Noninvasive Ventilation Success and Failure Risk Factors: The Role of Upper Airways

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Abbreviations

ALS	Amyotrophic lateral sclerosis
ARF	Acute respiratory failure
cmH_2O	Centimeters of water
COPD	Chronic obstructive pulmonary disease
EPAP	Expiratory positive airway pressure
FiO_2	Fraction of inspired oxygen
HMEs	Heat-moisture exchangers
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
IPAP	Inspiratory positive airway pressures
NIV	Noninvasive ventilation
PSRs	Pulmonary stretch receptors
PVA	Patient-ventilator asynchrony
RARs	Rapidly adapting receptors
UA	Upper airways

Introduction

Noninvasive ventilation (NIV) refers to the provision of ventilatory support through the patient's upper airways (UA) using a mask or similar device. This technique is distinguished from those which bypass the upper airways with a tracheal tube, laryngeal mask, or tracheostomy and are therefore considered invasive.

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The use of NIV to treat respiratory failure has spread widely throughout the world with a wide spectrum of pathologies treated and settings of application [1–3].

Over the past 20 years, several studies were designed to assess the outcome of NIV and several factors have been identified that increase its success rate.

Similarly, NIV failure, defined as need for intubation or death, relies on numerous factors. However, the pathophysiology of NIV failure is incompletely understood.

An important difference in the application of NIV versus invasive ventilation is, evidently, the involvement of the upper airways. During invasive ventilation the endotracheal tube bypasses the upper airways, and the cuff of the endotracheal tube provides an airtight seal in the trachea; in contrast, during NIV the upper airways may play a role in the efficiency of delivered ventilation [4].

Noninvasive Ventilation Failure

Over the past 20 years, several studies have been designed to assess the outcome of NIV. Failure of NIV is usually defined as (a) need for intubation because of lack of improvement in arterial blood gas tensions and clinical parameters after 1–3 h of ventilation; (b) clinical deterioration and subsequent intubation during hospital stay, and (c) death [5].

The failure rate of NIV varies from 5 to 60% of the treated cases, depending on numerous factors, including the type and severity of acute respiratory failure (ARF), the timing of NIV application, inappropriate ventilation pressures, the patient's clinical condition (i.e., the coexistence of other organ failures besides respiratory failure), the expertise of the team, and the intensity of care provided by the environment [6].

Based on data from randomized controlled trials, NIV failure occurs in three identified time points: (1) immediate failure (within minutes to <1 h), due to weak cough reflex, excessive secretions, intolerance, agitation or hypercapnic encephalopathy syndrome, and patient-ventilator asynchrony; (2) early failure (from 1 to 48 h), due to poor arterial blood gas and the inability to promptly correct them, increased severity of illness, and the persistence of a high respiratory rate with respiratory muscles distress; and (3) late failure (after 48 h), which can occur after an initial favorable response to NIV and may be related to sleep disturbances and severe comorbidities [5].

Immediate Noninvasive Ventilation Failure

Patients with a depressed cough reflex are unable to spontaneously clear their airways, thus creating an excessive burden of respiratory secretions which is likely to cause NIV failure [7].

In such a clinical scenario, adequate secretion management with manual or mechanical techniques may be advisable before NIV is declared failed or

contraindicated: particularly, the suction of secretions with fiber-optic bronchoscopy performed by an experienced team may increase the chance of NIV success [8, 9].

Patients undergoing NIV often present with a heterogeneous spectrum of neurological alterations (from psychomotor agitation and confusion to soporous status, delirium, and coma) which may potentially lead to NIV intolerance.

Paradoxically, if the sensorium is severely depressed, NIV is more likely tolerated, but as patient awakens, a status of agitation and/or delirium frequently occurs, especially in elderly patients, and induces patient to refuse remaining on ventilation [10].

Especially in the first few minutes of adaptation to this "new mode" of breathing, patient tolerance has been shown to be critical for NIV feasibility and success, while the presence of psychomotor agitation induces the lack of necessary cooperation in patients who do not tolerate the mask and the pressurized air pushed by the ventilator. In these conditions, despite the assistance provided also by an experienced nurse team, severe patient-ventilator asynchrony, major air leaks, and patient's attempts in removing the interface may make impossible for the physician to provide an adequate NIV [11].

An integrated strategy based on explaining the technique, asking the patient's preference for the interface, and initiation at low pressures followed by stepwise increases may be helpful to overcome agitation.

However, the use of judicious sedation may be beneficial in some patients for symptom relief and improved patient tolerance and compliance. Physicians should aim to achieve an ideal sedation level that keeps the patient awake or easily arousable, and comfortable. Sedation must be performed by a highly experienced team providing a close monitoring and prompt availability of intubation since an unduly delay may increase the risk of serious systemic complications and, eventually, of death [12].

Patient-ventilator asynchrony (PVA) can be defined as a lack of coordination between the patient and the ventilator [13].

The PVA prevalence is variable since it depends on numerous factors, including timing and duration of observation, detection technique, patient population (e.g., severity of illness, underlying diagnosis), type of asynchrony, ventilation mode and settings (e.g., trigger, flow, and cycle criteria), and confounding factors (e.g., state of wakefulness, sedation) [14].

Several factors affect the occurrence of PVA and they can be related to patient characteristics (e.g., respiratory mechanics, effort) and to the ventilator (e.g., trigger asynchrony, flow asynchrony, cycle asynchrony, mode asynchrony). Moreover, the interface used can be a potential cause of PVA through two mechanisms: (1) it promotes air leaks, and (2) the interface can contribute to mechanical dead space and rebreathing, thus increasing respiratory drive and dyspnea [15].

Asynchrony can easily be detected by an evaluation of symptoms and a physical examination of the patient, particularly taking into account number of spontaneous breaths vs. ventilator-delivered breaths and accessory muscle use. Also, the close observation of the flow, volume, and pressure waveforms on the ventilator can be used to assess for patient-ventilator interactions [16].

The systematic research for asynchronies may be useful in driving the operators' choices and allows an "optimized ventilation," driven by the analysis of the waveforms generated by ventilators, which may have a positive effect on physiological and patient-centered outcomes [17].

Patient-ventilator asynchrony is a potential cause of NIV failure since it causes a series of adverse clinical effects and is associated with unwanted outcomes, such as discomfort, dyspnea, increased/wasted work of breathing, worsening of pulmonary gas exchanges, increased respiratory effort, diaphragmatic injury, decreased quantity and quality of sleep, increased need for sedation, prolonged mechanical ventilation, and longer ICU and hospital stay [14].

Late Noninvasive Ventilation Failure

Late failure can occur after an initial favorable response to NIV and may be related to severe comorbidities and sleep disturbances including an abnormal electroencephalographic pattern, disruption of the circadian sleep cycle, and decreased rapid eye movement sleep [18].

The occurrence of sleep disturbances during noninvasive ventilation is related to different factors. First, during sleep physiological parameters (muscle tone, heart rate, breathing, blood pressure, and metabolic rate) change and may interfere with the efficacy of ventilation [12].

Vice versa, the influence of mechanical ventilation on the quality of sleep is not entirely unambiguous. Mechanical ventilation can cause sleep disruptions through various mechanisms like the occurrence of PVA which can increase respiratory effort, the sedation's effect on sleep architecture, and noise-related sleep fragmentation. However, even if there is a consensus in the literature that mechanical ventilation is probably a factor causing sleep disruptions, it must be considered that sleep disturbances are also related to the severity of disease and noninvasive ventilation can reduce patient effort, improve gas exchange, and thus indirectly improve their quality of sleep [19].

Noninvasive Ventilation Intolerance

Although NIV is generally perceived as more comfortable for patients than IMV, the rate of NIV failure due to patients' intolerance is reported to be variable between 9 and 25% [11, 20–23].

As described above, neurological alterations and the presence of PVA could be cause of NIV intolerance and consequent failure. Moreover, as the duration of NIV increases, patients may develop ventilation-related complications which may lead them to refuse ongoing NIV prompting its discontinuation and subsequent requirement for endotracheal intubation. Ventilation-related complications can be divided into major NIV complications (pneumonia, barotrauma, hemodynamic effects) and minor NIV complications which include interface-related complications (arm

edema and deep venous thrombosis, carbon dioxide rebreathing, claustrophobia, discomfort, facial skin lesions, noise, and patient-ventilator asynchrony) and air pressure- and flow-related complications (air leaks, nasal or oral dryness and nasal congestion, lower airway dryness) [24].

In expert hands, potential remedies can be considered to avoid some minor complications and to reduce the risk of NIV failure, need for IMV, or the chance of death. Discomfort is mainly related to the interface since different models of NIV masks can produce different levels of tolerance. Moreover, all attachment systems were considered variably uncomfortable against the skin, and tolerance may decrease by tightening the straps in an attempt to reduce air leaks. This condition may require a change to a different strap system or mask in order to reduce the discomfort. Air leakage is virtually universal during NIV and depends on sealing features of the interface. Large air leaks decrease the FiO_2 and arterial oxygen saturation and increase ventilation asynchronies and rebreathing of exhaled gas, all of which increase chances of NIV failure. Hence, air leaks must be monitored closely and taken care of promptly. During NIV, nasal or oral dryness is usually indicative of air leaking through the mouth with consequent loss of the nasal mucosa capacity to heat and to humidify inspired air. Nasal mucosa progressively dries and releases inflammation mediators that increase nasal congestion and resistance, thus reducing tidal volume and patient comfort. Strategies to decrease the airway dryness and congestion during NIV should be carefully considered from the beginning of NIV.

During NIV, cool and dry gases alter the tracheobronchial mucosa inducing airway dryness. By drying secretions and desquamating mucosal epithelium, NIV may cause mucous plugging and atelectasis. To avoid this problem, humidification devices, heated humidifiers and HMEs, are used for both short-term and long-term humidification during NIV [24, 25].

It shall be considered that, in order to provide patient comfort as to optimize the chances of success during NIV, judicious use of sedation during NIV can be a valuable option for some patients at risk of intubation due to mask intolerance, because of pain, discomfort, claustrophobia, or agitation. This reasoning is helpful within the first few hours of NIV when the patient needs to adapt and later when prolonged ventilation is required [26].

Sedation can facilitate ventilation, calms anxiety, promotes sleep, and modulates the autonomic system responses to stress, such as tachycardia and hypertension, with a final improvement of patient's adaptation to NIV [26, 27].

Previous studies have addressed the efficacy of sedation during NIV, using dexmedetomidine [28–30], midazolam [30], propofol [31], and remifentanil [32].

The intrinsic characteristics and clinical effects of the various pharmacological categories must be considered when choosing the drug, especially regarding the effects exerted on patient's own respiratory drive.

Benzodiazepines should preferentially be avoided in the elderly due to the risk of a paradoxical state of delirium [33].

In addition, the benzodiazepines' pharmacokinetics profile is prone to accumulation in the case of obese patients or in those subjects with renal injury or low albumin levels [34].

Propofol has a rapid pharmacokinetic profile, but sedation regimen dose must be decided carefully since it has shown to adversely affect the breathing pattern, the respiratory drive, and gas exchange, proportionally to the rate of its infusion [35].

Dexmedetomidine, a selective α2 agonist with intrinsic properties of sedative and analgesic effects, may be useful thanks to its limited effect on the respiratory pattern. Its main adverse effects are bradycardia and hypotension, and in literature there is evidence of it being superior to midazolam in terms of pharmacokinetics manageability [27].

Remifentanil is a short-acting opioid that has also proven to be safe and effective to achieve optimal sedation in case of intolerance to NIV [32].

Regardless of the drug adopted, evaluation for agitation before starting therapy and subsequent sedation assessments are of pivotal importance during NIV. The use of subjective scales (e.g., Richmond Agitation-Sedation Scale) at regular time intervals allows to provide the desired target of sedation [12].

The Role of Upper Airway in the Failure of NIV

Noninvasive Ventilation and Upper Airway Physiology

Currently, the relationships between NIV efficiency and upper airways (UA) are not completely understood. On one side, ventilator settings during NIV affect physical conditions such as pressure, flow, and temperature which contribute to determine the patency of the UA. On the other side, this effect implies that deviant behavior of the UA may play a role in the failure of NIV.

Therefore, to achieve optimal management of ventilated patients, it is of utmost importance to understand the normal anatomy and physiology of UA and the changes induced by pressure, flow, and temperature.

The UA comprise the nose, oral cavity, pharynx, and larynx. The nose and oral cavity are mainly static in their conducting function, whereas the pharynx and larynx predominantly are muscular structures and thus may alter the patency of the UA [4].

Receptors in the upper and lower airways modulate activity of the UA muscles. The most prominent receptors are the bronchopulmonary C-fiber receptors, rapidly adapting receptors (RARs), and slowly adapting pulmonary stretch receptors (PSRs).

C-fiber receptors are excited both by large mechanical deformations and chemical stimuli. Their activation evokes inhibitory effects (apnea or bradypnea; hypotension and bradycardia) and can result in closing of the UA by glottic narrowing by activation of laryngeal muscles.

RARs respond in reaction to mechanical and chemical stimuli and produce mainly excitatory effects such as tachypnea. When the laryngeal mucosa is stimulated, RAR reflexes elicit laryngoconstriction and bronchoconstriction, which may be part of the glottal closure seen during cough.

PSRs do not affect patency of the UA but modulate the respiratory cycle: they terminate inspiration and extend expiration. PSRs are activated by stretching the airway wall and fire throughout the respiratory cycle (tonic activity) or in response to lung inflation (phasic activity).

Respiration and in particular patency of the UA depend on a complex, but incompletely understood, interplay between several inhibitory and excitatory pathways [36–40].

NIV may affect some physical conditions such as pressure, flow, and temperature and therefore affects patency of the UA [41].

Previous studies have tested the impact of NIV-derived positive pressure with a nasal interface in the UA of healthy subjects. The protocol included the delivery of three different levels of inspiratory positive airway pressures (IPAP: 10, 15, and 20 cmH_2O), in the presence of 5 cmH_2O of expiratory positive airway pressure (EPAP), using controlled and spontaneous modes. The authors concluded that incremental IPAP does not always lead to improvements in lung ventilation, so they suggest that the use of a two-level positive-pressure ventilator in controlled mode is less predictable and less stable compared to volumetric ventilators. This observation may be explained by the significant narrowing of the glottis caused by adduction of the vocal cords for all patients undergoing positive pressure [42, 43].

Another study evaluating glottis patency in the acute exacerbation of COPD with NIV found that high pressures using different ventilatory modes did not cause UA obstruction, but increased respiratory volume, perhaps because the protective and normal reflex response at high pressures does not occur in COPD patients. The main reason invoked is the alteration of the C-fiber receptors' response to chemical stimulus with narrowing of the glottis, due to chronic inhalation of carbon dioxide. Therefore, this may be the reason for the high-intensity ventilation effectiveness in COPD patients [44].

In addition to the positive pressure delivered by the ventilator, the interface used can also induce changes in the patency of the UA. Particularly, caution needs to be used when applying oronasal masks because this can cause posterior displacement of the tongue inducing partial obstruction of the oropharyngeal airway. On the contrary nasal masks are thought to produce a differential pressure gradient between the nasopharynx and oropharynx, thus causing a pneumatic splinting, and this phenomenon pushes the soft palate and the tongue anteriorly away from the posterior pharyngeal wall [45, 46].

Another important aspect to consider is that positive-pressure ventilation can induce hyperventilation and cyclic hypocapnia. This effect has been shown to promote intermittent obstruction of the UA through active glottis closures in normal subjects when either awake or asleep [47, 48].

Asynchronies are generally related to the interaction between the activity of the inspiratory muscles and the ventilator response; however, as far as explained so far, it is evident that during NIV it is also important that the ventilator acts in synchrony with the UA muscles [4, 49].

Noninvasive Ventilation and Upper Airway Pathology

The efficacy of NIV delivery can be also greatly compromised by alterations in the UA patency or spasticity.

In patients with obstructive sleep apnea or obesity hypoventilation syndrome, soft tissue collapse of UA can significantly decrease their diameter and increase airflow resistance, particularly in the supine position, thus provoking oropharyngeal obstructive events [44, 50].

Neuromuscular patients with upper motor neuron involvement and impairment of bulbar function, particularly amyotrophic lateral sclerosis (ALS), are more likely to fail NIV due to UA spasticity [51, 52].

The alteration common to neuromuscular disease patients is respiratory muscle weakness, which varies highly according to the underlying disease. Weakness may affect three main muscle groups: inspiratory muscles (diaphragm, parasternal, scalene, and accessory muscles), expiratory muscles (external intercostal and abdominal muscles), and muscles of the upper airways (palatine, pharyngeal, and genioglossal muscles) [53].

Patients with bulbar muscle weakness present epiglottic flapping which may be an explanation for the failure of NIV therapy per se. Moreover, the way NIV is applied can aggravate this condition since the use of high-pressure values could worsen the epiglottic dysfunction and result in the occlusion of the laryngeal space [54, 55].

Predictors of Noninvasive Ventilation Success

Several factors have been identified that increase the success rate of NIV. These factors include careful selection of patients, properly timed intervention, a comfortable and well-fitting interface, coaching and encouragement of patients, careful monitoring, and a skilled and motivated nursing team.

The prediction of NIV success inevitably depends even on the ability to predict its failure.

From the beginning of NIV usage, several tries have been made to predict NIV success, as early intubation may reduce hospital mortality, in patients experiencing NIV failure. Different scores, more or less easy to apply, have been tried.

In 2017, a composite score, the HACOR score, which includes heart rate, acidosis, state of consciousness, oxygenation, and respiratory rate, recorded after the first hour of treatment, has shown to predict NIV failure with high sensitivity and high specificity, in patients suffering from hypoxemic respiratory failure. The study results indicate that the HACOR score can be used in patients with different disease severity; then, though the NIV failure rate is different between patients who have received different diagnoses and also for different ages, the HACOR score achieves a good predictive power independently from them. The HACOR score shows moreover lower values in patients who successfully undergo NIV, but it does not improve after 1 h in patients with NIV failure. Therefore, it can be also used to assess the efficacy of NIV. A HACOR score of 5 as cutoff value has a good predictive power

for NIV failure. At 1 h after NIV initiation, 87.1% of patients with a HACOR score of >5 required intubation, and 81.6% of patients with HACOR score ≤ 5 did not require intubation. These values indicate that the risk of NIV failure is high in patients with a HACOR score of >5. Further, the high-risk patients who receive early intubation meet lower hospital mortality than those who receive a late intubation. Thus, the HACOR score can be used to establish the necessity for intubation too and so avoid late intubations [56].

In the year 2020, a small monocenter study, inspiring to HACOR score, enrolls 329 patients suffering from respiratory failure of various etiology who need to be treated with assisted mechanical ventilation, and try to pack a score composed by five items, collected at the beginning of hospitalization in an emergency department and before starting the NIV, to predict its failure. These, in order of weight on the score, were the presence of lactacidemia greater than 8 mmol/L, a pH below 7.30, a systolic blood pressure below 90 mmHg, a heart rate greater than 110 beats per minute, and a peripheral oxygen saturation of less than 90%. Three risk classes have been then identified, low (score 0–1), moderate (score 2–4), and high (score > 5), which have shown a sensitivity to predicting noninvasive mechanical ventilation failure of 72.27% [57].

In another study with a larger cohort of nonsurgical patients, from 127 different US centers, who underwent NIV as the first ventilation methodology for the treatment of respiratory failure due to various causes, not later than 2 days after hospitalization, 10 items were evaluated, which included the number of organ failure, principal diagnosis, acute physiological parameters, and chronic disease comorbidities. This score applies regardless of the cause of respiratory failure and stratifies patients into three risk classes, high, intermediate, and low; it does not require the evaluation of laboratory parameters, so it can be applied to all patients, even in the earliest stages of hospitalization, who are immediately subjected to NIV. Among its weaknesses, however, there is the lack of control of the same entry parameters after 1 or 2 h, a time universally considered to evaluate the effectiveness of NIV. The use of this score is however to be considered innovative, because in other works have been prepared scores that tried to predict the failure of the NIV, but in specific pathology settings [58].

Conclusions

Noninvasive ventilation failure, defined as need for intubation or death, relies on numerous factors like weak cough reflex, neurological alterations, patient-ventilator asynchrony, sleep disturbances, and severe comorbidities. A poor tolerance and compliance can also be responsible for NIV failure.

An important difference in the application of NIV versus invasive ventilation is, evidently, the involvement of the upper airway which might play a role in the efficiency of delivered ventilation.

Currently, the relationship between noninvasive ventilation outcome and upper airway is not completely understood.

It is known that respiration and in particular patency of the UA depend on a complex, but incompletely understood, interplay between several inhibitory and excitatory pathways.

On one side, ventilator settings during NIV affect physical conditions such as pressure, flow, and temperature which contribute to determine the patency of the upper airway.

On the other side, this effect implies that deviant behavior of the UA may play a role in the failure of NIV.

Careful selection of patients, properly timed intervention, a comfortable and well-fitting interface, coaching and encouragement of patients, careful monitoring, and a skilled and motivated nursing team are factors that can increase the success rate of NIV.

Several tries have been made to predict NIV success, as early intubation may reduce hospital mortality, in patients experiencing NIV failure. Different scores, more or less easy to apply, have been tried, and their use, regardless of which one is chosen, must become an integral part of the daily evaluation of the patient in NIV, even in non-ICU settings, as the prediction of NIV success inevitably depends even on the ability to predict its failure.

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