

Non-Invasive Ventilation with PAV mode in Rehabilitation for
Patients with Chronic Obstructive Pulmonary Disease:
Systematized Review and Meta-Analysis

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Abstract

Background: High-intensity exercise therapy is recommended for the treatment of Chronic Obstructive Pulmonary Disease (COPD) patients; however, limitations in exercise capacity often arise due to symptoms of dyspnea and reduced ventilatory capacity. Incorporating Non-invasive Positive Pressure Ventilation (NPPV) into exercise therapy holds the potential to enhance exercise performance. Proportional Assist Ventilation (PAV) developed considering synchronization between the patient and the ventilator, may offer continuous ventilatory support tailored to the patient's inspiratory effort and lung mechanics. This makes PAV a promising mode suitable for rehabilitation efforts involving increased inspiratory effort during exercise. This study aims to systematically examine the effectiveness of employing NPPV with the PAV mode in exercise therapy for COPD patients.

Methods: We conducted a search on PubMed, CINAHL, EMBASE, and the Cochrane Central Register of Controlled Trials for relevant articles. The inclusion criteria encompassed randomized controlled trials or crossover trials that compared the PAV mode with other conditions in patients with COPD. The primary outcomes were set as the Borg scale and exercise endurance time. In the secondary outcomes, minute ventilation, respiratory rate, oxygen uptake, heart rate, and work rate were examined. Summary estimates of the effect were calculated using the mean difference, along with accompanying 95% confidence intervals. Risk of bias was assessed using the Cochrane Collaboration's tool for RCTs.

Results: Nine studies were included. The Borg Scale (Dyspnea) was significantly lower in patients using the PAV mode compared to spontaneous breathing without mechanical ventilation, sham, or CPAP modes. There was no significant difference in the Borg Scale (Leg). Exercise endurance time was significantly longer in patients using the PAV mode compared to spontaneous breathing without mechanical ventilation, sham, or CPAP modes.

Conclusion: The use of NPPV with PAV mode during exercise therapy in COPD patients may lead to alleviation of breathlessness and improvement in exercise tolerance.

Keywords: Proportional Assist Ventilation (PAV), Chronic Obstructive Pulmonary Disease (COPD), Non-invasive Positive Pressure Ventilation (NPPV), systematized review, meta-analysis

List of abbreviations

COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
PAV	Proportional Assist Ventilation
NPPV	Noninvasive Positive Pressure Ventilation
QOL	Quality of Life
ADL	Activities of Daily Living
RCT	Randomized Controlled Trial

1. INTRODUCTION

1.1. Background Information

Chronic Obstructive Pulmonary Disease (COPD) is a progressive, irreversible condition characterized by airflow obstruction. The most challenging symptom for COPD patients is dyspnea, significantly impacting patient's quality of life (QOL).¹ The severity of dyspnea, rather than the disease classification based on forced expiratory volume in 1 second (FEV1), has been shown to predict prognosis.² Among various treatment modalities, aside from smoking cessation and pharmacological therapy, respiratory rehabilitation plays a crucial role. Respiratory rehabilitation has demonstrated improvements in exercise capacity, reduced exertional dyspnea, and enhanced QOL.³ Within respiratory rehabilitation, exercise therapy plays a central role, addressing overall endurance, muscle strength training, and activities of daily living (ADL) training to alleviate and prevent muscle atrophy and disuse syndrome due to dyspnea.

Currently, in exercise therapy for COPD patients, intensity is considered crucial, and high-intensity exercise therapy is recommended in guidelines.^{3, 20} Low-intensity exercise therapy has shown limited improvements in exercise capacity for COPD patients, while reports indicate improved exercise capacity, cardiorespiratory function, and peripheral muscle adaptation with high-intensity exercise therapy.^{4,5} However, a significant challenge arises from the limitations on high-intensity exercise therapy for COPD patients due to respiratory symptoms and decreased ventilatory capacity.^{21, 22, 23}

Assistance from mechanical ventilation may enhance patients' exercise tolerance, enabling COPD patients to engage in higher intensity exercise therapy. Noninvasive Positive Pressure Ventilation (NPPV) is a form of mechanical respiratory support that can be temporarily employed without invasive intubation. By assisting inspiratory muscles, reducing dyspnea, and redistributing blood flow from respiratory muscles to skeletal muscles, NPPV has been shown to improve exercise capacity.^{6, 7} Currently, the widely used mode in NPPV is Continuous Positive Airway Pressure (CPAP) mode. In this mode, a constant positive pressure is applied to the patient. The use of CPAP mode is reported to be associated with expected improvements in dyspnea and exercise tolerance.^{8, 9, 6}

The tolerability of mechanical ventilation is crucial, and NPPV is often discontinued due to discomfort.²⁴ Improving tolerability involves enhancing the patient-device synchrony with the mechanical ventilator.²⁷ Proportional Assist Ventilation (PAV) is a relatively new mode developed considering synchrony between the patient and the ventilator. It can consistently provide ventilatory support based on the patient's inspiratory effort and lung mechanics. In invasive mechanical ventilation management, PAV mode has garnered attention as a mode suitable for the weaning period aiming at ventilator liberation, with large-scale randomized comparative trials currently underway to validate this.¹⁰ Given its characteristics, PAV mode holds potential as a suitable mode for rehabilitation involving increased inspiratory effort during exercise.²⁵

Moreover, COPD patients exhibit abnormalities in lung mechanics such as compliance and resistance, making ventilatory support based on lung mechanics crucial for improving synchrony. PAV mode theoretically could provide effective respiratory assistance in COPD patients with reduced exercise tolerance.^{12, 26} Presently, there have been multiple reports of Randomized Controlled Trials (RCTs) utilizing the PAV mode of noninvasive ventilation in COPD patients,^{12, 13} but these studies are relatively small in scale, lacking systematic reviews or meta-analyses. The current guidelines do not specifically address the use of NPPV in respiratory rehabilitation for COPD patients.^{3, 20} To carefully consider its application to patients, there is a need to gather and consolidate knowledge in this regard.

1.2. Objectives

In this study, we aimed to investigate the effectiveness of utilizing NPPV in PAV mode for exercise therapy in patients with COPD. Our focus was on comparing the use of NPPV in PAV mode with scenarios where respiratory assistance is not employed or when the commonly used CPAP mode is utilized. Specifically, we sought to assess whether employing NPPV in PAV mode could reduce respiratory distress and enhance exercise tolerance in patients, compared to situations where conventional CPAP mode or no respiratory assistance is utilized.

We conducted a systematized review and followed the procedure of a meta-analysis to synthesize data from the included studies in order to comprehensively examine existing literature on this subject.

2. METHODS

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement guidelines to construct this review. Due to the sole involvement of a reviewer, this review is categorized as a systematized review. Consequently, it has not been registered with PROSPERO.

2.1. Eligibility Criteria

In evaluating the effectiveness of the intervention, we focused on the research design, particularly randomized trials. Randomization is the only way to prevent systematic differences in confounding factors.¹⁹ One reviewer included both randomized parallel studies and crossover studies that investigated the efficacy of PAV mode compared to other modes (not specifically defined) for patients with COPD. In this study, we did not include the concept of 'exercise' as a keyword in the search formula. The reason for this decision was that including it resulted in very few hits, potentially missing many relevant studies. However, during the full-text review stage, we included only studies that verified either the Borg scale or exercise endurance time, which are primary outcomes, and excluded those without either. As a result, only studies examining the effects of exercise were included.

Additionally, studies on invasive mechanical ventilation and those targeting patients during acute exacerbation of COPD were excluded.

2.2. Database Search Strategy

We searched PubMed, CINAHL, EMBASE, and the Cochrane Central Register of Controlled Trials for eligible articles. Our last search update was December 18, 2023. Utilizing keywords derived from previous literature ¹⁰, the search terms included "COPD and its synonyms" AND "PAV and its synonyms" AND "randomized controlled study or cross-over study, and their synonyms." The detailed search strategy is documented in the Appendix A. We screened abstract citations for inclusion, retrieved potentially relevant studies, and adjudicated study eligibility.

2.3. Data Extraction and Outcome setting

In this study, we designated Borg scale (measuring perceived breathlessness and lower limb fatigue) and exercise endurance time as the primary outcomes. Additionally, to elucidate the mechanistic background of the primary outcome, we included minute ventilation, respiratory rate, oxygen uptake (VO₂), heart rate, and work rate as secondary outcomes. From each study, we extracted treatment effects using the mean along with standard deviation wherever possible. The following data were extracted from each study: Borg scale (Dyspnea), Borg scale (Leg), Exercise endurance time, Minute ventilation, Respiratory rate, Oxygen uptake (VO₂), Heart rate, and Work rate. The Borg Scale is a 10-point scale utilized to assess subjective difficulty and fatigue during exercise. A lower numerical value indicates fewer symptoms. The Borg scale (Dyspnea) specifically refers to the sensation of breathlessness and respiratory difficulty. The Borg scale (Leg) assesses fatigue in the legs during exercise. Values recorded during each exercise session were extracted. Exercise endurance time represents the duration, in minutes, during which the exercise therapy was sustained and was uniformly extracted. Minute ventilation (L/min), Respiratory rate (breaths/min), Oxygen uptake (VO₂, L/min), Heart rate (beats/min), and Work rate (Watts) were also extracted, with units standardized, from measurements recorded during exercise. In instances where specific numerical values were not explicitly stated in the text, data were extracted from figures if precise values could be accurately inferred.

2.4. Statistical Analysis

For each parameter, we conducted comparisons among PAV mode, spontaneous breathing only (without mechanical ventilation), sham ventilation (simulated ventilation), and CPAP mode.

To statistically combine the data from the included studies, the 95% confidence intervals (CI) was transformed into standard deviation.¹⁹ Summary estimates of the effect were calculated using the mean difference, along with accompanying 95% CIs. And we evaluate the heterogeneity using the Cochran's Q test, a Chi-square test, with a threshold p value of

less than 0.1. The impact of heterogeneity on outcomes was assessed using I^2 statistic. Forest plots were used to summarize the results.

The choice between fixed-effect or random-effect models was based on statistical heterogeneity. If $p < 0.1$ with the Chi-square test or $I^2 > 50\%$, a random-effects model was used; otherwise, the fixed-effect model was used.

We conducted a subgroup analysis for the severe COPD (Classified as severe COPD or falling into GOLD stages III or IV) group and those with a high exercise therapy work rate (70% or more of their maximum power).

For analyses that included six or more studies, we created funnel plots and conducted Egger's test to assess publication bias. Analyses with five or fewer included studies did not allow for a statistically meaningful assessment of publication bias. Standard deviations and mean differences were utilized for each result.

Review Manager (Cochrane Collaboration) was employed for these analyses. Only Egger's test was performed using R.

2.5. Assessment of Risk of Bias

For each individual trial, we assessed the risk of bias based on Cochrane methodology. The risk of bias assessment utilized the Cochrane Collaboration's tool¹⁹, evaluating the following items for each trial:

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other bias

We selected either "Low risk," "High risk," or "Unclear risk" for each evaluation item.

2.6. Assessment of Cross-over studies

In general, when analyzing crossover trials, attention must be given to carry-over effects and the risk of bias. For our study, we selected stable COPD patients as the target population and evaluated the temporary effects during exercise therapy. Given the transient nature of the intervention's effect, we considered crossover trials to be suitable and included them in our analysis.

Furthermore, for each individual trial, we assessed carry-over effects and the risk of bias following the Cochrane methodology¹⁹. We adopted data for each intervention's measurements when average and standard error or 95% CI were individually available. In this study, we employed an analytical approach where we utilized all measurements from each intervention, treating the trials as if they were parallel-group trials for each intervention.

3. RESULTS

3.1. Results of the Database Search

In accordance with the search strategy, we systematically conducted database searches, yielding a total of 340 records. Following the elimination of duplicate entries, 275 records underwent a screening process based on their titles and abstracts. Subsequently, 24 records were subjected to a comprehensive full-text assessment. After careful evaluation, a final selection resulted in the inclusion of 9 records in the study. Among these, 2 featured a randomized parallel design, while the remaining 7 followed a randomized crossover design. The detailed overview of the search process is depicted in Figure 1. And the characteristics of the included studies are summarized in Table 1. The randomization process was examined in the full text of each literature, and it was confirmed that quasi-RCTs were not included in this study.

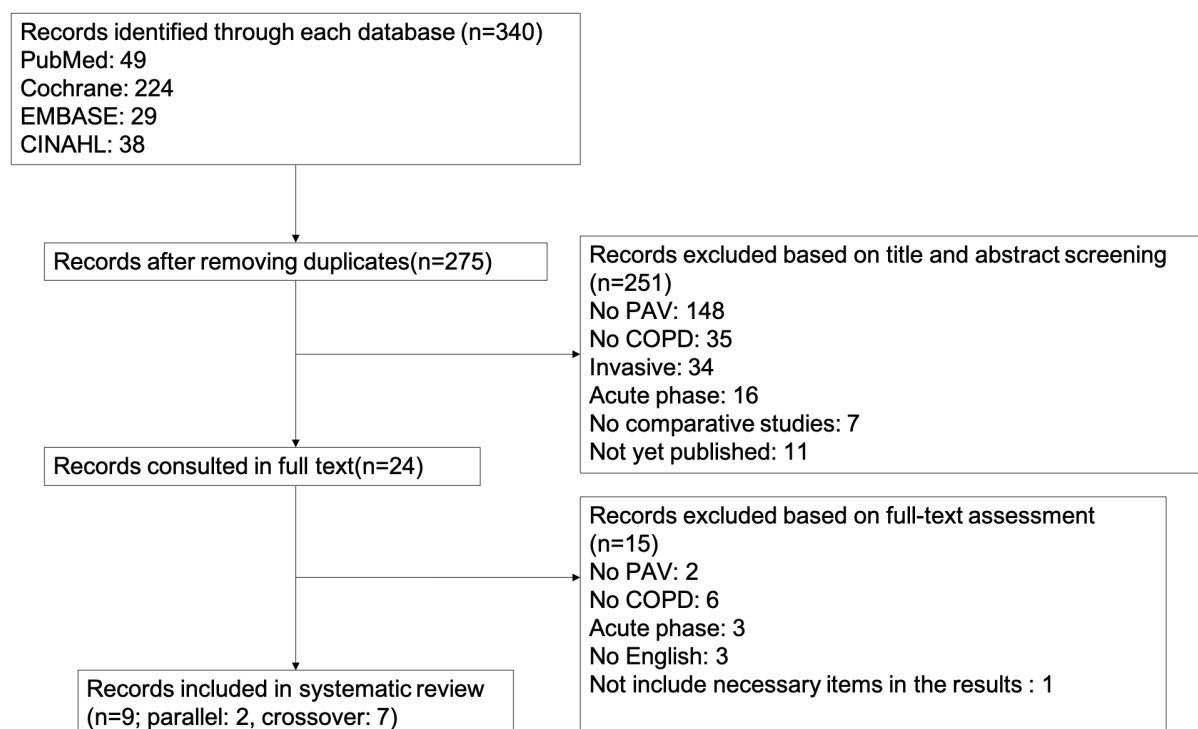


Figure 1: Study selection.

Table 1: Characteristics of included studies

Author/year (Country)	Study type	Each Sample size (%female)	Total Sample size (%female)	Mean Age	Population (meanFEV1, %predicted)	Exercise and time course
Dolmage/1997 ¹¹ (Canada)	Randomized crossover design	PAV 10 vs Spont 10 vs Sham 9 vs CPAP 8 vs PAV+CPAP 9	10 (30)	59	Moderate - Severe COPD (59)	a cycle ergometer at 60-70% of their maximal work rate Each single session was conducted at the same time at least one day apart a cycle ergometer at 80% of their maximal work rate
Bianchi/1998 ¹² (Italy)	Randomized crossover design	PAV 15 vs Spont 15 vs Sham 15 vs CPAP 15	15 (6.7)	64	Severe COPD (32)	Exercise at 8am and 12pm in random order over 2days a cycle ergometer at 50-70% of their maximal work rate
Bianchi/2002 ¹³ (Italy)	Randomized parallel design	PAV 9 vs Spont 10	33 (0)	PAV 64 Spont 65	COPD (no mention of severity)	6weeks of 3 hours sessions held 3times a week a cycle ergometer at 70% of their maximal work rate
Hawkins/2002 ¹⁴ (United Kingdom)	Randomized parallel design	PAV 10 vs Spont 9	19 (10.5)	PAV 68 Spont 66	Severe COPD	6weeks of 30 minutes sessions held 3times a week upper limbs activity with the arm elevation test
Roberta/2006 ¹⁵ (Italy)	Randomized crossover design	PAV vs Spont vs PSV	8 (0)	65	COPD (no mention of severity) HOT (40)	40 minutes sessions in the morning in random order with

Silva/2008 ¹⁶ (Brazil)	Randomized crossover design	PAV 16 vs Sham 16	16 (0)	Not specified	COPD GOLD stage II /III/IV (not specified)	breaks on the same day a cycle ergometer at 70-80% of their maximal work rate Performed single exercises on different days in random order
		PAV 20 vs Spont 20		Not specified		a cycle ergometer at 70-80% of their maximal work rate
Carrascossa/2010 ¹⁷ (Brazil)	Randomized crossover design		20 (0)		Moderate-to- severe COPD (not specified)	Performed in random order on the same day with a 30 minute break in between
		PAV 6 vs Spont 6 vs Sham 6 vs CPAP 6	6 (25)	65.2	COPD GOLD stage III/IV (33. 3)	a cycle ergometer at 80% of their maximal work rate Performed in random order on separate days, one day apart
Koch/2020 ⁷ (Brazil)	Randomized crossover design	PAV 9 vs Spont 9 vs Sham 9	9 (33)	62	COPD GOLD stage III/IV (40)	a cycle ergometer at 75% of their maximal work rate Performed in random order on separate days

* PAV: Proportional assist ventilation, PSV: Pressure support ventilation, CPAP: Continuous positive airway pressure, Sham: pseudo-ventilation, Spont: Spontaneous breathing without mechanical ventilation

3.2. Primary Outcome

3.2.1. Borg Scale for Dyspnea

The Borg Scale (Dyspnea) was assessed in a total of seven studies, with six studies comparing PAV with spontaneous breathing, five studies comparing PAV with sham, and three studies comparing PAV with CPAP.

In the comparison between PAV mode and spontaneous breathing, a meta-analysis utilizing a fixed-effects model, encompassing 131 patients from 6 studies, demonstrated a statistically significant reduction in Borg Scale (Dyspnea) among patients using the PAV mode compared to those with spontaneous breathing (weighted mean difference (WMD) -0.77; 95% CI: -1.32 to -0.21; $p=0.007$; $I^2=48\%$) (Fig. 2).

For the comparison between PAV mode and sham, the meta-analysis using a fixed-effects model, involving 111 patients from 5 studies, indicated a significant decrease in Borg Scale (Dyspnea) for patients utilizing the PAV mode compared to those with sham (WMD -1.05; 95% CI: -1.79 to -0.32; $p=0.005$; $I^2=48\%$) (Fig. 2).

In the comparison between PAV mode and CPAP, a meta-analysis utilizing a fixed-effects model, including 59 patients from 3 studies, exhibited a significant decrease in Borg Scale (Dyspnea) for patients using the PAV mode compared to those with CPAP (WMD -1.01; 95% CI: -1.99 to -0.02; $p=0.04$; $I^2=0\%$) (Fig. 2).

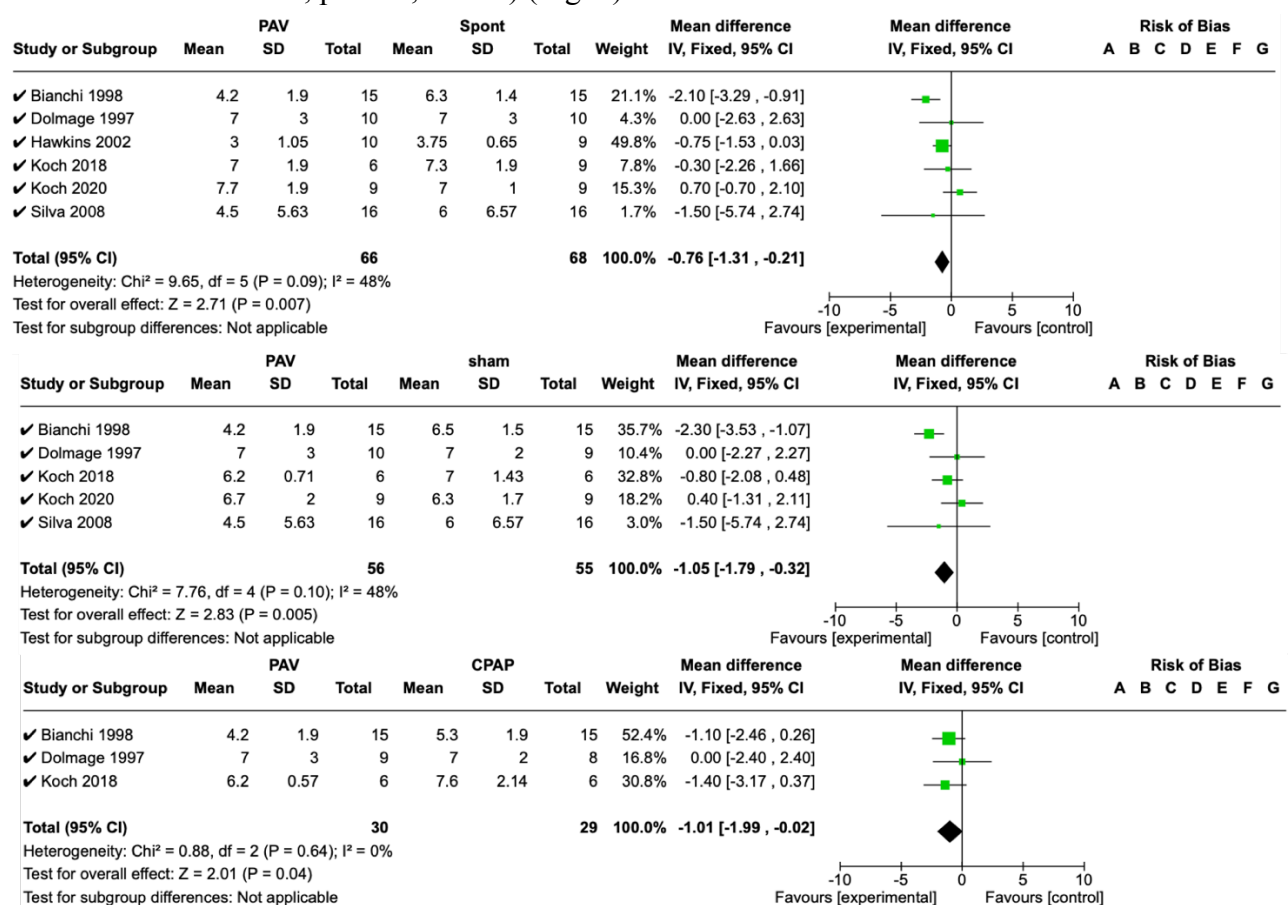


Figure 2: Results of Borg scale Dyspnea

3.2.2. Borg Scale for Leg fatigue

Borg Scale (Leg fatigue) was reported in five studies, but results for the PAV mode were not documented in two of them.

In the comparison between PAV mode and spontaneous breathing, a meta-analysis using a fixed-effects model, involving 80 patients from three studies, revealed no significant difference in Borg Scale (Leg fatigue) between patients using PAV mode and those with spontaneous breathing (WMD -0.69; 95% CI: -1.94 to 0.57; $p=0.28$; $I^2=0\%$) (Fig. 3).

For the comparison between PAV mode and sham, the meta-analysis using a fixed-effects model, including 80 patients from three studies, showed no significant difference in Borg Scale (Leg fatigue) between patients using PAV mode and those with sham (WMD -0.71; 95% CI: -1.87 to 0.46; $p=0.23$; $I^2=0\%$) (Fig. 3).

Regarding the comparison between PAV mode and CPAP, results were reported in only one study, precluding the conduct of a meta-analysis.

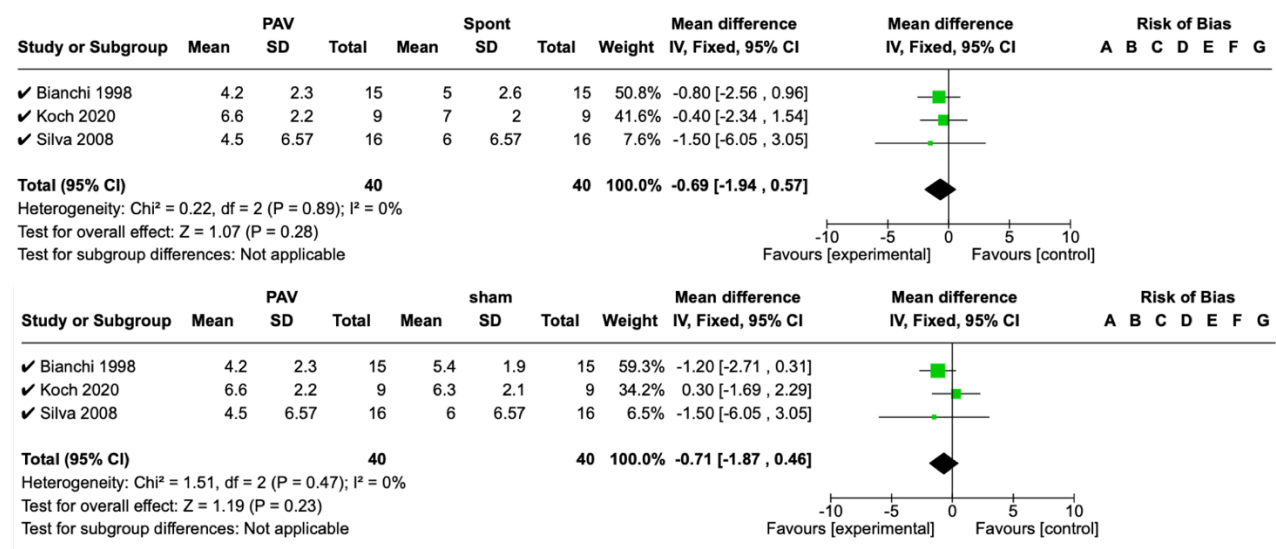


Figure 3: Results of Borg scale Leg

3.2.3. Exercise endurance

Exercise endurance was assessed in a total of seven studies, with four studies comparing PAV with spontaneous breathing, five studies comparing PAV with sham, and three studies comparing PAV with CPAP.

In the comparison between PAV mode and spontaneous breathing, a meta-analysis using a fixed-effects model, involving 109 patients from four studies, demonstrated that patients using PAV mode had significantly longer exercise endurance compared to those with spontaneous breathing (WMD 2.60; 95% CI: 1.04 ~ 4.15; $p=0.001$; $I^2=0\%$) (Fig. 4).

For the comparison between PAV mode and sham, the meta-analysis using a fixed-effects model, including 111 patients from five studies, indicated that patients using PAV mode had

significantly longer exercise endurance than those with sham (WMD 1.77; 95% CI: 0.84~2.70; $p=0.0002$; $I^2=26\%$) (Fig. 4).

Regarding the comparison between PAV mode and CPAP, results from three studies involving 59 patients showed, in a meta-analysis using a fixed-effects model, that patients using PAV mode had significantly longer exercise endurance than those with CPAP (WMD 1.83; 95% CI: 0.34~3.33; $p=0.02$; $I^2=5\%$) (Fig. 4).

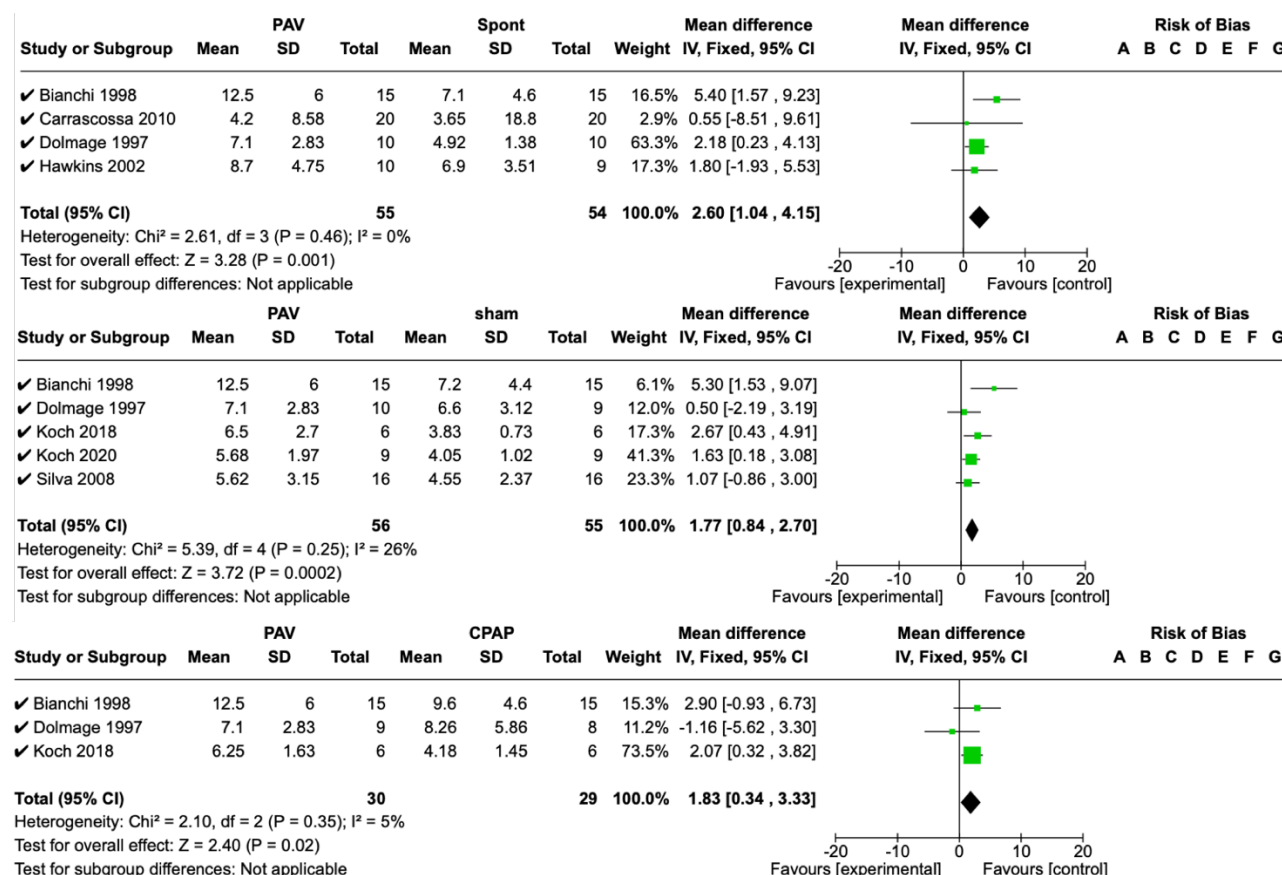


Figure 4: Results of Exercise endurance

3.3. Secondary Outcome

We conducted a meta-analysis using a fixed-effect model to compare Minute Ventilation, Respiratory rate, Heart rate, Oxygen uptake, and Work rate among patients undergoing PAV mode, spontaneous breathing (without mechanical ventilation), sham ventilation, and CPAP mode.

For Oxygen uptake in the comparison between PAV mode and CPAP mode, and for Work rate in the comparisons between PAV mode and sham, as well as PAV mode and CPAP mode, only one study reported the respective outcomes, precluding the possibility of meta-analysis.

The results of the meta-analysis consistently showed no significant differences between patients using PAV mode and those in the other conditions across all parameters. A summary of the results is shown in Table 2.

Table 2: Results of Secondary outcomes

Outcomes	Number of studies	Total sample size	Summary estimates WMD (95%CI)	I^2 (%)
Minute Ventilation	PAV vs Spont 5	105	1.50(-0.12, 3.12)	38
	PAV vs sham 4	99	4.01(-0.16, 8.19)	0
	PAV vs CPAP 2	47	0.98(-6.02, 7.99)	0
Respiratory rate	PAV vs Spont 4	81	-2.27(-4.80, 0.27)	0
	PAV vs sham 4	99	-0.26(-2.78, 2.26)	0
	PAV vs CPAP 2	47	-1.55(-6.04, 2.95)	0
Heart rate	PAV vs Spont 4	72	0.86(-5.73, 7.44)	16
	PAV vs sham 4	99	1.24(-5.59, 8.07)	0
	PAV vs CPAP 2	47	1.78(-7.45, 11.01)	0
Oxygen uptake (VO ₂)	PAV vs Spont 3	84	0.09(-0.04, 0.23)	0
	PAV vs sham 2	51	0.07(-0.10, 0.23)	5
	PAV vs CPAP 1	-	-	-
Work rate	PAV vs Spont 3	69	1.41(-5.57, 8.39)	0
	PAV vs sham 1	-	-	-
	PAV vs CPAP 1	-	-	-

WMD: weighted mean difference

3.4. Sub-group analysis

In this study, subgroup analyses were conducted focusing on two groups: one restricted to patients with severe COPD and the other limited to high-intensity exercise, defined as 70% or more of their maximum power.

Regarding the analysis of the Borg Scale leg fatigue, subgroup analyses were not conducted for the comparison of PAV mode vs. Spont and PAV mode vs. sham in the high exercise intensity group since the subgroups matched the primary outcome group.

For the comparison of PAV mode vs. CPAP mode in the severe COPD group and the high exercise intensity group, only one study reported results for each, preventing a comprehensive analysis.

In the case of Borg Scale dyspnea, analyses for the comparison of PAV mode vs. Spont and PAV mode vs. sham were conducted using a random-effects model due to $I^2 > 50\%$. Other comparisons utilized a fixed-effects model. Detailed results are presented in Table 3.

For Borg Scale dyspnea, both in the severe COPD group and the high exercise intensity group, patients using the PAV mode showed significantly lower values compared to those

using spontaneous breathing, sham, and CPAP modes.

Regarding Borg Scale leg fatigue, there was no significant difference observed in patients with severe COPD who used the PAV mode compared to those using spontaneous breathing or sham, respectively.

For exercise endurance, both in the severe COPD group and in the high exercise intensity group, patients using the PAV mode demonstrated significantly longer durations compared to those using spontaneous breathing, sham, and CPAP modes.

These results were consistent with the primary outcome.

Table 3: Results of Subgroup analysis

Outcome/ Subgroup	Number of studies	Total sample size	Summary estimates WMD (95%CI)	<i>I</i> ² (%)
Borg scale Dyspnea				
Severe COPD	PAV vs Spont 4	79	-0.79(-1.36, -0.22)	67
	PAV vs sham 3	60	-1.17(-1.95, -0.38)	71
	PAV vs CPAP 2	42	-1.21(-2.29, -0.13)	0
Exercise work rate at more than 70%	PAV vs Spont 5	111	-0.80(-1.36, -0.23)	57
	PAV vs sham 4	92	-1.18(-1.95, -0.40)	56
	PAV vs CPAP 2	42	-1.21(-2.29, -0.13)	0
Borg scale Leg fatigue				
Severe COPD	PAV vs Spont 2	48	-0.62(-1.92, 0.68)	0
	PAV vs sham 2	48	-0.65(-1.85, 0.55)	28
	PAV vs CPAP 1	-	-	-
Exercise work rate at more than 70%	PAV vs Spont 3	-	-	-
	PAV vs sham 3	-	-	-
	PAV vs CPAP 1	-	-	-
Exercise Endurance				
Severe COPD	PAV vs Spont 2	49	3.56(0.88, 6.23)	43
	PAV vs sham 3	60	2.26(1.10, 3.41)	40
	PAV vs CPAP 2	42	2.21(0.62, 3.80)	0
Exercise work rate at more than 70%	PAV vs Spont 3	89	3.31(0.75, 5.88)	6
	PAV vs sham4	92	1.94(0.95, 2.93)	32
	PAV vs CPAP 2	42	2.21(0.62, 3.80)	0

WMD: weighted mean difference

※If the subgroup corresponds to the primary outcome group, it is not specified.

3.5. Risk of Bias

The risk of bias for each study is detailed in Figure 5. In all trials, random sequence generation using computers or similar methods was implemented. Allocation concealment was performed in two trials^{17,11}, while in other trials, it remained unclear. Due to the nature of the study design, blinding of participants and researchers was nearly impossible. Given that the outcome, the Borg Scale, involves subjective assessment, there is a potential for participants to be influenced, but assessors are not affected. For other outcomes involving objective numerical values, the risk of bias was considered low. Also, dropouts were not observed in all trials except in three studies^{13,11,7}, and reporting bias was unclear in almost all trials.

Concerning crossover trials, the possibility of carry-over effects was considered, where the use of different setting modes sequentially might lead to habituation in the latter part of the trial, potentially influencing assessments to be lighter, or conversely, fatigue-induced heavier evaluations. However, to prevent habituation effects on assessments, all studies provided a sufficient familiarization period with artificial ventilation or exercise protocols before the actual crossover phases. Additionally, to prevent fatigue-induced impacts on assessments, a washout period with a break extending across days was implemented. While two studies^{4,15} conducted assessments on the same day, it was explicitly mentioned that adequate rest periods were provided.

Publication bias was assessed only in analyses with six or more trials, specifically for the Borg Scale (dyspnea) PAV vs Spont. In other analyses with five or fewer included trials, assessment was not feasible. The funnel plot is generally centered symmetrically around the target. (Figure 6) The result of the test for funnel plot asymmetry was $z = -2.37$, $p = 0.077$. Egger's test suggested that there is no publication bias ($p = 0.077$).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Bianchi 1998	+	?	-	-	+	?	+
Bianchi 2002	+	?	-	-	-	?	
Carrascossa 2010	+	+	-	+	+	+	-
Dolmage 1997	+	+	-	-	-	?	+
Hawkins 2002	+	?	-	-	+	+	
Koch 2018	+	?	-	-	+	+	+
Koch 2020	+	?	-	-	-	+	+
Roberta 2006	+	?	-	+	+	?	-
Silva 2008	+	?	-	-	+	?	+

Figure 5: Risk of bias

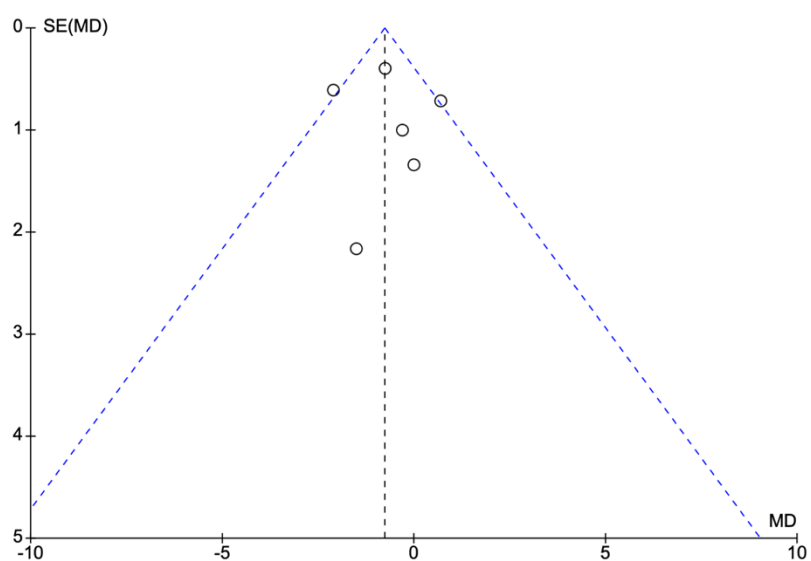


Figure 6: Funnel plot for Borg Scale(Dyspnea) PAV vs Spont

4. DISCUSSION

The key findings suggest that, in the context of exercise therapy for COPD patients, the use of PAV mode in NPPV may alleviate dyspnea measured by The Borg Scale and potentially extend exercise endurance, when compared to spontaneous breathing, sham, or CPAP modes. In COPD patients, as the severity advances, lung function deteriorates, and exercise therapy may be more hindered.^{21, 22, 23} The intensity of exercise therapy is crucial, with high-intensity exercise therapy being recommended.^{3, 20} Therefore, subgroup analysis was conducted, focusing on the severe COPD group and the high-load exercise group as subgroups deemed more suitable for assistance in exercise therapy. Results consistently showed a reduction in The Borg Scale (Dyspnea) and an extension of exercise endurance, whether narrowed down to the severe COPD group or the high-load exercise group. This suggests that support with PAV mode may be effective, even when narrowed down to subgroups more suitable for assistance in exercise therapy. On the other hand, there were consistently no significant differences observed in the Borg scale (Leg) across the results of this study.

In order to examine the mechanistic background for the effects of this intervention, an analysis was conducted on multiple circulatory respiratory parameters as secondary outcomes. Hypothetically, the use of PAV mode was expected to improve respiratory circulatory function, leading to an increase in oxygen uptake and work rate.²⁶ However, in this secondary outcome analysis, there were no significant differences between patients using PAV mode and those under other conditions for any of the analyzed parameters. While there was a significant difference in the primary outcomes of dyspnea and exercise endurance, the lack of significance in these secondary outcomes is not clear. One possible reason for this is that the use of PAV mode extended the exercise duration, resulting in an overall higher workload. Silva using near-infrared spectroscopy (NIRS) to measure muscle oxygenation during exercise, suggested the potential increase in peripheral muscle oxygen consumption along with the alleviation of respiratory muscle burden with PAV mode.¹⁶ While PAV mode provides respiratory muscle support, reducing dyspnea, it may simultaneously lead to an increased overall workload, potentially explaining the lack of changes in circulatory respiratory parameters and lower limb fatigue. Akoumianaki employed a method calculating exercise efficiency using the change in the rate of energy expenditure measured on an ergometer and the oxygen consumption measured by indirect calorimetry.²⁵ To further investigate the physiological mechanisms, a compilation of studies examining oxygen consumption in both respiratory and peripheral muscles, along with evaluating exercise efficiency, is needed.

The current modes in NPPV include CPAP mode, as well as Spontaneous/Time (S/T) mode and Pressure Support Ventilation (PSV) mode. However, comprehensive studies comparing these modes with PAV mode were not enough identified in this review. Given that S/T and PSV modes are also frequently employed, further research comparing these commonly used modes with PAV mode is warranted for a more thorough understanding of their respective efficacies and applications.

4.1. Strengths

Several strengths are emphasized in this study. Firstly, it is noted as the first systematized review and meta-analysis examining the use of PAV mode in NPPV. Given the limited scope of small-scale studies in this field prior to this analysis, the systematized review and meta-analysis contribute significantly, enhancing the impact and credibility of the findings.

Moreover, the analysis considers a wide range of outcomes, not limited to the current targets, which suggests the potential to propose future investigations regarding the use of PAV mode in NPPV for various outcomes.

4.2. Limitations

This study is subject to several limitations. Firstly, the reviewer was the sole author, and the systematic review procedure, which typically involves parallel reviews by multiple individuals, was not followed. It requires independent review to minimize potential bias. To mitigate this limitation to the best extent possible, the criteria for inclusion and exclusion were made as clear and simple as possible, and each decision was documented with individual justifications.

Secondly, the number of included studies is limited, and each study has a small sample size. Moreover, many of the included studies are cross-over studies. When analyzing crossover trials, it is crucial to be mindful of carry-over effects and risk of bias. In consideration of these factors, in this study, we conducted an assessment of publication bias using funnel plots and evaluated the bias in crossover trials (3.5. Risk of Bias). In doing so, we confirmed that carryover effects were not substantial, after consideration of factors such as the nature of the study and the proper setting of the washout period. However, to enhance the precision of the final analysis, the accumulation of data from future RCTs is desirable.

Thirdly, there is substantial heterogeneity in the study designs across studies. Specifically, the protocols for the exercise therapy intervention and the timing of outcome assessments vary among the studies. To address this, each publication was thoroughly reviewed, with references to the full text, figures, tables, and appendices consulted to scrutinize the timing of measurements such as the Borg scale and other numerical values. Every effort was made to adopt data from the most appropriate timing whenever possible.

The fourth limitation arises from the inherent nature of the research, where blinding of subjects is not feasible in any of the studies, posing a high risk of performance bias. In this study, considering the subjective nature of patient assessments using the Borg scale, bias in the results might have occurred under certain conditions. However, it's essential to note that this performance bias is inherently challenging to eliminate. To account for the potential impact of NPPV mask application itself, this study included a sham condition for comparison.

4.3. Implications for Practice

As mentioned in the introduction, while theoretically advantageous physiologically, the

acceptability of NPPV, including issues such as mask discomfort, poses challenges for patient tolerance.^{24, 27} Therefore, the clinical efficacy in improving patient outcomes remained unknown until tested. This systematized review and meta-analysis, by analyzing results from actual patient use, provides meaningful clinical data.

In a clinical setting, the use of the PAV mode in NPPV raises concerns about the risk of a run-away phenomenon where ventilation continues due to the inability to detect the beginning of exhalation, particularly in the presence of air leaks.²⁶ In this review, there was minimal documentation of adverse events within each study. However, most studies reported the completion of exercise therapy without dropouts, and there were no reports of significant adverse events or intolerance to NPPV application itself. In each of the studies, conducted with small sample sizes, the proposed protocols were feasible, and at least appeared to be achievable under the given conditions. Current guidelines do not specifically mention the use of NPPV in respiratory rehabilitation for COPD patients^{3, 20}. Furthermore, the PAV mode is a relatively new mode, and currently, the available ventilators are limited (Puritan Bennett 840/980® by Medtronic plc, BiPAP Vision® by Respirationics, and Evita4® by Dräger).^{28, 29} Moreover, the usage of the PAV mode is still low in Japan.³⁰ To appropriately consider its application to patients, there is a need to increase the number of studies and participants, evaluate the effectiveness, and comprehensively assess potential side effects.

4.4. Conclusions

In exercise therapy for COPD patients, the use of the PAV mode in NPPV may reduce dyspnea, as measured by The Borg Scale, and extend exercise tolerance compared to spontaneous breathing, sham, or CPAP modes. However, a definitive conclusion requires further large-scale studies.

5. References

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Appendix A: Database Search Strategy

("interactive ventilatory support"[MeSH Terms] OR "proportional assist ventilation"[Title/Abstract] OR "pav"[Title/Abstract] OR "proportional ventilation"[Title/Abstract] OR "proportional assist"[Title/Abstract] OR "closed-loop"[Title/Abstract] OR "closed-loop"[Title/Abstract] OR "closedloop"[Title/Abstract]) AND ("pulmonary disease, chronic obstructive"[MeSH Terms] OR "copd"[Title/Abstract] OR "chronic obstructive pulmonary disease"[Title/Abstract] OR "chronic obstructive lung disease"[Title/Abstract])) AND ("cross over studies"[MeSH Terms] OR "cross-over"[Title/Abstract] OR "cross-over"[Title/Abstract] OR "crossover"[Title/Abstract] OR ("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract]))