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RESEARCH ARTICLE

# AVAPS-NIV treatment in hypercapnic respiratory failure with insufficient response to fixed-level PS-NIV

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## ABSTRACT

### AVAPS-NIV treatment in hypercapnic respiratory failure with insufficient response to fixed-level PS-NIV

**Introduction:** *Noninvasive ventilation (NIV) for acute hypercapnic respiratory failure (AHRF) is an established treatment modality. Current evidence does not conclude any superiority between fixed pressure support (PS) and average volume-assured pressure support (AVAPS) modes. However, given the ability of rapid $PaCO_2$ decline in AVAPS mode, we hypothesized that COPD patients with AHRF who did not show the desired reduction in $PaCO_2$ with fixed-level PS-NIV might benefit from the AVAPS mode.*

**Materials and Methods:** *Patients admitted to the non-ICU pulmonary ward with acute exacerbation of COPD (AECOPD) and AHRF were included consecutively in this observational study. Patients with hypercapnic respiratory failure due to obesity-hypoventilation, neurological diseases, or chest wall deformities were excluded. All patients started NIV treatment with fixed pressure support (PS) and patients who did not reach clinical and laboratory stability under PS-NIV treatment were switched to the average volume-assured pressure support (AVAPS) mode of NIV.*

**Results:** *Thirty-five COPD patients with hypercapnic respiratory failure were included. Under PS-NIV treatment, 14 (40%) patients showed a 17.9 (-0.0–29.2) percent change in terms of $PaCO_2$, meaning no improvement or worsening. Therefore, these patients were treated with AVAPS mode. Arterial $PaCO_2$ and pH levels significantly improved after AVAPS-NIV administration. AVAPS-NIV treatment created a significantly better $PaCO_2$ change rate than using PS-NIV [-11.4 (-22.0 - -0.5) vs 8.2 (-5.3–19.5), p= 0.02]. Independent predictors of AVAPS mode requirement were higher Charlson Comorbidity Index [OR= 1.74 (95% CI= 1.02–2.97)] and higher $PaCO_2$ upon admission [OR= 1.18 (95% CI= 1.03–1.35)]. Thirteen (92.8%) patients reaching significant clinical stability with AVAPS-NIV were able to return to fixed-level PS-NIV and maintain acceptable $PaCO_2$ levels.*

**Conclusion:** *Our study demonstrated that patients can benefit from AVAPS-NIV despite insufficient response to fixed-level PS-NIV.*

**Key words:** *Hypercapnic respiratory failure; NIV treatment; avaps; copd exacerbation*

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**ÖZ**

**Hiperkarbik solunum yetmezliğinde sabit basınç destekli NIV tedavisine yetersiz yanıtta AVAPS-NIV tedavisi uygulaması**

**Giriş:** *Noninvaziv ventilasyon (NIV) akut solunum yetmezliğinde (ASY) yer etmiş bir tedavi seçeneğidir. Mevcut çalışmalar sabit düzeyde basınç desteği (PS) ile ortalama volüm garantili basınç desteği (AVAPS) modları arasında üstünlük konusunda fikir birliğine varmamıştır. Bu çalışmada hipotezimiz; avaps modu ile elde edilen hızlı $PaCO_2$ düşüşü göz önünde bulundurularak, akut hiperkarbik solunum yetmezliği ile başvuran KOAH hastalarında PS-NIV ile hedeflenen $PaCO_2$ düzelmesine ulaşılamadığı durumlarda AVAPS modunun kullanımının faydalı olabileceğidir.*

**Materyal ve Metod:** *Göğüs hastalıkları servisinde KOAH akut alevlenme ilişkili hiperkarbik ASY ile takip edilen hastalar sırayla bu gözlemsel çalışmaya dahil edilmiştir. Hiperkarbik ASY obezite-hipoventilasyon, nörolojik hastalıklar ve göğüs duvarı deformiteleri ile ilişkilendirilen hastalar çalışma dışı bırakılmıştır. Tüm hastalara PS-NIV desteği başlanmış ve hedeflenen klinik ve laboratuvar stabiliteye ulaşılamayan hastalar AVAPS modda takibe alınmıştır.*

**Bulgular:** *Hiperkarbik solunum yetmezliği olan 35 KOAH hastası çalışmaya dahil edilmiştir. On dört (%40) hastada PS-NIV desteği takiplerinde $PaCO_2$ düzeyinde %17,9 (-0,0–29,2) oranında değişim izlenmiş yani kan gazı parametrelerinde düzelme olmamış veya kötüleşme gözlenmiştir. Bu sebeple hastalara NIV desteği AVAPS moduna geçilmiştir. AVAPS-NIV tedavisi ile arteriyel kan gazında pH ve $PaCO_2$ düzeylerinde anlamlı düzelme izlenmiştir. AVAPS modunun kullanımı sabit PS modunun kullanımına göre daha iyi oranda $PaCO_2$ yanıtı ile ilişkilendirilmiştir [-11,4 (-22,0 - -0,5) vs 8,2 (-5,3–19,5), p= 0,02]. Hastalarda AVAPS moduna geçiş ihtiyacını öngören bağımsız parametreler ise yüksek Charlson komorbidite indeksi [OR= 1,74 (95% CI= 1,02–2,97)] ve başvuruda yüksek $PaCO_2$ düzeyi [OR= 1,18 (95% CI= 1,03–1,35)] olarak belirlenmiştir. AVAPS moduna ihtiyaç duyan hastaların 13 (%92,8)'ünde klinik stabilizasyon sağlandıktan sonra sabit basınçlı PS moda geçiş yapılabilmiş ve kabul edilebilir $PaCO_2$ düzeyleri korunmuştur.*

**Sonuç:** *Çalışmamız, sabit düzeyde PS ile yeterli düzelme göstermeyen hastaların AVAPS modundan fayda görebileceğini işaret etmektedir.*

**Anahtar kelimeler:** *Hiperkarbik solunum yetmezliği; NIV tedavisi; avaps; koah atak*

## INTRODUCTION

Noninvasive ventilation (NIV) for acute respiratory failure (ARF) is an established treatment modality. NIV is recommended in acute hypercapnic respiratory failure (AHRF) due to chronic obstructive lung disease (COPD) exacerbation, ARF due to cardiogenic pulmonary edema, and ARF in immunocompromised patients or post-operative settings (1). NIV in the treatment of respiratory failure due to COPD exacerbation results in better survival, decreased need for intubation, and better and rapid improvement in arterial pH and $PaCO_2$ (2).

Healthcare professionals have many choices for ventilatory modes of NIV. Fixed-level pressure support (PS) mode of NIV delivers inspiratory and expiratory airway pressure in a fixed preset manner but does not guarantee delivered tidal volume. Average volume-assured pressure support (AVAPS) mode automatically adjusts pressure support within settings to provide a target tidal volume and therefore sustains adequate ventilation even in changing airway resistance, inspiratory effort, lung compliance, or body position (3).

There are few studies on AVAPS-NIV use in acute settings and COPD patients with respiratory failure, and the results are conflicting (3). Current evidence does not conclude any superiority between PS and AVAPS modes, however, $PaCO_2$ reduction in some studies is greater in the AVAPS-NIV group compared to the PS-NIV group (3-7).

### Objectives

Given the ability of rapid $PaCO_2$ decline in AVAPS mode, we hypothesized that COPD patients with AHRF who did not show the desired reduction in $PaCO_2$ with fixed-level PS-NIV might benefit from AVAPS mode. The primary objective of our study is to evaluate the performance of AVAPS-NIV on $PaCO_2$ measurements. Secondary outcomes are the effects of AVAPS-NIV treatment on length of stay and intubation rates.

## MATERIALS and METHODS

### Subjects

The study was designed as an observational study in a tertiary care pulmonary clinic, which retrospectively included patients admitted to the non-ICU pulmonary ward with acute exacerbations of COPD (AECOPD) and hypercapnic respiratory failure. AECOPD was defined as an acute event characterized by the worsening of the patient's respiratory symptoms beyond normal variation and leading to a change in medication (8). Hypercapnic respiratory failure was defined as arterial pH≤ 7.35 and $PaCO_2$> 45 mmHg (1). Respiratory support was considered if the patient

presented with acute respiratory failure leading to acute or acute-on-chronic respiratory acidosis or respiratory rate> 24 breaths/minute despite optimum medical treatment (1).

Patients with hypercapnic respiratory failure due to obesity-hypoventilation, neurological diseases, or chest wall deformities were not included in this study. Patients with contraindications for NIV treatment were excluded from the study. Exclusion criteria included pneumothorax, pulmonary embolism, difficulty with secretion clearance, upper airway obstruction, ventricular arrhythmia, myocardial ischemia, hemodynamic instability despite fluid treatment, facial deformities, recent surgery of cranium or upper gastrointestinal system, lack of cooperation, altered consciousness not due to hypercapnia.

**Interventions**

Ventilation support was provided by the same noninvasive ventilator (Philips, Respironics Inc, Murrysville, PA, USA). All patients received fixed-level pressure support NIV upon admission. Patients using home NIV devices started the treatment with previously used pressure support settings (9). Patients who did not use NIV treatment at home started the treatment in a standardized manner. In the fixed-level pressure-support (PS) mode of NIV, inspiratory airway pressure (IPAP) and expiratory airway pressure (EPAP) were initially set as 10 cm $H_2O$ and 4 cm $H_2O$, respectively. Airway pressures were gradually adjusted according to patients' tolerance and arterial blood gas analysis. IPAP was incremented by 2 cm $H_2O$ and EPAP was incremented by 1 cm $H_2O$ in each adjustment, up to 25 cm $H_2O$ and 10 cm $H_2O$ respectively (10). Oro-nasal masks compatible with patients' face sizes with an oxygen port were used in all patients. Supplemental oxygen flow was adjusted to maintain oxygen saturation between 88-92%. All patients were advised to use NIV for 18 hours/day in the beginning and were disconnected for an hour for each meal. Patients who didn't reach clinical and laboratory stability under fixed pressure support (PS) were switched to using the average volume-assured pressure support (AVAPS) mode of NIV. Clinical and laboratory stability was defined as Glasgow Coma Scale score= 15, respiratory rate< 24 breaths/minute, oxygen saturation≥ 90%, and normalized arterial pH with $PaCO_2$ reduction. In the volume-targeted mode of NIV initial settings were as follows; target tidal volume was calculated as 6-8 mL/kg of body weight, maximum IPAP was set as 20 cm $H_2O$, minimum IPAP and EPAP were set as 10 cm $H_2O$ (10). Using NIV-AVAPS mode EPAP was set according to previous NIV-PS mode EPAP values to ensure adequate oxygen saturation (11). All settings were adjusted in 1-4 hours after the NIV AVAPS mode of treatment according to patients' tolerance and arterial blood gas analysis. Keeping in mind that these patients did not respond well to NIV-PS, the aim of the frequent controls was to avoid a delay in escalation to invasive mechanical ventilation and prevent higher mortality related to late and/or urgent intubation (1). IPAP was incremented by 2 cm $H_2O$ up to 30 cm $H_2O$ and target tidal volume was incremented by 50-100 mL in each adjustment. Back-up frequency was 10 breaths/min and inspiratory time was between 0.5-2.0 s (10,12).

Arterial sampling was obtained via vascular puncture from the radial artery. Arterial blood gas analysis was evaluated within one and four hours after adjusting NIV settings and might change in frequency depending on the patient's condition and treatment response. Arterial blood gas analysis was measured more frequently in patients with confusion, low pH, and high $PaCO_2$ levels. Duration of NIV was decreased in patients showing clinical and laboratory stability. After reaching 12-14-hour/day of NIV support without any deterioration, pressure support was also decreased. Stable patients under the AVAPS mode of NIV treatment were re-assigned to use PS mode. Compliance with NIV was encouraged at all times.

Endotracheal intubation or intensive care unit transfer was considered in case of cardiac or respiratory arrest, decreased consciousness (Glasgow Coma Scale score≤ 11), psychomotor agitation, aspiration, vomiting, hemodynamic instability, thoracic-abdominal paradoxical movement, discordance with NIV or oxygen saturation below 80% despite maximum oxygen supplementation, arterial pH< 7.25 or pronounced increase in $PaCO_2$.

Decisions on NIV support and changes within and between treatment modes were made by an experienced team of pulmonary physicians in a specialized ward. In addition to NIV support, COPD patients received exacerbation therapy including bronchodilators, intravenous antimicrobial therapy, and systemic corticosteroids as deemed necessary by the attending physician.

### Measurements and Outcomes

A detailed structured form, including risk factors, smoking status, disease history, and comorbid conditions was completed for each patient. Biochemical results and blood cell counts were recorded at admission. NIV parameters such as mode, EPAP, IPAP, tidal volume and daily use of treatment, arterial blood gas analysis upon admission, and changes during NIV treatment were evaluated. Long-term oxygen therapy (LTOT) use and domiciliary NIV was recorded according to patients' statements. Dyspnea severity was assessed using the modified Medical Research Council (mMRC) Dyspnea Scale.

### Statistical Analysis

Data was analyzed using Statistical Package for Social Sciences (SPPS) version 22. Means and standard deviations were reported for normally distributed continuous data, and medians and inter-quartile ranges (ICR) for non-normally distributed continuous data. Differences between the two groups' means in independent samples and paired samples were analyzed with Student's t-test and a paired sample t-test, respectively. Differences between the two groups' medians in independent samples and paired samples were analyzed with Mann-Whitney U and Wilcoxon tests, respectively. Repeated measures analysis of variance was used to evaluate changes in blood gas analyses. The greenhouse-Geisser correction was used when the sphericity assumption was violated. Categorical variables were compared by the Chi-square test. Candidate risk factors related to AVAPS requirement were evaluated firstly by univariate analysis and then possible risk factors with p values below 0.15 were evaluated by multiple logistic regression model to identify independent predictors of AVAPS requirement. Values of $p< 0.05$ were considered statistically significant.

### Ethical Considerations

The institutional ethics committee approved the study protocol (Date: 10/06/2020, Number: 2020-10/30). Written and oral informed consent were taken from all participants. The study was conducted in compliance with the Declaration of Helsinki.

## RESULTS

We included 35 COPD patients with hypercapnic respiratory failure with a mean age of 70.7 ± 7.8 years. The study population included 26 (74.3%) males and 4 (11.4%) current smokers. The Charlson comorbidity index was 3 (2-6) points with the most frequent comorbidities hypertension (37.1%) and arrhythmia (31.4%). The most frequent symptoms before admission were dyspnea (97.1%) and purulent sputum (45.7%). The clinical characteristics of the study population are presented in Table 1.

All patients started NIV treatment in PS mode. The mean maximum IPAP pressure during PS-NIV treatment was 17.5 ± 4.0 and the mean maximum EPAP pressure during PS-NIV treatment was 8.3 ± 2.4 in the study population. The first control recorded at 8.5 (3.7–16.5) hours after PS-NIV treatment revealed a -0.29 (-15.9–13.1)% change from baseline in $PaCO_2$ measurements. After 24 (14.5–39) hours of PS-NIV treatment, the study population showed 2.2 (-10.4–11.8)% improvement in $PaCO_2$.

**Table 1.** Clinical characteristics and laboratory measurements

| | **Study population (n= 35)** |
|---|---|
| Age (years) | 70.7 ± 7.8 |
| Gender; male sex, n (%) | 26 (74.3) |
| Current smokers, n (%) | 4 (11.4) |
| Smoking, pack/year | 48.0 (30.0-50.0) |
| Charlson comorbidity index | 3.0 (2.0-6.0) |
| Comorbidities, n (%) | |
| Bronchiectasis | 3 (8.6) |
| OSA | 3 (8.6) |
| Cor pulmonale | 2 (5.7) |
| Heart failure | 9 (25.9) |
| Using domiciliary NIV, n (%) | 17 (48.6) |
| Using LTOT, n (%) | 22 (62.9) |
| Pneumonia upon admission, n (%) | 21 (60.0) |
| pH | 7.35 ± 0.06 |
| $PaO_2$ (mmHg) | 67.3 (55.3-104.0) |
| $PaO_2$ (mmHg) | 58.7 ± 12.0 |
| $HCO_3$ (mmol/L) | 29.4 ± 4.8 |
| Length of stay (days) | 8.5 (6.0-13.0) |
| IMV, n (%) | 2 (5.7) |
| ICU, n (%) | 3 (8.5) |

Data was expressed as numbers (percentages), mean ± SD or median (IQR).
mMRC: Modified medical research council dyspnea scale, OSA: Obstructive sleep apnea, NIMV: Noninvasive ventilation, LTOT: Long-term oxygen treatment, IMV: Invasive mechanical ventilation, ICU: Intensive care unit.

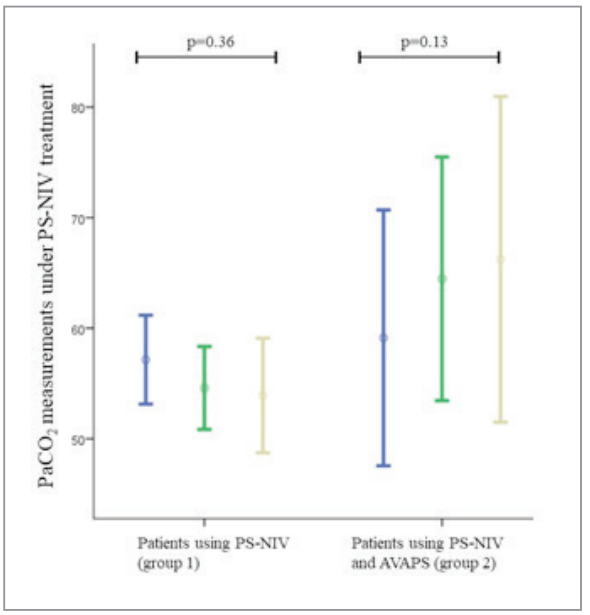


**Figure 1.** $PaCO_2$ measurements during fixed-level PS-NIV treatment in Group 1 and Group 2.
While patients in Group 1 showed a trend of decrease in $PaCO_2$ levels in response to PS-NIV treatment (56.1 ± 8.4 vs 53.9 ± 7.8 vs 53.9 ± 10.4, p= 0.36), patients in Group 2 showed a trend of increase in $PaCO_2$ levels (60.0 ± 7.8 vs 62.5 ± 11.6 vs 66.2 ± 14.0, p= 0.13) under PS-NIV treatment. Patients in Group 2 needed a change of NIV mode from fixed-level PS-NIV to AVAPS-NIV due to a lack of improvement in $PaCO_2$ levels.

During follow-up, after 28.0 (16.5–95.0) hours of PS-NIV treatment 14 (40%), patients showed 17.9 (-0.0–29.2) percent change in $PaCO_2$, meaning no improvement or worsening. Therefore, these patients started treatment in AVAPS mode instead of fixed-level PS mode (Figure 1). A comparison of the course of arterial blood gas analyses is detailed in Table 2. Patients who needed a change in NIV mode to AVAPS (Group 2) had similar age, comorbidities, history of NIV use, pneumonia in chest x-ray, and laboratory parameters such as leukocyte count, brain natriuretic peptide and C-reactive protein with patients who continued PS-NIV (Group 1). However arterial blood gas analysis upon admission in terms of arterial pH and $PaCO_2$ were different between groups. Clinical characteristics and laboratory measurements of the two groups are compared in Table 3.

Group 2 received AVAPS-NIV treatment with an IPAP maximum of 8.9 ± 1.9 and EPAP of 8.9 ± 1.9 for 96.0 (72.0–132.0) hours. Arterial $PaCO_2$ and pH levels significantly improved after AVAPS-NIV administration (Figure 2, Table 4). After 4.0 (3.0–10.0) hours of AVAPS-NIV treatment, $PaCO_2$ showed a -9.52 (-23.9–4.2) % change and after 19.5 (9.0–24.0) hours of AVAPS-NIV treatment, $PaCO_2$ showed -11.4 (-22.0 – -0.5) % improvement. Within Group 2, using AVAPS-NIV for 19.5 (9.0–24.0) hours created a significantly better $PaCO_2$ change rate than using PS-NIV for 21.0 (10.0–24.0) hours [-11.4 (-22.0 – -0.5) vs 8.2 (-5.3–19.5), p= 0.02].

Treatment with AVAPS-NIV was changed to PS-NIV after reaching clinical and laboratory stability in 13 (92.8%) patients following 96.0 (72.0–132.0) hours of treatment. The first control within 24.0 (12.0–24.0) hours of returning to PS-NIV revealed a stable arterial $PaCO_2$ (56.3 ± 9.3 vs 54.7 ± 7.4, p= 0.54).

Independent predictors of AVAPS mode requirement were evaluated with a multiple logistic regression model (Table 5). Higher Charlson comorbidity index [OR= 1.74 (95% CI= 1.02–2.97)] and higher $PaCO_2$ upon admission [OR= 1.18 (95% CI= 1.03–1.35)] were significantly related to an increased risk of AVAPS-NIV requirement.

Patients in Group 2 had a longer length of hospital stay compared to Group 1 [11 (8.0–15.5) vs 8.0 (5.0–9.0), p= 0.008]. However, ICU and intubation requirements were only present in Group 1 patients (Table 3).

## DISCUSSION

AVAPS mode provided a greater reduction in $PaCO_2$ compared to PS-NIV in patients with hypercapnic respiratory failure due to AECOPD who did not respond to PS-NIV in terms of $PaCO_2$ reduction.

Claudett et al. were the first to demonstrate the benefits of AVAPS mode over PS mode in patients with hypercapnic respiratory failure with hypercapnic encephalopathy due to AECOPD. Using AVAPS mode enabled a better recovery from hypercapnic encephalopathy with better control over $PaCO_2$, respiratory rate, and higher IPAP (4). The length of stay and duration of NIV treatment didn't differ between AVAPS or fixed-level PS modes. Magdy et al. and Oscroft et al. evaluated stable hypercapnic patients in randomized trials and found that AVAPS-NIV led to a more significant correction in daytime $PaCO_2$ than PS-NIV (5,11). COPD patients using AVAPS-NIV due to hypercapnic respiratory failure with compensated arterial pH tended to have lower

**Table 2.** Arterial gas analysis during fixed-level PS-NIV treatment

| | 1st control under PS-NIV treatment | 2nd control under PS-NIV treatment | 3rd control under PS-NIV treatment | p |
|---|---|---|---|---|
| **pH** | | | | |
| Overall patients | 7.36 ± 0.06 | 7.37 ± 0.05 | 7.37 ± 0.06 | 0.70 |
| Group 1 | 7.37 ± 0.05 | 7.39 ± 0.05 | 7.38 ± 0.06 | 0.34 |
| Group 2 | 7.35 ± 0.01 | 7.35 ± 0.05 | 7.35 ± 0.06 | 0.53 |
| **$PaCO_2$, mmHg** | | | | |
| Overall patients | 57.7 ± 8.3 | 57.1 ± 10.1 | 56.9 ± 12.3 | 0.68 |
| Group 1 | 56.1 ± 8.4 | 53.9 ± 7.8 | 53.9 ± 10.4 | 0.36 |
| Group 2 | 60.0 ± 7.8 | 62.5 ± 11.6 | 66.2 ± 14.0 | 0.13 |
| **$PaO_2$, mmHg** | | | | |
| Overall patients | 67.9 (53.0-91.5) | 86.5 (62.5-116.2) | 65.9 (53.9-96.6) | 0.04 |
| Group 1 | 70.7 (55.0-92.8) | 90.5 (60.7-115.0) | 64.4 (51.6-116.2) | 0.12 |
| Group 2 | 60.4 (49.5-91.5) | 74.6 (66.4-123.0) | 67.1 (61.9-89.7) | 0.31 |
| **$HCO_3$ mmol/L** | | | | |
| Overall patients | 30.3 ± 4.4 | 30.6 ± 4.4 | 30.9 ± 5.8 | 0.95 |
| Group 1 | 30.3 ± 4.5 | 30.4 ± 4.4 | 29.3 ± 5.9 | 0.31 |
| Group 2 | 30.0 ± 4.5 | 31.1 ± 4.1 | 33.9 ± 4.5 | 0.04 |

Data was expressed as numbers (percentages), mean ± SD or median (IQR).
Group 1: Patients treated with only PS-NIV
Group 2: Patients treated with AVAPS-NIV after a period of PS-NIV treatment with no improvement or worsening of $PaCO_2$.

$PaCO_2$ levels than patients using PS-NIV, in a randomized controlled trial conducted by Oscroft et al (6). Türk et al. found no difference between PS-NIV and AVAPS-NIV treatments in terms of $PaCO_2$ change in six days. But the comparison of $PaCO_2$ curves during treatments revealed that in the first 48 hours AVAPS-NIV had a decreasing effect on $PaCO_2$ while PS-NIV did not (7). Another study indicating faster improvements in $PaCO_2$ with AVAPS mode compared to PS-NIV mode in an emergency department setting with patients treated for AHRF was conducted by Gören et al. In this randomized control trial, clinical outcomes such as intubation and ICU requirement and in-hospital mortality were not significantly different (13). These added benefits in $PaCO_2$ reduction are mostly due to the ability of AVAPS mode to reach preset volume despite changes in patients' effort, lung compliance, and lung resistance (14). Although AVAPS-NIV mode reaches higher inspiratory ventilatory pressures, additional leaks in the ventilator circuit have little effect on minute ventilation (14,15).

However, Cao et al. compared AVAPS and PS modes in a mixed group of patients with COPD, asthma, bronchiectasis, and OSAS, and found similar success in terms of $PaCO_2$ reduction within six hours (10). Positive airway pressure, intubation rate, length of stay, and duration of NIV treatment were also similar between AVAPS and PS modes. A comparison of AVAPS and S/T modes in an ICU setting showed higher IPAP levels in AVAPS mode but equivalent benefits in both settings in terms of pH and $PaCO_2$ normalization and in-hospital mortality (16). In line with these studies, Crisafulli et al. compared stable hypercapnic COPD patients using AVAPS and PS modalities and found no superiority in AVAPS-NIV over PS-NIV in terms of $PaCO_2$ control (17).

Studies comparing the effect of AVAPS mode with fixed-level PS on $PaCO_2$ in obesity hypoventilation syndrome also showed conflicting results. Murphy et al. evaluated daytime $PaCO_2$ in a randomized population of super-obese patients with chronic respiratory failure. Patients treated with either AVAPS or fixed-level PS treatment showed improvements in gas exchange, health-related quality of life, and control of sleep-disordered breathing. There wasn't any significant difference between groups in terms of $PaCO_2$ decline (18). In addition, a cross-over study

**Table 3.** Comparison of clinical characteristics and laboratory measurements

| | Patients using PS-NIV (Group 1) (n= 21) | Patients using PS-NIV and AVAPS (Group 2) (n= 14) | p |
|---|---|---|---|
| Age, years | 71.9 ± 8.2 | 69.1 ± 7.1 | 0.30 |
| Sex, male | 16 (76.1) | 10 (71.4) | 0.52 |
| Current smokers, n (%) | 0 (0.0) | 4 (30.8) | 0.57 |
| Smoking, pack/year | 35.0 (20.0-50.0) | 50.0 (47.5-60.0 | 0.08 |
| mMRC | 3 (2-4) | 3 (3-4) | 0.19 |
| Charlson comorbidity index | 2 (1-5) | 5 (3-6) | 0.02 |
| Comorbidities, n (%) | | | |
| Bronchiectasis | 2 (9.5) | 1 (7.1) | 0.65 |
| OSA | 2 (9.5) | 1 (7.1) | 0.60 |
| Cor pulmonale | 0 (0.0) | 2 (14.3) | 0.15 |
| Heart failure | 4 (19.0) | 5 (35.7) | 0.43 |
| Using domiciliary NIV, n (%) | 10 (47.6) | 7 (50.0) | 0.50 |
| Using LTOT, n (%) | 15 (71.4) | 7 (50.0) | 0.46 |
| Pneumonia upon admission, n (%) | 13 (61.9) | 8 (57.1) | 1 |
| Leukocyte count, (K/μL) | 11.7 ± 5.1 | 8.9 ± 4.5 | 0.09 |
| Neutrophil, (%) | 71.7 (64.2-83.2) | 70.5 (65.0-81.5) | 0.98 |
| CRP | 5.8 (1.8-10.2) | 6.0 (2.4-11.3) | 1 |
| Procalcitonin | 0.08 (0.03-0.15) | 0.08 (0.03-0.73) | 0.63 |
| BNP | 104.0 (24.7-309.7) | 158.0 (80.0-900.0) | 0.60 |
| pH | 7.37 ± 0.06 | 7.32 ± 0.05 | 0.01 |
| $PaO_2$, mmHg | 67.4 (46.8-98.2) | 66 (58.0-133.2) | 0.60 |
| $PaCO_2$, mmHg | 53.9 ± 10.4 | 65.9 ± 10.8 | 0.002 |
| $HCO_3$, mmol/L | 28.8 ± 4.9 | 30.4 ± 4.5 | 0.34 |
| Length of stay, days | 8.0 (5.0-9.0) | 11 (8.0-15.5) | 0.008 |
| IMV, n (%) | 2 (9.5) | 0 (0) | 0.51 |
| ICU, n (%) | 3 (14.2) | 0 (0) | 0.22 |

mMRC: Modified medical research council dyspnea scale, OSA: Obstructive sleep apnea, NIMV: Noninvasive ventilation, LTOT: Long-term oxygen treatment, CRP: C-reactive protein, BNP: Brain natriuretic peptide, IMV: Invasive mechanical ventilation, ICU: Intensive care unit.

designed by Kelly et al. in patients with nocturnal hypoventilation who did not use any NIV prior to the study found that mean pressure support was significantly lower in volume-targeting NIV support, however, oxygen saturation and overnight transcutaneous $PCO_2$ did not show a significant difference between treatments (19).

In our study, risk factors associated with AVAPS-NIV requirement due to insufficient response to fixed-level PS-NIV were higher Charlson comorbidity index and higher $PaCO_2$ upon admission. This finding is in accordance with the research about NIV failure. NIV failure rate in AHRF in COPD patients is between 13.4-24% (12,21-25). Previous studies defined $PaCO_2$ and arterial pH upon admission as the best predictors of NIV failure (26-28). Correction of arterial pH and rapid reduction in $PaCO_2$ are also qualified as predictors of NIV success (20,29-31). High APACHE II scores and low Glasgow coma scale scores are also associated with NIV failure (29,32). Independent risk factors for mortality in COPD patients treated with NIV are age and Glasgow coma scale score, according to Fiorino et al (12). Çiftçi et al. evaluated the clinical efficacy of AVAPS mode in AHRF due to COPD exacerbation in the ICU setting and showed failure of AVAPS treatment in 23.6% of the patients. Failed treatment was independently

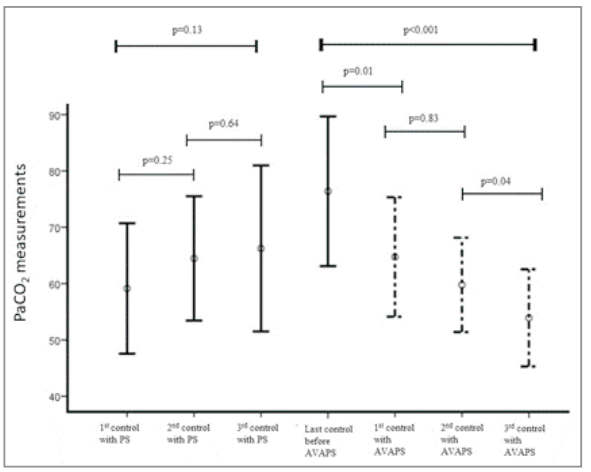


**Figure 2.** $PaCO_2$ measurements during NIV treatment in Group 2 patients.
Patients in Group 2 did not show improvement under fixed-level PS-NIV treatment in terms of $PaCO_2$ (60.0 ± 7.8 vs 62.5 ± 11.6 vs 66.2 ± 14.0, p= 0.13). However, these patients showed significant improvement under AVAPS-NIV treatment (70.6 ± 11.2 vs 62.3 ± 11.0 vs 61.7 ± 10.1 vs 56.7 ± 10.7, p= 0.001).

associated with a worse percentage change of $PaCO_2$ in two hours and higher APACHE II scores. Patients who failed AVAPS-NIV treatment had higher comorbidity indices and more frequent coronary artery disease (33). In our study, patients with insufficient response to PS-NIV also had more frequent cor pulmonale and heart failure comorbidities as well as higher Charlson comorbidity indices. Heart and lung interactions during mechanical ventilation might play an important role in this relation. Changes in lung volume and airway pressure with increased intra-thoracic pressure lead to increased pulmonary vascular resistance, increased external pressure on the heart, and a decrease in venous return to the heart. These alterations might have a negative effect on ventricular ejection, especially from the right ventricle (34).

In our study population, 13 (92.8%) patients reaching significant clinical stability with AVAPS-NIV were able to return to fixed-level PS-NIV and maintain acceptable $PaCO_2$ levels. This is especially important in patients who need NIV treatment at home. Due to economic challenges and regulations of the social security system, it is often not possible to obtain a respiratory device with AVAPS mode in COPD patients.

### Limitations

This study is not designed as a randomized control trial however all patients started a standardized treatment in the same experienced clinic with fixed-

**Table 4.** Arterial gas analysis during AVAPS-NIV treatment in Group 2 (n= 14)

| | Last control under PS-NIV treatment | 1st control under AVAPS-NIV treatment | 2nd control under AVAPS-NIV treatment | 3rd control under AVAPS-NIV treatment | p |
|---|---|---|---|---|---|
| pH | 7.31 ± 0.06 | 7.35 ± 0.07 | 7.37 ± 0.05 | 7.40 ± 0.05 | <0.001 |
| $PaCO_2$ | 70.6 ± 11.2 | 62.3 ± 11.0 | 61.7 ± 10.1 | 56.7 ± 10.7 | 0.001 |
| $PaO_2$ | 71.5 (49.3-99.0) | 53.1 (41.4-72.6) | 69.3 (56.1-82.5) | 67.3 (55.7-98.3) | 0.29 |
| $HCO_3$ | 30.7 ± 6.0 | 31.5 ± 7.3 | 32.5 ± 5.4 | 32.7 ± 4.5 | 0.31 |

**Table 5.** Independent predictors of AVAPS requirement

| | Univariable regression analysis | | | Multivariable regression analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | p | OR | 95% CI | p |
| Age | 0.95 | 0.87-1.04 | 0.29 | - | - | - |
| Using LTOT | 0.46 | 0.11-1.97 | 0.30 | - | - | - |
| Using domiciliary NIMV | 1.28 | 0.32-5.13 | 0.72 | - | - | - |
| mMRC | 1.93 | 0.77-4.82 | 0.15 | - | - | - |
| Charlson comorbidity index | 1.46 | 1.02-2.09 | 0.03 | 1.74 | 1.02-2.97 | 0.04 |
| Leukocyte count | 1.0 | 1.0-1.0 | 0.10 | 1.00 | 0.99-1.00 | 0.11 |
| $PaCO_2$ upon admission | 1.14 | 1.02-1.26 | 0.01 | 1.18 | 1.031.35 | 0.01 |

mMRC: Modified medical research council dyspnea scale, NIMV: Noninvasive ventilation, LTOT: Long-term oxygen treatment.

level PS-NIV and had a standardized follow-up period. Therefore, we could analyze and compare the effect of PS-NIV with AVAPS-NIV treatment on the same patients. Although there are studies comparing the effects of fixed-level PS-NIV and AVAPS-NIV treatment in hypercapnic respiratory failure, AVAPS-NIV treatment of patients with insufficient response to fixed-level PS-NIV is a relatively new approach.

Data on leaks, breathing frequency, and delivered tidal volume were not recorded due to the observational nature of our study. However, these parameters should be approached carefully because of the drawbacks of data quality and differences between ventilator models (3).

Data on abnormal nocturnal events are not recorded but patients with OSA or OSA symptoms are scarce in our study and showed no difference between groups.

Patients with hypercapnic respiratory failure due to obesity-hypoventilation, neurological diseases, and chest wall deformities were excluded from the study. This led to a homogeneous population in terms of physiopathological changes.

## CONCLUSION

Our study demonstrated that COPD patients with hypercapnic respiratory failure can benefit from AVAPS-NIV despite insufficient response to fixed-level PS-NIV. AVAPS mode facilitates a rapid recovery in arterial blood gas measurements.

**Ethical Committee Approval:** This study approval was obtained from Uludağ University Faculty of Medicine Clinical Research Ethics Committee (Decision No: 2020-10/30, Date: 10.06.2020).

## CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

## AUTHORSHIP CONTRIBUTIONS

Concept/Design: NAAÖ, AU, ED

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Data acqusition: SM, FC, EU, MK

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Clinical Revision: NAAÖ, ED, AGD, FC, EU, MK

Final Approval: All of authors

## REFERENCES


1. *Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidelines: Noninvasive ventilation for acute respiratory failure. Eur Respir J 2017; 50(2): 1602426. https://doi.org/10.1183/13993003.02426-2016*
2. *Ram FS, Picot J, Lightowler J, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2004; (3): CD004104. https://doi.org/10.1002/14651858.CD004104.pub3*
3. *Piper AJ. Advances in non-invasive positive airway pressure technology. Respirology 2020; 25(4): 372-82. https://doi.org/10.1111/resp.13631*
4. *Briones Claudett KH, Briones Claudett M, Chung Sang Wong M, Nuques Martinez A, Soto Espinoza R, Montalvo M, et al. Noninvasive mechanical ventilation with average volume assured pressure support (AVAPS) in patients with chronic obstructive pulmonary disease and hypercapnic encephalopathy. BMC Pulm Med 2013; 13: 12. https://doi.org/10.1186/1471-2466-13-12*
5. *Magdy DM, Metwally A. Effect of average volume-assured pressure support treatment on health-related quality of life in COPD patients with chronic hypercapnic respiratory failure: A randomized trial. Respir Res 2020; 21(1): 64. https://doi.org/10.1186/s12931-020-1320-7*
6. *Oscroft NS, Chadwick R, Davies MG, Quinnell TG, Smith IE. Volume assured versus pressure preset non-invasive ventilation for compensated ventilatory failure in COPD. Respir Med 2014; 108(10): 1508-15. https://doi.org/10.1016/j.rmed.2014.07.010*
7. *Türk M, Aydoğdu M, Gürsel G. Effects of modes, obesity, and body position on non-invasive positive pressure ventilation success in the intensive care unit: A randomized controlled study. Turk Thorac J 2018; 19(1): 28-35. https://doi.org/10.5152/TurkThoracJ.2017.17036*
8. *2020 Global strategy for prevention, diagnosis and management of COPD. Available from: https://goldcopd.org/2020-gold-reports/*
9. *Tuggey JM, Elliott MW. Titration of non-invasive positive pressure ventilation in chronic respiratory failure. Respir Med 2006; 100(7): 1262-9. https://doi.org/10.1016/j.rmed.2005.10.012*
10. *Cao Z, Luo Z, Hou A, Nie Q, Xie B, An X, et al. Volume-targeted versus pressure-limited noninvasive ventilation in subjects with acute hypercapnic respiratory failure: A multicenter randomized controlled trial. Respir Care 2016; 61(11): 1440-50. https://doi.org/10.4187/respcare.04619*
11. *Oscroft NS, Ali M, Gulati A, Davies MG, Quinnell TG, Shneerson JM, et al. A randomised crossover trial comparing volume assured and pressure preset noninvasive ventilation in stable hypercapnic COPD. COPD 2010; 7(6): 398-403. https://doi.org/10.3109/15412555.2010.528084*

12. *Fiorino S, Bacchi-Reggiani L, Detotto E, Battilana M, Borghi E, Denitto C, et al. Efficacy of non-invasive mechanical ventilation in the general ward in patients with chronic obstructive pulmonary disease admitted for hypercapnic acute respiratory failure and pH < 7.35: A feasibility pilot study. Intern Med J 2015; 45(5): 527-37. https://doi.org/10.1111/imj.12726*

13. *Gören NZ, Şancı E, Ercan Coşkun FF, Gürsoylu D, Bayram B. Comparison of BPAP S/T and average volume-assured pressure support modes for hypercapnic respiratory failure in the emergency department: A randomized controlled trial. Balkan Med J 2021; 38(5): 265-71. https://doi.org/10.5152/balkanmedj.2021.20137*

14. *Oscroft NS, Smith IE. A bench test to confirm the core features of volume-assured non-invasive ventilation. Respirology 2010; 15(2): 361-4. https://doi.org/10.1111/j.1440-1843.2009.01691.x*

15. *Nilius G, Katamadze N, Domanski U, Schroeder M, Franke KJ. Non-invasive ventilation with intelligent volume-assured pressure support versus pressure-controlled ventilation: Effects on the respiratory event rate and sleep quality in COPD with chronic hypercapnia. Int J Chron Obstruct Pulmon Dis 2017; 12: 1039-45. https://doi.org/10.2147/COPD.S126970*

16. *Akbaş T, Altun G. Treatment of critically ill patients with acute hypercarbic respiratory failure by average volume-assured pressure support mode. Clin Respir J 2021; 15(9): 973-82. https://doi.org/10.1111/crj.13401*

17. *Crisafulli E, Manni G, Kidonias M, Trianni L, Clini EM. Subjective sleep quality during average volume assured pressure support (AVAPS) ventilation in patients with hypercapnic COPD: A physiological pilot study. Lung 2009; 187(5): 299-305. https://doi.org/10.1007/s00408-009-9167-1*

18. *Murphy PB, Davidson C, Hind MD, Simonds A, Williams AJ, Hopkinson NS, et al. Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: A randomised controlled trial. Thorax 2012; 67(8): 727-34. https://doi.org/10.1136/thoraxjnl-2011-201081*

19. *Kelly JL, Jaye J, Pickersgill RE, Morrell MJ, Simonds AK. Randomized trial of 'intelligent' autotitrating ventilation versus standard pressure support non-invasive ventilation: Impact on adherence and physiological outcomes. Respirology 2014; 19(4): 596-603. https://doi.org/10.1111/resp.12269*

20. *Janssens JP, Metzger M, Sforza E. Impact of volume targeting on efficacy of bi-level non-invasive ventilation and sleep in obesity-hypoventilation. Respir Med 2009; 103(2): 165-72. https://doi.org/10.1016/j.rmed.2008.03.013*

21. *Kaya A, Ciledağ A, Caylı I, Onen ZP, Sen E, Gülbay B. Associated factors with non-invasive mechanical ventilation failure in acute hypercapnic respiratory failure. Tuberk Toraks 2010; 58(2): 128-34.*

22. *Devi P, Raja R, Kumar R, Shah A, Ansari SI, Kumar B. Invasive versus non-invasive positive pressure ventilation in chronic obstructive pulmonary disease complicated by acute respiratory failure. Cureus 2019; 11(8): 5418. https://doi.org/10.7759/cureus.5418*

23. *Smith DB, Tay GTP, Hay K, Antony J, Bell B, Kinnear FB, et al. Mortality in acute non-invasive ventilation. Intern Med J 2017; 47(12): 1437-40. https://doi.org/10.1111/imj.13632*

24. *Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: A multicentre randomised controlled trial. Lancet 2000; 355(9219): 1931-5. https://doi.org/10.1016/S0140-6736(00)02323-0*

25. *Walkey AJ, Wiener RS. Use of noninvasive ventilation in patients with acute respiratory failure, 2000-2009: A population-based study. Ann Am Thorac Soc 2013; 10(1): 10-7. https://doi.org/10.1513/AnnalsATS.201206-034OC*

26. *Ambrosino N, Foglio K, Rubini F, Clini E, Nava S, Vitacca M. Non-invasive mechanical ventilation in acute respiratory failure due to chronic obstructive pulmonary disease: Correlates for success. Thorax 1995; 50(7): 755-7. https://doi.org/10.1136/thx.50.7.755*

27. *Nava S, Ceriana P. Causes of failure of noninvasive mechanical ventilation. Respir Care 2004; 49(3): 295-303.*

28. *Plant PK, Owen JL, Eliott MW. Non-invasive ventilation in acute exacerbations of chronic obstructive pulmonary disease: Long term survival and predictors of in-hospital outcome. Thorax 2001; 56(9): 708-12. https://doi.org/10.1136/thx.56.9.708*

29. *Garpestad E, Brennan J, Hill SN. Noninvasive ventilation for critical care. Chest 2007; 132(2): 711-20. https://doi.org/10.1378/chest.06-2643*

30. *Soo Hoo GW, Santiago S, Williams AJ. Nasal mechanical ventilation for hypercapnic respiratory failure in chronic obstructive pulmonary disease: Determinants of success and failure. Crit Care Med 1994; 22(8): 1253-61. https://doi.org/10.1097/00003246-199408000-00009*

31. *Singh VK, Khanna P, Rao BK, Sharma SC, Gupta R. Outcome predictors for non-invasive positive pressure ventilation in acute respiratory failure. J Assoc Physicians India 2006; 54: 361-5.*

32. *Confalonieri M, Garuti G, Cattaruzza MS, Osborn JF, Antonelli M, Conti G, et al. A chart of failure risk for noninvasive ventilation in patients with COPD exacerbation. Eur Respir J 2005; 25(2): 348-55. https://doi.org/10.1183/09031936.05.00085304*

33. *Çiftci F, Çiledağ A, Erol S, Öz M, Acar D, Kaya A. Evaluation of the feasibility of average volume-assured pressure support ventilation in the treatment of acute hypercapnic respiratory failure associated with chronic obstructive pulmonary disease: A pilot study. J Crit Care 2017; 39: 232-7. https://doi.org/10.1016/j.jcrc.2016.12.023*

34. *Mahmood SS, Pinsky MR. Heart-lung interactions during mechanical ventilation: The basics. Ann Transl Med 2018; 6(18): 349. https://doi.org/10.21037/atm.2018.04.29*