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How do I wean a patient with acute hypercapnic respiratory failure from noninvasive ventilation?

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Abstract Noninvasive ventilation (NIV) has been increasingly used for the management of different etiologies of acute hypercapnic respiratory failure (AHRF). Although NIV implementation has been framed well by the guidelines, limited number of studies evaluated the NIV weaning strategies, including a gradual decrease in the level of ventilator support and/or duration of NIV as well as abrupt discontinuation, once respiratory acidosis and distress have resolved. None of the methods have yet been established to be superior to the other in terms of the success rate of weaning and duration of NIV; as well as mortality, length of stay (LOS) in hospital, respiratory ICU (RICU), and ICU. Patient-derived factors, such as etiology of AHRF, disease severity, history of prior NIV use, and clinical status can help to predict NIV weaning outcome and eventually choose the best method for each individual. In this paper, we have described the strategies for weaning a patient with AHRF from NIV and provided a quick guide for implementation of these data into daily practice based on our experience in and the current scientific evidence.

Clinical case

A 73-year-old female was hospitalized because of exacerbation of chronic obstructive pulmonary disease (COPD) with acute-on-chronic respiratory failure. She was cachectic (Body mass index: 18 kg/m^2), an ex-smoker (with a history of one-hundred-pack-years), on inhalers at home, and was using long term oxygen therapy (LTOT) for the last 3 years, but suboptimal (3 h/day on average). She had hypertension and cardiac arrhythmia with moderate functional limitation (i.e. short of breath with light activities and unable to perform two or more activities of daily living).

Abbreviations: ABG, Arterial blood gas; AHRF, Acute hypercapnic respiratory failure; COPD, Chronic obstructive pulmonary disease; EPAP, Expiratory positive airway pressure; ICU, Intensive care unit; IMCU, Intermediate care unit; IPAP, Inspiratory positive airway pressure; LTOT, Long term oxygen treatment; NMD, Neuromuscular disease; NIV, Noninvasive ventilation; OHS, Obesity hypoventilation; RR, Respiratory rate; AAA13, aaaaaa13; AAA14, aaaaaa14.
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On arrival to emergency department; she was started on noninvasive ventilation (NIV) because of her increased respiratory distress (accessory muscle use with RR: 30 bpm, HR: 120 bpm, Systolic/diastolic BP: 150/125 mmHg) and arterial blood gas result, revealing acute hypercapnic respiratory failure (AHRF) (pH: 7.29, PaCO2: 69 mmHg, PaO2: 54 mmHg, HCO3: 28 mmol/L, SatO2: 86% on room air). She was transferred to the respiratory ward to continue her management regarding COPD exacerbation and AHRF.

On admission day 2, the patient's clinical and gas-exchange status significantly improved (pH: 7.35, PaCO2: 61.6 mmHg, PaO2: 88.7 mmHg, HCO3: 29.6 mmol/L, SatO2: 97.7% on IPAP: 20/EPAP: 6 cmH2O, inspired oxygen fraction (FiO2): 0.28). We decided to wean the patient gradually off NIV.

Introduction

Noninvasive ventilation is effective in the management of different etiologies of acute hypercapnic respiratory failure (AHRF), especially for exacerbation and post-extubation weaning phase of COPD patients, as well as for palliative purposes.[1,2] The use of NIV in non-COPD causes of AHRF, such as acute decompensation of the obesity-hypoventilation syndrome (OHS) or neuromuscular diseases (NMD), has also been incorporated into clinical practice, although this has been based on mainly cohort studies.[2-4] On the other hand, NIV can also be utilized for the management of acute hypoxemic respiratory failure; including immune-compromised patients, post-operatively, patients with acute cardiogenic pulmonary edema, or Covid-19 pneumonia.[1,5,6]

Although NIV implementation for the management of AHRF has been framed well by the guidelines,[1,2] the strategies for weaning from NIV have not been well-defined yet. Most of the time, clinicians decide on NIV weaning intuitively according to their expertise and daily clinical practice. Unnecessarily prolonged use of NIV can lead to increased morbidity and even mortality, due to complications, including facial skin lesions or NIV-related pneumonia, as well as to the increased duration of hospitalization and cost.[7-12] Attempting extubating a patient as soon as he/she recovers from the primary disorder leading to respiratory failure is recommended to decrease complications associated with intubation[13]; similarly, NIV should be stopped as soon as the acute episode is has passed.[2] On the other hand, premature discontinuation of NIV can also result in worsening of respiratory status, with possible reinstitution of NIV. This risk might be extremely likely, especially in patients with a high risk of nocturnal hypoventilation (i.e. partial arterial pressure of carbon dioxide increase during sleep $>$10 mmHg), such as severe COPD, OHS, NMD, or chest wall disorders.[4,14,15] Keeping all of these important physiological points in mind, here is the critical question: When is the best time for weaning from NIV for whom?

Despite the wide range of studies available on weaning from invasive mechanical ventilation;[13,16,17] few numbers of studies have evaluated the NIV weaning strategies in patients with AHRF, especially with COPD.[18-27] Once the patient's general condition improves, NIV can be discontinued either by the patient (e.g. NIV intolerance) or by the physician (based on clinical findings, such as normalization of pH as well as respiratory status) or by protocol. In comparison to physician-directed weaning, protocol-directed discontinuation of NIV can reduce the duration of NIV and ICU stay as well as the mortality.[18,19,28] The strategies for weaning can be currently grouped into three, including a gradual decrease in the level of ventilator support and/or duration of NIV as well as abrupt discontinuation.[2,20-24,29] The 2016 BTS/ICS guidelines state that NIV can be discontinued in AHRF due to exacerbation of COPD, by reducing the daytime periods of ventilation in 2 to 3 days, based on clinical criteria, before being discontinued overnight.[2] Stepwise decrease in NIV duration, as recommended,[2] was shown to have no difference in NIV withdrawal success rates compared to abrupt discontinuation of NIV,[21,22] except for a longer intermediate care unit stay.[22] Similarly, in a recent RCT performed on 90 COPD patients, the success rate of weaning was similar between abrupt discontinuation, stepwise decrease in ventilator support level, and stepwise decrease in NIV duration arms; although the duration of NIV use and length of hospital stay were lower in first two groups.[23] Therefore, abrupt removal of NIV can be an acceptable option for spontaneously breathing patients of COPD, whereas the clinical status and disease severity can alter the physician's choice.

For non-COPD patients recovering from an episode of AHRF, a referral to a home ventilation service for assessment of 'domiciliary NIV use' has been recommended, while continuing 'nocturnal NIV' till to the accomplishment of the evaluation.[2] The presence of ongoing respiratory failure, in-hospital stability of NIV, and local care pathways can affect the decision on the location and timing of this assessment.[30] Recently, hospital discharge with positive airway pressure management was shown to reduce mortality in patients with OHS or suspected of having OHS.[31]

Patient-derived factors [such as etiology of AHRF (such as COPD vs. non-COPD causes), disease severity, history of prior NIV use, clinical status (for example rapid shallow breathing index (RSBI), bicarbonate level or pH$<$7.35 just before weaning] can help to predict NIV weaning outcome and eventually to choose the best method for each individual.[23,24,26,27] In the sole multicenter RCT, including both COPD and non-COPD patients, all three tested strategies were similarly effective in terms of NIV weaning success; while the presence of restrictive respiratory disorder due to obesity as an underlying lung disease was a predictor of failure, in contrast to COPD as a predictor of success (unpublished data under review).[24] In the future, additional research is required on weaning strategies/processes in non-COPD patients.

It is essential to decide the timing and methodology of NIV discontinuation after recovering from AHRF in adults, to improve patient outcomes. In this context, we aimed to describe and discuss the course of weaning and various weaning protocols, based on the most recent available literature and our experience both on COPD and non-COPD populations. Thereby, a practical guide for daily practice was intended.

When to start weaning from NIV in a patient recovering from AHRF?

The process of liberating patients from NIV generally referred to as weaning, should be planned as soon as the patient is initiated on NIV. The optimal timing for initiation

of weaning is as important as the methods of NIV discontinuation. These can differ based on the underlying etiology of AHRF (COPD vs. non-COPD) and the severity of the disease.

The 2016 BTS/ICS guideline states that discontinuation from NIV can be planned in AHRF due to acute exacerbation of COPD, in whom NIV is successful (pH ≥7.35 achieved, resolution of underlying cause and symptoms, respiratory rate normalized) following the first 24 h or longer duration on NIV[2]. Patients can be screened daily by the physician or respiratory therapist for the clinical criteria to be met before the weaning attempt, as summarized in Table 1.[22-24,29] If patients pass the baseline screening criteria, they can be discontinued from NIV onto nasal/Venturi oxygen at the minimal level (maximum of 5 L/min) to achieve the same oxygenation targets of NIV. If they also pass the re-assessment criteria after 1-4 h of spontaneous breathing with supplementary oxygen, the weaning process can be initiated. While pH>7.35 was mostly used as criteria, two of the studies used pH>7.30 as cut-off for screening.[18,26] However, a recent study[27] pointed pH<7.35 before weaning as a predictor of weaning failure. The physicians should keep in mind that more liberal criteria can increase the chance of earlier weaning with reduced rate of NIV complications and the duration of NIV and hospital stay; while stricter criteria can lead to a greater rate of withdrawal success, as in the case of extubation.[31]

Chronic obstructive pulmonary disease patients with persistent hypercapnia after recovering from AHRF have a poor prognosis with high rates of readmission and mortality within one year.[32] Actually, a relevant proportion (25%) of COPD patients in GOLD stage 3 and 4 exhibits chronic hypercapnia.[14] The long-term domiciliary NIV treatment can improve daytime hypercapnia and admission-free survival with no to little benefit in quality of life of those patients.[33] 'Normalization of PaCO2' has been recommended previously, for the COPD patient to be weaned off NIV,[2] indirectly increasing possibility of initiation of long-term NIV in hospital. However, based on emerging evidence, currently, reassessment for 'long-term NIV' has been suggested at 2−4 weeks after resolution, since nearly one fifth of the patients are no longer hypercapnic by then.[34-36]

Once non-COPD patients (such as exacerbation of NMD or OHS) or COPD patients with suspected or known sleep apnea syndrome have achieved clinical stability and the underlying cause of exacerbation has resolved, consideration can be given to in or outpatient assessment of OHS or overlap syndrome as well as domiciliary use of NIV, which can reduce mortality.[30,34] These patients cannot be weaned off NIV and may require in-hospital continuation and transition to long-term NIV, as suggested by home ventilation services.[2,34]

How to wean the patient from NIV?

Although NIV implementations for AHRF due to different etiologies have been described in detail,[1,2] the weaning methodology has not been well-defined yet by the guidelines. There are different weaning protocols recommended for invasive mechanical ventilation;[13,16,17] however, there have been no definitive recommendations for NIV weaning published in global guidelines yet,[1,2] except for Spanish and Indian guidelines.[29,37] Monitoring PaCO2 on and off NIV can be a useful guide for the withdrawal process,[2] in addition to other clinical parameters, including vitals, pH, and SatO2 levels. Patients can be considered as 'weaning failure'; if NIV reinstitution or intubation criteria[19,38,39] (Table 2) are met during the weaning phase/ right after NIV discontinuation, or if weaning is not possible. The time to define whether weaning is successful or not varies among studies from 2 to 8 days, the most common threshold being 3-5 days (Table 1).

Protocol-directed versus physician-directed weaning

NIV has generally been withdrawn depending on either by decision of the physician based on clinical findings with gas exchange status, or by the patient's demand (such as in NIV intolerance). On the other hand, the weaning can be protocolized. Duan et al compared those two strategies in 73 patients with COPD using NIV>24 h for AHRF.[18] In the protocol-directed arm, patients passing daily screening for NIV weaning criteria were discontinued by respiratory therapists from NIV directly onto oxygen with a nasal cannula till the patient was discharged. If the patient's clinical condition

Table 1 Clinical criteria for readiness to be weaned off NIV.[20, 22-25,29]

Baseline *(under NIV use)*	After 1-4 hour of spontaneous breathing *(with supplementary oxygen)*
pH ≥7.35	pH≥7.35
Decrease from initial PaCO2 (at NIV start)≥10%	Increase of PaCO2≥ 20 % of baseline
PaO2>60 mmHg, PaO2/FiO2>150, or SaO2≥90% on FiO2<50%	SaO_2 ≥88-92% with a FiO_2≤40%
RR < 25-30 bpm	RR 8-30 bpm
HR 50-120 bpm	HR 50-120 bpm
Systolic BP 90-180 mmHg without vasopressors	Systolic BP 90-180 mmHg without vasopressors
Body temperature 36-38°C	Body temperature 36-38°C
Neurologic score of Kelly≤ 2 (i.e. Alert. Follows simple,3-step complex commands)	Kelly score ≤2
No need for sedation	Absence of severe dyspnea (i.e. BORG>4)

BP: Blood pressure, *HR*: Heart rate *NIV*: noninvasive ventilation, *PaO2*: Partial arterial oxygen pressure, *RR*: Respiratory rate, *SaO2*: Oxygen saturation.

Table 2 Criteria for NIV re-institution or intubation.

NIV Re-institution	Intubation*	
	The major criteria	The minor criteria
RR <8 or >30 bpm Systolic BP <90 or >180 mmHg without vasopressors HR <50 or >120 bpm Neurologic score of Kelly >2 SaO_2 <90% with a $FiO_2 \geq 40\%$ pH<7.35 More than 20% increase in PaCO2 than the one recorded at start of weaning Presence of severe dyspnea (BORG>4).	Respiratory arrest Respiratory pauses with unconsciousness Severe hemodynamic instability Intolerance leading to discontinuation of the device.	Reduction ≥30% of basal PaO2/FiO2 ratio Increase of ≥20 % of PaCO2 Worsening of alertness based on the Kelly scale (≥1 point) New onset or persistent respiratory distress Exhaustion Secretion accumulation despite the use of aggressive physio-therapy and cough assist.

BP: Blood pressure, *FiO_2*: Fraction of inspired oxygen, *HR*: Heart rate *NIV*: noninvasive ventilation, *PaO2*: Partial arterial oxygen pressure, *RR*: Respiratory rate, *SatO2*: Oxygen saturation.
* The presence of one major criterion or two minor criteria for at least 1 h was considered indicative of the need for intubation, as previously reported.[19,38,39]

worsened as given in the protocol, NIV was reinstituted with daily screening to wean. By this method, the authors showed that NIV duration (-1.8 days) and length of ICU stay (-2.3 days) decreased as compared to the physician-directed method. Reduction in 28-day mortality was also shown as a benefit of protocols.[19] Accordingly, NIV weaning using a standardized protocol can provide better outcomes, with the prevention of prolonged NIV use due to an unplanned approach.[28]

Weaning strategies

There are few studies regarding methods of weaning from NIV.[22-24] Based on these studies, the strategies can be grouped into three (Table 3):

a) A gradual decrease in duration of NIV

Weaning can be started with the liberation of the patient from NIV during the daytime and then nighttime support can be gradually reduced. It has been recommended as such by BTS/ICS guideline,[2] which stands on a randomized trial designed by Plant et al. to compare the effect of NIV and standard medical treatment among patients with acute exacerbation of COPD, but not comparing different methods of NIV withdrawal.[40] Cuvelier et al.[41] gradually decreased duration of daytime NIV first, with close monitoring of clinical and ABG findings, in non-COPD patients (n=58) and COPD (n=42). When daytime NIV was stopped, the possibility of stopping nocturnal NIV was then assessed, on the basis of the patient's clinical condition and ABG values at the end of the following day. Inability to stop NIV for at least eight consecutive days (after two attempts) because of worsening clinical status, a rise in PaCO2 with respiratory acidosis (pH ≤7.35) and/or recurrent AHRF without any identifiable cause was considered as long-term NIV dependency, which was observed more frequently in non-COPD group (39 vs. 19%, respectively). Damas et al used a similar approach in a prospective cohort study, including 78 patients with acute exacerbation of chronic respiratory failure.[20] All of the patients were weaned successfully with a shorter duration of NIV use, compared to prior studies. But authors suggested other less time-consuming strategies.

b) A gradual decrease in ventilator support levels and duration of NIV

Another way of weaning from NIV could be a gradual decrease in ventilatory support with periods of spontaneous respiration. Nava et al used NIV as a weaning method for intubated COPD patients failing T-piece trial.[42] The authors gradually decreased the level of pressure support by 2 or 4 cmH2O per day in patients with hypercapnic ARF, who were successfully weaned from INV onto NIV, as long as they tolerate. They also allowed patients to breathe spontaneously with increasing duration. At the end of 3 h of spontaneous breathing if the patient's clinical condition and ABG findings are stable, patient was considered to be weaned off successfully. Moretti et al used the similar NIV weaning method with gradual decrease in pressure support and PEEP values in their study searching for incidence and causes of late NIV failure, recognition of which is critical since prolonged application of NIV can delay the time of intubation, leading to very poor prognosis.[43] While the inspiratory pressure support can be reduced by 2-4 cmH2O every 4-6 h with vitals and blood gas monitoring till IPAP<8 and EPAP<4 cmH2O to withdraw completely;[23] this reduction can also be supported with a concomitant decrease in duration of NIV use.[29]

c) Abrupt discontinuation of NIV

As the patient meets the weaning criteria, NIV can be stopped at once. Lun et al reported no significant difference in NIV withdrawal success rates between this strategy (25 patients) and a gradual decrease in NIV duration (35 patients) (56% vs. 74%, respectively, p=0.139).[21] The significant decrease in NIV duration (a median of 0 vs. 3 days, p<0.001)) was not reflected by the length of hospital stay.

Table 3 Weaning strategies.[24]

Gradual decrease in duration of NIV	In day 1, daytime (6 am-10 pm) maximum of 8 h, nighttime (10 pm-6 am) at least 6 h From day 2 NIV can be decreased at least 2 h/day each at the daytime and nighttime When a patient reaches the duration of NIV use as 4 hper 16 hduring daytime, without the presence of any reinstitution criteria, it can liberate definitively from NIV.
Gradual decrease in ventilator support levels and duration of NIV	In day 1, daytime maximum of 8 h, nighttime at least 6 h; from day 2 the daytime NIV decreased at least 2 h/day and nighttime discontinuation was considered similarly. The level of pressure support can be decreased by 2-4 cmH2O per 4 h during daytime, with no change at night time. If the patient deteriorates or cannot tolerate the change, the pressure support can be kept the same and the pressure support can be decreased the next day. When a patient reached to the level of PS of 8 cmH20, without the presence of any reinstitution criteria, it can liberate definitively from NIV.
Abrupt NIV discontinuation	Patients can be disconnected from NIV and oxygenated with a nasal cannula. Oxygen flow can be limited to a maximum of 5L/min.

The study was criticized as under-powered.[44] In a larger study by Sellares et al, no significant differences were reported in terms of weaning success, NIV dependency, 6-month hospital readmission, or survival between immediate withdrawal and 3 further days of nocturnal NIV, except for a shorter RICU stay (-1 day) in prior arm.[22]

Which strategy is better?

Comparison of a gradual decrease in duration of NIV or level of inspiratory pressure support with immediate withdrawal in 90 patients with COPD showed similar success rates for weaning; whereas the immediate withdrawal group had the lowest duration of NIV use and hospital stay as compared to the other two methods (p=0.001).[23] Recently, our group compared the above 3 strategies in a multicenter, multinational RCT including 197 patients with COPD and non-COPD causes.[24] The median duration of total NIV use after randomization and length of stay (LOS) in the intermediate care unit was shorter in the abrupt discontinuation group ($p<0.001$, and p=0.044, respectively), but this significant difference was lost after adjustments for variables differing between groups at the baseline. Rates of weaning failure and intubation, mortality, and domiciliary NIV prescription, as well as LOS in hospital were also similar between groups. As a conclusion, abrupt discontinuation can be feasible in clinically stable, spontaneously breathing COPD patients recovering from AHRF.[22-24,45] This recommendation was supported by 53% of recently published Spanish consensus members,[37] whereas the Indian guidelines recommend the adoption of any of the three strategies.[29]

High flow nasal cannula is a relatively new treatment that has been suggested as a complementary therapy during breaks off NIV.[46,47] It was associated with better comfort and improved respiratory rate and dyspnea compared to low flow oxygen, during NIV breaks.[47] It can shorten NIV duration and probably increase NIV weaning success in AHRF. High flow nasal cannula can be an alternative to NIV after partial reversal of respiratory acidosis, especially in patients not tolerating NIV with a potential to deliver bronchodilator treatment as well.[49] However, there is not sufficient evidence yet.[48-50]

Reasons for weaning failure

Monitoring clinical and physiological factors throughout this process can help the physicians to predict the outcomes, such as prevention of AHRF relapse after discontinuation, reducing the duration of NIV and hospital stay, complications, or mortality. On the other hand, the patient may not be weaned successfully and can get intubated and/or discharged on NIV.

Predictors of weaning failure can be listed as the presence of restrictive respiratory disorder due to obesity as underlying lung disease, severe functional limitation, history of prior NIV use, time spent on NIV, higher PaCO2 and lower pH at enrollment, HCO3 concentration, and a $pH<7.35$ before weaning, poorer Glasgow Coma Scale.[23,24,27] On the other hand; the presence of COPD as underlying lung disease, location of NIV initiation (wards and intermediate care unit as opposed to emergency departments and ICUs), rapid shallow breathing index (i.e. respiratory rate /tidal volume) just before NIV turned off <67.4 can predict weaning success.[24,26] As a result, those patients with bad prognostic factors (such as non-COPD cause of AHRF) should be monitored cautiously during the weaning period. Additionally patients on NIV can be followed up routinely with rapid shallow breathing index, for optimal timing of weaning.

Weaning failure can be associated with increased morbidity and mortality.[29] In the only real-life observational study for NIV weaning in AHRF due to COPD exacerbations, 39% of patients failed weaning with adaptation to domiciliary ventilation.[25] However, the timing of recovery of hypercapnia is crucial as mentioned above and is likely to have the most important impact on long term NIV. Reassessment of hypercapnia in 2-4 weeks after the initial episode is recommended for identifying patients who are most likely to benefit from

long-term NIV.[34,35] Non-COPD causes of AHRF (such as OHS or NMD) can require home ventilation services as mentioned above.[2] Despite no previous neurological history, it was suggested that NMD be investigated in patients difficult to wean from ventilator support.[51]

Continuation of the clinical case

Our patient passed the readiness criteria (Table 1) both on NIV and spontaneous breathing (with nasal oxygen 2lt/min). Since she had cardiovascular co-morbidities and functional limitation, she was started on weaning strategy of gradual decrease in ventilator support levels and duration of NIV. However, her clinical status declined on weaning day 2 with emerging fever, tachypnea, tachycardia, increased cough, phlegm and severe respiratory acidosis (pH 7.30). She was diagnosed with pneumonia, started on modified antibiotic regimen and continued back on NIV with increased pressure and duration. After 5 days of treatment, the patient passed again readiness criteria, and she was weaned off NIV successfully using the same strategy in 3 days. The patient was discharged on LTOT with an appointment for an assessment at 'home ventilation services' two weeks later, since she had hypercapnia without acidosis at discharge.

Conclusion

It is important to know the timing and methods of weaning from NIV for patients recovering from AHRF, since inappropriate discontinuation can result in increased morbidity and mortality. Clinical status and disease severity may play a part in choosing the best method. None of the methods have yet been clearly established to be superior to the others in terms of relapse of AHRF in COPD patients after liberation from NIV, as well as mortality and long-term ventilator dependence. Therefore, abrupt removal of NIV can be a better option for uncomplicated cases of COPD to decrease the rate of NIV complications, while any of the methods can be adopted based on the patient's characteristics. Last but not least; we need more robust evidence for alternative NIV weaning strategies in different patient subgroups with AHRF.

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