



Monaldi Archives for Chest Disease

eISSN 2532-5264

<https://www.monaldi-archives.org/>

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Monaldi Arch Chest Dis 2026 [Online ahead of print]

To cite this Article:

Gamal Ahmed M, Sadek SH, Khaleel WGE. **Immediate versus gradual noninvasive ventilatory pressure-or-duration step-down in chronic obstructive pulmonary disease patients: a randomized trial.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2026.4092

Submitted: 3-05-2026

Accepted: 25-08-2026

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Immediate *versus* gradual noninvasive ventilatory pressure-or-duration step-down in chronic obstructive pulmonary disease patients: a randomized trial

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Contributions: Montaser Gamal Ahmed, Samiaa Hamdy Sadek, Waleed Gamal Eddin Khaleel: conception, design, medical writing, revision of the manuscript. Waleed Gamal Eddin Khaleel, Montaser Gamal Ahmed: data collection. Montaser Gamal Ahmed: statistical analysis.

Conflict of interest: the authors declare that they have no conflicts of interest.

Ethics approval and consent to participate: the study was approved by the institutional review board and ethical committee of Faculty of Medicine- Assiut University in compliance with the Helsinki Declaration, IBR.no 04-2023-300094.

Informed consent: written informed consent was obtained from all participants or their legally authorized representatives before enrollment in the study.

Patient consent for publication: not applicable.

Availability of data and materials: the datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of generative artificial intelligence and artificial intelligence-assisted technologies in the writing process: the authors declare that no generative artificial intelligence or artificial intelligence-assisted technologies were used in the preparation of this manuscript.

Trial registration: ClinicalTrials.gov. NCT07133711.

Abstract

Despite the proven role of noninvasive ventilation (NIV) as an effective treatment for acute hypercapnic respiratory failure (AHRF) in patients with chronic obstructive pulmonary disease (COPD), no clear agreement has been reached regarding the ideal weaning strategy. This study aimed to compare three NIV weaning strategies in terms of efficiency and safety among COPD patients with AHRF. A total of 105 COPD patients stabilized on NIV were enrolled in this randomized clinical trial and equally distributed into three groups (n=35 each): duration step-down (group A), pressure step-down (group B), and immediate withdrawal (group C). The primary endpoint was successful weaning within 48 hours. Secondary outcomes included duration of NIV use, lengths of ICU and hospital stay, predictors of weaning failure, and complication rates. The results of this study indicated that successful weaning rates differed significantly among the groups, being highest in group A (82.9%), followed by group B (74.3%), and lowest in group C (54.3%) ($p<0.01$). Compared with other strategies, immediate withdrawal was associated with higher rates of weaning failure. Although NIV duration was significantly shorter in group C ($p<0.001$), complication rates and post-discharge outcomes were similar across the three groups. In this trial, gradual duration- and pressure-based step-down strategies were associated with higher rates of successful NIV weaning than immediate withdrawal, with the highest observed success rate in the duration-based step-down group.

Key words: weaning strategies, COPD, non-invasive ventilation, RICU.

Introduction

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) remains a significant reason of hospitalization, causing significant load on the health care system. Approximately one in five patients develops hypercapnic respiratory failure, either on presentation or during hospitalization, a condition related to increased risk of death [1]. For patients with AECOPD complicated by hypercapnic respiratory failure, noninvasive ventilation (NIV) is considered the best therapeutic option. Its application has resulted in significant decrease in the need for invasive mechanical ventilation, hospital and ICU length of stay, death and improve outcomes [2,3]. NIV is a cornerstone of acute hypercapnic respiratory failure management in COPD exacerbations, reducing the need for endotracheal intubation in appropriately selected patients [4]. Weaning strategies for invasive mechanical ventilation (IMV) have been studied [5,6]. These findings have led to the development of standardized principles and practices for IMV weaning, whereas similar guidance for NIV discontinuation is still inadequate.

Prior studies evaluating the use of NIV in acute respiratory failure have verified considerable heterogeneity in weaning strategies [7-9]. Two principal strategies are employed by clinicians for NIV weaning: a gradual reduction in the level and/or duration of NIV support over hours to days, or immediate withdrawal [10]. The need for protocolized approaches to NIV liberation has been stressed to reduce patient discomfort, minimize complications, and decrease the economic strain on healthcare services [11,12]. Evidence regarding the optimal NIV withdrawal strategy remains inconclusive. Some studies favor gradual pressure- or duration-based step-down, whereas others support immediate withdrawal [12,13]. Interpretation is limited by small single-center samples and heterogeneous patient severity, weaning criteria, protocols, outcome definitions, and follow-up periods. Consequently, the optimal approach remains uncertain. So this study aims to compare the three NIV weaning strategies: stepwise reduction in duration of use, stepwise reduction in pressure support, and immediate withdrawal in patients with AECOPD.

Materials and Methods

This study was carried out between May 2023 and October 2025 in a Respiratory Intensive Care Unit (RICU). We enrolled patients admitted to the RICU with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) who met the indications for noninvasive ventilation (NIV) [3]. The study was designed as a parallel-group randomized clinical trial. Ethical approval was obtained from the Scientific Ethics Committee of the Faculty of Medicine

(IRB No. 04-2023-300094), written informed consent was obtained from a legally authorized representative before patient enrollment. No formal a priori power calculation was performed. A pragmatic, feasibility-based approach was used to determine the sample size, with consideration of the anticipated recruitment capacity over the study period. With equal allocation of 35 patients to each study group, this study enrolled 105 patients totally. Participants were randomized 1:1:1 using a computer-generated sequence prepared by an investigator independent of recruitment, clinical management, and outcome assessment. Allocation was concealed using sequentially numbered, opaque, sealed envelopes opened after enrollment and baseline assessment. Participants and treating clinicians could not be blinded because of the nature of the interventions.

We included patients with AECOPD admitted to the RICU who required NIV for acute or acute-on-chronic hypercapnic respiratory failure despite standard treatment, defined by pH ≤ 7.35 and PaCO₂ > 45 mmHg. Additional indications included persistent distress, tachypnea, accessory muscle use, or paradoxical breathing. Patients were conscious, cooperative, able to protect their airway, and hemodynamically stable [3]. Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations were used to diagnose COPD, based on clinical features and prior spirometric confirmation of persistent airflow limitation (post-bronchodilator FEV₁/FVC < 0.70) [14]. Exclusion criteria encompassed one or more of the following: age < 18 years, prior use of domiciliary NIV, presence of tracheostomy, contraindications to NIV, and respiratory failure attributable to causes other than COPD. Patients requiring immediate endotracheal intubation and invasive mechanical ventilation at screening or before randomization were also excluded.

A meticulous medical history and full clinical examination were performed for all included patients. Arterial blood gas (ABG) samples were obtained as part of routine clinical care. Measurements were performed at RICU admission, prior to randomization, 2 hours and 48 hours post-randomization, and additionally as clinically indicated. All samples were analyzed using a blood gas analyzer (Instrumentation Laboratory GEM Premier 3000 blood gas electrolyte analyzer, Lexington, MA, USA). Via Acute Physiology and Chronic Health Evaluation (APACHE) II score, we determined illness severity for the enrolled patients [15].

Noninvasive ventilation (NIV) was administered by a Puritan-Bennett 840 ventilator (Puritan-Bennett Corporation, Pleasanton, CA, USA). Patients were ventilated in pressure support mode with a backup respiratory rate (S/T mode), starting with an inspiratory positive airway pressure (IPAP) of 15–20 cmH₂O and an expiratory positive airway pressure (EPAP) of 6–8 cmH₂O,

with a backup rate of 12–16 breaths/min. The fraction of inspired oxygen (FiO_2) was titrated to maintain $\text{PaO}_2 \geq 60$ mmHg and oxygen saturation of 88–92%, guided by arterial blood gas analysis [16]. The treating physicians determined the initial NIV settings, subsequent pressure adjustments, and other management decisions prior to study enrollment. All participants received standard care, including inhaled bronchodilators, corticosteroids, and antibiotic therapy, according to the clinical judgment of the treating physicians. No study-specific intervention was initiated until patients fulfilled the predefined criteria for NIV weaning readiness. Patients were considered suitable for weaning when the following conditions were accomplished: arterial $\text{pH} \geq 7.35$, $\text{SpO}_2 > 90\%$ on $\text{FiO}_2 \leq 50\%$, respiratory rate ≤ 25 breaths/min, heart rate ≤ 120 beats/min, systolic blood pressure ≥ 90 mmHg, and absence of clinical signs of respiratory distress [13]. Patients meeting the above criteria were randomized in a 1:1:1 ratio into three groups.

Group A (stepwise reduction of duration): NIV use was gradually reduced in terms of daily duration, starting with 16 hours on the day of randomization (day 0), followed by 12 hours on day 1 (including 6–8 hours overnight), then limited to 6–8 hours overnight on day 2, with complete discontinuation on day 3.

Group B (stepwise reduction of pressure support): Pressure support was gradually reduced by 2–4 cm H_2O at intervals of 4–6 hours, with continuous monitoring of clinical parameters and arterial blood gases, until IPAP < 8 cm H_2O and EPAP < 4 cm H_2O were reached, after which NIV was discontinued.

Group C (immediate withdrawal): NIV was discontinued immediately, and patients were monitored on spontaneous breathing.

Patients were continuously monitored with care to vital signs and arterial blood gas parameters until complete discontinuation of NIV across all study groups.

Successful weaning was established when patients sustained spontaneous breathing for at least 48 consecutive hours in the absence of respiratory distress, with arterial $\text{pH} > 7.35$ and $\text{PaO}_2 > 60$ mmHg while breathing via a mask at $\text{FiO}_2 \leq 0.5$ [17].

Study outcomes

The primary outcome was the frequency of successful NIV weaning among the three study groups. Secondary objectives included the identification of predictors of weaning failure, as well as comparison of total NIV duration, complication rates, hospital length of stay, and in-hospital mortality among the study groups. Successful weaning was defined as completing the

allocated strategy followed by 48 consecutive hours without NIV reinstitution or endotracheal intubation. This observation period began after the final planned NIV session in the duration step-down group, after protocol completion and NIV discontinuation in the pressure step-down group, and immediately after discontinuation in the immediate withdrawal group. Weaning failure was recorded at NIV reinstitution or intubation during this period. Time to outcome extended from randomization to completion of the 48-hour observation period for successful cases or to the failure event for unsuccessful cases.

Statistical analysis

SPSS software (version 22.0; IBM Corp., Armonk, NY, USA) was used for statistical analysis for this study. Continuous variables are stated as mean $\pm$ standard deviation (SD), while categorical variables are presented as number (percentage), as proper. We used one-way analysis of variance (ANOVA) or the Kruskal–Wallis test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables, as appropriate for comparisons among the three groups. A two-tailed P value < 0.05 was considered statistically significant.

Results

Among 150 COPD patients with acute hypercapnic respiratory failure, 45 were excluded due to predefined criteria, including home noninvasive ventilation (NIV) use (n=13), coexisting obstructive sleep apnea (OSA) (n=20), and the need for invasive ventilation (n=12). The remaining 105 patients, who achieved clinical stability and justified criteria for weaning from NIV, were equally distributed to one of three groups: Group A duration step-down, Group B pressure step-down, or Group C immediate withdrawal (35 patients in each group) as shown in *Supplementary Figure 1*. No patients were lost to follow-up.

The mean age ranged from 62.1 to 65.1 years, and males predominated in all three groups. Age, sex distribution, body mass index, smoking status, and Glasgow Coma Scale at admission were comparable among the three groups. Likewise, the frequency of comorbid conditions did not vary significantly between groups (Table 1). Arterial blood gas parameters at admission showed no significant between-group differences in pH, PaCO₂, PaO₂, or SpO₂. Baseline measurements prior to randomization including pH, PaCO₂, PaO₂, FiO₂, systolic blood pressure, respiratory rate, heart rate and duration of NIV usage were comparable through the studied groups. Also, NIV settings at randomization, including inspiratory positive airway pressure IPAP and expiratory positive airway pressure EPAP, were similar among the three

arms. Pre-randomization SpO₂ was the only variable that differed significantly among groups, being slightly lower in Group A than in Groups B and C (93.7±1.7%, 94.7±1.8%, and 94.4±1.9%, respectively; p=0.027). Overall, the three study arms were well balanced at baseline (Table 2).

Early post-weaning evaluation shown no significant intergroup differences in pH (p = 0.544), PaCO₂ (p = 0.556), PaO₂ (p = 0.328), or ΔPaCO₂ (p = 0.818). Likewise, respiratory rate, heart rate, and SpO₂ did not vary significantly among the groups (p = 0.893, p = 0.804, and p = 0.625, respectively). At the late post-weaning assessment, no significant differences were detected amongst the three groups regarding pH (p = 0.463), PaCO₂ (p = 0.203), or ΔPaCO₂ (p = 0.784). Likewise, vital signs, including respiratory rate, heart rate, and SpO₂, remained comparable among the groups (p = 0.408, p = 0.928, and p = 0.331, respectively) available in *Supplementary Table 1*.

Figure 1 illustrated the serial changes in arterial blood gas parameters and respiratory rate following NIV weaning. PaCO₂ decreased significantly after randomization in all groups; however, it remained stable thereafter only in the duration and pressure step-down groups, whereas a significant increase was observed between 2 and 48 hours following immediate withdrawal (P = 0.037). Arterial pH remained unchanged throughout follow-up. PaO₂ increased significantly only in the duration step-down group, while respiratory rate decreased significantly in both gradual weaning groups but remained unchanged following immediate withdrawal.

Within-group repeated-measures analysis demonstrated significant temporal changes in PaCO₂ in all three study groups (*Supplementary Table 2*). In both the duration step-down and pressure step-down groups, PaCO₂ decreased significantly from pre-randomization to 2 hours and remained stable thereafter, as no significant difference was observed between 2 and 48 hours (both P >0.05). In contrast, although the immediate withdrawal group showed a significant initial reduction in PaCO₂ at 2 hours, PaCO₂ increased significantly between 2 and 48 hours (P = 0.037), indicating less stable maintenance of carbon dioxide control following abrupt NIV discontinuation.

Arterial pH remained stable throughout follow-up in all three groups, with only a small increase between pre-randomization and 48 hours in the duration step-down group. PaO₂ increased significantly over time in the duration step-down group, whereas no significant temporal changes were observed in the pressure step-down group. In the immediate withdrawal group, PaO₂ showed a numerical decline after NIV discontinuation; however,

pairwise comparisons did not reach statistical significance. Respiratory rate decreased significantly over time in both gradual weaning groups but remained unchanged in the immediate withdrawal group.

Rate of successful weaning within 48 hours differed significantly among the study groups, with the highest success observed in the duration step-down group (82.9%), followed by the pressure step-down group (74.3%), and the lowest rate in the immediate withdrawal group (54.3%) ($p = 0.008$) (Table 3).

The duration of cumulative post-randomization NIV exposure differed significantly among the three groups ($P < 0.001$), being longest in the duration step-down group (34.9 ± 0.8 h), followed by the pressure step-down group (32.8 ± 7.2 h), and shortest in the immediate withdrawal group (18.8 ± 6.0 h). Likewise, the time from randomization to final outcome determination varied significantly across the study groups ($P < 0.001$). Patients assigned to duration step-down required the longest interval to reach the final study outcome (119.3 ± 11.1 h), followed by the pressure step-down group (72.6 ± 19.3 h), whereas the immediate withdrawal group had the shortest time (38.7 ± 16.4 h). This reflected the additional time required to complete the assigned gradual weaning strategy before initiation of the predefined 48-hour post-weaning assessment in Groups A and B, while patients experiencing weaning failure were classified immediately when the first predefined failure criterion occurred.

Re-initiation of NIV during 48 hours occurred more frequently in the immediate withdrawal group (28.6%) compared with the pressure step-down (17.1%) and duration step-down (11.4%) groups ($p = 0.031$). Although the need for intubation or mortality among the studied groups were numerically higher in the immediate withdrawal group, these differences were not statistically significant ($p = 0.339$, $p = 0.128$ respectively). Similarly, duration of ICU and hospital stay did not change significantly among the three groups ($p = 0.100$ and $p = 0.198$, respectively) (Table 3).

As shown in *Supplementary Table 3*, patients who achieved successful NIV weaning had a significantly longer duration of NIV before randomization than those with failed weaning (53.0 ± 10.6 vs. 47.6 ± 12.4 h, $P = 0.039$). Successful weaning was also associated with a lower respiratory rate at 2 hours (18.34 ± 3.16 vs. 22.55 ± 5.09 breaths/min, $P < 0.001$) and lower APACHE II scores (8.04 ± 3.16 vs. 15.45 ± 3.76 , $P < 0.001$). In addition, patients with successful weaning demonstrated significantly greater reductions in PaCO₂ from baseline at both 2 hours [-4.0 (-7.0 to -1.0) vs. 5.0 (-0.5 to 11.0) mmHg, $P < 0.001$] and 48 hours [-5.5 (-9.0 to -2.0) vs. 7.0 (2.0 to 12.0) mmHg, $P < 0.001$]. In contrast, maximum IPAP and EPAP, admission GCS,

arterial pH and PaCO₂ at admission and randomization, and FEV₁% did not differ significantly between patients with successful and failed weaning (all P >0.05).

Univariate logistic regression analysis identified immediate withdrawal as a significant predictor of NIV weaning failure compared with the duration step-down strategy (OR 4.07, 95% CI 1.35–12.26; P = 0.013). Higher APACHE II scores (OR 1.84, 95% CI 1.45–2.34; P <0.001), higher PaCO₂ at 2 hours (OR 1.07, 95% CI 1.01–1.12; P = 0.020), and higher respiratory rate at 2 hours (OR 1.30, 95% CI 1.15–1.47; P <0.001) were associated with increased odds of NIV weaning failure. Conversely, longer pre-randomization NIV duration (OR 0.96, 95% CI 0.92–1.00; P = 0.029), higher PaO₂ at 2 hours (OR 0.89, 95% CI 0.85–0.94; P <0.001), and higher SpO₂ at 2 hours (OR 0.65, 95% CI 0.54–0.79; P <0.001) were associated with lower odds of weaning failure. Age, sex, admission GCS, FEV₁, pre-randomization arterial blood gas parameters, FiO₂, respiratory rate, and the pressure step-down strategy were not significantly associated with NIV weaning failure (all P >0.05) as shown in *Supplementary Table 4*.

Variables identified as clinically relevant and/or associated with NIV weaning failure in the univariate analysis were entered into the multivariable logistic regression model (Table 4). After adjustment for potential confounders, higher APACHE II score remained an independent predictor of NIV weaning failure (adjusted OR 2.01, 95% CI 1.47–2.75; P <0.001). In addition, immediate withdrawal was independently associated with a significantly higher risk of weaning failure compared with the duration step-down strategy (adjusted OR 14.19, 95% CI 1.65–121.76; P = 0.016). In contrast, FEV₁ (% predicted), pre-randomization PaCO₂, pre-randomization NIV duration, and the pressure step-down strategy were not independently associated with weaning failure after multivariable adjustment (all P >0.05).

NIV-related complications were comparable among the three arms, with no statistically significant differences found in pressure ulcers (p = 0.850), air leak (p = 0.818), nasal dryness (p = 0.929), gastric distension (p = 0.873), aspiration (p = 0.771), and healthcare-associated pneumonia (p = 0.895). Similarly, no significant differences were observed in post-discharge outcomes, including re-hospitalization within 30 days (p = 0.247) and discharge therapy requirements which included both continuation of pre-existing LTOT and newly prescribed respiratory support following hospitalization (p = 0.925) (*Supplementary Table 5*).

Receiver operating characteristic analysis showed that APACHE II had excellent discrimination for NIV weaning failure across all strategies (AUC 0.900–0.975; all P ≤0.002), with optimal cut-offs of >12.5 for duration step-down and >10.5 for the other groups. Two-hour PaCO₂ was

predictive only in the pressure step-down group (AUC 0.756, 95% CI 0.579–0.934; $P=0.024$), whereas pre-randomization PaCO_2 was not predictive in any group (*Supplementary Table 6*).

Discussion

The present randomized trial compared three strategies for discontinuation of non-invasive ventilation (NIV) in COPD patients recovering from acute hypercapnic respiratory failure. The principal finding was that gradual withdrawal, particularly the duration step-down strategy, resulted in a significantly higher successful weaning rate and a lower frequency of NIV reinstitution than immediate withdrawal. Although intubation, mortality, ICU stay, hospital stay, and NIV-related complications were comparable among the three strategies, gradual withdrawal was associated with a more favorable weaning outcome. Furthermore, higher APACHE II score and the immediate withdrawal strategy independently predicted weaning failure, whereas patients with successful weaning demonstrated greater early reductions in PaCO_2 and lower respiratory rates during follow-up.

Our findings are generally consistent with previous studies evaluating different NIV weaning strategies. Purohit et al. reported a numerically higher rate of successful NIV withdrawal using a duration step-down strategy than immediate withdrawal, although the difference did not reach statistical significance [18]. Similarly, Venkatnarayan et al. observed comparable overall weaning success among duration step-down, pressure step-down, and immediate withdrawal strategies and concluded that abrupt discontinuation may be feasible in carefully selected patients [19]. Differences from previous studies may reflect variations in patient selection, disease severity, weaning criteria, randomization timing, and outcome definitions. In our study, randomization occurred only after predefined clinical and gasometric stability criteria were met, minimizing baseline physiological differences among groups.

Serial within-group analysis demonstrated sustained improvement in PaCO_2 after both gradual weaning strategies. In contrast, the immediate withdrawal group exhibited a significant increase in PaCO_2 between 2 and 48 hours after NIV discontinuation, indicating less stable maintenance of carbon dioxide control following abrupt withdrawal. Likewise, respiratory rate declined progressively only in the gradual weaning groups, consistent with a more stable pattern of ventilatory recovery following NIV discontinuation. Although arterial pH and PaO_2 showed only modest temporal changes, these findings collectively support the concept that gradual withdrawal facilitates a smoother transition from assisted to spontaneous breathing while maintaining physiological stability. Importantly, arterial blood gas values remained

comparable between groups at individual assessment time points, indicating that the observed differences reflected temporal recovery patterns rather than persistent between-group physiological differences.

The physiological mechanisms responsible for successful NIV weaning are likely multifactorial [20-22]. Previous physiological studies have demonstrated that discontinuation of positive-pressure ventilation may increase inspiratory effort before complete recovery of respiratory muscle function [20,21]. Likewise, transient deterioration in pulmonary mechanics and exercise tolerance has been observed immediately following NIV withdrawal despite relatively stable arterial blood gases. Although these physiological studies were performed predominantly in patients receiving chronic NIV, they support the concept that gradual withdrawal may facilitate a more progressive transition to unsupported breathing. Nevertheless, because inspiratory effort, work of breathing, oesophageal pressure swings, intrinsic positive end-expiratory pressure, diaphragmatic function, and patient-ventilator asynchrony were not directly assessed in the present study, these mechanisms remain hypothetical.

Our multivariable analysis identified both disease severity and the selected weaning strategy as independent determinants of NIV weaning outcome. Higher APACHE II score remained the strongest independent predictor of weaning failure, emphasizing the major influence of acute illness severity on the ability to sustain spontaneous breathing after discontinuation of ventilatory support. This finding is consistent with previous studies demonstrating that higher APACHE II scores independently predict NIV failure in patients with acute hypercapnic respiratory failure [15,23]. Immediate withdrawal was also independently associated with a substantially greater risk of weaning failure than the duration step-down strategy, suggesting that abrupt discontinuation may expose susceptible patients to recurrent ventilatory insufficiency despite initial clinical stabilization. In addition, patients with successful weaning demonstrated greater early reductions in PaCO₂ and lower respiratory rates during follow-up. These findings suggest that early improvement in alveolar ventilation and unloading of the respiratory muscles reflect more complete recovery from the acute episode, whereas persistent hypercapnia and tachypnea may identify patients at increased risk of recurrent respiratory failure requiring NIV reinstitution. Similar associations between persistent hypercapnia, elevated respiratory rate, and unsuccessful NIV weaning have recently been reported in prospective studies of respiratory ICU patients [24].

Although some secondary outcomes were not statistically significant, modest reductions in recurrent respiratory failure and NIV reinstitution may remain clinically relevant by preventing deterioration, invasive ventilation, and patient discomfort. Therefore, these findings should be interpreted considering both the magnitude and clinical relevance of the observed effects, rather than statistical significance alone.

NIV-related complications and 30-day rehospitalization were comparable among the three groups, with no reported barotrauma. These findings suggest that NIV withdrawal strategy has little effect on safety when standardized protocols and careful monitoring are applied, consistent with previous studies of clinically stabilized COPD patients [25].

Conclusions

The present study demonstrates that gradual withdrawal of NIV, particularly using a duration step-down strategy, achieved higher successful weaning rates and reduced the need for NIV reinstitution compared with immediate withdrawal in COPD patients recovering from acute hypercapnic respiratory failure. Higher APACHE II score and immediate withdrawal independently predicted weaning failure.

Limitations of the study

This study was strengthened by its randomized design, balanced baseline characteristics, standardized weaning criteria, and serial assessment of clinical and gasometric outcomes. However, its single-center setting and modest sample size may limit generalizability and statistical power for infrequent outcomes and multivariable analyses. Direct assessments of inspiratory effort, oesophageal pressure, work of breathing, diaphragmatic function, patient–ventilator interaction, and validated dyspnea scores were unavailable, limiting mechanistic interpretation. Moreover, subgroup ROC analyses included relatively few weaning failures and require external validation. Finally, longer-term post-discharge outcomes were not assessed.

Recommendations

In COPD patients presenting with acute hypercapnic respiratory failure, these findings support the use of gradual weaning strategies, duration step-down, especially among those with higher disease severity or persistent hypercapnia.

List of Abbreviation

AECOPD: Acute exacerbation of chronic obstructive pulmonary disease.

APACHE II: Acute Physiology and Chronic Health Evaluation II.

COPD: Chronic obstructive pulmonary disease.

EPAP: Expiratory positive airway pressure.

FEV₁: Forced expiratory volume in one second.

FiO₂: Fraction of inspired oxygen.

IPAP: Inspiratory positive airway pressure.

NIV: Noninvasive ventilation.

OR: Odds ratio.

PaCO₂: Partial pressure of carbon dioxide.

PaO₂: Partial pressure of oxygen.

SpO₂: Peripheral oxygen saturation.

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Online supplementary material

Supplementary Figure 1. Flow diagram of patient screening, exclusion, randomization, and outcomes among the study population (n=150).

Supplementary Table 1. Arterial blood gas parameters and vital signs across study groups at different time points following noninvasive ventilation weaning (n=105).

Supplementary Table 2. Within-group repeated-measures analysis of arterial blood gas parameters and respiratory rate following noninvasive ventilation weaning according to the allocated weaning strategy.

Supplementary Table 3. Comparison of baseline clinical characteristics, ventilatory settings, and arterial blood gas parameters between patients with successful and failed noninvasive ventilation weaning (n=105).

Supplementary Table 4. Univariate logistic regression analysis of predictors of noninvasive ventilation weaning failure (n=105).

Supplementary Table 5. Complications and post-discharge outcomes among the study groups (n=105).

Supplementary Table 6. Receiver operating characteristic analysis for predicting noninvasive ventilation weaning failure according to weaning strategy.

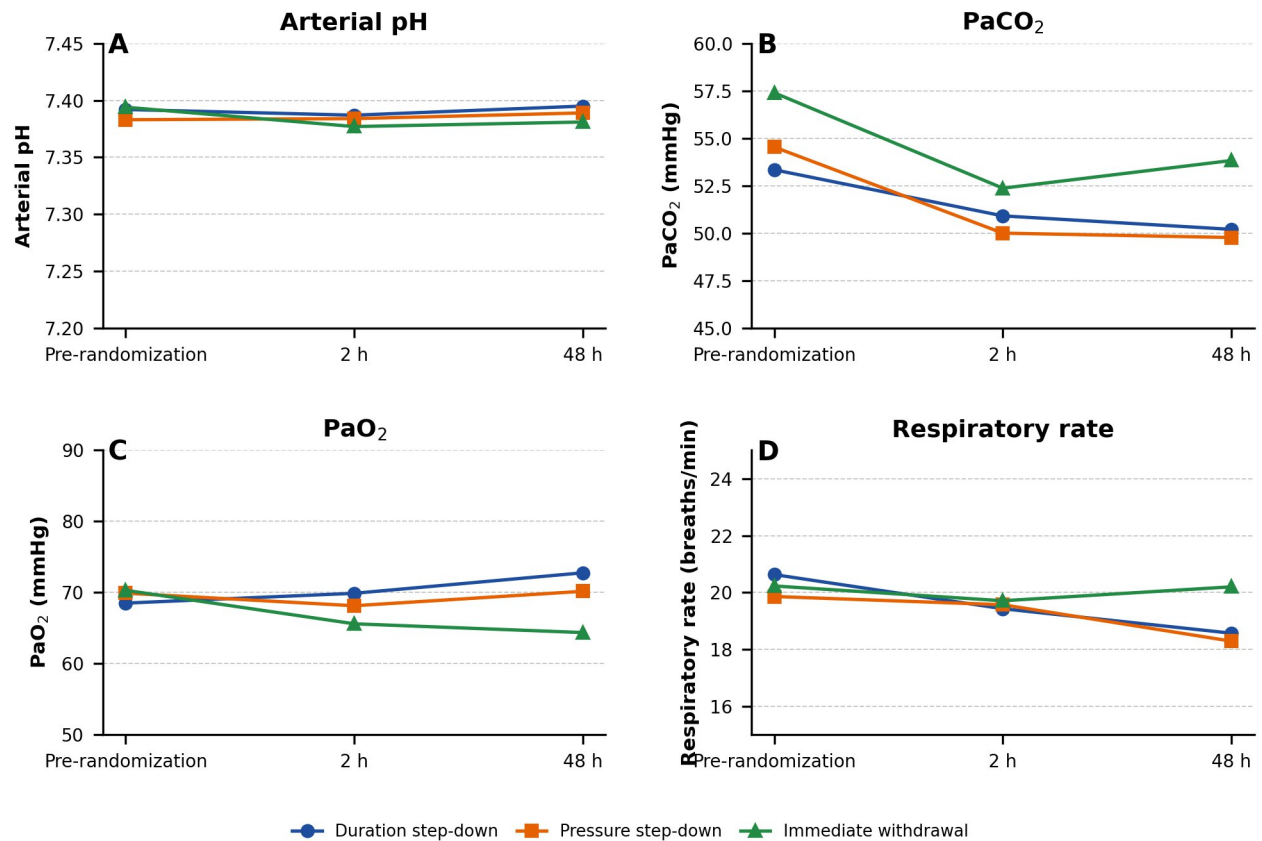


Figure 1. Serial changes in arterial blood gas parameters and respiratory rate following non-invasive ventilation (NIV) weaning according to the allocated weaning strategy. Mean ($\pm$ SD) values of arterial pH, arterial partial pressure of carbon dioxide (PaCO₂, mmHg), arterial partial pressure of oxygen (PaO₂, mmHg), and respiratory rate (breaths/min) measured at pre-randomization (T1), 2 hours after randomization (T2), and 48 hours after complete NIV discontinuation (T3) in the duration step-down, pressure step-down, and immediate withdrawal groups. Within-group temporal changes were analyzed using one-way repeated-measures analysis of variance followed by Bonferroni-adjusted pairwise comparisons. SD, standard deviation.

Table 1. Demographic and clinical characteristics at baseline across the study groups (n=105).

Variable	Group A: duration step-down (n=35)	Group B: pressure step-down (n=35)	Group C: immediate withdrawal (n=35)	P
Age, years (mean ± SD)	65.1±5.8	63.9±6.1	62.1±4.7	0.097
Male sex, n (%)	24 (68.6)	28 (80.0)	22 (62.9)	0.077
Body mass index, kg/m ² (mean ± SD)	27.0±4.1	25.9±5.1	27.6±3.3	0.073
Smoking status, n (%)				0.585
Current smoker	12 (34.3)	8 (22.9)	11 (31.4)	
Ex-smoker	14 (40.0)	15 (42.9)	13 (37.1)	
Non-smoker	9 (25.7)	12 (34.3)	11 (31.4)	
GCS at admission (mean ± SD)	13.7±1.0	13.5±0.7	13.3±1.0	0.200
Hypertension, n (%)	20 (57.1)	19 (54.3)	17 (48.6)	0.765
Diabetes mellitus, n (%)	11 (31.4)	12 (34.3)	12 (34.3)	0.918
Ischemic heart disease, n (%)	6 (17.1)	11 (31.4)	7 (20.0)	0.103
Chronic kidney disease, n (%)	7 (20.0)	5 (14.3)	6 (17.1)	0.818
Previous long-term oxygen therapy, n (%)	9 (25.7)	7 (20.0)	8 (22.9)	0.850
Exacerbations in the previous year (mean ± SD)	2.1±1.0	2.2±1.0	2.3±1.0	0.843
Pre-randomization APACHE II score (mean ± SD)	10.0±4.7	9.6±4.1	11.1±5.2	0.506
Baseline FEV ₁ (% predicted) (mean ± SD)	44.9±15.4	43.5±14.2	42.8±11.6	0.931

Comparisons among the three groups were performed using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables, as appropriate. A two-tailed P value < 0.05 was considered statistically significant. Abbreviations: GCS, Glasgow Coma Scale; COPD, chronic obstructive pulmonary disease; APACHE II, Acute Physiology and Chronic Health Evaluation II; FEV₁, forced expiratory volume in one second.

Table 2. Vital signs, arterial blood gas, and ventilatory parameters at initiation of NIV and pre-randomization among the three groups (n=105).

Variable	Group A: duration step-down (n=35)	Group B: pressure step-down (n=35)	Group C: immediate withdrawal (n=35)	p
ABG at admission				
pH (mean ± SD)	7.29±0.03	7.30±0.03	7.30±0.03	0.261
PaCO ₂ , mmHg (mean ± SD)	68.1±13.5	67.8±9.9	68.9±10.3	0.902
PaO ₂ , mmHg (mean ± SD)	61.4±4.6	61.5±5.6	61.7±5.7	0.951
SpO ₂ , % (mean ± SD)	88.8±3.0	89.0±2.5	88.9±2.9	0.925
Pre-randomization ABG				
pH (mean ± SD)	7.39±0.04	7.38±0.03	7.39±0.03	0.335
PaCO ₂ , mmHg (mean ± SD)	53.3±7.6	54.5±7.7	57.4±7.4	0.091
PaO ₂ , mmHg (mean ± SD)	68.5±7.5	69.9±8.9	70.3±7.9	0.607
SpO ₂ , % (mean ± SD)	93.7±1.7	94.7±1.8	94.4±1.9	0.027*
Pre-randomization vital sign				
FiO ₂ (mean ± SD)	0.35±0.06	0.36±0.06	0.38±0.07	0.170
Respiratory rate, breaths/min (mean ± SD)	20.6±2.7	19.9±2.5	20.2±2.7	0.563
Heart rate, beats/min (mean ± SD)	101.3±14.3	98.7±13.1	94.1±14.9	0.107
Systolic blood pressure, mmHg (mean ± SD)	127.4±19.2	121.5±19.4	124.9±17.2	0.374
NIV parameters at randomization				
Duration of NIV use before randomization, h (mean ± SD)	52.1±10.2	51.2±12.0	50.8±12.1	0.335
IPAP, cmH ₂ O (mean ± SD)	17.6±1.2	17.6±1.3	18.1±1.5	0.369
EPAP, cmH ₂ O (mean ± SD)	5.0±0.9	5.1±0.8	5.1±0.8	0.854

PaCO₂, partial pressure of carbon dioxide; PaO₂, partial pressure of oxygen; SpO₂, peripheral oxygen saturation; FiO₂, fraction of inspired oxygen; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure.

Table 3. Primary and secondary clinical outcomes following NIV weaning among the study groups (n=105).

Outcome	Group A: duration step-down (n=35)	Group B: pressure step-down (n=35)	Group C: immediate withdrawal (n=35)	p
Successful weaning after 48-hour observation, n (%)	29 (82.9)	26 (74.3)	19 (54.3)	0.008*
NIV reinstitution during the 48-hour post-weaning assessment, n (%)	4 (11.4)	6 (17.1)	10 (28.6)	0.031*
Need for intubation, n (%)	2 (5.7)	2 (5.7)	4 (11.4)	0.339
Mortality (ICU/in-hospital), n (%)	0 (0.0)	1 (2.9)	2 (5.7)	0.128
Cumulative post-randomization NIV exposure, h (mean $\pm$ SD)	34.9 $\pm$ 0.8	32.8 $\pm$ 7.2	18.8 $\pm$ 6.0	<0.001*
ICU length of stay, days (mean $\pm$ SD)	6.5 $\pm$ 2.3	7.5 $\pm$ 2.0	7.4 $\pm$ 2.2	0.100
Hospital length of stay, days (mean $\pm$ SD)	10.0 $\pm$ 2.8	11.2 $\pm$ 3.5	11.3 $\pm$ 3.4	0.198
Time from randomization to outcome determination, h (mean $\pm$ SD)	119.3 $\pm$ 11.1	72.6 $\pm$ 19.3	38.7 $\pm$ 16.4	<0.001*

Cumulative post-randomization NIV exposure was defined as the total number of hours during which NIV was delivered after randomization, including protocol-directed NIV during gradual withdrawal and any NIV administered following reinstitution after initial discontinuation. Time to outcome represents the elapsed time from randomization to final outcome determination. For successful cases, it included completion of the assigned NIV withdrawal strategy followed by 48 consecutive hours without NIV reinstitution or endotracheal intubation. For failed cases, it ended at the occurrence of the first predefined failure criterion. Statistical comparisons among the three groups were performed using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test, and the chi-square test or Fisher’s exact test as proper. P value less than 0.05 was a significant.

Table 4. Multivariable logistic regression analysis of independent predictors of NIV weaning failure (n=105).

Variable	β (B)	SE	Adjusted OR (Exp(B))	95% CI	p
FEV ₁ (% predicted)	-0.055	0.033	0.95	0.89–1.01	0.094
APACHE II score	0.698	0.160	2.01	1.47–2.75	<0.001*
Pre-randomization PaCO ₂ (mmHg)	-0.120	0.066	0.89	0.78–1.01	0.069
Pre-randomization NIV duration (h)	-0.031	0.037	0.97	0.90–1.04	0.391
Pressure step-down group	1.405	1.036	4.08	0.54–31.07	0.175

Multivariable logistic regression analysis was performed to identify independent predictors of NIV weaning failure. Variables entered into the multivariable model were selected based on clinical relevance and/or a P value <0.10 in the univariate analysis. The duration step-down group served as the reference category for weaning strategy. Adjusted odds ratios (ORs), 95% confidence intervals (CIs), and corresponding P values are presented. ORs >1 indicate increased odds of NIV weaning failure, whereas ORs <1 indicate reduced odds of failure. APACHE II, Acute Physiology and Chronic Health Evaluation II; FEV₁, forced expiratory volume in one second; NIV, non-invasive ventilation; PaCO₂, arterial partial pressure of carbon dioxide; OR, odds ratio; CI, confidence interval; SE, standard error. A two-sided P value <0.05 was considered statistically significant.