and ACE Course on COPD) to decrease dynamic hyperinflation. The hyperinflated alveoli may compress their adjunct capillaries (West zone 1) and behave as dead space. Therefore, in patients with obstructive lung disease, if a decrease in VT results in reduction of hyperinflation and dead space, it may result in a lower $PaCO_2$ for the same of even lower minute ventilation (see Figure 10).

4. 2. 5. Respiratory rate, Inspiratory/expiratory ratio, inspiratory plateau

The choice of respiratory rate (RR) complements the choice of VT with the aim of reaching a minute ventilation which will achieve a target PCO_2. The choice of RR also includes the choice of inspiratory to expiratory ratio (I:E) as well as the addition (or not) of inspiratory plateau. In patients ventilated in controlled modes there is no need to try to match the mechanical to the neural respiratory rate or inspiratory time as these modes are used in patients lacking spontaneous breathing activity.

As several constraints tend to limit VT, there is usually a need for a RR higher than the normal 12-18 br/min (for adults). Clearly, RR cannot be increased indefinitely as sufficient time for passive expiration has to be allowed otherwise dynamic hyperinflation will develop. The time required for passive expiration is proportional to the respiratory system resistance and compliance (time constant, τ=R*C). Therefore, patients with ARDS who have low resistance and compliance require short expiratory time while patients with obstructive lung disease who have high resistance and normal compliance require prolonged expiratory time. Observation of the expiratory flow waveform provides information on the adequacy of expiratory time (Figure 9). Manipulation of expiratory time can be achieved not only through changes in RR but also in I:E ratio (Figure 13). The normal I:E ratio is between 1:1.5 and1:2 but in patients with obstructive lung disease longer expiratory times with ratios 1:3 – 1:6 are prefered to allow lung emptying (see module on COPD).

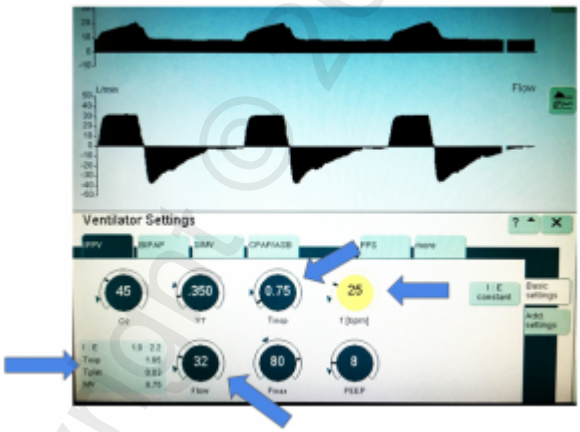

Figure 13:Inspiratory to Expiratory ratio, Plateau time, RR, Inspiratory Flow. Mechanical Ventilation module, ESICM Academy, 2018

Figure 13: In volume control mode I:E ratio, Plateau time, RR, Flow and VT are interconnected by their mathematical relationship and not dependent on the patient.

A setting of RR of 25 br/min means that each breath will last Ttot= 60/25 =2.4sec.

The user may choose an inspiratory time (for example 0.75sec) which will result in an expiratory time of Te = Ttot-Ti = 2.4 - 0.75 = 1.65sec and an I:E ratio of 0.75:1.65 = 1:2.2.

If the user would like to increase expiratory time, and depending on the type of ventilator, either inspiratory time or I:E ratio has to be modified accordingly. An inspiratory plateau time increases mean intrathoracic pressure and acts as a second, higher level, of PEEP that helps improve oxygenation. The addition of inspiratory plateau time could benefit patients with ARDS, but should be avoided in patients with obstructive lung diseases

where the aim is to provide maximum expiratory time. Again, depending on the ventilator brand, the inspiratory plateau is set as an absolute time or as a percent of inspiratory time. In this case, flow is computed based on the set total inspiratory time and volume. In some ventilators the operator chooses the inspiratory time, tidal volume and inspiratory flow. To achieve an inspiratory plateau, the chosen flow has to deliver the set tidal at a shorter time than the set inspiratory time. Luckily in all ventilator brands these calculations are presented on the ventilator setup screen, so the user does not have to perform them manually.

The addition of an inspiratory plateau - that is time with the lungs inflated at tidal volume- will provide additional time of high intrathoracic pressure. This can be seen as a higher level of PEEP. Thus, an inspiratory plateau would be desired to improve oxygenation. On the other hand, if flow limitation is the main problem then an inspiratory plateau would necessitate a decrease in expiratory time for the same RR which would compromise lung emptying. Furthermore, the inspiratory plateau increases mean airway/intrathoracic pressure affects hemodynamics just as high PEEP does.

In patients ventilated in pressure control mode, the inspiratory time will determine the tidal volume for a given inspiratory pressure setting as shown in Figure 12. Therefore, in patients ventilated in a pressure control mode, a change in tidal volume can be made by changing either inspiratory pressure or time. A prolongation of the time the alveoli remain inflated to the tidal volume before expiration in pressure control - like the inspiratory plateau in VC - can be implemented by selecting an inspiratory time to achieve conditions of zero flow at the end of inspiration.

Note

at end-inspiration the plateau and driving pressure (Ppl-PEEP) will be the same for the same tidal volume whether the patient is ventilated in volume or pressure control mode. This is determined by respiratory system compliance:

$$CRS = \frac{VT}{P_{pl} - PEEP}$$

In text References

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(Pham, Brochard and Slutsky. 2017; Vaporidi et al. 2020; Levine et al. 2008; Henderson et al. 2017; Beitler et al. 2019; Palmer et al. 2019; van den Boom et al. 2020; Grieco, Chen and Brochard 2017; Yoshida et al. 2018)

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4. 3. Assisted modes of ventilation

As discussed above, when a patient's effort triggers the delivery of positive pressure, the mode is termed 'assisted.' The choice of ventilating a patient in an assisted mode implies that the patient is able to trigger the ventilator at an 'acceptable' rate, but, the pressure

generated by the patient's respiratory muscles is insufficient to maintain adequate ventilation to achieve the target PCO_2. The ventilator is therefore needed to contribute to the work of breathing.

There a variety of modes of delivery of positive pressure after triggering. The modes of assisted ventilation include:

- Pressure support: constant pressure is provided during inspiration. The level of assist is constant and not related to the patient's effort. The delivered volume depends on the level of assist, patient's effort, and total respiratory system compliance (Figure 1).
- Volume support: a pre-set volume is provided after triggering. The level of assist decreases with increasing the patient's effort. The delivered volume is constant and does not depend on the patient's effort
- PAV and NAVA: a pressure is delivered, proportional to the patient's effort or diaphragmatic activity, respectively. Both the level of assist and the delivered volume increase with increasing patient effort (Figure 2, Figure 3).

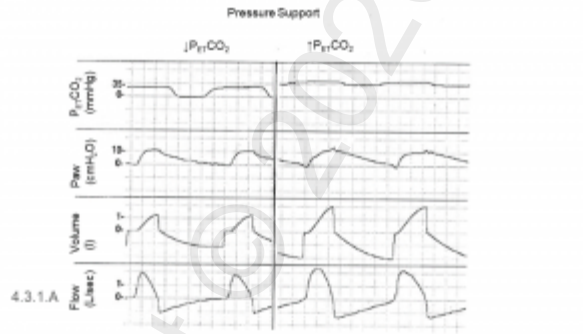

Figure 1: Assisted modes of ventilation – Level of assist in relation to patient's effort – In Pressure Support.

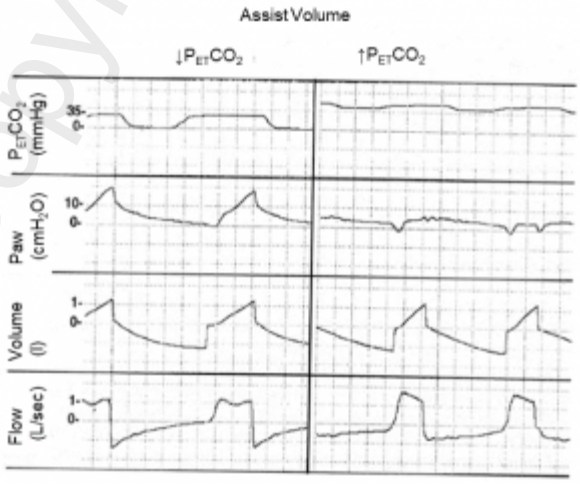

Figure 2: Assisted modes of ventilation – Level of assist in relation to patient's effort – In Assist-Volume.

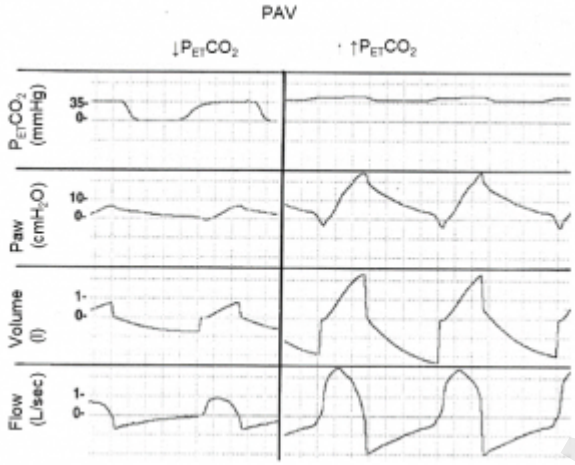

Figure 3: Assisted modes of ventilation – Level of assist in relation to patient's effort – In Proportional-assist Ventilation.

Figure 1, Figure 2, Figure 3: Response of ventilator-provided support in experimentally increased patient effort an increase in $PETCO_2$. In Pressure Support (Figure 1) assist level remains unchanged at the set level of pressure. In Assist-Volume (Figure 2) the level of assist decreases so that the delivered volume remains unchanged. In Proportional-assist ventilation ((Figure 3), the level of assist increases proportionally to the patient's effort. From Mitrouska J, Xirouchaki N, Patakas D, Siafakas N, Georgopoulos D (1999) Effects of chemical feedback on respiratory motor and ventilatory output during different modes of assisted mechanical ventilation. Eur Respir J 13:873-882

In all assisted modes, the necessary ventilator settings required for the proper function of the ventilator include:

- Inspiratory trigger mode and corresponding setting
- Mode and level of assist
- Pressurisation rate or rising time (in pressure support mode)
- Expiratory trigger mode and corresponding setting
- PEEP and FiO_2

Note

During assisted ventilation, the target is not only to achieve adequate gas exchange, but also to protect the lung from the excessive stretch, to maintain adequate but not excessive diaphragm contraction during inspiration, and to match the mechanical to the neural timing of the breath. Therefore, setting the ventilator in assisted modes is more challenging than in controlled modes, because the pressure generated by the patient's respiratory muscles is not (routinely) measured, and the interactions between the patient's control of breathing system and the ventilator-delivered breaths can be very complex.

Note

Although VILI has only been studied during controlled mechanical ventilation, there is no reason to believe that high distending pressures are not just as harmful during assisted ventilation. Thus, it appears reasonable at the moment to avoid high tidal volumes and distending pressures during assisted ventilation.

Note

In proportional ventilation, the assist provided by the ventilator is proportional to the inspiratory effort of the patient. The ventilator follows the patient's effort and amplifies it to a degree determined by the physician. Two proportional ventilator modes are currently available, the proportional assist ventilation (PAV) and the Neurally Adjusted Ventilatory Assist (NAVA).

4. 3. 1. Pressure Support

Pressure support is the most commonly used mode of assisted ventilation in clinical practice. With this mode, the ventilator, once triggered, provides a pre-set level of constant pressure. The level of assist is independent of the patient's effort. This pressure (Pvent) is added to the patient's muscle pressure (Pmus) and as a result, the patient's effort is augmented. Thus, the patient's muscles and the ventilator can be considered as pressure generators arranged in series where Ptot = Pvent + Pmus. Similarly to Pressure Control mode, during inspiration the equation of motion indicates that

$$P_{tot} = P_{vent} + P_{mus}$$

Similarly to Pressure Control mode, during inspiration the equation of motion indicates that

$$P_{toti} = P_{vent} + P_{mus(i)=V'*Ri+VTi*Ei}$$

Therefore the resulting tidal volume and inspiratory flow-time profile depend on 1) Pmus, 2) Pvent and 3) mechanical properties (i.e.Rrs and Ers) of respiratory system. The basic waveforms during Pressure Support are shown in Figure 4.

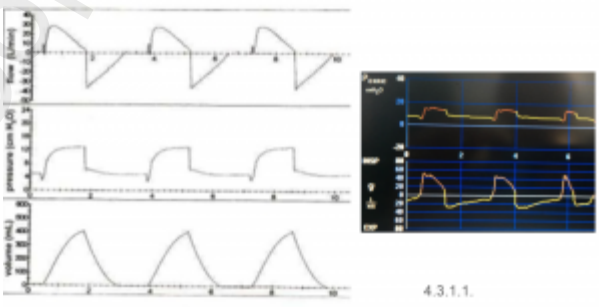

Figure 4: Waveforms in Pressure Support Ventilation. Mechanical Ventilation module, ESICM Academy, 2018

Figure 4: Pressure, Flow and volume waveforms during Pressure Support: note that the shape of waveforms is similar to pressure control ventilation, but because Pmus differs from breath to breath, the waveforms of each breath also have small differences.

Inspiratory trigger

Flow or Pressure triggering requires the patient to decrease the flow or pressure, respectively in the ventilator circuit to the pre-set level. When pressure triggering is selected, a part of the patient's effort is 'consumed' or 'wasted' in decreasing circuit pressure to the set threshold before the ventilator inspiratory valve opens, and inspiratory flow begins. Flow triggering is thus preferred, and the usual setting is 2-3 l/min (See also ACE part III).

Problems during triggering phase

1. Triggering delay and Ineffective effort

At the beginning of a breath in mechanically ventilated patients with obstructive lung disease and dynamic hyperinflation, the inspiratory muscles start contracting at volumes above passive FRC where alveolar pressure is positive (PEEPi). In this case, in order to trigger the ventilator the patient must first counterbalance PEEPi in order to decrease alveolar pressure below external PEEPe. Therefore, a portion of Pmus is dissipated to counteract PEEPi (elastic threshold load) and as a consequence, there is a delay between the beginning of inspiratory effort and the triggering. In some cases the inspiratory effort of the patients is not able to counterbalance PEEPi resulting in the inability to trigger the ventilator (ineffective effort). Ineffective efforts may occur in the absence of dynamic hyperinflation in patients with severe respiratory muscle weakness. Triggering delay and ineffective efforts can be best detected by recording esophageal pressure, but careful inspection of flow tracings may help identify ineffective efforts (Figure 5).

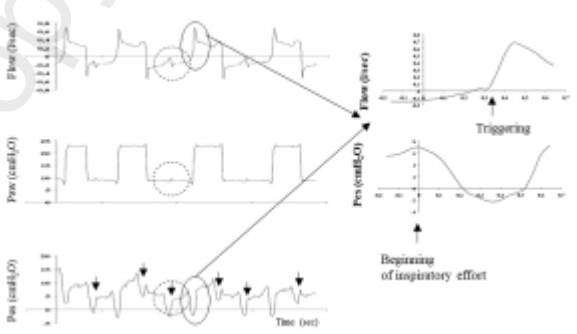

Figure 5:Triggering delay and ineffective effort

Figure 5: Flow, airway pressure and oesophageal pressure recordings from a patient ventilated in Pressure Support mode. Small arrows on the oesophageal pressure tracing indicate patient's inspiratory efforts. Note that several efforts (dotted circle) are not

followed by inspiratory flow and increase in airway pressure (ineffective efforts). Note also the delay between the initiation of the patient's effort and the initiation of mechanical breath (ovals, and magnified tracing on the right).Georgopoulos D, Prinianakis G, Kondili E. Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies Intensive Care Med. 2006 Jan;32(1):34-47.

The strategies aiming to decrease the triggering delay and ineffective efforts are 1) measures that decrease the magnitude of dynamic hyperinflation (decrease tidal volume by decreasing pressure support or decrease expiratory resistance by bronchodilators), 2) interventions which increase Pmus during the triggering phase (decrease sedation), 3) application of external PEEP and 4) decrease the threshold for triggering and/or use flow triggering. (See table 1)

Table 1: Different forms of patient-ventilator dyssynchrony. ESICM Academy 2018.

Table 1: Different forms of patient-ventilator dyssynchrony, during triggering phase ,their predisposing factors, and the possible interventions for eliminating or reducing them.

Abbreviations:

- DH: Dynamic Hyperinflation
- PEEP: Positive –end-expiratory Pressure
- PEEPi: intrinsic Positive –end-expiratory Pressure
- PS: Pressure support
- V'th Flow threshold for cycling off
- TIM : mechanical inspiratory time
- TIN:neural inspiratory time
- Paw: Airway pressure

Note

Flow distortion due to cardiac oscillation might be confused with ineffective efforts, particularly if the stroke volume of the patient is relatively high. The short duration (<0.3 sec) and the rapid frequency (close to heart rate) of flow distortion suggest cardiac oscillation rather than ineffective efforts.

Auto-triggering

Auto triggering refers to the phenomenon whereby the ventilator is triggered in the absence of patient effort (Figure 6). This phenomenon may be caused by a random 'noise' in the circuit, like circuit leaks, presence of water, or cardiogenic oscillators combined with a low threshold for triggering. Hiccoughs may also trigger the ventilator. Auto-triggering may occur with any triggering mode when zero end-expiratory flow remains for some time before the next inspiration, usually when respiratory drive and respiratory system time constant are low. Interventions to manage auto-triggering include correction of circuit issues if present and increase in triggering sensitivity (mainly for cardiogenic oscillation-trigger). Hiccoughs usually create significant intrathoracic pressure swings which cannot be managed by increasing triggering sensitivity, so only pharmacological interventions are helpful.

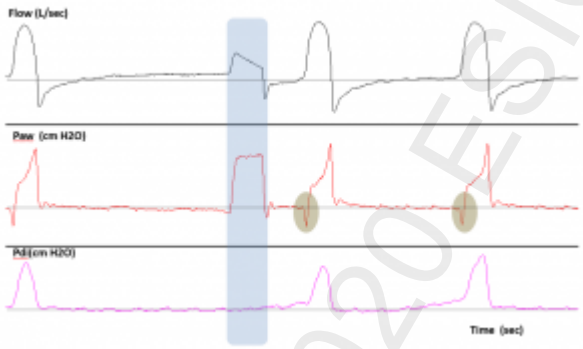

Figure 6: Autotriggering. ESICM Academy 2018.

Figure 6: Autotriggering. Airway pressure (Paw), flow and diaphragmaticl pressure (Pdi) curves of a patient ventilated on Pressure Support Ventilation are illustrated. As indicated by the absence of Pdi increase, there is no inspiratory effort before the second mechanical breath (autotriggered breath, see blue shaded area). We can observe that, in comparison to patient triggered breaths, where a decrease in Paw is observed before the start of mechanical inflation (grey shaded areas), there is no distortion in the Paw- (no decrease in Paw) and flow-time curve in the autotriggered breath. Moreover, the shape of the inspiratory flow-time curve is different compared to that of patient-triggered breaths. Notice the absence of dynamic hyperinflation in this patient (expiratory flow returns to zero after each breath).

Setting the Level of Assist in Pressure Support

The ideal level of assist is such that the patient's needs for ventilation are satisfied while his/her inspiratory muscles are active during inspiration, but not excessively, to prevent distress and fatigue. The choice of assist level (in cmH_2O of pressure) will be based on the derived ventilatory variables such as VT and resulting VE, and the clinical evaluation of the patient's effort and comfort. This level is adjusted by trial and error. As the level of assist is stable during pressure support ventilation, the ventilator cannot adapt to changing the patient's needs for ventilation. This is why over- or under- assist may occur. In the case of under-assist, the compensatory mechanisms of the patient's control of the

breathing system will lead to an increase in muscle pressure and/or respiratory rate. When this is insufficient, signs of respiratory distress and/or hypercapnia will develop (Figure 7). In the case of over-assist, the patient will relax the respiratory muscles after triggering. Recent studies indicate that high assist, which can lead to complete respiratory muscle relaxation after triggering, may induce diaphragmatic disuse atrophy (Figure 8). In patients with obstructive lung disease, high levels of assist resulting in high tidal volume may induce dynamic hyperinflation and ineffective efforts . Over-assist may also promote apneas and periodic breathing when the PaCO2 is below the patients' apneic threshold

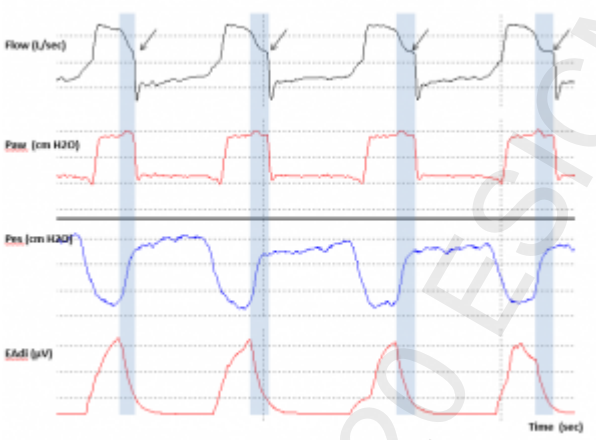

Figure 7: High assist in a patient ventilated with pressure support ventilation.. ESICM Academy 2018.

Figure 7: High assist in a patient ventilated with pressure support ventilation. Observe the square shaped airway pressure (Paw) and the abrupt decrease in inspiratory flow to flow threshold for cycling off towards the end of inspiration (arrows). There is also a significant cycling off delay (blue shaded area), seen often at high assist levels. Esophageal pressure (Pes) and electrical activity of the diaphragm (EAdi) decrease rapidly but mechanical inflation continues. Importantly, expiratory muscles contract during the whole expiration.

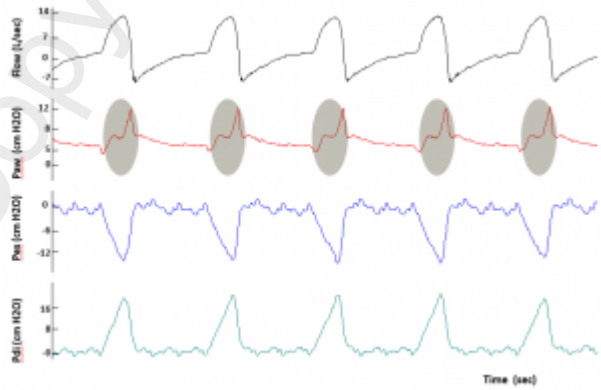

Figure 8: Flow, airway pressure (Paw), esophageal pressure (Pes) and transdiaphragmatic pressure (Pdi) waveforms in a patient ventilated with pressure support ventilation. ESICM Academy 2018.

Figure 8: Flow, airway pressure (Paw), esophageal pressure (Pes) and transdiaphragmatic pressure (Pdi) waveforms in a patient ventilated with pressure support ventilation. Observe the vigorous contraction of inspiratory muscles (Pdi increase) during the mechanical inspiration. The magnitude of this contraction causes a rounded inspiratory flow and a large decrease of Paw from the expected square-shaped form during inspiration. Rounded flow and Paw decrease are signs of low ventilator assist with respect to patients ventilator demands.

Rising time

With new-generation ventilators, the user may modify the time in which pressure delivered by the ventilator reaches the pre-set value (Figure 9). The equation of motion predicts that the rising time impacts the shape of the flow-time waveform. An instantaneous increase of pressure to the desired level is associated with a sharp increase in inspiratory flow. A slower increase in rising time eliminates the sharp increase in inspiratory flow. This is because when pressure reaches its final value the opposing effect of elastic recoil (due to volume increase during the rising time) decreases the driving pressure (i.e. Paw+Pmus-Pel) for flow. Very low rising time may cause a round shape of the inspiratory flow graph. When patient's ventilatory demands are high, a high inspiratory flow is required at the beginning of the breath, and thus, the patient would benefit from a short rising time. In the presence of leaks (that cannot be corrected) lower inspiratory flows will reduce leaks, and thus, in such cases longer rising times would be preferred.

Note that a rounded shape in inspiratory flow is observed when the patient continues to increase his/her inspiratory muscle pressure during mechanical inspiration.

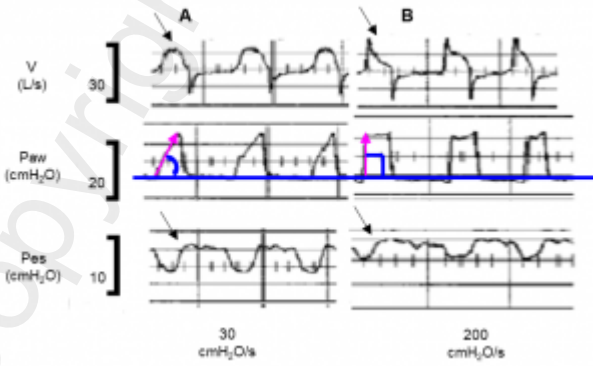

Figure 9:Rising time.ESICM Academy 2018.

Figure 9: Flow, airway pressure and oesophageal pressure recordings from a patient ventilated in Pressure Support mode, with long (A) and short (B) rising time. A slow increase in rising time (smaller angle at pressure waveform) is associated with a rounded shape of inspiratory flow because when pressure reaches its final value the opposing effect of elastic recoil has increased. On the contrary an instant increase of pressure to set level (angle at pressure waveform close to 90^{o}) is associated with a sharp increase in

inspiratory flow.Georgopoulos D, Prinianakis G, Kondili E. Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies Intensive Care Med. 2006 Jan;32(1):34-47.

Expiratory trigger or Cycling off

The aim of the expiratory trigger setting is to match as closely as possible the mechanical inspiratory time to the neural inspiratory time. The most commonly used expiratory trigger, or cycling off criterion, is to determine the amount of decrease of inspiratory flow, reasoning that, when inspiratory effort declines, so does the inspiratory flow. This decrease in inspiratory flow is expressed as an absolute value or a percentage of the peak inspiratory flow. This threshold can be modified by the user, thus changing the duration of mechanical inspiration. It is important for the physician to recognise expiratory asynchrony during PS ventilation.

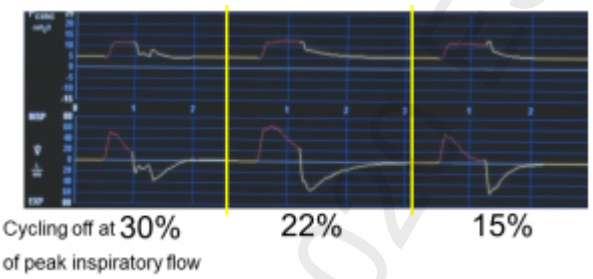

Figure 10:Cycling off. Mechanical Ventilation module, ESICM Academy, 2018

Figure 10: Pressure and flow waveforms during pressure support ventilation with cycling off set at different % of peak inspiratory flow. Note the progressive increase in mechanical inspiratory time as the set cycling off % is decreased.

Problems during cycling off

The decline of inspiratory flow depends on the shape and magnitude of the pressure generated by the patients' respiratory muscles, the pressure provided by the ventilator, and the respiratory system mechanics. It is therefore impossible for the clinician to estimate in advance the 'correct' value for the cycling off criterion to match the patient's neural timing of the breath. As a result the selected cycling off may result in termination of the mechanical breath either before (premature) or after (delayed) the end of the patient's neural breath. It is important for the clinician to understand this mismatch between the mechanical and neural timing of the breath by interpreting the ventilator waveforms.

1. Premature termination of mechanical inspiration

The opening of the exhalation valve is followed by reversal of flow from inspiratory to expiratory. Expiratory flow instantly achieves its highest value, determined by the elastic recoil pressure at end-inspiration, the airway pressure (i.e. PEEP) and the expiratory resistance (respiratory system + ventilator circuit). Thereafter, flow decreases

exponentially to zero following the decrease in elastic recoil pressure. If the patient continues to generate inspiratory pressure (negative pressure), the expiratory flow pattern will be affected, as shown in Figure 11. An abrupt change of the expiratory flow towards zero after the opening of the exhalation valve indicates that inspiratory muscles continue to contract after the end of mechanical inspiration. The contraction of the inspiratory muscles oposes lung emptying, and appears as decrease in expiratory flow. Relaxation of inspiratory muscles eliminates this opposing pressure and the expiratory flow returns to the shape and values determined by the elastic recoil pressure and resistive properties of the patient and expiratory circuit. Inspiratory effort may sometimes be strong enough to not only decrease expiratory flow to zero but also to reach the triggering threshold. In such cases one inspiratory effort triggers the ventilator twice, a phenomenon called ‘double triggering’ (Figure 12). In pressure support the duration of the second breath is usually relatively short because the inflation of the lung stars at lung volumes well above the passive FRC and as a result the driving pressure for inspiratory flow is relatively low. On the contrary, in assist-volume the ventilator once triggered delivers the pre-set volume, which adds to the remaining volume from the previous breath resulting in high distending pressures. The phenomenon of premature termination of mechanical inspiration can be observed when patient’s effort is relatively strong and prolonged, the time constant of the respiratory system is short, the level of pressure support is low, and the cycling off set at a relatively high flow threshold. Therefore, presence of premature cycling off may help the clinician recognize that the patient’s respiratory drive is high, the ventilatory demands are not met, and the respiratory system compliance is low (short time constant), and thus the corrective actions should address all these problems and not only the duration of mechanical inspiration. Increasing pressure support and decreasing cycling off flow threshold will prolong inspiratory time and may resolve premature cycling off. Yet, in some patients, the presence of high ventilatory demands and low lung compliance may indicate that the patient is at risk of self-inflicted lung injury and likely not ready for spontaneous breathing (See Table 2).

	Type of asynchrony	Definition	Causes	Ventilator Waveform characteristics	Suggested interventions
Cycling off phase	Delayed opening of expiratory valve	T_I/T_{TOT}	- Long time constant of the respiratory system (Obstructive lung disease) -High Assist level -ΔΗ -Low V'rb	-A small spike (↑Paw) in Paw near the end of breath. - Abrupt decrease in inspiratory flow followed by an exponential decline toward the end of mechanical inspiration	Increase V'rb, -Decrease the PS level -Decrease the rise time -Measures to decrease DR
	Premature opening of expiratory valve	T_I/T_{TOT}	-Short time constant (restrictive lung disease, ARDS) -High V'rb -Low PS level	-Zero or low inspiratory flow for short time instantaneously after flow decreases to PEEP level -Convex pattern of expiratory flow	-Decrease V'rb, -Increase the PS level -Decrease rising time
	Double triggering	One inspiratory effort triggers the ventilator twice	-Strong inspiratory efforts		Decrease#TA, -Increase the PS level -Decrease rise time -Decrease ventilation demands

Table 2: Different forms of patient-ventilator dyssynchrony, during cycling off phase.ESICM Academy, 2018.

Table 2: Different forms of patient-ventilator dyssynchrony, during cycling off phase ,their predisposing factors, and the possible interventions for eliminating or reducing them.

Abbreviations:

- DH: Dynamic Hyperinflation
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- PS: Pressure support
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- TIM : mechanical inspiratory time
- TIN:neural inspiratory time
- Paw: Airway pressure

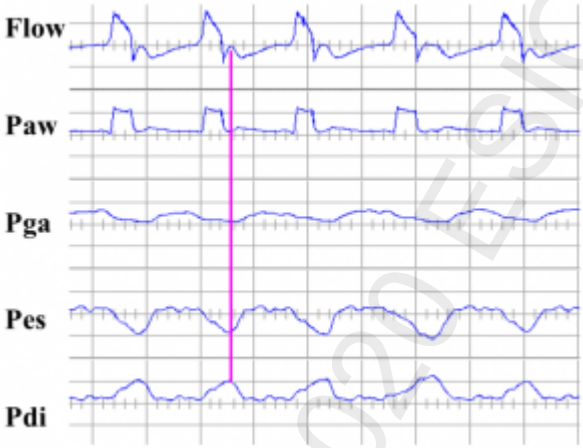

Figure 11:Cycling off - premature opening of exhalation valve

Figure 11: Flow, airway pressure, gastric, oesophageal and transdiaphragmatic pressure recordings from a patient ventilated in Pressure Support mode. Inspiratory muscle pressure continues after the cycling off criterion is reached and the mechanical inspiration is terminated, resulting in distortion of expiratory flowGeorgopoulos D, Prinianakis G, Kondili E. Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies Intensive Care Med. 2006 Jan;32(1):34-47.

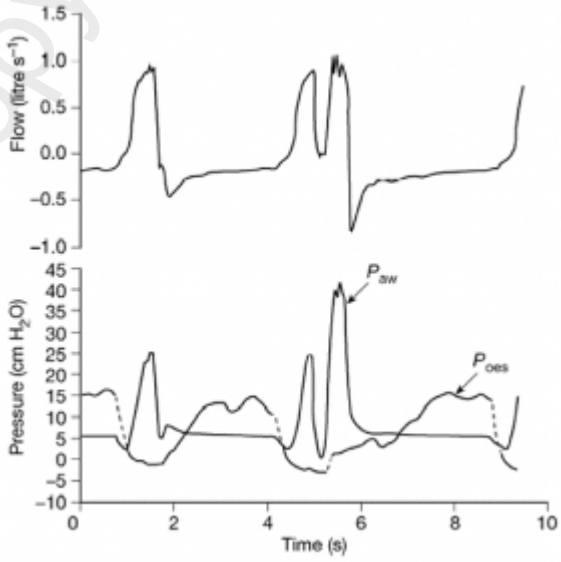

Figure 12:Double triggering. Mechanical Ventilation module, ESICM Academy, 2018

Figure 12: Flow, airway pressure and oesophageal pressure recordings from a patient ventilated in Pressure Support mode. A prolonged inspiratory effort decreases flow and triggers the ventilator twice in the same breath.

2. Delayed opening of exhalation valve

Identification of the delayed opening of the exhalation valve in relation to neural inspiration using the basic waveform is difficult, particularly if the patient does not use expiratory muscles. Relaxation of inspiratory muscles well before the end of mechanical inspiration results in pressure, flow and volume waveforms similar to those obtained with passive inflation, with a rather sharp decrease in inspiratory flow followed by an exponential decline (Figure 13). Delayed opening of the exhalation valve is usually caused by excessive support (low respiratory drive), long time constant of the respiratory system of the patient and cycling off set at a relatively low percentage of peak flow. Management of delayed cycling off includes decreasing the level of support and increasing the cycling off flow threshold See also table 2.

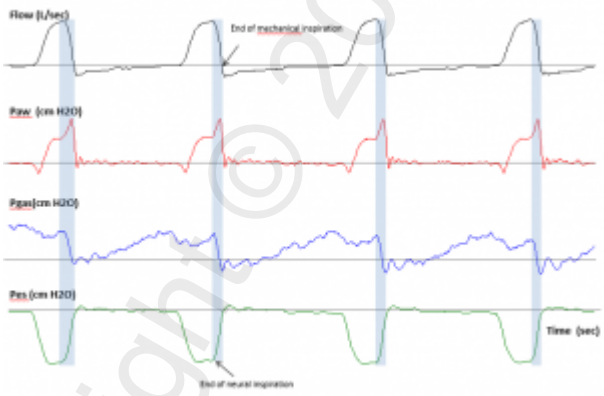

Figure 13:Delayed opening of exhalation valve. ESICM Academy, 2018.

Figure 13: Flow, airway pressure (Paw), gastric pressure (Pgas) and esophageal pressure (Pes) waveforms in a patient ventilated with Pressure Support Ventilation. There is a significant time delay (blue shaded area) between the end of neural inspiration, recognized by a rapid increase in esophageal pressure, and the end of mechanical inspiration, signified by the termination of inspiratory flow (inspiratory flow equals zero). Observe the rapid increase of Paw towards the end of mechanical inspiration, indicating inspiratory muscles relaxation.

In text References

(Georgopoulos, Prinianakis and Kondili. 2006; Kondili et al. 2009; Kondili et al. 2006; Zambon et al. 2016; Hess 2005; Meza et al. 1998; Vaporidi et al. 2020; Bertoni, Spadaro and Goligher. 2020)

4. 3. 2. Proportional Assist Ventilation (PAV)

Proportional Assist Ventilation (PAV) delivers assistance in proportion to the patient's respiratory drive and mechanical obstacles to the inspiratory breath (i.e. resistance and elastance).

Triggering in PAV+ is identical to conventional assisted ventilator modes. After triggering, the ventilator monitors inspiratory flow and volume and generates pressure which is, at any time during inspiration, the sum of the instantaneous flow and volume multiplied by a predetermined gain factor (% assist).

$$Paw = (V' * Rrs + VT * Ers)$$

where Paw is instantaneous airway pressure, V' is instantaneous inspiratory flow, VT is instantaneous lung volume above end-expiratory level, Rrs the respiratory system resistance and Ers the respiratory system elastance. The % percentage of offloading is set by the caregiver. The maximum % assist is 95% of the measured values of elastance and resistance. The pressure muscles need to develop (Pmus) is reduced by the % assist. When assist is set to zero, breathing is unassisted and Pmus undertakes the whole work of inspiration. When assist is set to 50%, half of the inspiratory work is performed by the patient and the other half by the ventilator. As Pmus declines towards the end of neural inspiration, inspiratory flow gradually decreases and when it reaches a preselected threshold, the ventilator terminates pressure generation.

PAV+ has utilises software that allows automatic and noninvasive measurement of respiratory system mechanics. At random intervals of 4 to 7 breaths, the ventilator applies a 300 msec pause maneuver at the end-inspiration (Figure 34).

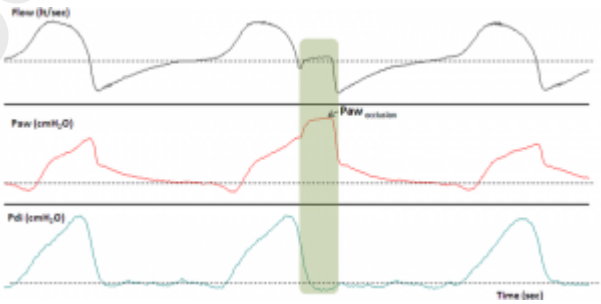

Figure 14:Waveforms in PAV+ ventilation. Mechanical Ventilation module, ESICM Academy, 2018

Figure 14: Flow, Airway Pressure (Paw) and transdiaphragmatic pressure (Pdi) vs. time curves in a patient ventilated with PAV+. Notice an end-inspiratory pause maneuver during the second breath (shaded area). The maneuver is performed near the end of the neural breath when Pdi declines to zero and, therefore, there is no patient effort. Flow is zero, so that respiratory system resistance is zero. Paw measured at the end of the maneuver is the Paw occlusion pressure used to calculate respiratory system compliance.

Airway pressure at the end of the occlusion (Pawocclusion) is measured and Ers and compliance (Crs=1/Ers) are calculated as follows:

$$Ers = \frac{(Pawocclusion - PEEP)}{VT}$$

and

$$Crs = \frac{VT}{(Pawocclusion - PEEP)}$$

where PEEP is positive end–expiratory airway pressure. In the presence of PEEPi (dynamic hyperinflation), the calculated value of Ers overestimates respiratory system elastance (and the calculated Crs underestimates respiratory system compliance).
The measurement of Rrs is performed during the expiration that follows the pause maneuver. Assuming that the expiratory flow early in exhalation is driven by the elastic recoil pressure (i.e. alveolar pressure, Palv), the software identifies three points on the expiratory flow-time curve corresponding to peak flow and 5 msec and 10 msec later. At these points Palv and total expiratory resistance (RTOT) are calculated as follows:

$$Palv = Pawocclusion - \Delta V x Ers$$

$$RTOT = \frac{(Palv - Paw)}{V'}$$

where ΔV is the exhaled volume up to the point of interest and V’ and Paw are the corresponding expiratory flow and airway pressure, respectively. The values of RTOT at these points are averaged and an estimate of RTOT is obtained. RTOT is the sum of the flow-dependent resistance of the endotracheal tube (Rtube) and that of the respiratory system (RrsPAV). Rtube is calculated using the following equation:

$$Rtube = a + bV'$$

where a and b are constants, depending on tube length and diameter, estimated using in vitro testing. RrsPAV is derived by subtraction of Rtube from RTOT.

Advantages and limitations of PAV+

PAV+ may be particularly helpful in several conditions but there are also contraindications to its use (Table 3).

The main advantages of PAV+ are:

- Improved patient-ventilator synchronisation as ventilator assist follows the patient's effort both in terms of timing and ventilator support necessary.
- Continuous measurement and display of respiratory system mechanics.
- Less risk of lung overdistension, since this mode does not interfere with the operation of lung protective innate reflexes (i.e. Herring-Breuer).

Conditions that may result in inappropriate assist level with PAV+ are:

- The presence of a large difference between inspiratory and expiratory resistance (i.e. patients with obstructive lung disease). PAV+ measures expiratory resistance assuming that the difference between inspiratory and expiratory resistance is small. If the difference is large, the calculated Rrs is inaccurate and so is the assist level.
- Conditions that depress the respiratory centre (i.e. central nervous system diseases, sedatives, metabolic or respiratory alkalosis etc), affect respiratory muscle output (polyneuropathy, muscle fatigue, Guillain Barre, myasthenia gravis, muscle relaxing drugs etc) or reduce the magnitude of the force generated by the diaphragm (e.g. in hyperinflation). As PAV+ follows patient effort, there is a risk of hypoventilation in the above conditions.
- Excessive assist (runaway). Runaway occurs when % assist is greater than the sum of Ers and Rrs at a particular point during inflation. As a result, the ventilator continues to deliver volume despite the fact that the patient has terminated his/her inspiratory effort. The volume will continue to increase until an alarm limit (pressure or volume) is activated, the compliance of the respiratory system is decreased because the respiratory system approaches total lung capacity or when expiratory muscles are recruited by the patient. With PAV+, runaway occurs rarely and only when the % of assist approaches 90%.
- Dynamic hyperinflation. Following triggering, pressure delivery in PAV+ is driven by patient effort. In the presence of dynamic hyperinflation, triggering delay will reduce the fraction of the patient's effort that is being assisted. In addition, the calculated values of Crs and RTOT underestimate the actual values if PEEPi is present.
- The presence of leaks. In this case, the ventilator misinterprets the flow and volume escaping the circuit as a continuous patient effort and extends its assist delivery into exhalation. The effect of a large bronchopleural fistula is similar.

Conditions where PAV+ is particularly beneficial	Conditions where PAV+ might be problematic	Conditions where PAV+ is contraindicated
Considerable patient-ventilator asynchrony	Dynamic hyperinflation	Deep sedation, central apneas, CNS deficits
Monitoring of lung mechanics helpful	Severe neuromuscular disease	Muscle paralysis
High or variable ventilator demand		Marked hemodynamic compromise
Concern for lung over-distension		Bronchopleural fistula
Difficult to wean patients		
Periodic breathing		

Table 3:Applicability of PAV+ in different clinical conditions. Mechanical Ventilation module, ESICM Academy, 2018

Table 3: In the left column the physician should specifically prefer PAV+ or switch other assisted modes to PAV+. In the middle column PAV+ is not contraindicated and should be tried but specific supervision of patients is warranted.

Setting the ventilator in PAV+

The following algorithm to set PAV+ has been proposed by Xirouchaki et al in a randomised controlled study of 208 critically ill patients:

- Correct ideal body weight, endotracheal tube size and maximum airway pressure (40 cmH2O) must be set. Setting airway pressure limit is important, since it will protect the lungs from overdistention.
- Triggering, initial PEEP and fraction of inspired oxygen (FIO2) are set using common criteria. PEEP can be titrated according to changes in compliance: PEEP should be increased as long as compliance improves due to lung recruitment. In the absence of further Crs change, PEEP escalation should be stopped.
- The initial % level of assist must be sufficiently high to support the patient but not too high to cause over-assist and runaway. Starting with a 70% assist is a reasonable approach. If there is distress at 70% assist, possible reasons are the presence of delayed triggering due to dynamic hyperinflation or very low compliance. PEEP increase may improve distress in both conditions. If distress at 70% assist continues, % assist can be increased in steps of 5% up to 90% provided that there is no runaway phenomena. A high respiratory rate or a low VT (i.e. 3-4 ml/Kg) do not necessitate action if there are no other signs of respiratory distress. Weaning with gradual decrease of % assist as long as the patient shows no signs of distress and blood gas targets are met follows the same rationale as in other modes of assisted ventilation.
- When changing from a conventional mode to PAV+, we may observe: no change in breathing pattern, rapid shallow breathing (an indication of the presence of significant number of ineffective efforts on previous modes) or apnoea (an indication of over-assist on previous modes). Waiting a few minutes is important to see how the breathing pattern evolves before deciding on the next step.

Note

An increase in PEEPi from 0.9 cm H_2 O to 3.5 cmH_2 O in PAV+ has been shown to decrease the portion of supported inspiratory effort from 86% to 66%.

In text References

(Akoumianaki, Kondili and Georgopoulos 2012; Kondili et al. 2006; Xirouchaki et al. 2008)

4. 3. 3. Neurally Adjusted Ventilatory Assist (NAVA)

Neurally Adjusted Ventilatory Assist (NAVA) is based on the continuous recording of the electrical activity of the diaphragm (EAdi). The EAdi signal is proportional to the intensity of the diaphragmatic contraction. The more the diaphragm contracts, the greater the level of support delivered by the ventilator. The EAdi signal is obtained through a dedicated feeding tube with a mounted distal array of multiple electrodes. This signal is processed to provide the highest possible quality of signal (Figure 15). An EAdi increase above a predetermined value triggers the opening of the inspiratory valve. The ventilator then provides pressure (Paw) which is an amplification of the spontaneous EAdi:

$$Paw = NAV\,Alevel * EAdi$$

where Paw is the pressure provided by the ventilator in cmH_2O, NAVA level (in cmH2O/μV) is the amplification factor of EAdi and EAdi the electrical activity of the diaphragm in μVolt. When EAdi decreases by a percentage in relation to its maximum value, the inspiratory phase is terminated and the exhalation valve opens. The triggering and cycling off criteria as well as the NAVA level are determined by the physician (Figure 16).
For safety reasons, the triggering of the ventilator in NAVA follows a ‘first come first serve’ approach. This means that the caregiver, besides EAdi triggering, determines a pneumatic (flow or pressure) triggering criterion, as in conventional assisted modes. The criterion that will be satisfied first (EAdi or pneumatic) will trigger the ventilator. Moreover, in the presence of a problem in the EAdi signal (noise, malfunction, removal of the catheter etc.), the ventilator will be automatically switched to pressure support ventilation with settings selected by the physician.

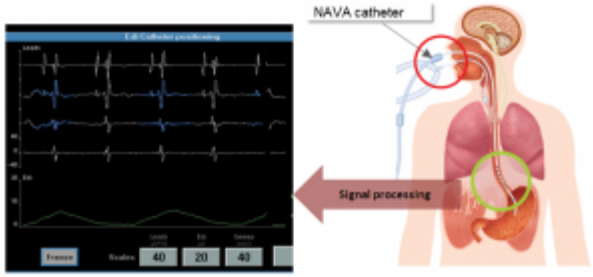

Figure 15:Recording of diaphragm electrical activity during NAVA. Mechanical Ventilation

module, ESICM Academy, 2018

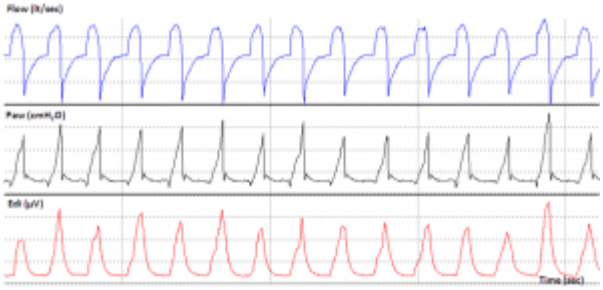

Figure 16:Flow, airway pressure (Paw) and diaphragmatic electrical activity (Edi) vs. time waveforms in a patient ventilated with NAVA. Mechanical Ventilation module, ESICM Academy, 2018

Setting the ventilator in NAVA

FiO_2 and PEEP settings in NAVA follow the same principles as in other ventilator modes. The EAdi inspiratory trigger is usually set to a default value of 0.5 µVolts, meaning that an EAdi increase of 0.5 µVolts above its minimum value will trigger the inspiratory phase. A 70% decrease in EAdi from its maximum value cycles-off the ventilator. The most challenging issue is the titration of the NAVA level. The NAVA level has units of cmH20/µV and the available range is between 0-15 $cmH_20/\mu V$. A NAVA level of 0 cmH20/µV is considered similar to CPAP. Several approaches have been proposed to adjust the NAVA level at the bedside:

- NAVA level can be set through the 'NAVA preview' function of the ventilator Servo-i screen. This function estimates the NAVA level required to obtain the same peak pressure as during pressure support ventilation.
- Brander et al described a two-phase response during NAVA level escalation: in the first phase, NAVA level escalation leads to Paw and VT increase. Above a that, any further increase will be associated with a relatively unchanged Paw and VT due to the activation of feedback control mechanisms. The ideal NAVA level is considered to be the inflection point from the first to the second phase.
- An alternative approach is to determine the EAdi during a spontaneously breathing trial (no ventilator assist). Then NAVA level can be titrated to decrease the EAdi recorded during the spontaneous breathing trial by 60%.

Irrespective of the initial NAVA level selected, NAVA level should be subsequently titrated according to patient comfort, signs of respiratory distress and observation of the flow, pressure and EAdi waveforms. If the support provided is too high, the nerve centres receive negative feedback leading to less support. This is detection by a difference in flow or pressure in the system from one cycle to the next. If the diaphragmatic contraction is

insufficient, positive feedback will cause a more powerful EAdi signal and thus more support. As the patient respiratory function improves, EAdi decreases at the same NAVA level and NAVA level can be then reduced in a stepwise manner.

In text References

(Brander et al. 2009; Rozé et al. 2011)

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4. 4. Modes of ventilation with combinations of triggering and pressurisation variables

In modern commercially available ICU ventilators there are over fifty different ‘modes’ of ventilation. These do not represent completely different ways of delivering positive pressure ventilation, but rather using several combinations of triggering/cycling off and pressurisation variables in the basic modes described above. Knowledge of the basic principles of ventilation modes allows the user to understand any such ‘new’ mode.

Several modes permit the combination of controlled and assisted breaths. In modern ventilators, all ‘control’ modes are ‘assist-control’. This means a triggering threshold is selected, and if the patient triggers the ventilator, the breath will be assisted in the same way the control breath is delivered. Spontaneous intermittent mandatory ventilation (SIMV) is similar to volume assist-control, but if and how (by pressure or volume) the spontaneous breaths will by supported is set separately by the user.

Bi-level ventilation modes allow patients to breath spontaneously during any phase of the ventilator cycle, as the ventilator switches at pre-set intervals from a low level of pressure (P-low) to a high level of pressure (P-high). Again, spontaneous breaths can be supported (pressure support) or not. Airway pressure release ventilation (APRV) is similar to Bi-level ventilation using an inverse I:E ratio.

In several modes, the user chooses a target minute ventilation and the modes to provide the assisted and the mandatory breaths. These can be any combination of pressure and volume controlled. The ventilator continuously calculates the delivered volume and estimates if mandatory breaths are required to achieve the set minute ventilation. A commonly used such mode is mandatory minute ventilation (MMV).

The choice of pressure as controller leads to a delivered volume that is dependent on the mechanical properties of the respiratory system which may vary. In several pressure control or support modes, a minimum ‘safe’ tidal volume is set. If this is not reached, the ventilator adjusts the pressure delivered to meet the set ‘safe’ tidal volume.

Finally, as artificial intelligence evolves, new ventilator software have become available. These have algorithms that continuously change ventilator settings (for example decrease/increase pressure support) after measuring the dependent variables of ventilation. The aim is to substitute the physician in selecting setting in well-described

situations. For example, the gradual decrease of pressure support during weaning. It is questionable at the moment whether a given patient will have a course that is predictable enough to allow ventilator management by these algorithms.

In text References

(Tobin and Alex. 1994; Chatburn and Mireles-Cabodevila. 2011)

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5. Weaning the patient from mechanical ventilation

Although often life-saving, mechanical ventilation is associated with several life-threatening complications. Accordingly, it is important to discontinue mechanical ventilation and extubate the patient at the earliest possible opportunity.

5. 1. Definitions

Weaning is defined as the entire process of liberating the patient from mechanical support and the endotracheal tube.

Weaning failure is defined as the failure to pass spontaneous-breathing trial or the need for reintubation or NIV support within 48 hours (for some authors within 72 hours) following extubation.

Extubation failure is defined as the need for reintubation

The majority of patients can be successfully extubated after one spontaneous breathing trial (SBT) and are categorised as having undergone ‘simple weaning’. Patients who can be successfully extubated after the second or third SBT within seven days from the first attempt are categorised as having undergone ‘difficult weaning’. Patients who require more than three SBTs or longer than seven days from the first attempt before successful extubation are categorised as having undergone ‘prolonged weaning.’ The proportion of patients in each weaning group varied between different studies and ranged from 30-59% in the simple weaning, 26-40% in the difficult weaning and 6-30% in prolonged weaning groups.

Weaning failure significantly affects patient outcomes. Numerous studies have shown that patients who undergo prolonged weaning have significantly higher ICU mortality rates compared to those with simple and difficult weaning. Patients who fail extubation and need reintubation have a much higher mortality rate than patients successfully extubated ranging from around 30 to 50% compared to 5-10% for successful extubation.

5. 2. The course of weaning

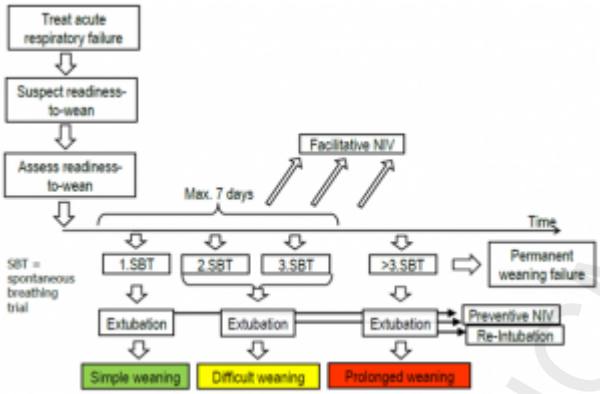

Figure 1:Schematically represents the course of the weaning process. (Adapted with permission from Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, et al. Weaning from mechanical ventilation. Eur Respir J 2007; 29(5): 1033–1056. PMID 17470624)

First step:

The weaning process starts at the time that the illness that led to the need for mechanical ventilation has (at least partially) resolved.

Second step:

Readiness-to-wean should be suspected early in the course of mechanical ventilation and assessed by objective criteria.

Table 1: Readiness to wean criteria
Satisfactory oxygenation: e.g., PaO_2 / FiO_2 >200 mmHg (27 kPa) with PEEP ≤ 5 cm H_2O
Hemodynamic stability: e.g. no continuous vasopressor infusion
Adequate level of consciousness: Patient awake or easily aroused
Adequate Cough & secretion management: Patient able to cough effectively, as roughly assessed by the presence of coughing in response to endotracheal aspiration
Respiratory physiology criterion: Rapid shallow breathing index RSBI < 100 after 2 minutes of a spontaneous breathing trial

Note

The RSBI index is the ratio of respiratory rate to tidal volume after 2 minutes of

spontaneous breathing trial. RSBI was first introduced by Yang and Tobin and represents a sensitive screening test for early detection of readiness-to-wean. It can identify those who have a chance of passing a confirmatory SBT. It does not identify those who actually pass the SBT

In text References

(Boles et al. 2007; Yang and Tobin. 1991; Tobin 2006)

Third step:

Spontaneous Breathing Trial (SBT)

Once the readiness to wean has been confirmed in the presence of the criteria mentioned above, an SBT should be conducted.The SBT is needed to confirm the patient's ability to breathe without assistance.

How to perform a Spontaneous Breathing Trial

Weaning guidelines suggest performing the SBT with no (T-piece strategy) or little ventilator assistance (low levels of inspiratory pressure support or continuous positive airway pressure). Ideally, SBT should be performed using the T-piece method, as that is the method that most accurately simulates the post-extubation physiological conditions.

Performing an SBT by applying low inspiratory pressure support (up to 7 cmH2O) with or without continuous positive airway pressure has been shown to decrease the work of breathing significantly, and may overestimate the patient's ability to handle post-extubation workload.

Duration of SBT

In the majority of the patients, a 30 min trial is adequate in identifying a successful or failed SBT. However, SBT might have to last for longer (up to 120 min) in patients at high-risk for reintubation such as elderly patients and those with COPD, heart failure, or neuromuscular disorders.

Note

During the initial few minutes of the SBT, the patient should be attentively monitored, before judgment is made to continue the SBT.

Criteria defining the success of SBT (Table 2)

Table 2: Criteria of successful SBT

Respiratory rate < 35 breaths/minute
Good tolerance to spontaneous breathing trials
Heart rate < 140 /minute or heart rate variability of >20%

$SatO_2$>90% or PaO_2> 60 mmHg (8 kPa)on FiO_2<0.4
Systolic blood pressure >80 and <180 mmHg or <20% change from baseline
No signs of increased work of breathing or distress *

Accessory muscle use, paradoxical or asynchronous rib abdominal cage movements, intercostal retractions, nasal flaring, profuse diaphoresis, agitation

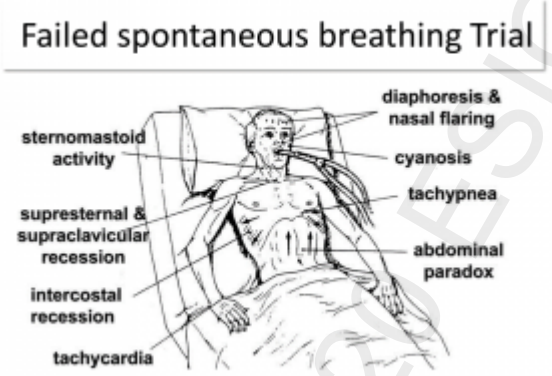

Figure 2: Clinical signs of SBT failure. Deepak Talwar, Vikas DograJ Assoc Chest Physicians 2016;4:43-9

Table 3: Criteria of failure of SBT (see Figure 2)

Clinical criteria

- Diaphoresis
- Nasal flaring
- Increasing respiratory effort
- Tachycardia (increase in Heart rate >40 bpm)
- Cardiac arrhythmias
- Hypotension
- Apnea

Gas exchange criteria

- Increase of $PetCO_2$>10 mm Hg
- Decrease of arterial pH <7.32
- Decline in arterial pH>0.07
- PaO_2<60 mmHg (8 kPa) with an FiO_2>0.40 (PaO_2/FiO_2 ratio <150 {20 kPa})
- Fall in SpO2>5%

Fourth step: Extubation

Following a successful SBT, the patient should undergo assessment for and removal of the endotracheal tube.

In text References

(Thille, Richard and Brochard. 2013; Perren and Brochard. 2013; Vallverdu. 1998; Epstein, Ciubotaru and Wong. 1997; Schmidt et al. 2017; Heunks and van der Hoeven. 2010; Boles et al. 2007; Tobin and Alex. 1994; Sklar et al. 2017)

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5. 3. Diagnostic approach to weaning failure

The majority of patients can be extubated after the first SBT. A patient failing a weaning test or extubation is automatically allocated to the difficult-to-wean group.
The most common causes of failing a SBT are:

- Incomplete resolution of critical illness
- Errors in assessing readiness to wean
- Presence of a new problem

Numerous studies have investigated the risk factors for weaning failure. Patients at a high risk for extubation failure are those >65 years of age and those with underlying chronic cardiovascular or respiratory disease.

Following a failed SBT and before performing a new SBT, the physician should determine the reason of failure and subsequently develop an appropriate treatment strategy.

5. 3. 1. Pathophysiological determinants of weaning failure

The pathophysiology of weaning failure is complex and multifactorial. Determination of the pathophysiological factors that cause weaning failure requires a dedicated clinician with in-depth knowledge of the pathophysiology of weaning failure (Figure 3).

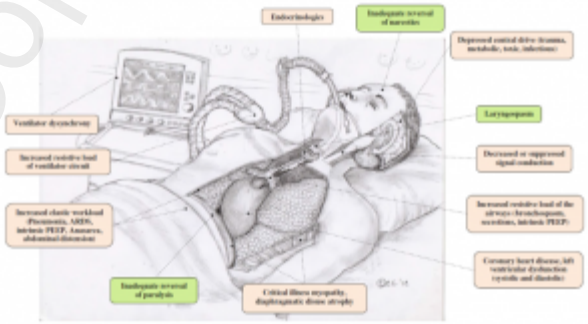

Figure 3: Adapted with permission from Perren A Brochard L Managing the apparent and hidden difficulties of weaning from mechanical ventilation.Intensive Care Med (2013) 39:1885–1895 with permission

The primary pathophysiologic mechanisms related to weaning failure include:

- Respiratory pump insufficiency
- Cardiovascular dysfunction
- Neuromuscular disorders
- Psychological factors
- Metabolic/ endocrine diseases, alone or combined.

5. 3. 1. 1. Respiratory pump insufficiency

Respiratory pump insufficiency is probably the most common cause of weaning failure and may result in an imbalance between respiratory muscle workload and respiratory neuromuscular capability (Table 4).

Decreased respiratory neuromuscular capacity	**Increased respiratory muscle workload**
Decreased respiratory center output	Increased ventilatory requirements
Phrenic nerve dysfunction	Increased CO_2 production
Respiratory muscle pump dysfunction	Increased deadspace ventilation
Hyperinflation	Increased mechanical loads
Decreased oxygen delivery	Increased airway resistance
Respiratory acidosis	Increased dynamic lung elastance
Mineral and electrolyte abnormalities	Increased intrinsic PEEP
Malnutrition	
Respiratory muscle fatigue	
Critical illness neuromyopathy (CINM)	
Ventilator-Induced Diaphragmatic Dysfunction	

Table 4: Respiratory neuromuscular capability

Increased mechanical workload

An increase in the load on the respiratory muscle pump may result from increased ventilatory requirements and/or increased mechanical load (Table 5). Physiological studies indicate that compared to patients who are successfully extubated, patients with COPD who failed an SBT exhibit substantially higher respiratory workload, expressed either as higher inspiratory airway resistance and/or higher elastance and PEEPi.

Increased airway resistance	Reduced compliance
Tube (small diameter, sputum retention, kinking)	**Chest wall**
Central airways	Elevated abdominal pressure
Tracheostomy malposition	Pleural fluid and ascites
Sputum plug	Pneumothorax
Vocal cords and laryngeal injury	Obesity
Tracheomalacia or tracheal stenosis	Flail chest
Small airways	Cyphoskoliosis
Bronchospasm	**Lung**
Mucosal oedema	Intrinsic positive end-expiratory pressure(PEEPi)
Excessive secretions	Alveolar filling (edema, pus, and collapse), ARDS
	Atelectasis
	Interstitial lung disease and fibrosis
	Pneumonia

Table 5: Load on the respiratory muscle pump

Laryngeal injuries (both structure injury and abnormal vocal cord mobility) may significantly increase mechanical workload and are considered as a cause of post-extubation stridor and extubation failure. A recent prospective study including patients extubated after more than 24 h, showed a high incidence of laryngeal injuries. Moreover, in patients who needed reintubation, laryngeal granulation and vocal cord abnormalities were frequently observed.

Note

In patients who meet extubation criteria and judged at high risk for post-extubation stridor, a cuff leak test should be performed before extubation.

Impaired respiratory neuromuscular capability

Adequate respiratory capability requires a structurally intact respiratory pump and adequate signal transmission from the respiratory centre to the inspiratory muscles. The leading causes that may result in impaired respiratory capability are summarised in Table 4.

Respiratory centre depression may rarely be the cause of weaning failure and is usually due to sedatives and opioids overdose. On the other hand, respiratory muscle dysfunction is believed to be a predominant mechanism of weaning failure, in particular in patients with COPD. Geometrical distortion of the respiratory muscles due to dynamic hyperinflation is considered the primary causative factor. Critical illness neuromyopathy (Critical illness polyneuropathy and /or myopathy) may also be considered as a common cause of weaning failure. This is seen particularly in patients with sepsis, COPD or in those who have received treatment with corticosteroids, and/or neuromuscular blockers. Of particular importance is the presence of Ventilator-Induced Diaphragmatic Dysfunction (VIDD) as the cause of weaning failure. An observational study reported that compared to those with simple weaning, patients who underwent prolonged and difficult weaning had a significantly higher prevalence of VIDD. In addition, a recent study showed that

diaphragm atrophy developing during mechanical ventilation was specifically associated with substantial delays in liberation from mechanical ventilation.
Impaired respiratory neuromuscular capability may also present as a result of the development of respiratory muscle fatigue. Tension Time Index (TTI) is a physiological variable that quantifies the magnitude and duration of inspiratory muscle contraction (mainly the diaphragm). Studies in patients during SBT, have shown that TTI increased over the course of the trial in patients who failed, whereas it remained unchanged in those who were successfully extubated. Moreover, some of the patients who failure weaning developed a TTI higher than 0.15. This value has been associated with respiratory muscle fatigue.

In text References

(Perren and Brochard. 2013; Tadie et al. 2010; Vassilakopoulos, Zakynthinos and Roussos. 1998; Boles et al. 2007; Jubran and Tobin. 1997; Purro et al. 2000; Tobin and Alex. 1994; Dres et al. 2017; Goligher et al. 2018)

5. 3. 1. 2. Cardiovascular Dysfunction

Cardiovascular dysfunction as a cause of weaning failure was initially described in 1988 by Lemaire et al., in patients with obstructive lung disease. Since then, cardiovascular impairment has been increasingly recognised as an essential cause of weaning failure in patients with known or previously unrecognised left heart disease. Although the precise incidence of cardiovascular dysfunction as the cause of weaning failure is unknown , many studies have reported significant high incidence rates. Heart failure can be responsible for up to 42% of unsuccessful SBT in a large cohort of medical ICU patients, whereas a more recent study, reported an incidence of 59% of weaning induced pulmonary oedema (WiPO) in weaning failure.
The transition from mechanical ventilation to spontaneous breathing imposes an additional load on the cardiovascular system. This is because a decrease in intrathoracic pressure significantly affects preload and afterload of both right and left ventricles and is associated with increased oxygen consumption by the respiratory muscles. Several studies have shown that in patients with or without preexisting cardiac disease, weaning is associated with a significant reduction in left ventricle ejection fraction, increased left ventricular afterload, increased adrenergic tone, increase in myocardial O_2 consumption and decreased compliance of left ventricle. As a result, some patients may present with myocardial ischemia, acute heart decompression, and WiPO. Both cardiac disease and COPD are independent risk factors of WiPO. Fluid overload in patients with or without pre-existing left ventricular dysfunction is recognised as a cause of weaning and extubation failure. Positive fluid balance the day before extubation is a strong risk factor for extubation failure. Multiple studies have demonstrated that baseline values and changes in Brain Natriuretic Peptide (BNP), an indirect index of ventricular expansion and volume overload, are significantly higher in patients with weaning failure than in patients with successful extubation. See Figure 3.

Notes

- In patients with pre-existing left cardiac disease (systolic or /and diastolic dysfunction), as the result of the remarkable increase of pulmonary artery occlusion pressure (PAOP), clinical symptoms and signs of cardiogenic pulmonary oedema are usually observed within a few minutes on SBT.
- Recent findings emphasise the role of LV diastolic dysfunction with preserved LV ejection fraction as a contributor to weaning failure. In a cohort of ICU patients, weaning failure was more frequently due to varying degrees of LV diastolic than systolic dysfunction.
- COPD patients are at high risk of weaning failure of cardiac origin. Gas exchange abnormalities, vigorous inspiratory efforts, increased work of breathing, and increased adrenergic tone are the most significant pathophysiologic factors.
- Patients with concomitant pre-existing COPD and LV disease have a substantially high risk to experience acute LV dysfunction and WiPO.

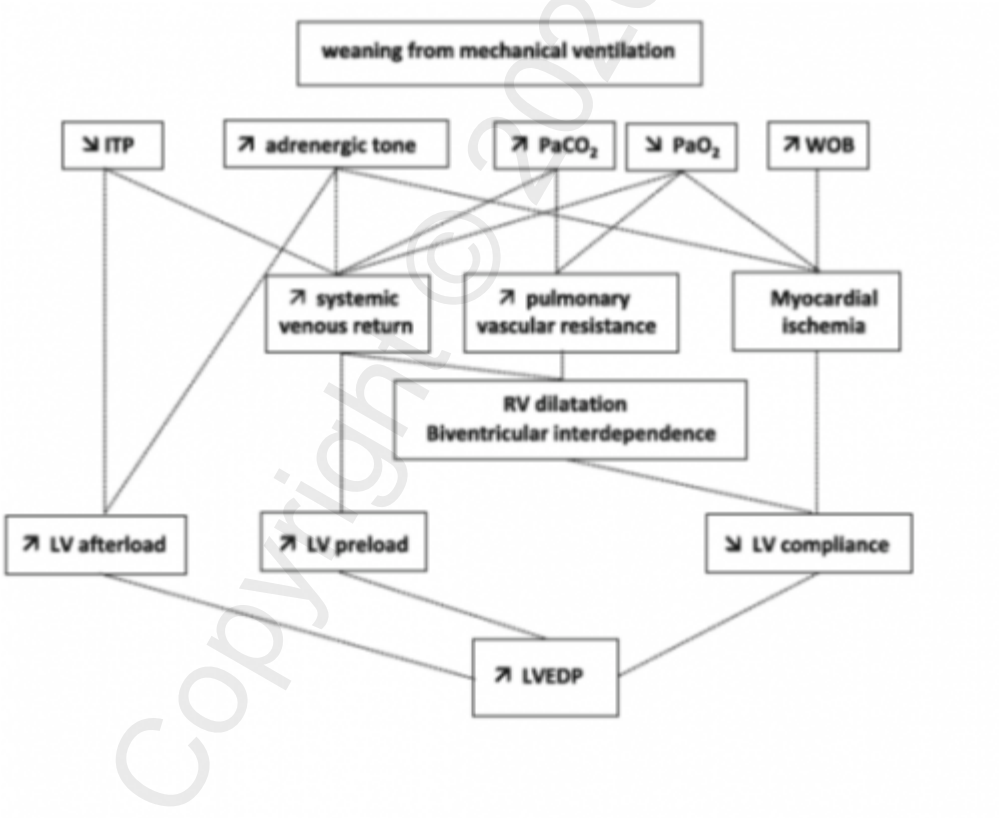

Figure 4: Main mechanisms, potentially involved in the development of weaning induced pulmonary edema.

Figure 4: Main mechanisms, potentially involved in the development of weaning induced pulmonary edema. ITP:intra-thoracic pressure, LV: left ventricular, LVEDP: left ventricular end-diastolic pressure, PaO_2 : oxygen arterial pressure, $PaCO_2$ carbon dioxide arterial

pressure, RV: right ventricular, WOB: work of breathing Adapted with permission from Teboul JL. Weaning-induced cardiac dysfunction: where are we today?.Intensive Care Med 2014 Aug;40(8):1069-79.

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5. 3. 2. Other causes of weaning failure

Brain dysfunction and psychological disturbances

Brain dysfunction in patients who have weaning failure is mainly caused by delirium. Delirium, as assessed by the CAM-ICU (see the ACE Course on sedation, analgesia and delirium) has been significantly associated with difficult weaning and a higher risk of failed extubation. Psychological disturbances other than delirium, such as anxiety and depression have also associated with failed extubation.

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5. 4. Diagnostic workup and management of weaning failure

The diagnostic approach approach and management of the most common causes of weaning failure are summarised in the following tables **(6,7,8,9)**

Table 6: Respiratory pump insufficiency as cause of weaning failure. Diagnostic approach and therapeutic interventions.

Cause	Diagnostic approach	Therapeutic interventions
Increased inspiratory muscle work load	• Inspection of Flow, Paw waveforms • Assessment of gas exchange • Measurement of dynamic compliance, PEEPi, inspiratory resistance • Lung- abdomen ultrasound- chest radiography • Assessment of upper airway /tube patency (bronchoscopy) • Cuff leak test (in patients at high risk for post -extubation stridor	• Treat underlying disease • Optimize airway function (bronchodilation), steroids • Tracheotomy (rarely)
Impaired respiratory neuromuscular capability	• Measurement of MIP- Pdimax • Bedside ultrasound (Loss of diaphragm descent or thickening) • Bilateral phrenic nerve stimulation	• Optimize sedation /analgesia • Muscle training • Early Mobilization • Minimize patient-ventilator asynchrony • Rest if respiratory muscle exists • Provide adequate energy intake

Abbreviations:

- PEEPi: Intrinsic positive –end expiratory pressure
- MIP: Maximal inspiratory pressure
- Pdimax : Maximal trans-diaphragmatic pressure

Table 7: Cardiac dysfunction as cause of weaning failure. Diagnostic approach and therapeutic interventions.

Diagnostic approach	Therapeutic interventions

• 12 lead ECG before and during SBT
• Echocardiography before and after SBT
• Monitor SvO2 during SBT
• BNP measurement
• Rule out myocardial ischemia- Consider coronary angiography
• Pulmonary artery catheter
	• **Optimize fluid balance**
	  ◦ Diuretics
	  ◦ Restrictive fluid management
	• **Reduce afterload**
	  ◦ Inotropes ,Vasodilators (dobutamine, levosimental, Nitrates)
	• **Treat appropriately if myocardial ischemia exists**
	  ◦ (b-blockers, anti-platelet therapy ,Hb optimization, PCI)

Abbreviations:

- SBT: Spontaneous breathing Trial
- SvO2: Mixed venous oxygen saturation
- Hb: Hemoglobin
- PCI: Percutaneous Coronary Intervention

Table 8: Brain dysfunction and psychological disturbances as cause of weaning failure. Diagnostic approach and therapeutic interventions.

Cause	Diagnostic approach	Therapeutic interventions

• Brain dysfunction • Delirium and • Other cognitive disorder	• CAM –ICU • Screening Depression, Anxiety, Sleep disturbances • Sleep assessment	• Optimize sedation • Early mobilization • Provide appropriate pharmaceutical treatment (anxiety depression , Delirium) • Dexmedetomidine • Optimize ICU environment • Implementation of Sleep promoting measures

Abbreviations:

- CAM –ICU :Confusion Assessment Method for the ICU

Table 9: Metabolic and endocrine abnormalities as cause of weaning failure. Diagnostic approach and therapeutic interventions.

Cause	Diagnostic approach	Therapeutic interventions
Metabolic and endocrine abnormalities	• Measurements of electrolyte and glucose • Measurement of hormone plasma levels	• Glucose control, Keep electrolytes with in normal limits Provide hormone replacement in case of deficiency

5. 4. 1. The role of NIV in the management of weaning failure

NIV has been used at three different time points during the weaning process (Figure 5)

- To facilitate extubation
- To prevent reintubation in high-risk patients
- To treat postextubation acute respiratory failure

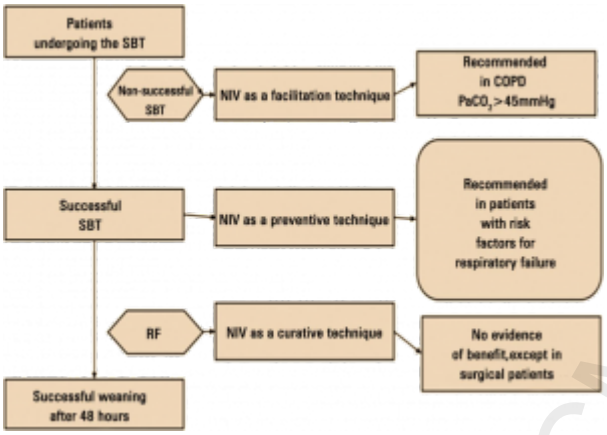

Figure 5:Diagnostic approach and management of the most common causes of weaning failure. Brazilian recommendations of mechanical ventilation 2013. Part 2 J Bras Pneumol. 2014;40(5):458-486

NIV To Facilitate extubation

NIV is used as a weaning method in patients who usually do not meet standard extubation criteria and cannot withstand a weaning test. A recent meta-analysis revealed that in patients with COPD with hypercapnia this form of NIV application is associated with a reduced duration of invasive mechanical ventilation, decreased length of ICU stay and lower incidence of nosocomial pneumonia.

NIV for Prevention of post-extubation respiratory failure

Early NIV application after extubation prevents post-extubation respiratory failure, decreases re-intubation rates and ICU mortality in patients at high risk for extubation failure. High risk for extubation failure was defined as patients >65 years old with underlying chronic cardiovascular or respiratory disease.

Treatment of post-extubation respiratory failure

Two large randomised studies not only failed to prove any benefit of NIV as rescue therapy in post-extubation respiratory failure, but showed an increase in ICU mortality if they are used. This was mainly attributed to delayed reintubation. Nevertheless, in a very selected group of patients, mainly with COPD, a trial of NIV could be considered as long as it does not delay reintubation in case of failure.

In text References

(Nava 1998; Burns et al. 2014; Nava et al. 2005; Ferrer et al. 2006; Esteban et al. 2004; Keenan et al. 2002; Yeung et al. 2018)

5. 4. 2. The role of tracheostomy

Performing a tracheostomy is currently common in patients with COPD requiring prolonged mechanical ventilation. However, the right timing and the impact on outcome remains debatable. Some studies in patients with prolonged weaning have shown that a tracheostomy did not favorably influence ICU survival. Other studies reported that a tracheostomy performed in ICU for long-term mechanically ventilated patients was associated with lower ICU and in-hospital mortality rates. From a physiological point of view, compared to the endotracheal tube, the tracheostomy in these patients may significantly reduce airway resistance and dead space. Hence the work of breathing and ventilation requirements are reduced. Efforts should be made to identify patients who might benefit from a tracheostomy to avoid unnecessary prolonged mechanical ventilation.

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(Durbin CG 2010; Diehl et al. 1999)

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6. Complications of Mechanical Ventilation

6. 1. Ventilator Induced Lung Injury (VILI)

Mechanical ventilation can aggravate or even induce lung injury leading to an entity that is histopathologically indistinguishable from ARDS, termed ‘Ventilator Induced Lung Injury’ (VILI). VILI is a key contributor to morbidity and mortality in patients with ARDS. Spontaneous inspiratory efforts and patient-ventilator asynchrony may further exacerbate lung injury.

6. 1. 1. Mechanisms of ventilator-induced lung injury

The pathophysiology of VILI is characterised by:

- Increased infiltration: Ventilation with high distending pressures increases infiltration through an increase in transmural vascular pressure and/or a decrease in lung interstitial pressure. Moreover, mechanical ventilation can lead to surfactant depletion or inactivation. It can lead to an increase in alveolar surface tension along with decreases in the peri-microvascular pressure (pressure in the perivascular space surrounding extra-alveolar vessels).
- High alveolo-capillary permeability: Lung overinflation may damage the alveolo-capillary barrier increasing the epithelial and endothelial permeability. The combination of increased infiltration and high alveolo-capillary permeability is responsible for the interstitial and alveolar oedema.
- Leukocyte activation and release of proinflammatory mediators which contribute to pulmonary and systemic inflammatory response known as ‘biotrauma.’ Proinflammatory mediators and cytokines implicated in the pathogenesis of biotrauma include: tumor necrosis factor (TNF-a), interleukin IL-1β, IL- 6, IL-8, macrophage inflammatory protein (MIP-2), nuclear factor-κB (NF-κB).

6. 1. 2. Physiological determinants of VILI

Mechanisms related to ventilator settings

The two main mechanisms of VILI are regional alveolar overdistention resulting from high levels of lung stress and strain and cyclical opening and closing of alveolar units (atelectrauma).

Lung stress is the pressure difference between the alveoli and the lung surface and strain is the deformation of the lung relative to its original size, resulting from stress.

In clinical practice, we quantify the stress amplitude by estimating the driving pressure (DP = Pplat –PEEP) measured during end-inspiratory and end-expiratory occlusion. This represents the amplitude of stress applied to the respiratory system as a whole. The stress specifically exerted on the lung is quantified by the change in the distending pressure of the lung when VT is delivered and is called the driving transpulmonary pressure (DPL). DPL is defined as the difference between the end-inspiratory transpulmonary pressure (PLendinsp) and the end-expiratory transpulmonary pressure (PLendexp): DPL = PLend-insp - PLend-exp = (Pplat-Pesendinsp) – (PEEP-Pesendexp). Oesophageal pressure is measured with an oesophageal catheter which is assumed to be eqivalent to the pleural pressure. It is difficult to accurately determine lung stress because:

1. The lung is non uniformly expanded and pleural pressure measured in one site could differ to the pleural pressure in other lung regions.
2. Alveolar pressure cannot be directly measured but is considered to equal airway pressure during inspiratory and expiratory occlusions. However, some alveoli do not communicate with the airways because they are collapsed or filled with fluid or mucus.
3. n diseased lungs stress is concentrated between aerated and non aerated alveolar units.

Lung strain can be static which equals VT, or dynamic which is calculated as the ratio of VT to functional residual capacity (FRC). Because static strain fails to incorporate the size of the aerated lung (the lower the size of the aerated lung the higher the strain applied at the same VT), dynamic strain better assesses the risk of VILI caused by VT. Lung stress and strain are two faces of the same coin as shown by the following equation:

$$PL = ELspec * \frac{VT}{FRCorStress} = ELspec * Strain$$

where ELspec is the tissue elastance of the lung and averages 12cmH_2O.

Respiratory rate and the inspiratory flow rate express how many times (respiratory rate) and how fast (flow rate) a potential harmful stress and strain is applied to the lung and are also implicated in the pathogenesis of VILI.

All mechanical ventilation factors -tidal volume, driving pressure, flow, resistance, respiratory rate, and PEEP - are expressed by the mechanical power, which is the energy delivered over time.

The same applied stress, strain and/or mechanical power may have considerably different effects depending on the heterogeneity of the lung parenchyma. Neighboring alveoli are mechanically interdependent. Alveolar units located at the margins of atelectatic lung regions can collapse and reopen with each tidal breath. This phenomenon, known as atelectrauma, subjects these alveoli to high shear strain with each breath. Heterogeneously inflated regions of the lung may act as stress raisers, amplifying local mechanical stress.

The role of spontaneous breathing

Spontaneous breathing in mechanically ventilated patients may improve lung ventilation/perfusion matching and shunt by recruiting dorsal atelectatic regions, prevent ventilator-induced diaphragmic atrophy, and reduce sedation requirements. However, spontaneous breathing may itself worsen lung injury, with or without MV, a phenomenon described as ‘patient self-inflicted lung injury’ (P-SILI). There are several mechanisms related to P-SILI:

1. Vigorous spontaneous breathing decreases pleural pressure, increases transpulmonary pressures and tidal volumes exacerbating lung stress and strain for the same lung mechanics. These changes can be detrimental in injured lungs.
2. Normally, spontaneous effort induces a uniform change in pleural pressure throughout inspiration. However, in conditions of lung injury, inspiratory effort produces a more negative pleural pressure in the dependent compared with the non-dependent lung regions. As a result, air moves from non-dependent to dependent areas early in inspiration causing significant distention of the dependent areas and lung injury aggravation. This mechanism is described as the pendelluft phenomenon.
3. NNegative intrathoracic pressure resulting from spontaneous breathing activity increases venous return and raises the transmural pressure of the pulmonary vessels, increasing the propensity to oedema.
4. Patient-ventilator asynchrony, mainly double triggering and breath stacking may further augment transpulmonary pressures and tidal volumes despite lung-protective strategies.

6. 1. 3. Strategies to protect from VILI

The main strategies to protect from VILI are summarised in Table 1. They can be divided into ventilator and non-ventilator strategies.

Table 1: Summary of strategies to minimise VILI

STRATEGY	TARGET	RATIONALE	LIMITATIONS
VT/PBW	4-6 ml/kg/PBW	Estimates static strain	Does not take into account the size of the aerated lung.
Pplat	<30 cmH_2O	Pplat as a surrogate of stress	The 'safe' Pplat may result in excessively low or high stress
VT/FRC	1.5-2.0	Takes into account the size of the aerated lung	Methods to measure FRC complex, cumbersome or risky.
PLendinsp	<20-25 cmH_2O	The stress in the lungs at a given lung volume	Requires esophageal catheter. Static value. No clear boundaries for PL have been defined.
DP	<14cmH_2O	Individualizes VT to lung size (Crs). The strongest predictor of mortality in recent studies.	Safe upper limit not known. DP is affected by ECW which may vary among patients.
DPL	Not known, probably <12cmH_2O	Assesses lung stress independently from the effects of ECW	Esophageal manometry required. No safe upper limit for DPL.
PEEP	Individualized	Improves inhomogeneity by recruiting closed alveoli and preventing cyclic collapse	May aggravate strain (response to PEEP should be assessed). PEEP titration should be individualized
Mechanical power	Not known	Incorporates the contribution of respiratory rate and inspiratory flow to VILI	Not investigated. Target not identified
Prone position	>16hrs/session. Early in severe ARDS	Increases lung homogeneity and size of aerated lung.	Complexity, risk of complications

Neuromuscular blockade	Cisatracurium infusion In severe ARDS	Low transpulmonary pressure, improved patient-ventilator interaction, anti-inflammatory properties of cisatracurium.	Critical illness associated neuromyopathy, Ventilator-induced diaphragmatic dysfunction.

6. 1. 3. 1. Ventilator strategies

Strategies to protect from excessive stress and strain

To prevent excessive lung stress and strain during MV, tidal volume and pressure can be selected as follows:

- VT to target a predicted body weight (PBW) of approximately 6 ml/kg (ARDS Network protocol). Further reductions of VT (4-5 ml/kg/PBW) are proposed to maintain an inspiratory plateau pressure (Pplat) ≤ 30cmH_2O. However, the same VT is associated with different levels of strain depending of the size of the aerated lung.
- VT adjusted to reduce dynamic strain (VT/FRC). VILI occurs when dynamic strain is higher than 1.5-2.0. Dynamic strain calculation, however, requires the measurement of FRC.
- VT adjusted by calculation of DP. Although mortality increases steeply at DPs above 14 cmH_2O, a safe DP threshold has not been identified yet.
- Estimation of PL. Although reliable targets for safe limit of end-inspiratory PL are lacking: a study identified a PL of 27cmH_2O as a safe upper limit while other investigators suggest considerably lower end-inspiratory PL values, < 13-15 cmH_2O.

Note

A recent meta-analysis of >3000 patients detected higher survival in patients with DP ≤14cmH_2O and found that a lower DP was the strongest predictor of improved outcome among the various ventilator variables. Changes in VT, Pplat and PEEP did not influence survival at a constant DP.

Note

Unfortunately, ventilation strategies that target VT, DP, Pplat, PL represent global measurements of respiratory system and lung mechanics, that poorly reflect the effects of mechanical ventilation at each alveolar unit.

Strategies to reduce lung heterogeneity

The main ventilator strategy to reduce lung heterogeneity is the application of PEEP. PEEP has two main effects:

(a) Prevents end-expiratory collapse of unstable alveolar units (units that open and close

with every breath). This minimises the risk of atelectrauma.
(b) Increases the number of aerated alveoli. This improves lung compliance and homogeneity. Hence, shear strain and injury at the margins between aerated and collapsed lung tissue are further reduced.

Patients with ARDS do not respond uniformly to an increase in PEEP. Some exhibit reductions in the collapsed lung while others exhibit minimal lung recruitment. Increases in PEEP will raise end-inspiratory stress in both groups. However, in the first group, the recruitment of lung units will reduce mechanical strain and atelectrauma decreasing dead space ventilation and shunt. In the second group the increased stress without recruitment will worsen mechanical strain causing additional distension of already aerated alveoli and dead space ventilation.

Therefore, before applying PEEP we must first assess whether the lung is recruitable and then select the adequate PEEP.

Lung recruitability may be assessed by performing a recruitment maneuver (RM), which is an intentional application of elevated transpulmonary pressure aiming to reopen previously collapsed lung units, thus increasing the lung units available for gas exchange. Different techniques of RM have been proposed. As sufficient evidence is lacking on which technique is superior, in every day clinical practice, the choice of technique for performing an RM is determined by personal preference.

The ideal technique would not be complicated and time-consuming to perform, provide sustainable alveolar recruitment to correct and prevent hypoxemia and improve lung mechanics (improving ventilation) while having a low incidence of complications/adverse effects. RM is considered a safe intervention. Transient hypotension and desaturation commonly occur, whereas other more serious adverse events, such as barotrauma are infrequent.

Technics of recruitment maneuver
Sustained inflation s the RM that has probably been used most commonly. A common approach has been to set the ventilator to CPAP mode and increase the pressure to 30–40 cm H_2O for 30–40 s

Stepwise, RM has being proposed more recently and different variants have been reported.
In one approach on pressure control ventilation at fixed inspiratory pressure (15cmH_2O) above PEEP, PEEP is progressively increased from 20 cmH_2O to 30 cmH_2O, to 40 cmH_2O every 2 min, reaching a maximum peak pressure of 55 cmH_2O. PEEP is then titrated at 3 min intervals to 25 cmH_2O, 22.5 cmH_2O, 20 cmH_2O, 17.5 cmH_2O, to a minimum of 15 cmH_2O until an oxygen saturation decrease of 1% to 2% is observed. At this point, lung de- recruitment is supposed to occur. The lung is then re-recruited before the ‘optimal PEEP’ is set at 2.5 cmH_2O above the de-recruitment point.

In an alternative approach, on volume control ventilation at a fixed VT of 6 mL/IBW kg, PEEP is increased in increments of 2–5 cm H_2O. Each step lasts for 3–5 min unless there is an adverse effect (hypotension, desaturation) that prompts a decrease in PEEP to the previous step. At each step the driving pressure (Pplat _PEEP), compliance, SpO_2, and blood pressure are monitored. PEEP is increased if there is evidence of recruitment: (decreased driving pressure, Pplat_30 cm H_2O, or increased SpO_2. PEEP is decreased to the previous step if there are indications of overdistention: increased driving pressure, Pplat above 30 cm H_2O, hypotension, or decreased SpO_2.

High-frequency Oscillatory Ventilation (HFOV)

High-frequency Oscillatory Ventilation (HFOV) consists of a simple circuit where oxygenated, humidified gas (bias flow) is passed across the path of an oscillating membrane at a set frequency (usually 3-15 Hz) generating VT well below anatomic dead space (1–3 mL/kg PBW).The fraction of inspired oxygen (FiO_2) and the mean airway pressure (Paw) determines the PaO_2 while the frequency of oscillations, their pressure amplitude and the inspiratory time determine the $PaCO_2$. Theoretically, the very low VT limits overdistension while the high mean Paw may both recruit collapsed alveoli and prevent cyclic recruitment-derecruitment of unstable lung units. HFOV should be considered in patients with severe ARDS who have failed conventional ventilator strategies and should be performed in centres with expertise in using this mode of ventilation.

Note

in two recent large randomised trials, ventilation with HFOV was associated with a difference in mortality and possible harm compared to conventional ventilation. However, there are limitations in each of these trials e.g. higher doses of sedation, fluids, vasopressors and neuromuscular blocking agents in the HFOV groups.

6. 1. 3. 2. Non ventilator strategies to protect from VILI

Non ventilator strategies to protect from VILI include:

- Prone positioning
- Neuromuscular blockade
- Extracorporeal dioxide removal ($ECCO_2R$) and the extracorporeal membrane oxygenation (ECMO)

Prone positioning alters the distribution of lung ventilation and lung perfusion. In the healthy lung, ventilation favors ventral lung regions because alveolar size decreases from ventral to dorsal regions. In contrast to ventilation, pulmonary perfusion preferentially distributes to the dorsal lung regions. In patients with ARDS, lung oedema further diminishes the aeration of dorsal regions and aggravates shunt in these regions (high

perfusion, less aeration). Prone position increases the aeration of dorsal lung units. The redistribution of aeration does not impair gas exchange in the ventral region, while pulmonary perfusion remains preferentially distributed to the dorsal lung regions. Therefore, alveolar/perfusion matching improves, shunt fraction decreases, and gas exchange is improved. Moreover, the more homogenous lung ventilation and the increased size of the aerated lung protect the lung from abnormal stress and strain and mitigate the risk of VILI. A recent multicentre randomised controlled trial (PROSEVA) found that placing patients with severe ARDS (PaO_2/FiO_2<150 mmHg) in the prone position for at least 16 hours/day improved survival compared to the semirecumbent supine position.

Note

Prone positioning sessions should be initiated early in the course of severe ARDS, applied for extended periods (>10-12 hours/session) and must be combined with other lung protective strategies (small VT, low Pplat and driving pressures, individualised PEEP titration etc).

The exact beneficial mechanism of neuromuscular blockade in ARDS is unknown. It is hypothesised that lower transpulmonary pressure, along with improved patient-ventilator interaction, facilitates lung-protective ventilation. Another hypothesis is that cis-atracurium has anti-inflammatory properties by blocking the nicotine-acetylcholine receptor a1 signaling. In a multicentre randomised controlled trial in 340 patients with moderate-to-severe ARDS, early neuromuscular blockade decreased 90-day mortality. A subsequent study in 1006 patients with ARDS did not demonstrate survival benefit from early 48-hr administration of cisatracurium. A recent meta-analysis concluded that neuromuscular blocking agents may be beneficial in refractory hypoxemia and prevent barotraumas but further studies are required to assess its effects on mortality. Taking into consideration the potentially detrimental effects of P-SILI, it is prudent to consider neuromuscular blockade at the early stages of severe ARDS in mechanically ventilated patients with spontaneous inspiratory efforts.

Extracorporeal strategies include extracorporeal dioxide removal ($ECCO_2R$) and extracorporeal membrane oxygenation (ECMO). $ECCO_2R$ can be used when the application of lung-protective ventilation is impeded by hypercapnia and acidosis. Of note, $ECCO_2R$ allows the application of ultra-protective lung ventilation with very low VTs (3-4 ml/kg/PBW). ECMO may be considered in persistent hypoxemia. The multicenter, international EOLIA trial demonstrated a no statistically significant but clinically relevant (11%) reduction in mortality in the patients with severe ARDS treated with veno-venous ECMO compared with standard lung-protective ventilation. ECMO carries a moderate risk of major hemorrhage and cannula- and circuit-related complications. While extracorporeal strategies allow ultra-protective ventilation and are more efficient in addressing hypoxemia, the optimal targets for ventilator settings, the group of patients that will mostly benefit, and the impact on long term outcomes is still unknown.

In text References

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6. 2. Ventilator Induced Diaphragmatic Dysfunction (VIDD)

6. 2. 1. Definition

Ventilator-induced diaphragmatic dysfunction (VIDD) is defined as a loss of diaphragmatic force-generating capacity specifically related to the use of mechanical ventilation (MV). VIDD is related explicitly to MV and cannot be solely explained by other factors such as sepsis, drugs, or metabolic derangements, although these factors may further exacerbate diaphragmatic weakness. Unlike ICU-acquired weakness, in VIDD phrenic nerve signal transmission and signal transduction at the neuromuscular junction is normal or even increased.

The prevalence of VIDD is unknown. Studies have shown that diaphragmatic dysfunction is two times more frequent than ICU-acquired weakness, while 80% of patients with ICU-acquired weakness have diaphragmatic dysfunction. VIDD delays liberation from MV and is associated with difficult weaning and weaning failure and prolongs ICU stay.

6. 2. 2. Pathophysiology

Diaphragmatic weakness in VIDD is due to both atrophy and contractile dysfunction. The main histopathological and biochemical changes are:

- muscle fibre atrophy
- muscle fibre remodeling
- muscle fibre injury (disrupted myofibrils, increased numbers of vascular structures and abnormal mitochondria).

Mechanical ventilation may cause VIDD through:

1. Over-assistance where diaphragmatic contraction is either abolished (controlled MV) or suppressed to deficient levels (high levels of ventilator support). This leads rapidly to disuse atrophy of the diaphragm due to an increase in proteolysis coupled with depressed protein synthesis. Proteolysis is activated within 6 hrs of controlled MV and is associated with increased oxidative stress. Disuse diaphragmatic atrophy affects nearly 50% of mechanically ventilated patients.
2. Under-assistance where excessive diaphragmatic load causes diaphragmatic injury and contractile dysfunction.
3. Patient-ventilator asynchrony associated with eccentric diaphragmatic contractions (contractions while the diaphragm is lengthening). Ineffective efforts or reverse triggering at the expiratory phase could predispose the diaphragm to eccentric loading.
4. Longitudinal atrophy associated with high PEEP. When PEEP is applied to the lung and end-expiratory lung volume increases, the diaphragm shortens at end-expiration which experimentally induces a decrease in the number of sarcomeres along the length of the diaphragm muscles fibres. This atrophy may impair the

length-tension relationship of the diaphragm so that when PEEP is acutely reduced or removed (i.e., during weaning), the overstretching of the diaphragm above its optimal length impairs its performance.

Note

12 hrs of controlled MV results in a 15% reduction of diaphragmatic fibres and this reduction approaches 30% after 18-24 hrs of MV. Both controlled and assisted MV (with high assist) can induce diaphragmatic atrophy albeit at a slower rate.

6. 2. 3. Diagnostic approach

The presence of VIDD should be considered in any mechanically ventilated patient experiencing difficulties in weaning. The diagnostic approach of VIDD includes:

- Exclusion of other causes of weaning failure
- Assessment of the respiratory muscle strength
- Assessment of diaphragmatic strength
- Diaphragmatic ultrasonography

Causes of weaning failure other than VIDD such as underlying lung diseases, drugs, electrolyte disturbances, malnutrition, congestive heart failure, central nervous system disorders, and neuromuscular disorders should be considered and evaluated accordingly.

Respiratory muscle strength is most commonly assessed through the measurement of maximum inspiratory pressure (MIP). MIP is easily measured at the bedside but it assesses all inspiratory muscles and not specifically the diaphragm. It is affected by lung diseases and is effort dependent.

The gold standard for diaphragmatic strength evaluation is the measurement of maximal transdiaphragmatic pressure (Pdimax, the difference between esophageal and gastric pressure) in combination with transdermal phrenic nerve (magnetic) stimulation. This technique requires oesophageal and gastric balloon placement and equipment for magnetic stimulation.

Ultrasonography of the diaphragm is easy to perform and non-invasive. It allows assessment of diaphragmatic function and structure and may exclude other causes of weaning failure (e.g. heart failure, pneumonia etc). Two ultrasonography parameters are evaluated: diaphragmatic excursion and thickening fraction of the diaphragmatic muscle during inspiration. Thickening fraction is defined as thickness at end-inspiration minus thickness at end-expiration divided by thickness at end-expiration. A diaphragmatic excursion less than 1cm and a thickening fraction < 30% have been associated with weaning failure.

Note

Patients may suffer from VIDD even if they don’t have weaning difficulties.

6. 2. 4. Prevention and Management

Approximately 60% of patients experience severe VIDD at the time of their first spontaneous breathing trial. VIDD develops rapidly after instigation of MV, and the longer the duration of MV, the more serious the damage to the diaphragm. Excessive or insufficient inspiratory effort during MV, patient-ventilator asynchrony, and MV duration are the main factors contributing to VIDD. Therefore, limiting the duration of MV (mainly controlled MV), promoting patient-ventilator synchrony, and targeting an optimal inspiratory effort are critical factors in eliminating the risk of VIDD. Pharmacological interventions to treat VIDD, such as antioxidants and protease inhibitors, are currently under investigation.

In text References

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6. 3. Ventilator Associated Pneumonia (VAP)

Definition-Epidemiology

Ventilator-associated pneumonia (VAP) is defined as pneumonia that occurs more than 48 hours following endotracheal intubation and invasive mechanical ventilation. It represents half of all cases of hospital-acquired pneumonia and is estimated to occur in 10-27% of all mechanically ventilated patients. It is the second most common infection in the Intensive Care Unit (ICU). The risk of VAP is higher in the first 5 days following mechanical ventilation (3% risk/day) and declines thereafter (2%/day between days 5-10 and 1%/day after the 10th day of ventilation).

Clinical impact

VAP is the leading cause of death related to nosocomial infections in critically ill patients. All-cause mortality rates associated with VAP range from 20% to 50% and mortality directly related to VAP is estimated at 9-13%. Mortality depends on the causative organism and the severity of the underlying medical illness. VAP prolongs the length of mechanical ventilation and hospitalisation.

Prevention

Measures proved to prevent VAP include:

- Head-of-bed elevation
- Alcohol-based hand washing policy
- Early discontinuation of MV

The use of NIV as a means to prevent intubation and avoid re-intubation and to decrease the duration of mechanical ventilation (early weaning and extubation) plays an essential role in decreasing the incidence of VAP.

The role of other suggested measures (stress ulcer prophylaxis, early tracheostomy, subglottic secretion drainage, conical and polyurethane endotracheal tube cuffs, silver/antibiotic coated endotracheal tubes, prophylactic probiotics, selective digestive decontamination and oral care with chlorhexidine) remain controversial.

In text References

(Kalil et al. 2016; Magill et al. 2013; Klompas et al. 2016)

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