

SCIENTIFIC INVESTIGATIONS

Effect of continuous positive airway pressure on maximal exercise capacity in patients with obstructive sleep apnea: a systematic review and meta-analysis

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Study Objectives: Exercise capacity is impaired in obstructive sleep apnea (OSA). There are conflicting reports on the effect of continuous positive airway pressure (CPAP) on maximal exercise capacity. The objective of this review was to determine if there is a change in exercise capacity and anaerobic threshold following CPAP treatment in OSA patients.

Methods: We conducted a systematic review and meta-analyses to summarize the changes in peak rate of oxygen uptake ($\dot{V}O_2$ peak) or maximum rate of oxygen uptake ($\dot{V}O_2$ max) and anaerobic threshold (AT) during cardiopulmonary exercise testing following CPAP intervention in patients with OSA. A systematic literature review was conducted to identify published literature on markers of $\dot{V}O_2$ peak, $\dot{V}O_2$ max, and AT pre- vs post-CPAP using a web-based literature search of PubMed/MEDLINE, Embase, CINAHL, and Cochrane review (CENTRAL) databases. Two independent reviewers screened the articles for data extraction and analysis.

Results: The total search of all the databases returned 470 relevant citations. Following application of eligibility criteria, 6 studies were included in the final meta-analysis for $\dot{V}O_2$ peak, 2 studies for $\dot{V}O_2$ max, and five studies for AT. The meta-analysis showed a mean net difference in $\dot{V}O_2$ peak between pre- and post-CPAP of $2.69 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, $P = .02$, favoring treatment with CPAP. There was no difference in $\dot{V}O_2$ max or AT with CPAP treatment (mean net difference $0.66 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ [$P = .78$] and $-144.98 \text{ mL} \cdot \text{min}^{-1}$ [$P = .20$] respectively).

Conclusions: There is a paucity of high-quality studies investigating the effect of CPAP on exercise capacity. Our meta-analysis shows that $\dot{V}O_2$ peak increases following CPAP treatment in patients with OSA, but we did not observe any change in $\dot{V}O_2$ max or AT. Our findings should be considered preliminary and we recommend further randomized controlled trials to confirm our findings and to clarify the peak and maximum rates of oxygen uptake adaptations with CPAP therapy.

Keywords: continuous positive airway pressure, obstructive sleep apnea, aerobic exercise, physical activity, cardiopulmonary exercise test

Citation: Fletcher HV, Cho PSP, Loong SL et al. Effect of continuous positive airway pressure on maximal exercise capacity in patients with obstructive sleep apnea: a systematic review and meta-analysis. *J Clin Sleep Med*. 2020;16(11): 1847–1855.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Exercise capacity is impaired in obstructive sleep apnea. It is unclear if exercise capacity and anaerobic threshold change in obstructive sleep apnea patients after continuous positive airway pressure treatment. This systematic review and meta-analyses summarized the changes in peak rate of oxygen uptake, maximum rate of oxygen uptake, and anaerobic threshold with continuous positive airway pressure intervention.

Study Impact: A web-based literature search included PubMed/MEDLINE, Embase, CINAHL, and Cochrane review (CENTRAL) databases. The analysis finds a significant change in peak rate of oxygen uptake but does not support a change in maximum rate of oxygen uptake or anaerobic threshold after continuous positive airway pressure treatment. More randomized controlled trials are recommended to confirm our conclusions.

INTRODUCTION

In the UK, it is estimated that 1.5 million adults have obstructive sleep apnea (OSA), with under a third currently diagnosed and being treated.¹ OSA increases the risk of developing hypertension,² cardiovascular disease, obesity, stroke events, and diabetes.^{3,4} Cardiorespiratory fitness can be measured by assessing volume of oxygen ($\dot{V}O_2$), which is the rate of oxygen uptake during cardiopulmonary exercise testing, with $\dot{V}O_2$ max representing the maximum value under ideal conditions and $\dot{V}O_2$ peak representing the highest value achieved

within the constraints of the individual or study conditions. These markers can be used to prognosticate cardiac and respiratory disease in patients with high cardiorespiratory risk.^{5–7} A $\dot{V}O_2$ peak has been reported in OSA patients^{8–13}.

A recent systematic review and meta-analysis reported lower maximal exercise capacity in OSA patients compared to healthy individuals.^{14,15} Continuous positive airway pressure (CPAP) is the first-line treatment for significant OSA. Several studies have assessed the effect of CPAP treatment on behavior, metabolism, and energy expenditure.^{14,17–18} Interest also lies with the objective measures of physical activity and exercise training interventions

in addition to CPAP treatment in OSA patients.^{18–20} Associations between physical activity and OSA patients indicate that patients are neither physically capable nor psychologically motivated to exercise.^{8,21–24} However, CPAP has been shown to have a favorable effect on physical activity in patients with OSA. A basis for change could be through a change in motivation (based on symptomatic improvement) or a fundamental change in oxidative capacity. Few systematic reviews have investigated the literature comparing pre- and post-CPAP treatment in maximal exercise capacity ($\dot{V}O_2$ peak and $\dot{V}O_2$ max) and AT markers.

To our knowledge, no systematic review or meta-analyses has been conducted to summarize the changes in maximal exercise capacity with CPAP intervention in patients with OSA. Therefore, the main objective of this systematic review and meta-analysis was to determine if there were changes in maximal exercise capacity ($\dot{V}O_2$ max and $\dot{V}O_2$ peak) and anaerobic threshold following CPAP treatment in OSA patients. A secondary aim was to explore if other physiological markers altered the effect of CPAP on maximal exercise capacity and AT.

METHODS

PRISMA

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement and recommendations were followed (www.prisma-statement.org). The study is registered on PROSPERO [ID number 138158] (www.crd.york.ac.uk/prospero/). No public or patient involvement occurred in this study.

Search strategy

A systematic literature review was conducted to identify published literature that investigated maximal exercise capacity and AT in OSA patients before and after CPAP treatment. A web-based literature search included PubMed/MEDLINE, Embase, CINAHL, and Cochrane review (CENTRAL) databases. Search terms were selected to reflect the intervention, population, and outcome parameters to allow for the specific comparison of the intervention to be assessed by using PICO, (P: adults, I: CPAP, C: pre- and post-treatment, O: maximal exercise capacity and AT).

The search terms included a combination of terms and medical subject headings (MeSH) and or exploded with in databases. For the treatment, condition, and outcomes, search terms used were “continuous positive airway pressure” OR “APRV Ventilation Mode” OR “Airway Pressure Release Ventilation” OR “Bilevel Continuous Positive Airway Pressure” OR “Biphasic Continuous Positive Airway Pressure” OR “CPAP Ventilation” OR “Continuous Positive Airway Pressure” [MeSH Terms] OR “Continuous Positive Airway Pressure” OR “Nasal Continuous Positive Airway Pressure” OR “nCPAP Ventilation” AND “Sleep Apnea, Obstructive” OR “Apnea, Obstructive Sleep” OR “OSAHS” OR “Obstructive Sleep Apnea” OR “Obstructive Sleep Apnea Syndrome” OR “Sleep Apnea Hypopnea Syndrome” OR “Sleep Apnea Syndrome, Obstructive” OR “Sleep Apnea, Obstructive” [MeSH Terms] OR “Sleep Apnea, Obstructive” OR “Syndrome, Obstructive Sleep Apnea” OR “Syndrome, Sleep Apnea, Obstructive” OR “Syndrome,

Upper Airway Resistance, Sleep Apnea” OR “Upper Airway Resistance Sleep Apnea Syndrome” AND “Acute Exercise” OR “Aerobic Exercise” OR “Exercise” [MeSH Terms] OR “Exercise” OR “Exercise Training” OR “Exercise, Aerobic” OR “Exercise, Isometric” OR “Exercise, Physical” OR “Isometric Exercise” OR “Physical Activity” OR “Cardiopulmonary Exercise Testing”.

Terms were searched with all possible combinations using Boolean logical operators. An additional search of bibliographies was conducted to identify any relevant articles. Mendeley Reference Manager software (version 1.19.4; Mendeley Ltd., London, United Kingdom) was used to manage all references.

Eligibility criteria

Inclusion criteria were: published peer reviewed articles conducted in adult humans with a diagnosis of OSA and with an apnea-hypopnea index or respiratory disturbance index score of > 10 events/h on polysomnography. Articles were authors’ original work and only articles published in English were retained. Only articles reporting maximal exercise capacity ($\dot{V}O_2$ max and $\dot{V}O_2$ peak) and AT as means and standard deviations were included. Only articles with clear trial designs were included. Accepted study designs included within group comparison of pre- vs post-CPAP treatment. There was no restriction on the length of the CPAP treatment and no date limits set for the articles. Nonrandomized studies were included.

Articles were excluded if exercise or physical activity interventions were implemented in addition to CPAP treatment. Conference articles were also excluded.

Reviewing procedure and data extraction

Searches of the databases were conducted in December 2018. All obtained references were retained, with data collection being conducted by 2 review authors (HF and PC). The first level of review involved title and abstract screening and removal of duplicated and irrelevant articles and those not published in English. Remaining articles then underwent full text review and assessment against the prespecified eligibility criteria by 2 review team members independently. Disagreements over eligibility of potential articles were resolved through discussion with a third reviewer (KL).

Data extraction was performed for retained articles. Principle summary measures were the differences in $\dot{V}O_2$ max, $\dot{V}O_2$ peak, and AT pre- vs post-CPAP. The following variables were also systematically extracted: (1) author, (2) publication year, (3) participants, (4) apnea-hypopnea index cut-off, (5) sample size, (6) age, (7) duration of CPAP, (8) design, (9) units of measurement, (10) pre-CPAP $\dot{V}O_2$ peak or $\dot{V}O_2$ max/pre-CPAP AT, (11) post-CPAP $\dot{V}O_2$ peak and $\dot{V}O_2$ max/post-CPAP AT (**Table 1** and **Table 2**).

Statistical analysis

The mean $\dot{V}O_2$ max, $\dot{V}O_2$ peak, and AT were compared pre- and post-CPAP. Where $\dot{V}O_2$ max values were not explicitly reported, the mean and standard deviation values of $\dot{V}O_2$ max or $\dot{V}O_2$ peak were estimated by using uncertainty analysis.²² $\dot{V}O_2$ max and $\dot{V}O_2$ peak were expressed in $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. AT was expressed in $\text{mL}\cdot\text{min}^{-1}$.

Table 1—Summary of findings for articles reporting $\dot{V}O_2$ peak.

Author	Year	AHI Cut-off events/h	Baseline AHI/RDI events/h	Sample Size (n)	Age (years)	Duration of CPAP	Adherence to CPAP (hrs · n ⁻¹)	Design	$\dot{V}O_2$ peak or $\dot{V}O_2$ max (mL · min ⁻¹)	Pre (mL · kg ⁻¹ · min ⁻¹)	Post (mL · kg ⁻¹ · min ⁻¹)
Taguchi ²⁶	1997	Not reported	62.5 ± 8.6	6	44.7 ± 13.7	7 days	Not reported	Q	$\dot{V}O_2$ max (mL · min ⁻¹)	22.13 ± 4.56*	25.9 ± 4.8*
Ozsarac ²⁵	2014	> 30	40.7 ± 19.6	65	48.76 ± 9.2	4 weeks	6.2 ± 0.9	Q	$\dot{V}O_2$ max (mL · min ⁻¹)	22.5 ± 6.6*	21.3 ± 5.3*
Alonso-Fernández ¹⁰	2006	> 10	43.6 ± 26.6	31	53 ± 13	12 weeks	6 ± 1	RCT	$\dot{V}O_2$ peak	24.53 ± 6.15	25.1 ± 8.58
Goel ²⁷	2015	> 10	35.32 ± 16.99	15	56.5 ± 9.1	4 weeks	Not reported	Q	$\dot{V}O_2$ peak (mL · min ⁻¹)	12.83 ± 3.3*	17.46 ± 4.44*
Lin ²⁸	2004	RDI ≥ 30	47.3 ± 15.7	20	43 ± 8	2 months	Not reported	Q	$\dot{V}O_2$ peak	20.41 ± 3.31	26.3 ± 4.29
Mortari ²⁹	2017	> 30	61.7 ± 23.4	16	52.8 ± 10.8	3 months	6.7 ± 2**	R	$\dot{V}O_2$ peak	27.81 ± 9.91	29.71 ± 7.83
Pendharker ³⁰	2011	> 15	48.1 ± 33.1	15	49 ± 6	3 months	5.8 ± 2s	Q	$\dot{V}O_2$ peak	17 ± 4.2	16.6 ± 3.5
Quadri ³¹	2017	> 30	45.4 ± 14.9	12	58 ± 9.7	2 months	Not reported	Q	$\dot{V}O_2$ peak	21.1 ± 3.8	23.4 ± 4.3

Data are presented as n or mean ± SD, unless reported otherwise. *Original data in articles in mL/min, uncertainty analysis used to change. **Extrapolated from the total hours usage data over 3 months (603 ± 180 written in article). AHI = apnea-hypopnea index, CPAP = continuous positive airway pressure, OSA = obstructive sleep apnea, OSAHS = obstructive sleep apnea hypopnea syndrome, Q = quasi-experimental single group designed study, R = retrospective study, RCT = randomized controlled trial, RDI = respiratory disturbance index, $\dot{V}O_2$ max = peak rate of oxygen uptake, $\dot{V}O_2$ peak = maximum rate of oxygen uptake.

Table 2—Summary of findings for articles reporting anaerobic threshold.

Author	Year	Sample Size (n)	Age (years)	Duration of CPAP	Design	AT (L · min ⁻¹ or mL · min ⁻¹)	Pre (mL · min ⁻¹)	Post (mL · min ⁻¹)
Goel ²⁷	2015	15	56.5 ± 9.1	4 weeks	Q	mL · min ⁻¹	703 ± 215	926 ± 248
Lin ²⁸	2004	20	43 ± 8	2 months	Q	L · min ⁻¹	910 ± 140*	1280 ± 120*
Ozsarac ²⁵	2014	65	48.76 ± 9.2	4 weeks	Q	L · min ⁻¹	1000 ± 300*	900 ± 200*
Quadri ³¹	2017	12	58 ± 9.7	2 months	Q	mL · min ⁻¹	1229.5 ± 212.9	1399.2 ± 372.7
Taguchi ²⁶	1997	6	44.7 ± 13.7	7 days	Q	mL · min ⁻¹	985 ± 161	1050 ± 139

Data are presented as n or mean ± SD, unless reported otherwise. *Original data in articles in mL/min, uncertainty analysis used to change. AT = anaerobic threshold, CPAP = continuous positive airway pressure, Q = quasi-experimental single group designed study, R = retrospective study, RCT = randomized controlled trial.

Heterogeneity analysis was used to provide an estimation of the variability due to heterogeneity. An I² index of > 60% reflects increasing heterogeneity.²³ Sensitivity analysis was performed for $\dot{V}O_2$ max, $\dot{V}O_2$ peak, and AT using Cochrane Q test.²⁴

Effect sizes were calculated for random effects models using Review Manager (RevMan, Version 5.3.; The Nordic Cochrane Centre, Copenhagen, Denmark) and reported as mean net difference and 95% confidence intervals.²⁴

For subanalysis, tests of normality and Spearman rank tests were performed using Prism (Version 8.3.0 for Windows; GraphPad Software, La Jolla, CA).

RESULTS

Study selection process is presented in **Figure 1**, a PRISMA flow diagram. The total search of all the databases provided 470 relevant citations. After the first and second stages of screening, 8 articles remained that reported $\dot{V}O_2$ max or $\dot{V}O_2$ peak pre- and post-CPAP treatment in OSA patients, of which 2 reported

$\dot{V}O_2$ max^{25,26} and 6 reported $\dot{V}O_2$ peak.^{10,27–31} Five articles met the inclusions criteria for reporting AT pre- and post-CPAP treatment in OSA patients^{25–28,31} (**Figure 2**).

Description of studies

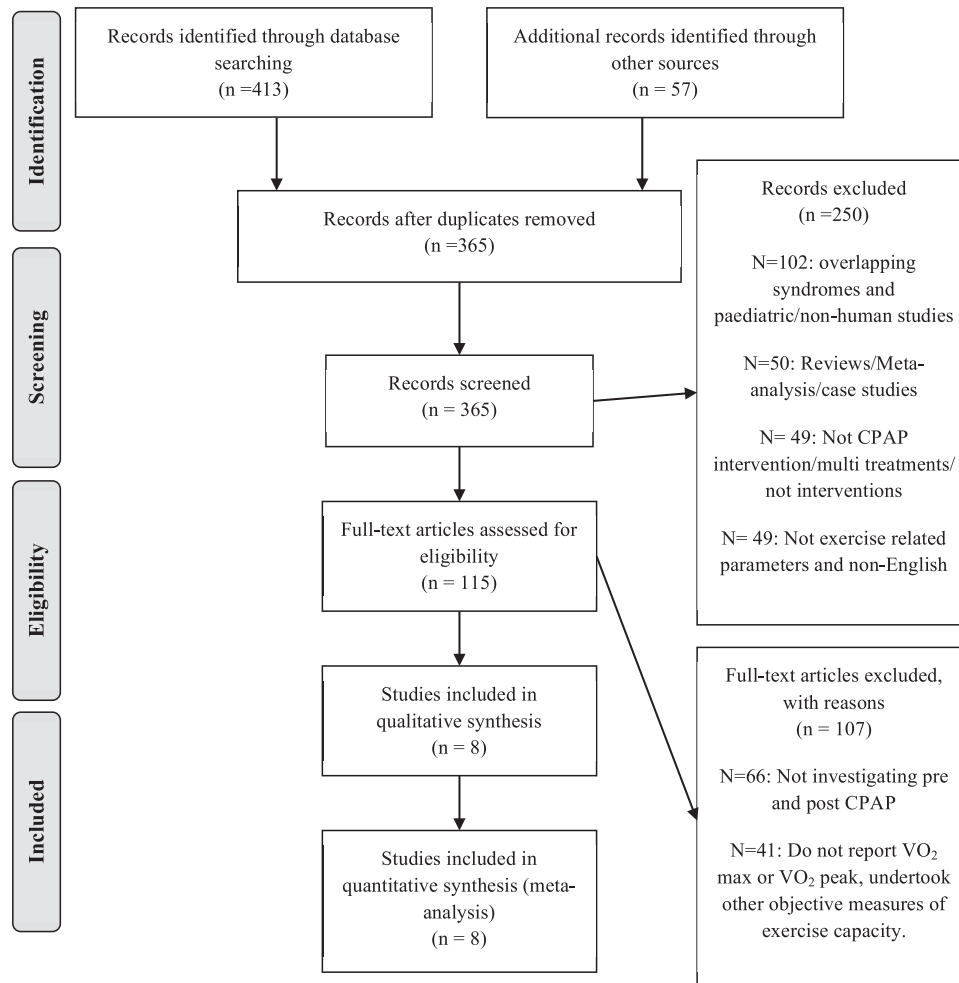
The characteristics of the articles are presented in **Table 1** and **Table 2**. The sample size of all the included studies was 175 patients, of whom 18.9% were female. The mean age ranged from 43 to 58 years. Baseline apnea-hypopnea index or respiratory disturbance index ranged between 35 and 62 events/h, signifying a cohort of patients with severe OSA.

The total sample sizes of the studies retained for the meta-analyses of $\dot{V}O_2$ max,^{10,27–31} $\dot{V}O_2$ peak,^{25,26} and AT^{25–28,31} were 71, 104, and 119 patients, respectively.

Analysis of publication bias

Overall the quality of the evidence of CPAP improving $\dot{V}O_2$ max, $\dot{V}O_2$ peak, and AT in patients with OSA was graded as high and the risk of bias as unclear (**Table 3**). The quality

Figure 1—PRISMA flow diagram $\dot{V}O_2$ max and $\dot{V}O_2$ peak, for the selection of articles identified and evaluated during the selection process.



CPAP = continuous positive airway pressure, OSA = obstructive sleep apnea, $\dot{V}O_2$ max = maximum rate of oxygen uptake, $\dot{V}O_2$ peak = peak rate of oxygen uptake.

of the one RCT study was low risk of bias.¹⁰ All of the quasi-experimental, single-group–designed studies were considered as having very low/unclear quality.^{25–31}

Effect of CPAP on $\dot{V}O_2$ max and $\dot{V}O_2$ peak

The mean $\dot{V}O_2$ max net difference between pre- and post-CPAP in patients with OSA was $-0.66 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($P < .78$) not reaching statistical significance. Mean $\dot{V}O_2$ max, pre-CPAP, and post-CPAP expressed a 95% CI of -5.38 to -4.05 (Figure 3, Figure S1 in the supplemental material, and Table 1).

The mean $\dot{V}O_2$ peak net difference between pre- and post-CPAP in patients with OSA was $-2.69 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($P < .02$) favoring treatment with CPAP and reaching statistical significance. Mean $\dot{V}O_2$ peak, pre-CPAP and post-CPAP expressed a 95% CI of -4.96 to -0.41 (Figure 4, Figure S2 in the supplemental material, and Table 1).

Effect of CPAP on anaerobic threshold

Mean net difference (95% CI) AT before and after CPAP treatment was -144.98 (-368.65 to -78.68) $\text{mL} \cdot \text{min}^{-1}$ ($P < .20$)

(Figure 5, Figure S3 in the supplemental material, and Table 2).

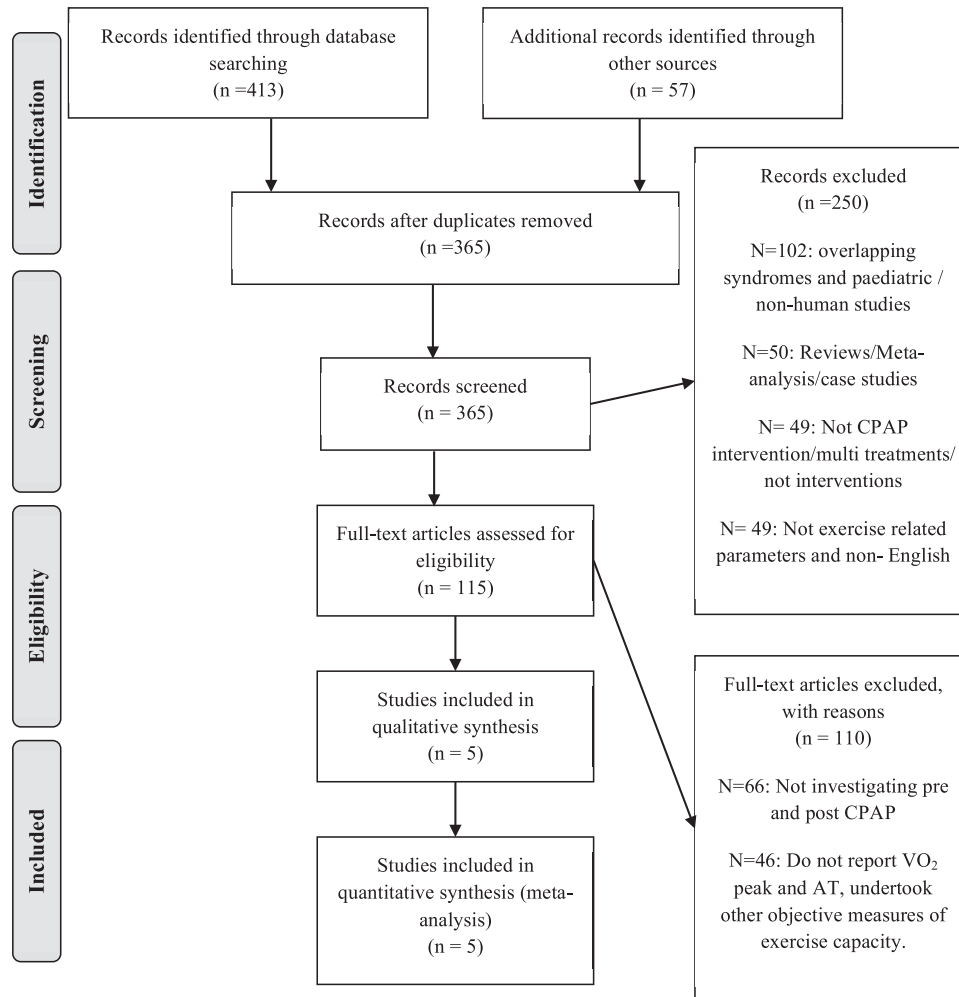
Subanalysis

Table 4 shows the Spearman correlation coefficients between baseline patient characteristics and change in $\dot{V}O_2$ max and $\dot{V}O_2$ peak ($\Delta\dot{V}O_2$ max and peak) with CPAP within the included studies. There was a significant inverse relationship between the $\Delta\dot{V}O_2$ max and peak and baseline body mass index (BMI) ($r = -.785, P = .027$). There was no significant correlation between $\Delta\dot{V}O_2$ max and peak and age or pre-CPAP $\dot{V}O_2$ max and peak (Table 4). There was no statistically significant association between the change in AT and baseline BMI.

Sensitivity analysis

The heterogeneity I^2 index (Cochrane Q test) was 66% between the studies reporting $\dot{V}O_2$ max (Figure 3) and 65% in the $\dot{V}O_2$ peak articles (Figure 4). The heterogeneity I^2 index between the studies reporting AT was 93% (Figure 5). Further removal of one article (Ozsarac et al, 2014) improved heterogeneity to 59%

Figure 2—PRISMA flow diagram anaerobic threshold, for the selection of articles identified and evaluated during the selection process.



AT = anaerobic threshold, CPAP = continuous positive airway pressure, OSA = obstructive sleep apnea.

(Figure 6), suggesting that this article skewed the heterogeneity of the data analysis, although this cannot be concluded due to the small sample of articles included in this systematic review.

DISCUSSION

Our systematic review was conducted to assess the effect of CPAP therapy on $\dot{V}O_2$ max, $\dot{V}O_2$ peak, and AT in OSA patients. The meta-analysis showed a statistical increase in $\dot{V}O_2$ peak with CPAP therapy, but there was no change in $\dot{V}O_2$ max. There was no effect on AT with CPAP therapy.

A beneficial effect of CPAP on $\dot{V}O_2$ is plausible since $\dot{V}O_2$ peak is dependent on levels of oxygen delivered to vital organs and is an indirect assessment of cardiac output.³² CPAP is known to improve left ventricular function, cardiac index, and thus arterial oxygen content, constituting the rationale for benefit in patients with heart failure.^{33,34} Furthermore, CPAP treatment has been shown to significantly reduce cardiovascular risk or stroke in patients with severe OSA, and assessment of

$\dot{V}O_2$ has been linked to cardiovascular risk profiling.^{4,35} Others suggest that CPAP may rebalance the autonomic nervous system leading to greater exercise performance.³¹ It has also been postulated that CPAP could improve $\dot{V}O_2$ by affecting a decrease in the production of reactive oxygen species such as interleukin-8, tumor necrosis factor α , and interleukin-6, resulting in improvements in cardiovascular, ventilatory, and musculoskeletal systems.²⁷

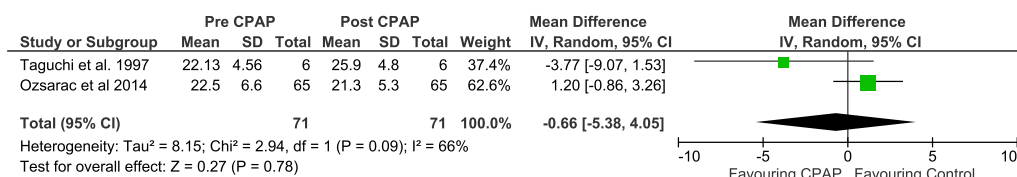
Our finding of the improvement in $\dot{V}O_2$ peak but not $\dot{V}O_2$ max may be explained by true differential effect from CPAP or by methodological limitation due to the lack of data on $\dot{V}O_2$ max. $\dot{V}O_2$ max is defined as the true $\dot{V}O_2$ maximum value, but its measurement can prove challenging for some patients due to their inability to complete the protocol (for example, due to fatigue, joint pain, lack of fitness). $\dot{V}O_2$ peak, by contrast, is considered a “system-limited” peak oxygen uptake,³⁶ defined as the maximum observed value within the capability of the patient and accounting for any such constraints. It is possible that CPAP therapy facilitates an improvement in $\dot{V}O_2$ peak by improving a patient’s systemic

Table 3—Results of the quality analysis of the included studies.

Quality Criteria	Alonso-Fernández ¹⁰	Goel ²⁷	Lin ²⁸	Mortari ²⁹	Ozсарac ²⁵	Pendharker ³⁰	Quadri ³¹	Taguchi ²⁶
Sample randomization	Yes	No	No	No	No	No	No	No
Comparison between treatments	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Blinding of participants	Yes	No	No	No	No	No	No	No
Description of measurement	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Statistical analysis	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Defined inclusion/exclusion criteria	Yes	No	Yes	Yes	Unclear—exclusion only	Yes	Yes	No
Report of follow-up	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear
Risk of bias*	Low	High	High	Unclear	High	Unclear	Unclear	High

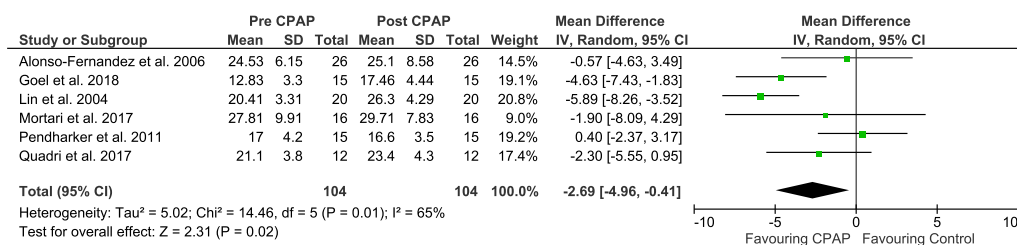
*Risk of bias assessment: Yes (high) = 0–4, unclear = 5–6, No (low) = 7.

Figure 3—Forest plot for mean $\dot{V}O_2$ max in $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ pre- and post-CPAP treatment in OSA patients.



CPAP = continuous positive airway pressure, IV = random-effect model, SD = standard deviation.

Figure 4—Forest plot for mean $\dot{V}O_2$ peak in $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ pre- and post-CPAP treatment in OSA patients.



CPAP = continuous positive airway pressure, IV = random-effect model, SD = standard deviation.

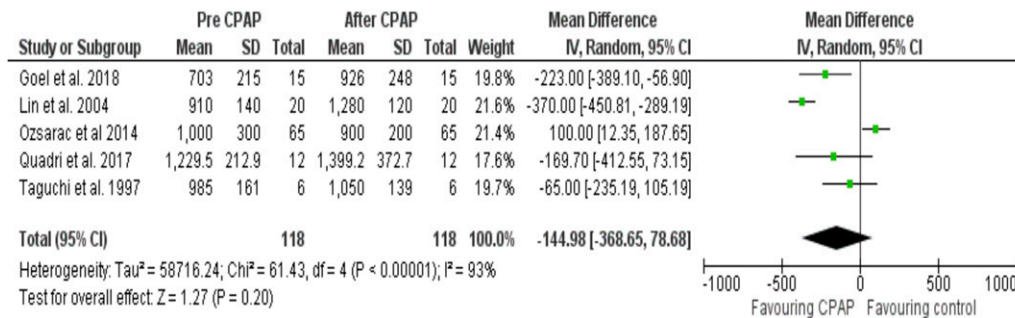
limitations, without affecting the true $\dot{V}O_2$ max. To alter an individual’s $\dot{V}O_2$ max requires exercise training that is conducted at the right intensities, duration, and type of training,³⁷ and CPAP alone may not result in a change in oxidative capacity. Alternatively, we are cognizant that there was very limited data on $\dot{V}O_2$ max available for inclusion in our meta-analysis. Only 2 studies reported $\dot{V}O_2$ max, of which 1 study dominated the weighting in the analysis.²⁵ This study found no change in $\dot{V}O_2$ max despite reported adequate CPAP adherence, but the adherence levels were self-reported by patients and this is recognized to be prone to overestimation by as much as 50%.³⁸ We therefore caution making definitive conclusions on the effect of CPAP on $\dot{V}O_2$ max until further data is available.

Our meta-analysis showed that $\dot{V}O_2$ peak increased by 2.69 $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ with CPAP therapy. There is a paucity of data on the minimum clinically important difference (MCID) of $\dot{V}O_2$, particularly in patients with OSA, but values ranging

between 1.5 and 2.0 $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ have been reported in other groups of patients using either anchor-based, distribution-based, or arbitrarily defined methods.^{39,40} Others have defined “responders” to interventions based on detectable differences in $\dot{V}O_2$ greater than the technical error of measurement, which may range from 1.5 to 1.8 $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.^{41,42}

The subgroup analysis within this review found a relationship between baseline BMI and $\Delta\dot{V}O_2$ max and $\dot{V}O_2$ peak, with higher baseline BMI being associated with smaller changes in $\dot{V}O_2$ max and $\dot{V}O_2$ peak with CPAP treatment. Patients with higher BMI levels are more likely to have additional comorbidities that could interfere with the ability to alter $\dot{V}O_2$ max and $\dot{V}O_2$ peak. A higher BMI is associated with significantly increased risk of cardiovascular morbidity and mortality compared to normal BMI.⁴² Unfortunately, not all of the studies in our systematic review reported the baseline BMI or weight data, thus the resultant sample size was low. Further studies are needed to

Figure 5—Forest plot for mean AT in mL · min⁻¹ pre- and post-CPAP treatment in OSA patients.



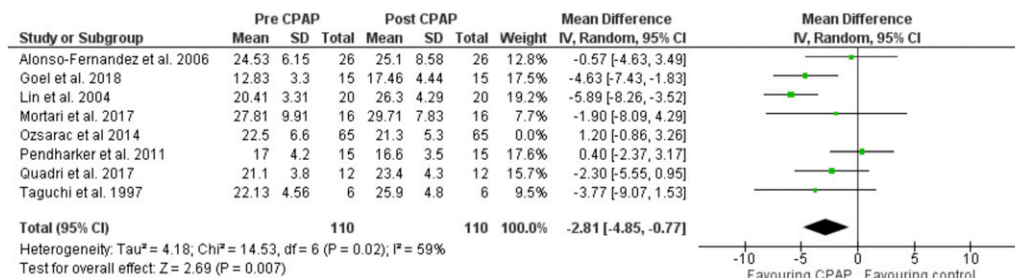
CPAP = continuous positive airway pressure, IV = random-effect model, MD = mean difference, SD = standard deviation.

Table 4—Spearman correlation coefficients between change in exercise capacity following CPAP therapy and baseline patient characteristics.

	Change in $\dot{V}O_2$ max and peak vs Baseline BMI	Change in $\dot{V}O_2$ max and peak vs Age	Change in $\dot{V}O_2$ max and peak vs Baseline $\dot{V}O_2$ max and peak	Change in AT vs Baseline BMI
Spearman <i>r</i>	-.78	-.09	-.42	-.50
<i>P</i> -Value (two-tailed)	.02	.84	.29	.45

AT = anaerobic threshold, BMI = body mass index, $\dot{V}O_2$ max = maximum volume of oxygen uptake, $\dot{V}O_2$ peak = peak rate of oxygen uptake.

Figure 6—Forest plot for mean $\dot{V}O_2$ max & peak in mL · kg⁻¹ · min⁻¹ pre- and post-CPAP treatment in OSA patients with 1 author removed to show the change in heterogeneity.



CPAP = continuous positive airway pressure, IV = random-effect model, SD = standard deviation.

investigate this observation. Age and pre-CPAP $\dot{V}O_2$ max and $\dot{V}O_2$ peak levels did not affect the $\Delta\dot{V}O_2$ max and $\dot{V}O_2$ peak with CPAP.

Our meta-analysis did not find a statistically significant improvement in AT with CPAP therapy. AT represents the change from aerobic to anaerobic metabolism during exercise and is utilized to determine and observe exercise rehabilitation or programs within a variety of diseases, such as COPD.⁴³ In the clinical setting, AT can provide an index of the functional state of patients.⁴⁴ Studies have shown that exercise at AT is associated with steady state blood lactate response; however, though it was not clarified whether exercise at a power output above the calculated AT also resulted in constant blood lactate levels.^{42,43} AT was not the primary outcome in any of the studies included in this meta-analysis. Additionally, AT is a derived measurement from $\dot{V}O_2$ data, and the techniques in measurement of the marker could be disputed. We

found no relationship between baseline measures and Δ AT with CPAP.

Several of the studies within this systematic review included younger patients, with the mean age ranging from 43- to 58-years-old. This could suggest a slightly atypical OSA cohort; however, we do recognize that OSA patient cohorts can vary in demographics. The majority were male patients, consistent with OSA prevalence data. Our cohort of patients had a high baseline apnea-hypopnea index representative of severe OSA. It is possible that the effect of CPAP on exercise capacity may differ depending on disease severity, and therefore our findings should not be generalized to patients with milder disease.

The quality analyses of the included articles within our systematic review identified a “high” risk of bias, and the funnel plots demonstrated a publication bias by non-inverse funnel shaped plot (**Figure S1**, **Figure S2**, and **Figure S3**). Furthermore, an

unavoidable concern is that only one study was a randomized controlled trial.¹⁰ Only two other studies compared treatments types.²⁷ Common limitations across all studies were the small sample sizes, which limit the generalization of the results.^{28,31–32} These findings highlight the current dearth of high-quality studies in this field and emphasize the need for more randomized controlled trials.

Our study has some limitations. We reported AT in $\text{mL} \cdot \text{kg}^{-1}$ rather than $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; this was due to the lack of weight data within some of the studies, and unfortunately this prevents direct comparison or the ability to fully assess oxidative capacity. CPAP adherence was reported in only 4 out of 8 studies (Table 1). Of those, CPAP usage ranged from 5.8 hours per night to 10 hours per night. CPAP adherence of 4 hours or more is usually considered the minimum satisfactory level in clinical practice, although some authors suggest that less can potentially still have clinical benefits.⁴⁵ Two studies with a negative treatment effect did not report CPAP adherence data, and it is possible that insufficient CPAP usage affected those results. Finally, the duration of CPAP therapy across the studies was not uniform, ranging from 7 days to 3 months. Seven days of CPAP is sufficiently long to correct OSA and the associated arousals and hypoxia events.⁴⁶ Indeed, we observed a positive treatment effect on $\dot{V}O_2$ in the study that conducted 7 days of CPAP²⁶; however, it is possible that studies of longer duration encounter different changes in motivation or oxidative capacity, which we were not able to account for and thus could have influenced the results.

CONCLUSIONS

We have identified a paucity of high-quality studies investigating the effect of CPAP therapy on exercise capacity in patients with OSA. The results of our meta-analysis showed that $\dot{V}O_2$ peak significantly increases following CPAP treatment in patients with OSA. There was no significant change in $\dot{V}O_2$ max or AT with CPAP. We recommend further randomized controlled trials to confirm our findings and to clarify the $\dot{V}O_2$ adaptations with CPAP therapy.

ABBREVIATIONS

AT, anaerobic threshold
 BMI, body mass index
 CPAP, continuous positive airway pressure therapy
 OSA, obstructive sleep apnea
 $\dot{V}O_2$ max, maximal rate of oxygen uptake
 $\dot{V}O_2$ peak, peak rate of oxygen uptake
 $\dot{V}O_2$, volume of oxygen

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ACKNOWLEDGMENTS

Authors' contributions: conception and design: HF, PC, SL, and KL; participants screening: HF; study recruitment: HF; data analysis: HF, SL, and LEP; interpretation of data: HF, PC, SL, LEP, SB, and KL; drafting manuscript: HF, PC, SL, LEP, ASP, SB, and KL; revised manuscript: HF, PC, SL, LEP, ASP, SB, and KL.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication March 18, 2020

Submitted in final revised form July 3, 2020

Accepted for publication July 7, 2020

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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. The authors declare no conflicts of interest.