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Comparison of immediate withdrawal and stepwise reduction in duration of non-invasive ventilation in chronic obstructive pulmonary disease patients presenting with acute hypercapnic respiratory failure

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Abstract

There is no universally acceptable protocol for the withdrawal of non-invasive ventilation (NIV) in chronic obstructive pulmonary disease (COPD) patients presenting with acute hypercapnic respiratory failure (AHcRF). This study was carried out to evaluate immediate against stepwise reduction in NIV. Sixty COPD patients with AHcRF who were managed with NIV were randomized into two groups: immediate NIV withdrawal (group A) and stepwise reduction of NIV duration (group B). The rate of successful NIV withdrawal, time to recurrence of hypercapnic respiratory failure, total duration of NIV use, and hospital length of stay (LOS) were compared among the two groups. NIV was successfully withdrawn in 51/60 (85 %) patients. NIV was successfully withdrawn in 24/30 (80%) patients in group A and 27/30 (90%) patients in group B (p=0.472). The total duration of NIV use was significantly lower in group A (38.97±17 hours) as compared to group B (64.3±7.74 hours) (p<0.0001). LOS was significantly lower in group A (5.8±1.6 days) as compared to group B (7.7±0.61 days) (p<0.0001). To conclude, immediate withdrawal of the NIV after recovery from respiratory failure among patients with exacerbation of COPD is feasible and does not increase the risk of weaning failure.

Introduction

Non-invasive positive pressure ventilation (NIV) is the preferred initial mode of ventilatory support for chronic obstructive pulmonary disease (COPD) patients presenting with acute hypercapnic respiratory failure (AHcRF). Over the years, multiple studies on patients with invasive mechanical ventilation (IMV) have resulted in definite criteria and protocols for weaning from IMV. Akin to IMV, there are well-defined indications for putting a patient on NIV; however, there are no universally accepted guidelines on how to take the patient off NIV. An early study by Duan *et al*. comparing protocol-directed *vs.* physician-directed weaning in NIV patients concluded that protocol-directed weaning decreased the duration of NIV and intensive care unit (ICU) stay [1]. This small but landmark study brings out a very important issue of protocolized weaning in patients on NIV. There has been a marked heterogeneity in the weaning strategies used among previous studies that aimed at studying the utility of NIV in acute respiratory failure. The 2016 American Thoracic Society/European Respiratory Society guidelines state that NIV can be discontinued in COPD patients presenting with AHcRF by progressively reduc-

ing the daytime periods of ventilation in 2 to 3 days before being discontinued overnight. These guidelines also emphasize the need for more trial data for optimal NIV withdrawal strategy [2].

Hence, this study was planned to compare the rate of successful NIV withdrawal using two NIV weaning strategies, *i.e.*, immediate NIV withdrawal and stepwise reduction in duration of NIV. It was also aimed to compare the time to recurrence of hypercapnic respiratory failure from the time of NIV withdrawal in patients who fail to wean from NIV, the total number of hours of NIV use, the total length of hospital stay, and in-hospital mortality among the two groups.

Materials and Methods

Study design, patients and setting

The randomized study was conducted at a tertiary care teaching hospital in India over 18 months. All COPD patients admitted to the pulmonary medicine ward or ICU who required only NIV during the hospital stay were screened for enrollment in the study after clinical stabilization and resolution of the underlying cause of AHcRF. Patients not requiring inspiratory positive airway pressure (IPAP) >16 cm H_2O and expiratory positive airway pressure (EPAP) >8 cm H_2O were then kept on unassisted breathing with Venturi oxygen for 4 hours at the minimal concentration to achieve the same oxygenation targets of NIV. If, after 4 hours of unassisted breathing, patients were clinically stable as defined by arterial pH≥7.35, oxygen saturation (SpO2) >90% on the fraction of inspired oxygen (FiO2) ≤50%, respiratory rate ≤25/min, heart rate ≤120/min, systolic blood pressure ≥90 mm Hg, and no signs of respiratory distress such as agitation, diaphoresis, or anxiety, they were included. Patients who were on home NIV, patients who required NIV for respiratory failure due to diseases other than COPD, and patients with comorbid illnesses like heart failure, chest wall deformity, obstructive sleep apnea, and coronary artery disease were excluded. Written informed consent was taken from the patients or legally authorized representatives. Initial NIV settings, pressure changes, as well as other management decisions, before enrollment in the study, were left to the discretion of the treating physicians, and the study investigators were not involved in the same till the patient satisfied the inclusion criteria for weaning. All the patients received nursing care and medical management as per the standard departmental protocol throughout the study. Patient data was collected from the time of admission and randomized into the following two groups (1:1) using a variable block randomization method with a block size of 4 using sealed envelopes for group allocation (Figure 1).

The immediate withdrawal of NIV group – group A (Gp A) – included patients who received the conventional Venturi oxygen mask. The setting of FiO2 was the same as used before randomization. Oxygen therapy was administered for as long as patients needed; if the oxygenation target could be achieved without supplemental oxygen, then patients were observed on room air.

The stepwise reduction of duration group – group B (Gp B) included patients for whom the duration of NIV was reduced to 16 hours on the day of randomization (day 0), then reduced to 12 hours on day 1 (including 6-8 hours of overnight use), 6-8 hours of overnight use on day 2, and complete withdrawal on day 3.

Vitals and blood gases were monitored till 48 hours after the complete withdrawal of NIV in all the groups. All patients received standard medical treatment with inhaled bronchodilators, systemic steroids, and antibiotics as deemed appropriate by the treating physician. Patients were monitored closely for any signs of weaning failure. The criteria of weaning failure were the appearance of any one of the following features – respiratory rate >25/min or increase of >50%; heart rate >110/min or increase >20%; SpO2<90% on FiO2 of 50%; arterial blood pH<7.35; or respiratory distress. The appearance of any one of these within 48 hours of withdrawal was considered a weaning failure. Such patients were restarted on NIV with pressures increased to previously tolerated levels. The study protocol was approved by the Ethics Committee of the institute.

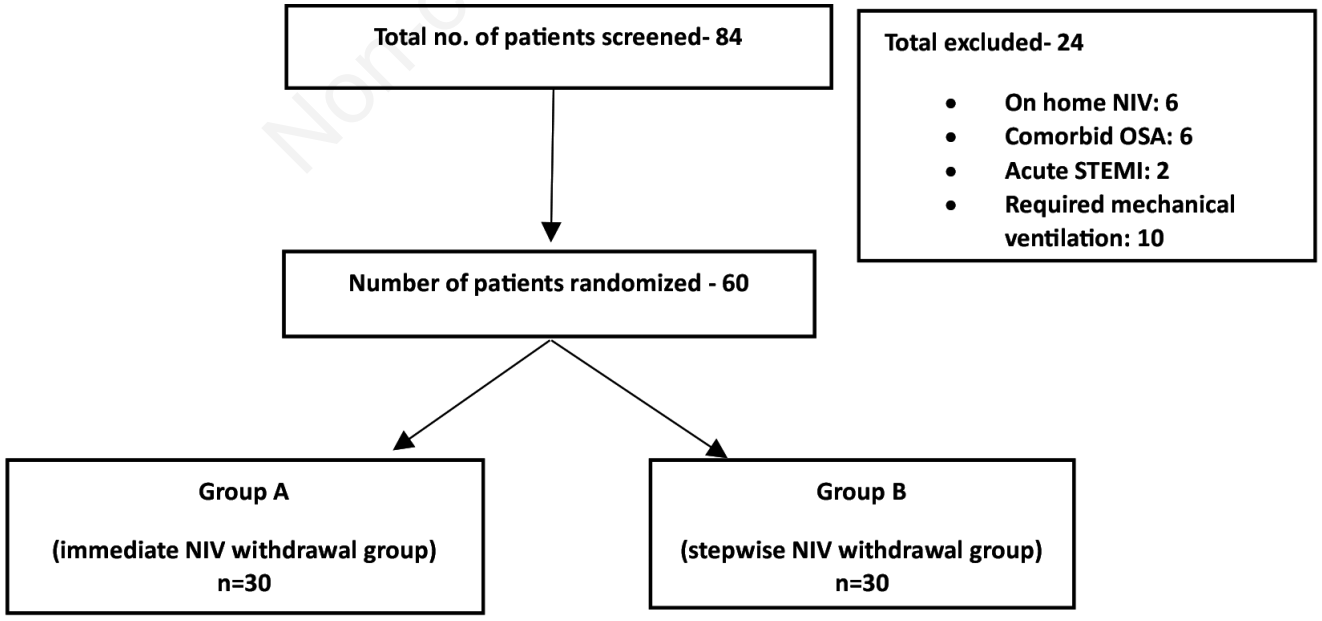

Figure 1. Recruitment of study subjects. NIV, non-invasive ventilation; OSA, obstructive sleep apnea; STEMI, ST-elevation myocardial infarction

Statistical analysis

The presentation of the categorical variables was done in the form of numbers and percentages (%). The quantitative data were presented as the means ± standard deviation and as the median with 25th and 75th percentiles (interquartile range). The data normality was checked by using the Kolmogorov-Smirnov test. In the cases in which the data was not normal, we used nonparametric tests. The following statistical tests were applied to the results: i) the comparison of the variables that were quantitative and not normally distributed in nature was analyzed using the Mann-Whitney test and variables that were quantitative and normally distributed in nature were analyzed using the independent *t*-test.; ii) the comparison of qualitative variables was analyzed using the Chi-Square test. If any cell had an expected value of less than 5 then Fisher's exact test was used.

The data entry was done in the Microsoft EXCEL (Redmond, WA, USA) spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software ver 25.0 (IBM, Chicago, USA). For statistical significance, a p-value of less than 0.05 was considered significant.

Results

A total of 84 COPD patients presenting with AHcRF were screened for the study. Twenty-four patients were excluded due to various reasons (6 patients were on home NIV, 6 patients had comorbid OSA, 2 patients presented with acute STEMI, and 10 patients required endotracheal intubation and mechanical ventilation). Sixty patients fulfilling the inclusion criteria, who were managed with NIV and were clinically stable after 4 hours of unassisted breathing, were randomized into the following two groups: I) immediate withdrawal of NIV (Gp A) (n=30); ii) stepwise reduction of duration (Gp B) (n=30). All patients completed the study.

The two groups were comparable in terms of baseline characteristics [age, gender, body mass index, smoking status, biomass fuel exposure, Glasgow Coma Scale (GCS) and Acute Physiology and Chronic Health Evaluation II (APACHE II) score at admission, and blood gas parameters), as shown in Table 1. NIV was successfully withdrawn in 24/30 (80%) and 27/30 (90%) patients in Gp A and Gp B respectively (p=0.472). There was no statistically significant difference in the time to recurrence of hypercapnic respiratory failure from the time of NIV withdrawal in patients who failed to wean from NIV among the two groups (14.5±6.8 hours in Gp A *vs.* 20±2 hours in Gp B). The two groups were similar in terms of the duration of NIV use before randomization (32.17±8.22 hours in Gp A *vs.* 32.37±7.76 hours in Gp B). However, the total duration of NIV use (in hours) and hospital length of stay (LOS) were significantly less in Gp A as compared to Gp B (32.17±8.22 hours in GA *vs.* 64.3±7.74 hours in Gp B). There was no in-hospital mortality in both groups.

We performed a *post-hoc* analysis of patients who failed and succeeded in NIV weaning among both groups. We found that there was a significant difference in NIV duration before randomization (hours), IPAP max (cm H_2O), EPAP max (cm H_2O), GCS score at admission, APACHE II score at admission, pH at admission, pH at randomization, partial pressure of carbon dioxide in arterial blood (PCO_2) (mmHg) at admission, PCO_2 (mmHg) at randomization, between patients who succeeded and failed NIV withdrawal ($p<0.05$), as shown in Table 2.

Based on the above findings, we further evaluated pH and PCO_2 at admission for predicting successful weaning outcomes using the receiver operating characteristic (ROC) curve (Figure 2). Interpretation of the area under the ROC curve (AUC) showed that the performance of PCO□ at admission (mmHg) [AUC 0.913; 95% confidence interval (CI): 0.811 to 0.970) was outstanding. The discriminatory power of pH at admission (AUC 0.83; 95% CI: 0.711 to 0.915) was excellent. Among both parameters, PCO_2 at admission (mmHg) was the best predictor of a successful outcome at a cut-off point of ≤89.4 with an AUC of 0.913 for correctly predicting a successful outcome. The sensitivity, specificity, and positive predictive value (PPV) of PCO_2 at admission (mmHg) for predicting successful weaning outcomes were 80.39%, 88.89%, and 97.1%, respectively. On the other hand, pH at admission (mmHg) had a sensitivity, specificity, and PPV of 66.67%, 88.89%, and 97.1%, respectively.

When we compared the two high-risk groups as defined by pH≤7.25 or PCO_2>89.4, we found that 54.54% in the immediate withdrawal group *vs.* 80% of patients in the stepwise withdrawal group had weaning success according to pH criteria (p=0.91), while according to PCO_2 criteria, 37.5% of patients achieved success in Gp A *vs.* 72% of patients in Gp B (p=0.07).

Table 1. Baseline characteristics of study population.

Characteristic	Group A (immediate NIV withdrawal) (n=30)	Group B (stepwise NIV withdrawal) (n=30)	p
Age in years, (mean±SD)	59.67±8.4	62.03±8.97	0.296
Male gender, n (%)	15 (50)	19 (63.33)	0.297
BMI in kg/m^2, (mean±SD)	23.71±2.14	24.44±2.27	0.743
Smoker, n (%)	20 (66.67)	22 (73.33)	0.573
Smoking index (mean±SD)	470±232.49	536.36±223.7	0.24
APACHE II score at admission (mean±SD)	17±1.6	16.63±1.92	0.425
GCS score at admission (mean±SD)	14.1±0.84	13.9±0.8	0.395
Blood gases at admission (mean±SD)			
pH	7.26±0.03	7.27±0.04	0.59
PCO_2 (mm Hg)	82.63±10.8	82.49±11.1	0.96
NIV use before randomization in hours (mean±SD)	32.17±8.22	32.37±7.76	0.988

NIV, Non-invasive ventilation; SD, standard deviation; BMI, body mass index; GCS, Glasgow Coma Scale; APACHE II, Acute Physiology and Chronic Health Evaluation II; PCO_2, partial pressure of carbon dioxide in arterial blood.

Table 2. Baseline parameters of patients with failed and successful weaning.

Baseline parameters	Success (n=51)	Fail (n=9)	p
NIV duration before randomization (hours)	30 (25-36)	37 (34-41)	0.022
IPAP max before randomization (cm H_2O)	16 (14-18)	22 (20-22)	<0.0001
EPAP max before randomization (cm H_2O)	6 (6-8)	8 (8-8)	0.003
GCS score at admission	14 (14-15)	13 (13-13)	<0.0001
APACHE II score at admission	16.57±1.75	18.22±1.09	0.008
pH at admission	7.27±0.04	7.24±0.02	<0.0001
pH at randomization	7.41±0.03	7.38±0.01	<0.0001
PCO_2 (mmHg) at admission	80.25±9.52	95.67±5.68	<0.0001
PCO_2 (mmHg) at randomization	50.26±5.59	58.89±4.04	<0.0001

NIV, non-invasive ventilation; SD, standard deviation; GCS, Glasgow Coma Scale; APACHE II, Acute Physiology and Chronic Health Evaluation II; PCO_2, partial pressure of carbon dioxide in arterial blood; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure.

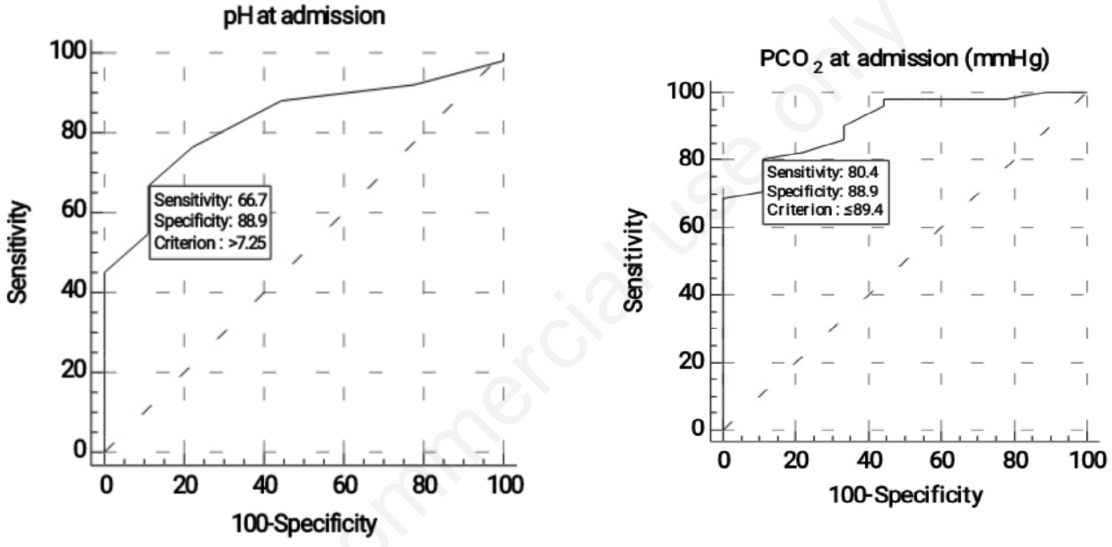

Figure 2. Receiver operating curve for pH and partial pressure of carbon dioxide in arterial blood (PCO2) (mm of Hg) at admission for predicting successful weaning outcome.

Discussion

NIV is an established indication in patients with acute exacerbations of COPD presenting with AHcRF [3]. Although different studies have defined factors predicting the outcome of NIV in terms of intubation and mortality in patients with severe AHcRF [4-6], these studies did not assess the best method to discontinue NIV. There is a paucity of information in defining a strategy to discontinue NIV, and, indeed, the optimal method to discontinue NIV after the recovery of an episode of AHcRF has not been established yet. Damas *et al*., in 2008, conducted a study to describe the performance of a weaning protocol based on progressive periods of NIV withdrawal in patients with acute exacerbations of COPD and concluded that strategies based on periods with and without NIV are effective and merit further investigation [7]. There has been a marked heterogeneity in the weaning strategies used among previous studies that aimed at studying the utility of NIV in acute respiratory failure (Table 3). This study was done to compare two different strategies of weaning from NIV, *i.e.*, immediate withdrawal and stepwise reduction in duration of NIV after recovery in COPD patients presenting with AHcRF.

In our study, NIV was successfully withdrawn in 24/30 (80%) and 27/30 (90%) patients in Gp A and Gp B, respectively. Our study did not demonstrate any significant difference in NIV withdrawal success rate between the immediate and stepwise withdrawal groups, as was the case in previous studies. The success rate of NIV weaning of immediate and stepwise withdrawal groups in a similar study by Hadda *et al.* was 76.6% and 86.6%, respectively [8]. Similarly, another study by Lun *et al.* also did not find any statistically significant difference in the NIV withdrawal success rate between the two groups [4]. However, both these studies were limited by a small sample size. A recent study by Sellares *et al*. that recruited 120 COPD patients and compared immediate withdrawal and an additional 3 days of nocturnal NIV support after recovery from respiratory failure did not find any statistically significant difference in the success rate of NIV withdrawal between these two strategies of weaning (83% and 87%: p=0.56) [9].

The duration of receiving NIV before randomization was com-

parable between the two groups. However, the total NIV duration was significantly less in the immediate withdrawal group as compared to the stepwise withdrawal group. This may be the result of the study design, as the NIV was immediately withdrawn in Gp A, whereas it was continued for 3 days after recovery from AHcRF in Gp B. Also, there was no significant difference in NIV parameters at randomization (IPAP, EPAP, IPAP max, EPAP max) between the two groups. These findings are consistent with those observed in a similar study by Hadda *et al*. [8].

Importantly, immediate withdrawal was not associated with any adverse outcome. LOS was significantly less in the immediate withdrawal group as compared to the stepwise withdrawal group. The shorter duration of hospital stay may translate into a lesser risk of hospital-acquired infections and NIV-associated complications. There was no significant difference in time to recurrence of hypercapnic respiratory failure after NIV withdrawal between the two groups. These results imply that immediate withdrawal is feasible in COPD patients presenting with AHcRF without any additional risk of weaning failure. There was no inpatient mortality among the two study groups. However, since the patients were not followed up after discharge from the hospital, long-term inferences on late recurrence of AHcRF and mortality cannot be made.

Among the patients who failed NIV weaning (n=9), 7 were subsequently withdrawn from NIV and discharged. Two patients continued to require NIV support and were discharged on home NIV. It was observed that patients who failed weaning received a longer duration of NIV with higher IPAP and EPAP before randomization, probably pointing towards a more severe disease exacerbation, which took a longer time to recover. Another probable explanation for this finding may be progressive hyperinflation, resulting from inappropriately higher initial ventilator settings, that led to patient-ventilator asynchrony with a high rate of unrewarded inspiratory efforts resulting in deventilation dyspnea [10]. These patients also had a poorer GCS at admission and a higher APACHE II score, also pointing towards a more severe disease process. They also had a lower pH and higher PCO_2 levels on admission, randomization, and outcome, a finding consistently noted in both groups. It can be inferred from the above observation that patients with lower pH and higher PCO_2 have a higher likelihood of failing NIV withdrawal and are probably candidates for more stringent monitoring and likely a more gradual NIV withdrawal. Based on these observations, we analyzed pH and PCO_2 at admission using the ROC curve to predict successful weaning outcomes. Although both these parameters performed well to predict successful weaning outcomes. PCO_2 at admission with a cut-off value of ≤89.4 mm of Hg had a high AUC of 0.91. The specificity, sensitivity, and PPV of PCO_2 cut-off of 89.4 were 80.39%, 88.89%, and 97.6%, respectively. Although there is always a trade-off between sensitivity and specificity (any increase in sensitivity will be accompanied by a decrease in specificity), overall PCO□ at admission of ≤89.4 mm Hg was the best predictor of successful outcome with maximum AUC. When we compared the two high-risk groups as defined by pH≤7.25 or PCO_2>89.4, we found that 54.54% in the immediate withdrawal group *vs.* 80% of patients in the stepwise withdrawal group had weaning success according to pH criteria (p=0.91), while according to PCO_2 criteria, 37.5% of patients achieved success in immediate withdrawal *vs*. 72% of patients in stepwise withdrawal group (p=0.07). Although these findings show a favorable trend towards the use of stepwise NIV withdrawal in COPD patients with PCO_2 at the admission of >89.4 mm Hg, the results are not statistically significant. Larger studies with a bigger sample size may be able to confirm these findings.

Table 3. Studies of non-invasive ventilation weaning in chronic obstructive pulmonary disease patients.

Study name	Strategy for NIV withdrawal	Results
Lun *et al.* (2013) [4], (n=60)	35 immediate withdrawal *vs.* 25 stepwise withdrawal. Weaning protocol: NIV duration was reduced to 16 hours on the day of randomization (day 0), then reduced to 12, 8, and 0 hours on days 1-3, respectively.	No statistically significant difference in the success rate. NIV successfully stopped in 74.3% and 56% of the stepwise and immediate withdrawal groups, respectively (p=0.139).
Selares *et al.* (2017) [9], (n=120)	Weaning protocol: 61 patients received three additional nights of NIV *vs.* direct NIV discontinuation in 59 patients. The primary outcome was relapse of AHcRF within 8 days after NIV discontinuation.	No differences in relapse of AHcRF after NIV discontinuation [10 (17%) *vs.* 8 (13%) for the direct discontinuation and nocturnal NIV groups, respectively, p=0.56]. No differences in long-term ventilator dependence, hospital stay, and 6-month hospital readmission or survival.
Hadda *et al.* (2020) [3], (n=90)	Three groups of 30 subjects each – (group A - immediate withdrawal; group B - stepwise reduction of pressure support PS reduced by 2-4 cm H_2O every 4-6 hours till IPAP of <8 cm of H_2O and EPAP of <4 cm of H_2O was attained, f/b complete NIV withdrawal; Group C - stepwise reduction of duration NIV was reduced to 16 hours on the day of randomization (day 0), then reduced to 12 hours on day 1 (including 6-8 hours of overnight use), 6-8 hours of overnight use on day 2, and complete withdrawal on day 3.	NIV was successfully withdrawn in 23/30 (76.6%) in group A, 27/30 (90%) in group B, and 26/30 (86.6%) in group C (p=0.31).
Damas *et al.* (2008) [10], (n=65)	Weaning strategy: during the first 24 hours in each 3 hours, one hour without NIV (except during the night period), on the second day in every 3 hours, two hours without NIV (except during the night period) and on the third day NIV was used during the night period.	All patients completed the weaning protocol with no re-institution of NIV or invasive ventilation during hospitalization.

NIV, non-invasive ventilation; PCO_2, partial pressure of carbon dioxide in arterial blood; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure; AHcRF, acute hypercapnic respiratory failure; PS, pressure support; f/b, followed by.

This study is one of the few studies addressing the important issue of protocolized weaning of NIV in COPD patients presenting with AHcRF. The study was conducted following good clinical practices for biomedical research involving human subjects, including prior approval of study protocol by the institutional Ethics Committee.

There are a few limitations of this study that need to be addressed. First, it was a single-center study with a small sample size, and therefore, the results may not be generalizable. Secondly, our enrollment criteria of IPAP<16 and EPAP<8 means that a previous reduction of IPAP and EPAP was performed as weaning process in a few patients who required higher pressures in the initial period before randomizing them into two weaning arms. This may have introduced a potential bias in the interpretation of results. Thirdly, patients on home/domiciliary NIV and patients using NIV for indications other than COPD were excluded from the study. Therefore, the results cannot be applied to patients using NIV for indications other than COPD. Fourthly, it was an open-label study where both patients and investigators were aware of the intervention. Last, since patients were not followed up after discharge from the hospital, late recurrence of AHcRF or mortality was not assessed in this study.

Conclusions

Immediate NIV withdrawal is feasible and non-inferior to a stepwise reduction of the duration of NIV as a weaning strategy. Further, the immediate NIV withdrawal strategy results in a reduced total duration of NIV and LOS without any significant increase in the risk of weaning failure. However, patients with high PCO_2 at admission (>89.4 mm Hg) may be candidates for stepwise withdrawal of NIV.

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