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APPLICABILITY OF NON-INVASIVE VENTILATION IN COVID-19 PATIENTS

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Introduction. Non-invasive ventilation (NIV) has revolutionized the management of respiratory failure, providing an alternative to invasive mechanical ventilation (IMV) with reduced risks and complications. Amid the COVID-19 pandemic, the importance of NIV has been accentuated, necessitating a comprehensive understanding of its evolution, types, and clinical applications. This review aims to elucidate the key aspects of NIV, including its modes, indications, comparative effectiveness, and factors influencing success and failure. By synthesizing existing literature, this study seeks to provide valuable insights into the optimal use of NIV in various respiratory conditions, particularly in the context of COVID-19.

Material and methods. Narrative literature review. Bibliographic search in the PubMed, NCBI and Google Academic databases, using the keywords: "NIV", "NIV modes", "CPAP", "respiratory conditions", "ARDS", "HFNC", "success predictors", "failure predictors", "early intervention", "COVID-19", "clinical application", which were combined with each other. The final bibliography included 80 references.

Results. The review highlights the evolution of NIV technology and its various modes, including Continuous Positive Airway Pressure (CPAP), Bilevel Positive Airway Pressure (BiPAP), Proportional Assist Ventilation (PAV), and Average Volume Assured Pressure Support (AVAPS). Indications for NIV encompass a wide range of respiratory conditions, with comparative effectiveness studies indicating its efficacy in conditions such as Chronic Obstructive Pulmonary Disease (COPD) exacerbations and Acute Respiratory Distress Syndrome (ARDS). Success and failure predictors for NIV underscore the importance of early intervention, appropriate patient selection, and meticulous monitoring to optimize outcomes and mitigate complications.

Conclusion. NIV represents a vital therapeutic modality for managing respiratory distress, offering advantages over IMV in select cases. The evolution of NIV technology has led to the development of various modes, catering to diverse clinical scenarios. However, success with NIV hinges on timely intervention, appropriate patient selection, and vigilant monitoring to prevent complications. In the context of the COVID-19 pandemic, NIV assumes heightened significance, necessitating a nuanced approach to its clinical application.

Key words: non-invasive ventilation, CPAP therapy, high flow nasal cannula, ARDS, COVID-19.

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ЗАСТОСУВАННЯ НЕІНВАЗИВНОЇ ВЕНТИЛЯЦІЇ У ПАЦІЄНТІВ ІЗ COVID-19

Цивиржич І.

Неінвазивна вентиляція (НІВ) революціонізувала лікування дихальної недостатності, пропонуючи альтернативу інвазивній механічній вентиляції (ІМВ) зі зменшенням ризиків і ускладнень. Під час пандемії COVID-19 важливість НІВ набула більшого значення, вимагаючи глибшого розуміння її еволюції, типів та клінічного застосування. Цей огляд має на меті розкрити ключові аспекти НІВ, включаючи її режими, показання, порівняльну ефективність та фактори, що впливають на успіх і невдачу. Узагальнивши наявну літературу, дослідження дає цінні знання щодо оптимального використання НІВ за різних респіраторних станів, особливо в контексті COVID-19. **Матеріали та методи.** Огляд наративної літератури. Бібліографічний пошук у базах даних PubMed, NCBI та Google Академія за ключовими словами: «НІВ», «режими НІВ», «CPAP», «респіраторні стани», «ГРДС», «HFNC», «прогноз успіху», «прогноз невдачі», «раннє втручання», «COVID-19», «клінічне застосування», які були скомбіновані між собою. Фінальна бібліографія включала 80 джерел.

Результати. Огляд висвітлює еволюцію технології НІВ та її різні режими, включаючи постійний позитивний тиск у дихальних шляхах (CPAP), двофазний позитивний тиск у дихальних шляхах (BiPAP), вентиляцію з пропорційною допомогою (PAV) та підтримку тиску з гарантією середнього об'єму (AVAPS). Показання до застосування НІВ охоплюють широкий спектр респіраторних станів, а дослідження порівняльної ефективності демонструють її результативність у разі загострень хронічної обструктивної хвороби легень (ХОЗЛ) та гострого респіраторного дистрес-синдрому (ГРДС). Прогнозування успіху та невдачі при НІВ підкреслює важливість раннього втручання, правильного відбору пацієнтів і ретельного моніторингу для оптимізації результатів і зменшення ускладнень.

Висновок. НІВ є важливим терапевтичним засобом для лікування дихальної недостатності, пропонуючи переваги над ІМВ у вибраних випадках. Еволюція технології НІВ призвела до розвитку різних режимів, що відповідають різноманітним клінічним ситуаціям. Однак успіх НІВ залежить від своєчасного втручання, правильного відбору пацієнтів і пильного моніторингу для запобігання ускладненням. У контексті пандемії COVID-19 НІВ набуває особливого значення, що вимагає більш детального підходу до її клінічного застосування.

Ключові слова: неінвазивна вентиляція, CPAP-терапія, високопоточний назальний канюль, ГРДС, COVID-19.

Introduction. *Noninvasive ventilation (NIV)* is defined as the provision of ventilatory assistance to the lungs without an invasive artificial airway [1].

Noninvasive ventilators consist of various devices, including negative- and positive-pressure units. Until the early 1960s, negative-pressure ventilation in the form of tank ventilators was the most common type of mechanical ventilation used outside the anesthesia suite [1].

NIV is well recognized as an effective strategy to avoid endotracheal intubation with adverse complications (e.g., ventilator-associated pneumonia) in patients with various forms of hypercapnic respiratory failure, immunosuppression, and specific postoperative conditions [2].

During the past few years, the main application of NIV has been in chronic obstructive pulmonary disease (COPD) exacerbations. In addition to being a weaning strategy for COPD patients from invasive mechanical ventilation (IMV), the use of NIV has resulted in a significant reduction in mortality rate, nosocomial pneumonia, and weaning failure [2].

Moreover, it is crucial to note that during the COVID-19 pandemic, NIV emerged as a crucial tool in managing respiratory distress in affected individuals. Its widespread application as a user-friendly device played a vital role in saving lives, particularly in cases where invasive ventilation posed higher risks or was unavailable.

Material and methods. To ensure comprehensive coverage of relevant literature, a systematic search was conducted in PubMed, clinicaltrials.gov, and rcpjournals.org. The search strategy involved employing keywords such as "NIV", "NIV modes", "CPAP", "respiratory conditions", "ARDS", "HFNC", "success predictors", "failure predictors", "early intervention", "COVID-19", and "clinical application". These keywords were combined in various permutations to maximize search efficiency.

Inclusion criteria comprised full-text articles in English, published in recognized journals before June 2024. Priority was given to critical literature, meta-analysis, randomized studies, and those with substantial patient cohorts. Ultimately, the final bibliography included 80 references, providing a robust foundation for the analysis and discussion in the review.

Results and discussion

Types of non-invasive ventilation and indications in various pulmonary and respiratory pathologies

The most common NIV modes are CPAP and BiPAP (or BPAP). These modes can provide respiratory support and a fraction of inspired oxygen (FiO_2) equal to 100% in a closed-loop [3].

CPAP provides continuous positive airway pressure to patients with spontaneous breathing. This mode can support breathing at high flow rates of air or a mixture of air and oxygen as one set pressure, typically between 3 and 20 cmH_2O [4]. By improving the ventilation-perfusion mismatch and respiratory compliance, CPAP reduces the degree of hypoxemia through alveolar recruitment.

BiPAP mode is considered when applying CPAP to non-intubated adult patients through different interfaces. It allows clinicians to control ventilation using two different pressures (IPAP and EPAP) to improve ventilation and make breathing easier. High inspiratory pressure offloads the patient's breathing effort, while the lower pressure preserves an acceptable alveolar volume and prevents the collapse of unstable alveoli during expiration. Pressure support (PS) is calculated by the difference between IPAP and EPAP, where the difference should be at least 8 cmH_2O [5].

Compared to CPAP, BiPAP is preferred in patients with respiratory acidosis (PCO_2>40 mmHg and pH<7.35), COPD, obesity, and respiratory muscle fatigue. The initial settings in BiPAP mode are PS of 5 cmH_2O, PEEP of 5–10 cmH_2O), and titrating the FiO_2 to reach SpO_2 ≥94%, RR ≤25 bpm, and a VT of 6 mL/Kg predicted body weight. Moreover, monitoring should be done every 30 minutes during the 60 minutes trial duration [6–8].

Indications

Several causes of acute respiratory failure (ARF) are now considered appropriate for NIV therapy and are listed in Table 1. The European Respiratory Society/American Thoracic Society (ERS/ATS) Task Force for NIV offered recommendations and suggestions

on clinical applications of NIV in 2017 [10]. At the outset, it is imperative to emphasize that the interface used to apply NIV may be crucial to its efficacy in any individual patient.

Table 1

NIV indications [11]

Indications for Use of Noninvasive Ventilation in the Acute Care Setting
Airway Obstruction
COPD (A) Asthma (B) Cystic fibrosis (C) Obstructive sleep apnea or obesity hypoventilation (B) Upper airway obstruction (C) Facilitation of weaning in COPD (A) Extubation failure in COPD (B)
Hypoxemic Respiratory Failure
ARDS (C) Pneumonia (C) Trauma or burns (B) Acute pulmonary edema (use of CPAP) (A) Immunocompromised patients (A) Restrictive thoracic disorders (C) Postoperative patients (B) Do-not-intubate patients (C) During bronchoscopy (C)
Note: *NIV-Non-invasive ventilation; COPD – Chronic obstructive pulmonary disease; (A) – multiple randomized controlled trials: recommended; (B) – at least one randomized controlled trial: weaker recommendation; (C) –case series or reports: can be attempted, but with close monitoring; ARDS – Acute respiratory distress syndrome; CPAP – continuous positive airway pressure [11].*

The factors influencing the results of non-invasive ventilation

NIV should be viewed as a "crutch" that assists patients through a period of ARF. At the same time, reversible factors are being treated, helping them avoid IMV (invasive mechanical ventilation) and its attendant complications.

To optimize the chance of success, NIV should be used early when patients first develop signs of incipient respiratory failure. In addition, predictors of success help identify patients most likely to benefit (Table 2). The selection process might be viewed as taking advantage of a "window of opportunity": the window opens when the patient first requires ventilatory assistance and closes when the patient becomes too unstable.

Based on the predictors of success and criteria used in prior controlled trials, it is recommended the following three-step selection process: (1) ensure that the patient has an etiology of respiratory failure likely to respond favorably to NIV and (2) identify patients in need of ventilatory assistance by using clinical and blood gas criteria. Patients with mild respiratory distress and only mild gas exchange abnormalities are likely to do well without ventilatory assistance. Good candidates are those with moderate to severe dyspnea, tachypnea, and impending respiratory muscle fatigue, as indicated by the use of accessory muscles of breathing or abdominal paradox. The level of tachypnea used as a criterion depends on the underlying diagnosis. With COPD, candidates for NIV usually have respiratory rates exceeding 24 breaths per minute, but with hypoxemic respiratory failure, respiratory rates are usually higher, in the range of 30–35 breaths per minute.

The third step excludes patients for whom NIV would be unsafe. If respiratory arrest is imminent, the patient should be promptly intubated because the successful initiation of NIV requires some time for adaptation. Patients who are medically unstable with hypotensive shock, uncontrolled upper gastrointestinal bleeding, unstable arrhythmias, or life-threatening ischemia are better managed with IMV. Additionally, NIV should not be used for patients who are uncooperative, are unable to protect their airways or clear secretions adequately, or are intolerant of masks. The use of NIV merits caution after recent upper gastrointestinal or airway surgery [11].

Table 2

NIV indications [11]

Lower acuity of illness (APACHE score)
Ability to cooperate; better neurologic score
Ability to coordinate breathing with ventilator
Less air leakage; intact dentition
Hypercarbia, but not too severe ($PaCO_2$ between 45 and 92 mm Hg)
Acidemia but not too severe (pH between 7.1 and 7.35)
Improvements in gas exchange and heart and respiratory rates within the first 2 hours

Note: *NIV – Noninvasive ventilation; APACHE – Acute Physiology and Chronic Health Evaluation; $PaCO_2$ – Arterial partial pressure of carbon dioxide.*

Failure criteria of non-invasive ventilation and indications for conversion to mechanical ventilation

Whenever NIV is used, however, caution must be taken into account that NIV failure may occur in some patients, which was reportedly associated with adverse outcomes of patients [12].

NIV failure is often defined as the need for invasive mechanical ventilation with endotracheal intubation [13–15]. Despite convenience and ease, failure is not uncommon with NIV.

Clinical literature reported that the incidence of NIV failure varies significantly from 5% to 60%, depending on the causes of ARF and the morbidity, etc. [9; 16]. The incidence of NIV failure was reported approaching about 50% in patients with community-acquired pneumonia and acute respiratory distress syndrome (ARDS) [14; 15]. Results of clinical trials demonstrated that NIV failure was independently associated with some bad clinical outcomes, such as increased morbidity and mortality [9; 14; 15]. Therefore, it is crucial to identify the factors that can predict patients who cannot benefit from NIV as early as possible so that patients can be endotracheally intubated and ventilated with IMV if necessary [14].

The effectiveness of NIV depends on the etiology of respiratory failure; therefore, not all diseases will benefit from NIV in the same way [17]. The prediction of NIV failure is significant in preventing delayed intubation and an increased risk of morbidity and mortality [12]. The risk of NIV failure determines the intensity of monitoring needed [9]. One approach to determine the need for monitoring is to assess the patient's risk of NIV failure [9]. Some of these are simple bedside assessments, such as the ability to cough, respiratory rate, etc. Other methods require analysis to determine arterial blood gases (ABG). Other methods require proven evaluation protocols: Acute Physiology and Chronic Health Evaluation (APACHE) II or Simplified Acute Physiology Score (SAPS) II.

Some novel clinical scoring of the NIV failure among patients with ARF have proven their usefulness.

Liengswangwong et al. [18] demonstrated that NIV failure was associated with heart rate >110 bpm, systolic BP <110 mmHg, SpO2 < 90%, arterial pH < 7.30, and serum lactate. In addition to all these factors that we can evaluate, the team's experience in charge of these patients is not less critical due to the speed at which the changes occur. A patient with multiple risk factors for NIV failure should be placed in a closely monitored setting, such as an ICU or a step-down respiratory unit.

Three critical periods for detecting NIV failure have been defined [9]:

1. Immediate failure (within minutes to <1 h),
2. Early failure (1–48 h),
3. Late failure (after 48 h).

The risk factors of NIV failure based on timing are summarized in Table 3.

Table 3

The risk factors of NIV failure based on timing

Time	Risk factors
Immediate	1. Weak cough reflex and/or excessive secretions
	1. Hypercapnic encephalopathy and coma
	2. Psychomotor agitation
	3. Patient-ventilator asynchrony
Early Hypoxemic ARF	1. Baseline ABG and inability to correct gas exchange (P/F ratio less than 150)
	2. Baseline severity scores (SAPS II>
	3. The presence of ARDS/pneumonia/sepsis/multiorgan failure
	4. Increased respiratory rate (>
	5. Miscellaneous: Delay between admission and NIV use, number of fiber optic bronchoscopes performed, duration of NIV use, increase in radiographic infiltrates within the first 24h, causal diagnosis as *de novo*
Early Hypercapnic ARF	1. Baseline ABG and inability to correct gas exchange (pH<7.25)
	2. Increased severity of disease
	3. Increased respiratory rate (>35 breaths/min)
	4. Mixed indices:
	GCS, APACHE II score, respiratory rate, and pH
	Respiratory rate, random glucose level and APACHE II
	Anemia and WHO-PS
	5. Miscellaneous: Poor nutritional status, increased heart rate, higher baseline C-reactive protein/white blood cell count, lower serum K^+, airway colonization by non-fermenting gram-negative bacilli
Late	1. Sleep disturbance
	2. Functional limitation
	3. Possible initial improvement in pH
	4. Hyperglycemia

Note: *NIV – Non-invasive ventilation; ARF – Acute respiratory failure; ABG - arterial blood gas; SAPS II – Simplified Acute Physiology Score ; ARDS – acute respiratory distress syndrome; APACHE II – Acute Physiology, and Chronic Health Evaluation; GCS – Glasgow coma scale; P/F - ratio of PaO2 to FiO2; WHO-PS – World Health Organization performance status, adapted by Ozyilmaz et al. [9].*

The HACOR score (Heart rate, Acidosis, Consciousness level, Oxygenation, and Respiratory rate) has been proposed as a bedside tool for predicting NIV failure [19].

Predicting NIV failure in patients with ARF is very important to prevent delayed intubation and an increased risk of morbidity and mortality. The factors involved will depend on the characteristics of respiratory failure and their etiology. Adequate follow-up will be necessary at each NIV treatment.

The results of the use of non-invasive ventilation in SARS CoV2 Infection (COVID-19)

Traditionally, in hypoxemic ARF in acute respiratory distress, one of the main concerns is the increased mortality associated with intubation delay. Thus, NIV has been widely questioned as a support method. In a recent international observational study that included 2.813 patients with acute respiratory distress (ARDS), those initially treated with NIV (15%) and severe hypoxemia (PaO_2/FiO_2 < 150 mm Hg) had higher mortality (36.2%) than those ventilated invasively (24.7%) [20]. In contrast, HFOT (high flow oxygen therapy) has emerged as a non-invasive strategy for avoiding intubation and invasive ventilation. Based on these previous experiences in hypoxemic ARF and NIRS (non-invasive respiratory support), as the first phase of the COVID-19 epidemic overflowed, several guidelines from different countries recommended early intubation of critically ill patients with COVID-19 and ARF, also as a means of protecting healthcare workers from cross-infection [21; 22].

One of the main reasons for recommending early intubation in patients with COVID and ARF would be the use of NIRS techniques that delay rather than prevent intubation. This delay, while maintaining spontaneous respiratory pattern with tachypnea and high tidal volume, may lead to the worsening of the so-called patient self-induced lung injury (P-SILI).

P-SILI has been linked to various pathophysiological phenomena: (a) increased effort, both inspiratory and expiratory, can lead to an increase in transpulmonary pressure (stress) and strain (increase in volume concerning its baseline value). The intensity of the inspiratory effort has been correlated as a surrogate of the neural drive associated with relapse in patients with COVID-19 [23]; (b) inhomogeneity in gas distribution, with areas with different time constants and intrapulmonary gas redistribution between them (pendelluft phenomenon); and (c) changes in pulmonary perfusion [24].

On the other hand, the defenders of NIRS techniques (high nasal flow and positive pressure, either CPAP, or bilevel positive airway pressure (BiPAP)) argue that they can avoid unnecessary endotracheal intubations and that the liberal use of invasive ventilation and its associated consequences (muscular atrophy and ventilation-associated infections) may lead to increased mortality.

The experience in the use of NIRS in COVID-19 comes mainly from retrospective observational studies, with extremely variable failure rates, ranging between 20 and 60%, and biased populations (i.e., age-selected, Intensive care Unit (ICU) or ward environments). A meta-analysis about non-invasive ventilatory support (HFOT was excluded) as a therapeutic option outside the Intensive Care Units included 3,377 patients. Overall mortality was 38%, although it is possible to distinguish the group of patients without therapeutic limitation (19%) from that of patients with orders of no intubation (72%). Mortality in patients with NIV failure who were ultimately intubated was 45% [25].

No prospective studies focused on the outcome of patients with direct intubation vs. a previous trial with non-invasive support. A recent meta-analysis that included

8.944 patients showed no benefit of early intubation compared to intubation delayed more than 24 h after admission to the ICU, neither in mortality nor in days of mechanical ventilation. Mortality was also not significant in patients who received treatment with high nasal flow or non-invasive ventilation compared to those who did not receive such treatment before intubation [26].

Therefore, the available data suggest that the use of NIRS does not seem to lead to a worse prognosis compared with direct orotracheal intubation.

Non-invasive support modalities. Escalating algorithms and the role of combined therapies

Since the beginning of the pandemic, heterogeneous recommendations about the most preferred modality (HFOT, CPAP, NIV) have appeared in the literature. Whereas some societies emphasized the need for early orotracheal intubation, others recommended a trial with non-invasive ventilatory support, with essential differences in the first-line modality: most experts recommended HFOT, although others preferred treatment with positive pressure systems (mainly CPAP) and even with specific interfaces (helmet) [27].

The use of high nasal flow in non-COVID hypoxemic ARF is supported by high-quality controlled studies that show a decrease in mortality compared to conventional oxygen therapy and non-invasive ventilation, especially in patients with a PaO_2/FiO_2 ratio lower than 200. In addition, it is a better-tolerated technique when compared with CPAP [24]. Moreover, the distribution of tidal volume is more homogeneous than conventional oxygen therapy, protecting the lung against P-SILI [28]. On the other side, the PEEP effect achieved is usually less than with accurate positive pressure systems and it should take into account that the combination of high FiO_2 and low PEEP values maintained has long been associated with de-recruitment phenomena (resorption or denitrogenation atelectasis) in patients with acute lung injury [29]. As maintained, supraphysiological oxygen levels were associated with increased mortality in a large, unselected multicenter cohort of critically ill patients [30], a close monitoring and later adjustment of inspired FiO_2 in C ARDS patients seems adequate.

In clinical practice, in a survey that included responses from 502 units from 40 countries, high nasal flow was the most widely used NIRS modality (53%) in cases of mild-moderate ARF, followed by systems of positive pressure (47%) [31]. In the same way, a study carried out in an ICU setting highlighted the heterogeneity of treatments between the different origins of the participants, although HFOT was the most used strategy (47%) followed by CPAP/NIV (26%) and early direct intubation (7%) [32]. In fact, in an expert consensus based on the Delphi method, 97% of them agreed that HFOT can be considered as an alternative strategy for oxygen support before invasive mechanical ventilation and should be used in patients who are unable to maintain SpO_2 > 90% using oxygen delivery through a Venturi mask or may be used in patients with increasing oxygen requirement to avoid endotracheal intubation [33].

The second therapeutic option for the treatment of ARF is the positive pressure devices, either CPAP or pressure support. The effect of expiratory positive pressure prevents alveolar collapse and improves ventilation-perfusion relationships and, ultimately, pulmonary gas exchange. The addition of pressure support can theoretically contribute to unloading inspiratory muscles. However, in hypoxemic ARF, the use of positive pressure systems, except for acute cardiogenic lung edema, remains controversial. In fact, the expert consensus in the respiratory management of ARF in COVID-19

recommended only NIV in the presence of mixed respiratory failure (hypoxemia and hypercapnia) and in selected patients with increased work of breathing [33]. The increased respiratory drive characteristic in COVID patients and their relatively preserved lung mechanics (compliance) can lead to high tidal volumes when using pressure support. High tidal volumes (>9.2 or 9.5 ml/kg) under NIV are associated with increased mortality [20], probably related to "unprotective" mechanical ventilation. On the other hand, high-quality pressure ventilators equipped with monitoring capabilities can help to monitor reliably and continuously the respiratory rate and tidal volume reliably and continuously, except for helmet interface use.

Early experiences with treatment with positive pressure have already demonstrated a superiority compared to conventional oxygen therapy in terms of preventing orotracheal intubation, even with a moderate sample size [34]. Among the positive pressure modes, the most widely used has been CPAP. In a meta-analysis that included 3.377 patients treated with positive pressure systems outside the Intensive Care Units, a total of 2.764 patients were treated with CPAP and 1.855 with helmet interface [25].

Regarding the efficacy of avoiding intubation, in the previously mentioned meta-analysis, from the 75% of survivors in the group of patients who were candidates for intubation, 31% required IMV, and 43% only NIRS [25]. In a study including patients who were candidates for intubation and invasive ventilation but who could not receive such treatment due to the shortage in the context of the massive influx of patients, intubation was avoided in 37% of patients who were managed only with CPAP [35]. Similar results (40% efficacy) were reported by Noeman-Ahmed et al. [36]. Somewhat better results were reported in a group of patients with moderate ARF (PaO_2/FiO_2 < 200 and RR < 30), with 85% of successful management exclusively with CPAP [37]. A meta-analysis including more than 4.700 patients showed that CPAP and NIV were equally employed (48.4 vs. 46%). Interestingly, almost half of the patients exposed to CPAP/NIV failed the non-invasive support trial, and only half of the failing cases were eligible for intubation. Finally, mortality was higher in patients treated with NIV (35.1%) than in patients treated with CPAP (22.2%), even though the number of failures was similar in each group [38].

In a matched retrospective of COVID-19, patients admitted to the ICU, the four therapeutic, supportive therapies (oxygen therapy, high nasal flow, non-invasive ventilation, and direct intubation) were compared. The group with the highest mortality received non-invasive ventilation [39]. Both scenarios were retrospectively studied by Colaianni et al. [40] in a clinical study conducted under a careful algorithm for managing ARF in COVID patients. The first step was HFOT and prone position. In case of failure, a CPAP trial, combined with periods of HFOT, was initiated. The first step had a failure rate of 10/65, but mainly due to CPAP intolerance. The failure rate in the second group (HFOT + CPAP) was 20/48. Mortality in intubated patients was 55%. Of note, a combination of modalities is not uncommon in clinical practice, especially pauses in CPAP/NIV therapy using HFOT, for example, for feeding breaks [40].

The duration of non-invasive support. Failure criteria. How to deescalate.

The duration of NIRS in COVID patients seems clearly longer than in non-COVID patients but with huge variability. In the meta-analysis by Cammarota et al. [25] the mean time of non-invasive support (CPAP-NIV) until orotracheal intubation in patients with NIRS failure ranged between 72 and 137 h. In responders, the mean time of total duration of NIRS ranged between 2 and 12 days.

This long NIRS time may increase the probability of late failure, with a worsening prognosis if intubation is required. This point has been the subject of research in a few studies. In an observational study Boscolo et al. [41] determined that the ventilation time prior to admission to the ICU was one of the determining factors of mortality in patients in whom NIV failed. Although there were no significant differences between patients who were directly intubated and those who underwent failed NIV trial prior to intubation, the authors found a significant increase in mortality in patients with a duration of ventilation >48 h outside the ICU [41]. Similarly, Vaschetto et al. determined that CPAP use time ≥ 3 days was an independent predictor of mortality in the event of CPAP failure and intubation [42].

Given these data, it seems especially important to closely monitor patients under NIRS who are treated for more than 72 h with any supportive therapy. In the event of late deterioration in respiratory conditions in these patients, orotracheal intubation and invasive mechanical ventilation should be considered immediately. In addition to the classic criteria for invasive ventilation (hemodynamic instability, decreased level of consciousness, appearance of signs of muscle fatigue, or development of unmanageable tracheal secretions), predefined respiratory conditions for intubation should be protocolized, especially in late failure. It is also essential to rule out pulmonary embolisms as a potential cause of acute oxygenation alterations, the incidence of which has been shown to be higher in COVID patients under ventilatory support [43].

The efficacy of NIV, including both bilevel positive airway pressure (BiPAP) and continuous positive airway pressure (CPAP), in patients with ARF secondary to coronavirus disease 2019 (COVID-19) is still debated [44]. Some authors believe that NIV represents a questionable option and that controlled mechanical ventilation should be established as soon as possible because of the risks of patient self-inflicted lung injury and delayed intubation [45], but there is evidence in favor of early intu- bation in COVID-19 ARF. Recent studies showed that a short NIV trial could be beneficial to treat COVID-19 mild-to-moderate hypoxemic ARF [46].

Recently, a simple nomogram and online calculator has been developed to identify patients with COVID-19 who are at risk of NIRS failure (including both HFNC and NIV). The patients might benefit from early triage and more intensive monitoring. The nomogram was based on age, number of comorbidities, ROX index, Glasgow coma scale score, and use of vasopressors on day 1 of NIRS [47].

The prediction of NIV failure in patients with ARF is significant to prevent a delayed intubation and an increased risk of morbidity and mortality. The factors involved will depend on the characteristics of respiratory failure and their etiology. An adequate follow-up will be necessary at each NIV treatment.

In summary, it would be cautious to consider orotracheal intubation in those patient candidates who, after 48–72 h of NIRS, do not present significant clinical improvement, as well as in those patients with acute worsening of a previously stable situation or with highly compromised respiratory conditions ($PaO_2/FiO_2 < 100$).

Conclusion. Non-invasive ventilation (NIV) represents a vital therapeutic modality for managing respiratory distress, offering advantages over invasive mechanical ventilation (IMV) in select cases. The evolution of NIV technology has led to the development of various modes, catering to diverse clinical scenarios. Indications for NIV span a spectrum of respiratory conditions, with evidence supporting its efficacy and safety,

particularly in conditions such as COPD exacerbations and ARDS. However, success with NIV hinges on timely intervention, appropriate patient selection, and vigilant monitoring to prevent complications.

For any kind of respiratory support employed, it is mandatory to monitor the efficacy in a short time frame. In the absence of response, prompt orotracheal intubation and invasive ventilation needs to be considered, if the patient is a candidate for full therapy. If the condition of the patient under NIRS remains stationary after 48–72 h, orotracheal intubation should also be considered. Not all the patients may be candidates for invasive ventilation. For those patients with DNI orders who receive non-invasive ventilatory support, high mortality can be expected. It should be taken into account while starting or maintaining potentially futile treatments (in cases without response) that are not free from secondary effects and may pose relevant discomfort in dying patients. In the context of the COVID-19 pandemic, NIV assumes heightened significance, necessitating a nuanced approach to its clinical application. This review provides valuable insights and guidance for clinicians navigating the complexities of NIV usage, emphasizing its pivotal role in respiratory care.

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