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Course Title: Mechanical Ventilation in Respiratory Therapy

Topic List:-

Chapter

Mechanical Ventilation in the Trauma Patient

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Abstract

In this chapter, we discuss the unique ventilatory strategies of the trauma patient. Injuries can be direct to the lung resulting from the trauma or indirect because of other injury to the body. We will discuss the airway and ventilation management and concerns in a patient with chest trauma, abdominal trauma, head trauma, orthopedic, and burn injury. The chapter will explain lung-protective strategies as well as innovative ventilation management techniques including extracorporeal membrane oxygenation.

Keywords: trauma, ventilation, burn, anesthesia, chest

1. Introduction

Trauma lung injury can result from a direct injury to the lung or secondary to injury elsewhere. The trauma and the associated aggressive resuscitation lead to bleeding, edema, and inflammation of the lungs. The trauma can result in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). The goal of the ventilation is to preserve the lung as well as the brain and other organs that are injured. Each form of traumatic injury results in an individualized approach to mechanical ventilation [1].

1.1 Lung-protective ventilation strategies in the trauma patient

The primary goal of the trauma patient is to avoid hypoxia and secondary tissue injury. Mechanical ventilation may be initiated for reasons other than respiratory compromise, such as brain injury, shock, intoxication, agitation, or combativeness. Lung-protective ventilation strategies aim to reduce the volume and pressure delivered to the lung. For example, the goal tidal volume is 6–8 mL/kg of predicted body weight regardless of the type of ventilation [1].

1.2 Modes of ventilation in the trauma patient

Volume-controlled ventilation (VCV) is the most used form of ventilation in the operating room. The tidal volume (Vt), respiratory rate, and FiO_2 are set by the operator. This mode guarantees delivery of a set Vt and minute ventilation. The Vt is not reached if the peak inspiratory pressure (PIP) exceeds a set limit [1].

Pressure-controlled ventilation (PCV) can be used. In this type of ventilation, the Vt delivered is variable and depends on the airway resistance and the lung/chest wall compliance. This mode is recommended in the case of severe ARDS to promote better gas exchange [1].

Airway pressure release ventilation (APRV) is useful for the patient that has suffered a blunt trauma, with pulmonary contusions and severe atelectasis. APRV is also indicated for patients with morbid obesity and pregnancy. This mode of ventilation is a time-triggered, pressure-limited, and time-cycled mode of ventilation. The patient is able to breathe spontaneously. This mode is excellent for recruitment of the collapsed lung [1].

High-frequency oscillation ventilation (HFOV) results in the rapid delivery of very small tidal volumes with the application of high mean airway pressures. This type of ventilation results in active exhalation and therefore reduces air trapping. This type of ventilation is useful for patients with severe pulmonary contusion, ALI/ARDS, and smoke inhalation injury [1].

Noninvasive positive-pressure ventilation (NIPPV) including continuous positive airway pressure (CPAP) and bi-level airway pressure (BiPAP) can be used to treat acute respiratory failure. This mode of ventilation can be used in the trauma patient as well. This is not recommended for patients with brain injury, intoxication, or facial trauma. It is also not recommended for patients that are at increased risk of aspiration [1].

2. Chest trauma

Chest trauma, and the subsequent complications of chest injury, is significantly prevalent and the second most common cause of mortality in trauma. Injury sustained to the thorax can cause enormous damage to the heart, lungs, and major vasculature.

Any mechanism of injury to the chest wall or underlying organ systems has the potential to cause acute life-threatening issues with respiration. Mechanical ventilation, as it relates to the resulting complications of contusions, hypoxemia, and hemorrhage that occupy the spaces left behind by traumatic events, will be discussed throughout this chapter. Understanding the pernicious effects on respiratory mechanics and respiratory physiology helps the clinician to determine the timing of intubation and where the patient would most benefit on the spectrum of invasive ventilation.

2.1 Respiratory physiology in chest trauma

Injuries to the chest requiring mechanical ventilation may affect respirations in a variety of ways. Damage to the integument, musculoskeletal, nervous, or circulatory supply confined within and around the thoracic cavity can vastly change the physiology of respirations. Similarly, damage to the airways and lungs can significantly impede proper ventilation and oxygenation. As such, we can reduce respiratory compromise into two distinct circumstances: respirations compromised by altered mechanics of breathing, and respirations compromised by direct damage to the airway and lungs. Injuries to the respiratory system can also be categorized as being either penetrating or blunt in origin; however, the need for mechanical ventilation may exceed this distinction.

Integument provides a barrier from foreign organisms and elasticity, which is essential for expansion and contraction of the lungs; hindrance of integument

by injuries, such as in the case of burns or circumferential eschars, limits the compliance of the respiratory system and often necessitates positive pressure ventilation.

Skeletal trauma most commonly involves rib fractures. Splinting, caused by painful respirations and often associated with factures involving the ribs, sternum, vertebrae, clavicles, or scapulae as well as injuries to soft tissue or muscle, can lead to atelectasis, hypoxemia, and pneumonia. Disruption to breathing mechanics by a flail chest, when two or more ribs are fractured in two or more places, and by hemopneumothorax, whereby the thoracic cavity is occupied by blood or air, may impede lung expansion and limit tidal volumes as well as oxygenation. Massive thoracic trauma is often accompanied by significant abdominal trauma. Diaphragmatic injury inhibits the lungs' ability to expand and contract. Invasion of the lung cavity by penetrating wounds, bone spurs, and the like creates a discordance within the respiratory system, inhibiting lung expansion, and reversing physiology to an open cavity [2].

Damage to respiratory parenchyma, including alveoli, alveolar ducts, and bronchioles, will impede gas exchange. High kinetic energy to the chest wall commonly causes pulmonary contusions and is the most frequently diagnosed intrathoracic injury associated with blunt trauma.

Tracheobronchial wounds, and more rarely esophageal damage, can have profound consequences. Structural damage may result in tension pneumothorax, pneumomediastinum, and subcutaneous emphysema. Most importantly, damage to the tracheobronchial tree can create an immediate threat to oxygenation and perfusion, a situation requiring swift discovery, appropriate intubation technique in a patient with diminished respiratory reserve, and isolation of injury for surgical manipulation, exposure, and repair.

Vascular injury, cardiac injury, and cardiac tamponade may impair circulation *via* massive hemorrhage, diminished preload because of decreases in venous return, and impediments to cardiac ejection from impedance on myocardium [3, 4].

2.2 Pulmonary contusion

Blunt trauma often results in pulmonary contusion. The early signs of tachypnea, rhonchi, wheezing, or hemoptysis may indicate pulmonary contusion. Changes may not be visible on a chest X-ray for up to 4–6 hours. Pulmonary contusions usually resolve in 7 days, which are managed easily by treating with permissive hypercapnia, conservative fluids, routine lung recruitment, positive end-expiratory pressure (PEEP), and lung-protective ventilation [1].

2.3 Hemothorax

The most common cause of a hemothorax is the rupture of intercostal vessels. Chest tube placement is recommended to access the rate of blood loss. Massive hemothorax, >1500 ml or one third of a patient's blood volume, often requires emergent surgery [1].

2.4 Bronchopleural fistulas

Bronchopulmonary fistula is a communication between proximal and distal airways and the pleural space. Mechanical ventilation can be difficult. The mean airway pressure should be kept low. Some experts recommend PCV due to the ability to control the pressure gradient more precisely. Lung isolation may be required

if the leak is too large for proper ventilation. This can be achieved with main stem intubation, double-lumen tube, or bronchial blocker depending on the location of the fistula. The use of HFOV has been reported in some cases in addition to extra-corporeal membrane oxygenation (ECMO) [1].

2.5 Choosing the appropriate mechanical ventilation for a chest trauma patient

2.5.1 Non-invasive ventilation

Provided the patient is hemodynamically stable without significant associated injury such as traumatic brain injury or severe abdominal trauma, non-invasive ventilation (NIV) techniques should be attempted. NIV has become common in acute chest trauma as it limits the hazard of further damaging the contused lung, which is at risk for diminished oxygenation and diffusion issues. Furthermore, NIV removes the risk of ventilator-induced lung injury, and many of the complications associated with endotracheal intubation should be considered prior to intubation attempts [5].

2.5.2 Indications for intubation

Respiratory compromise is depicted in many facets. Decreased tidal volume, increased respiratory rate, inadequate chest compliance, pleural compromise, failed lung mechanics, high oxygen requirements, and severe associated injuries (e.g., head trauma) are all situations that could require intubation. These indications are not absolute. These situations can quickly spiral out of ventilatory control. Surmounting a response prior to catastrophic failure and respiratory compromise is essential (**Table 1**) [6–8].

2.5.3 Ventilator settings in chest trauma

Initial ventilator settings in chest trauma are based on a lung-protective strategy. The Vt should be set between 4 and 8 mL/kg of ideal body weight with the plateau pressure < = 30 cm H_20. While positive end-expiratory pressure (PEEP) has well-established benefits in ICU and ARDS patients, it is initially withheld to evaluate the level of pulmonary injury, barotrauma, air leaks, and pulmonary shunt. The FiO_2 should be set = 1.0 and then titrated to an appropriate arterial oxygenation (PaO2). The respiratory rate should be set to 15–25 breaths per minute and then increased as need to achieve the desired PaCO2. Limiting plateau pressure to 30 cm H_20 will help protect lung physiology (**Table 2**) [6–8].

Indications for intubation in a chest trauma patient
• Hemodynamic instability
• Decreased respiratory reserves
• Hypoxemia (PaO_2 < 60 mmHg)
• Tachypnea
• Hypercarbia
• Glasgow coma scale of 8 or less

Table 1.
Indications for intubation in a chest trauma patient [6–8].

Initial ventilator settings in the chest trauma patient
• Tidal volumes between 4 and 8 mL/kg of ideal body weight
• FiO_2 = 1.0, titrated to arterial oxygenation
• Avoid PEEP
• Rate 15–25 breaths per minute

Table 2.
Initial ventilator settings in the chest trauma patient [6–8].

3. Abdominal trauma

Abdominal trauma can result from compression of the organs, deceleration injury, or penetrating trauma such as a stab or gunshot. It is important to first determine whether the injury is superior (above the diaphragm), inferior (inguinal ligament and symphysis pubis), or lateral (anterior axillary lines). The location of the injury helps to determine the organs involved [9].

The pain from an abdominal trauma can lead to poor shallow respirations, increased respiratory rate, and a decreased ability to clear secretions. This can result in a secondary pneumonia. The use of early mechanical ventilation has been correlated with a decreased risk of pneumonia, but after 5 days of ventilation that risk of pneumonia begins to increase again [10].

A patient presenting to the operating room with an abdominal injury requires a rapid sequence induction with intubation secondary to the high risk of aspiration. Most trauma patients are considered a "full stomach" and have delayed gastric emptying secondary to the high catecholamine levels from the stress of the trauma [9].

3.1 Abdominal compartment syndrome

Abdominal compartment syndrome can result from increased intra-abdominal pressure secondary to massive fluid resuscitation (bowel edema) or continued bleeding. Intra-abdominal pressures exceeding 20–25 mmHg can result in poor circulation and tissue perfusion as well as decreased cardiac output. The abdominal compartment syndrome can lead to respiratory dysfunction that will present as high peak pressures, decreased tidal volume, worsening atelectasis, and hypercarbia. Emergent surgery is required to release the abdominal pressure [9].

4. Head trauma

Traumatic brain injury (TBI) resulting from a trauma has a primary and secondary injury component. The primary injury results from the initial trauma and resulting mechanical deformation of the skull and brain tissue. The secondary injury is a result of the progressive insult to the neurons (**Table 3**) [11].

4.1 Brain injury and acute lung injury (ALI)

Head injury can occur as an isolated trauma or along with other injuries to the trauma patient. Isolated head injuries have been shown in clinical and experimental studies to cause lung damage soon after the injury. Neurogenic pulmonary edema can occur due to the release of catecholamines. In addition, the injured brain can display a systemic inflammatory response, which can result in injury to the

	Causes of brain injury
Primary brain injury	• Disruption of vascular structure • Compression of neuronal and glial tissue • Axonal injury
Secondary brain injury	• Astrocyte and neuronal swelling • Hypoperfusion • Increased free radicals • Inflammation • Cellular necrosis • Axonal degeneration • Systemic insults: hypotension, hypoxemia, hypoglycemia, hypocarbia, and hypercarbia

Table 3.
Causes of brain injury [11].

epithelial cells in the lungs. Subsequent mechanical ventilation (MV) can cause further pulmonary injury and strategies to minimize further damage to the lungs should be employed [12].

Mechanical ventilation in a patient with both a brain injury and ALI requires a balance between the principles that guide brain injury and the mechanical ventilation required to be protective of the lung. High PEEP can lead to elevated intrathoracic pressure, which results in decreased cerebral venous drainage and therefore poor cerebral perfusion. This effect is seen less in patients with ALI and ARDS; therefore, PEEP can often be safely applied in these patients. The key is to maintain the patient's volume status and mean arterial pressure. Also, the PEEP must be lower than the patient's intracranial pressure (ICP). The goal is to apply the lowest level of PEEP possible to still maintain oxygenation. Head elevation, avoiding tight endotracheal ties around the neck, and maintaining normocapnia are all important measures to monitor when ventilating a patient with head and lung injury [13].

Hypoxia, hypercarbia, and hypocarbia should be avoided in patients with a brain injury. Oxygenation should be monitored with a continuous pulse oximeter (goal >90%) and the PaO_2 should be >60 mmHg. Hyperventilation can result in cerebral vasoconstriction and brain ischemia. Prolonged hyperventilation is not recommended and should be avoided in the first 24 hours after injury. Hyperventilation should only be used as a temporizing measure [11].

4.2 Prolonged mechanical ventilation in the head injury patient

Prolonged mechanical ventilation in the patient with a traumatic brain injury presents a unique set of goals, first, to avoid further increased ICP and to optimize cerebral blood flow (CBF). Maintaining adequate oxygenation is critical to ensuring adequate cerebral perfusion pressure (CPP). Another goal is to reduce the risk of ARDS. In a multicenter study of ventilated patients with severe brain injury, higher tidal volumes were associated with increased risk of ALI. Lower PaO_2/FiO_2 ratio and higher respiratory rate were also independent predictors of ALI in the same study [14]. Low tidal volumes and permissive hypercapnia are recommended. One systemic review of intubated patients showed a tidal volume range of 6–8 ml/kg may reduce the risk of ARDS [15].

When ARDS develops along with TBI, management can be more difficult. ARDS NET strategies to improve ventilation can conflict with the goal of maintaining CPP.

Increasing PEEP up to 15 cm H_2O has a clinically insignificant effect on CPP; however, permissive hypoxia can lead to increased cerebral blood flow and increased CPP. ICP monitoring is suggested to monitor the effects of MV on CPP [12].

4.3 High-frequency percussive ventilation (HFPV) in head injury

Some studies show good results with HFPV in trauma patients with or without head injury. Using HFPV has resulted in improved oxygenation and reduced ICP [13].

5. Orthopedic trauma

Trauma management of a multiply-injured patient will require stabilization of pelvic and long bone fractures in as timely a manner that is safely possible. Research has shown that early stabilization of these fractures can reduce pain and improve patient outcomes. This includes a decrease in length of hospital stay and a reduction in pulmonary complications [16].

Patients with pre-existing pulmonary disease are at an even greater risk for significant pulmonary complications after a polytrauma. A chest X-ray or computed tomography (CT) scan is recommended on arrival to determine a baseline [16].

5.1 Fat embolism

Fat embolism syndrome (FES) is a result of the micro-embolism of fat and bone marrow from a patient's long bones [16]. Intraoperative transesophageal echocardiography performed on patients undergoing a long bone repair shows that most have some microembolization of fat and marrow [17]. This embolization can result in a varying degree of symptoms, including a significant acute inflammatory response [16, 17]. Most patients will not have a clinical impact. About 3–10% of patients will have clinically significant symptoms. The symptoms are usually progressive and develop over 12–72 hours. The most significant symptoms result in acute respiratory arrest and cardiac arrest [16].

The patient can present with hypoxia, tachycardia, mental status change, and a petechial rash. The rash is usually present on the upper body, including the conjunctiva, oral mucosa, neck, axilla, chest, and arms. Elevated pulmonary artery pressure and decreased cardiac output are seen with direct monitoring. When these symptoms arise, there are tests that can help confirm the diagnosis. These include testing for fat globules in the blood and urine, anemia, thrombocytopenia, and elevated ESR. A chest X-ray will often show bilateral alveolar infiltrates [16, 17].

The treatment for FES is supportive. The treatment for hypoxia requires early recognition and supplemental oxygenation, and may require ventilation management. Patients often require oxygen and PEEP. They may need long-term mechanical ventilation [16].

6. Burn injury

6.1 Smoke inhalational injury

Smoke inhalation is associated with increased mortality in a burn patient. Inhalational injury can be caused by the superheated air or the toxic compounds found in the smoke. These toxic compounds can include ammonia, sulfur, chlorine, and nitrogen dioxide [18].

There should be an increased suspicion of inhalational injury in any burn patient that presents with singed facial hair, carbonaceous deposits in the oropharynx, and blood carboxyhemoglobin levels greater than 10%. The chemical components of smoke can cause a significant inflammatory response that can lead to bronchospasm and impaired ciliary function. Lung necrosis and edema can lead to airway obstruction and atelectasis [19].

Signs and symptoms of inhalational injury include increased respiratory rate, increased secretions, stridor, dyspnea, use of accessory muscles, and facial burns. The first phase of inhalational injury includes asphyxia and acute toxicity. The second phase of inhalational injury begins at 24–96 hours after the injury and is the result of cellular level damage to the lungs. The treatment of inhalational injury includes ventilatory support, early pulmonary toilet, and nebulization therapy [18].

6.2 Carbon monoxide toxicity

Carbon monoxide is a byproduct of combustion. It is the cause of 80% of deaths associated with smoke inhalation from its ability to saturate hemoglobin at very low partial pressures. Burn patients with carbon monoxide toxicity may present with a normal pulse oximeter reading. It is important to always check arterial concentrations of oxy- and carboxy-hemoglobin. The treatment of carbon monoxide poisoning is oxygen therapy (**Table 4**) [18, 19].

6.3 Airway injury

Upper airway injury is often due to thermal heat injury. This leads to swelling and upper airway obstruction due to edema of the oropharynx (**Table 5**) [18].

Carbon monoxide saturation %	Symptoms
<15%	Rare symptoms
15–20%	Headache Nausea Confusion Tinnitus
20–40%	Neurological symptoms Disorientation Nausea Fatigue
40–60%	Cardiac dysrhythmias Brain injury Hallucinations Combativeness
>60%	Death

Table 4.
Carbon monoxide toxicity symptoms [18, 19].

Classic symptoms of impending airway obstruction:	• Stridor • Hoarseness • Dysphagia

Table 5.
Classic symptoms of impending airway obstruction in the burn patient [19].

Indications for immediate tracheal intubation:	• Respiratory distress and impending airway compromise (increased respiratory rate, increased secretions, stridor, dyspnea, and progressive hoarseness.)
	• TBSA burn >60%
	• Evidence of inhalational injury
	• Cardiovascular instability
	• Central nervous system depression

Table 6.
Indications for immediate tracheal intubation in the burn patient [18, 19].

6.4 Ventilator strategies in the burn patient

Patients with a large percentage of burn, burns to the head and neck, and inhalational injury will have an increased likelihood of need for mechanical ventilation. The large fluid load required to treat a burn can result in fluid overload to the lungs. Early bronchoscopy after intubation can help with the removal of secretions and burn-related debris and can help to reduce the length of time required for mechanical ventilation [10].

Non-invasive ventilation can be used for awake patients with minimal facial trauma that are stable hemodynamically. This can be started early upon arrival to the hospital (**Table 6**) [10].

Invasive mechanical ventilation can be lung-protective at low tidal volumes. Airway pressure release ventilation (APRV), high-frequency percussive ventilation (HFPV), and high-frequency oscillatory ventilation (HFOV) have been studied and shown useful in burn patients and to improve morbidity and mortality in comparison to VCV. These provide better oxygenation at lower FiO_2 than conventional ventilation with minimal effects on hemodynamics. APRV can be used to improve lung recruitment and oxygenation. There is no marked improvement in mortality, but it has been shown to stabilize alveoli, reduce edema of the alveoli, and helps to prevent the development of ARDS [10, 13].

6.5 Extubation of the burn patient

Extubation of a burn patient should be based on the patient hemodynamics, fluid resuscitation, inhalational lung injury, and existing airway abnormalities. Burn patients often receive large volumes of fluid resuscitation, which can result in airway edema. Burn patients also require large amounts of opioids for pain control. This results in burn patients often requiring prolonged intubation and ventilation. The criteria for extubation should be similar to those of non-burn patients: resolution of intoxications, ability to follow commands, pain-controlled, gag reflex, and appropriate cough. Burn patients need to be able to protect their airway from aspiration. An early tracheostomy should be considered for patients with long-term respiratory failure. While early tracheostomy has the benefits of improved communication, oral and tracheal hygiene, and improved patient comfort, it has not been associated with improved outcome [18, 19].

7. Extracorporeal membrane oxygenation (ECMO) in the trauma patient

Polytrauma is the leading cause of death among adults. This is often secondary to hemorrhagic shock, hypoxia, acute respiratory distress syndrome (ARDS),

hypothermia, coagulopathy, and brain injury. The lung is often the first organ to fail in a severe trauma. ECMO has been used for nearly two decades, and its use has been gradually expanded to treat severe trauma patients, but the indications are uncertain and clinical outcomes are variable. The mortality of a severe trauma patient on ECMO is still high. There is much research needed on the proper initiation time for ECMO in the trauma patient and which patients will have the most benefit from ECMO. The safety and efficacy of ECMO still needs to be studied [20].

7.1 What is ECMO?

ECMO is a simplified version of the heart-lung machine used in open heart surgery. It is a method of gas exchange outside the body, so the lungs are exposed to minimal volume, pressure, rate, Fio_2, and they potentially have some time to recover [10]. ECMO can provide adequate tissue oxygenation, help in rewarming, and infuse large amounts of blood products quickly [20].

7.2 Complications of the trauma patient on ECMO

Complications associated with a trauma patient on ECMO include bleeding and thrombotic complications. Patients also presented with abdominal compartment syndrome, lung and brain edema, and pancreatitis [20].

8. Conclusion

As cases of severe trauma continue to increase, more and more trauma patients will be arriving in the operating rooms and intensive care units. It is important to understand how the mechanism of injury in a trauma affects the goals and types of mechanical ventilation required. The understanding of these individual cases will lead to improved patient outcomes.

Conflict of interest

The authors declare no conflict of interest.

DOI: http://dx.doi.org/10.5772/intechopen.101578

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Chapter

Ventilation Strategies in Obese Patients

Pavol Pobeha

Abstract

Obesity is an increasingly prevalent disease and is a root and complication of conditions necessitating mechanical ventilation. Obese patients require a careful approach due to the particular manner of how ventilatory mechanics is affected, if obstructive sleep apnea (OSA) is present. The two main diagnoses we may encounter while ventilating these patients are obesity hypoventilation syndrome (OHS) and chronic obstructive pulmonary disease (COPD) in an obese patient, which has been recently proposed as a novel phenotype of COPD. The excessive amount of fat in the abdomen, chest wall, and around upper airways warrants the use of special ventilation modes and settings. This chapter provides insight into which issues should be considered when ventilating an obese patient, either in acute or chronic conditions. We stress the importance of acknowledging the high risk of OSA and how OSA affects the ventilation algorithms.

Keywords: non-invasive ventilation, obesity hypoventilation syndrome, COPD, overlap syndrome, sleep-disordered breathing, ventilation strategies

1. Introduction

Obesity is a disease with prevalence increasing significantly; about a third of the world's population is overweight or obese. The number of obese people has doubled in the last 20–30 years, and this trend continues [1]. This is closely related to the increase in the number of obese patients admitted to the intensive care units (ICU) as well as those requiring mechanical ventilation. The specificity of obesity in critically ill patients lies in the increased risk of infections, impaired respiratory drive, respiratory mechanics as well as the presence of sleep-disordered breathing [2]. A frequently mentioned diagnosis linking respiratory failure and obesity is obesity hypoventilation syndrome (OHS), but obesity also affects patients with other diseases, including respiratory and lung diseases. It is necessary to mention patients with chronic obstructive pulmonary disease (COPD), where a subset of obese patients benefits from a different approach to diagnosis and treatment compared to low-weight patients. This chapter aims to clarify the issue of respiratory failure in obesity and its treatment using mechanical ventilation in both acute and chronic conditions.

2. Mechanisms of respiratory failure development in obesity

The development of respiratory failure in obesity is a gradual and often long-term process. Although the proportion of individual factors may vary from patient to patient, the disease results from a complex of the following mechanisms [3–6]:

- Reduction of vital capacity and functional residual capacity due to the mass of abdominal and subcutaneous chest fat
- Upper airway narrowing and collapse during sleep—obstructive sleep apnea (OSA)
- Accumulation of fat deposits in the respiratory system with increased lower airways resistance
- Increased work of breathing (increased respiratory load)
- Hypoxic pulmonary vasoconstriction
- Fluid overload associated with nocturnal rostral fluid shift
- Rapid eye movement (REM) associated hypoventilation
- Impaired respiratory mechanics—muscle weakness
- Central leptin resistance—deterioration of the respiratory drive
- Accumulation of serum bicarbonate—reduction of ventilatory response to carbon dioxide (CO_2)

All these pathomechanisms affect the development and course of the disease in individual patients and should be considered in the diagnosis and treatment of respiratory failure and the setting of ventilation strategies. Guideline for mechanical ventilation generally distinguishes recommendations for the treatment of patients with obstructive pulmonary disease and restrictive diseases and separately for the diagnosis of obesity hypoventilation syndrome [7–9]. However, as obesity is present in various diseases and the above-mentioned pathomechanisms contribute to the clinical picture, in the following, we will mention the specifics of the treatment of respiratory failure in multiple diseases.

3. Obesity hypoventilation syndrome

Obesity hypoventilation syndrome is standardly defined by the combination of:

- Obesity with body mass index (BMI) ≥ 30 kg m^{-2}.
- Daytime hypercapnia—arterial CO_2 tension ($PaCO_2$) ≥ 45 mm Hg.
- Sleep-disordered breathing.
- The diagnosis of OHS cannot be made if an alternative explanation for hypoventilation (e.g., neuromuscular, mechanical, or metabolic disease) is present [10].

As the development of hypoventilation in OHS is gradual, the diagnosis is in most cases made at a stable stage, when the patient is examined in a sleep laboratory for symptoms of sleep-disordered breathing [10]. Approximately one-third of patients are diagnosed at the point of acute-on-chronic hypercapnic respiratory

failure [11], and these patients often require critical care. Comorbidities such as heart failure (usually with preserved ejection fraction), pneumonia, and sepsis contribute to the acute condition. A major problem in the acute and long-term management of these patients is that instead of making a correct diagnosis of OHS, other diseases such as COPD or asthma are misdiagnosed [12, 13]. The misdiagnosis of obstructive pulmonary disease without adequate lung function examination incorrectly directs treatment to the application of bronchodilators instead of adequate respiratory support.

3.1 Classification of OHS patients

Based on the presence of OSA and hypoventilation, three phenotypes of patients with OHS were observed [14, 15]:

- **Severe OSA**—free of REM sleep hypoventilation. This phenotype is characterized by a lack of CO_2 washout capacity after obstructive apnea episodes.

- **Isolated OHS**—characterized by morbid obesity (BMI often ≥40 kg m^{-2}), severe hypercapnia and REM sleep hypoventilation without the presence of OSA.

- **Combined OHS and OSA**.

Polysomnographic (PSG) findings for individual phenotypes are shown in **Figure 1**.

Figure 1 describes the excerpts of polygraphic recordings displaying from the top oxygen saturation, thoracic respiratory effort, airflow, and snoring. The first excerpt of severe OSA is exhibiting short interapneic intervals with oxygen saturation rising above 90%. The second excerpt illustrates low baseline oxygen saturation with further desaturations after apneic events. The third excerpt shows low baseline saturation with no desaturations reflecting isolated hypoventilation.

The classification is based on observations and medical evidence. It is a fact that a significant proportion of patients with OHS have concomitant OSA (near 70%

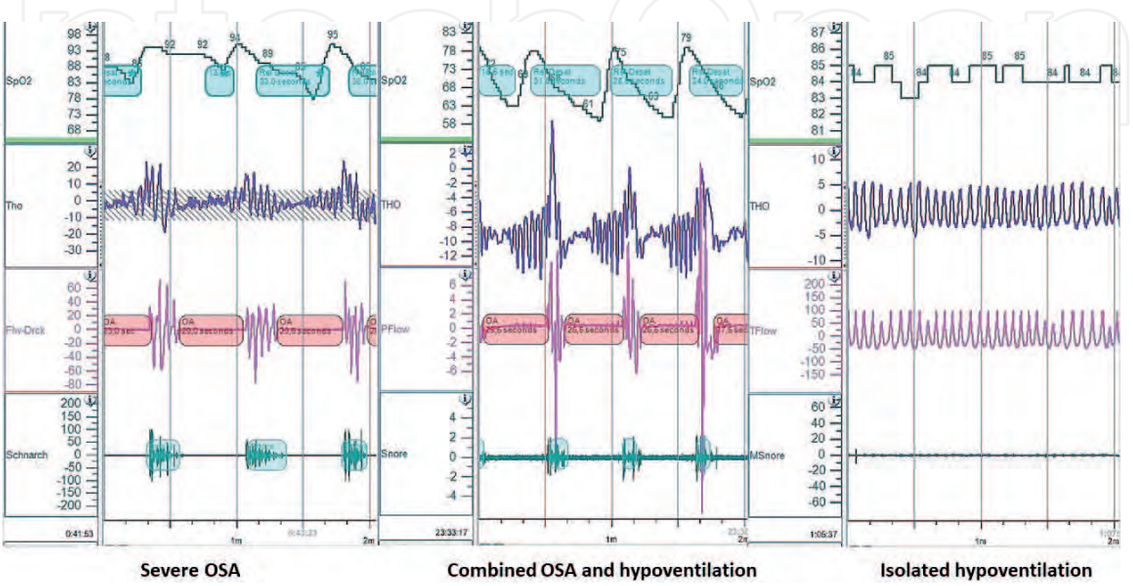

Figure 1.
Phenotypes of OHS.

of patients have severe OSA), and its presence should be presumed in treatment, especially in acute situations [14]. In a stable state, it is appropriate to devote time to the precise diagnosis, differential diagnosis, and titration of treatment.

3.2 Ventilation strategies in acute hypercapnic respiratory failure and OHS

While continuous positive airway pressure (CPAP) treatment may be appropriate for OHS and chronic hypercapnic respiratory failure, noninvasive ventilation (NIV) is the method of choice for acute or acute-on-chronic respiratory failure. It is a better alternative to invasive ventilation because it significantly reduces patient morbidity and mortality and reduces the risk of reintubation [7, 15].

3.2.1 Indications for NIV in acute hypercapnic respiratory failure in OHS

In an obese patient with a known or suspected diagnosis of OHS who meets the criteria for initiating ventilation support, noninvasive ventilation should be considered the first treatment modality.

Acute ventilatory support in OHS patients is indicated if the following criteria are met [16]:

- $PaCO_2 \geq 45$ mm Hg.
- Respiratory acidosis with $7.1 < pH < 7.35$.
- Severe breathlessness, tachypnea (≥23 breaths per min).

3.2.1.1 Notes

- Severe respiratory acidosis increases the risk of NIV failure but is not an obstacle to this treatment. It is possible to start a trial with NIV and be prepared for urgent endotracheal intubation.
- NIV can also be indicated in some hospitalized obese hypercapnic patients with daytime somnolence, sleep-disordered breathing, and/or right heart failure in the absence of respiratory acidosis [17].

3.2.2 Examinations and procedures before the start of the NIV

Before starting treatment with NIV, it is necessary (assuming patient safety—no delay of NIV) to perform the following procedures:

- Blood collection for arterial blood gas (ABG) analysis. An arterialized capillary blood sample (e.g., by heat) is an alternative
- Electrocardiography (12 lead)
- Chest radiography
- Search for and treatment of reversible causes of respiratory failure
- To determine in advance an individual plan for possible escalation of treatment (e.g., for do not intubate patients) [17]

3.2.3 Management of NIV in acute OHS patient

In the case of acute OHS, the NIV should be started immediately. OHS patients with severe daily sleepiness may be so somnolent that they cannot participate in placing their face masks. Treatment should be provided by staff experienced in NIV, and the patient should be placed in a high dependency unit (HDU) or intensive care unit (ICU) for close monitoring [17].

3.2.3.1 Important notes on the management of acute NIV in OHS

- **Interface**—Face mask (oronasal/full-face mask) is preferred in acute settings and very obese patients because of high pressures and mouth breathing [15]. Proper mask fitting is the key to successful NIV. It is advisable to choose the appropriate size mask (masks too large for the patient's face are more likely to leak) and adjust the restraining straps so that the mask is so loose that it seals well. In the case of skin lesions or bruises with an oronasal mask, it is possible to try the rotation of the masks (regular alternation of different masks; for example, total face mask or under nose full-face mask—e.g., Amara view, Dreamwear full-face—Philips Respironics™).

- **Ventilation mode**—Ventilation modes with backup respiratory rate are recommended in acute settings, for example, spontaneous-timed (ST) or pressure controlled (PC) mode, depending on the ventilation device and physician's experience.

- **Expiratory positive airway pressure (EPAP)/positive end-expiratory pressure (PEEP)**—It should be at least 8 cm H_2O [7, 15, 17]. It is possible to start with pressure 6 cm H_2O and gradually titrate upwards to improve tolerance and oxygenation, reduce respiratory load and control upper airway obstruction (snoring reduction). EPAP higher than 13–14 cm H_2O can be poorly tolerated, and too high EPAP reduces the possibility of achieving sufficient pressure support (depending on the ventilation device). Since comorbid sleep apnea is present in sleep, it is necessary to optimize EPAP during sleep. Software analysis of ventilation is helpful in subsequent parameter adjustments. Effective EPAP can be titrated manually, alternatively using specific modes, for example, AVAPS-AE™ (Philips Respironics) or auto-ST (Löwenstein medical) [18].

- **Inspiratory positive airway pressure (IPAP)**—It should be initiated at least 8 cm H_2O higher than EPAP. The difference between EPAP and IPAP, that is, pressure support (PS), should be increased gradually (up to 30 cm H_2O) to achieve a sufficient chest wall excursion and tidal volume (measured or estimated by a ventilator), but patient tolerance must be achieved [11, 15, 16].

- **Ensuring the target volume**—The use of ventilation pressure-controlled modes with target tidal volume settings such as average volume assured pressure support-AVAPS™ (Philips Respironics) or target volume (Löwenstein medical) is not necessary. However, in extremely obese patients with marked respiratory asynchrony in NIV, these modes can be used, as the ventilator can compensate for changes in lung compliance (e.g., patient position changes or tidal volume variability in-breaths triggered spontaneously or by device). Target tidal volume should be calculated and targeted at 8 (maximum 10) mL kg^{-1} ideal body weight [15]. PS (IPAP settings—IPAP

minimum-maximum) should be in an acceptable range (starting 4 cm H_2O above EPAP) to allow the device to reach the desired tidal volume. The rate of pressure change (to adjust tidal volume) is suitable to choose medium to fast. Volume-targeted ventilation modes are accompanied by higher mask air leaks but can (assuming good mask fitting) improve breathing synchronization instead of changing to other modes.

- **Backup rate**—Setting the backup respiratory rate in the range of 12–14 is the prevention of central apnea and hypoventilation during sleep [19].

- **Inspiratory time**—For mandatory breaths should be at least 1.2 s (up to 1.5 s). For ventilation devices with the possibility of setting the inspiratory and expiration ratio (I-E ratio), it is suitable to set it 1:2–1:1 [20].

- **Oxygen**—Oxygen inhalation is an extreme risk for OHS patients as it worsens hypoventilation [21]. In the stable and acute stage, oxygen is considered an additional treatment to NIV. In acute NIV, the amount of oxygen must be increased gradually to achieve saturation above 90% [11, 14–16].

- **Forced diuresis**—In acute-on-chronic respiratory failure in OHS, fluid overload commonly contributes to the severity of the disorder. Forced diuresis may be helpful initially [17].

- **Phlebotomy**—Hyperviscosity associated with secondary erythrocytosis may impair oxygen delivery in OHS patients. Phlebotomy may be considered in a patient with very high hematocrit as a part of intensive care therapy, provided that NIV is treated effectively and with sufficient oxygenation [11].

3.2.3.2 Contraindications to the use of NIV

Absolute:

- facial burns, severe facial deformity—inability to put on a mask
- gastrointestinal bleeding or ileus
- significant hemoptysis
- undrained pneumothorax
- inability to protect the airway, for example, fixed airway obstruction

Relative:

- copious respiratory secretions
- hemodynamic instability (cardiogenic shock, myocardial infarction)
- severe hypoxemia and acidosis (pH < 7.1)—predictors of NIV failure
- confusion/agitation
- coma—however, hypercapnic coma can be reversed using NIV [22, 23]

3.2.3.3 Monitoring in acute NIV

Patients treated with NIV require intensive care and careful monitoring, including:

- Monitoring: Respiratory rate, oxygen saturation, end-tidal CO_2, blood pressure, transcutaneous measurement of carbon dioxide ($TCCO_2$)
- Observation: Dyspnea, paradoxical abdominal movements, mask leaks, asynchrony with ventilator
- Measurements: Glasgow coma scale (GSC), acute physiology and chronic health evaluation (APACHE) score
- Labs: Blood gas analysis (sampling after 1–2 h of NIV, followed by 6–12 h for the first 24 h)
- Waveforms: Analysis of NIV parameters [23]

3.2.3.4 Failure of acute NIV and indication of endotracheal intubation in OHS

Despite careful monitoring and proper ventilation, NIV failure may occur in some cases. There is no exact algorithm to determine when to indicate intubation, but it is necessary to know the most common predictors of NIV failure [23–25]:

- excessive unintentional air leaks
- high severity score on admission (pH < 7.25, APACHE II score > 29)
- excessive respiratory secretions
- intolerance and noncompliance with NIV
- polymorbidity
- severe hypoxemia and low level of $PaCO_2$
- pneumonia
- low level of bicarbonates (HCO_3)—possible link to renal failure
- short duration of NIV
- minimal or no change in pH after 1–2 h of NIV
- no reduction in respiratory rate after 1–2 h of NIV

3.2.3.5 Further recommendations after successful acute ventilation in OHS

Data show that patients with a diagnosed or suspected diagnosis of OHS have a higher risk of death if they are discharged from the hospital without home positive airway pressure (PAP) treatment. Therefore, it is appropriate to set these patients for NIV treatment (ideally with pressure settings as in

hospitalization or with auto-PAP settings) and to schedule an early examination in the sleep laboratory and titration of PAP treatment (within 3 months) [26]. In patients acutely ventilated invasively, the use of NIV is an appropriate weaning strategy, as it effectively prevents respiratory failure in the first 48 h after extubation [24]. In patients requiring tracheostomy for prolonged invasive ventilation, it is advisable to perform decannulation and adjustment to home NIV after successful weaning instead of indicating long-term mechanical ventilation via tracheostomy.

3.3 Ventilation strategies in chronic hypercapnic respiratory failure and OHS

Initiating treatment of OHS patients in a stable stage allows assessing the ventilation strategy carefully. The choice of appropriate treatment should be based upon the severity of clinical state, the laboratory, functional and polysomnographic findings, reasonable cost-effectiveness, and the physician's experience. Clinical practice and literature data do not favor treatment by either CPAP or NIV as they are comparable, though some studies acknowledge certain benefits of NIV over CPAP.

3.3.1 Comparison of effectivity of CPAP and NIV

In the medium-term treatment, both CPAP and NIV have improved:

- Daytime hypercapnia, sleepiness [27]
- Health-related quality of life [28]
- Polysomnographic measures [29]
- Structural and functional echocardiographic measures [30]

NIV was superior to CPAP in terms of:

- Lung functions and 6 min walking test
- The rapidity of blood gases improvement [28]

In the long-term treatment, both CPAP and NIV have improved:

- Number of hospitalization days [31]
- Pulmonary hypertension and left ventricular diastolic dysfunction [32]

The concerns about the potentially harmful effect of NIV of hemodynamics due to the application of unphysiological positive pressure have been addressed by utilizing impedance cardiography, but it has not shown any deleterious impact on ventricular function [33].

The one undeniable benefit of CPAP over NIV is its lower cost [34]. The novel guidelines for the management of OHS by the American Thoracic Society [26] propose a switch of treatment from NIV to CPAP once the patient has achieved significant clinical improvement. This switch has been shown to be feasible and even favored by patients [35].

3.3.2 Obstructive sleep apnea

The one defining feature of OHS is its high prevalence of OSA, mainly of severe degree (estimated in around 70% of OHS patients). Thus, in patients with an apnea-hypopnea index (AHI) cut-off ≥30 episodes/h, it is reasonable to start with CPAP, as the primary aim is to alleviate obstruction in the upper airways, which might lead to the eventual resolution of chronic hypercapnia. For the patients without severe OSA, we should aim to improve the mechanics in the respiratory system and depression of the respiratory center; that is why NIV is used as an initial treatment.

3.3.3 Failure of CPAP

The patients initially set on CPAP should be monitored for signs of CPAP failure. In that case, a switch to NIV is warranted. The definition of CPAP failure is inconsistent among different researchers. Some of the criteria used for CPAP failure in OHS patients were:

- Insufficient improvement of oxygen saturation on CPAP:
  - Oxygen saturation below 90% for more than 20% of total sleep despite adequate abolition of apneas and hypopneas [36]
  - Oxygen saturation < 85% or hypercapnia despite maximal CPAP [37]
  - Oxygen saturation below 90% for more than 30% of titration night [38]
  - Oxygen desaturation < 80% over 10 min [9]
- Persistence of apneic and hypopneic episodes [37]
- Insufficient improvement of CO_2 levels
  - ≥5 min-long increase in nocturnal $PTcCO_2$ > 55 mm Hg and in $PaCO_2$ ≥ 10 mm Hg compared to the awake state [9]
  - Daytime $PaCO_2$ > 45 mm Hg [38]

The choice of criteria for CPAP failure should be suited for the practice of a particular sleep laboratory, and it should be consistent over time.

Careful evaluation is necessary to avoid deeming inadequate patient compliance as CPAP failure.

It is important to note that a failure of CPAP during titration does not necessarily lead to failure of the CPAP treatment [36]. A single or few titration nights of CPAP may falsely display a failure, when in fact, a more extended period of treatment (2–3 months) might be necessary for CPAP to be effective. The length of a trial should be adapted according to the convenience of a sleep laboratory.

3.3.3.1 Predictors of CPAP failure

The high proportion of CPAP failure in OHS patients has led to identifying certain predictors when CPAP should be tried with a reasonable expectation of success and when to proceed straight to NIV.

Recognized CPAP failure predictors were:

- awake oxygen saturation < 94% and PaO_2 < 68 mm Hg [37]
- daytime $PaCO_2$ > 53 mm Hg [15]
- BMI ≥ 50 kg m^{-2} [15, 39]
- significant comorbidities [40]
- acute respiratory failure [39]
- and clinician's preference [39]

Generally, worse blood gases [38], higher obesity, significant comorbidities, and clinician's preference warrant the trial of NIV in the first step.

3.3.4 Setup strategies of NIV

Novel increasingly intelligent auto-titrating devices are able to adjust to a patient's ventilatory need depending on his/her body position or the sleep stage.

- Volume targeted pressure support assures sufficient ventilation but may potentially lead to sleep disturbance.
- Auto-titrating EPAP allows to maintain the patency of upper airways and alleviates concomitant sleep apnea [18].
- Standard ST mode is not inferior to the novel modes but requires precise and gradual titration, which is time-consuming.

Similarly, as the OHS patients are monitored for signs of CPAP failure, patients with NIV should be checked frequently, as there is a possibility of improvement of the respiratory center sensitivity, and a switch from NIV to CPAP might be considered.

4. Chronic obstructive pulmonary disease (COPD)

COPD is a serious disease with an increasing prevalence, accompanied by a high risk of respiratory failure [41]. Unlike OHS, COPD is a disease where, in addition to the failure of the ventilatory pump (muscle weakness, shortening of the diaphragm), lung disease (obstructive airway disorder) is added [42]. The severity of the situation and the fact that it is a progressive disease also affect the management of respiratory failure. The use of NIV in COPD is common practice today. This treatment has clearly been shown to be effective in acute exacerbations of COPD (AECOPD) [43] and has long been a controversial topic in chronic indications [44]. However, recent studies have provided clear evidence in favor of treatment (including the effect on survival), and the greatest benefit of NIV has been present with higher pressures in NIV settings for maximum CO_2 reduction, in patients with higher basal $PaCO_2$ values, and in those who achieve high treatment compliance [45–47]. In the management of hypercapnic respiratory failure in COPD, there is growing evidence of the effectiveness of so-called high-intensity NIV (HI-NIV) [48].

However, many studies and guidelines perceive COPD as a single disease and do not reflect the existence of different phenotypes, comorbidities, and the need for a unique approach to them. One of them is an obese patient with COPD.

4.1 Obese patient with COPD

Several respiratory societies perceive COPD, not as a single homogeneous airway disease but also distinguishes between several phenotypes characterizing differences between patients [49, 50]. In intensive care units, patients with COPD often appear to be classified as a classic "Blue bloater." These patients are generally classified as chronic bronchitis phenotype, but its definition does not fully describe such a complex clinical trait. On the contrary, there is increasing evidence that this trait of COPD patients is characterized by different radiological findings than those seen in emphysema, and it is associated strongly with obesity and frequently also with OSA [51]. The prevalence of obesity among COPD patients is also very high and variable (18–54%) [51, 52]. Obesity is strongly linked with the presence of OSA, and in COPD patients requiring inpatient pulmonary rehabilitation, the number of obese patients with OSA increases significantly [53]. The presence of obesity and the COPD-OSA overlap syndrome appears to be a key factor in the pathogenesis and development of clinical signs of the blue bloater trait. This statement is underlined with evidence that the severity of static hyperinflation is negatively associated with the apnea-hypopnea index in both COPD and non-COPD patients surviving acute hypercapnic respiratory failure [54]. This evidence is following data showing that overlap syndrome increases the risk of respiratory failure, pulmonary hypertension, and COPD exacerbations [55]. In line with the above literary data [56], a new "obese patient with COPD" phenotype (characterized by predominantly chronic bronchitis, less hyperinflation, metabolic and cardiovascular comorbidity, sleep apnea symptoms, that is, daytime sleepiness, snoring, nonrefreshing sleep, and/or hypercapnic respiratory failure) was proposed [57] with a recommendation of screening for sleep-disordered breathing in this group of patients [50].

4.2 Ventilation strategies in acute exacerbation of COPD in obese patients

Acute exacerbation of COPD (AECOPD) is a severe condition that requires urgent intervention, and recommendations for its treatment are well known [41]. NIV has an irreplaceable place in the management of AECOPD in the event of acute or acute-on-chronic respiratory failure [17, 43]. In a patient with COPD who is obese, it should be borne in mind that obesity is probably one of the predominant factors predisposing to respiratory failure. Other possible factors such as cardiogenic edema, infection, uncontrolled excessive oxygen therapy, or pneumothorax should not be forgotten [17]. Because NIV effectively prevents endotracheal intubation and survival in patients with AECOPD [23, 58], it should be indicated whenever a patient meets the criteria for initiation.

4.2.1 Indications for NIV in acute hypercapnic respiratory failure in COPD

Acute ventilatory support in AECOPD is indicated in the same criteria as in OHS patients:

- $PaCO_2 \geq 45$ mm Hg
- Respiratory acidosis with $7.1 < pH < 7.35$
- Severe breathlessness, tachypnea (≥23 breaths/min)

4.2.1.1 Notes

It should be emphasized that controlled low-flow oxygen therapy (to achieve a saturation of 88–92%) is the basis for treating respiratory insufficiency in COPD. However, if respiratory acidosis develops or progresses (pH < 7.35) during careful monitoring of this treatment, NIV is recommended [7, 23].

4.2.2 Examinations and procedures before the start of the NIV

Examinations before the start of NIV are recommended the same as in Section 3.2.2. A chest radiograph is necessary to determine whether the deterioration of the patient's condition is caused by pneumothorax or pulmonary edema.

4.2.3 Management of NIV in an obese patient with AECOPD

A patient with AECOPD with respiratory acidosis is at extreme risk of early death, and early intervention is necessary [59]. NIV is highly effective in this indication but does not replace the standard treatment of AECOPD, which must be given in each case. NIV should be started as soon as it is confirmed that regulated oxygen therapy is failing. In the case of AECOPD, as in the case of OHS, CPAP is not an appropriate treatment (as respiratory support). The method of choice is bilevel ventilation [7, 17, 23]. In treating obese patients with COPD, we can generally proceed from the procedures in OHS, with certain specifics for airway disorder.

4.2.3.1 Important notations on the management of NIV in obese patients with AECOPD

- **Interface**: Since mouth breathing predominates in AECOPD, we prefer the oronasal (full-face) mask. Prevention of skin lesions is necessary, and mask rotation is useful. In case of failure to use the mask, helmet ventilation may be a suitable alternative.

- **Humidification**: Humidified ventilatory circuits are necessary for patients with airway disease.

- **Ventilation mode**: Spontaneous-timed (ST), pressure-controlled (PC) mode, allowing you to set the backup frequency.

- **EPAP**: For COPD, it is standardly recommended to set EPAP to exceed intrinsic PEEP in the airways (usually 5–6 cm H_2O). Because obese patients with COPD have a high risk of OSA, it is necessary to proceed as in the diagnosis of OHS and increase EPAP to eliminate upper airway obstruction (which is a condition for successful NIV).

- **IPAP**: The inspiratory pressure settings are like those in an acute patient with OHS. The purpose is to ensure sufficient pressure support, unloading of respiratory muscles, and reduction of respiratory work. It is necessary to achieve the required tidal volume, chest excursions, decrease respiratory rate, and eliminate the diaphragmatic paradox. IPAP can start at 15 cm H_2O, titrates upwards gradually in the range of 20–30, which are commonly used to manage AECOPD (mostly in pH < 7.25) [17, 44, 60]. However, patient tolerance is fundamental, and pressure increases must be gradual and monitored.

- **Ensuring the target volume**: Using ventilation pressure-controlled modes with target tidal volume settings can be useful, well-tolerated, and effective in managing AECOPD in obese patients. In addition, from a practical point of view, in an acute state, automatic modes (e.g., AVAPS™, target volume) require less intervention by staff (in terms of parameter titration) than in simple bilevel modes. In COPD, tidal volume can be targeted at 6 (maximum 8) mL kg^{-1} ideal body weight [60]. The rate of pressure change (to adjust tidal volume) is suitable to choose medium to fast (in super-obese patients).

- **Backup rate**: Backup respiratory rate should be set at 15 breaths/min [23].

- **Inspiratory time**: For mandatory breaths, 0.8–1.2 s according to breathing frequency. I-E ratio can be set 1:2–1:3 [20, 23]. For ventilators with the possibility of setting the inspiratory ramp and rise time, it is advisable to set them so that the patient has enough time to inhale and, in the case of prolonged expiration, allow him/her to exhale effectively.

- **Oxygen**: Standardly added to the ventilation circuit to achieve a saturation of 88–92%.

- **Monitoring choices and contraindications to NIV** are the same as in OHS (Section 3.2.3).

4.2.3.2 Failure of acute NIV and indication of endotracheal intubation in AECOPD

Predictors of NIV failure have already been mentioned in Section 3.2.3. The documented percentage of NIV failure ranges widely from 5 to 40% (depending on the predictors of failure, patient selection, and staff experience with NIV). Analysis of several studies has shown that the most significant predictor of NIV failure is pH 1 h after the onset of NIV, followed by the severity of the underlying disease and patient compliance [61]. If the pH after 1–2 h of NIV is below 7.25, respiratory rate > 25/min, or new confusion or distress appears, consider intubation [17]. Nevertheless, if NIV adds to patient distress and intubation has been inappropriate, NIV should be discontinued, and palliative care measures adopted [17].

In case of NIV failure and planning for escalation of treatment to invasive mechanical ventilation (IMV), it is necessary to [23, 60]:

- monitor and document parameters and signs indicating intubation

- document and provide a decision in "do not intubate" patients

- discuss the management with the patient and family

- plan intubation before late failure of NIV

4.2.4 Further recommendations after successful acute ventilation in COPD

NIV may be an appropriate option in patients who have survived intubation and invasive mechanical ventilation and require continued treatment for chronic respiratory failure. However, in ventilator-dependent patients requiring ventilation for 12 h or more, tracheostomy may be considered and is highly recommended if

the ventilation time exceeds 16 h per day. In this case, it is necessary to provide a ventilation device with an integrated battery [17, 40]. There are at least two reasons why we can assume that patients who have survived AECOPD with a need for NIV or IMV will be candidates for long-term home ventilation. The first is that obese patients with COPD have probable or known sleep-disordered breathing and will require some form of PAP treatment [53, 56]. Secondly, an episode of acute hypercapnic respiratory failure (AHRF) is a milestone in the course of the disease that predicts adverse development and prognosis [17]. In contrast to OHS (where weight reduction can reverse the course of the disease), this fact supports the planning of long-term ventilation treatment in obese patients with COPD. Therefore, clinicians should discuss the management of possible future episodes of AHRF with patients following an episode requiring ventilatory support because there is a high risk of recurrence [17]. Timing of indications for home mechanical ventilation (HMV) in COPD is a debated topic and ultimately depends on the decision of the patient and the physician. If the patient's condition after AHRF is stable, does not require continued ventilation, he/she may be discharged from the hospital with a scheduled early follow-up. It is recommended to reassess postacute NIV COPD patients 2–4 weeks after clinical recovery. NIV should be considered if the pCO_2 remains >7 kPa (53 mm Hg) [47] or if sleep-disordered breathing is detected in a sleep study.

4.3 Ventilation strategies in stable obese COPD patients

COPD is a disease associated with a high risk of developing chronic respiratory insufficiency [41]. Despite long-standing discussions about whether long-term NIV can affect the course and prognosis of the disease, the reality is that more than a third of patients treated are patients with lung and airways diseases [62]. Moreover, we now know that long-term NIV positively affects the quality of life and symptoms and improves survival [46, 47]. Thus, the question is not whether to ventilate COPD patients, but which COPD patients benefit from NIV and when it should be initiated.

4.3.1 Overlap syndrome COPD-OSA

Obese patients with COPD are very likely to have OSA simultaneously, commonly referred to as overlap syndrome [63]. The prevalence of these diseases in the general population is up to 10%, but in severely ill patients with COPD, the prevalence of OSA may be much higher, especially in the obese [53]. The coexistence of both diseases leads to a combination of continuous hypoxia (due to COPD) and chronic intermittent hypoxia (during sleep in apnea episodes due to OSA) in patients, which contributes to the development of the described clinical phenotype (Section 4.1) [57]. CPAP is the standard treatment for OSA and overlap syndrome [64]. However, CPAP treatment alone is more suitable for normocapnic patients with COPD, as it may not be effective in reversing hypoventilation and hypoxemia. Options should be carefully considered, and if nocturnal hypoxemia persists despite CPAP treatment, NIV may be an appropriate treatment instead of adding oxygen therapy to CPAP. In COPD patients diagnosed with OSA in the sleep laboratory, CPAP has been shown to fail in more than one-fifth. Although there are no clear limits to the efficacy of CPAP, treatment failure and NIV indication are more common in patients who are more obese, have worse lung function, hypercapnia, and more severe hypoxemia (with a longer desaturation time below 90% during nocturnal PSG) [65].

4.3.2 Indications for NIV in chronic hypercapnic respiratory failure in COPD

There is not only one criterion for indicating long-term NIV in COPD, which is confirmed by common practice that patients need to be approached individually [7, 9, 44, 66]. Long-term NIV may be indicated at a stable stage of COPD or after overcoming an acute exacerbation, meeting specific criteria, and considering the patient's needs. An important factor influencing the decision on the need for NIV is the presence of OSA. Contrary to the diagnosis of OHS with severe OSA, in the case of COPD-OSA overlap and hypercapnia, CPAP is not an appropriate option. CPAP may be effective in normocapnia in this case, but in hypercapnic COPD and the likelihood of progression of the underlying lung disease, NIV is the treatment of choice.

Long-term NIV may be indicated in well-established COPD (treated according to guidelines) in which there are persistent symptoms of chronic hypoventilation (hypercapnia), **and at least one of the following criteria is met:**

- chronic daytime $PaCO_2 > 50$ mm Hg
- nocturnal hypercapnia with $PaCO_2 > 55$ mm Hg
- daytime hypercapnia with $PaCO_2$ 45–50 mm Hg and nocturnal rise in transcutaneous CO_2 ($PTCCO_2$) ≥ 10 mm Hg
- stable daytime hypercapnia with $PaCO_2$ 45–50 mm Hg and at least two hospitalizations for hypercapnic respiratory failure within the past 12 months
- overlap syndrome COPD-OSA and daytime hypercapnia with $PaCO_2 > 45$ mm Hg
- after overcoming an acute exacerbation, if the need for respiratory support persists (based on clinical estimation)

4.3.3 Examinations before the start of long-term NIV

Blood gas collection and chest X-ray are recommended as standard. If possible, it is advisable to carry out a sleep study, preferably with the measurement of transcutaneous capnometry. Finally, the examination of lung functions is critical. Although this is not indicated directly in COPD exacerbation, in patients with a controversial diagnosis (especially in an obese patient), a misdiagnosis of COPD is common. Planning spirometry and possible body plethysmography with a distance from exacerbation before setting for long-term NIV will make it possible to clarify the diagnosis and set up treatment effectively.

4.3.4 Management of long-term NIV

Because patients with COPD form a wide range of different phenotypes, making precise recommendations on setting long-term NIV is not easy. In recent years, various approaches have been used, including the so-called low-intensity NIV (LI-NIV) and high-intensity NIV (HI-NIV) [44, 66]. The main difference is that HI-NIV uses higher values of IPAP and backup frequency to achieve normocapnia [48]. This approach has been shown in clinical trials to be effective in improving symptoms and quality of life and even in improving survival [45–47]. NIV was most effective

in those COPD patients where IPAP over 18 cm H_2O was used, baseline $paCO_2$ was over 55 mm Hg, and NIV was used overnight for more than 5 h [44]. Another option is to use volume-targeted ventilation modes. In COPD, their use is equally effective compared to HI-NIV [67]. It can make sense to obese patients with COPD because they allow them to better adapt to current and later patient needs when set up correctly.

4.3.4.1 Important notes on the management of long-term NIV in obese patients with COPD

- **Interface**: The choice of mask for long-term NIV is at the patient's and the physician's discretion but must ensure adequate ventilation and low leakage (e.g., in mouth breathers).

- **Ventilation modes and pressure settings**: Spontaneous-timed (ST) is the best option for long-term NIV. Automatic modes can be used to titrate settings, especially EPAP. The pressure setting is similar to AECOPD; the aim is to ensure airway patency (eliminate obstructive apnea). IPAP titration in chronic respiratory insufficiency may be less steep than in acute conditions. We can start at IPAP 12 cm H_2O and gradually increase above 18 cm H_2O (often between 20 and 30). We titrate the backup frequency slightly higher than in OHS. However, the basis is to ensure patient tolerance and compliance. Target volume modes can be used in obese patients like in AECOPD.

- **Oxygen**: In hypercapnic COPD, inhalation of oxygen through a nasal cannula is risky due to the progression of hypoventilation. If the NIV alone is insufficient to maintain saturation above 90%, it is advisable to add oxygen to the ventilation circuit.

5. Conclusion

This chapter aimed to discuss different approaches to the treatment of respiratory failure depending on the situation and diagnosis in obese patients. Up-to-date information from evidence-based medicine and international guidelines was used in the preparation of the chapter. Although COPD and OHS are different diagnoses with different prognoses, in obese patients, they are associated with the presence of sleep-disordered breathing. It is obstructive sleep apnea that seems to be a key factor contributing to the clinical picture of the so-called obese patient with COPD, and early diagnosis and treatment can reverse the negative impact of the disease on patients' health.

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Chapter

Mechanical Ventilation in Neurocritical Patients

Thierry Hernández-Gilsoul, Jose de Jesús Vidal-Mayo and Alan Alexis Chacon-Corral

Abstract

Patients under neurocritical care may require mechanical ventilation for airway protection; respiratory failure can occur simultaneously or be acquired during the ICU stay. In this chapter, we will address the ventilatory strategies, in particular the role of protective lung ventilation, and the potential increase in intracranial pressure as a result of permissive hypercapnia, high airway pressures during recruitment maneuvers, and/or prone position. We will also describe some strategies to achieve mechanical ventilation liberation, including evaluation for tracheostomy, timing of tracheostomy, mechanical ventilation modalities for weaning and extubation, or tracheostomy weaning for mechanical ventilation.

Keywords: mechanical ventilation, neurocritical

1. Introduction

Neurological critically ill patients represent an important group in the intensive care unit (ICU) worldwide. About 20% of these patients require mechanical ventilation (MV) of which 20–25% will develop acute respiratory distress syndrome (ARDS) [1, 2]. Ventilatory management is controversial in this kind of population due to the complexity of the event and singularity of each case with acute brain injury (ABI). This includes traumatic brain injury (TBI), intracerebral hemorrhage (ICH), aneurysmatic subarachnoid hemorrhage (aSH), acute ischemic stroke (AIS), and other entities associated with high intracranial pressure (ICP). Additionally, brain damage may be prevented by avoiding pulmonary and systemic injury associated with mechanical ventilation. Thus, this topic is particularly important, since respiratory failure is the most frequent extracerebral organic failure in patients with ABI [3].

Recently, the VENTILA group reported some interesting characteristics, in the evolution of the ventilatory management in neurological critically ill patients, in three cohorts of patients with mechanical ventilation (2004, 2010, and 2016) [4]. In this multicentric international report of 4152 patients, the main pathologies were intracerebral hemorrhage and traumatic brain injury. One of the main results was an increment in the use of lung protective ventilation through time (47% in 2004, 63% in 2010 vs 65% in 2016; $p<0.001$). However, there were no differences in other outcomes such as length of stay in ICU, length of stay in hospital, mortality in the ICU, and mortality in the hospital. Some variables were associated with mortality in multivariate analyses such as age > 75 years old (OR 1.80, CI 95% 1.40–2.30),

SAPS II (Simplified Acute Physiology Score II) > 50 points (OR 2.31, CI 95% 1.87–2.86), occurrence of organic failure within the first 48 h after ABI (OR 1.79, IC 95% 1.59–2.0), and etiology of ABI, specifically TBI (OR 1.8, CI 95% 1.4–2.3), ischemic stroke (OR 3.94, CI 95% 2.47–6.31), and cerebral hemorrhage (OR 3.96, CI 95% 2.59–6.06).

2. Brain-lung cross talking

Acute brain injury can create issues in lung function and vice versa. This bidirectional brain-lung interaction is supported in experimental models and basic studies in humans, which have shown several neuroinflammatory, autonomic, immunologic, and endocrine pathways [5]. According to the so-called two-stroke model, when ACL occurs, a lung injury associated with systemic inflammation due to a "catecholamine storm" appears, first hit; subsequently these events can trigger an increase in permeability into the pulomnary capillaries, vasoconstriction in the pulmonary arterioles and recruitment of inflammatory cells in the alveoli, second hit [6].

Hypoxemia and hypercapnia are associated with lung injury and amplify acute brain injury. Both situations reduce cerebral vascular resistance, which consequently raises cerebral blood flow and increases ICP. Also, they can increase the systemic inflammatory response and produce extracerebral organic failures. In the literature, this chain of events had been denominated *dangerous cross talk* [7, 8]. Thus, ventilatory management has been considered a strategy to avoid ventilator-induced lung injury (VILI) through the use of lung-protective ventilation.

3. Ventilatory management

The most recent guidelines related to this topic are provided by the European Society of Intensive Care Medicine [9]. Evidence about most of these recommendations remains at a low level; for this reason, we present the most general suggestions in order to give a safety and efficient ventilatory management to these patients.

3.1 Oxygenation and carbon dioxide (CO_2) targets

In patients with ABI, it is fundamental to guarantee an optimal oxygenation to avoid secondary brain injury [10]. It is recommended to target "normoxia" with a partial arterial pressure of oxygen (PaO_2) between 80-120 mmHg and or a peripheral oxygen saturation (SpO_2) of ≥95% in patients with or without intracranial hypertension [9, 11].

In addition, some evidence suggests that hyperoxia is an independent factor associated to greater mortality and outcomes driven by several mechanisms: vasoconstriction of brain arteries, synthesis of reactive oxygen species (ROS) and damage associated molecular patterns (DAMPs) [10]. In a clinical trial of patients with traumatic brain injury (TBI), which evaluated two oxygenation strategies (normobaric hyperoxia and normoxia), there were no differences in the hospital length of stay, but the modified Rankin scale at discharge and at 6 month follow-up was better in the normoxia group [12].

In relation to the minute ventilation settings (respiratory rate times tidal volume) to modify the CO_2 content of the blood, it is recommended to adjust the ventilation to maintain normal levels of arterial pressure of carbon dioxide ($PaCO_2$) between 35 and 45 mmHg. Traditionally, it was considered that patients with ABI (specially population with TBI) should be maintained with hyperventilation;

however, this situation can lead to cerebral vasoconstriction that can worsen cerebral tissue hypoxia and ischemia [13]. In a randomized clinical trial conducted by Muizelaar et al., it found that patients with TBI undergoing systematic hyperventilation ($PaCO_2$ 25 ± 2 mmHg) had poorer outcomes at 3 and 6 months' follow-up compared with the normocapnia group ($PaCO_2$ 35 ± 2 mmHg). Deleterious findings were also documented in head injury patients who were managed with hyperventilation plus tromethamine addition as buffer [14]. Transient hyperventilation ($PaCO_2$ 30–35 mmHg) is only recommended as a rescue maneuver in cases of brain herniation [9].

3.2 Tidal volume (Vt)

Ventilation with Vt between 6 and 8 ml/kg of predicted body weight is considered a standard of ventilatory treatment in patients with ARDS and its application in general in patients under invasive ventilatory support. However, historically, neurocritical patients have been excluded from clinical trials that have evaluated this ventilatory therapeutic strategy due to the potential increase in intracranial pressure caused by hypercapnia and increased intrathoracic pressures [15].

In a multicenter cohort study, it was found that an average Vt of 9 ml/kg of predicted weight was used in this group of patients [15]. Additionally, it has been described that the use of high Vt has been associated with the development of ARDS in these patients [16] while other observational studies have found no evidence of this association; instead, driving pressure was the only ventilatory variable associated with the development of ARDS [17]. Likewise, there is no consistent evidence that the use of a Vt by itself increases intracranial pressure [15, 18].

A recent multicenter prospective study that used a strategy of low Vt (less than 7 ml/kg), moderate PEEP (6–8 cmH_2O), and a protocol for early extubation was associated with more days free of mechanical ventilation and lower mortality at 90 days, with no serious adverse events associated with this intervention [19]. Condensing this information, the administration of Vt of 6–8 ml/kg is suggested to maintain a plateau pressure of less than 25 cmH_2O and a driving pressure of less than 15 cmH_2O [8, 11, 13].

3.3 Positive end expiratory pressure (PEEP)

Implementation of PEEP associated with low Vt in the pulmonary protective ventilation strategy has been associated with better clinical outcomes, even in patients without ARDS [20]. Its use has been a useful strategy in neurocritical patients where oxygenation and ventilation are essential. The PEEP level has been considered a potential indirect maneuver that increases ICP in a directly proportional way. This led Asehnoune et al. to study the use of PEEP and its effect on intracranial pressure, comparing PEEP levels less than or greater than 5 cmH_2O; no clinically significant differences of episodes of intracranial hypertension were seen [19]. Boone et al. analyzed 341 patients with ABI, in which nonsignificant effects of PEEP on ICP or cerebral perfusion pressure (CPP) were documented [21]. Furthermore, in a study of patients with aSH divided into groups according to respiratory compliance, those with decreased respiratory compliance (<45 ml/cmH_2O) did not show changes in the hemodynamic variables, including CPP at diverse levels of PEEP [22].

In another prospective study of 20 patients with TBI with brain-tissue oxygenation ($P_{bt}O_2$) monitorization, an increase in the level of PEEP from 5 to 10 cmH_2O (24.60 ± 6.84 to 26.55 ± 7.09; $p = 0.0001$) and from 10 to 15 cmH_2O (26.55 ± 7.09 to 29.05 ± 7.07; $p = 0.0001$) significantly increased $P_{bt}O_2$ in these patients, without significant changes in ICP or CPP [23].

Therefore, it is recommended to administer a sufficient PEEP (5–8 cmH_2O) to maintain adequate oxygenation. In cases where PEEP is greater than 10–15 cmH_2O, it is suggested that advanced neuromonitoring be used to adjust this variable optimally [11, 13, 24].

3.4 Prone positioning

Mechanical ventilation in the prone position is also a standard of treatment for patients with moderate-severe ARDS, since it reduces mortality in addition to improving oxygenation, respiratory mechanics, and ventilation-perfusion imbalance. However, due to the potential increase in ICP and reduction in CCP, these patients have also been excluded from clinical studies to evaluate this intervention [13].

In an observational study of patients with aSH, who fulfilled criteria for ARDS within the first 2 weeks, a significant increase in oxygenation was found (97.3 ± 20.7 mmHg in the supine position to 126.6 ± 31.7 mmHg in the prone position) as well as an increase in $P_{bt}O_2$ (26.8 ± 10.9 mmHg to 31.6 ± 12.2 mmHg; $p < 0.0001$) with a good tolerance of the intervention (prone position for 14 hours). In contrast to a concomitant increase in ICP and a decrease in CPP, however, overall, the benefit in systemic oxygenation was greater than the effects on cerebral perfusion and intracranial pressure [25].

In the same way, other observational studies have reported that this maneuver improves patient oxygenation and $P_{bt}O_2$ with a tendency to increase ICP but without reducing CPP. One report with 8 patients showed a significant increase in oxygenation with an increase in ICP and CPP as well as an improvement in $P_{bt}O_2$ [26]. Roth et al. found in a retrospective study that patients had a significant increase in oxygenation with an increase in ICP without significant changes in CPP [27].

Recommendations in this group of patients suggest ventilation in the prone position. In patients with moderate-severe ARDS without evidence of intracranial hypertension, it is a safe and effective strategy. However, the risks and benefits of the intervention should be considered, and the patient must have multimodal monitoring to determine the effects on both systemic and cerebral hemodynamics and oxygenation [9, 11].

3.5 Alveolar recruitment maneuvers

Another controversial aspect is the use of alveolar recruitment maneuvers, due to the potential risk of increasing intracranial pressure with reduction of CPP [13]. In systematic reviews and meta-analysis of ARDS studies, it was found that this intervention is associated with an improvement in the oxygenation of patients but without effects in other outcomes such as mortality or duration of mechanical ventilation [28, 29].

In studies carried out in this population, conflicting results have been found regarding the efficacy of this intervention to improve oxygenation; however, regarding neurological variables, some studies described an increase in ICP associated with a decrease in CPP without improvement in oxygenation [30, 31]; another study found that recruitment maneuvers significantly affected cerebral hemodynamics [32].

Although the most recent guidelines for ventilatory management of these patients do not issue any recommendation due to limited evidence [9], expert recommendations suggest that this intervention can be considered individually in patients with acute brain injury and concomitant ARDS with an invasive neuromonitoring for the potential risks and benefits of these maneuvers [8, 13].

4. Extracorporeal life support (ECLS)

Extracorporeal membrane oxygenation ventilation (ECMO) and extracorporeal CO_2 removal ($ECCO_2R$) have gained popularity for patients with hypoxemic respiratory failure refractory to conventional ventilation strategies; however, because the evidence for this intervention is anecdotal in this patient population [33, 34] and there is a risk of catastrophic complications in patients with ABI (especially intracranial hemorrhage due to the need for routine anticoagulation), there is no consensus to carry out this intervention in neurocritical patients [9, 11, 13]. Heparin-free regional citrate anticoagulation, like in renal replacement circuits, may offer an alternative to this problem [35]. The use of regional citrate anticoagulation continuous veno-venous hemofiltration (RCA-CVVH) connected to an ECMO circuit, with low heparin or heparin-free ECMO, has been reported [36].

In an experimental model of severe hypercapnic acidosis, regional anticoagulation with citrate solution achieved the anticoagulation goal as well as standard heparin anticoagulation but did not improve CO_2 removal and led to more hypocalcemia and hypotension [37].

5. Weaning from mechanical ventilation

Historically, the population of neurocritical patients has been considered at high risk of failure to extubation (from 10 to 38% failure), and hence there is delayed withdrawal of mechanical ventilation which is associated with higher rates of ventilator associated pneumonia (VAP) and airway injury; longer mechanical ventilation and ICU length stay, and higher mortality [15, 38, 39].

The recommendations of the international guidelines for the withdrawal of mechanical ventilation do not contemplate specific aspects for this population [40, 41], in addition to the fact that certain general aspects of these consensuses are not applicable for neurocritical patients:

- The process by which the patient is on mechanical ventilation is not resolved in most cases of patients with ABI [3, 39, 42].

- Evaluation of the state of consciousness (and, therefore, the ability to follow commands) is altered in a significant proportion of patients. In addition, scales used for the neurological evaluation in neurocritical patients on mechanical ventilation do not precisely discriminate success versus failure after extubation [40, 41]. Some studies have found that a score greater than 8 or greater than 10 in Glasgow Coma Scale (GCS) is associated with a successful withdrawal from mechanical ventilation [43, 44], while other series found that neither the GCS [42] nor the FOUR scale [45] was associated with successful extubation.

There is evidence that multidisciplinary and standardized protocols in these patients are associated with better outcomes and a higher rate of successful withdrawal from mechanical ventilation [46, 47]. One tool designed for this population is the VISAGE score by Asehnoune et al [44]. This score was derived from a multicenter prospective cohort that included a heterogeneous population of patients with ABI (n = 437), of which 77.3% had a successful extubation. From the multivariate analysis of the factors associated with successful extubation, 4 variables with significant association were found that made up the VISAGE score: visual pursuit, swallowing attempts, age under 40 years, and GCS greater than 10 points (**Table 1**). According to the original validation study, a score on this scale greater than or equal to 3 points

A score ≥ 3 is associated with 90% extubation success; each variable has a value of 1 point • Age < 40 years • Visual pursuit • Swallowing attempts • Glasgow coma score > 10 points
[44].

Table 1.
VISAGE score.

has a sensitivity of 62%, specificity of 79%, positive predictive value of 90%, negative predictive value of 39%, positive likelihood ratio of 2.9, and negative likelihood ratio of 0.5 to predict extubation success. This scale represents a practical tool for use in the patient's bed, for which several experts have recommended its clinical use; however, external validation in other patient cohorts is still pending [48, 49].

In a systematic review with meta-analysis, Wang et al. found that other variables associated with extubation failure in neurocritical patients are the presence of pneumonia, atelectasis, mechanical ventilation for more than 24 h, a score of GCS lower than 8 (OR = 4.96.95% CI = 1.61–15.26, p = 0.005), the inability to follow orders (OR = 2.07.95% CI = 1.15–3.71, p = 0.02), thick secretions, and alteration in cough reflex [50]. Another score that evaluates the ability to protect the airway has been proposed (the Airway score), which takes into consideration variables such as the amount and quality of respiratory secretions, gag and cough reflex, and patients with a score of less than 6 who are candidates for IMV withdrawal. Nevertheless, it should be considered that there is a wide variability in the qualitative assessment of respiratory secretions and that there is no extensive external validation of this tool [51].

Regarding the actual evidence of tracheostomy performance, it has been observed that intensivist achieves more frequently tracheostomies in neurocritical patients (up to 45%) compared to general patients in the ICU [52]. The theorical benefits of tracheostomy are that it decreases the work of breathing and improves patient comfort when compared to an endotracheal tube. Tracheal stoma that does not generate pain after 48–72 h of tracheostomy placement. Reduction or suspension of sedation and opioid analgesia, as well as less work of breathing are the theorical benefits that generate greater patient comfort. Contrary to general belief, there is no evidence that it decreases the frequency of tracheal stenosis associated with prolonged ventilation. Even more, an endotracheal cannula also requires the inflation of a balloon to isolate and protect the airway from bronchoaspiration; thus, tracheal stenosis is also a complication, which according to a case study is more complicated (infraglottic stenosis) and may not resolve more frequently compared to tracheal stenosis acquired with an orotracheal tube [53].

According to this information and consensus, it is recommended to consider to facilitate the withdrawal of mechanical ventilation in the following cases: infratentorial lesions, inability to protect the airway (inadequate management of respiratory secretions), altered central respiratory drive, slow or unfavorable neurological recovery, and patients with recurrent extubation failure.

However, the precise indications for its performance and the timing of the intervention remain poorly defined in the literature [38, 48, 54].

A highly controversial aspect is the performance of "early tracheostomy," which has been defined as placing it within the first 7 days [55] (there are reports that define it from day 5 to day 10) of mechanical ventilation [56, 57].

Large series of patients that have compared early versus late tracheostomy have not found a benefit in terms of mortality, although there is a trend of better

outcomes in the early tracheostomy group, such as reduction in the frequency of ventilator-associated pneumonia, fewer days of mechanical ventilation, and a shorter length of stay in intensive care [58, 59]. In the SETPOINT study (Stroke-related Early Tracheostomy vs. Prolonged Orotracheal Intubation in Neurocritical care Trial) that randomized 60 patients with stroke or cerebral hemorrhage to early tracheostomy (day 1–3 of mechanical ventilation) versus standard tracheostomy (between 7 and 14 days), no difference was found in the primary endpoint, which was the length of stay in the ICU (median, interquartile range [IQR] 8, 16–28 days versus 17 [13–22] days, median difference: 1 [−2 to 6]; $p = 0.38$) although in the intervention group, mortality in the ICU and at 6 months was significantly lower (10 versus 14%; $p < 0.01$ and 27% versus 60% $p = 0.02$), without finding other differences in other secondary outcomes [60].

The CENTER-TBI study that was a prospective European multicenter cohort of adult patients with head trauma found that the factors associated with the decision to perform a tracheostomy were older age (HR = 1.04, 95% CI 1.01–1.07; $p = 0.003$), GCS less than or equal to 8 (HR = 1.70, 95% CI = 1.22–2.36 at 7; $p < 0.001$), thoracic trauma (HR = 1.24, 95% CI = 1.01–1.52, $p = 0.020$), hypoxemia (HR = 1.37, 95% CI = 1.05–1.79, $p = 0.048$), and absence of pupillary reactivity (HR = 1.76, 95% CI = 1.27–2.45 at 7; $p < 0.001$). Additionally, a wide heterogeneity was identified in the frequency (7.9–50.2%) and timing of early tracheostomy practice (0–17.6%) in

	Points
Neurological function	
Dysphagia (4 points)	4
Observed aspiration (3 points)	3
GCS on admission < 10 (3 points)	3
Neurological lesion	
Brain stem (4 points)	4
Ischemic stroke > 2/3 middle cerebral artery territory (4 points)	4
ICH volume > 25 ml (4 points)	4
Hydrocephalus (4 points)	4
Space-occupying cerebellar (3 points)	3
Diffuse lesion (3 points)	3
Extracerebral organ function-procedure	
APACHE II score > 20 (4 points)	4
Sepsis (3 points)	3
Additional respiratory disease (3 points)	3
PaO_2/FiO_2 < 150 (2 points)	2
LIS score > 1 (2 points)	2
Neurosurgical intervention (2 points)	2

A score > 8 in combination with an estimate of an experienced neurointensivist suggests prolonged ventilation and need of tracheostomy.
GCS = glasgow coma scale. ICH = intracerebral hemorrhage. PaO_2 = partial arterial pressure of oxygen. APACHE II = acute physiology and chronic health evaluation II. LIS = lung injury score.
[62, 63].

Table 2.
SET score to estimate tracheostomy need after severe stroke.

this cohort. Late tracheostomy (after 7 days) was associated with worse neurological outcomes and a longer stay in the intensive care unit [61].

In acute cerebrovascular events (ischemic stroke, cerebral hemorrhage, and aSH), a specific score for predicting tracheostomy has been designed and tested in these patients. The SET score (**Table 2**) that combines various variables from 3 items (neurological evaluation, characteristics of the injury, and extracerebral organic procedure/function) is the one with the greatest external validation for use in this population. A SET score of >10 points has a sensitivity of 64–81%, a specificity of 57–86%, and an area under the curve of 0.74 (95% CI 0.68–0.81) [62, 63].

In terms of an invasive procedure without complications, percutaneous tracheostomy is practically equivalent to surgical tracheostomy. Some systematic reviews with meta-analyses have found that the former has fewer stoma infections, with similar rates of bleeding and other procedural complications [64–66].

6. Conclusion

Neurocritical patients represent a particularly challenging subgroup for ventilatory management due to coexistence of acute brain injury associated with other organ failure, the most frequent being respiratory failure. Management of mechanical ventilation should prevent secondary brain injury by ensuring optimal ventilation and oxygenation. The use of additional strategies to standard management of pulmonary protective ventilation (high PEEP, recruitment maneuvers, and extracorporeal circulatory support) in patients with refractory respiratory failure should be individualized and be accompanied by advanced neuromonitoring (invasive measurement of intracranial pressure and cerebral tissue pressure oxygen). It is important to avoid a late withdrawal of mechanical ventilation using adjuvant scales such as the VISAGE score; theorical benefits from tracheostomy include reduction and suspension of sedation and opioid analgesia as well as patient comfort due to lower work of breathing and may be considered in patients with slow neurological recovery, failure to extubation, and those patients with dysphagia or altered state of consciousness resulting from a primary injury to the central nervous system.

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Chapter

Mechanical Ventilation for Patients with COPD

Ozlem Ediboglu

Abstract

Mechanical ventilation is a lifesaving therapy in patients who have acute respiratory failure due to chronic obstructive pulmonary disease (COPD). Mechanical ventilaton either invasive or non-invasive has an important role in the management of acute exacerbation of COPD (AECOPD). AECOPD required hospitalizaton had increased mortality and poor prognosis. Ventilatory management success related to understanding physiopathology of the disease. Clinicians must be aware of deterioration of clinical signs of COPD patients. The most appropriate treatment should be performed at optimal time. Some COPD patients are at high risk for prolonged mechanical ventilation due to COPD is a progressive disease.

Keywords: mechanical ventilation, COPD, respiratory failure

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major global health problem which has high morbidity and mortality [1]. COPD is characterized by chronic inflammation of the airways and lung parenchyma. The most important physiologic abnormality is worsening of expiratory airflow limitation due to increased airway resistance and decreased elastic recoil [2]. Patients who have fexpiratory airflow limitation cannot breath normally and due to dynamic hyperinflation increase work of breathing. These physiologic changes are deteriorated unless avoid risk factors because of COPD is a progressive disease and can be complicated with different severity of acute exacerbation [1–4].

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is described an acute worsening of the clinical condition of the COPD patient [5]. Clinical features are highly variable and AECOPD has a negative impact of patients' health status and outcomes [1, 6–8]. The reported mortality associated with a AECOPD is variably at 11% to 32% [9]. The mortality rate and costs are much higher in some patients requiring mechanical ventilation [10, 11]. In severe AECOPD, it is crucial to recognise acute respiratory failure (ARF) immediately and to decide appropriate treatment. ARF is defined as the inability to maintain the delivery of oxygen and/or removal of carbon dioxide acutely. Worsening gas exchange and consequently hypercapnia and/or hypoxemia occur in arterial blood gas sample (ABG) analysis [12].

2. Non-invasive ventilation

Mechanical ventilation either invasive or non- invasive is lifesaving treatment for acute respiratory failure. It is targeted by non - invasive ventilation (NIV)

to minimize risks of mechanical ventilation and maximize patients' safety and comfort. Hence NIV is successful to provide alveolar ventilation and gas exchange as invasive mechanical ventilation (IMV); NIV accepted widely as the first choice in treating AECOPD patients with ARF [13–24]. NIV therapy success is related to appropriate patient selection and early application [14, 25–27]. The appropriate patient means that is alert, co-operative, compliant and has no contraindications [28].

NIV is applied after initial treatment if the pH remains <7.30 and after exclusion of reversible precipitating causes such as a pneumothorax, the depressant effect of uncontrolled oxygen therapy, or the excessive use of sedatives [29–31]. According to GOLD guide, NIV is considered at least one of these conditions; respiratory acidosis, weakness of respiratory muscles, severe dyspnea, increased work of breathing, accessory muscle using, intercostal retraction, paradoxal breathing and persistant hypoxemia with oxygen therapy [32]. Main determinants are experience of the clinician, place of the NIV therapy, clinical condition and theurapeutic requirement of patient [33, 34].

NIV can be apply with all ventilators used in IMV support [35]. It's important to known technical specialities and settings by clinician. Portable ventilators, intermediate ventilators and ICU ventilators has been used [33, 36]. Portable ventilators are named according to targeted parameter as volume and pressure ventilators. The synonim name is portable device is bilevel or BiPAP (Bilevel positive airway pressure) ventilator. Clinicians must be aware of difference between settings of the two devices: While adjusting IPAP (inspiratory positive airway pressure), EPAP (expiratory positive airway pressure) levels setting in BiPAP device, pressure support (PS = IPAP - EPAP) and EPAP levels in ICU ventilators [33, 37]. Bi-level pressure support ventilators are simpler to use, cheaper, and more flexible than other types of ventilator currently available. ICU ventilators have full monitoring and alarm capability and can be given up to 100% FiO_2 when needed [30, 33]. Whole appropriate equipment must be ready to iniciate the NIV therapy as single/double lumen circuit, nasal/oronasal NIV mask by different size [38]. Mask selection is more important than ventilator. In acute setting, oronasal mask is well tolerated and preferred by many clinicians [14, 38, 39].

NIV is contraindicated in these situations; respiratory or cardiac arrest, hemodynamic instability, inability to use mask, excessive secretion, high risk for aspiration, and uncooperative patient.

Initially it is began with low pressure levels as IPAP 8–10 cm H_2O and EPAP 4–5 cm H_2O. According to patient's clinical status, pressure levels can be increased. Monitorization of clinical signs, parameters of mechanical ventilation and gas exchange at the bedside are very important. Especially clinician must be follow and record subjective symptoms like anxiety, consciousness, delirium, agitation, sedation, analgesia, patient comfort, dyspnea, tolerance of mask. All the time NIV therapy, physiological response like respiratory rate (RR), using accessory muscle, heart rate (HR) and rhythm, blood pressure (BP) must be recorded. After the first 1–2 hours ABG must be done. We must consider intubation, if no improvement in ABG, deterioration in level of consciousness, NIV poorly tolerated, and inadequate secretion clearance [1, 7, 21, 40].

NIV failure is associated with hospital mortality, length of hospital and ICU stay [41]. NIV failure indicators are found as initial pH <7.25, Glascow Coma Scale (GCS) <10, Acute Physiology and Chronic Health Evaluation (APACHE) II score > 25, severe comorbidity, asynchrony, leaks [7, 42], existing pneumonia, and bad initial response (no change RR, pH and $paCO_2$) [14, 43]. The potantial causes NIV failure are defined that poor patient selection, progression of the underlying disease, wrong interface, wrong ventilator, inappropriate ventilator settings

and clinican's inexperience [44]. In a study, HACOR scores (heart rate, acidosis, consciousness, oxygenation, respiratory rate) be defined as a potential tool for clinical physicians to identify NIV failure earlier [45]. Patient tolerance to NIV is a critical factor determining its success in avoiding endotracheal intubation [46]. The most important point of the tolerance to NIV is optimal synchrony between the patient's spontaneous breathing activity and the ventilator's set parameters, known as "patient–ventilator interaction" [47]. Clinician can detected an asynchrony index (AI) (%) via visual inspection of asynchrony events (ineffective triggering, auto-triggering, premature cycling, double triggering and delayed cycling). AI is identified as number of asynchrony events/total RR X 100% and above 10% was accepted as severe asynchrony [44]. In a multicenter study, severe asynchrony was found 43% [48]. The level of pressure support and the existing of leaks were found independent predictive factors of severe asynchronies and severe asynchronies were detected 30% of patients [49]. Patient-ventilator synchrony is related to better success of NIV. For this reason, in case of asynchrony, the most appropriate strategies should be followed to improve synchronization with NIV [44].

3. Invasive mechanical ventilation

Endotracheal intubation should be done any one of the following criteria immediately: respiratory arrest, loss of consciousness, psychomotor agitation requiring sedation, hemodynamic instability with a systolic BP less than 70 or greater than 180 mmHg, HR less than 50 beats/minute with loss of alertness, gasping for air. These criteria are named major criteria. Intubation was suggested any two of the following criteria also named minor criteria; RR >35 breath/min, worsening acidemia or pH < 7.25, paO_2 < 40 mmHg or paO_2/FiO_2 < 200 despite oxygen therapy, decreasing level of consciousness [50]. Before intubation preoxygenation is essential. Intubation with the rapid sequence induction and cricoid pressure to reduce the risk of aspiration should ideally be performed by an experienced clinician [51].

After intubation, its targeted to improve gas exchange abnormality and to avoid auto-PEEP ($PEEP_i$) [7, 52]. Dynamic hyperinflation(DHI) may exist before intubation or induced by mechanical ventilation. The minute volume (MV) should be adjusted to pH and not to the $PaCO_2$ levels. Clinicians should be avoid overventilation and $paCO_2$ levels should decreased gradually. It is important to provide lower MV (RR x tidal volume (TV)) and higher inspiratory flow rate which has allow longer expiratory time. Any mode can be used, either assist control (AC), synchronized intermittent mandatory ventilation with either volume or pressure target (SIMV-VS, SIMV-PS), or pressure support ventilation(PSV). Clinician's experience is the most important determinant of mode selection. Initial ventilator settings are recommended like that; TV: 6–10 ml/kg, FiO_2: 1.0, RR: 10–14 breaths/minute, no PEEP, inspiratory flow rate: 80–100 liter/minute with square waveform [1, 2, 4]. Monitoring the lung mechanics on ventilator graphic screen continously and detecting any sign of DHI or $PEEP_i$ are very important. The clinicians should be followed existing any clinical signs to avoid the complications of DHI. The most important complications of DHI are hypotension, hemodynamic collaps, barotrauma and increased work of breathing (WOB) [51, 53]. Therefore, that strategies must be applied by clinicians to reduce auto-PEEP; providing the longest expiratory phase that is possible, reducing patient ventilatory demand and MV, and reducing airflow resistance by bronchodilators and steroids [1].

Barotrauma is an important risk at the COPD patients. Elevated peak inspiratory pressure (PIP) does not reflect the alveolar pressure in patients with bronchospasm.

Alveolar pressure can be detected with plateau pressure (P_{plat}) and suggested PIP < 50 cmH_2O, P_{plat} < 30 cmH_2O to avoid barotrauma [1].

Quantifying $PEEP_i$ is a difficult and favored process. $PEEP_i$ amount of proportionated with degree of bronchial obstruction. Different techniques can be used to calculate $PEEP_i$. Clinicians can directly measure by occluding the expiratory port for 1–3 seconds at end expiration or by using expiratory hold maneuver on new ventilators. Static $PEEP_i$ can be measured in this way only in sedatized patients without active respiratory effort. The $PEEP_i$ can then be calculated by subtracting the external PEEP from the total PEEP. If there is spontan respiratory effort of the patient, dynamic $PEEP_i$ can be determined by simultanously recording esophageal pressure and airflow tracings. It is measured at end expiration as the negative deflection of esophageal pressure to the point of zero flow. The dynamic $PEEP_i$ is usually measured lower than static $PEEP_i$ by reason of different longer of time constant [1, 2, 4, 53, 54]. While $PEEP_i$ is determined extrinsic PEEP ($PEEP_e$) at 80% of $PEEP_i$ should be added to reduce patient triggering effort. Ventilator trigger sensitivity must be justify minimal [1, 4, 6, 51, 55, 56].

Weaning should begin once the cause of the exacerbation is adequately treated and the patient is hemodynamically stable. Physiologic parameters must be followed intensively. It's targeted MV < 15 L, RR < 30 breaths/minute, TV > 325 ml, rapid shallow breathing index (RSBI) <105, maximum inspiratory pressure (MIP) < −15. Although the superiority did not found among each other, different strategies were used to weaning. Daily spontaneous breathing trail (SBT) is one way of identifying patients stable to wean and it may reduce the number of ICU days. While decreasing gradually of PS has not been shown to be superior to SBT, PSV is preferable by many clinicians. Using NIV to facilitate weaning is accepted by multiple RCT [14, 15, 52, 57, 58].

4. High flow oxygen therapy

Long term oxygen therapy (LTOT), is used mainly in COPD patients with chronic hypoxemia [32]. High flow oxygen therapy (HFOT) is a new technique for delivering oxygen. There are many studies using HFOT instead of conventional oxygen therapy (COT) recently. HFOT was well tolerated and was sensed as comfortable. By using this system, oxygen delivery trends provided to be lower, and $paCO_2$ levels could be measured significant decreased. HFOT could be accepted as an alternative treatment to NIV due to it generates a modest degree of positive pressure almost 5–6 cmH_2O. It provides a more physiological humidification and heating of the airways. In this settings, HFOT has been used with different aims, as an alternative to COT, and NIV [59–62].

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Chapter

Weaning from Mechanical Ventilation

Liran Statlender and Pierre Singer

Abstract

Weaning off mechanical ventilation (MV) is a process that ultimately ends with a patient's liberation from the ventilator. As extubation failure worsens prognosis, every effort should be made to safely extubate the patient when the clinical condition allows it. There are several methods and techniques to assess whether a patient is ready for weaning. The clinician should choose the proper method for each patient to minimalize the risk of extubation failure. When liberation from MV is not possible, tracheostomy and transferring the patient to a long-term rehabilitation ward may be required. If this is not feasible, palliative care should be considered.

Keywords: weaning, extubation, spontaneous breathing trial (SBT), rapid shallow breathing index (RSBI)

1. Introduction

Weaning from mechanical ventilation (MV) is the process by which a patient is liberated from a ventilator. It begins with a readiness assessment and ends with liberation, usually by extubation. A successful weaning process should discriminate patients who might fail in the extubation and need reintubation from those who might be successful and maintain spontaneous breathing without mechanical support. This is important, as extubation failure and reintubation worsen prognosis and increase risk of mortality, length of stay, length of ventilation, and ventilation-associated events [1].

Ventilation duration affects the weaning process. If a patient was ventilated for a short time (e.g., during a surgical procedure, trauma patient emergency work-up and treatment), it is usually possible to liberate the patient from MV immediately at the end of the procedure without any special difficulties. Of course, patient characteristics matter in these cases (more caution is mandated in a fragile patient than in a young patient). However, longer time of ventilation due to severe respiratory failure or other severe injury or inflammatory process usually mandates a more structured weaning process, which this chapter describes [2, 3].

2. Readiness for weaning

A daily assessment of readiness for extubation should be performed in every ventilated patient. This screening is important to identify patients who might be successfully weaned and to avoid premature extubation in patients who are not ready yet.

The first consideration when weaning a patient from MV is whether the disease that necessitated MV is controlled and in recovery phase. If the disease process is active and not controlled, the patient should not be considered ready for extubation [4].

The second consideration is respiratory function, both oxygenation and ventilation [5]:

1. Oxygenation

   a. $paO_2/FiO_2 > \sim 260$

   b. $FiO_2 < 0.4$

   c. Positive end expiratory pressure (PEEP) < 5 cmH_2O

   If these criteria are not met, it is likely that the patient needs considerable oxygen supplementation.

2. Ventilation

   a. pH > 7.25

A lower pH represents a great load on the respiratory system.

These criteria are considered conservative. For example, early works considered paO_2/FiO_2 of 150 as satisfactory for extubation consideration. Later works suggested a higher cutoff of 260–290 [6–8]. Nevertheless, in specific subgroups of patients, these criteria should be slightly adapted. For example, in patients who suffer interstitial lung disease (or other chronic hypoxic diseases), a $paO_2/FiO_2 > 120$ can be used. In patients who suffers from obstructive lung disease, pH and pCO_2 should be close to the patient's baseline level.

The third consideration is cardiovascular function. Initiation of MV unloads the work of breathing from the patient. Cessation of MV imposes this work on the patient again and adds work to the cardiac output. Moreover, as positive end-expiratory pressure (PEEP) decreases afterload, discontinuation of MV increases afterload, potentially worsening heart failure. Therefore, it is necessary that a patient be hemodynamically stable before weaning (no more than a small and stable rate of vasopressors) [9].

The fourth consideration is neurological status. A patient can be considered ready for extubation if they are alert and cooperative. It is necessary that the patient not be under the effect of IV sedation drugs [4], which might cause respiratory depression (opiates, benzodiazepines, propofol). A small dose of IV sedatives that do not cause respiratory depression (dexmedetomidine, ketamine) is acceptable. Enteral or transdermal analgesia and sedation are possible, as long as the doses are stable and the patient is cooperative.

It is worth emphasizing the importance of patient cooperation. After extubation, the patient will usually have to promote cough, cooperate with respiratory therapy, and might need some support in the form of non-invasive ventilation (NIV) or supplementary oxygen. Failure to cooperate with any of these might lead to re-intubation and thus it is important to achieve the patient's cooperation.

Another issue of neurological status is muscle power, especially the ability to cough [10]. Although specific maneuvers to assess respiratory muscle strength are not superior to current maneuvers to assess weaning probability success, it is important to evaluate the patient's ability to cough, as coughing evacuates secretions and

prevents aspiration. Whenever a patient seems too weak or not able to perform cough mechanics, the risk of aspiration and re-intubation increases.

Other factors to consider are hemoglobin [11] and temperature [12]. Although both are not mandatory and critical to be completely normal before extubation, it is worth confirming that the patient being assessed for weaning is not developing a new problem such as sepsis, bleeding, or hemolysis (any of which might impose further load on the respiratory system and mandate intubation by itself). If so, it might be better to hold off on the weaning process.

2.1 Weaning predictors

When a patient seems ready for extubation, it is possible to perform some measurements as predictors of successful weaning. As no predictor is 100% sensitive and specific, and as some are cumbersome to perform, it is not mandatory to use any of these predictors. Some use weaning predictors in a structured fashion, while others use them only in cases of doubt whether the patient is ready or not [13–15].

The best studied predictor is the Rapid Shallow Breathing Index (RSBI), which is calculated by dividing the tidal volume (in liters) by the respiratory rate (Vt/f). To calculate this predictor, the patient has to breath spontaneously, without any support, for 1 minute, during which the tidal volume and the respiratory rate are measured. Though this measurement is sometimes performed while disconnecting the patient from the ventilator (measurement by external spirometer), it is acceptable to measure RSBI 1 minute after setting the ventilator on zero pressure support and zero PEEP. An RSBI of 105 is considered the cutoff for extubation failure. RSBI >105 has good correlation with extubation failure (negative predictive value 95%), and thus it is advised to delay extubation. However, RSBI <105 does not guarantee successful weaning, as its positive predictive value is about 80%. Interestingly, using automatic tube compensation increases RSBI sensitivity for successful extubation [13, 16, 17].

Other predictors include p/F ratio, dead space measurement, minute ventilation, compliance of respiratory system, work of breathing, P0.1 (inspiratory effort at 0.1 seconds inspirium), maximal inspiratory pressure (MIP), P0.1/MIP, diaphragmatic sonography, tension-time index (TTI), CROP index, CORE index, Weaning Index (WI), and Integrative Weaning Index (IWI). **Table 1** provides more detail about these predictors [13, 18–24]. Although some of these have been shown to better predict successful or unsuccessful extubation than RSBI, there is only slight improvement in prediction, and all these slightly better predictions are more cumbersome to perform than RSBI.

2.2 Spontaneous breathing trial (SBT)

Whether any weaning predictor is used or not, assessing a patient for extubation requires a spontaneous breathing trial. Several techniques are possible, but the basic principle is the same. The spontaneous breathing trial (SBT) is a short period of time in which the patient is breathing spontaneously, with support as minimal as necessary to overcome the endotracheal tube or without support at all. Among the different techniques are using a T-piece device and ventilating using pressure support mode with pressure support (PS) of 0 cmH_2O and PEEP 0 cmH_2O, or PS 0 cmH_2O and PEEP 5 cmH_2O (CPAP), or PS 7–8 cmH_2O and PEEP 5 cmH_2O. There are controversial results from several studies regarding the superiority of specific techniques. Some studies found no difference, while others have shown better success rates with PSV 8 cmH_2O and PEEP 0 cmH_2O compared to T-piece [25]. In any case, FiO_2 during SBT should be 0.4 or lower.

Predictor name	Description	Successful extubation cutoff	Sens	Spec	PPV	NPV
RSBI	RR/Vt	≤105	0.97	0.64	0.78	0.95
Dead space	$\frac{P_{aCO_2} - P_{eCO_2}}{P_{aCO_2}}$	≥0.58*	0.88	0.85	0.62	0.98
Minute ventilation	RR × Vt	≤15	0.78	0.18	0.55	0.38
Dynamic compliance	$\frac{Vt}{PIP - PEEP}$	≥33	0.72	0.50	0.65	0.58
WOB	Vt × P_{TP}	Not defined				
$P_{0.1}$	Pressure at 0.1 sec during maximal inspiratory effort	≤−4.2	0.87	0.61	0.87	0.61
MIP	Maximal pressure during maximal inspiratory effort	≤−25	0.73	0.28	0.75	0.26
$P_{0.1}$/MIP	$\frac{P_{0.1}}{MIP}$	≤−14	0.98	0.61	0.88	0.92
Diaphragm sonography	Sonographic measurement of diaphragm thickness	<24%	0.93	0.58	0.69	0.89
TTI	$\frac{MAP \times T_i}{MIP \times T_{TOT}}$	≥0.18*	1	1	1	1
CROP	$\frac{C_{DYN} \times MIP \times \frac{P_{aO_2}}{P_{AO_2}}}{RR}$	≥13	0.81	0.57	0.71	0.70
CORE	$\frac{C_{DYN} \times \frac{MIP}{P_{0.1}} \times \frac{P_{aO_2}}{P_{AO_2}}}{RR}$	≥8	1	0.95	0.96	1
IWI	$\frac{C_{RS} \times Sat_{O_2}}{RSBI}$	≥25	0.97	0.94	0.99	0.86

**Dead space and TTI predict failed extubation.*
Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; RSBI, rapid shallow breathing index; RR, respiratory rate; Vt, tidal volume; P_{aCO_2}, arterial partial pressure of carbon dioxide; P_{eCO_2}, end tidal partial pressure of carbon dioxide; PIP, peak inspiratory pressure; PEEP, positive end expiratory pressure; P_{TP}, transthoracic pressure; MIP, maximal inspiratory pressure; TTI, tension time index; MAP, mean airway pressure; Ti, inspirium time; T_{TOT}, total time of inspirium + expirium; Cdyn, dynamic compliance of lung; P_{aO_2}, arterial pressure of oxygen; P_{AO_2}, alverolar pressure of oxygen; RR, respiratory rate.

Table 1.
Weaning predictors and their diagnostic value.

From a historical point of view, SBT was found to shorten weaning time more than previously used methods of weaning such as PSV gradual decrease, IMV gradual decrease, or no SBT at all [4, 26]. In recent years, an automated mode of SBT has been possible due to the development of closed-loop ventilators. These ventilation modes are mainly pressure controlled/pressure supported, but their settings are changed automatically by the ventilator based on oxygen saturation and end tidal monitoring. Upon activation of automated SBT modes, the ventilator decreases support and monitors physiological parameters including heart rate (from saturation pulse), oxygen saturation, respiratory rate, tidal volume, compliance, end tidal CO_2, and RSBI. After completing SBT for a predefined time, the ventilator alerts whether the patient is ready for extubation or not. There is paucity

of data comparing automated SBT to manual SBT, but results seem promising, with a possibility of automated SBT shortening MV duration [27].

When first introduced, the recommendation was to perform SBT for 2 hours. Later studies showed no difference in outcomes with SBT lasting only 30 minutes. When there is a suspicion regarding patient strength, it seems logical to perform longer SBT [28].

As SBT is somewhat challenging for the patient, its endpoint is mainly clinical [5]. To successfully pass the SBT, the patient should remain calm during the test, without any stress signs such as tachycardia, tachypnea, elevated/decreased blood pressure, desaturation, restlessness, feeling uncomfortable, increased effort in breathing, diaphoresis, or new complaints such as chest pain. If any of these occur, the patient has failed the SBT and should remain ventilated. In case of doubt, it is possible to obtain an arterial blood gas (ABG) sample to assess adequacy of oxygenation and ventilation. An ABG sample is also warranted in the case of chronic obstructive pulmonary disease (COPD).

If a patient passes the SBT successfully, extubation should be performed. If a patient fails the SBT, the ventilator should be set to the pre-SBT settings and a workup should be done to determine cause of failure reason and proper treatment. In this case, a daily SBT should take place.

3. Extubation

Once the patient has successfully passed an SBT, extubation should be performed. However, one must pay attention to the patient's ability to remove secretions on their own. Nursing staff should be asked about amounts of secretions and frequency of secretion suctions. Also, patient cough mechanics should be assessed clinically. It is possible that a patient will be screened successfully for extubation and pass an SBT but still suffer from a large amount of secretions or muscle weakness. Suction frequency greater than once every 2 hours is considered unsafe for extubation. Peak expiratory flow during cough <60 L/min is also considered unsafe for extubation. If this is the case, postponing extubation is advised [29].

In select groups of patients who are considered to have risk factors for post-extubation stridor, usually due to laryngeal edema, a cuff leak test is necessary before extubation. This test is not mandatory in all patients, as without any risk factors the leak test is not sensitive nor specific. Risk factors for laryngeal edema include age older than 80 years, female gender, prolonged ventilation (more than 1 week), large-diameter endotracheal tube (more than 8 mm for males and 7 mm for females; smaller diameters are appropriate if the patient is short), CT imaging with endotracheal tube diameter >0.45 than tracheal diameter, Glasgow Coma Scale (GCS) < 8, traumatic intubation, and history of asthma. Any one of these endanger the patient for stridor and therefore mandate performing a cuff leak test. The cuff leak test is performed by deflating the endotracheal tube cuff and measuring the difference between the inspired tidal volume to the expired tidal volume (during volume-controlled ventilation). Generally, when a patient suffers from laryngeal edema, there will be small air leak, if any. Usual cutoffs that support this diagnosis are leak of <110–130 ml or <12–24% of the inhaled tidal volume. If the cuff leak test is positive (i.e., the patient suffers from laryngeal edema), a course of steroids should be given (methylprednisolone 20 mg every 6 hours) before next evaluation [30].

When the patient is ready for extubation, all necessary arrangements should be made to perform the procedure safely. The physician who performs the extubation

must keep in mind that despite taking all precautions, the patient might fail immediately and be prepared for reintubation. This is the main theme of the extubation.

Once the decision to extubate the patient is made, FiO_2 of the ventilator should be set to 1. This is the preoxygenation for possible reintubation. All the equipment needed to intubate must be within grasp, including sedation drugs, laryngoscope, endotracheal tube (usually half the size of the current tube), suction tube, and resuscitation cart. If prior intubation of the patient was difficult, then the method that was finally used should be available. Before extubation, a suction is performed within the tube and oral cavity to prevent aspiration. The patient is placed in the upright position and a short explanation about the procedure is given. Extubation itself is performed either with a bag valve mask (e.g., Ambu bag) without one. With an Ambu bag the cuff is deflated, and small positive pressure is constantly applied with the bag while pulling the tube out. Without a bag, the patient is asked to take a deep breath and hold. In that time the cuff is deflated, and the tube is quickly removed. The purpose of both techniques is to set exhalation by the patient as the first movement without the tube to decrease the chance of aspiration.

3.1 Post extubation management

Usually, immediately after extubation the patient is supported by oxygen. Respiratory therapies are advised shortly after the extubation to support secretion removal. Closed monitoring for any sign of respiratory distress is mandatory to allow intervention and reintubation, if necessary, as soon as possible after respiratory distress appears.

About 85% of patients are at low risk of reintubation. Usually, these patients are managed with low-flow oxygen (nasal prongs, simple mask). Occasionally, a patient will be more comfortable with a high-flow nasal canula (HFNC), even without overt hypoxemia. Patients in this group should be monitored closely for 12–24 hours, and if there are no alarming events, they can be discharged from the ICU afterwards (considering no other active ICU problems) [2, 31].

About 15% of patients are at high risk of reintubation within 48 hours of extubation. These patients should be closely monitored and treated accordingly to avoid reintubation. High-risk patients are considered those whose cough is ineffective, who need secretion suction at a frequency greater than one suction every 2 hours, who are in positive fluid balance, who were intubated because of pneumonia. Who are not fully conscious, and who suffer from congestive heart failure (CHF) or COPD. Treatment should be focused with the etiology of deterioration (frequent secretion suction, diuretics, etc.) [1].

Applying HFNC or NIV to these patients seems beneficial in some instances, but this has not been proven. Applying NIV to all extubated patients was not found efficient in all studies performed. In select patients, immediate use of HFNC or NIV might be beneficial, especially in those patients who suffer from COPD or CHF. Both of these patient populations have specific indications for PEEP and therefore have better outcomes when extubated directly to bilevel positive airway pressure (BiPAP). HFNC was found to be non-inferior to NIV, in that instance [32, 33].

When a patient develops respiratory failure after extubation, applying NIV or HFNC might be harmful, as usually it does not prevent reintubation, but rather only postpones it. As such, when the patient finally goes to reintubation, their muscle fatigue is greater than before the NIV/HFNC challenge [4, 34]. Therefore, when a patient starts to deteriorate after extubation, careful monitoring should be performed. If an etiology of deterioration is evident, it must be treated aggressively (suction of secretions, CHF treatment, etc.). If no such reason is apparent, or if treatment response is not sufficient, it is better to reintubate the patient than to challenge with NIV/HFNC.

Reintubation is a bad prognostic factor. Usually, reintubated patients are hospitalized for a longer time (both in ICU and in hospital), suffer from more infections, and have higher mortality rates [1].

4. Management of SBT failure and the difficult-to-wean patient

Approximately 60% of patients manage to pass their first SBT and are extubated successfully. These patients are classified as having simple extubation. About 40% of patients do not pass their first SBT and thus will be classified (initially) as difficult to wean (**Table 2**). These patients should undergo workup to determine why SBT failure occurred. While determining reasons for failure, daily SBT should take place. Most patients who are difficult to wean will require up to three SBTs or 7 days to pass an SBT [2].

Several pathophysiological processes might cause SBT failure. These are classified according to the main system that compromises the patient.

1. Respiratory/ventilatory: hypoxemia, V/Q mismatch, sepsis (excessive CO_2 production), increased airway resistance (COPD/asthma), dynamic hyperinflation, increased secretions, atelectasis, pleural effusion, pneumothorax, ventilator circuit malfunction

2. Cardiac: CHF deterioration, fluid overload

3. Neurological: decreased respiratory drive, oversedation, delirium, anxiety

4. Muscular: respiratory muscle weakness, electrolyte disorders (hypophosphatemia, hypomagnesemia, hypocalcemia, hypokalemia), neuropathy or myopathy, underfeeding, protein catabolism, hypothyroidism

Usually, a careful patient examination involving history review, physical examination, ventilator graph analysis, basic laboratory examination, and imaging studies might reveal the reason and aid treatment.

During the time between SBTs the patient should be ventilated in settings that will maintain oxygenation and ventilation targets, in accordance with lung protective ventilation principles. Usually, PSV mode would apply. However, the patient must be comfortable with PSV settings. In addition, to allow respiratory muscles to rest, some patients may require mandatory ventilation.

Once the process that is suspected to have failed the previous SBT is treated, the patient can undergo another SBT. Usually, this SBT should be longer than the previous one, about 2 hours. The SBT technique should be the same as the previous attempt. However, if CHF is suspected as the reason for SBT failure, it might be better to perform an SBT with a T-piece. This will allow to examine whether the patient can tolerate absence of PEEP.

If the patient successfully passes the SBT, an extubation should be performed. However, if the patient fails, the SBT should be halted at the first signs of failure to decrease fatigue of respiratory muscles.

4.1 Prolonged weaning/prolonged mechanical ventilation

Patients who are not able to pass an SBT in three consecutive attempts or who take more than a week to pass are considered to be going through prolonged weaning. Although they represent the minority (about 10%), these patients are at increased risk of death and are likely to need tracheostomy [3].

Group	Description	Proportion of patients (%)
Simple weaning	Successful extubation at the first attempt of weaning process	85
Difficult weaning	Failure of extubation or SBT at the first attempt, but successful extubation with two further attempts and within 1 week	10–15
Prolonged weaning	At least three failures of extubation or SBTs or duration of weaning process is longer than a week	5

Adapted from Boles et al. [2]

Table 2.
Weaning process classification.

Assuming the acute illness has already recovered, and those pathologies that might cause SBT failure were also treated, the most prominent reason for prolonged MV is imbalance between respiratory system load and capacitance. In other words, patients who need prolonged MV are patients whose respiratory systems cannot meet the physiological demands of the body, whether because of lung pathology (abnormal lung mechanics), respiratory muscle weakness, or neurological dysfunction [31].

Medically, a patient who needs prolonged MV should undergo tracheostomy. This is done to improve patient communication, decrease sedation, ease nursing treatment, and allow for transfer to a long-term weaning facility. With coordination of physicians, nurses, physical therapists, clinical dietitians, and social workers, long-term weaning facilities focus on weaning and rehabilitation. As reasons of prolonged MV are multifactorial, there is no accepted strategy to liberate a patient from the ventilator, and a tailored approach to each patient is feasible.

Outcomes of long-term rehabilitation wards are as follows:

- About 55% of patients are successfully weaned. Average time to wean is approximately 30 days (at the rehabilitation ward). Approximately 40% of these patients survive 1 year.

- About 15% of patients remain ventilator dependent (inability to wean within 3 months). One-year survival in this group is about 20%.

- About 30% of patients die during admission.

One-year survival is variable among different studies, in the range of 25–75%. Most likely, this represents variability in patients' baseline characteristics [35].

Upon diagnosing a patient as one who needs prolonged MV, it is important to discuss this with the patient (or the patient's next of kin/primary caregiver/legal guardian) and explain the chances of remaining ventilator dependent and possible quality of life. If patient expectations are not possible to meet, it seems appropriate to discuss the option of palliative care.

5. Conclusion

Weaning is the process of liberating a patient from MV. Whenever a patient is ventilated for more than 24 hours, the weaning process should be a structured process. **Figure 1** presents the weaning process as performed in our unit. This allows for patient safety and avoids unnecessary extubation failures, which worsen prognosis.

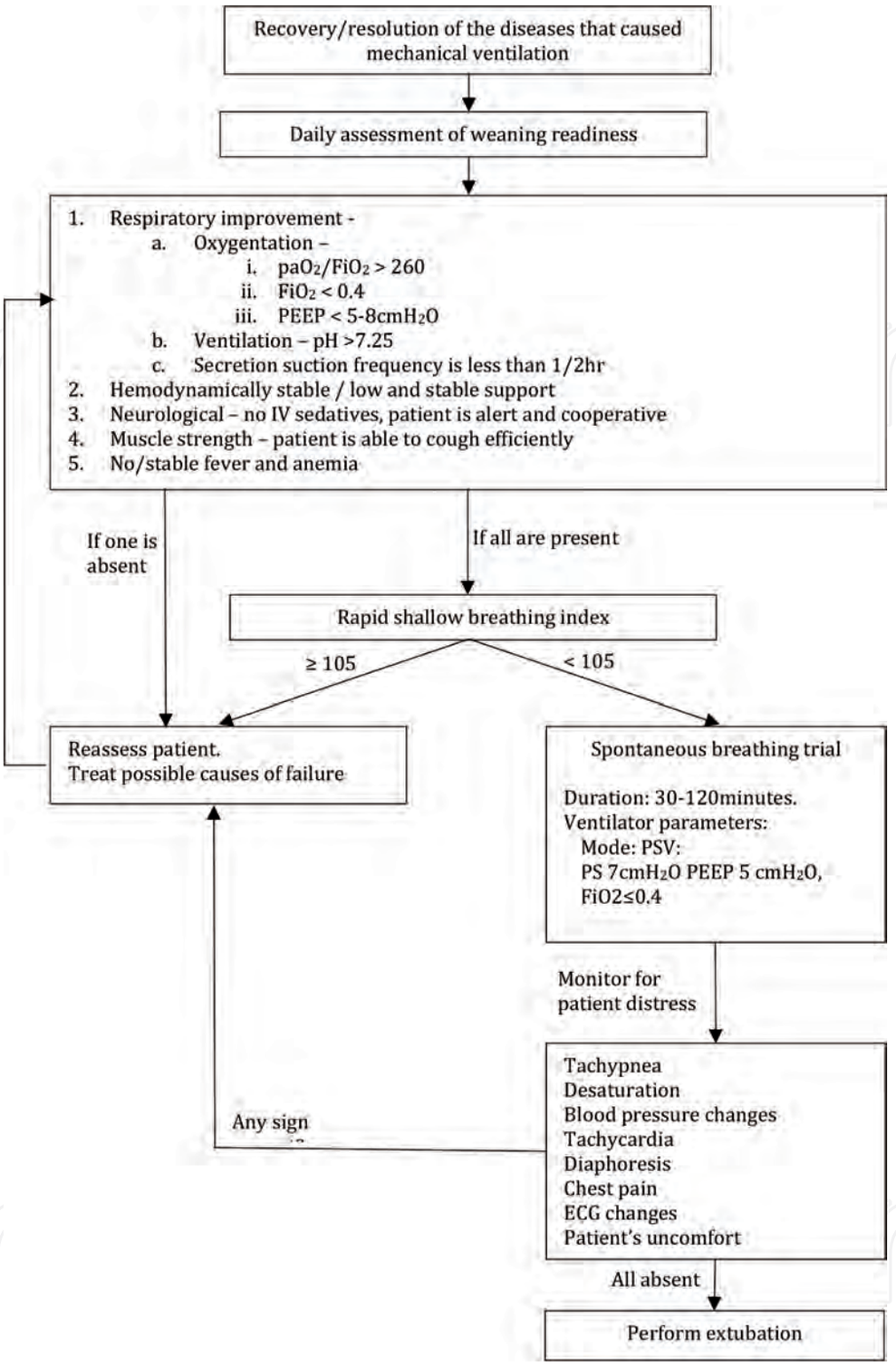

Figure 1.
Suggested flow chart of weaning process.

In most cases, the patient will be extubated without complications. In a minority of cases, special attention should be given to pathological processes that might endanger the patient to extubation failure. In severe cases, weaning will be a long process performed in dedicated ward.

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Chapter

How Medical Conditions Affect the Weaning of Mechanical Ventilation

Iuri Christmann Wawrzeniak, Karolinny Borinelli de Aquino Moura and Eder Chaves Pacheco

Abstract

Weaning from mechanical ventilation is a common process in critically ill patients and its failure is related to worsening outcomes. A better understanding of the subject is necessary to change these unfavorable results. This chapter will review the approach to weaning from mechanical ventilation in special groups of critically ill patients. The chapter will also review the causes of failure to wean from MV along with strategies for improving evaluation and approach of the patient with difficult and prolonged weaning from mechanical ventilation. Therefore, the presence of this topic in a book on mechanical ventilation is fundamental and relevant.

Keywords: critical illness, intensive care unit, respiratory failure, mechanical ventilation, mechanical ventilator weaning

1. Introduction

Mechanical ventilation (MV) is a lifesaving intervention in critically ill patients. MV is commonly used for postoperative respiratory failure, trauma, pneumonia, sepsis, heart failure (HF), chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS) [1, 2]. After the condition that caused the use of MV improves, the process of removing invasive ventilatory support begins, which is called weaning from MV [3, 4]. The MV weaning process is crucial and frequent in the critically ill patient's recovery. Almost 50% of the total duration of MV is dedicated to weaning patients [3]. However, some patients may fail to wean from MV despite all criteria in a planned extubation. This extubation failure is reported in around 10–20% of critically ill patients and, consequently, this weaning failure group has a high mortality when compared to patients who successfully weaned from MV [5–9].

The MV weaning and failure process have been studied since the 70s and 80s [10–13]. Milic-Emili questioned that the MV weaning performed in this period was more based on art than science because there were few scientific studies on the topic [14]. Studies in subsequent decades evaluated the best ventilatory mode to perform weaning from MV as well as predictors of weaning from MV [15–19]. After advances in the study of MV weaning, guidelines were formulated establishing

better criteria for evaluating the weaning process [20, 21]. Despite this, there are still different ways to practice MV weaning among intensive care units (ICU) in different countries, suggesting the need for more studies on the topic [4].

This chapter aims to review the weaning from MV in special subgroups. How to evaluate and to manage MV weaning will be discussed.

2. Weaning from mechanical ventilation in special groups

The cause of weaning failure may be related to individual or associated dysfunctions (respiratory, muscular, cardiac, neurological, endocrine, metabolic and iatrogenic). However, understanding the pathophysiology of MV weaning failure can be complex in some cases and it is not always fully understood, making its treatment difficult (**Figure 1**). When a patient does not pass a weaning trial, structural evaluation could help to identify factors that played a role in that specific patient. Moreover, it is important to know and to understand peculiarities of some critical patient subgroups in order to achieve more successful weaning. The **Table 1** summarizes the main characteristics, assessment and management of the main groups of patients in the process of weaning from mechanical ventilation admitted to an ICU.

2.1 Chronic obstructive pulmonary disease

In COPD patients, the weaning process is more difficult, prolonged and has higher failure rates than general populations. The higher failure rates in COPD patients can be attributed, at least in part, to the underlying pathophysiology of the disease. In COPD patients with acute respiratory failure, dynamic hyperinflation and the generation of intrinsic PEEP are the main factors that causes increased intrathoracic pressure, which lead to increased work of breathing, MV-induced injury, asynchrony, dyspnea, hemodynamic worsening, in addition to MV dependence and weaning failure [22]. In this population, the use of prophylactic non-invasive ventilation (NIV) after extubation is also recommended, considering this group of patients is at high risk of failure. The use can be extended to immediate extubation for NIV of COPD patients who have failed T-tube spontaneous

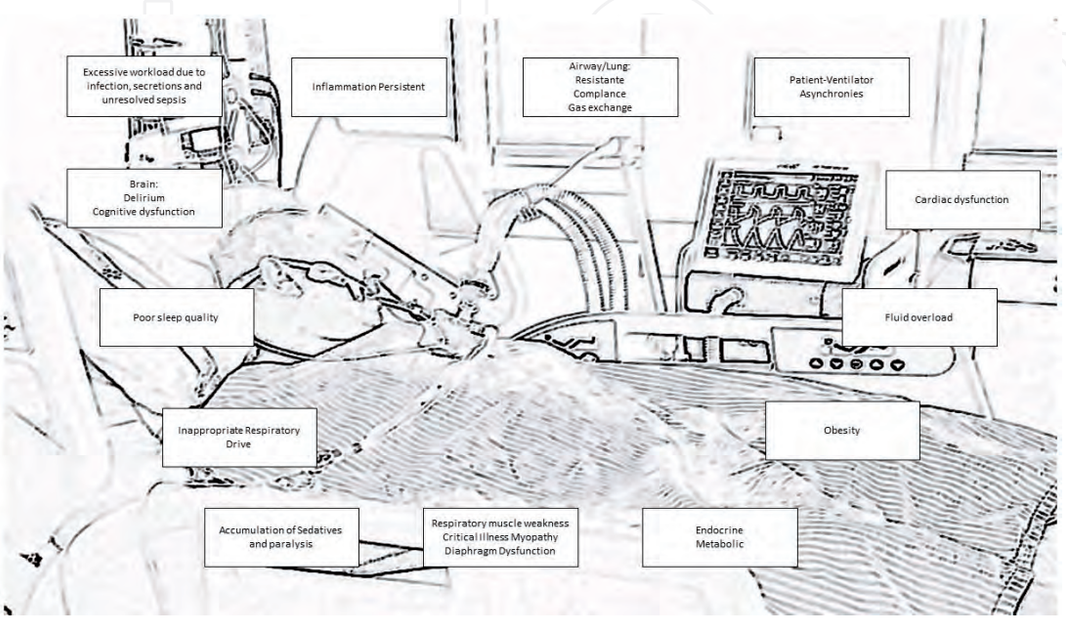

Figure 1.
Aspects of mechanical ventilation weaning failure.

Group	Characteristics	Assessment and Management
COPD	Higher weaning failure and MV dependence Dynamic hyperinflation and intrinsic PEEP	Extubation for NIV
Heart Failure	Increased left ventricular preload which afterload with reduction of the left ventricular ejection fraction	Electrocardiogram and an echocardiography Collecting a pro-brain N-terminal natriuretic peptide/central venous blood gas SvO2 Medications can also be used to optimize ventricular function – inotropic Volume overload should be adjusted - diuretics Extubation for NIV to maintain a PEEP
Neurological Dysfunction	Reduction in the level of consciousness did not impede successful extubation Ability to handle secretions and airway protection are relevant	Daily screening to assess MV weaning CAM-ICU Performing non-pharmacological and pharmacological measures for delirium
Neuromuscular Diseases	Neuromuscular alterations are relatively common Primary neuromuscular disturbance ICU-acquired muscle weakness Diaphragmatic muscle weakness can also impair weaning	Avoiding exposure to medications and hyperglycemia Motor rehabilitation
ARDS	The dangerous of excessive spontaneous ventilation with higher respiratory demands and loss of the protective-ventilation strategy Increased lung volumes, higher respiratory drive, breath stacking, pendelluft and patient-ventilator asynchrony	Evaluation of MV weaning does not differ from others patients Caution in the higher respiratory patients demands and its ventilatory repercussions
Obesity	The large weight on the rib cage can causes alveolar collapse	Higher PEEP during the pre-extubation period to prevent alveolar collapse Use of NIV
Prolonged Weaning	~10% of critically ill intubated patients High mortality Chronic critical illness	Multidisciplinary rehabilitation Swallowing dysfunction Tracheostomy Discussion of treatment goals
Others Care	Conditions for Weaning Progress: • Adequate neurological status • Ability to cough and to manage respiratory secretions • Improvement of oxygenation • Hemodynamic stability	Use of protocols for weaning MV Daily screening for weaning with predictors Use of NIV in ICU patients at high risk for reintubation HFNC reduces the ventilatory work by supplying the demand and reversing the hypoxemic through of a high airflow therapy Cuff Leak Test: high risk of post-extubation stridor (traumatic intubation, prolonged intubation, large endotracheal tube, high cuff pressures, women and reintubation after unplanned extubation) Systemic corticosteroids recommended to patients with fail the cuff leak test Weaning Failure Causes: respiratory, muscular, cardiac, neurological, endocrine, metabolic and iatrogenic

Legend: MV, mechanical ventilation; NIV, non-invasive ventilation; CAM, confusion assessment method; HFNC, High-flow nasal cannula; COPD, chronic obstructive pulmonary disease; PEEP, positive end-expiratory pressure; ARDS, acute respiratory distress syndrome.

Table 1.
Weaning from mechanical ventilation in special groups.

breathing trial (SBT), with evidence of reduced length of stay in the ICU, nosocomial pneumonia and 60-day mortality, when compared to those weaned through invasive pressure support ventilation. These findings were corroborated by a recent meta-analysis [22, 23].

2.2 Heart failure

SBT causes spontaneous respiratory movements, which generate negative pressures and consequently hemodynamic repercussions. Negative intrathoracic pressures cause increased left ventricular (LV) preload which increases LV afterload and, ultimately, reduces left ventricular ejection fraction. This reduction in ejection fraction during an SBT can precipitate or worsen heart failure. Thus, if there are volume overload or systolic or diastolic left ventricular dysfunction, SBT can cause cardiorespiratory decompensation with pulmonary edema, reduced oxygen transport and insufficient cardiac output [24]. Furthermore, SBT can cause or worsen myocardial ischemia as a result of reduced left ventricular compliance, pulmonary edema and/or increased respiratory effort. To assess a possible cardiac dysfunction as a cause of weaning failure, it is suggested to perform an electrocardiogram and an echocardiography, in addition to collecting a pro-brain N-terminal natriuretic peptide and a central venous blood gas measuring SvO2.

An accurate diagnosis of the mechanism of cardiac dysfunction is needed to better guide therapy. In difficult-to-wean patients, additional medications can also be used to optimize ventricular function [24, 25].

Volume overload should be adjusted before performing a SBT because it has been associated with worse weaning outcomes [24]. It can be treated with diuretics or hemodialysis and after that, direct extubation for NIV can be used in order to maintain a positive end-expiratory pressure. When there is evidence of heart pump failure, reduction in afterload and/or use of inotropic agents (such as dobutamine or milrinone) may be considered. Furthermore, the improvement in pulmonary mechanics itself will improve cardiac performance by reducing the afterload of the left ventricle [24].

2.3 Neurological dysfunction

The decision to extubate comatose neurocritical patients is complicated. Previous studies have shown that the reduction in the level of consciousness is a good predictor of extubation failure [26]. Coplin et al. have challenged common sense showing that patients with a Glasgow Coma Scale (GCS) 8 did not impede successful extubation [27]. Moreover, the delayed extubation in this population was related to more ventilator-associated pneumonia (VAP) and longer intensive care unit and hospital stays [28, 29]. Also, according to the study by Coplin et al., the professional should avoid prolonged intubation when the level of consciousness is the only reason to maintain MV. Navalesi et al. demonstrated that a daily screening to assess MV weaning is recommended for patients with neurological diseases to reduce the duration of MV [30]. Strategies that include protective ventilation, early enteral nutrition, standardization of antibiotic therapy for nosocomial pneumonia, and systematic testing to assess readiness for extubation showed an association with a reduction in MV time in brain injured patients [31].

There are still other concerns about the neurological status of patients able to wean from MV. A study has shown that the change in cognitive function had been associated with a four times greater risk of unsuccessful extubation [32]. The ability to handle secretions and airway protection is also a relevant issue. In addition, the causes of acute brain dysfunction in difficult-to-wean patients should be

considered, such as delirium, which is very common. The CAM-ICU can be a good tool to assess delirium in intubated ICU patients and performing non-pharmacological and pharmacological measures can help in symptomatic management. Improving hospital environments, for example, with poor noise and ICU-beds near to windows, besides frequent reassurance, touch, verbal orientation and family members presence can improve delirium symptoms [33]. Furthermore, it is important treating potential causal factors such as pain, constipation, infection and withdrawal of precipitating medications such as benzodiazepines and others [25]. In case of hyperactive delirium unresponsive to non-pharmacological measures, antipsychotics can be used for symptomatic management. Although there are no clinically significant differences between the classes of antipsychotics, haloperidol is one of the most used and studied.

2.4 Neuromuscular diseases

Weaning from MV requires adequate neuromuscular activity to overcome the impedance of the respiratory system and maintain adequate alveolar ventilation to eliminate carbon dioxide and ensure a metabolic balance. For this to happen, a generation of the stimulus by the central nervous system, adequate transmission via spinal respiratory motor neurons, respiratory muscles and neuromuscular junctions are necessary. Modifications anywhere of this complex system can contribute to MV weaning failure. Peripheral neurological alterations can also be the cause of weaning failure. Neuromuscular alterations are relatively common, being reported in up to 62% of patients in some studies [34]. Primary neuromuscular disturbance, such as Guillain-Barré syndrome, myasthenia gravis and motor neuron diseases, are usually diagnosed prior to intubation. Occasionally new diagnoses will occur as the difficulty of weaning from MV develops and is investigated.

In the ICU, the most common is secondary neuromuscular diseases, especially muscle weakness acquired in the ICU. It is a pure axonal disease, affecting mainly the peripheral nerves and muscles, symmetrical and bilateral and predominantly proximal. Prevalence between 50 and 100% is estimated in studies and is associated with disease severity, multiorgan dysfunction, exposure to corticosteroids, hyperglycemia and prolonged ICU stay [35–38]. Diaphragmatic muscle weakness can also impair weaning and its assessment can be challenging at the bedside, as the tests are either invasive and/or depend on the patient's ability to understand and to cooperate. There are studies that demonstrate an association between ICU-acquired muscle weakness and longer weaning duration or failure [34, 39–41]. Diaphragmatic muscle weakness can also impair weaning and its assessment can be challenging at the bedside, as the tests are either invasive and/or depend on the patient's ability to understand and to cooperate. There are studies that demonstrate an association between ICU-acquired muscle weakness and longer weaning duration or failure.

2.5 ARDS

In the early stages of MV in patients with acute respiratory distress syndrome (ARDS), the use of protective-ventilation strategies is recommended, as well as the use of neuromuscular blockers, prone position and extracorporeal membrane oxygenation (ECMO) in more severe cases [42]. However, during weaning from MV in patients with ARDS, this protective-ventilation strategy may be lost, mainly due to the influence of spontaneous ventilation with higher respiratory demands [43]. The increased lung volumes, higher respiratory drive, breath stacking, pendelluft and patient-ventilator asynchrony besides to delirium and ICU-acquired paresis may influence weaning from MV and should be considered in the assessment of patients with ARDS [44].

In addition, the use of the arterial-to-inspired oxygen (PaO2/FiO2) ratio to demonstrate improvement in hypoxemia, does not always translate into improvement in inflammatory response and weaning success [45]. Then, the premise for the beginning of weaning from MV based on PaO2/FiO2 ratio (resolution or improvement of the cause that led the patient to MV) is not always a good predictor to weaning success. Moreover, the management of MV weaning in these patients through consensus on weaning from MV generally does not include this specific group of patients [20, 21, 46]. Studies have shown that a greater proportion of patients have difficult and prolonged weaning when compared to the general ICU population [29, 47]. Therefore, regarding current knowledge, the evaluation of MV weaning does not differ in general from other patients. However, this subgroup has a particular pathophysiology that can influence and delay the evolution of the withdrawal of invasive ventilatory support.

2.6 Obesity

Obese patients, with a body mass index (BMI) > 30, have specific problems during MV. The large weight on the rib cage can cause alveolar collapse in some conditions and gravity can influence pulmonary mechanics [48]. In a study of obese patients with ARF, mortality was reduced by 50% when the choice of PEEP was guided with an esophageal catheter (EsoC) and electrical impedance tomography (EIT) [49]. During the process of weaning of MV is crucial to pay attention to the work of breathing, because the increased negative pleural pressure in these patients can led to a compression of the diaphragm in to the rib cage and can induce atelectasis in patients with muscle weakness [49]. Therefore, obese patients may benefit from higher PEEP during the pre-extubation period, making pleural pressure more positive and preventing alveolar collapse [50]. After extubation, positive pressure in the smaller airways can be maintained through by NIV, preferably in a sitting position, to avoid abdominal cavity compression of the diaphragm and inducing collapse by undermining the mechanics of the rib cage [51].

3. Prolonged weaning and some considerations

Prolonged weaning concerns about 10% of critically ill intubated patients and is associated with a high mortality [19, 27, 52]. Patients with prolonged weaning are associated with chronic critical illness [53]. The multidisciplinary rehabilitation group is very important to treatment [54]. Physical therapy will be very important to assess the patient's tolerance and exercise. Swallowing dysfunction can complicate the extubation process and its evaluation is essential for the return to normal eating habits [55]. Short daily cuff down trials with a speaking valve are performed to induce vocal cords to exert their original function during expiration. Tracheostomy may be considered as a useful adjunct for easier care of the patient, especially for mobilization and better comfort [56, 57]. A randomized controlled trial suggested that tracheostomized patients were more rapidly separated from the ventilator by repetitive T-tube trials than with a gradual reduction of PSV without influencing survival at 12 months [58]. Assessment with the patient and family should address explicit discussion of realistic versus futile treatment goals [59].

4. Future perspectives

More recently, tools such as ultrasound, EsoC and EIT have helped to predict MV weaning. The EsoC can be useful in the objective assessment of respiratory

effort, estimating transpulmonary pressure and autoPEEP [60]. On the other hand, ultrasound can be useful in providing information through visual assessment and in obtaining objective measurements of cardiorespiratory variables at different stages of weaning. A study by Haji et al. showed that loss of pulmonary aeration and left ventricular diastolic dysfunction are more frequent in patients who fail extubation [61]. Additionally, several studies have shown that the use of the EIT can help to evaluate weaning from MV. Bickenbach et al. and Lima et al. showed loss of recruitment and lung homogeneity during SBT [62, 63]. Studies in specific populations, such as patients with COPD, are ongoing and partial results indicate that those who fail the SBT ventilate more the anterior lung regions [64].

5. Conclusions

The weaning from MV in critically ill patients is a common and fundamental process in the ICU. The understanding the withdrawal of invasive ventilatory support and identifying possible causes of weaning failure are essential. The use of SBT trial and predictors guide weaning from MV. Some subgroups should be better valued to better individualize MV weaning and avoid reintubation associated with worse outcomes.

Conflict of interest

"The authors declare no conflict of interest."

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Chapter

Palliative Withdrawal of Mechanical Ventilation and Other Life Supports

Lauren F. Goodman

Abstract

Palliative or compassionate withdrawal of mechanical ventilator support at the end of life aims to optimize comfort, alleviate suffering, and allow a natural death in patients for whom life supports are not achieving desired goals. Palliative withdrawal is a medical procedure and must be treated as such. Appropriate planning and preparations are required to optimize patient comfort, which is the goal of the procedure. Many institutions have a "one size fits all" approach to this process, but individual patient factors require consideration to meet the patient's needs. Some of these factors include patient pathophysiology (airway edema, airway trauma, hemoptysis, secretions), current treatment modalities (ventilator settings, medications including sedatives, vasopressors, inotropes, inhaled agents, neuromuscular blockade agents), and patient and family values and preferences. This chapter will discuss the implications of each of these factors and propose methods for successful transitions to comfort-focused care. Case vignettes will demonstrate the thought processes involved and model optimal management. Common ethical considerations and questions regarding palliative withdrawal of life support will also be discussed.

Keywords: Palliative, terminal, Withdrawal, comfort care, end of life

1. Introduction

Palliative or compassionate withdrawal of mechanical ventilator support at the end of life aims to optimize comfort, alleviate suffering, and allow a natural death in patients for whom life supports are not achieving desired goals. Medical ethics discussions have shifted significantly over the decades since critical care was first developed. It is now generally, though not universally, accepted that withdrawal of life support is equivalent to withholding of life support. Some now argue that withdrawal may be ethically superior to withholding life support, as withholding assumes the life support will not achieve the patient's goal, while withdrawal occurs only after this assumption has been proven true [1].

2. Decision-making process

A patient with capacity must be given the opportunity to participate in decision-making. This can be challenging when medical interventions limit audible speech, as with an oroendotracheal or nasoendotracheal tube. While sometimes

time-consuming, solutions such as computers or tablets with keyboards, phones with texting capabilities, sign language, letter boards, or simply pen and paper, can allow a patient to ask questions and express their own values, goals, and preferences. Some patients with a tracheostomy tube in place can generate audible fricative speech, even when the cuff must remain inflated for respiratory support. Some patients with either tube can mouth words clearly enough to be understood, though this can be difficult for both patient and medical team. The powers of the Power of Attorney may be limited by the patient, or by local laws, but generally allow the surrogate to make medical decisions on the patient's behalf when the patient is unable or chooses to defer. Capacity for medical decision-making is a complex construct and can vary over time, and with the decision to be made. Some patients are unable to process any significant medical information. Some are able to process and express clear and consistent preferences about simpler matters but not complex ones. As with language interpretation, these interpretations must be made by a member of the medical team and not exclusively by family or friends of the patient, and must be confirmed with the patient in other ways, such as nodding or shaking their head to confirm or refute accuracy.

A patient with capacity can also choose to defer to their legal surrogate, and in many jurisdictions can select and assign Power of Attorney for Health Care to one or more people to speak for them.

Still others are able to understand, manipulate, and ask questions about the medical information presented to them, and to express clear, consistent decisions on their own behalf.

3. When to discuss withdrawal of life supports

Ideally, physicians discuss with each patient their prior experiences, values, preferences, goals, and minimal acceptable outcomes prior to onset of critical illness, and prior to initiation of life supports. This is often not possible, sometimes due to the acute nature of some critical illnesses, and sometimes due to patient factors such as unwillingness to discuss these issues. Unfortunately, this is also sometimes due to physicians' and medical teams' discomfort with, inadequate time for, or failure to recognize the necessity of such discussions.

Regardless of whether routine or baseline discussions of experiences, values, preferences, and goals have occurred, the onset of critical illness is an important prompt to discuss or rediscuss these thoughts. Ideally, at the beginning of a patient's critical illness, their physician discusses with the patient or surrogate, or with both, the presumed diagnosis, the treatment options, and the likely outcomes of each and how soon the outcomes are anticipated. The patient or surrogate ideally understands and integrates this information and selects the treatment that gives them the best chance of recovery within the parameters of acceptable risk and acceptable burdens or suffering defined by that individual patient. After learning the patient's risk and burden tolerance, the physician confirms and documents the treatment plan, including any limits set by agreement with the patient or surrogate. The physician should then schedule a date to discuss progress, or lack of improvement, and further options with the patient or surrogate, unless new findings or changes require significant discussions sooner. This constitutes a time-limited trial, which is a useful framework for acknowledging the uncertainty of outcomes of critical illness [2].

If the patient is not improving to the extent they themselves would require to make continuing current life supports acceptable, or if the patient, or surrogate acting in the patient's best interest, finds the current life supports too burdensome despite good efforts at symptom management by the medical team, it is important to discuss the option of palliative withdrawal of life supports.

When multiple life supports are present, and the patient or surrogate and team are considering withdrawing one form of life support, it is necessary to consider whether or not the other forms of life support present are contributing to achievable medical goals. If any form of life support is not helping the patient progress toward achievable goals, potential withdrawal should be considered and discussed.

4. How to withdraw mechanical ventilation

Palliative withdrawal is a medical procedure and must be treated as such. Appropriate planning and preparations are required to optimize patient comfort, which is the goal of the procedure. Many previously published works, and many institutions have a "one size fits all" approach to this process, but individual patient factors require consideration to meet the patient's needs. Unfortunately, for understandable reasons, at this time there are exceedingly few studies of how to perform any part of this procedure. Therefore, many aspects require logical consideration and expert opinion to guide practice, as well as consideration of the individual patient's condition, needs, preferences, and goals.

Evidence suggests family satisfaction is increased when a step-wise approach to withdrawal of life support is used [3].

4.1 Ventilator weaning vs. immediate discontinuation

Older literature regarding palliative withdrawal of life supports generally describes either universal weaning or universal immediate discontinuation. More recent literature and guidelines take a more patient-centered, case-specific approach and recommend consideration of the patient's current ventilator support requirements and level of symptoms [4]. For patients on moderate or high ventilator support, it is recommended to wean ventilator support - specifically positive end inspiratory pressure (PEEP), potentially pressure support, and fraction of inspired oxygen (FiO2) - in a step-wise approach, titrating opioids and benzodiazepines especially to control dyspnea and anxiety respectively.

For example, for a patient who is on assist control volume control with a set rate of 14, tidal volume 6 mL/kg ideal body weight, PEEP of 14 cmH2O, and FiO2 60%, it would be advisable to achieve comfort with medications before initiating weaning, then reduce PEEP and FIO2 to 10–12 and 40% respectively, titrate medication boluses to achieve and maintain comfort, and continue to wean ventilator support every 15-30 minutes as tolerated.

4.1.1 Mode

Modern ventilators allow for a wide variety of mandatory, intermittent mandatory, assisted breath, and entirely spontaneous modes. Each mode has potential benefits and potential burdens to the patient.

When transitioning to comfort measures, patient condition and clinician comfort with managing the various modes will determine optimal mode for weaning or continued support. A patient who is awake, alert, and requires little ventilator support may be most comfortable right away with low levels of pressure support and PEEP. A patient with poor lung compliance or with neurologic or myopathic limitations to breathing may require a more sensitive trigger or a more controlled mode that ensures volume delivery, and for some, having a minimum breath frequency is necessary for comfort.

4.1.2 Rate

In modes with a set minimum rate, reducing a rapid set rate may unmask intrinsic tachypnea, which may be physiologic, or may be due to pain or anxiety. In synchronized intermittent mandatory ventilation settings, reducing the set rate may increase the frequency of spontaneous breaths; depending on the level of support provided with these spontaneous breaths, patients may feel more dyspnea if under-supported, or less dyspnea if their respiratory efforts are sufficiently supported.

4.1.3 Peep

Reducing PEEP can allow pulmonary edema, alveolar secretions, or pulmonary hemorrhage to become more prominent. Some patients may experience increased cough and may have difficulty expectorating the secretions. A stepwise approach, reducing PEEP by 2–4 cmH2O per step, may allow for titration of symptom control medications. Most ventilators have backup apnea settings that cannot be discontinued. For patients who are maintained on ventilator support throughout the comfort care process, it is important to remind families and team members that the ventilator will continue to deliver breaths even after the patient has died.

4.1.4 Oxygen

Some patients are asymptomatic or relatively asymptomatic with hypoxemia, while others note symptoms with even relatively small reductions in oxygenation. Again a stepwise approach, reducing by approximately 20% per step, allows for symptom management with medication titration. Supplemental oxygen through the ventilator can be weaned to as low as 21%, especially if the plan is for discontinuation of ventilator support without supplemental oxygen.

4.1.5 Tidal volume

Since the first ARDSnet trial publication [5], when tidal volumes are set on the ventilator, they are commonly set to a low tidal volume, lung protective strategy of 8 mL or less per kilogram of ideal body weight. Some patients find this strategy uncomfortable, as it forces small, limited volume breaths. If ventilator support is to be continued, especially if awaiting arrival of family members, or another significant event, continuing the current set volume is typical, but liberalizing the set volume somewhat may improve comfort.

4.1.6 Drive pressure, inspiratory pressure, or pressure support

These terms all refer to pressure added by the ventilator for the inspiratory phase of each breath to inflate the lungs and generate a tidal volume. The size of the tidal volume depends on the pressure administered and on the patient's lung and airway compliance. For patients with acute lung injury or acute respiratory distress syndrome, the pressure is generally set to target lung protective low tidal volumes. For patients without lung injury, the pressure requirement may be fairly low, or may be set to allow more liberal breath sizes for comfort.

4.2 Extubating vs. maintaining oro- or nasoendotracheal tube

Many institutions, and some older articles written about the process of palliative withdrawal of life supports, have a near-universal practice of removing the patient's

oral (or nasal) endotracheal tube. It is generally assumed that patients and families prefer extubation and will be more comfortable after removal of the tube. However, there are some important considerations that may limit or worsen patient comfort after removal of these tubes. Airway compromise caused by edema, trauma, masses, or other lesions may make removal of the oro- or nasoendotracheal tube risky for causing or allowing burdensome symptoms to occur. Similarly, significant hemoptysis or secretions, whether purulent or edematous, may require excessive effort by the patient to clear, and may limit comfort after extubation.

Decades ago, some institutions also routinely removed tracheostomy tubes at end of life. Unless there are specific patient-centered reasons to do so, this is no longer recommended.

4.3 Sedatives, analgesics, anxiolytics

4.3.1 Basal rate titration vs. bolus dose administration

As with enteric opioid medication administration, as needed bolus dose administration and titration should be the mainstay of symptom management. Anecdotally, ICU physicians and nurses often treat opioid and benzodiazepine infusions as though they have the pharmacokinetic and pharmacodynamic properties of vasopressors in terms of time to peak effect and time to steady state. This is not consistent with the actual activity of these medications, and can cause both ineffective symptom management initially, and excessive dosing later in the patient's course.

Pharmacologic principles must be remembered and utilized in the management of infusions of opioids and benzodiazepines. When a patient has significant symptoms, bolus doses can and should be administered as often as the time to peak effect for the drug in question. If the bolus dose is effective in controlling symptoms, the dose can be repeated after time to peak effect when it is needed again. If the dose is only moderately helpful for symptom control, the dose can be increased by 50% at the next administration to improve efficacy. And if the dose is minimally or ineffective, the dose can be doubled at the next dosing interval, or an alternative medication can be considered.

4.3.2 Propofol

Propofol is an anesthetic and sedative without analgesic properties. Some institutions restrict use without a secured airway. However, it can have benefits, including control of seizures, and may occasionally be a helpful adjunct to symptom control for those with severe anxiety, for example, where the patient prefers deep sedation over the possibility of experiencing their severe symptoms at end of life.

4.4 Inhaled vasodilator agents

There are no significant studies to inform best practices on withdrawal of inhaled pulmonary vasodilators. Generally it is probably reasonable to discontinue the agent at the start of transition to comfort measures, before weaning any ventilator settings. Based on half life, symptoms may become significant or severe approximately 15 minutes after discontinuing nitric oxide, or 25 minutes after discontinuing inhaled epoprostenol. Opioid administration as needed for dyspnea or chest pain, and benzodiazepine administration as needed for anxiety after discontinuation are the mainstays of management.

4.5 Neuromuscular blockade agents

Medication must be stopped and effect must be absent prior to withdrawal of life support to ensure ability to demonstrate any discomfort they are experiencing, and to avoid active euthanasia by this mechanism. Even if practicing in a jurisdiction where active euthanasia is legal, withdrawing life support in the presence of neuromuscular blockade is not acceptable because of the temporary and avoidable inability to actively monitor for symptoms and address them during the process.

Ethically, this differs from palliative withdrawal of life support in a neurologically devastated person who is intrinsically unable to demonstrate discomfort during end of life care because their inability to demonstrate discomfort is permanent and irreversible. In this case, for a patient whose surrogate feels the patient would not wish to continue life sustaining treatments, best practice is to aggressively treat for potential symptoms, using changes in vital signs as markers for possible distress and treating accordingly.

Ideally, neuromuscular blockade infusion can be stopped at the initiation of the transition to comfort measures and the effect allowed to wear off gradually as the drug is metabolized. Cessation of neuromuscular blockade allows patients to physically express whether symptoms such as pain, anxiety, dyspnea, or other forms of distress are present.

However, in some instances, patients may have such severe hypoxemia that oxygenation may start to falter before the drug effect is entirely resolved, sometimes to the point that the patient could die before physical symptoms can be fully assessed. In such situations, reversal of neuromuscular blockade may be considered, with neostigmine and glycopyrrolate for any agent, or with sugammadex for rocuronium or vecuronium only.

4.6 Dialysis

When to discontinue dialysis is highly dependent on the patient's situation. For patients with volume overload who are on continuous dialysis, continuing volume removal at least until the time of ventilator withdrawal or extubation may improve comfort by reducing pulmonary edema and whole body anasarca.

For patients with end-stage renal disease, some patients tolerate dialysis well and feel better with continuing it. In the United States, patients who enroll in hospice for a terminal diagnosis not related to their end-stage renal disease may be able to continue outpatient dialysis for a time; this is generally situation-dependent.

4.7 Vasopressors and inotropes

Optimal timing of withdrawal of vasopressors and inotropes is dependent on the situation. For less responsive patients, some physicians recommend discontinuing these early in the course of withdrawal of life supports, to induce a hypotensive or hypoperfusion-related encephalopathy, with the hope of reducing experience of symptoms through this mechanism. Other physicians elect to continue pressors until symptoms are noted to be well controlled after completion of palliative ventilator weaning or withdrawal to ensure medications can be circulated through the body to maximize their effect. Still other physicians discontinue vasopressors and inotropes concurrent with early palliative ventilator withdrawal. To date, there are no studies examining optimal timing; clinical judgment regarding which strategy will most likely meet the individual patient's values, goals, and preferences in light of their condition is needed.

4.8 Pacemakers and implanted cardiac defibrillators

Implanted Cardiac Defibrillators (ICDs) should be deactivated as soon as transition to comfort measures is started, if not already deactivated with DNR order. Implanted pacemakers are typically not deactivated unless the pacemaker function is felt to be significantly prolonging the dying process. Temporary pacemakers are typically deactivated at some point during the withdrawal process; timing can be considered similar to vasopressors.

4.9 Lines, drains, and tubes

At the time of transition to comfort care, the medical team should discuss all lines, drains, and tubes in place and decide whether to maintain or remove each. Urinary catheters may be maintained or removed depending on patient preference and perceived comfort. Temporary central venous catheters and tunneled central venous catheters can generally be maintained unless causing discomfort; temporary catheters may be considered for removal if the patient will be discharged to a setting where use of the catheter may not be feasible.

Nasogastric and orogastric tubes can generally be removed unless continued gastric decompression is necessary or unless there are medications that absolutely must be continued for comfort after extubation. Orogastric tubes should almost always be discontinued if extubation is planned due to significant risk of gagging and oropharyngeal discomfort. Surgical drains and wound vacuum systems should be discussed with the surgical or wound care team.

Pulmonary arterial catheters and arterial lines generally do not improve comfort and should be removed at initiation of transition to comfort measures.

Chest tube management depends on the indication for placement. If a chest tube was initially placed for pneumothorax and maintained in place only because of continued positive pressure ventilation, clamping and removal can be considered, especially if ventilator support will be discontinued. Chest tubes placed for significant, symptomatic pleural effusions likely should be continued to allow continued pleural drainage, unless pleurodesis has occurred. Those placed for pneumothorax that has not resolved likely should also be maintained and kept to suction to avoid symptomatic expansion of the pneumothorax. In all cases, the patient's condition should be the driving factor in decision-making.

4.10 Artificial hydration and nutrition

The limited benefits and significant risks, harms, and symptoms induced by artificial hydration and nutrition should be discussed with the patient or surrogate prior to the palliative withdrawal process. Ideally these should be discontinued hours before initiation of the withdrawal process to avoid full stomachs or fluid overload. Patients who are able to express desire to eat or drink after extubation should be allowed to do so with caution and support, with a focus on comfort and quality of life.

5. Other consideration

5.1 Brain death

Jurisdictions may vary in their laws regarding management of patients diagnosed as brain dead. In some, the local organ procurement organization must be

notified and allowed to assess the patient for donation before withdrawal of life supports can be considered.

5.2 Organ and tissue donation

Depending on local or national laws regarding organ and tissue donation, the local organ procurement organization may be required to be notified prior to initiation of the withdrawal process. It may also be required to allow the agency to assess the patient and discuss potential for donation with the patient or surrogate.

Ethically, clinicians involved in the patient's care should not be involved in discussing organ or tissue donation. Perceived or real pressures to procure organs for other patients can adversely affect both decision-making processes of the patient or family and of the medical team. This can also erode the patient's trust in the medical team to prioritize their needs and care. Discussions regarding organ and tissue donation should occur between the patient or family and procurement specialists not involved in the patient's care.

6. Process of palliative ventilator withdrawal

6.1 Time out

Prior to the initiation of palliative withdrawal of life supports, the care team should convene to discuss the patient's condition and formulate a plan consistent with the patient's and family's goals, values, and wishes, and making every effort to minimize or at least control symptoms. This process should be a formal, focused discussion and should occur before initiation in every case. The discussion should include the physician, bedside nurse, and respiratory therapist (RT) at least, ideally should include the chaplain, and the clinical pharmacist when needed.

Topics for discussion during the time out must include plans regarding timing of and method for withdrawing each form of life support, symptoms anticipated due to withdrawal of each life support, and plans for managing these symptoms. The team should also clarify which team member is to be the first point of contact if initial symptom management strategies are insufficient, or if other issues arise.

Where required, the local organ procurement organization must be notified of the plan for palliative withdrawal of life supports and anticipated or possible patient death prior to initiation of the process.

The bedside nurse in particular must be given support and time to focus exclusively or nearly exclusively on the patient undergoing transition to comfort measures, to ensure a smooth transition with excellent symptom management.

Prior to initiation of any steps in the process of withdrawal, the appropriate Do Not Resuscitate order must be signed by the appropriate medical team member. Remaining full code while undergoing palliative withdrawal of life supports is completely counter to the goals of the process; it is absolutely predictable that at some point after withdrawal, cardiopulmonary arrest will occur and require either cessation of efforts based on futility, or require re-initiation of some forms of life support. At best, life supports required at this point might be the same as those in use prior to withdrawal, but more likely would include additional supports to sustain a condition that would at best be equal to the patient's condition at the initiation of withdrawal. If the patient or surrogate desires resuscitative efforts at time of death, current management should be continued. This can include agreed-upon plans to limit escalation (e.g., not adding additional pressors, dialysis, or other new therapies), or to plan to discuss progress, or lack thereof, at a specified date and time, typically a few days.

The patient, surrogate, and family should be asked about what cultural or spiritual practices related to death and dying are meaningful to them, and efforts should be made to support these needs and wishes. These can include Last Rites or specific prayers to be said prior to death, creating memorial items before or after death, and rituals regarding cleaning and care of the patient's body after death. Some memorial items such as handprints, hand casts, recordings, and ECG tracings, can be made fairly easily and inexpensively. Some family members may wish to preserve locks of hair. It is essential to ask open ended questions and not project what the patient or family 'should' or 'should not' want at this point.

Once the plan is created and agreed upon, it should be reviewed with the patient as able, and with the family, to their desired level of detail. Anecdotally, many families and most patients are satisfied hearing that the plan for transition and withdrawal has been discussed and agreed upon by everyone participating, and has been designed to maximize the patient's comfort.

Once transition has started, the bedside nurse should update the designated point of contact for the medical team to discuss any inadequately controlled symptoms or changes in clinical status.

After the patient's death, family should be allowed and encouraged, but never forced, to assist in caring for the patient's body after death. Specific cultural or religious practices regarding care and monitoring of the body after death should be elicited and respected.

7. Case examples

7.1 Case 1: a 'simple' case

Mrs. A is a 78 year-old woman with chronic obstructive lung disease with chronic hypoxic and hypercarbic respiratory failure, and pulmonary cachexia. Her baseline oxygen requirement is 3 liters of oxygen by nasal cannula around the clock. She has been in the intensive care unit (ICU) for three weeks with acute on chronic respiratory failure due to chronic obstructive pulmonary disease (COPD) exacerbation and pneumonia, which have been fully treated. She has failed non-invasive ventilation repeatedly and was reintubated for the third time four days ago. She has spent a total of 16 days on the ventilator thus far. She has mild to moderate secretions and is able to expectorate them without distress. She is on assist control volume control with a tidal volume set at 6 mL/kg ideal body weight, requiring peak inspiratory pressure of 20, rate set at 12, PEEP of 5, and FiO2 35%.

She has a good cuff leak, but failed her spontaneous breathing trial this morning for dyspnea and tachypnea. She requests palliative extubation as she is not amenable to tracheostomy or prolonged ventilatory support.

She is awake, alert, able to write long coherent paragraphs about her understanding of the situation and about her wishes regarding her further care. Her spouse and children are understandably sad but supportive of her wishes, agreeing that this request is consistent with her long-stated wishes regarding prolonged life support. She is on no sedation and reports feeling comfortable on assist control.

After confirming the patient has capacity and is expressing a consistent choice with internally consistent logic based on good understanding of her medical condition, and answering any questions she or her legal surrogate or family have, the physician should discuss with the bedside nurse, RT, and when needed, the ICU charge nurse, to ensure the nurse and RT will have time to properly devote to this patient as the transition to comfort measures occurs. They should discuss what

as-needed medications she has been given over her ICU stay, and what her response has been to each, to determine what she is likely to need during the withdrawal process, and orders for these medications should be placed.

The physician or nurse should ask the patient and family if they wish to visit with a chaplain and when. If a chaplain visit is desired prior to transition to comfort measures, the chaplain should ensure they ask about any specific spiritual or cultural practices they wish to observe. If the chaplain's visit is declined, the physician and nurse should coordinate to explore culture or spiritual needs and wishes related to the transition process.

After the appropriate Do Not Resuscitate order is signed, and preparations for symptom management are made, and the patient and family are ready, as she is already on minimal ventilator settings, a spontaneous breathing trial should be initiated again, and comfort medications titrated to maintain her comfort with minimal ventilator support. Once she is comfortable on minimal ventilator support, she can be extubated when she and her family are ready, placed on oxygen via supplemental nasal cannula as is her baseline, and treated with the minimal effective dose of an opioid as needed for pain or dyspnea, or benzodiazepine as needed for primary anxiety, and supported until death or transition to another location for further care.

7.2 Case 2: a more challenging case

Mr. B is a 57 year-old with a remote mid-thoracic spinal cord injury with paraplegia but no known chronic respiratory insufficiency who was admitted to the intensive care unit 2 weeks ago for septic shock due to urinary tract infection with secondary bacteremia. He was initially intubated for respiratory fatigue after hours of working to compensate for lactic acidosis, but developed acute respiratory distress syndrome (ARDS) requiring PEEP of 18 cmH2O at most, FiO2 80–100%, with a set respiratory rate of 34. He has required pressors for the past two weeks, and developed renal failure requiring continuous renal replacement therapy for the past week. He requires deep sedation to maintain ventilator synchrony, and is encephalopathic and agitated when sedation is lightened. When updated at a meeting to discuss his clinical condition and values, preferences, and goals, his legal surrogate states he would not accept prolonged life support measures, including a tracheostomy, a longer-term feeding tube, or more than a few weeks of ventilator support or dialysis. The surrogate feels he has 'had enough' and would not want to continue current management; he feels the patient would wish to have Last Rites administered by a priest, and has no other specific requests for rituals surrounding death.

His code status is changed to Do Not Resuscitate. As soon as is feasible, family and friends are allowed a few hours to visit and say goodbyes. The patient's priest comes to the hospital and administers Last Rites. The patient's nurse and respiratory therapist are relieved of some of their other duties for a time, to be allowed to provide dedicated care to this patient. As discussed in the time out prior to withdrawal, first medications and therapies that do not improve his comfort are discontinued. Renal replacement therapy is then stopped and the machine is removed from the room. Vasopressors are then stopped. Blood pressure falls to a MAP of 50 mmHg but stabilizes, and heart rate increases from 90 to 110 and stabilizes.

His face appears calm and he is synchronous with the ventilator. His current opioid and benzodiazepine infusion rates are continued. Ventilator weaning is initiated; rate is reduced by 4–6 breaths per minute, FiO2 is reduced by 10%, and PEEP by 2 cmH2O simultaneously. Tidal volume is not changed, or may be increased slightly to improve comfort. Any respiratory distress or apparent anxiety are treated

with boluses of opioids or benzodiazepines or both, and once controlled, rate, FiO2, and PEEP are weaned again with ongoing boluses and titration of bolus doses as warranted by his symptoms. His SpO2 falls to 60%, but his vital signs remain fairly unchanged. Once he is weaned to 30% with a PEEP of 6, and a set rate of 14 with a total rate of 18, and he appears comfortable based on lack of grimacing and lack of restlessness, the oroendotracheal tube is removed. Additional doses of opioids are given as needed for respiratory discomfort, and benzodiazepines are given as needed for evidence of anxiety. Family remains at the bedside until he dies.

7.3 Case 3: an unusual circumstance

Mr. C is a 30 year-old man with relapsed acute myeloblastic leukemia who develops severe tumor lysis syndrome after induction chemotherapy and is transferred to the ICU for management. He is started on a bicarbonate infusion and IV fluids. He is placed on BiPAP to support his respiratory compensation for acidemia while arrangements are made to start continuous renal replacement therapy, but is unable to maintain respiratory compensation for acidemia and is intubated. His respiratory rate is moderate, with minimal pressure and oxygen requirements. He remains remarkably alert, calm, and coherent after medications given for intubation wear off. After discussion of his overall condition, in which he has fully participated, he writes out clearly that he wants to transition to comfort care. The medical team discusses his physiologic derangements and recalls his extremely high respiratory rate prior to initiation of bicarbonate infusion. After a short spontaneous breathing trial in which he remains somewhat tachypneic but does not feel distressed.

He requests his code status be changed to Do Not Resuscitate and Do Not Intubate; these orders are completed. He is extubated to allow him to speak with his family. Continuous renal replacement therapy is continued for a few more hours until the cassette requires changing, at which time the set-up is taken down and not restarted. Bicarbonate infusion is continued to ameliorate his acidemia in hope of preventing dyspnea due to tachypnea. He is offered opioids for dyspnea when he appears to have respiratory distress and allowed to choose whether or not he feels he needs them, as well as being allowed to request them when needed. After several hours of good conversations with his family, he feels his breathing is tiring out and requests more frequent opioids, even if this means he may be too sleepy to interact with family. Opioids are given to relieve his dyspnea and respiratory distress. When the bicarbonate infusion bag is nearly empty, the rate is reduced and opioids are titrated to comfort before the bag is completed and the infusion stopped. His breathing pattern becomes irregula as he is no longer able to maintain compensation, and he appears comfortable until and through his death.

7.4 Case 4: a very challenging case

Mx. D is a 37 year-old person with antiphospholipid antibody syndrome and patent foramen ovale, with multiple deep venous thromboses and pulmonary emboli in the past, on therapeutic anticoagulation, develops diffuse alveolar hemorrhage and acute hypoxic respiratory failure requiring intubation and mechanical ventilation. They are treated with steroids and inhaled tranexamic acid, and chronic anticoagulation is held. They unfortunately have several seizures and are found to have multiple embolic strokes with severe hemorrhagic conversion, including several of the cerebellum and visual cortex. On meeting with their family including parents who are their legal surrogate, they feel that the likely long-term impairments caused by the strokes would be unacceptable given their career as a dancer, and that they would not want to continue disease-directed therapies.

Given the continued moderate and occasionally large volume hemoptysis requiring suctioning through the oroendotracheal tube, the patient's sibling, who is a respiratory therapist, expresses concern about the patient's ability to breathe comfortably if extubated. Code status is changed to Do Not Resuscitate prior to transition to comfort care. Ventilator support is weaned down to the lowest PEEP level at which the patient appears comfortable. Pressure support, SIMV-PSV, and APRV with only a small difference between high and low PEEP. The medical team advises their family that the ventilator will continue to trigger after the patient's death, as the ventilator's apnea backup settings can be minimized but not completely discontinued. Their comfort is maintained with opioid and benzodiazepines as needed until death.

7.5 Case 5: organ procurement

Ms. E is a 25 year-old woman with a long-standing history of opioid abuse including ingestion and injection- both subcutaneous and intravenous- of prescription opioid pills, and injection of heroin and fentanyl. She has suffered several overdoses requiring hospitalization and brief periods of intubation and mechanical ventilation in the past, has undergone rehab including some periods of abstinence, but has unfortunately suffered multiple relapses. Five days ago she was found unresponsive with agonal breathing at home after last speaking to family by phone hours earlier. MRI of the brain and serial head CT scans over several days in the ICU showed diffuse anoxic injury with severe edema and progressive herniation. Her clinical exam with normal electrolytes, normal temperature, and normal pCO2 and pH progresses to demonstrate no brainstem reflexes.

Several forms of testing clearly demonstrate brain death. The medical team informs and consoles her family, and requests the chaplain and social worker to further assist in supporting the family. The bedside nurse contacts the local organ procurement organization, whose representative comes to the hospital and reviews Ms. E's case. She is noted to be a self-registered organ donor, and is deemed to be a candidate for donation of multiple organs. The representative from the organ procurement organization discusses with her family the process of assessing her and preparing for potential organ donation. She is maintained on mechanical ventilation via oroendotracheal tube. Pituitary failure is managed with IV levothyroxine, DDAVP, and hydrocortisone. Blood pressure is maintained with vasopressors. When assessment is complete and the organ procurement organization and explant surgeons are available, she is taken to the operating room with a solemn procession in her honor, where life supports are withdrawn simultaneously. Cardiac death occurs 20 minutes later, and all viable organs are harvested for transplantation.

8. Conclusions

The above discussions, and the case examples, are not exhaustive of the situations clinicians may find themselves facing in the course of caring for patients. They are examples of some of the more common conditions that require consideration and flexibility for patient-centered management. Far from a simple, 'one size fits all' process, they illustrate that palliative withdrawal of life supports is a medical procedure that requires thoughtful collaboration and consideration to provide each patient with the most comfortable transition to end of life care possible.

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Chapter 3

Noninvasive Ventilation in Neuromuscular Diseases

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.77173

Abstract

Respiratory muscle weakness is the main contributor to respiratory imbalance in patients with neuromuscular diseases (NMD). In the advanced stages of the disease, patients develop a chronic respiratory failure due to muscle weakness, which is the principal cause of death among these patients. Respiratory muscle weakness ultimately causes alveolar hypoventilation, initially nocturnal, and later daytime respiratory failure. The signs and symptoms of early respiratory muscle weakness are discrete, namely: dyspnoea on effort, orthopnea, insomnia, frequent nocturnal awakenings, morning headache, loss of appetite, excessive daytime sleepiness, depression, anxiety, and marked fatigue. The management of respiratory failure in neuromuscular diseases requires the use of non-invasive ventilation (NIV) to assist the respiratory muscles in order to correct the alveolar hypoventilation and ameliorate gas exchange. NIV thus slows down the decline of forced vital capacity thereby improving the patient's quality of life, physical activity and hemodynamics, normalization of blood gases, slight improvement in other physiological measures, and maximal mouth pressures and increases survival. NIV support should be offered to all patients who present with early signs of ventilatory failure as it is probably the most effective among treatments in prolonging life in neuromuscular patients.

Keywords: non-invasive ventilation, respiratory failure, neuromuscular diseases

1. Introduction

Neuromuscular diseases (NMD) are a group of diseases that affect the nerves that control voluntary muscles, including respiratory muscles in more advanced stages, that varies according to underlying disease [1]. The weakness of the respiratory muscles causes alveolar hypoventilation, initially during sleep, and then leading to respiratory insufficiency in the

daytime [1, 6]. Respiratory infections, in which neuromuscular patients are predisposed, usually aggravate the evolution of respiratory insufficiency.

Muscle weakness affects three categories of muscles involved in breathing:

- Inspiratory muscles, which contribute to the act of ventilation and voluntary inspiration.
- Expiratory muscles performing forced expiration and forced expiratory flow.
- Bulbar muscles, which have a glottic function, thus contributing to swallowing/speech, increased intra-thoracic pressure and cough [4, 9, 13].

Affection of inspiring muscles in NMD leads to dyspnoea, orthopnea, alveolar hypoventilation and hypercapnia. Alveolar hypoventilation occurs initially during rapid eyes movement sleep (REM) sleep, then in non-REM sleep, leading to morning hypercapnia and later in the evening hypercapnia as well as hypoxia [2, 3, 8, 13]. The weakness of the expiratory muscles leads to an inefficient clearance of the airway, ineffective cough, thus predisposing to respiratory infections. Affecting bulbar muscles causes swallowing and speech disturbances, aspiration secretions, reduced airway clearance, and recurrent respiratory infections [1, 6, 8, 13].

Existing studies have shown, mostly uncontrolled trials, that non-invasive ventilation (NIV) in neuromuscular diseases improved quality of life, physical activity and hemodynamic, normalization of blood gases and slight improvement in other physiological measures, such as the vital capacity and maximal mouth pressures [1, 3, 5, 6, 11, 12].

Monitoring of patients diagnosed with NMD is essential for the early detection of signs of respiratory failure and the establishment of NIV at an early stage of respiratory distress.

2. Signs and symptoms of respiratory failure in neuromuscular diseases

2.1. Symptoms

The symptoms of respiratory muscle weakness depend on the speed of its development. When the onset is subacute (for example, in Guillain-Barre syndrome), the predominant symptoms are dyspnoea and orthopnea, or sometimes respiratory arrest. These symptoms are often accompanied by those of bulbar weakness and inability to clear respiratory secretions. The symptoms of respiratory failure may easily be overlooked and should be specifically sought in any patient with rapidly progressive weakness, especially when the bulbar muscles and shoulder girdle are affected [4, 8, 9, 11].

When respiratory muscle weakness develops gradually, inadequate respiration usually occurs first during sleep. Symptoms of nocturnal hypoventilation include a broken sleep pattern, nightmares, nocturnal confusion, morning headache, daytime fatigue, mental clouding and somnolence [4, 8, 9, 11].

Symptoms	Signs
Dyspnea to minimal effort or speech	Tachypnea
Orthopnoea	The use of auxiliary respiratory muscles
Frequent nocturnal awakenings	Paradoxical abdominal movements
Excessive daytime sleepiness	Reducing the amplitude of the thoracic movements
Daytime fatigue	Ineffective cough
Morning headaches	Sweating
Difficulty to expectorate secretions	Tachycardia
Apathy, loss of appetite	Morning confusion, hallucination
Hypomnesic concentration deficiency and memory impairment	Weight loss
Difficulty sleeping	Dry mouth or hypersalivation

Table 1. Signs and symptoms of respiratory failure in neuromuscular diseases.

Rapidly progressive NMD	Variable progression	Slowly progressive or non-progressive
Amyotrophic lateral sclerosis (ALS)	Limb girdle muscular dystrophy	Spinal muscular atrophy
Duchene muscular dystrophy (DMD)	Miopathies Nemaline miopathy Metabolic miopathy	Poliomyelitis, post-polio syndrome
	Merosin negative congenital muscular distrophy	Facio-scapulohumeral muscular dystrophy
		Becker muscular dystrophy

Table 2. Classification of Neuromuscular disorders (NMD) according to evolution [1].

Exertional dyspnoea is encountered less frequently in neuromuscular patients than in those with other cardiorespiratory disorders, particularly when the patient has reduced mobility. Dyspnoea when lying flat or immersed in water specifically suggests weakness of diaphragm [4, 9].

2.2. Signs

A patient with severe respiratory muscle weakness or respiratory failure may appear overtly breathless and may be using accessory muscle of respiration. The patient may be unable to speak in complete sentences or take deep breaths to command. Inability to count from 1 to 20 in a single breath indicates significant reduction of vital capacity (VC) or forced vital capacity (FVC) [4, 9, 11]. Paradoxical abdominal motion (inwards movement of the abdominal wall with inspiration) suggests significant weakness of the diaphragm. The combination

of hypoxemia and respiratory acidosis may produce mental clouding or somnolence. It is also important to assess the bulbar musculature, weakness of which can hinder clearing of respiratory secretions and so allow aspiration. Most of the patients with respiratory muscle weakness resulting from a neuromuscular condition have limb weakness. Acute respiratory failure in patients with neuromuscular disorders is often precipitated by respiratory infection [4, 8, 9, 11].

Particular attention should be paid to:

- Presence or absence of bulbar weakness.
- A tall, thin face (congenital myopathy, myotonic dystrophy)
- Ptosis of ophthalmoparesis (myasthenia)
- Fasciculation (motor neuron diseases)
- Paraspinal muscle wasting (acid maltase deficiency)
- Skin rash (dermatomyositis)

The main signs and symptoms of respiratory failure in the NMD can be found in **Tables 1** and **2**.

3. Course of neuromuscular disorders

Neuromuscular disorders can be divided into slowly progressive, rapidly progressive and NMD with variable progression; understanding the speed of progression of the disease is important in deciding the appropriateness of NIV [1, 2].

In the rapidly progressive NMD, the prototype of this category is Duchenne muscular dystrophy (DMD). Monitoring these patients begin in early ambulance stage, when the patient can walk independently, by using serial spirometry, sleep studies and blood gases, for capturing early FVC decline and respiratory disturbance in REM and non-REM sleep [11, 14].

In general, reducing FVC demonstrated by spirometry does not correlate very well with the occurrence of dyspnea as a symptom at these patients. Therefore, monitoring of clinical signs and symptoms of respiratory disturbance is not enough. Alveolar hypoventilation, secondary to respiratory muscular weakness, initially occurs in REM sleep, and it can be early diagnosed by using polysomnography. In a later stage, sleep disturbances occur both in REM and non-REM sleep, resulting in morning hypercapnia, and in the final stages, it also occurs during the daytime [11, 14].

The classical spirometry measuring FVC has some limitation in detecting moderate inspiratory muscle weakness; performing lung function test in supine position, could improve the value of FVC [16]. In DMD and other rapidly progressive NMD, initial evaluation using

spirometry, polysomnography, blood gases and SaO2 is performed once a year, subsequently two times a year, and in advanced stages at 3 months [11, 14]. In slowly progression NMDs and those with variable progression, annual monitoring is sufficient.

4. Monitoring evolution of NMD

From a functional stand point, neuromuscular patients can be classified as following:

- Ambulant patients, who can walk without any help.
- Non-ambulant patients, who cannot stand seated without any help.
- Non-ambulant patients, who can stand seated without any help, but cannot walk without any help [14].

The monitoring of the patients is in relation with the specific neuromuscular disease and the rate of progression of the disease in each patient. It is recommended that the respiratory evaluation be done every 3–6 months, less frequently for ambulant patients, and more frequently for the nonambulant patients, and where the disease progresses at a faster pace.

Methods for respiratory monitoring in NMD:

- Spirometry
- Pulse oximetry
- Blood gases or capnography
- Polysomnography and/or cardiorespiratory polygraph
- Manometry for measurement of maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP)
- Cough peak flowmetry
- Sniff nasal inspiratory pressure (SNIP)

Spirometry and lung function testing are useful for detection of reducing FVC [11, 21] It can be applied while the patient is standing, however, classical spirometry measuring FVC has some limitations in detecting moderate inspiratory muscle weakness, spirometry in supine position is recommended. When measured FVC is in the supine position, vital capacity is lower, especially in patients with diaphragmatic weakness. Supine vital capacity may be useful in monitoring disease progression [11, 20]. A vital capacity of <1.11 liters predicted risk of chest infection with a sensitivity of 90.5% and a specificity of 70.8% [11].

Peak flowmetry during cough [cough peak expiratory flow (PEF)] allows efficient evaluation of coughing. A cough with PEF <270 ml/min suggests ineffective coughing [16].

Pulse oximetry can be used for highlighting hypoxemia during day, but also for guiding during the clearance of the airways. If the O_2 saturation is lower than 94%, clearance of the airways must be initiated. Continuous night pulse oximetry can be used for screening of the nigh time hypoxemia. Currently, it is not recommended to routinely monitor SaO_2 at home, more studies being required for this issue [11, 14, 16].

Blood gases or capnography allows the assessment and evaluation of the initial morning hypercapnia; then, it becomes permanent. Blood gases should be performed if $SaO_2 < 94\%$ and the patient do not have lung disease [16, 17]. In children with NMD, the use of capnography is preferred, a noninvasive method, in order to determine the transcutaneous CO_2, and to monitor the exchange of gases routinely [11, 14].

Polysomnography represents a diagnostical investigation option for respiratory disturbances during sleep and during alveolar hypoventilation in NMD and is the most pertinent indicator for proposing NIV [10, 21]. Polysomnography (**Figures 1** and **2**) is useful in nonambulant patients who cannot stand without any help and can be used for initiation and titration of the respiratory support, more specifically non-invasive ventilation. If polysomnography is not available, the cardiorespiratory polygraph is recommended, with a minimum of four channels: O_2 saturation, cardiac frequency, nasal flow, and chest movements during sleep [11, 14, 16].

A specific evaluation of respiratory muscle strength is the measurement of maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), and sniff nasal pressure (SNIP). In some patients, specifically in NMD with bulbar determination, some discrepancies are registered between the maximum inspiratory pressure (MIP) and sniff nasal pressure (SNIP). As a consequence of the discrepancies, it is recommended to do both tests, taking note to select the highest pressure [11, 16].

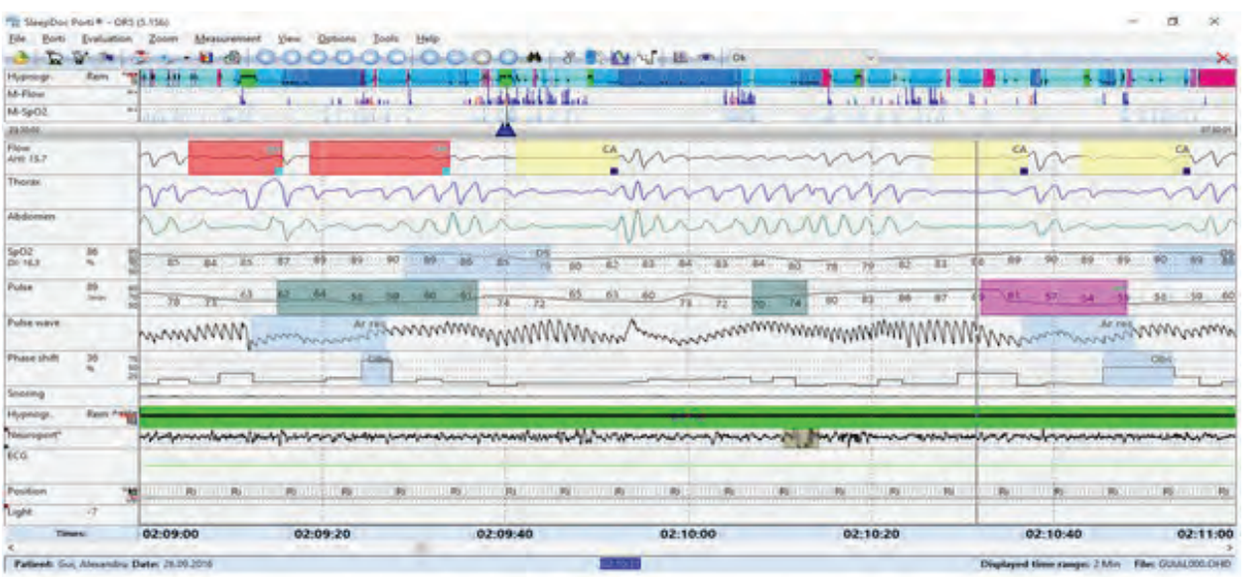

Figure 1. Polysomnography in 9 years old patient with Central Core Myopathy. Obstructive and central apnoea, AH1 = 15,7/hour of sleep, desaturation in O2 in REM sleep.

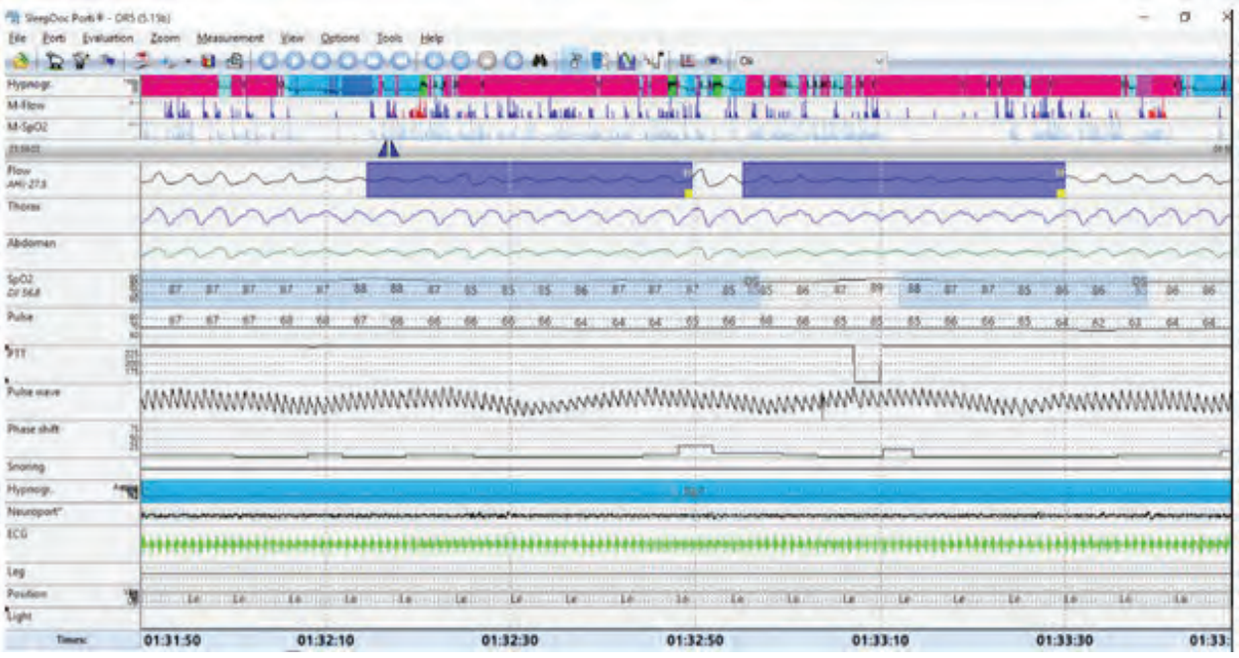

Figure 2. Polysomnography in a patient aged 45 years with ALS generalized form, spastic tetraplegia, pseudobulbar syndrome, syalorrhoea, eating difficulties, dyspnoea. Epoch with predominantly hypopneic flow, accompanied by desaturations in O_2, in stage N_2, morning PCO_2 = 51 mmHG.

5. Indications and contraindications for long-term NIV in NMD

The most frequent indications for NIV in NMD are:

- Amyotrophic lateral sclerosis (ALS)
- Duchenne's muscular dystrophy
- Becker's muscular dystrophy
- Steinert's muscular dystrophy
- Myasthenia gravis
- Spinal muscular atrophy [2, 7, 13, 15]

Depending on the natural evolution of neuromuscular disease to respiratory distress, NIV can be introduced to the management of the disease as soon as possible.

Contraindications for NIV in NMD:

- Facial burns/trauma/facial surgery or recent upper respiratory tract surgery
- Anatomical or functional obstruction
- Gastrointestinal or ileus bleeding

- Vomiting
- Hypersalivation
- Severe hypercapnia or severe respiratory acidosis (pH < 7.1)
- Without patient's consent for setting up NIV [2, 7, 15].

6. Neuromuscular diseases and long-term NIV: when?

There is plenty of evidence that precociously introducing NIV to the neuromuscular patient brings improvements in the quality of life and even prolongs survival. The question the clinician must ask is: when is the optimum moment for starting NIV with the neuromuscular patient?

NIV must be initiated when:

- The neuromuscular patient shows signs and symptoms of respiratory disturbances
- pCO_2 in the morning >45 mmHg
- FVC < 50% predicted value
- MIP or SNIP<60 mmHg
- Nocturnal SaO_2 < 88% for more than 5 min while under room air [1, 2, 14, 17].

Or

- FVC < 80% predicted value plus any symptoms or signs of respiratory impairment
- SNIP or MIP < 65 cm H_2O for men or 55 cm H_2O for women plus any symptoms or signs of respiratory impairment, particularly orthopnoea [17].

The classical indications to start NIV, when pCO_2 > 45 mmHg or when a patient has an exacerbation, as markers for respiratory failure could be too late. The history of neuromuscular diseases has a prolonged period of discrete symptoms of respiratory impairment, but with variable period of nocturnal hypoventilation. Performing polysomnography every year in a neuromuscular patient, as a routine method of disease monitoring, we can identify nocturnal hypoventilation very early and NIV could be started early [10]. Starting NIV earlier in the course of respiratory failure should be accompanied by a significant improvement in quality of life, and probably in prolonging life. There is no data for the moment to demonstrate this [10].

7. Introducing NIV in NMD, ventilator choices, interfaces

Non-invasive ventilation in NMD improved or corrected diurnal hypoxemia and hypercapnia, improved nocturnal hypoventilation and increases maximal respiratory pressures [7, 11, 14, 15, 22].

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From the clinical point of view, NIV improved quality of life, control of symptoms of sleep related breathing, for example, headaches, sleep fragmentation, decreased daytime sleepiness, increased ability to perform daily activities, provide patients with sense of control and autonomy in advance stages, reduce hospitalizations and prolonged survival [1, 2, 3, 7].

Type of ventilators for long-term NIV:

- Pressure-support ventilator
- Volume-targeted ventilator: deliver known tidal volumes, but most machines have a limited capacity to correct leaks, leading to underventilation
- Hybrid mode ventilator: pressure-targeted volume-assured mod

Bi-level positive airway pressure ventilator (BiPAP), spontaneous/timed (S/T) mode is the most common type of pressure-support ventilator used for long-term NIV in NMD. There is a lack of study to compare different types of ventilators used for long-term NIV. But, pressure-targeted ventilators tend to be lighter and cheaper and also comfortable to the patient than volume-targeted ventilators [6, 11, 18].

Intelligent volume-assured pressure support (iVAPS) is a hybrid mode ventilator, providing constant automatic adjustment of pressure support (PS) to achieve a target ventilation determined by the patient's pathology [11, 18]. iVAPS demonstrated, in small studies, similar arterial

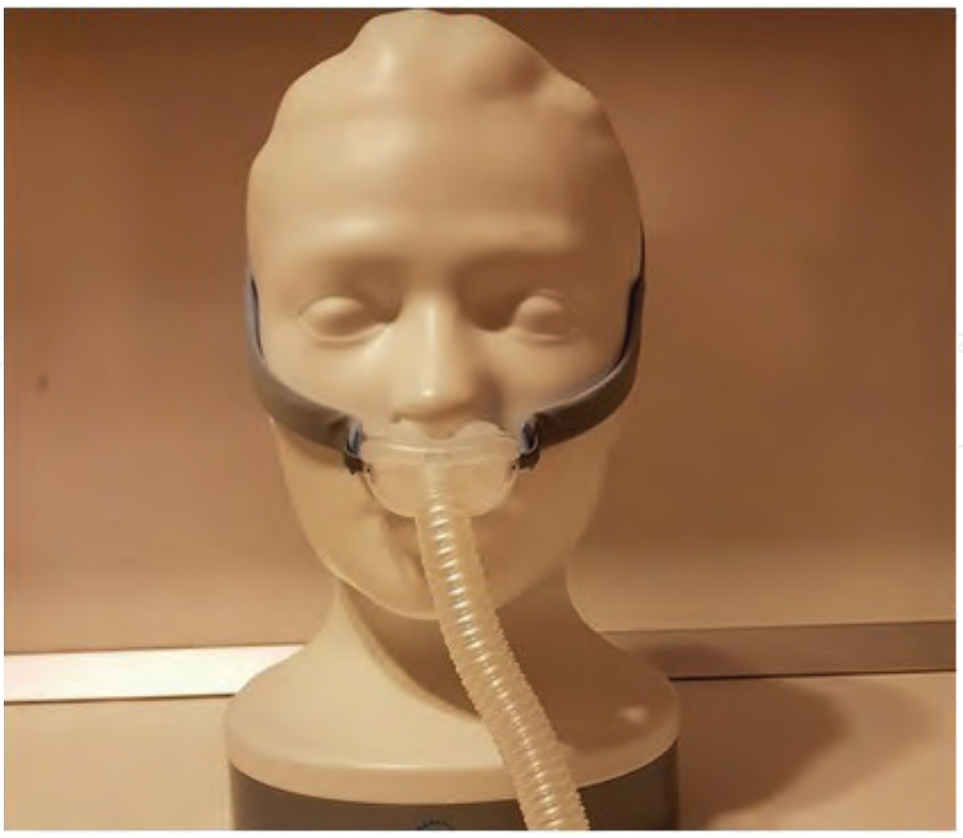

Figure 3. Choosing the interfaces: Pillow mask.

blood gases control to BiPAP, but iVAPS had higher overnight adherence, due to better patient-ventilator synchrony; there was no difference in outcome between ventilator modes for spirometry, respiratory muscle strength, sleep quality, arousals or O_2 desaturation index [11, 18].

7.1. Choosing the interfaces

Extremely important for good compliance to NIV is choosing the right interfaces. Nasal mask and pillow mask are best suited for cooperative patients that have a lower severity of the disease, or for children, needed low to moderate pressures only (< 20 cm H_2O). It also allows the patient to speak, drink, cough and clear his/her secretions while receiving the treatment. Nasal masks are more prone to leaks and the effectiveness is limited in patients with nasal obstructions, septal defects or other kind of deformities. Nasal and pillow mask are more comfortable for the patient than orofacial mask [11, 38, 39].

Orofacial mask, which encompass the mouth and nose are best suited for less cooperative patients who have more or less severe illnesses. It particularly fits patients who are mouth-breathing and edentulous and they are contraindicated in claustrophobic patients. Orofacial mask does not allow the patient to talk or eat and it is more uncomfortable for the patient than nasal or pillow mask [11, 38, 39].

Nasal mask, pillow mask and orofacial mask are illustrated in **Figures 3–5**.

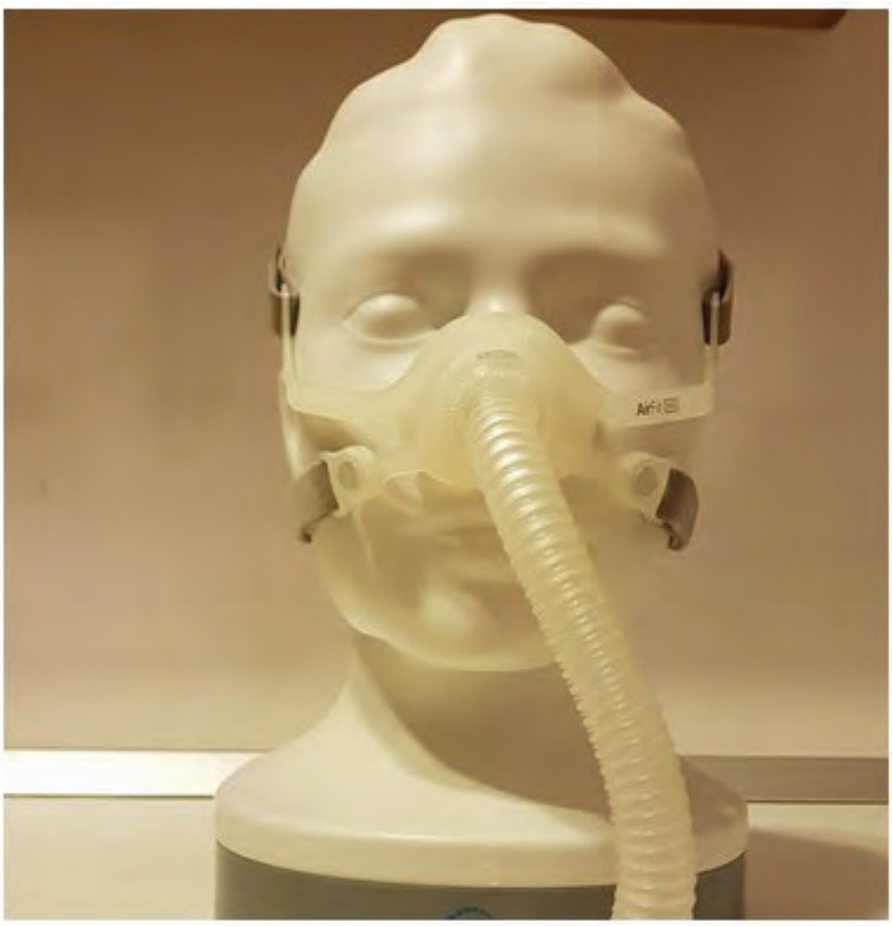

Figure 4. Choosing the interfaces: Nasal mask.

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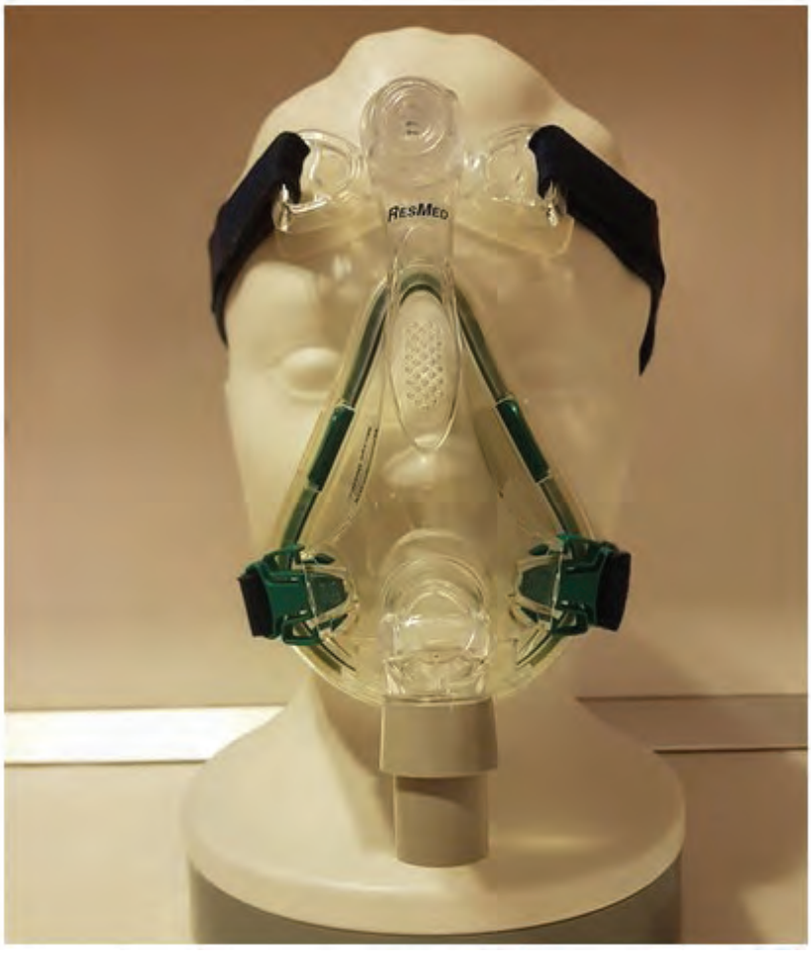

Figure 5. Choosing the interfaces: Orofacial mask.

7.1.1. Adverse effects and complications of NIV

The majority of adverse events of NIV are related to the mask: discomfort, skin rush, claustrophobia, nasal ulceration nasal congestion, eyes irritation, nasal or oral dryness. This mask related adverse events could be easily resolved by changing the interface and adding humidifier for the dryness of the mucosa.

Other NIV complications are aspiration pneumonia, pneumothorax or hypotension, with a low frequency < 5% [11, 38, 39].

8. Monitoring NIV in NMD

Effectiveness of NIV depended on a several factors: settings, interfaces, compliance and adherence of the patient to his ventilator. For obtaining a good compliance and adherence to NIV, monitoring NIV is crucial. The minimum requirement is a sleep study recording continuous oximetry, capnography or blood gases.

The frequency of monitoring NIV is depending of the cases; for new cases, monitoring is required to be done more often, every few weeks, until established that we obtained correction

of nocturnal hypoventilation and blood gases. In stable cases on home-ventilation, with slowly progressive or non-progressive disease, annual assessment is sufficient [11, 38]. The new type of ventilators provided a compliance card, which permitted a minimum set of data to monitor: hours of usage, AHI index, leaks.

8.1. Using ultrasound to monitor NIV in NMD

One of the main causes of morbidity and mortality in patients with neuromuscular diseases (NMD) is respiratory failure. The diaphragm acts as the main respiratory muscle during inspiration and accounts for 70% of the inspired air volume during regular breathing [19]. The diaphragm function can indirectly be analyzed by techniques such as fluoroscopy and chest radiography, which are non-specific and also ionizing exams [23]. Ultrasound (US) as a non-invasive, radiation-free imaging tool, allows an accurate, reproducible and safe assessment of diaphragm anatomy and function at the bedside [24–27]. Ultrasound has been shown to be similar in accuracy to most other imaging modalities for diaphragm assessment [28].

8.1.1. Technique of diaphragmatic ultrasound (US) assessment

With ultrasound, the diaphragm is typically identified by its deep location, curved shape and muscular echo-structure. Longitudinally it has a mixed echogenic appearance, consisting of hypo echoic (dark) muscle fibers separated by two hyper echoic (bright) layers: peritoneum and pleura (**Figure 6**).

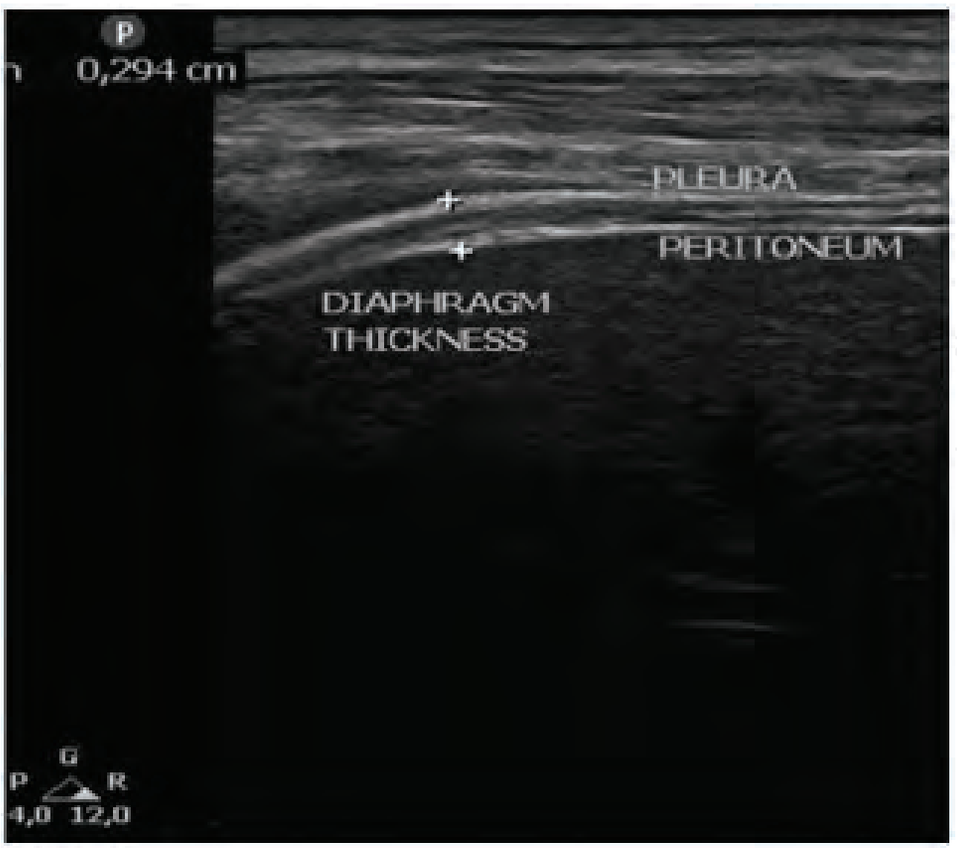

Figure 6. Normal US appearance and thickness of the diaphragm.

Patients are typically examined during spontaneous respiration to help identify the diaphragm moving. The supine position of the patient is preferred, because there is less overall variability, less side-to-side variability, and greater reproducibility [29]. Also, it could identify any paradoxical movement.

The right diaphragm can be visualized through the liver window. Visualization of the left diaphragm could be sometimes more difficult because of the smaller window of the spleen.

Classically, there are two methods to evaluate the diaphragm: the analyses of the movement of diaphragmatic dome using the M mode and the measurement of diaphragmatic thickness and the thickening during inspiration in the area of apposition using the B mode.

The anterior subcostal view is preferred for evaluation of diaphragm excursion. It requires a lower frequency, ideally curvilinear, transducer (2–6 MHz) placed between the mid-clavicular and anterior axillary lines (**Figure 7**), so that the ultrasound beam could reach the posterior third of the diaphragm. B mode is used to visualize the diaphragm moving toward or away from the transducer. Imaging is then changed to M mode with the line of sight positioned in order to obtain maximum excursion (**Figure 8**). Either dome of the diaphragm can be evaluated using the liver and spleen window and the amplitude of excursion can be measured on M mode, and diaphragm velocity can be calculated (**Figure 8**).

For an intercostal view, a higher frequency linear array transducer (7–18 MHz) is placed at the anterior axillary line, with the transducer positioned to obtain a sagittal image at the intercostal space between the 7th and 8th, or 8th and 9th ribs (**Figure 9**). The zone of apposition is assessed for measurement of the diaphragm thickness and echogenicity.

8.1.2. Measurements

Diaphragm thickness is measured at the zone of apposition during inspiration or expiration using the intercostal approach. The average thickness of the diaphragm is 0.22–0.28 cm in healthy volunteers [30]. Diaphragm thickness less than 0.2 cm, measured at the end of expiration, have been proposed as the cut-off to define diaphragm atrophy [31].

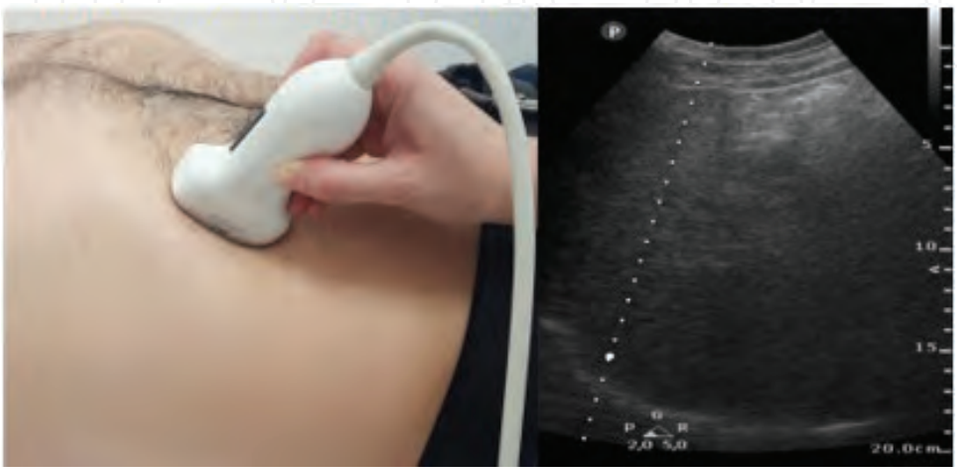

Figure 7. Diaphragm assessment in anterior subcostal view.

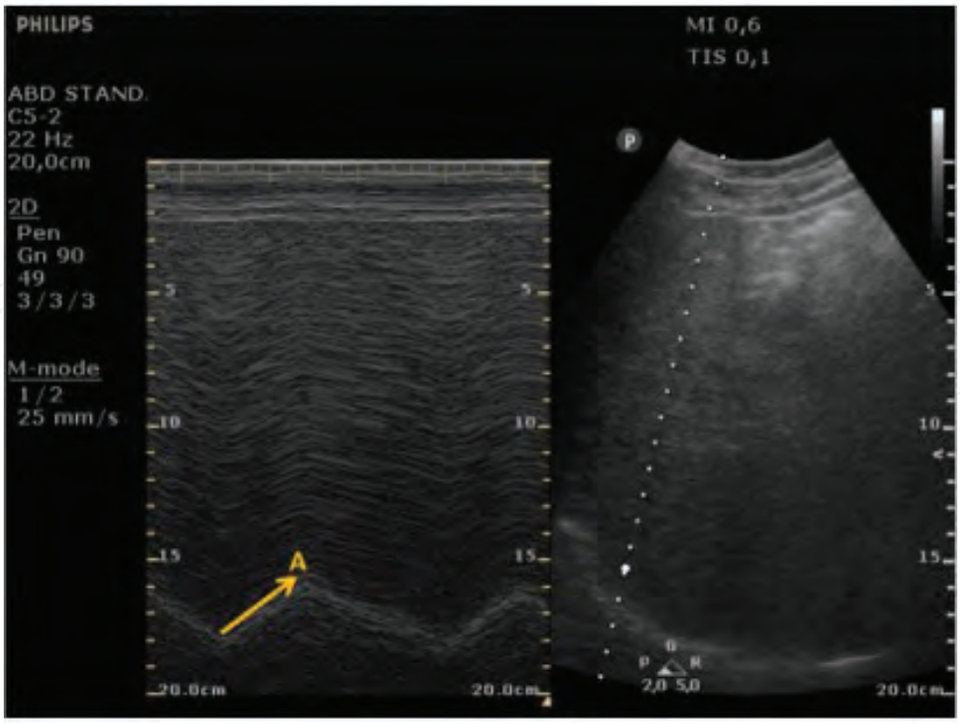

Figure 8. Assessment of diaphragm movement in M mode and 2D mode (A-wave amplitude).

Muscle fibers shorten with contraction and cause muscle thickening. A chronically paralyzed diaphragm is thin, atrophic, and does not thicken during inspiration. The measurement of thickness alone may miss an acutely paralyzed diaphragm with normal thickness or could incorrectly identify atrophy in a low weight individual with a healthy, yet thin, diaphragm. Therefore, the degree of diaphragm thickening has been proposed to be more sensitive than measurement of thickness alone [32]. Thickening fraction (TF) was calculated as: [thickness at end-inspiration (TEI)–thickness at end-expiration (TEE)]/TEE and expressed as a percentage (TEI thickness at end-inspiration; TEE thickness at end-expiration). Diaphragm thickening of less than 20% is proposed to be consistent with paralysis [32].

Diaphragm movement is recorded using the M mode assessment of the dome in the anterior subcostal view. The diaphragm is seen as a single thick echogenic line, and its movements with respiration can be plotted against a time curve. Measurement of the amplitude of excursion can be used to compare movement of the two hemi-diaphragms and for follow-up of diaphragmatic function (**Figure 8**). The normal range of motion from the resting expiratory position to full inspiration in adults has been reported to range from 1.9 cm in normal breathing to 9 cm in deep breathing [33]. Excursion greater than 2.5 cm in adults has been proposed as a cut-off for excluding severe diaphragm dysfunction [34]. Diaphragm weakness is indicated by less than normal amplitude of excursion on deep breathing with or without paradoxical motion on sniffing. Some variations are mentioned related to sex, age, weight or height.

Figure 9. Diaphragm assessment in intercostal view, using a high frequency linear probe.

8.1.3. Clinical application

Mechanical ventilation is associated with decreased muscle weight and alterations in contractile properties of the diaphragm within 48 h of intubation [35]. Diaphragm dysfunction may contribute to weaning failure, even in patients with no obvious reason to suspect phrenic nerve or diaphragm pathology. Decreased diaphragm excursion on M-mode ultrasound has been shown to predict weaning failure, with a 1.4 cm cut-off for the right hemidiaphragm and 1.2 cm for the left hemidiaphragm [36].

In critically ill patients under non-invasive ventilation, the diaphragm thickness and the thickening fraction (TF) are decreased as the level of pressure support increased (5, 10, 15 cm H_2O). The measurements done in the zone of apposition during tidal ventilation showed that, during NIV, thickening of the diaphragm is due to muscle effort and not due to increase in pulmonary volume induced by ventilation [37].

TF could be used in the ICU setting to assess diaphragmatic function and could contribute to respiratory workload in various situations, including ventilator-induced diaphragmatic dysfunction and ICU-acquired paresis [32].

9. Conclusions

Non-invasive ventilation in neuromuscular diseases should be introduced earlier in the evolution of respiratory failure, for obtaining maximum benefit for the quality of life, control of

symptoms, increased ability to perform daily activities, reduce hospitalizations and prolonged survival. Choosing the ventilator, the most appropriate interface, the ventilation mode, and periodic monitoring of the NIV is essential in obtaining success.

Abbreviations

ALS	Amyotrophic lateral sclerosis
BiPAP	bi-level positive airway pressure ventilator
DMD	Duchenne muscular dystrophy
FVC	forced vital capacity
iVAPS	intelligent volume-assured pressure support
NMD	neuromuscular disease
NIV	non-invasive ventilation
pCO_2	arterial pressure of CO_2
PS	pressure support
REM	rapid eyes movement sleep
S/T	spontaneous/timed
SNIP	sniff nasal pressure
US	ultrasound
TF	thickening fraction
MIP	maximum inspiratory pressure
MEP	maximum expiratory pressure

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Chapter 4

Noninvasive Monitoring of Manual Ventilation during Out-of-Hospital Cardiopulmonary Resuscitation

Andoni Elola, Erik Alonso, Elisabete Aramendi and Unai Irusta

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.77172

Abstract

Cardiopulmonary resuscitation (CPR) consisting of chest compressions and assisted ventilation is crucial to treat out-of-hospital cardiac arrest (OHCA). It is well reported that quality of manual ventilations, in terms of rate and volume, is suboptimal, with a high incidence of hyperventilation, which is linked to poor outcomes. The lack of a noninvasive technology to monitor ventilations during out-of-hospital CPR precludes feedback on ventilations to the rescuer, and it handicaps the evaluation of the effect of ventilations on the outcome of the patient. This chapter addresses the possibilities and challenges of monitoring the quality of manual ventilations in current defibrillators. Methods are proposed to monitor ventilations based on the thoracic impedance and the capnogram. These methods can be integrated in defibrillators used in both basic and advanced life support. The algorithms are described, and the accuracy of the methods to monitor the ventilation rate and the quality metrics of the ventilations is reported using real OHCA episodes. The accuracy and limitations of the methods as well as the implications of integrating them in the treatment of patients in cardiac arrest are discussed.

Keywords: manual ventilation, cardiopulmonary resuscitation, out-of-hospital cardiac arrest, thoracic impedance, capnogram

1. Introduction

Sudden cardiac arrest is the sudden cessation of effective blood circulation due to heart failure. If not treated promptly, cardiac arrest can lead to sudden cardiac death within minutes [1]. Sudden cardiac death is one of the leading causes of death in the industrialized world [2, 3].

Although the overall incidence depends on the definition and inclusion criteria applied by each study, it is documented that it ranges from 150,000 to 530,000 person-year in the United States, and about 275,000 in Europe [1, 2, 4].

Most cardiac arrest occur in the out-of-hospital setting [5]. There are two levels of treatment for out-of-hospital cardiac arrest (OHCA), basic life support delivered by emergency medical technicians and advanced life support (ALS) with the intervention of clinicians. Despite important progress in epidemiology, profiling and treatment of OHCA in the last decades, the survival rates to hospital discharge are dismally low, with rates between 8.4 and 10.7% [2, 6].

In OHCA, the first minutes are crucial as the chances of the patient to survive decrease about 10% per minute [7]. The chain of survival defines the key steps to treat a person in cardiac arrest. Two of the most important links of the chain are early defibrillation and early cardiopulmonary resuscitation (CPR). Defibrillation is delivered either by an automated external defibrillator (AED) or by more advanced monitor defibrillators used by ALS clinicians. The objective of CPR is to maintain a minimum oxygenated blood flow to the heart and brain until advanced care is available.

Quality of CPR is a key factor for the survival of OHCA patients. The 2015 resuscitation guidelines recommend that chest compression are provided with a rate of at least 100 compressions per minute and a depth of 5 cm [8]. During CPR, two ventilations may be given between series of chest compressions before intubation. Lay rescuers should open the airway using a head-tilt-chin-lift maneuver and blow steadily into the mouth while watching for the chest to rise, as shown in **Figure 1** [9]. The time taken to give a ventilation should be around 1 s, with no more than 5 s for two ventilations. After intubation, the resuscitation guidelines recommend CPR including continuous bag-mask ventilation with and without supplementary oxygen, as shown in **Figure 2**. The recommended ventilation rate is about 1 breath every 5–6 s, or about 10–12 breaths per minute [11]. However excessive ventilation, either by rate or tidal volume is

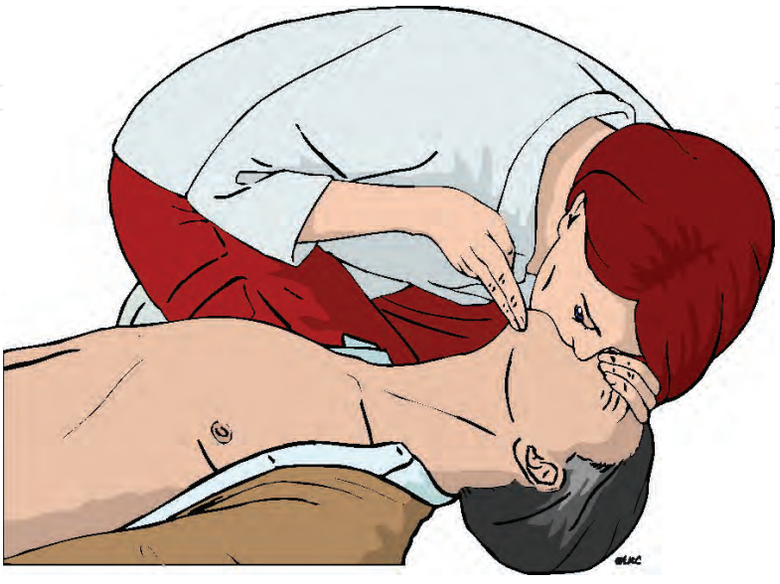

Figure 1. Head-tilt-chin-lift maneuver to provide ventilations. Extracted from [9].

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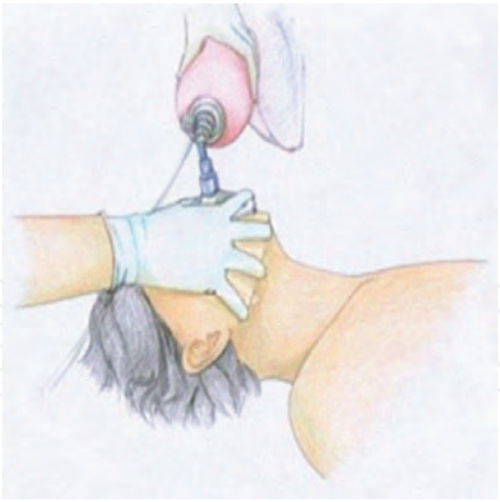

Figure 2. Bag-mask ventilation. Extracted from [10].

common during resuscitation [12–16]. Several analyses on OHCA episodes report rates ranging from moderate (14 min^{-1}) to severe (>20 min^{-1}) hyperventilation.

The negative effect of hyperventilation during CPR is well known: it increases intrathoracic pressures, reshapes the oxygen dissociation curve (increasing oxygen affinity) and behaves as a cerebral vasoconstrictor [17, 18]. Many studies have also proven that it contributes to a lower coronary perfusion pressure and to hemodynamic deterioration in animals [19, 20]. All these factors decrease the probability of survival of a patient in cardiac arrest, so the monitoring and evaluation of ventilation during CPR.

The real-time monitoring of the instantaneous ventilation rate during OHCA would enable feedback to the rescuers, so they could adhere to current guidelines. Furthermore, retrospective evaluation of the ventilation rates may help in debriefing to improve the quality of CPR provided by emergency medical services. Unfortunately, no commercial systems are available for BLS or ALS defibrillation equipment that give real-time feedback to the providers, and no automatic methods are available for debriefing on the quality of ventilation. Several quality metrics have been proposed to monitor quality of ventilations in OHCA [21], such as the mean value of ventilations delivered per minute and the fraction of minutes with hyperventilation (FMH), that is ventilation rates above 15 min^{-1}.

The automated computation of those ventilation quality values requires ventilation detection algorithms based on signal processing of the biomedical signals recorded by commercial equipment. Nowadays, equipment to monitor gas exchange during ventilations is not routinely used in OHCA, in contrast to the ubiquitous mechanical ventilators used in-hospital. In the BLS scenario, the biomedical signals recorded by AEDs through the defibrillation pads (see **Figure 3**) are most frequently the electrocardiogram (ECG) and the thoracic impedance (TI). Ventilations are visible in the TI as fluctuations in the waveform with every insufflation of oxygen into the chest of the patient. For more advanced monitor-defibrillators, as the ones used by medical experts in ALS, additional modules like the capnogram are available. Capnography monitors the partial pressure of the CO_2 in the respiratory gasses, and reflects high concentration during the exhalation phase of every ventilation.

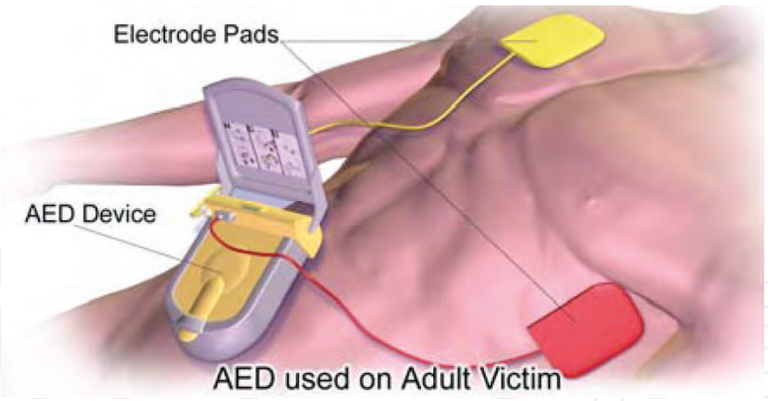

Figure 3. Automated external defibrillator with electrode pads attached to a patient.

In this chapter, the feasibility of monitoring the ventilation rate is analyzed using first the TI and then the capnogram. Automatic methods to detect ventilations are described, and their accuracy reported with OHCA datasets. The performance of the algorithms is reported in terms of sensitivity (SE), the percentage of correctly detected ventilations, and positive predictive value (PPV), the percentage of detected ventilations that are true ventilations. The validity of those methods to monitor the instantaneous ventilation rate and to evaluate the quality of ventilation is also analyzed. Finally, this chapter concludes with a discussion of several key points to be considered before these methods could be integrated into commercial equipment.

2. Thoracic impedance for ventilation monitoring

The TI is measured though the defibrillation pads of a defibrillator attached to the chest of the patient in the anterolateral position, as shown in **Figure 3**. A high frequency excitation current (20–100 kHz at 1–5 mA) is applied through the pads and the resulting surface potential measured to compute the impedance by applying Ohm's law. The TI may show different components:

- *Baseline component*: a baseline impedance value of 50–120 Ω depending on the position of the pads and on the patient's sex, chest size and body mass [22].
- *Chest compression component*: chest compressions cause variations in the cross-sectional area of the chest [23] and mechanical disturbances in the defibrillation pads that are reflected in the TI as fluctuations of amplitudes between 0.15 Ω and several ohms [24, 25].
- *Ventilation component*: ventilations produce variations in the cross-sectional area of the thorax [23]. Inflation of the lungs causes an increase in impedance because air is a poor conductor of electric current [25]. The TI shows a fluctuation from 0.1 Ω to 8 Ω with each ventilation [26, 27].
- *Circulation component*: the impedance shows a small fluctuation (<100 mΩ) with each effective heartbeat [26, 28, 29].
- *Additional noise and artifacts*: other noise and artifacts due to movement, electrode-skin contact, and so on can be present in the impedance [30].

All these components can be observed in **Figure 4**. From top to bottom, the ECG, TI, the compression depth (CD) of the chest compressions and the capnography are depicted. The TI shows a baseline around 105 Ω and fluctuations due to chest compressions (around 1 Ω), ventilations (0.5–1 Ω), and circulation (0.1 Ω). There is a perfect match between (1) compressions in the CD signal and fluctuations due to compressions in the TI signal, (2) the capnogram and fluctuations due to ventilations in the TI, and (3) effective heartbeats in the ECG and the circulation component in the TI. Two ventilations are visible in the TI, the fluctuations around 14 and 18 s, which correlate with increases of the CO_2 expired in the capnogram.

The TI has become a very useful signal in an OHCA in the last two decades and it is recorded by every commercial defibrillator, either AED or monitor/defibrillator. In 2002, Pellis et al. first suggested that ventilations (respirations) cause measurable fluctuations in the TI signal [27]. In an experiment with anesthetized male pigs, they found out that TI measurement at frequencies between 0.1 and 2 Hz showed fluctuations that were time coincident with the ventilations in the capnography signal.

Later in 2006, Losert et al. analyzed the feasibility of monitoring the ventilation characteristics during CPR using the TI signal acquired by the defibrillation pads of an AED [26]. They analyzed the correlation between the amplitude of the TI fluctuation due to ventilation and the tidal volume (400–1000 mL) given by a ventilator. They concluded that the TI

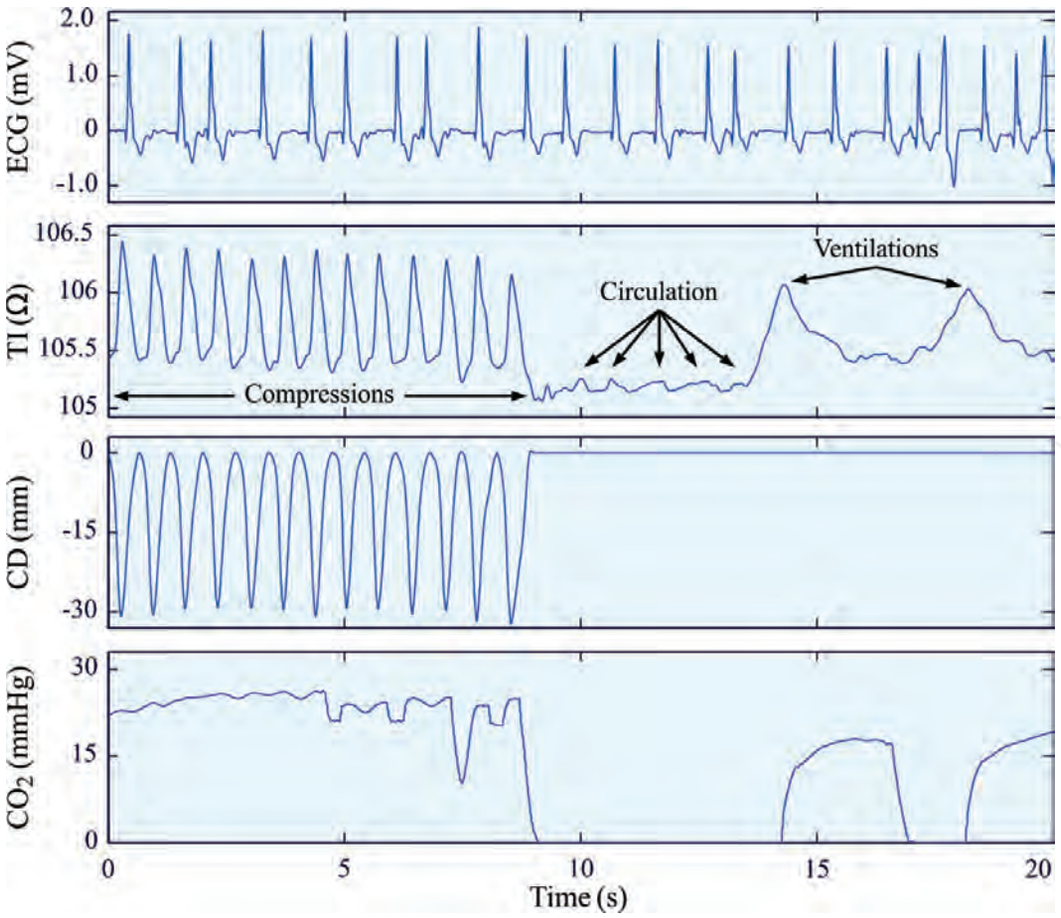

Figure 4. From top to bottom, the ECG, TI, CD and capnography signals are represented. Two ventilations are visible in the TI around 14 and 18 s.

allows to compute ventilation rates, inspiration and expiration times, but the amplitude of the TI fluctuation was not valid for exact tidal volume estimation. More recently, Roberts et al. also investigated the relationship between tidal volume and TI amplitude fluctuations but in mechanically ventilated children and using the TI acquired for two different placements of the defibrillation pads, anterior-apical and anterior-posterior positions [31]. The ventilations in the TI were detected as fluctuations above 0.4 Ω. The study concluded that although the linearity between tidal volume and TI fluctuation was high for each individual, it was not feasible to derive the exact tidal volume from the TI fluctuation for the pediatric population as a whole. The study also showed that the TI acquired via defibrillation pads could be used to accurately detect ventilations if delivered according to the guidelines (7–10 ml/kg tidal volume), with no significant differences between pad positions for ventilation detection. Nevertheless, for smaller volumes (<7 ml/kg), the sensitivity for ventilation detection decreased, suggesting that shallow ventilations during CPR might not be detected in the TI.

These evidences motivated Risdal et al. to propose a ventilation detector during CPR based on the TI signal [32]. After a preprocessing stage, the fluctuations in the TI due to chest compressions were suppressed using an adaptive filtering scheme [33]. The ventilation detector was based on a neural network classifier. The classifier decided whether each TI segment (1.4 s) analyzed was an expiration onset (maximum peak of the fluctuation in the TI) in the basis of waveform features extracted from the analyzed segment. This was a novel and complex approach to detect ventilations with excellent performance (SE/PPV of 90.4%/95.5%). However, ventilations were manually annotated in the TI signal and used as gold standard to evaluate the performance of the ventilation detector. Therefore, still there was the need for a more reliable validation using a robust independent gold standard. Furthermore, the complexity and computational burden of the method limited its application.

More recently, Edelson et al. developed two different ventilation detection algorithms, one based on the TI and other based on the capnography signal [34]. They hypothesized that capnography would be superior to TI for measuring ventilation rate, and that a combined algorithm would be more accurate than one based on a single signal. They obtained slightly better results in terms of SE/PPV for the capnography-based detector: 78%/87% for the TI-based detector, and 82%/91% for the capnography-based detector. As hypothesized the combination of both algorithms showed better performance. The lack of a gold standard (spirometry, flow or volume of the ventilations) independent of the signals used to develop the detectors might have affected the results.

2.1. An automated ventilation detector based on the TI

In this section, we present a study carried out to overcome the main limitations of the works described earlier and to cast some light on the reliability and accuracy of the TI to compute ventilation metrics. The study is aimed at (1) developing a simple ventilation detector based on the TI that might be incorporated into current commercial defibrillators; and (2) computing the CPR quality metrics related to ventilations in order to evaluate their accuracy against a robust gold standard.

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The dataset used to carry out the study consisted of OHCA episodes recorded through the Philips MRx monitor/defibrillator between 2006 and 2009 by the Tualatin Valley Fire and Rescue in Portland, OR, USA. Each episode contained concurrent TI and capnography signals for at least 30 min. The capnogram was considered the gold standard for the instants of ventilations which were manually and independently annotated by three experienced biomedical engineers. Intervals where the ventilation pattern was not clearly recognizable were excluded from the analysis. A total of 2575 min were analyzed, which included 17,586 ventilations. Episodes were randomly allocated to training and test sets, 32 and 31 episodes respectively. **Figure 5** shows an epoch of an episode included in the dataset of the study where capnography and TI signals are depicted, and the instants of ventilations are marked as black dotted lines on the capnogram.

The ventilation detector was developed using the training set and consisted of three different stages. First, a preprocessing stage where the TI was low-pass filtered at a cutoff frequency of 0.6 Hz to suppress fluctuations due to chest compressions as well as high frequency noise. In a second stage, the preprocessed TI signal, pTI, was analyzed to detect the local maxima and minima. Each local maximum and minimum were characterized by its time of occurrence, $t_{\max_i}$ or $t_{\min_i}$, and amplitude, $Z_{\max_i}$ or $Z_{\min_i}$, respectively as shown in **Figure 6**.

Each detected local maximum was a potential ventilation. To decide whether a maximum corresponded to a ventilation, the inflation amplitude ($A = Z_{\max_i} - Z_{\min_i}$) and inflation time ($d = t_{\max_i} - t_{\min_i}$) were first computed. Then, in the third stage, a decision algorithm decided if a local maximum was a ventilation based on A and d. Three were the requirements for a potential ventilation to be classified as ventilation. The value of d should exceed a minimum static threshold ($d_{\min} = 0.5$ s); the inflation amplitude, A, should be above a dynamic threshold (Th_v) that represents the weighted average of the minimum amplitude of the last 17 ventilations, and finally, the time interval between the actual fluctuation and last detected ventilation should exceed a refractory period ($T_{ref} = 1.4$ s).

This ventilation detector was used to detect the instants of ventilations, and these instants were used to compute the instantaneous ventilation rate, which is reported every 15 s as the ventilation rate provided in the last minute. The global quality metrics of every episode

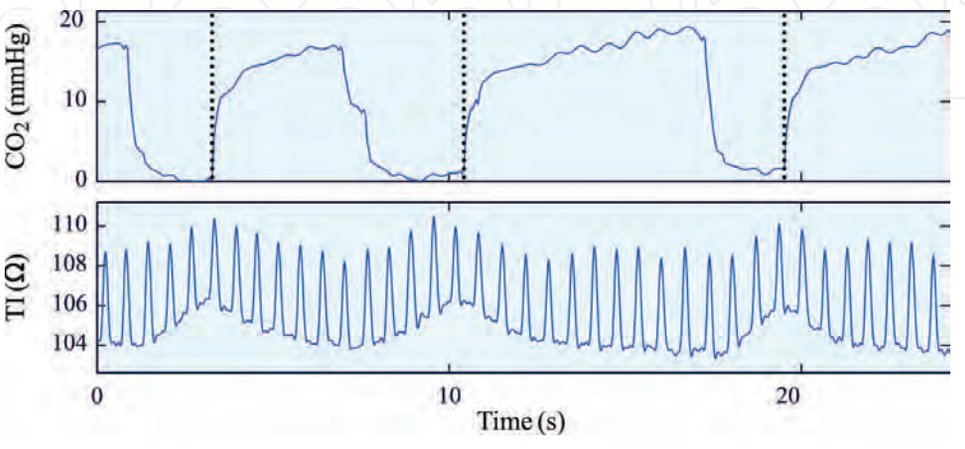

Figure 5. A segment of an episode of the dataset. From top to bottom, the capnogram and the TI. The black dotted lines represent the ventilations annotated in the capnogram.

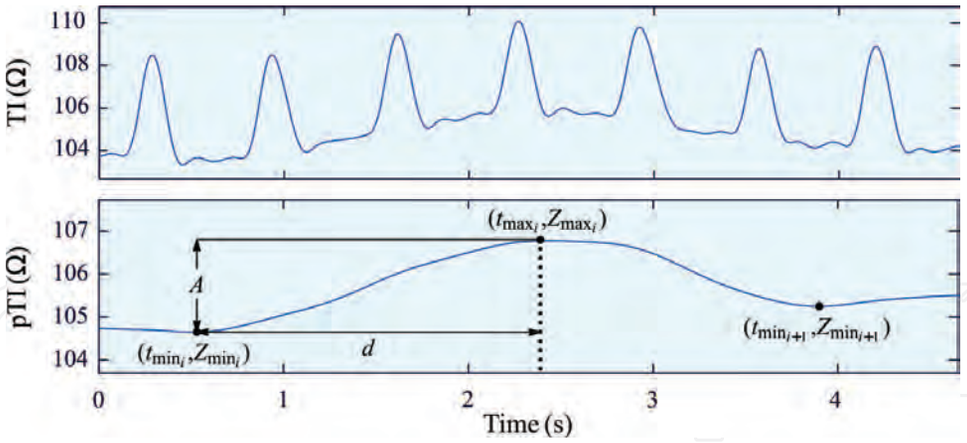

Figure 6. A short segment showing how preprocessing reveals the fluctuation caused by a ventilation. The inflation amplitude, *A*, and inflation time, *d*, are depicted as well as the local maximum and minima.

were also computed, namely the mean ventilation rate and the FMH, the latter to evaluate hyperventilation.

2.2. Evaluation of the ventilation detector

The feasibility and accuracy of the TI signal as a surrogate of the capnogram to measure ventilation metrics was evaluated using the test set. Distributions for each metric obtained from the TI and from the capnogram were analyzed independently applying the one sample Kolmogorov-Smirnov normality test. For normal distributions, the two-sample t-test was performed to test for equal means, and for not normal distributions, the Mann-Whitney U test was used to test for equal medians. The limits of agreement (LOA) between the values obtained from the TI and from the capnogram were analyzed using Bland-Altman plots for each metric.

The ventilation detector showed a median (interquartile range) SE of 92.2% (87.4–95.8), and a median PPV of 81.0% (67.2–90.5). These scores are similar to those reported by other authors as Risdal et al. [35] and Edelson et al. [34]. Nevertheless the proposed method was tested with an independent gold standard, annotated in the capnogram, and it requires a much simpler processing which would permit an easier integration in an AED.

Table 1 is a summary of the ventilation quality metrics computed from the TI and compared to those obtained from the capnogram. Data are presented as mean (standard deviation). The distributions of the FMH obtained from the TI and capnogram were not normal, although they did have equal medians ($p = 0.66$). Mean and instantaneous ventilation rates came from normal distributions. The mean ventilation rate and the FMH obtained from TI and capnogram showed equal means, with mean errors of 1.54 min^{-1} and 1%. That was not the case for the instantaneous ventilation rate, with different mean ($p < 0.001$) and a mean error of 3.30 min^{-1}.

Figure 7 shows the Bland-Altman plots for each ventilation quality metric, and the corresponding 95% LOA depicted with horizontal lines. For the quality metrics, both the mean

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Metric	Gold standard	TI	Error	*p*
Mean ventilation rate (min^{-1})	9.54 (2.94)	10.87 (2.68)	1.54 (1.44)	0.07
FMH (%)	11.39 (18.35)	10.09(16.88)	1.29 (2.59)	0.66*
Instantaneous ventilation rate (min^{-1})	10.23 (4.29)	13.09 (4.52)	3.30 (2.88)	<0.001

*The *p*-values obtained from the t-test and Mann–Whitney U test are expressed for each metric.

Table 1. Mean (SD) values computed from the gold standard and from the TI for each ventilation quality metric and the error.

ventilation rate and the FMH showed minor errors, with small LOAs. These results support the use of the TI to accurately evaluate the ventilation metrics when debriefing resuscitation episodes.

The Bland Altman plot for the instantaneous ventilation rate showed large LOAs, in the range of −8 to 5 ventilations per minute. These results question the accuracy of the method based on the TI to monitor the ventilation rate every 15 s.

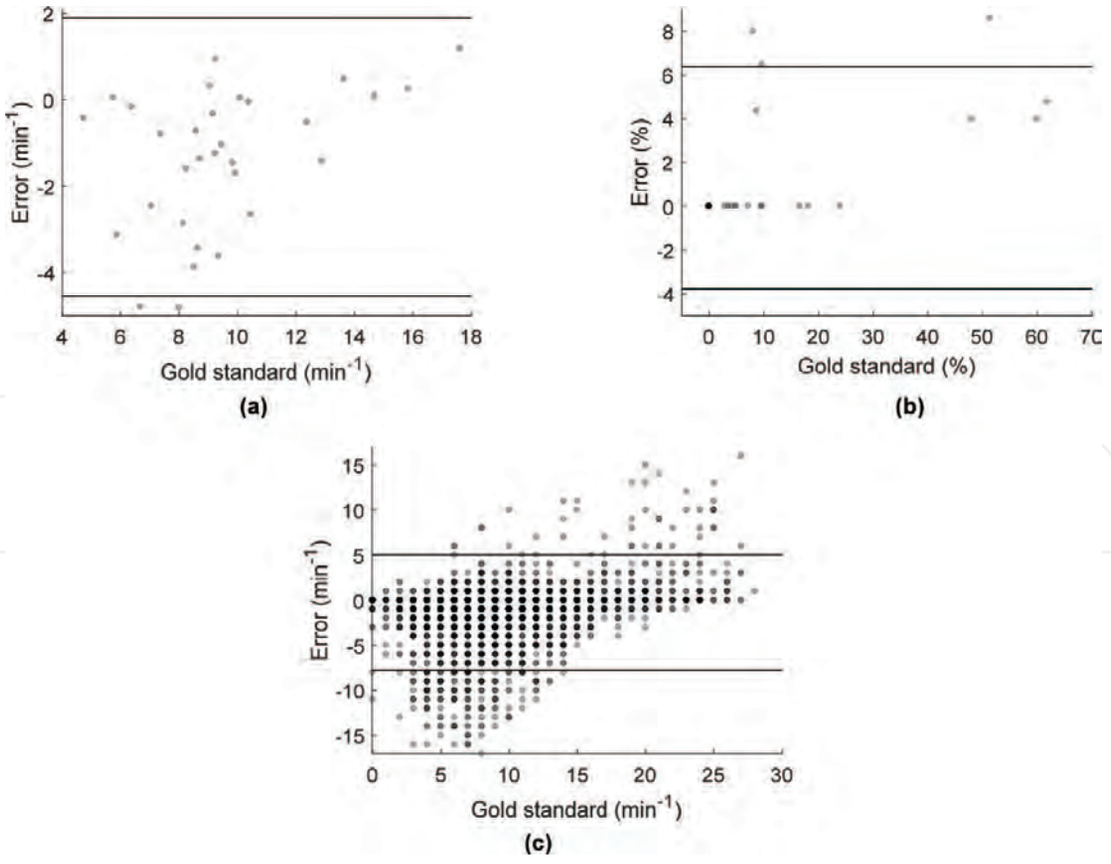

Figure 7. Bland-Altman plots for mean ventilation rate, FMH, and instantaneous ventilation rate are represented in a, b, and c panels respectively. The 95% LOA is depicted in black dashed lines.

3. The use of capnography to monitor ventilation rate

Capnography is a noninvasive monitoring technique that shows the partial pressure of the exhaled CO_2 of the patient over the time [36]. The initial use of the capnography signal (or capnogram) was for anesthesia monitoring, but its use has expanded to other fields such as emergency medicine as it provides information about CO_2 production levels, lung perfusion and alveolar ventilation among others [37]. Current resuscitation guidelines recommend the use of capnography to confirm endotracheal intubation, detect return of spontaneous circulation, monitor the effectiveness of chest compressions and monitor ventilation rate [8].

Advanced monitor/defibrillators used by medical personnel include modules that show the capnogram of the patient during CPR. In current commercial equipment, two main acquisition techniques are used: mainstream and sidestream capnography [38]. The mainstream technology has an infrared light sensor which is placed directly in the main way of expired flow to measure the absorption of CO_2. In sidestream, the expired gases are continuously aspirated from a 1–2 m long sampling tube, and the sensor is placed at the end. **Figure 8** shows the general structure of both acquisition technologies.

The capnogram shows the evolution of the CO_2 expired during the ventilations provided to the patient in cardiac arrest, where the cycle of every ventilation is visible. Four phases are visible in the cycle of each ventilation [39], as illustrated in **Figure 9**: the inspiration baseline (phase I), the expiration upstroke (phase II), the expiratory plateau (phase III) and the expiration down stroke (phase IV). The maximum value observed in the third phase is the so-called $EtCO_2$ (End-tidal CO_2). In hemodynamically stable patients, the value is about 35–45 mmHg, similar to the partial pressure of the CO_2 in the blood [37, 41]. During cardiac arrest, the elimination of CO_2 is reduced and it is accumulated in the tissues. This is because an abrupt

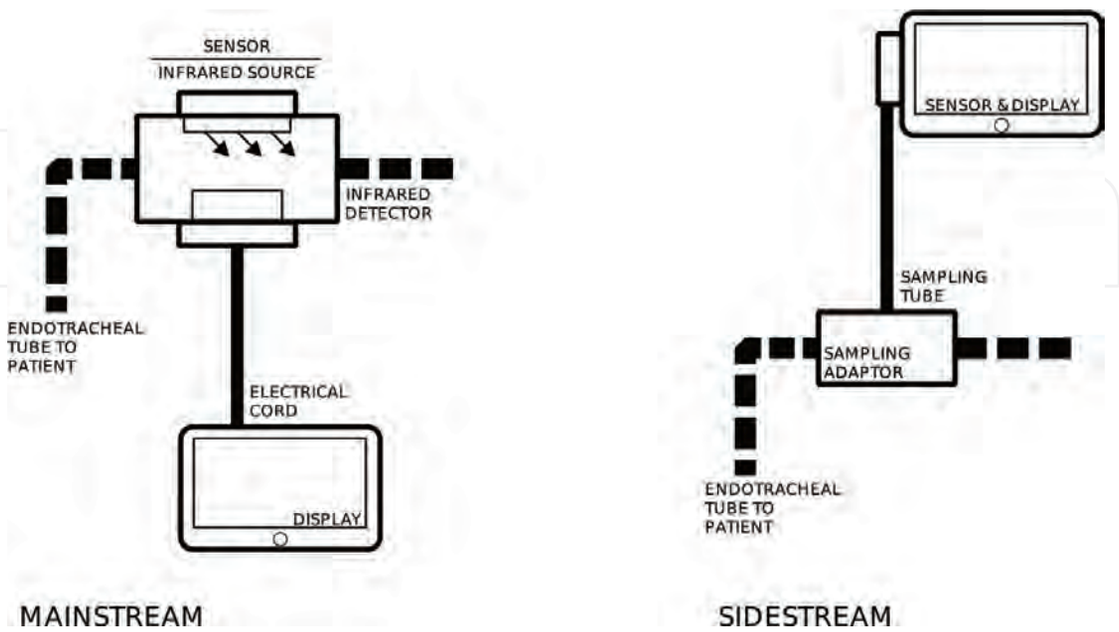

Figure 8. General schemes of mainstream and sidestream technologies to acquire the capnogram.

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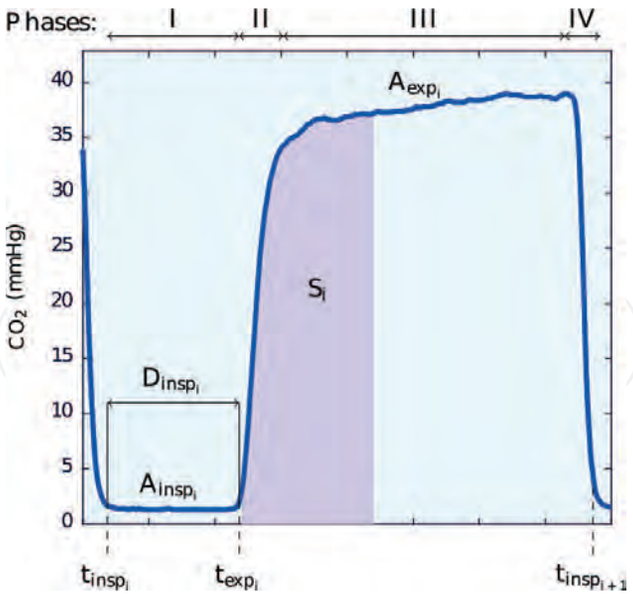

Figure 9. Basic waveform of the capnography signal during a cycle of ventilation. Four phases of the cycle and the features for automatic ventilation detection are shown. Adapted from [40].

decrease in cardiac output implies a reduced CO_2 transportation from the tissues to the lungs, and therefore $EtCO_2$ values decrease almost to zero. Effective chest compressions or recovering pulse make this value increase [42, 43].

During CPR, chest compressions may induce artifacts that corrupt the capnogram. Idris et al. [44] analyzed 210 patients and they detected artifacts in the capnography signal in 154 of 210 episodes, an incidence of 73.3%. More recently, Leturiondo et al. [45] reported an incidence of 42% (99 of 232 episodes showed artifacts). The source and level of the corruption is not well defined yet, and depends on both the patient and the way CPR is performed. Bottom panels of the cases represented in **Figure 10** show examples of the capnogram for four patients, uncorrupted in panels a and c, and corrupted by chest compression artifact in panels b and d. The interference caused by chest compressions complicate the design of automatic ventilation detection algorithms based on the capnogram that would permit the monitoring of ventilation rate and the retrospective debriefing of resuscitation episodes.

The first algorithm to automatically detect ventilations during CPR in the capnogram was proposed by Edelson et al. [34]. They used both the capnogram and the impedance signal to detect the ventilation instants, combining two finite-state-machines. The capnogram-based algorithm provided SE/PPV of 82%/91%. A similar algorithm was proposed by Leturiondo et al. [45] based exclusively on the capnogram with SE/PPV above 95% for uncorrupted intervals, and the accuracy decreased during chest compressions. Both proposals [34, 45] developed the algorithm using as ground truth the ventilations annotated manually in the impedance signal. As it can be observed in **Figure 10** the impedance signal is highly affected by the CPR artifact, and the amplitude of the fluctuations caused by ventilations is not constant, it has been reported to be nonlinear with the tidal volume for all the population [31]. Both factors question the reliability of the ground truth used to evaluate the algorithms.

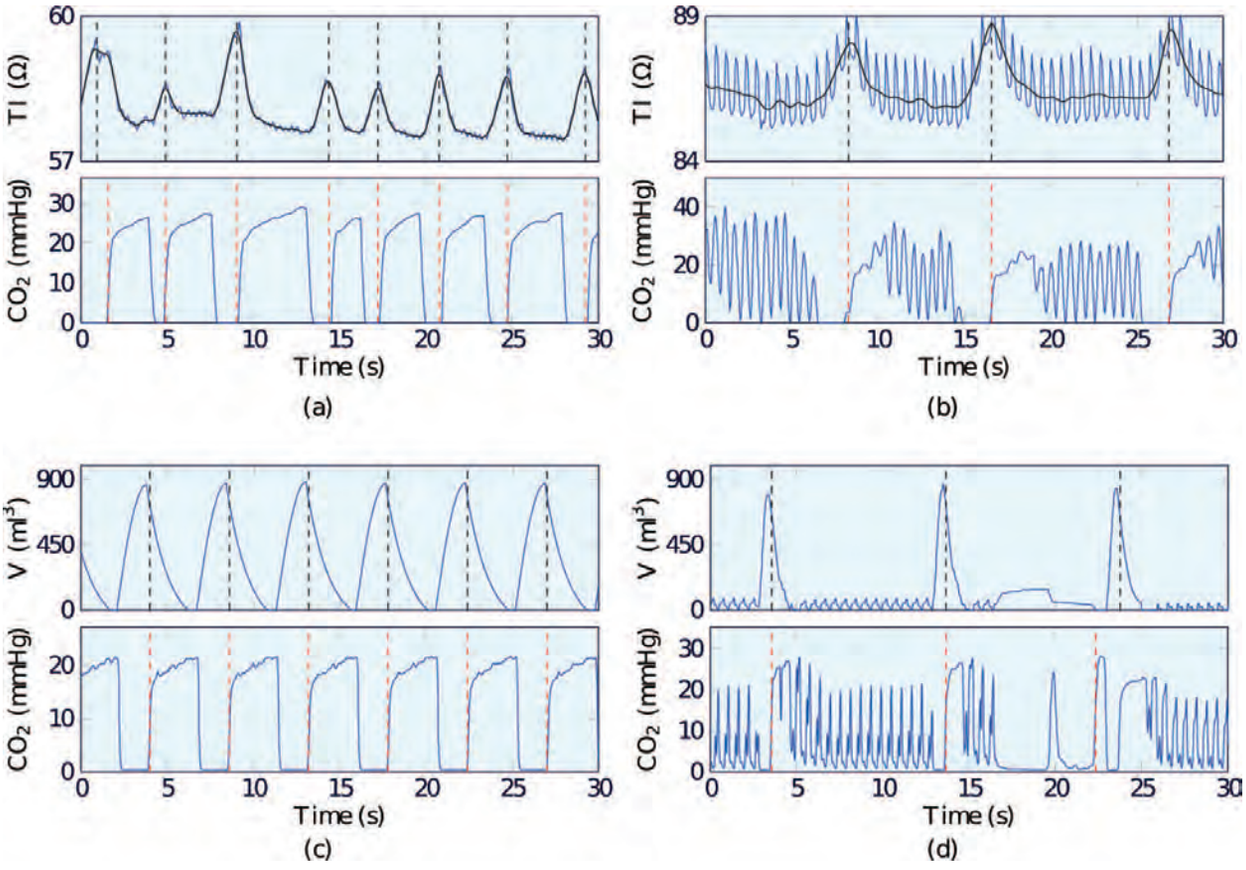

Figure 10. Examples of the capnogram (bottom) and the signal used to annotate the gold standard ventilations (top) are shown for the OHD (panels a and b) and for the IHD (panels c and d). For the OHD, the raw impedance signal (blue) and the filtered impedance signal (black) are shown, and for the IHD the volume signal. In both cases, black vertical lines show the annotated ventilations in the gold standard, and red vertical lines the detected ventilations in the capnogram.

3.1. An automated ventilation detector based on the capnogram

This section describes an algorithm developed using the gas exchange flow measured by a ventilator to annotate the ground truth for the ventilations instants [40]. To the best of our knowledge, this is the only ventilation detector tested with the most reliable ground truth.

Two datasets were used to develop and test the algorithm: an In-Hospital Dataset (IHD) and Out-of-Hospital Dataset (OHD). A total of 83 episodes (62 in-hospital and 21 out-of-hospital) were considered with a duration of 4880 min. The episodes included 16,899 and 29,841 ventilations, with a percentage of 38 and 8% of the time with compressions for the OHD and the IHD, respectively. The general characteristics of both datasets are summarized in **Table 2**. Each episode of the IHD contained the capnogram, and the airflow and air volume signals provided by the ventilator; the instants of the ventilations were annotated based on the volume of the flow signal, as shown in **Figure 10**. Chest compression intervals were identified by medical annotations and abrupt increases in arterial blood pressure. The cases in the OHD included the capnogram, the TI and the CD signals. The CD was used to identify chest compression intervals, while TI and CD were the ground truth to mark ventilations manually. **Figure 10** shows epochs of episodes included in both datasets. For each panel, the top figure shows the independent gold standard (volume signal for IHD and the thoracic impedance signal for OHD), and in the bottom the capnography. The ventilations

Parameter	OHD	IHD
Number of episodes	62	21
Total duration (min)	2545	2335
Total number of ventilations (% with CPR)	16,899 (38)	29,841 (8)
Instantaneous ventilation rate (min^{-1})	9.9 (8.7–13.1)	14.3 (12.6–18.2)
Minutes with hyperventilation per episode (%)	10 (2–35)	14 (0–88)

The instantaneous ventilation rate and minutes with hyperventilation are given per episode as median (interquartile range).

Table 2. Characteristics of both out-of-hospital (OHD) and in-hospital (IHD) datasets.

marked in the gold standard are depicted with black dashed lines. Both gold standards show fluctuations concurrently with the capnography signal for each ventilation. A total of 37 episodes randomly selected from the OHD dataset were used to design and train the algorithm; the test set was conformed with the remaining 25 cases of the OHD and the 21 IHD cases.

The method relies on the computation of the values corresponding to the features shown in **Figure 9**. First, the signal is preprocessed with a low-pass filter with a cutoff frequency of 10 Hz; then values of the waveform below 5 mmHg are set to zero. Potential ventilations are detected between the start of inspiration, t_{insp} (insufflation during ventilation), and the start of expiration, t_{exp} (deflation during ventilation). Both instants are computed based on the positive and negative peaks in the first difference of the signal. Then the following six features, depicted in **Figure 9** are computed:

- Duration of inspiration baseline, D_{insp}.
- Mean value of the signal during plateau, A_{exp}.
- Area of the first second of the expiratory plateau, S_{exp}.
- Relative increase of the signal, computed as:

$$A_r = \frac{A_{\exp} - A_{insp}}{A_{\exp}}, \tag{1}$$

where A_{insp} is the mean amplitude of the signal during inspiration baseline.

- Interval between actual potential ventilation and the last detected ventilation, t_{ref}.

The algorithm discriminates real ventilations based on fixed thresholds for D_{insp} and t_{ref}, and adaptive thresholds for A_{exp}, S_{exp} and A_r. The adaptation for the kth ventilation was computed based on the last p ventilations according to the following equation:

$$Th_k = \frac{w}{p} \sum_{n=k-p}^{k} x_n, \tag{2}$$

where w is a weighting factor between 0 and 1 and x_n represents the value of the feature for ventilation n. A more detailed description of the algorithm can be found in [40]. **Figure 10** shows examples of the algorithm performance. The black dashed lines represent the manual ventilation annotations in the gold standard, and the red dashed lines correspond to the ventilations detected by the algorithm.

As for the TI-based detector, the detected ventilations were used to compute the instantaneous ventilation rate, and the global ventilation metrics per episode.

3.2. Evaluation of the ventilation detector

The algorithm showed overall SE and PPV values above 99% and 97%, respectively. For the OHD, the median (interquartile range) SE and PPV per patient were 99.1 (96.9–99.8)% and 97.0 (95.9–98.9)%. When only the intervals with chest compressions were considered the SE and PPV were 99.0 (95.7–100)% and 97.6(94.8–100)%. For the IHD, SE and PPV were 100 (99.8–100)% and 100 (99.8–100)%. During compressions the performance dropped slightly to 99.8 (98.7–100)% and 98.3 (92.9–100)%, respectively.

The concordance correlation coefficient on ventilation rate measured as proposed in [46] was higher than 0.98 for both datasets, even during chest compressions. **Figure 11** shows the

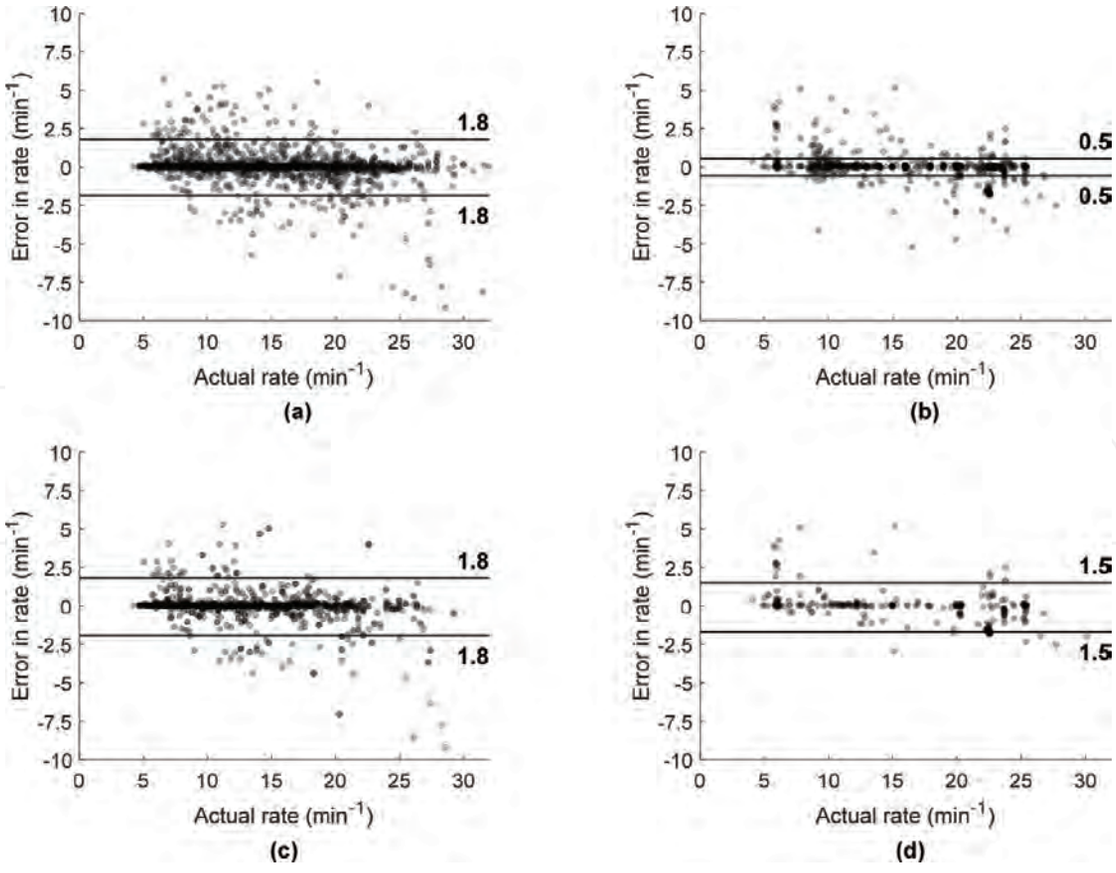

Figure 11. Bland-Altman plots for the instantaneous ventilation rate computed for the OHD (panels a and c) and for the IHD (panels b and d). The limits for the 95% level of agreement are depicted, in 1.82 and 1.8 min^{-1} (during chest compressions) for the OHD, and in 0.55 and 1.50 min^{-1} (during chest compressions) for the IHD.

	Gold standard	Algorithm	*p*
OHD			
Mean ventilation rate (min^{-1})	11.74 (10.34–15.47)	12.11 (10.56–15.37)	0.88
FMH (%)	2.56 (0–34.77)	2.50 (0–34.51)	0.94
Instantaneous ventilation rate (min^{-1})	9.07 (12.44–17.28)	9.23 (12.56–17.31)	0.79
IHD			
Mean ventilation rate (min^{-1})	14.02 (12.53–17.70)	14.02 (12.48–17.77)	1
FMH (%)	5.49 (0–81.08)	5.48 (0–80.39)	1
Instantaneous ventilation rate (min^{-1})	13.98 (12.98–18.98)	13.98 (12.98–18.98)	0.52

All *p* values were calculated using Mann-Whitney U test.

Table 3. Median (interquartile range) values computed from the gold standard and from the capnogram for each ventilation quality metric.

Bland-Altman plots and the 95% LOA between the gold standard and the algorithm, which was lower than 1.85 in any case. These results show that this capnogram-based method reliably estimates the instantaneous rate.

The detailed results for the ventilation quality metrics are shown in **Table 3**. It can be observed that the mean ventilation rate and the FMH showed equal distributions ($p > 0.05$) when compared to the ground truth for both the OHD and IHD episodes. The unsigned errors were close to zero for both metrics and for both datasets. These results support the use of this method to retrospectively debrief resuscitation episodes.

4. Discussion and conclusions

In this chapter, the monitoring of ventilations provided during out-of-hospital CPR was addressed with two objectives. First, giving feedback on the instantaneous ventilation rate to rescuers. Second, to allow retrospectively evaluation of ventilation rates and hyperventilation metrics during resuscitation episodes.

The analysis focused on the feasibility of the TI acquired by the defibrillation pads, and the capnogram to accurately report feedback on ventilation. Methods based exclusively on each of the signals were proposed and statistically evaluated. These methods could be integrated in commercial defibrillation equipment, the TI-based algorithm in any AED or monitor/defibrillators, and the capnogram-based algorithm in any equipment that includes capnography.

Several aspects deserved attention in the development of the algorithms. In the setting of the procedure, the gold standard was carefully selected. In the case of the TI, manual annotations were defined in the capnogram, as a result of the consensus of three experts. In the case of the capnogram, the independent signal used as gold standard was the gas volume exchanged measured by an external ventilator. In both cases, the gold standard was

annotated using an independent signal, including the gas exchange information, which is, in our opinion, the most reliable signal. This is a key factor when evaluating the accuracy and reliability of the methods.

In any case, the simplicity of the method was a priority. The algorithms proposed do not rely on complicated or computationally intensive signal processing techniques, so they could be integrated in current defibrillation equipment without much increase of computational requirements.

The scores obtained for the TI-based method are similar to those previously reported in terms of SE (around 90%), and slightly below for PPV. For the capnogram-based method, SE/PPV was both above 97% in any dataset, even when chest compressions were provided.

Both methods are valid to be integrated in the software provided to retrospectively review the quality of the ventilations. Errors below 2 min^{-1} in the mean rate and about 1% in the FMH for both the TI and the capnogram are sufficient for an accurate retrospective evaluation. The integration of these methods in the revision software provided by commercial equipment would permit debriefing on ventilation after cardiac arrest. The American Heart Association emphasizes the post-even analysis of the data, which contributes to the continuous quality improvement, closing the gap between the ideal and the actual performance of OHCA resuscitation. Excessive ventilation rates are often observed during CPR both out- and in-hospital cardiac arrest [14], and code team debriefing with audiovisual feedback has been associated with a decrease in mean ventilation rates from 18 to 13 min^{-1} [34, 47].

For the audiovisual feedback to the rescuer, the instantaneous rate should be provided to the rescuers, associated, if necessary with hyperventilation alarms. The instantaneous rate, as computed in the methods proposed, would permit feedback every 15 s, which is a reasonable compromise to follow the feedback and adhere to the recommendations of the guidelines. The method proposed on the capnogram was very reliable with errors below 2 min^{-1} for any dataset even during chest compressions. That was not the case for the TI, as the mean error for the instantaneous rate was above 3 min^{-1}. Two are the reasons that make difficult the automated detection of ventilations in the TI. First, the fluctuations caused by ventilations are very variable, even for the same patient, so adaptive thresholding is required for the algorithm. Panel a in **Figure 10** shows clear examples in which similar ventilation cycles in the capnogram appear with very different amplitudes in the impedance waveform. Therefore, it is very difficult to define a universally valid TI amplitude threshold for the detection of ventilations. Second, artifacts caused by chest compressions and other noise make difficult to automatically detect every ventilation.

Finally, it should be stated that the results and conclusions presented in this chapter are limited by the specific characteristics of the data used. Using the TI or the capnogram from other equipment, with different electronic circuitry and defibrillation pads, may require readapting the values and thresholds of the algorithms and may result in different values of the performance metrics.

Acknowledgements

This work has been partially supported by the Spanish Ministerio de Economía y Competividad, jointly with the Fondo Europeo de Desarrollo Regional (FEDER), project TEC2015-
64678-R, by the University of the Basque Country via project EHU16/18, the Ayudas a Grupos de Investigación GIU17/031 and the unit UFI11/16, and by the Basque Government through
the grant PRE_2017_1_0112.

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Chapter 5

Non-Invasive Ventilation of the Neonate

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.72395

Abstract

The use of mechanical ventilation in the past few decades has greatly contributed to the survival of critically ill neonates, both preterm and term. With this, however, has come an accompanied rise in certain complications and neonatal co-morbidities. Avoiding mechanical ventilation, or at least minimizing the time a neonate is intubated, is considered a critical goal in the care of these patients. Different modes of non-invasive ventilation have developed over the course of the time to help address these issues.

Keywords: non-invasive ventilation, neonate, preterm, prematurity, continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), nasal intermittent positive pressure ventilation (NIPPV), high flow nasal cannula (HFNC)

1. Introduction

Survival of premature infants has improved steadily since neonatal care became a national focus in the 1960's. A key component in this improvement is improved respiratory care, especially mechanical ventilation. Increased survival of vulnerable infants, however, is associated with complications and co-morbidities, some of which are directly caused by invasive ventilation. Therefore, minimizing exposure to mechanical ventilation is critical to the care of these babies. Gregory et al., in 1971, first described the use of continuous positive airway pressure (CPAP) to treat neonates afflicted with respiratory distress syndrome (RDS), which transformed respiratory care of neonates [1]. Subsequently, the use of CPAP and other forms of non-invasive ventilation have become the standard of care and have saved countless lives.

Non-invasive ventilation refers to any mode of respiratory support provided via the nasal airway of infants to support spontaneous breathing, without placement of an endotracheal tube. The most common non-invasive modes include nasal continuous positive airway

pressure (NCPAP), non-invasive intermittent mandatory ventilation (NIMV), and humidified high-flow nasal cannula (HHFNC). The ultimate goal of each of these devices is to prevent barotrauma, volutrauma, and atelectotrauma, all of which contribute to lung injury and long-term complications. Proposed mechanisms of lung protection due to non-invasive ventilation include mitigation of shear-type injury by maintenance of optimal end-expiratory lung volumes and prevention of cyclical collapse and over-distention of alveoli. Other potential benefits include lung-recruitment, improved gas exchange, and decreased work of breathing [2].

In this chapter, we will first explore historical aspects of the development of non-invasive ventilation in neonates. Then we will focus on specific respiratory mechanics unique to neonates and post-uterine adaptation. Finally, we will discuss specific non-invasive modalities.

2. Historical perspectives

Improved perinatal care, the advent of parenteral nutrition, advances in thermoregulation, and aggressive neonatal resuscitation have all contributed enormously to improved outcomes for neonates. Perhaps the most significant change, however, is a marked improvement in our ability to provide aggressive and sophisticated respiratory care and support to ever-smaller infants. In this section, we will focus on the historical development of innovative approaches to non-invasive ventilation in tiny premature infants.

Although Gregory et al. published the first modern description of the use of CPAP to treat RDS, a similar device was first described in 1914 by Professor August Ritter von Reuss [2]. This device resembled bubble CPAP, and consisted of an oxygen tank with tubing attached to the equivalent of a mask-and-bag device, with a simple valve to regulate oxygen flow. Unfortunately, it took almost six decades for this concept to gain acceptance. Prior to Gregory's description of CPAP, there was very little respiratory support that could be provided to neonates. In the 1940s and 1950s, the provision of supplemental oxygen was the sole therapeutic option for ill neonates [3]. It was during this time that two seminal discoveries were made. The first was the discovery that supplemental oxygen provided benefit to ill neonates, but that exposure to high concentrations led to blindness due to retinopathy of prematurity (ROP) [3]. The second was a report by Avery and Mead in 1959 describing increased surface tension in lung fluid recovered from preterm babies that had died from respiratory distress syndrome, and the observation that preterm infants lacked some sort of "surface-active agent" that could alleviate these forces [4].

Neonatology was still a relatively new field in the latter part of the 20th century, and 1963 was a pivotal year in its development. President John F. Kennedy's son, Patrick Bouvier Kennedy, was born 6 weeks prematurely and died from complications of respiratory distress syndrome on the third day of life [3]. This inspired rapid innovation in the development of new technologies geared towards critically ill neonates. Infant ventilators, blood gas machines, umbilical vascular catheterization and the development of the first true neonatal intensive care units all occurred in the late 1960s. As the field improved, survival rates for neonates with respiratory compromise began to improve as well, mainly due to the widespread use of infant ventilators.

Unfortunately, these advances were also associated with complications and many of these neonates were left with a form of chronic lung disease. This was first described in 1967 by Northway et al., who noted that prolonged exposure to mechanical ventilation and supplemental oxygen were likely to blame [5].

Subsequently, in 1971, Gregory et al., described the use of CPAP to treat neonates with respiratory distress syndrome, using either an endotracheal tube or a head box [2]. This use of CPAP represented an intermediate step that was more supportive than supplemental oxygen alone, was relatively easy to use, and seemed to avoid exposure to the injury associated with mechanical ventilation. The introduction of CPAP in neonates was not the only milestone that this decade produced; in 1972, Liggins and Howie published the results of a randomized controlled trial of antenatal steroids in mothers expected to delivery premature infants. They demonstrated that steroids accelerated fetal lung maturation and decreased the risk of respiratory distress syndrome and death by as much as half [3].

Despite the successes associated with CPAP and antenatal steroids, there were substantial concerns about risks. Specifically, some observers suggested that air leaks and pneumothoraces were more common with CPAP than mechanical ventilation. In addition, CPAP seemed to lead to gastric and abdominal distention of unclear clinical significance. Finally, there were fears that the devices themselves would predispose infants to neurological and cosmetic injury [2]. For these among other reasons, intermittent mandatory ventilation using an endotracheal tube was widely adopted, and quickly overtook CPAP as the standard of respiratory care for critically ill neonates. In addition, for about two decades, CPAP was largely replaced by non-invasive intermittent mandatory ventilation (NIMV). It involved using time-cycled, pressure-controlled breaths delivered by a mechanical ventilator via an oronasal mask or prongs [2].

In the late 1980s, there was renewed interest in CPAP and non-invasive ventilation, sparked by the seminal report in 1987 by Avery et al. which concluded that, among eight NICUs observed, the center with the most aggressive use of NCPAP had the lowest rates of chronic lung disease [6]. Coupled with the fact that the landscape of chronic lung disease, as originally described in 1967, was changing in both a clinical and histological sense due to prolonged exposure to mechanical ventilation, it was no surprise that non-invasive ventilation was resurgent. While CPAP was originally designed for the premature baby with respiratory distress syndrome, today it has multiple uses in neonates of varying ages and conditions. It is used to successfully treat transient tachypnea of the newborn, congenital pneumonia, meconium aspiration syndrome, primary pulmonary hypertension, as well as central apnea of prematurity and certain congenital upper airway lesions [2]. While the technology has certainly evolved quite a bit since Professor von Reuss' initial apparatus in 1914, CPAP and other forms of non-invasive ventilation have become the cornerstones of neonatal respiratory care.

3. Neonatal pulmonary mechanics

It is important to understand the core concepts of fetal and neonatal lung development, as well as basic pulmonary mechanics, to better understand the most appropriate respiratory

support modality. Fundamentally, the respiratory system is designed for the conduction and humidification of air into the lungs, uptake of oxygen from the ambient environment, and the removal of waste product in the form of carbon dioxide. All of this ensures that normal aerobic cellular metabolism is supported and that acid–base homeostasis is maintained.

The respiratory system develops through five distinct, yet overlapping phases: *embryonic*, *pseudoglandular*, *canalicular*, *saccular*, and *alveolar* [7]. While a full review of the embryology is not necessary for the understanding of neonatal respiratory care, it is important to note that each particular phase leads to unique respiratory difficulties and opportunities. Lung growth begins in the third week of gestation during the *embryonic* phase, with a small growth of diverticulum from the ventral wall of the foregut. This is often referred to as the primitive respiratory diverticulum or primitive lung bud [7]. Three rounds of branching and division also occur during this phase, leading to a left & right half as well as the formation of multiple tertiary bronchi. The vascular components of the respiratory system also begin their development during this phase. The *pseudoglandular* phase occurs from weeks 5–17, and this time period is notable for the completion of all bronchial divisions as well as formation of cilia and cartilage [8]. After this phase, any further lung growth is simply by the elongation, widening and hypertrophy of existing tissue. The *canalicular* phase is particularly important, as it encompasses 16–26 weeks of development and includes neonates of periviable gestational ages (ie, around 23 weeks gestation). Here, the earliest capillary beds begin to form, and areas of gas exchange start to develop. Many of the overlying epithelial cells also begin to thin out and improve the air-blood interface, further enhancing regions of gas exchange. More importantly, these cells also start to differentiate into type I pneumocytes that help form and stabilize the alveoli. Type II pneumocytes also start to appear, and these cells are vitally important in the production of endogenous surfactant [7, 8]. The canalicular stage is the earliest gestational age at which interventions can be provided. The *saccular* phase occurs from weeks 24–38 and leads to further development of alveolar ducts and conducting airways. Mucous and cilated cell growth also increases. Surfactant synthesis continues to improve, but overall production compared to full-term infants remains low [9]. This time period encompasses the bulk of premature infants, including those that are "late preterm." The relative structural immaturity coupled with insufficient (and often ineffective) surfactant production explains the need for respiratory support in this age group, even in infants born beyond 34 weeks gestation. Finally, the *alveolar* phase occurs from about 36 weeks – 8 years of age. This final stage is mainly characterized by further development of alveolar units, thinning of the air-blood interface, increased surface area for gas exchange, and increased numbers of type II pneumocytes, leading to enhanced synthesis of surfactant [7].

Throughout fetal development, fetal lung fluid is vital in the growth of normal lung structure. Fetal lung fluid is an isotonic fluid secreted by epithelial cells that helps promote growth and development. It is low in protein and high in chloride ions. Combined with contractions of fetal airway smooth muscle and fetal breathing in utero, these processes help promote the normal developmental process of lung growth. Fluid clearance is a process initiated by various labor mechanisms, and this also presents an area for maladaptation and one etiology of respiratory distress after birth [10].

Lung function in neonates, especially those born prematurely, is altered for a number of reasons. Structural issues include poorly developed lung parenchyma, airways and a highly elastic chest wall, and surfactant deficiency complicates these issues. This results in dramatic changes in normal lung mechanics and physiology, manifested by an overall state of abnormally decreased compliance, low functional residual capacity (FRC), and increased respiratory effort by the neonate [8]. This is further compounded by deranged gas exchange. If undertreated, each of these mechanisms may combine to cause respiratory failure. Antenatal steroids improve some of the structural and biochemical derangements, but post-natally the clinician must provide the correct level of respiratory support and surfactant when appropriate. The goal, as we will discuss, is resolve the skewed lung mechanics towards a more normal physiologic state by re-establishing FRC and decreasing work of breathing.

Functional residual capacity (FRC) is defined as the volume of air remaining in the lungs after a normal passive exhalation [8]. In most term, healthy neonates, this figure is typically about 20–30 mL/kg. To understand the significance of FRC in the management of neonatal respiratory care, it is important to understand normal transitional events in early postnatal life. During gestation, the developing fetus is entirely dependent on the placenta for gas exchange. This in-utero circulatory pattern consists of very limited pulmonary blood flow with intracardiac shunts in place to allow for adequate flow of blood to vital organs. The approximate oxygen saturation in a term fetus prior to delivery is about 60% [2]. When labor is initiated, epithelial lung cells halt their production of fetal lung fluid and begin to actively absorb it back into circulation. This process is triggered by thyroid hormone, glucocorticoids and epinephrine working in combination to change epithelial cells from chloride secreting to sodium reabsorption [11]. With the neonate's first spontaneous breaths, the lungs inflate and there is an increase in pulmonary arterial pO2 as well as activation of stretch receptors. This process, in conjunction with production of endogenous nitric oxide, dramatically reduces pulmonary vascular resistance [2]. As pulmonary vascular resistance continues to decrease, more pulmonary blood flow is established and oxygen saturations steadily increase to normal postnatal levels. The intra-cardiac shunts at the level of the ductus arteriosus and foramen ovale close due to increasing arterial oxygen content and increasing systemic vascular resistance from clamping of the umbilical cord, respectively. This process results in physiologic changes that can be witnessed in real time, as most healthy term neonates will obtain oxygen saturations greater than 90% by about 10 minutes of life.

For gas exchange to properly occur after birth, there must be an immediate interface between environmental oxygen and pulmonary blood flow at the alveolar-capillary level. Ventilation (V) and perfusion (Q) ratios reflect this physiologic state, and there are a number of ways that this process can be deranged. To allow for a normal VQ matching, there must be both an adequate alveolar gas volume and normal FRC [7]. If adequately sustained, either due to spontaneous respirations or assisted ventilation, FRC serves as an intrapulmonary pool of oxygen. Preterm infants and ill term infants are prone to a low FRC. This may lead to decreased compliance, increased airway resistance, increased work of breathing, increased pulmonary vascular resistance, hypoxemia, atelectasis, and impaired gas exchange [8]. Conversely, too much FRC from overinflation can also have negative effects and may lead to lung injury, air leaks and decreased cardiac output. Positive distending

pressure is therefore critical in recruiting collapsed alveoli and establishing optimal FRC in neonates that cannot achieve it spontaneously (**Figure 1**).

Specific mechanical and physical properties of the lung also play an important role in neonatal respiratory care. The elasticity of a system refers to the property of matter such that a system will tend to return to its original position when all external forces are abated [8]. In the neonate, the elastic properties of the lung refer to not just the parenchyma, but also the air exchange spaces, muscle, connective tissue and vasculature. In addition, there is also a recoil effect from surface tension in the alveoli, which is artificially increased with impaired surfactant production. Lastly, there are opposing elastic forces that may be provide by the chest wall to assist with lung expansion and air entry. All of these elastic forces form a complex, interdependent balance that may determine FRC [8].

The pressure required to inflate a lung is directly proportional to the volume of inflation – this is often referred to as Hooke's Law [7]. While this relationship is often seen as an extension of the elastic properties of the lung, it brings us to our next biophysical property of respiratory physiology. The compliance of a lung is strictly defined as the change in lung volume due to a change in distending pressure during normal breathing, expressed as a ratio [8]. This is an extension of Hooke's Law. Compliance may be further divided into static and dynamic compliance. Static compliance refers to the tendency of the lung to recoil to its original dimensions after a known volume of pressure is applied and then removed [2]. Dynamic compliance, on the other hand, is measured during spontaneous breathing and refers to the change in pressure from the end of exhalation to the end of inspiration for a given volume. It reflects both the intrinsic elastic and resistive properties of the lung [2]. The compliance of a given respiratory system includes both the lung and the chest wall. In neonates, the chest wall is primarily made up of cartilage and thus is a high compliance system. Conversely, the compliance of the

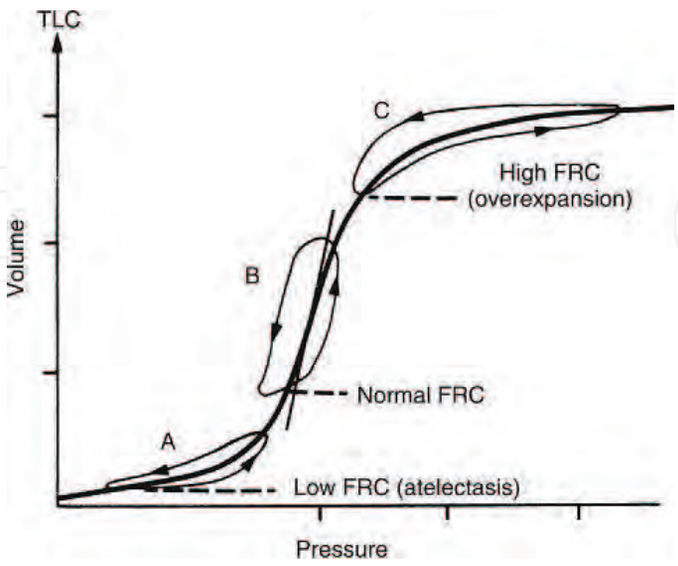

Figure 1. Compliance curve demonstrating different states of FRC. Area A represents poor lung volumes or collapse, where area C represents over distension of the lung. Area B demonstrates optimal lung volumes in which normal physiological FRC is maintained. Image used with permission by Elsevier Books, Inc.

lung is relatively low given surfactant deficiency and decreased alveolar radius, especially in premature infants [7]. This is a problematic scenario, as the balance of forces thereby is tilted towards lung collapse. This also negatively impacts FRC. Neonates respond by augmenting their FRC by increasing expiratory resistance through laryngeal abduction, clinically manifested as "grunting" [7]. Additionally, the higher respiratory rates seen in infants in low-compliant states creates relative gas trapping that helps slightly improve FRC [2]. The definitive treatment, however, is to deliver optimal PEEP via CPAP or another non-invasive modality to avoid atelectotrauma and to re-establish and sustain FRC (**Figure 2**).

The resistance to gas flow in a closed respiratory system is an important determinant of respiratory mechanics in neonates. Resistance is the direct result of friction, and can be defined as either viscous or airway resistance [2]. Viscous resistance refers to the resistance encountered by tissue elements as they touch and move past one another. Airway resistance refers to the resistance that occurs between moving gas molecules and between these molecules and the walls of the respiratory system [2]. Airway resistance makes up the majority of total resistance in a neonate. It is determined by the relationship between the velocity of gas flow, length of the airways, viscosity of the gas, and the diameter of the conducting airways. For laminar flow where all gas molecules move in an orderly fashion perfectly parallel to the walls of the airway, resistance is described by Poiseuille's law. This states that resistance is directly proportional to the product of the tube length and gas viscosity, and inversely proportional the airway radius to the fourth power [2]. Thus airway diameter is the critical determinant

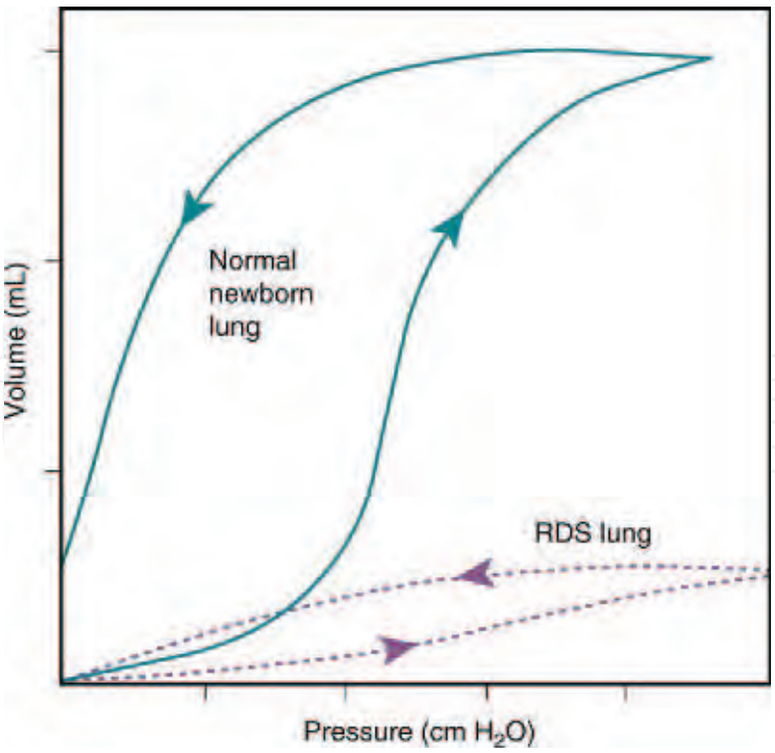

Figure 2. Comparison of compliance curves between a normal neonate (solid line) versus that of a neonate with RDS (dotted line). Note the very little volume change for an applied pressure seen in the infant with RDS due to the lack of surfactant and poor alveolar stabilization. Image used with permission by Elsevier Books, Inc.

of airway resistance, as even small changes in airway radius will have exponential effects on resistance. This effect in neonates is especially exaggerated as they have narrow airways relative to adults.

There is an inverse, nonlinear relationship between airway resistance and lung volume. This is due to the fact that airway size increases as FRC increases, therefore decreasing the total resistance of the system [2]. The converse is also true: any pathologic state in which low lung volumes occur will increase the airway resistance of that system. This is another lung mechanical property that is affected by the FRC. That is, application of adequate PEEP via non-invasive ventilation will establish optimal FRC, increase airway size, and decrease airway resistance [2].

One final concept to explore is work of breathing. Clinically, this term refers to the signs of respiratory distress exhibited by a patient. This can be manifested by tachypnea, grunting, intercostal retractions, or nasal flaring. Mathematically, work of breathing can be quantified as the energy needed to overcome the existing elastic and resistive forces. More specifically, this can be defined as the product of the force exerted and the volume of air displaced [2]. About two-thirds of this energy expenditure is used to overcome the elastic forces of the respiratory system, while one-third is used to overcome resistance [2]. While most clinicians recognize that a neonate exhibiting increased work of breathing is at risk for respiratory deterioration, it is important to realize that increased energy expenditure also results in increased oxygen consumption [8]. It is apparent that work of breathing can be decreased by the application of positive pressure via CPAP or some other non-invasive modality – but how? Of all the respiratory muscles, the diaphragm carries the majority of the workload. Like most skeletal muscles, its ability to generate optimal force is related to its initial relaxed position and the length of muscle fibers at the beginning of contraction [2]. Delivering PEEP via CPAP will not only help better inflate the lungs, but move the diaphragm into a more optimal position for contraction. In addition, PEEP may prevent atelectasis and move the neonate to a more ideal position on the pressure-volume curve where either extreme in atelectasis or over-distended are avoided, and instead optimal FRC is achieved [2, 12]. Lastly, one major role of the nasopharynx and lining of the upper airway is to provide warmth and moisture to inspired air. Non-invasive ventilation replaces the warming and humidification process required by the neonate, and in turn this may reduce metabolic demand [13].

4. Interface devices for providing non-invasive ventilation

Since Gregory's initial description of CPAP *via* a head-box, the technology used to provide continuous distending pressure to neonates has greatly evolved, first with the introduction of binasal prongs. Subsequently, both Kattwinkel et al. and Caliumi-Pellegrini et al. described non-invasive devices in which binasal prongs were connected to a ventilator to provide both flow and pressure [2]. This approach remained standard for a number of years. While the latter parts of this chapter will focus on each of the specific non-invasive modalities themselves, there is a considerable amount of overlap in terms of using the interface devices.

Devices such as "head boxes" or negative pressure boxes are purely of historical interest and are no longer in clinical practice. Facial masks can be used to provide CPAP provided that the mask is attached to a flow-inflating bag or a T-piece resuscitator (for more precise pressures generated). This is a commonly used approach in the delivery room for initial stabilization of neonates, but rarely used in a prolonged manner. Nasal masks, on the other hand, are often used to provide long-term support to neonates receiving non-invasive ventilation. This is typically with variable-flow devices or SiPAP [8]. Nasal prongs, however, are the most popular and effective way to provide non-invasive ventilation. Neonates are obligate nasal breathers so prongs provide the most reliable way of delivering consistent distending pressure [8]. If the infant's mouth is open, however, a large leak of pressure may occur and the neonate will not receive prescribed distending pressure. This may be addressed by using a chin strap or pacifier to keep the mouth closed. One other area where leak and loss of pressure can occur is at the nares; it is vital for nasal prongs to be large enough to fill the space within the nares to prevent this, but at the same time not so wide that they injure the surrounding mucosa and tissues [2, 8]. Long, thin prongs are generally avoided as they may increase the resistance in the system and even minor secretions can lead to significant obstruction and increased work of breathing. Endotracheal tubes are sometimes cut and used as "nasopharyngeal prongs." This practice is less common given all the previously described advantages of shorter binasal prongs. In addition, a recent Cochrane review also suggested that binasal prongs are simply more effective [14]. While we will explore some of the complications associated with non-invasive ventilation later in the chapter, skin and nasal trauma is perhaps the most commonly encountered issue. Adequate skin care requires assiduous nursing care, and often skin barriers are applied.

The pressure delivered by CPAP is typically *via* a continuous or variable flow device. Continuous flow was the method originally used in the 1970s and 1980s, and historically relied on gas flow generated from a ventilator [2]. Continuous-flow CPAP is still used today, typically *via* bubble or water-seal CPAP; this will be described in detail later in this chapter. Two of the most commonly used binasal prongs in continuous-flow CPAP are the Hudson (Hudson Respiratory Care, Inc., Arlington Heights, Illinois, USA) and Inca (Ackrad Laboratories, Inc., Cranford, New Jersey, USA) prongs. Argyle prongs are also occasionally used, but have fallen out of favor [14]. Many of these binasal prongs are interchangeable with different modes of non-invasive support, including CPAP, SiPAP/BiPAP or even nasal intermittent positive pressure ventilation (NIPPV) via a ventilator [15]. There are scant comparative studies in the literature comparing one prong type to another [2] (**Figure 3**).

Nasal masks are another avenue of providing non-invasive ventilation. The mask itself is connected to the pressure generator, typically a variable-flow device. Many units alternate the use of nasal masks with prongs to help prevent nasal and mucosal trauma. As with prongs, leaks can decrease the amount of pressure delivered to the patient. Therefore a proper seal around the nose must be maintained at all times. Very little data exists about the safety and efficacy of nasal masks versus prongs, and there are currently no reported studies of using NIPPV via nasal mask [2, 15] (**Figure 4**).

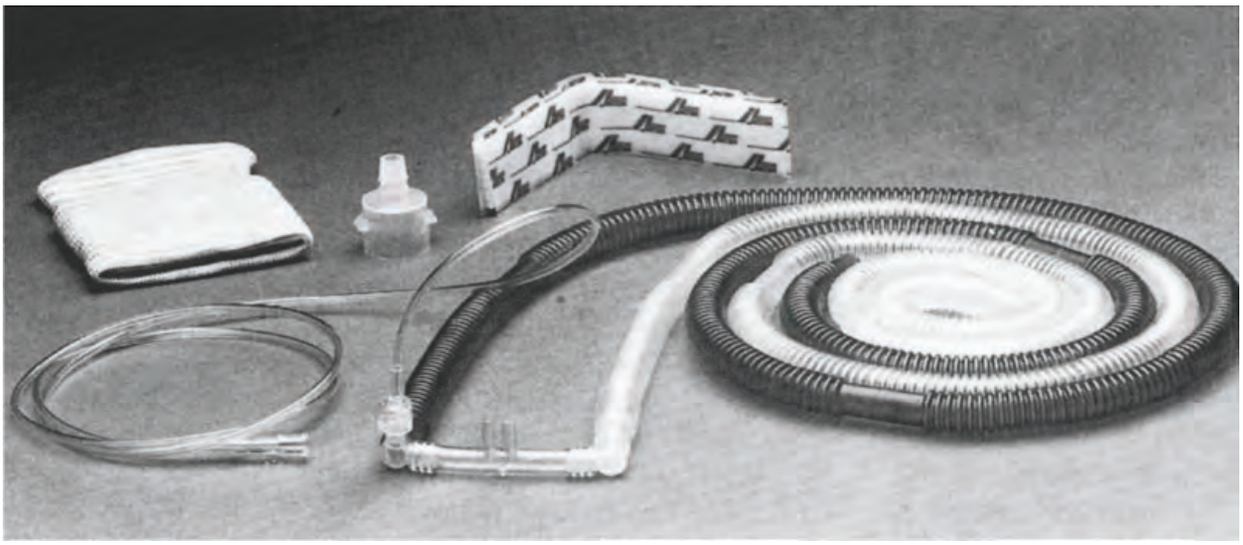

Figure 3. The Hudson NCPAP equipment very commonly used in many NICUs. Image used with permission by Elsevier Books, Inc.

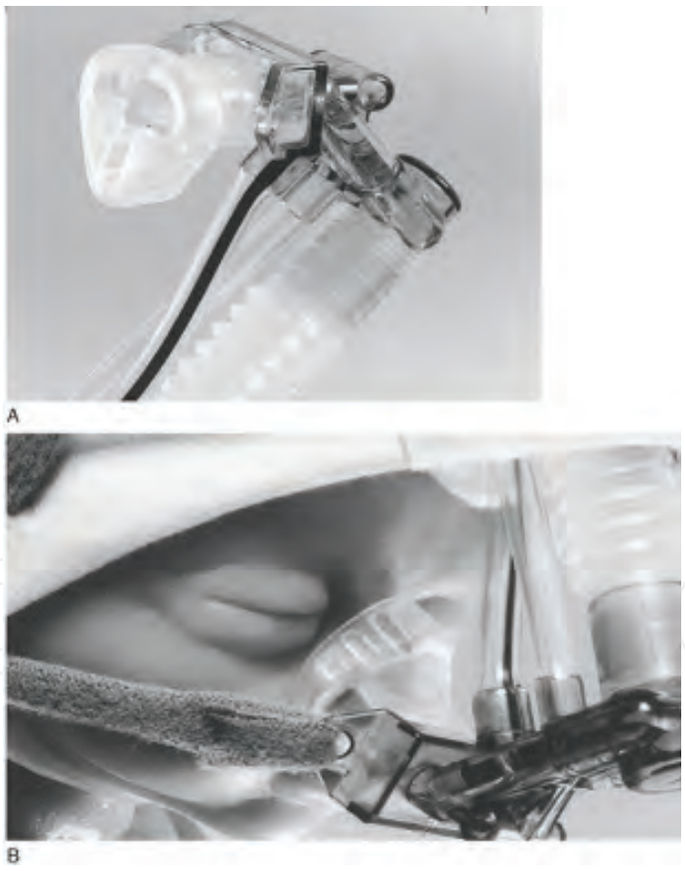

Figure 4. An example of a typical nasal mask used to deliver NCPAP with the infant flow driver device. Image used with permission by Elsevier Books, Inc.

While nasal cannulae (NC) are routinely used to provide supplemental oxygen, some distending pressure can be generated. The rate of gas flow, size of the cannulae, and degree of leak around the nares determine the amount of pressure generated [2]. Higher flow rates

delivered with relatively large sized nasal cannulae is termed "high flow nasal cannulae" (HFNC). Often heated and humidified, the physiology of respiratory support provided by HFNC is different than CPAP. The primary concern with a HFNC system is that depending on the flow rate and degree of leak, very high, uncontrolled positive pressure may be delivered. Not all HFNC devices contain "pop-off" valves to prevent this. These concepts will be explored later in this chapter. Finally, the RAM Nasal Cannula (Neotech, Valencia, California, USA) was originally designed to provide supplemental oxygen, but is a versatile interface device [2]. It has been used in various forms of CPAP as well as NIPPV *via* a ventilator. While at its core it is essentially another short binasal prong, it is designed with larger bore tubing to help reduce resistance and dead space. It has gained widespread use in many NICUs for its relative ease of use [2]. Early anecdotal reports also suggested lower rates nasal trauma. Concerns regarding the RAM Nasal Cannula have to do with the long segment of narrow tubing from the circuit connector to the prongs, creating a great deal of resistance. This can potentially lead to a sizeable drop in pressure and also raises concern about whether the clinician can accurately assess if the patient is receiving the desired distending pressure. It is important to also note that the use of the RAM Nasal Cannula in providing non-invasive ventilation is currently considered off-label use, as it is only approved for providing supplemental oxygen at this time.

5. Nasal continuous positive airway pressure (NCPAP)

Continuous positive airway pressure (CPAP) is positive pressure applied to the airways of spontaneously breathing neonates. As previously discussed, the primary function of the respiratory system is to move ambient air into the lungs for gas exchange. Any factor that limits this basic physiology will predispose the neonate to respiratory failure [8]. The inability to establish and maintain adequate lung volumes is perhaps the biggest risk factor for compromise. Low lung volumes and the resulting atelectasis may result in ventilation-perfusion mismatch and intrapulmonary shunting of blood. Oxygenation is typically affected the most, and while carbon dioxide can generally diffuse across biological membranes easily, its removal can be hampered by a low lung-volume state. Other mechanisms that contribute to respiratory distress in neonates include: retained lung fluid and pulmonary edema, suboptimal FRC, unstable chest wall with high compliance, upper airway more prone to collapse, poor laryngeal tone, and surfactant deficiency [8].

5.1. Physiological benefits of CPAP

CPAP alleviates many of physiologic derangements by increasing mean airway pressure and distending the airways to establish and maintain optimal FRC. By stabilizing and opening terminal alveoli, surface area for gas exchange is enhanced, and ventilation-perfusion mismatching is reduced. CPAP also improves diaphragmatic contractility. In addition, CPAP decreases the range of different opening pressure gradients between different areas of the lung and helps homogenize the total delivered tidal ventilations [8]. By better distending the individual alveolar units, CPAP also reduces the pressure needed to overcome surface tension. Surfactant is better preserved on the alveolar surface, further preventing atelectasis

and the resulting atelectotrauma. In addition, CPAP has been shown to reduce upper airway occlusion by increasing pharyngeal cross-sectional area and decreasing upper airway resistance [8]. Coupled with stabilization of the chest wall and improved compliance, CPAP also reduces work of breathing. Apnea of prematurity is a common issue for many neonates born before 35 weeks gestation. It is manifested by various episodes of apnea, bradycardia and oxygenation desaturation, or some combination of the three. While there is very limited evidence of CPAP being an effective treatment for apnea of prematurity, it is often clinically used in such a manner [2].

5.2. Methods of CPAP delivery

The pressure delivered via CPAP is either via a continuous flow or variable flow device. One of the most common methods of providing continuous-flow CPAP is what is referred to as bubble or water-seal CPAP [2]. Blended gas is first heated and humidified, then delivered to the neonate, typically *via* binasal prongs or a nasal mask. The distal end of the expiratory tubing is submerged in either 0.25% acetic acid or sterile water to a specific depth; this depth determines the level of CPAP generated [2]. The bubbles from the exhalation limb produce observable chest vibrations that could potentially enhance gas exchange. Furthermore, the applied gas flow rate to the CPAP device affects the degree of bubbling, suggesting that there may be a low-amplitude, high-frequency oscillatory effect to the lungs [13]. Initial studies that reported these findings, however, were using bubble CPAP delivered via a nasopharyngeal tube and not binasal prongs [2]. More studies are needed to determine if there exists an oscillatory waveform that enhances ventilation while on bubble CPAP.

Variable-flow CPAP has been in use since 1995 and was originally developed by Moa et al. to help reduce neonatal work of breathing [2]. These devices use dual injector jets directed towards each nasal prong to establish a constant airway pressure. In addition, when the neonate makes a spontaneous expiration, there is a "fluidic flip" in which the flow of gas is reversed and allowed to exit via the expiratory limb of the device. This phenomenon is enhanced due to the Coanda effect, in which gas tends to follow a curved surface [2]. The two most common variable-flow devices currently available are the Infant Flow (Cardinal Health, Dublin, Ohio, USA) and the Arabella system (Hamilton Medical, Reno, Nevada, USA). Some studies have indeed demonstrated less work of breathing and better synchrony in neonates on variable-flow devices compared to bubble CPAP. Others have found similar rates of extubation failure after randomization to either bubble CPAP or variable-flow CPAP following extubation from mechanical ventilation [2]. Despite these differences in the literature, there is no definitive evidence to suggest one mode of CPAP is superior. Many of these studies were done with neonates of various gestational ages and weights, which may confound the results further. Clearly, the clinician must be familiar with the device(s) available to them in their particular units and to be comfortable with their management.

5.3. Clinical management of CPAP

Determining the optimal CPAP level should be individualized to each neonate's underlying pathophysiology and should be aimed to obtain optimal without over-distention. This target

may change based on the neonate's disease course and postnatal age. The use of correctly sized binasal prongs with a chinstrap or pacifier to keep the mouth closed (if needed) is important to minimize any loss of pressure. Immediately after birth, most neonates of all gestational are started on a level of 5 or 6 cm H_2O, with escalation to 8–10 cm H_2O as needed [2, 8]. There is limited evidence, however, to suggest a singular approach to initiating or changing the CPAP level. Again, these decisions should be driven by the underlying pathophysiology and supported by clinical and laboratory measures when necessary. Many institutions have their own specific guidelines and goals, especially when caring for the very low birthweight or extremely low birthweight infant. In general, the CPAP level is deemed appropriate when the neonate's oxygenation and ventilation are satisfactory, the chest radiograph is optimally inflated, work of breathing is minimal, and the neonate is otherwise hemodynamically stable. When the CPAP level is too high, one may see signs of over-distention on the chest radiograph manifested by a flattened diaphragm or small heart size. Gas exchange may be worsened and, in severe cases, over-distention can reduce cardiac output leading to tachycardia and hypotension [8].

Weaning the neonate off CPAP is another area that should be driven by the underlying physiology and any continued need for respiratory support. This is typically possible when the neonate is requiring little to no supplemental oxygen, work of breathing is negligible, and there are few episodes of apnea, bradycardia, and desaturation [8]. While some institutions wean the CPAP level during this time, other institutions do not. An alternative method of weaning CPAP consists of "sprinting" the neonate off CPAP support for a period of time, which gradually increases until off entirely. This is not well studied and this method of "sprinting" may actually lead to CPAP weaning failure and may prolong the length of time ultimately spent on CPAP [8]. Additional questions include at what postnatal age to consider removal of CPAP, and what level of support (if any) should the neonate be transitioned to. The duration of CPAP is often driven by the neonate's gestational age even in the absence of significant lung disease, as very preterm infants often benefit from longer use of CPAP while their chest walls mature and offset the elastic recoil of the lungs [8]. While this may vary from one institution to another, typical goals for removing an extremely preterm neonate from CPAP are around 32–34 weeks postmenstrual age, when appropriate goals are achieved (ie, no work of breathing and/or minimal supplemental oxygen requirement, etc). When discontinuing CPAP, the neonate can either be taken directly to room air or transitioned to a lesser mode of support (typically some form of nasal cannula). Again, much of this decision-making is driven by the current lung disease (if any) being treated at the time, as well as any other factors that may predispose the neonate to continued need for respiratory support. For example, the neonate that is otherwise stable on a fairly low CPAP level, has no oxygen requirement, and is growing well can reasonably be taken to room air as the initial attempt at discontinuing CPAP. The neonate that still has a minimal oxygen requirement but otherwise meets other criteria for coming off CPAP can be taken to a nasal cannula.

5.4. BiPAP and SiPAP

Bilevel CPAP (BiPAP) or sigh intermittent positive airway pressure (SiPAP) has been marketed as a means of delivering alternating levels of distending pressure. Both are typically

used with the Infant Flow driver and can alternate between a lower and higher CPAP pressure throughout the respiratory cycle; some ventilators can provide this mode as well [2]. This method of support is not synchronized (synchrony is currently only available in Europe and Canada), and the neonate breathes spontaneously at both levels of support. This potentially creates two distinct FRCs [16]. The CPAP levels cycle at a specific rate. The higher pressure level is delivered during "inspiration", with typical values of 8–10 cm H_2O, but sometimes as high as 15 cm H_2O if using a patient triggered BiPAP device. Most SiPAP devices, on the other hand, will have a "sigh" pop-off that will prevent inspiratory PEEP from exceeding 10 cm H_2O. During "expiration", the neonate will breathe the lower pressure level, with typical values set at 4–6 cm H_2O. A higher "inspiratory time" is typically used, with some authors suggested as high as 1 second [8]. Lista et al. compared outcomes in preterm neonates with RDS that were initially supported with CPAP versus SiPAP [16]. They found that infants supported with SiPAP had a shorter duration of mechanical ventilation overall, needed less oxygen, and were discharged home sooner. A caveat of these studies is that it can be difficult to compare the actually distending mean airway pressure delivered between CPAP and BiPAP/SiPAP. The latter, with alternating levels of pressure, will typically generate a pressure that is 2–3 cm H_2O higher than CPAP [2]. It is quite possible that it is this higher overall level of pressure in addition to the cyclical tidal volumes delivered that result in benefit to the infant. A recent study in 2016 by Victor et al. aimed to compare the use of CPAP and BiPAP in infants born before 30 weeks' gestation and less than two weeks old using equivalent mean airway pressures [17]. They did not find any difference in extubation failures between the two groups, nor did they find any difference in total duration of mechanical ventilation, oxygen requirement at 28 days & 36 weeks corrected, or length of hospitalization.

6. Humidified high flow nasal cannula (HHFNC)

HHFNC use rapidly expanded in NICUs since 2005. The two major commercially available devices are Vapotherm (Exeter, New Hampshire, USA) and Fisher & Paykel (Auckland, New Zealand) [2]. While most clinicians refer to this technology as "HFNC," the delivered air undergoes a heating and humidification process. Traditional nasal cannula was limited to flow rates of 2 lpm of either 100% or blended oxygen for neaontes [13]. Higher rates of flow often caused significant drying of the airway mucosa, leading to irritation and mucosal trauma. The new HFNC systems create nearly 100%, allowing clinicians to use higher flow rates. This can vary from one institution to another. Some centers will use flow rates of up to 4 lpm, while others use rates as high as 8 lpm. Many of the same physiological benefits seen with the use of CPAP can be extrapolated to the use of HHFNC, as the higher flow rates has been shown in some studies to provide comparable distending pressure [2]. These benefits include improved pharyngeal tone, nasopharyngeal deadspace washout, decreased work of breathing, and maintenance of FRC [13]. The primary concern with the use of HHFNC is that it can potentially deliver unpredictable, uncontrolled and widely variable levels of distending pressure. Some studies using esophageal probes have measured the pressure delivered by HHFNC; this level is a determined not only by the flow rate delivered, but also the weight of the neonate and the size of the cannulae [2]. Neither of the two commercially available HHFNC

devices are capable of measuring the level of pressure provided. They do, however, have an internal pressure-limiting mechanism as a safety measure to prevent excessive pressures from reaching the patient [8]. Ultimately, though, there currently is no reliable way to calculate how much distending pressure is delivered. For that reason, it is vital that the nasal prongs selected allow for some leak around the nares so that extremely high pressures are avoided.

6.1. Clinical use of HHFNC

HHFNC has been tried in various domains of neonatal respiratory management, including as a means of avoiding extubation failure in premature neonates. There have been a handful of recent studies to look at this, and the general consensus seems to be that HHFNC was non-inferior to CPAP in terms of extubation failures [8]. The additional finding of less nasal and mucosal trauma was consistent across most of these studies. Overall, however, there is still insufficient evidence to suggest that HHFNC is equal or superior to CPAP in preventing extubation failure. Much of this has to do with wide variations in the previously mentioned study designs, use of different devices, and unknown severity of respiratory distress in enrolled patients [8]. These data are even more limited for extremely low birthweight infants or those born less than 28 weeks' gestation [13].

HHFNC has also been studied for treatment of apnea of prematurity and work of breathing. Saslow et al. (2006) evaluated the effects of CPAP and Vapotherm HFNC on work of breathing patterns in a crossover study of preterm infants requiring either support modality and weighing <2.0 kg at birth. They did not find any significant differences between the two groups [8]. Sreenan et al. (2011) also looked at stable premature infants in a crossover study of CPAP and HHFNC. They did not find any differences between the two modalities with respect to apnea, bradycardia, or desaturation events, oxygen requirement, or work of breathing [8]. This remains an area where success with HHFNC can certainly be achieved, but it is important to note that no definitive evidence exists to prove it is equally efficacious as CPAP.

6.2. Current best evidence regarding HHFNC use

In June 2015, an international group of experts met in Oxford, England to discuss the use of nasal high-flow therapy in neonatology. The goal of the meeting was to reach consensus among clinicians on how to best use and study HHFNC in neonates and to try to establish guidelines for its management [13]. At the time of their meeting, their review encompassed four current RCTs that involved over 1100 preterm infants [13]. The following is summary of the group's findings.

The Oxford group recommended that in general, HHFNC can be *considered* for most neonates in which CPAP would be used. This includes preterm infants with respiratory distress, increased work of breathing, or an oxygen requirement. Special consideration should be given to neonates with significant nasal trauma from CPAP use, as switching to HHFNC may allow the nares to heal [13]. The same level of monitoring and nursing care provided to a neonate on CPAP should be applied to a neonate on HHFNC [13].

As previously mentioned, one of the major differences at the level of the nasal prongs between CPAP and HHFNC is the desired amount of leak. With HHFNC, there must be a moderate

amount of leak around the nares to allow gas egress and to ensure that unpredictably high pressures do not occur. The group concluded that the prong dimensions be no greater than 50% of the diameter of the nares, and that the gas flow via HHFNC be heated between 34 and 37 degrees C [13]. Furthermore, the actual cannulae used should be per manufacturer recommendations, and components from different systems should not be mixed.

Individual institutions may have their own particular guidelines, but the Oxford meeting recommends starting with flows of 4–6 lpm for most preterm infants. Lower flow rates of 2–3 lpm may be acceptable for larger neonates closer to or at term [13]. A maximum flow rate of 8 lpm is recommended, and only in response to increased work of breathing or higher oxygen requirements. Escalation from HHFNC to a different support modality should be considered in cases of increased work of breathing, increased apnea, or oxygen requirements greater than 50% [13]. Weaning the flow rate can be considered once the neonate is stable for about 24 hours and on 30% or less oxygen, with one recommended approach of weaning the flow rate by 1 lpm every 12 hours as tolerated. Again, institutions may have their own weaning protocols. Discontinuing HHFNC can be considered once flow rates of 2–4 lpm are achieved, as 2 lpm is actually the lowest most devices will sustain, and the benefits of rates less than 3 lpm are actually unclear at this point [13].

6.3. Summary

A growing body of evidence seems to suggest that HHFNC is fairly safe and efficacious in supporting many preterm infants, however no definitive evidence exists. Flow rates of 2–8 lpm are generally acceptable, with careful attention to prong size and adherence to all manufacturer recommendations. Clearly, however, more research is needed. Specifically, more studies are needed to evaluate the use of HHFNC in extremely low birth weight infants and those born less than 27 weeks' gestation, as well as the potential use of HHFNC in delivery room resuscitation and during neonatal transport [13]. *This is one specific age group in which the evidence still overwhelmingly supports the use of CPAP as the initial mode of support*. More studies are also needed to compare different HHFNC devices, types of cannulas, and true flow rate recommendations based on weight and gestational age. Finally, the Oxford group strongly recommends that each institution devise and adhere to their own agreed-upon guidelines so that a standardized approach to the use of HHFNC can be applied and subsequently studied.

7. Nasal intermittent positive pressure ventilation (NIPPV)

Nasal intermittent mandatory ventilation (NIMV), also known as nasal intermittent positive pressure ventilation (NIPPV), refers to ventilation provided via a conventional ventilator in a non-invasive fashion. This is usually administered *via* short binasal prongs, the RAM Nasal Cannula, or a nasal mask [2, 8]. Depending on the type of ventilator and settings used, NIPPV is designed to deliver positive pressure throughout the respiratory cycle with defined, intermittent increases in pressure, often in synchrony with respiratory efforts [8]. This method of respiratory support was initially described in the early 1970s when *via* time-cycled inflations

using a ventilator with an oronasal mask [2]. In the 1980s, more than 50% of the level III NICUs in Canada were consistently using this method of respiratory support. Shortly after, it fell out of favor due to reports of facial neurological injuries and gastrointestinal perforations; subsequent studies regarding the use of NIPPV in neonates have not reported higher rates of these complications [2, 13]. Of note, nasal high-frequency ventilation (NHFV) is also described in the literature and is increasingly common in some centers in Europe. Given its relative new nature and lack of extensive comparative studies, it will not be discussed here.

7.1. Benefits of NIPPV

The physiological benefits of NIPPV are similar to other modes of positive pressure delivery. Specifically, NIPPV will expand the lung and recruit terminal alveoli, increase FRC, prevent atelectasis and atelectotrauma, and improve ventilation-perfusion mismatches [8, 18]. In addition, the positive pressure delivered helps splint the upper airways, improves laryngeal tone, and stabilizes the highly compliant neonatal chest wall. Synchronized NIPPV, or sNIPPV, has been shown in several studies to deliver higher tidal volumes than CPAP or non-synchronized NIPPV [13, 18]. In addition, all forms of NIPPV deliver additional positive pressure breaths, further increasing mean airway pressure. This in turn helps to further improve tidal volumes and reduces thoraco-abdominal asynchrony (especially true with sNIPPV), which has may reduce work of breathing and improve pulmonary mechanics [8]. Animal studies have also shown that the intermittent distending pressure above PEEP that NIPPV provides can more effectively recruit the lung than CPAP alone, leading to further improvements in FRC [13].

NIPPV has been studied in three major domains: preventing extubation failures, treating apnea of prematurity, and as the primary mode of treating respiratory distress in premature neonates. As of 2015, there have been ten randomized controlled trials comparing NIPPV with CPAP after extubation in premature infants. Friedlich et al. were the first to publish a study comparing CPAP with sNIPPV, and demonstrated that sNIPPV reduced extubation failures significantly [19]. In 2017, a Cochrane meta-analysis of these trials demonstrated a reduction in extubation failure (NNT = 4), but the studies included various NIPPV devices with a mix of synchrony versus asynchrony [8]. Furthermore, there was variability in the definition of extubation success. Despite these *caveats*, the conclusion from the review was that NIPPV may reduce extubation failure within 48 hours to one week after extubation more effectively than CPAP. No effect, however, was seen on chronic lung disease or mortality [18].

For treatment of apnea of prematurity, there are three studies comparing CPAP with NIPPV. The evidence is conflicting and there is no current recommendation whether NIPPV is superior to CPAP [8, 13]. A total of eight studies with 850 patients have looked at NIPPV as the primary mode of initial ventilation in premature neonates with respiratory distress syndrome, with the primary outcome being failure of non-invasive support and the need for intubation. The studies included different devices with mixed populations. Furthermore, some studies allowed the use of surfactant while others did not. As one might imagine, the results were mixed, with six of the trials essentially finding no difference between the two respiratory modalities [8]. As mentioned above, the strongest evidence in this area as demonstrated by

the 2017 Cochrane review appears to be the use of NIPPV to prevent extubation failure when used immediately after extubation [18].

7.2. Typical NIPPV settings

As with every mode of respiratory support, the settings applied to any particular neonate should be based on the particular device used and the underlying pathophysiology. Initial settings on NIPPV are typically similar to those of a mechanical ventilator, with two exceptions, applied peak inspiratory pressure (PIP) and inspiratory time (Ti). Higher PIP is often necessary as pressure is delivered via a nasal interface and pressure is attenuated prior to delivery to the lungs. Therefore, NIPPV PIP is typically started about 2–4 cm H_2O higher than that normally used for mechanical ventilation *via* an endotracheal tube [8]. This is then adjusted based on adequate chest rise and blood gas measurements. For similar reasons, slightly higher inspiratory times of 0.4–0.5 seconds are also typical, as breaths delivered nasally have more resistance to overcome versus those delivered via an endotracheal tube.

Weaning from conventional ventilator to NIPPV should be done according to the same general recommendations as for any other mode. The goal should be well inflated lungs with an adequate FRC and minimal work of breathing. Settings on NIPPV are typically similar to prior settings on mechanical ventilation at the time of extubation. While this will differ from one institution to the next, this typically consists of rates below 25 breaths/min, a PIP of less than 20 cm H_2O, and an oxygen requirement of less than 30–35%. PEEP can be variable depending on oxygen requirement and need for lung expansion, but ideally will be 6 cm H_2O or less [8].

8. Summary

Although the means of delivering non-invasive respiratory support are widely variable, with numerous interfaces, devices and modes, the underlying goal is the same for all. Each baby's physiology should be assessed and non-invasive respiratory support must be tailored to resolve the most important underlying pathophysiology. When properly supported, babies should be well oxygenated, with minimal work of breathing, infrequent apnea, and a stable respiratory status.

Acknowledgements

I would like to thank my colleagues, Drs. Schlegel and Shepherd, for all their support and guidance in undertaking this endeavor. Furthermore, I want to recognize all of the neonatal nurse practitioners, nurses, respiratory therapists, pharmacists, nutritionists, and occupational/physical therapists that work so tirelessly so that we can provide the best care for our most vulnerable patients.

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Chapter 6

Open-Circuit Mouthpiece Ventilation: Indications, Evidence and Practicalities

Michalis Agrafiotis, Konstantina Nikolaou, Dimitra Siopi and Diamantis Chloros

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73243

Abstract

Open-circuit mouthpiece ventilation (MPV) is a method of noninvasive ventilation, which can be used to provide full-time support, induce lung volume recruitment, increase cough efficacy, defer tracheostomy and possibly improve survival and quality of life in advanced-stage neuromuscular patients. MPV might also be applicable to other chronic respiratory diseases as well as in acute exacerbations of chronic obstructive pulmonary disease and can also be employed for the extubation of unweanable neuromuscular patients. A candidate for MPV should be able to rotate his neck adequately, grab the mouthpiece with his lips and maintain sufficient control of the upper airway muscles. MPV is usually provided in the volume assisted-controlled mode with a tidal volume between 0.7 and 1.5 L, zero PEEP and backup rate set to the lower allowed value, allowing the patient to define his own ventilatory pattern. The "low pressure" and "apnea" alarm should be switched off, if possible, or special setting adjustments should be used to prevent their activation. Comprehensive patient training and dedicated nursing time are important for the application of MPV. MPV is considered a safe method for the majority of the patients, but accidental mouthpiece loss is an important concern.

Keywords: noninvasive ventilation, tracheostomy, Duchenne muscular dystrophy, amyotrophic lateral sclerosis, home ventilation

1. Introduction: rationale for mouthpiece ventilation

Mouthpiece ventilation (MPV) is a unique method of respiratory support specifically intended to provide full-time ventilatory assistance mainly to patients with chronic ventilatory failure and limited or no ventilator-free breathing time [1–3]. Together with negative pressure ventilation, MPV is probably one of the oldest methods of noninvasive ventilatory support since it

was initially employed as an alternative to tracheostomy by poliomyelitis survivors 60 years ago [3]. However, it was the pioneering work of a few investigators over the last three decades, which popularized the use of MPV for the management of chronic ventilatory failure, and since 2013, several MPV modes have been incorporated into modern home ventilators [3, 4–10].

The main indication of MPV is the provision of full-time ventilatory support for patients with chronic progressive neuromuscular diseases (NMD). Many NMDs cause respiratory disease by involving inspiratory, expiratory and upper airway muscles, leading to sleep disordered breathing, reduced respiratory pump efficiency and weak cough [11, 12]. From the respiratory physician's point of view, the most characteristic pathophysiologic trait of these NMDs is chronic alveolar hypoventilation which appears initially during the rapid eye movement sleep stage and extends eventually throughout all sleep stages before manifesting during daytime [13]. At advanced disease stages cough function is also severely impaired predisposing to respiratory infections and atelectasis [11, 12]. The institution of noninvasive positive pressure ventilation (NIV) for the support of the feeble respiratory muscles at the early stage of nocturnal hypoventilation is the mainstay of management of these patients and has been shown to improve survival, quality of sleep and quality of life [14–19]. However, as disease progresses and respiratory muscles continue to weaken, ventilatory requirements extend into the daytime. For patients with limited or no ventilator-free breathing time (e.g. ventilator use for > 16 or 20 hours per day), many practitioners would suggest transition to invasive ventilation via tracheostomy [20]. Importantly, an additional role of tracheostomy is the facilitation of secretion clearance given that at advanced disease stages cough flows are invariably reduced [11, 12]. In a European survey involving patients managed with home ventilation, patients with NMDs were the most likely to receive ventilatory support for a prolonged period (>6 years) and to have undergone tracheostomy procedures [21]. Nevertheless, long-term tracheostomies have been associated with several disadvantages including loss of voice, tube-related injuries, increased care-giver burden and disturbed self-image [2, 3, 9]. Although most patients would show preference toward a continued noninvasive mode of management [6, 22], standard nasal or oronasal masks are not suitable for this task since they commonly cause difficulties in eating, drinking and speech, sense of claustrophobia, limited field of vision, impaired social interaction and pressure lesions [1–3].

An alternative method for continuous noninvasive ventilator support is based on the 24 hour use of MPV or the combination of MPV during the daytime with nocturnal nasal or oronasal mask ventilation (MV). This method is complemented by ancillary strategies of which the most important are the "air-stacking" maneuver and the glossopharyngeal breathing (GPB) technique [1–3]. A good candidate for MPV should be able to rotate his neck and grab the mouthpiece with his lips and also maintain good control of his upper airway muscles (**Figure 1**) [10]. MPV is usually delivered via a home ventilator in the volume-assist-control mode (VAC) with the tidal volume (Vt) commonly set between 0.7 and 1.5 L (to correct for air leaks), zero PEEP and a back-up respiratory rate ideally set to zero [1–3]. Therefore, the patient has the ability to define his pattern of breathing according to his own ventilatory needs by taking as many breaths as he requires and by modifying the quantity of leak [8].

Volume-target MPV facilitates the application of the "air-stacking" maneuver, which is performed by teaching the patient to stack consecutive volumes of air delivered from the

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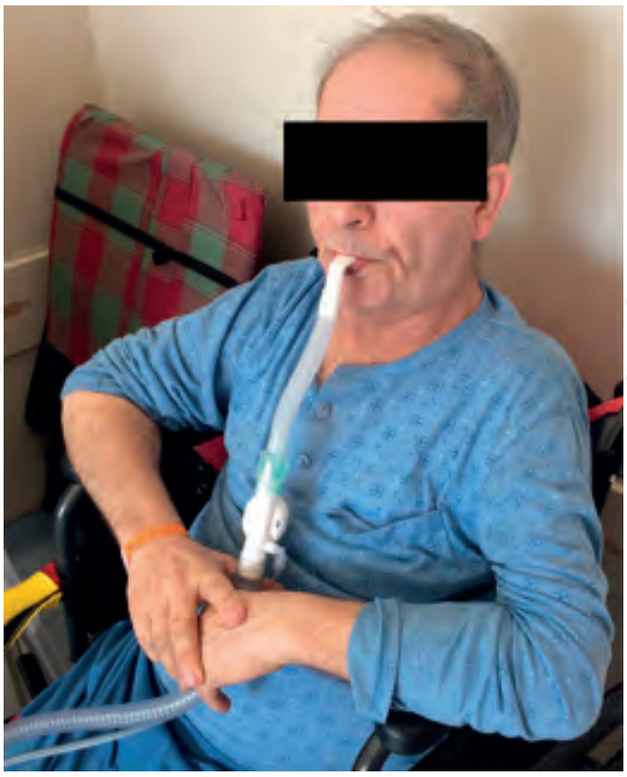

Figure 1. A patient with non-bulbar amyotrophic lateral sclerosis making use of mouthpiece ventilation (from Agrafiotis et al. [30], after permission).

ventilator until his lungs are maximally expanded. The maximum volume of air that can be held with a closed glottis is the patient's maximum insufflation capacity (MIC) [23]. The role of air-stacking is to preserve lung function by effecting lung volume recruitment and to avert chest wall strictures and contractures in patients with NMDs who experience a progressive decline in vital capacity (VC) [24, 25]. The difference MIC-VC depends directly on the integrity of glottic function and represents the amount of recruitable lung volume [24]. In a recent retrospective study of 151 patients with Duchenne muscular dystrophy (DMD), lung volume recruitment by air-stacking delayed the maximal VC decline by at least 5 years [26]. Other researchers have also reported a decrease in the rate of VC decline in patients with DMD [27] and a progressive increase in the MIC-VC difference, indicating a higher number of recruitable lung units [28]. In addition, lung expansion by air-stacking takes advantage of the increased respiratory system recoil pressure at high lung volumes to increase peak cough flow (PCF) and facilitate secretion clearance. In a group of 61 DMD patients, mean PCF increased from 137 to 236 L/min with the application of the air-stacking maneuver [29]. As an example, the application of air-stacking in a patient with amyotrophic lateral sclerosis (ALS) receiving MPV was associated with a MIC-VC difference of 0.4 L and an increase of PCF from 50 to 200 L/min [30]. Therefore, the use of MPV in combination with the air-stacking maneuver supports daytime ventilatory function and improves cough efficacy deferring tracheostomy.

GPB is another strategy commonly taught to MPV users. This technique is based on the use of the tongue to gulp consecutive boluses of air, while the glottis remains closed after each gulp to retain the inhaled air. By imitating the effects of a deep breath, GPB induces lung volume

recruitment and improves cough efficacy. In addition, GPB provides ventilator independency for patients with limited off-ventilator time and can be used as a rescue strategy in case of an accidental mouthpiece disconnection or ventilator failure [5, 6, 31].

During the last years, the use of MPV has also expanded to patients with other chronic respiratory diseases such as chest wall diseases [32] as well as to acute exacerbations of chronic obstructive pulmonary disease (COPD) [33, 34]. Nevertheless, despite the increasing interest in MPV, its application is limited to few centers specializing in noninvasive respiratory management [35]. Many practitioners are unfamiliar with its use, and several authors still consider tracheostomy as the most effective and secure method of ventilation for patients with advanced diseases [1].

In the rest of the chapter, we will present the evidence supporting the application of MPV for the management of respiratory disease and address several practical issues related to its use.

2. Evidence

2.1. Mouthpiece ventilation for full-time ventilatory support in neuromuscular patients

The application of MPV ventilation to 75 post-polio survivors with chronic respiratory failure was reported by Bach et al. [5]. All patients were using MPV as a major part of their respiratory support, but some (31%) were also using body respirators and the majority (88%) required full-time ventilator assistance. On average MPV was used for 1028 patient-years (14.8 years per person) for a total mortality of 1 death per 60.5 patient-years. Several of these MPV users married and some also joined the workforce.

Toussaint et al. [8] reported on 42 patients with DMD treated with MPV. Before introduced to MPV, all patients had diurnal hypercapnia by the end of the day while being treated optimally with nocturnal nasal ventilation. Survival at 1, 3, 5 and 7 years was 88, 66, 58 and 51%, respectively. Importantly, the use of MPV was associated with stabilization of VC, despite a deterioration in respiratory muscle strength, while transcutaneous CO_2 values improved. Some patients also reported improvements in dyspnea, appetite and swallowing. No important accidents or complications were observed over the 7-year follow-up period. VC was also preserved in a small cohort of 12 DMD patients who were prescribed MPV, a fact attributed to the concurrent use of lung volume recruitment strategies [36].

MPV was also compared to tracheostomy ventilation (TV) in 42 patients with DMD [9]. All tracheostomized patients (n = 16) used cuffless tubes and speaking valves connected in line with the ventilator circuit. While TV was associated with a higher incidence of tracheal injuries, mucous hypersecretion and lung infections, MPV users had a slightly higher incidence of weight loss and need for enteral feeding. Causes of death did not roughly differ between the two groups, however one MPV user died as a result of loss of mouthpiece during wheelchair malfunction, while a TV patient died during an endoscopic procedure.

Bedard and McKim [10] reported retrospectively on the use of MPV in patients with ALS. Of 37 patients in total, 27 were considered to be successful MPV users (consistent use > 1 month). The majority of the successful patients had less severe bulbar symptoms and demonstrated recruitable lung volume with MIC > VC. Importantly, all successful users experienced improved dyspnea scores and normalization of CO_2 values. For this group of patients, FVC decreased as disease progressed, but MIC was relatively preserved and MIC-VC difference increased. The majority of them could effect a PCF > 180 L/min with lung volume recruitment throughout disease course. In addition, a PCF > 180 L/min at initiation of MPV in successful users was associated with significantly better mean survival (637 vs. 240 days).

In addition, Khirani et al. [37] obtained questionnaires on quality of life issues from 30 neuromuscular MPV users. The majority of the patients reported reductions in dyspnea (73%) and fatigue (93%), and some of them also improvements in the ease of speech (43%) and swallowing (27%).

Overall, the above evidence indicates that MPV may defer tracheostomy, improve or stabilize clinically relevant lung function variables and possibly improve quality of life and confer a survival benefit to neuromuscular patients. The application of MPV seems relatively safe, although the possibility of mouthpiece loss is not a negligible concern. In addition, the concurrent use of other noninvasive aids, e.g. mechanical insufflation-exsufflation devices, might bias the interpretation of these studies. From this point of view, it is worth noting that in the study by Toussaint et al. [8], mechanical insufflation-exsufflation was available for only 7% of the patients. Nevertheless, further prospective studies are warranted to explore the impact of MPV on the outcomes of neuromuscular patients.

2.2. Mouthpiece ventilation for "unweanable" ventilator-dependent neuromuscular patients

MPV, sometimes combined with mechanical insufflation-exsufflation, has been successfully employed as a noninvasive method of weaning or removal of artificial tubes for patients with acute or chronic ventilatory failure, the majority of which had various NMDs. Many of these patients continued using MPV for several years [5, 6, 38]. A recent study [7] evaluated a simplified protocol for the extubation of neuromuscular patients with no ventilator-free breathing time. All patients (n = 157) who were normocapnic on invasive mechanical ventilation could maintain an SpO_2 > 95% for 12 hours on room air and could reverse desaturations with the use of mechanical insufflation-exsufflation device were extubated to noninvasive nasal, oronasal or mouthpiece volume assisted-controlled ventilation. Intensive use of mechanical insufflation-exsufflation was provided after extubation. Patients using MPV could determine the amount of volume they required and, when possible, could wean themselves *after* extubation by taking gradually fewer breaths from the mouthpiece. This protocol effected extubation success (defined as discharge without reintubation) in 157 (98%) of the patients, of whom 46% remained full-time ventilator-dependent. Although this study does not provide specific data with respect to each interface, it does exemplify the usefulness of mouthpiece for providing full-time ventilatory support without the requirement of an invasive tube.

2.3. Mouthpiece ventilation in other chronic respiratory diseases

Nicolini et al. [32] recruited 18 mechanical ventilation-naive patients with severe kyphoscoliosis in a prospective 4-year study, which evaluated the impact of combined diurnal MPV and nocturnal MV on lung function, clinical outcomes and health-related quality of life. They observed significant improvements in spirometric indices, blood gases, static mouth pressures, ventilatory drive and polygraphic variables at 6 months. In addition, patients reported improvements in quality of life aspects as sleep, physical well-being, eating, leisure, self-confidence and mood. Mortality at the end of the study period was 22.2%. When compared to a historical group of kyphoscoliotic patients who received only nocturnal MV, survival was better for the combined group at 180, 360 and 720 days.

2.4. Mouthpiece ventilation in acute respiratory exacerbations

There is limited evidence on the effectiveness, safety and tolerance of MPV in the setting of acute respiratory failure. A randomized cross-over prospective physiologic study compared four different interfaces with various internal volumes including a mouthpiece with minimal internal volume in critically ill patients. No difference was noted in gas change and respiratory effort variables, but the mouthpiece was associated with more leaks and asynchronies and a significantly less comfort on a visual analogue scale [39]. In a cross-over study which compared short-term mouthpiece and face mask tolerance in a cohort of 27 intensive care unit (ICU) patients treated for acute respiratory failure, five patients were withdrawn due to poor tolerance of the mouthpiece. For the remaining subjects and their nurses, facemask was associated with a nonsignificant better comfort, but mouthpiece required a significantly higher nursing time. While oxygenation and blood gases significantly improved with both interfaces, only face masks were associated with a significantly lower respiratory rate [40].

Some of the above findings were challenged by more recent clinical studies. Glerant et al. [33] conducted a retrospective matched case-control study in which MPV was compared to nasal MV and standard medical care in 87 COPD patients admitted to a respiratory ICU due to acute hypercapnic exacerbation of mild severity (average pH 7.3). In both groups, assist-control or pressure support modes were used. MPV was applied for 20 minutes every hour during the day and at less frequent intervals during the night. All MPV patients used a nose clips and had to hold the mouthpiece firmly and keep their mouth closed to avoid leaks. This study observed a nonsignificant lower intubation rate for MPV as compared to MV users (7 vs. 14%) and similar improvements in blood gases although these changes occurred much later in the MPV group, a fact attributed to a longer learning period for these patients. Overall, the duration of NIV and ICU stay did not differ between these two groups.

The same question was revisited by a recent randomized controlled trial. Nicolini et al. [34] randomized 50 COPD patients presenting with acute exacerbation of mild-moderate severity (pH 7.25–7.30) to receive either nasal MV or MPV in the pressure support mode. No case of NIV failure was observed, and blood gas values showed similar trends while the duration of NIV and hospital stay did not differ between the two groups. Common complications included skin breakdown for the MV group and gastric distention for the MPV group. However, tolerance and device acceptability was better for the MPV group.

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Criticism for both the abovementioned studies focused on the use of nasal masks in the setting of an acute exacerbation and the absence of long-term results. In addition, the study by Nicolini et al. [33] was underpowered to assess changes in blood gases, which was the primary outcome [41]. Pending the results of further investigations, MPV might be considered for COPD patients with a mild-moderate acute exacerbation who are intolerant of nasal or oronasal masks but retain a good level of consciousness and are not severely distressed in order to understand and apply this technique.

3. Practicalities in the application of mouthpiece ventilation

MPV is mainly indicated for neuromuscular patients with chronic ventilator failure when they develop daytime hypercapnia despite optimized nocturnal ventilatory support [8] or when they manifest deteriorating daytime breathlessness with increasing ventilator dependence [10]. MPV can be performed with (1) a home life-support ventilator, (2) a single or a double-limb circuit, (3) various types of mouthpieces, and (4) adjustable support arm or custom-made straps to mount the mouthpiece close to the head for patients with advanced motor disabilities (**Figure 2**). The presence of an exhalation valve in the circuit is not a prerequisite for the delivery of MPV; however, it might be necessary for switching to nocturnal MV for patients using non-vented circuits. The ideal candidate should be able to grab the mouthpiece with his lips and adequately rotate his neck [10]. MPV can be combined with MV during sleep or applied 24 hours per day using specifically designed interfaces [6, 31].

3.1. Patient education

Most of the patients considered for MPV have already been using MV for several years. Nevertheless, the experience of MPV is quite different and some patients may feel uncomfortable and express reluctance to continue. The application of MPV requires active participation

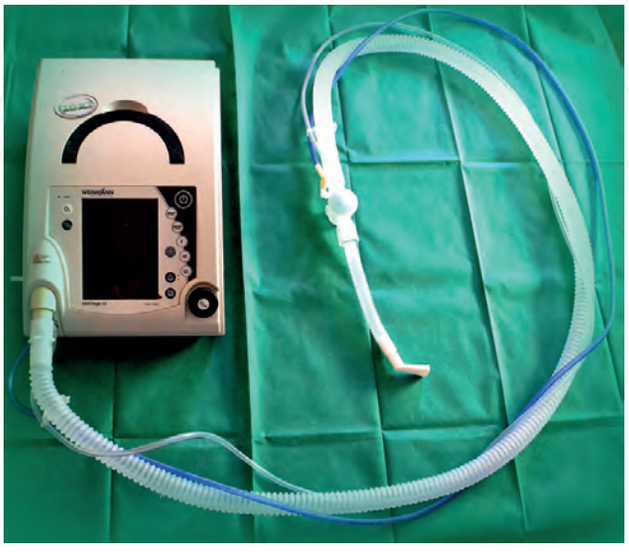

Figure 2. Setup for mouthpiece ventilation.

from the patient, increased nursing time and longer periods of training. We generally instruct patients to "sip" from the mouthpiece, in a manner similar to drinking a beverage using a straw (**Figure 1**). When this maneuver is applied, the soft palate moves posterocaudally sealing off the nasopharynx and minimizing nasal leaks. Importantly, the "sip" maneuver generates a higher negative pressure than maximum static inspiratory pressure, a fact that makes triggering easier for the frail neuromuscular patients [1].

3.2. Ventilator settings

The ventilator is usually set to the volume assisted-controlled mode with a Vt between 0.7 and 1.5 L, while PEEP (or EPAP) and backup rate are set to zero or to the lowest manufacturer-defined value. Recommendations on how to choose Vt and inspiratory time (Ti) are generally scarce [3]. If the patient is breathing comfortably while using MV, we begin with a similar Vt, albeit increased by 0.1–0.3 L to account for leaks and we commonly use a Ti at least as high as 1 s. Then we gradually increase Vt and/or Ti over several hours or days as much as tolerated. Many patients might have been using bilevel MV for many years before being introduced to volume-targeted MPV. While in bilevel ventilation, peak inspiratory flow is determined by the preset pressure, respiratory resistance and patient effort [42] in traditional volume-targeted ventilation inspiratory flow is ventilator-defined and is commonly delivered using a square waveform shape. Nevertheless, if the patient becomes severely breathless when switched to volume-targeted MPV, the use of a decelerating flow shape which delivers higher peak inspiratory flows at the start of the breath might be considered [43] . Generally, the patient should be able to define his own ventilatory pattern by determining the number of breaths and the quantity of leak [8]. Some experts would choose to use a pressure, rather than a flow-regulated, inspiratory trigger to avoid autotriggering [44]. However, despite the fact that in many new generation home ventilators only flow triggering is available, autotriggering with MPV seems to be less common than initially thought [37, 45]. Inspiratory trigger should be sensitive enough to reduce the work of breathing. However, since MPV users commonly fail to trigger the ventilator [45], a number of backup breaths could be set to ensure adequate ventilation and avert fatigue. On the other hand, machine-triggered breaths during patient disconnection from the mouthpiece might be a source of discomfort as a result of high flow on the user's face [45]. Nevertheless, in some newer generation ventilators, triggering can be simply effected by creating a small negative pressure at the mouthpiece ("kiss-trigger") [3, 37]. It must be noted that standard turbine ventilators are not designed to perform under conditions of rapidly changing load. A bench study which evaluated five different modern home ventilators observed significant swings in Vt when conditions of disconnection and reconnection were experimentally reproduced [46].

3.3. Alarms

One of the major problems in open-circuit systems is the prevention of "low pressure" and "apnea" alarm activation. As a general rule, these alarms should be switched off when possible or set to the lowest sensitive value allowed by the manufacturer. Several new generation home ventilators are more versatile in alarm customization with some even incorporating specifically designed software for MPV [37, 45]. Nevertheless, the use of high resistance mouthpieces together with smart combinations of Vt and Ti may create a sufficient back pressure which will

http://dx.doi.org/10.5772/intechopen.73243

prevent "low pressure" alarm activation, when the last cannot be switched off [37, 44]; practical recommendations for alarm customization for several home life-support ventilators have become recently available [45]. When 'apnea' alarming cannot be deactivated, a minimum of backup breaths should be set corresponding to the maximum allowed apnea time [44]. It should be noted, however, that at least in some types of ventilators, backup rate manipulation might also influence Ti, making alarm customization even more complicated [45].

3.4. Mouthpieces

There are a few types of mouthpieces available in the market nowadays, including angled 15 and 22 mm mouthpieces, straw-like as well as lip-sealing interfaces or orthodontic bite plates (**Figure 3**). The performance of these interfaces in the delivery of MPV has been assessed in a limited number of studies. Khirani et al. [37] compared three different angled mouthpiece configurations, a large mouthpiece (22 mm) and a small mouthpiece (15 mm) with and without a filter in a bench study which validated six different types of life-support home ventilators. The resistance was higher with the 15 mm mouthpiece with a filter, and this configuration was also

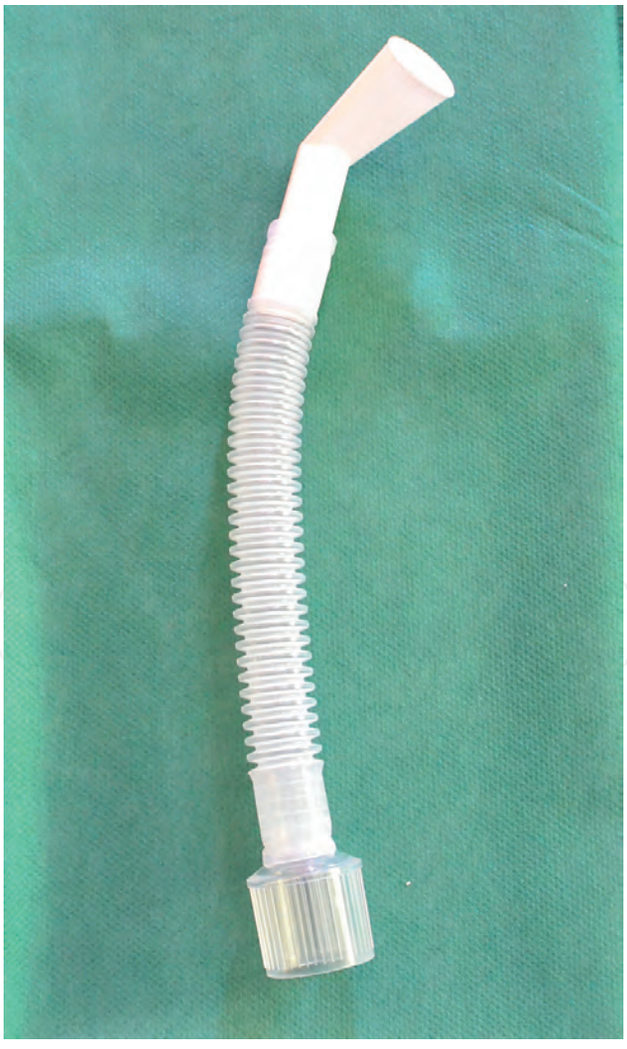

Figure 3. A 15 mm mouthpiece.

associated with a lower incidence of "low pressure" alarm activation. In another bench study, Ogna et al. [47] used four different home ventilators to compare the mechanical properties of various mouthpieces including a newly designed one. With respect to the most commonly used interfaces, respiratory resistance was lower with the 15 mm rigid-angled mouthpiece and higher with the straw mouthpiece. In volume-targeted modes with a Vt set to 1 L, both interfaces performed equally well across the different ventilators in delivering a volume close to the predetermined, while in pressure-targeted modes the effective pressure with the straw mouthpiece was slighter lower as a result of the increased resistance. The clinical implications of these findings remain unclear. For the time being, the choice of the interface should be tailored to the individual needs of each patient. An angled 15 mm mouthpiece seems to be a rational choice because its configuration increases resistance to the airflow preventing the activation of the "low pressure" alarm and in addition it is easier for the patient to grab [1]. If "low pressure" alarming persists, the addition of a filter to the circuit might be a simple and practical solution to the problem [37]. In addition, MPV can also be delivered during sleep with the use of specifically designed orthodontic bite plates or lip-sealing retention systems with attached Velcro straps to avoid disconnection. The use of these interfaces might cause desaturation, fragmented sleep and repeated arousals in a minority of the patients due to nasal leakage. Nasal pledges or clips can be applied to patients with significant nasal leaks [31].

3.5. Speaking and deglutition

Speaking is commonly problematic in patients with advanced respiratory disease as it requires higher than tidal inspiratory volumes and may slow the breathing rate causing breathlessness and fatigue [48]. If a patient on MPV needs to speak, he must take a large breath from the mouthpiece and then speak while expiration is driven by the expiratory muscles and the respiratory system recoil pressure. Nevertheless, speaking with the use of the mouthpiece might be associated with longer pauses (in order to breath in) and difficulties in choosing the right strategy for mouthpiece positioning and use [48].

Breathing and swallowing are normally competitive procedures and their coordination is disrupted in respiratory disease with respiration taking precedence over swallowing. Swallowing in neuromuscular patients is characterized by piecemeal deglutition, increased time to swallow a bolus and an increased number of swallows during inspiration. The institution of positive pressure ventilation stabilizes breathing and improves swallowing performance [49]. The practice of MPV should theoretically contribute to the restoration of swallowing and breathing coordination as users have to alternate between taking deep breaths from the mouthpiece and swallowing. In addition, MPV should also maintain the supraglottic pressure required for effective swallowing, while the high inspired volumes improve cough efficacy providing protection against aspiration [48]. Nevertheless, as disease progresses and ventilator-free time is reduced, less time is available for swallowing, while the presence of food in the mouth and in the pharynx does not allow patients to breath in safely. To deal with this problem, some patients use the ventilator to perform air-stacking in order to increase lung volume and afford longer periods of apnea without breathlessness [9]. Although weight loss and feeding problems in MPV users have been reported [9], it is not clear whether these should be attributed to the interface *per se* or to disease progression and increasing breathlessness.

It should be noted that a disconnection from the mouthpiece for eating and speaking might compromise effective gas exchange. In a small study including eight MPV users who were monitored with polygraghy during daily activities, most of the patients could speak and eat without ventilator assistance; however, prolonged disconnections (>3 min) (e.g. during meals) were associated with significant drops in SpO_2 and increases in transcutaneous PCO_2 [50].

3.6. Complications

A few complications associated with MPV have been so far reported, of which mouthpiece loss is the most important [9]. This complication can be avoided if the mouthpiece's position is secured using specifically designed support arms or customary-made straps. Fixation of the mouthpiece on the shoulders allows the interface to follow the patient's movements [8]. In addition, MPV users could be taught the technique of GPB to maintain ventilator independency in case of accidental mouthpiece loss [6, 31]. Other complications include salivation, aerophagia, abdominal distention and orthodontic problems [1, 2, 6, 51]. There are no available data on the management of excessive salivation in mouthpiece users. For more severe cases the administration of an anticholinergic agent such as amitriptyline might be considered [9, 52]. Aerophagia and abdominal distention are common complications of noninvasive ventilatory support and have been associated with respiratory distress and ventilator dependence [51]. For patients with gastrostomies, unclamping the gastric tube to "burp out" the air is a quick method to effect symptom relief. Sometimes a nasogastric or a rectal rube (for patients with colonic distention) might also be helpful [51]. For patients with persistent symptoms switching to pressure-targeted ventilation could be an option, although this mode is not suitable for the application of lung volume recruitment and air-stacking maneuvers. If the patient is maintained on a volume-targeted mode, setting a lower pressure limit to effect secondary pressure cycling is an alternative option. Vomiting and aspiration as a result of gastric distention as well as pneumothorax have been so far theoretical concerns, but they represent potentially life-threatening events [4, 53]. Orthodontic complications are not uncommon in long-term users; however, they pose mostly an esthetic rather than a functional concern and specifically designed orthodontic interfaces have become available in the market [6, 31, 53]. Patients on MPV and full-time ventilator dependence can safely undergo dental procedures using nasal interfaces as long as oxygen saturation is monitored and oxygen or sedatives are avoided [54].

4. Conclusion

MPV is a "re-discovered" method of noninvasive ventilation that can be used to provide full-time ventilatory support, recruit lung volume, improve cough efficacy, defer tracheostomy and possibly improve survival and quality of life in neuromuscular patients. MPV might also be beneficial for patients with other chronic respiratory diseases or in acute COPD hypercapnic exacerbation. The successful application of MPV requires careful selection of patient, interface, ventilator and alarm settings, increased nursing time and comprehensive patient training.

Conflict of interest

None for all authors.

Funding

This work was supported by the Hellenic Society of Respiratory and Occupational Lung Diseases

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