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Effect of respiratory rehabilitation techniques on the autonomic function in patients with chronic obstructive pulmonary disease: A systematic review

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Abstract

Patients with chronic obstructive pulmonary disease (COPD) show several extrapulmonary abnormalities such as impairment in the autonomic function (AF). Similarly, the use of respiratory training techniques such as controlled breathing techniques, noninvasive mechanical ventilation (NIMV), and oxygen supplementation for AF modulation in patients with COPD is popular in existing literature. However, the evidence to support their use is nonexistent. A systematic search of studies reporting on the effect of controlled breathing techniques, NIMV, and/or oxygen supplementation techniques on AF outcome parameters was conducted in three online databases: PubMed, Embase, and Web of Science. Following the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement, relevant studies were retained and qualitatively analyzed for evidence synthesis. The methodological quality in these studies was evaluated using the evidence based guideline development (EBRO) checklists per designs provided by the Dutch Cochrane Centre. Eighteen studies met the inclusion criteria of the review and were included and discussed. The evidence synthesis revealed that a strong and moderate level evidence supported oxygen supplementation and slow breathing techniques, respectively, in significantly enhancing the baroreceptor sensitivity (BRS) values in patients with COPD. The effect of the examined techniques on the heart rate variability and muscle sympathetic nerve activity was of a limited or inconsistent evidence. The findings from this review suggest that oxygen supplementation and controlled breathing techniques have profound positive influence on the BRS in patients with COPD. However, it is not fully clear whether these influence translates to any therapeutic benefit on the general AF of patients with COPD in the long term.

Keywords

COPD, sympathetic, parasympathetic, review, autonomic nervous system, respiratory training techniques

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex, heterogeneous, and highly prevalent clinical syndrome, which is associated with high morbidity and mortality.[1–3] The scourge of COPD, which is mainly as a result of aging and tobacco use, is on the increase and it is presently projected to be among the top three leading causes of mortality by the year 2020.[4] COPD is mainly characterized by a progressive and nonreversible airflow obstruction, and patients with the disease present

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with other numerous extrapulmonary abnormalities.[5,6] For example, conditions like chronic fatigue syndrome, arrhythmias, reduced exercise capacity, and impaired autonomic functions (AFs) have been repeatedly reported in patients with COPD.[7,8]

The AF in patients with COPD has been widely reported in literature due to its prognostic value in determining the cardiovascular health status of these patients. Unfortunately, the trends reflected in the results in most of these studies have shown that AF parameters like heart rate variability (HRV),[1,6] baroreceptor sensitivity (BRS),[9,10] heart rate recovery (HRR),[11] chemoreflex sensitivity,[12] skin sympathetic responses,[13] and the muscle sympathetic nerve activity (MSNA)[10,14,15] are significantly impaired. Similarly, there is also an increasing report on the use of nonpharmacological approaches for the management of patients with COPD. These approaches range from smoking cessation programs to, nutritional intervention, psychosocial support and in some cases surgical interventions.[16] A group of respiratory rehabilitation techniques such as hypoxic training/oxygen supplementation,[17–20] noninvasive mechanical ventilation (NIMV),[5,21–23] aerobic exercises,[24,25] and controlled breathing techniques[8,26–28] are also employed for a variety of important outcomes for patients with COPD. While the effect of these respiratory rehabilitation techniques on most COPD symptoms is clear, the evidence to support their effects on the AF outcomes is nonexistent. Therefore, a clear overview of the existing evidence regarding the effects of these techniques on AF is warranted. Also, it is necessary to make a distinction between various AF parameters with a view to highlighting possible clinical implications.

The aim of this systematic review is to provide a grade 2 evidence to support the effects of three distinct respiratory rehabilitation techniques, namely, controlled breathing, NIMV application, and oxygen supplementation on the AF parameters in patients with COPD. Conclusions regarding the evidence generated from the existing can shape the direction of future studies and also aid clinicians in making an informed choice regarding the use of respiratory rehabilitation techniques in the management of patients with COPD.

Materials and methods

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses.[29]

Information sources and search strategy

To identify relevant articles, the online databases of PubMed (1966 to August 23, 2015), Embase (1966 to August 23, 2015), and Web of Science (1955 to August 23, 2015) were searched for published articles. For PubMed, the search strategy was conducted using a combination of Medical Subject Headings (MeSH) terms in the following order: "(pulmonary disease, chronic obstructive [MeSH Terms]) AND autonomic function OR heart rate variability OR baroreceptor sensitivity OR muscle sympathetic nerve activity AND breathing exercises OR rehabilitation." For the Embase and Web of Science databases, two free-text keywords ("COPD AND autonomic function") were utilized for the search strategy. Search filters were applied to restrict search outputs in all three databases for article type (clinical trials), species (humans), and language (English). In addition, the reference list of the potentially relevant studies was screened to make the review as complete as possible.

Eligibility criteria

To be included in this systematic review, studies had to report on the effect of controlled breathing, NIMV, and/or oxygen supplementation (I) on AF outcomes (O) in patients with COPD (P).

Study selection

After de-duplication, the search results (articles) were screened based on title and abstract (for fulfillment of the review eligibility criteria). Thereafter, the full-text reports of articles that were considered potentially eligible and relevant were retrieved for further evaluation. The second round of evaluation of the studies was based upon six clearly stated predetermined inclusion criteria before any study was included in the review:

i. Study participants were clinically diagnosed with COPD using standardized measures (%FEV_1 predicted, global initiative for obstructive lung disease (GOLD), American Thoracic Society);
ii. Study design ranging from randomized controlled trials (RCTs), case–control, cohort, crossover, and cross-sectional studies, expert opinions, reviews, and letters were excluded;
iii. A respiratory rehabilitation technique was used for intervention, and this was delimited to

controlled breathing techniques, NIMV application, and oxygen supplementation;

iv. Reported any AF outcome measures;

v. Article was published in English language; and

vi. Full-text original research report, short communications such as congress proceedings and abstracts were excluded.

Qualification of searchers

Literature search and screening were conducted by two authors: JM (Master of Science in Physiotherapy) and PC (who has obtained the degree of PhD). Both authors have experience with systematic reviews.[30–34]

Data items and collection

Data regarding author information and year of publication, sample size and characteristics of participants, inclusion and exclusion criteria, respiratory training intervention, reported AF outcomes, main results, and conclusions were extracted from the included studies (Table 1).

Assessment of methodological quality

The checklists of the EBRO platform (an evidence-based guideline development in the Netherlands) present on the website of the Dutch Cochrane Centre (http://dcc.cochrane.org/) were used to assess methodological quality of the included studies. The appropriate checklist related to each study design was applied accordingly. All question items criteria used for the methodological quality evaluation are presented in Table 2.

The methodological quality was evaluated by two assessors (authors: JM and HDS) who were initially blinded from each other's evaluation. HDS is (Master of Science in Rehabilitation Sciences and Physiotherapy) a PhD candidate working on the "AF in patients with heart failure."

The assessors rated each question item with either a positive (+) or a negative (−) score. A positive score was obtained for each question item when questions items, if adequate, information were provided regarding: (i) the definition of the study population (both patients or control) reported in terms of place and time of recruitment, mean age, and sample size, (ii) selection bias sufficiently excluded stated in terms of the study population concerned or when a random sample of the source population with a participation rate at baseline of at least 70% was adopted, (iii) clearly defined exposure and assessment fulfilled if appropriately described in terms of duration, dosage, and frequency, (iv) clearly defined outcomes that are reproducible in terms of internationally accepted values, (v) outcome-assessment method clearly defined and adequate if they were presented in terms standardized AF outcome measures, (vi) blinding, if this was implemented during outcome assessment, (vii) follow-up period, if reported and was sufficiently long, (viii) selective loss-to-follow-up was excluded at analysis and also represented as the total number of dropouts or loss to follow-up >20%, and (ix) identification and consideration of confounders if and differences in medication use and patients characteristics were reported and accounted for.

A negative score (−) was allotted when noninformative description was provided to answer any of the question item or when the provided information was insufficient. After evaluating the included studies individually, the assessors met to compare their evaluation and to discuss areas of differences to obtain a consensus. Each study received a total methodological quality score by collating the number of positive item scores (+) over the number of question items. The scores were then converted into percentages (100%) in order to facilitate comparability across different study designs (Table 2). Only studies with high methodological quality (≥60%) were included for evidence synthesis.

Assessment of evidence synthesis

For each respiratory training technique, the evidence synthesis was based on specific AF outcome. In total, five possible evidence levels, namely, strong, moderate, limited, inconsistent, and no evidence could be reached. A strong evidence signifies consistent findings reported in at least three studies. Moderate evidence connotes consistent findings reported in two studies. A limited evidence was when results were found in only one study. Inconsistent evidence indicates conflicting findings in the available studies, while no evidence is when no study was available. Findings in two or more studies were considered to be consistent only when similar results formed at least 75% of the results in the studies evaluated.

Results

Study selection

As shown in Figure 1, a total of 724 hits were identified from the database search. After de-duplication,

Table 1. Characteristics of included studies.

Reference	Sample	Inclusion criteria	Intervention	Outcome	Results	Conclusion
Bartels et al.[35]	51 COPD; 63.18 ± 7.92 years	COPD: medically diagnosed (severe), no other active respiratory disease, maintain their normal daily routine and medications. All patients refrained from short-acting bronchodilators during assessment.	Oxygen supplementation: Acute administration of 31% $SuppO_2$ and CA; both treatments were randomized (double blind) by turns and patients breath at 12 breaths per minute.	BRS/ HRV	↑ BRS HF↑ LF/HF↓ LF=	$SuppO_2$ in COPD patients significantly and favorably alters autonomic modulation
Bartels et al.[36]	70 COPD (35♂, 35♀) 62.8 ± 8.5 years	COPD: %FEV_1: 30.4, %FVC: <70% (of predicted. All patients were medically diagnosed as moderate-severe, and they maintained daily routine and medications.	Oxygen supplementation: Acute administration of 31% $SuppO_2$ and CA. The intervention was delivered in a counterbalanced, randomized, double-blind crossover design.	BRS	BRS↑	Oxygen supplementation ameliorates BRS by changes in vasomotor activity
Barnerdi et al.[8]	15 COPD (10♂, 5♀) 52.2 ± 2.6 years 28 CON (13♂, 15♀) 47.2 ± 1.7 years	COPD: mild (GOLD I-II), smoking status (mixed), on medication such as B-agonists, anticholinergic, cortisone, and theophylline	Controlled breathing and oxygen supplementation: Acute administration of a 2-min controlled breathing at 15 breaths per minute (spontaneous breathing) and 2 min of controlled breathing at 6 breaths per minute (slow breathing). The treatments were randomly done by turns. Intervention also included progressive hypercapnic hyperoxia, isocapnic hypoxia, and oxygen administration were also done.	BRS	BRS↑	Slow breathing and oxygen administration improved BRS in patients with COPD
Borghi-Silva et al.[37]	19 COPD (19♂) 69 ± 8 years 8 CON (8♂) 68 ± 5 years	COPD: FEV_1 < 50%, FVC < 70% of predicted, (moderate severe), clinically stable, ex-smokers, sedentary, no other chronic diseases, B2-agonists, xanthene derivatives, and steroid treatments were suspended for 24 h to measurement time	NIMV Acute administration of BIPAP (1 min) comprising of IPAP, which was initially set at 6 cmH_2O (increased gradually at 2 cmH_2O per minute to a maximum of 14 cmH_2O), and EPAP, which was set at 3 cmH_2O (and increased gradually at 1 cmH_2O per minute to a maximum of 6 cmH_2O). The CG received only spontaneous breathing.	HRV	RMSSD= SDNN= HF= LF↑ LF(nu) ↑ HF(nu) ↓ LF/HF ratio↑	Ventilation improved but AF decreased as HF was significantly reduced while LF was significantly increased during BIPAP in patients with COPD

(continued)

Table 1. (continued)

Reference	Sample	Inclusion criteria	Intervention	Outcome	Results	Conclusion
Haider et al.[20]	18 COPD (10♂, 8♀) 51.7 ± 2.4 years 14 CON (5♂, 9♀) 47.7 ± 2.8 years	COPD: mild (GOLD I-II), normoxic, those on COPD were allowed to continue with their medications. Smokers and ex-smokers were allowed to participate.	Oxygen supplementation: 3 weeks (15 sessions) of passive interval hypoxic training for the TG for 3–5 times at 15% down to 12% of oxygen was administered progressively, meanwhile the placebo group received a constant normoxic air at 21% oxygen.	BRS/HRV	BRS↑ RRi↑	Patients with mild COPD with signs of cardiovascular autonomic abnormalities at baseline normalized (similar to healthy individuals) to following 3 weeks of hypoxic training.
Jaju et al.[6]	11 COPD (7♂, 4♀) 43.9 ± 20.6 years 6 CON (4♂, 2♀) 43.5 ± 14.6 years	COPD: FEV_1 < 60% predicted, no diabetes, CCF, or hypertension. The patients were allowed to continue medications. Patients had normal BMI (21.9 ± 5.52 kg/km^2)	Controlled breathing 3 months of PBE was administered once, which comprise the closing of one nostril with the thumb, and inhale slowly over (6), afterwards, both nostrils are close for another count of 6 s. The second nostril was then open for slow exhalation over 6 s. Thereafter, inhalation with the same nostril slowly over 6 s is done. This constituted a single sequence, which was repeated for a duration of 30 min/d for at least 5 d/wk.	HRV	HF= LF= LF(nu)= HF(nu)= LF/HF =	Vagosympathetic balance shifted toward the sympathetic in both patients with COPD, but it was not significant
Lewis et al.[19]	10 COPD: (7♂, 3♀) 73.9 ± 7.2 years	COPD: severe (GOLD III-IV). All patients were hypoxic but stable. Patients on drugs affecting ANS were excluded and they had other comorbidities like hypertension (pulmonary) and ischemic heart disease. Patients had normal BMI (24.8 ± 4.2 kg/km^2)	Oxygen supplementation: 3 sessions of LTOT was prescribed to be taken for 16 h per 24-h period at home. The sessions were at least 2 weeks apart.	HRV	RMSSDNN↑ SDNN↑ TP=	An increase in HRV multifractal properties following LTOT were observed. However, the beneficial effects was mainly expressed during the morning hours
Ramos et al.[27]	16 COPD (12♂,4♀): 64 ± 11 years	COPD: COPD (GOLD I-III), mean FEV_1 was 60 ± 25% of predicted. The mean weight was 66 ± 14 kg and BMI 24 ± 4 kg/m^2. No medication was taken 12 h prior to trials, non-ANS-associated diseases or comorbidities. They were asked to abstain from stimulating substances such as coffee and alcohol.	Controlled breathing Initial spontaneous breathing for 10 min (rest), then PLB for 8 continuous minutes and rest for another 10 min breathing spontaneously (recovery).	HRV	RMSSD↑ LF(nu)= HF(nu)= LF/HF ratio= LF/HF ratio is one outcome	Analysis of only the RMSSD index showed that PLB promoted increased parasympathetic activity.

(continued)

Table 1. (continued)

Reference	Sample	Inclusion criteria	Intervention	Outcome	Results	Conclusion
Raupach et al.[10]	15 COPD (11♂, 4♀) 60.9 ± 1.4 years 15 CON (11♂, 4♀) 60.7 ± 1.4 years	COPD: $FEV_1 \leq 60\%$ predicted (GOLD), and the mean BMI was 27 ± 1.1 kg/m^2. All were between 30 and 80 years. No diuretic medication was taken. The patients were also normoxic, had stable sinus rhythm, and nonsmoking. All those with comorbidities and those on sympathomimetic drugs were excluded.	Controlled breathing 15 breaths per minute for 4 min, followed by another 4 min respiration at 6 breaths per minute (3 s inspiration, 7 s expiration). Breathing at a rate of 6 breaths per minute was done using visual feedback.	MSNA/ BRS	BRS↑ MSNA↓	Slow breathing significantly enhanced BRS and MSNA in patients with COPD
Raupach et al.[15]	15 COPD (11♂, 4♀) 60.9 ± 1.4 years 15 CON (11♂, 4♀) 60.7 ± 1.4 years	COPD: $FEV_1 \leq 60\%$ predicted (GOLD), and the mean BMI was 27 ± 1.1 kg/m^2. All were between 30 and 80 years No diuretic medication was taken. The patients were also normoxic, had stable sinus rhythm and nonsmoking. All those with comorbidities and those on sympathomimetic drugs were excluded.	Controlled breathing IRL was performed while patients were breathing through a spirometer. Work of breathing was increased (tension-time index) by roughly 110% (from 0 to 10 hPa/L/s).	MSNA	MSNA=	Short term doubling the work of breathing does not affect sympathetic activation in COPD patients.
Reis et al.[26]	10♂ COPD 69 ± 9 years 9♂ CON 64 ± 5 years	COPD: $FEV_1 \leq 60\%$ predicted (GOLD II), FEV/FVC < 0.7 and the mean BMI was 23 ± 3.3 kg/m^2. The patients were stable clinically and were taking their normal medication (nonsmokers). CON: healthy and none of them had cardiac or metabolic diseases. COPD and CON matched by several parameters.	Controlled breathing Patients underwent 2min of spontaneous breathing at rest, then 4 min of R-SAM, which is a series of deep/slow inspirations and expirations to provide a pulmonary volume that varied from the TLC to RV. Each respiratory cycle was performed for 10-s (5 each for inspiration and expiration) corresponding to a breathing rate of 6 cycles/ min.	HRV	RMSSD= SDNN= LF= HF= LF(nu)= HF(nu)= LF/HF ratio=	COPD patients demonstrated impaired cardiac autonomic, which remained unchanged both at rest and during RSA-M when compared with healthy subjects who had improved HRV values.
Reis et al.[22]	10♂ COPD 69 ± 9 years 8♂ CHF 62 ± 8 years 10♂ CON 64 ± 5 years	COPD: $FEV_1 < 60\%$ (GOLD II), FVC < 0.7 predicted and the mean BMI was 23 ± 3.3 kg/m^2. Patients were clinically stable, nonalcoholics, sedentary, and they took their normal medication (bronchodilators). They were also nonsmokers, free from cardiac and metabolic diseases, and also avoided B2-agonists, xanthene derivatives, and steroids for 24 h before the experimental test.	NIMV I. Spontaneous breathing II: Randomly treated with three different levels of CPAP on the same day: sham ventilation, 5 cmH_2O (CPAP5) and 10 cmH_2O (CPAP10) for 10 min (randomized double-blind/ cross-sectional)	HRV	RMSSD↓ SDNN= LF= HF= LF(nu)↑ HF(nu)↓ LF/HF ratio= TP=	The results indicated that acute treatment NIMV led to altered HRV parameters and also significant negative effects occurred during CPAP10 patients with stable COPD.

(continued)

Table 1. (continued)

Reference	Sample	Inclusion criteria	Intervention	Outcome	Results	Conclusion
Rossi et al.[38]	17♂ COPD: 67.29 ± 6.87 years 15♂ CON 63.2 ± 7.96 years	COPD: GOLD II-IV and their mean BMI was 25.54 ± 4.44 kg/m^2. All smokers, alcoholics, and those with <2 months exacerbation, metabolic/cardiac disease cannot perform procedure were excluded. Those with other chronic comorbidities and those on ANS influencing medications were also excluded.	Controlled breathing Comprised of three 20-min phases—The first (rest) and third being spontaneous breathing, while the second phase is PLB. Protocol between 8 am and 12 pm in a room with temperature between 21°C and 23°C and relative humidity between 40% and 60%.	HRV	SD_1↑ SD_2↑ SD_1/SD_2= SDNN↑ RMSSD↑ LF↑ HF↑ LF/HF=	PLB led to improvements in both linear and nonlinear HRV parameters as well as in vagal activity in patients with COPD
Scalvini et al.[39]	11 COPD (8♂, 3♀) 65 ± 8 years 13♂ CON 51 ± 7 years	COPD: ATS criteria with chronic hypercapnia, FEV_1: 28 ± 9%, FVC: 42 ± 13% predicted, excluded patients with other comorbidities such as cancer and those who cannot perform the procedure.	Oxygen supplementation: Two groups of patients had an alternate application of both (a) control breathing while breathing room air in a tilted position and (b) control breathing with oxygen supplementation in a tilted position (intervention randomized in a AB-BA scheme)	HRV	SDRR= LF↑ HF=	Oxygen supplementation (therapy) only partially reversed ANS derangements in hypoxemic patients with COPD.
Sin et al.[23]	21 COPD (10♂, 11♀): 64.1 ± 9.7 years	COPD: all patients had clinical diagnosis of COPD, and ≥10 pack/yr smoking history. The FEV_1 of <70% was predicted. Patients were excluded if they had cardiac disease (coexisting), cognitive impairment, or a poor prognosis.	NIMV I: Training group (TG): 3 months of standard medical therapy plus nocturnal NIMV (4 cmH_2O of EPAP and 8 cmH_2O of IPAP). II: Control group (CG): 3 months of standard medical therapy plus sham NIMV (CPAP set at 4 cmH_2O).	HRV	24 h: TINN↑ SDNN↑ HRVI↑ *Nighttime*: HRVI↑ RMSSD= SDSD= SDNN index = SDNN index is one outcome SDANN↑	NIMV applied nocturnally over 3 months may improve HRV parameters in patients with COPD.
Skyba et al.[40]	23 COPD (18♂, 5♀) 68.2 ± 1.7 years	COPD: FEV_1: 45.5 ± 3.9% predicted; FVC: 66.1 ± 3.8% predicted (ATS/ERS) with acute exacerbation on β agonist and anticholinergics. Exclusion criteria were respiratory arrest, decreased level of consciousness, severe exacerbation of COPD requiring intubation	NIMV Acute NIMV using BIPAP technique for 60 min at a level of 4 cmH_2O of EPAP and 8 cmH_2O of IPAP in a spontaneous mode	HRV	LF↑ HF↑ VLF=	BIPAP may potentially cause sustained improvements in the autonomic control of heart rate. The LF also significantly increased only during post-BIPAP phase

(continued)

Table 1. (continued)

Reference	Sample	Inclusion criteria	Intervention	Outcome	Results	Conclusion
van Gestel et al.[28]	40 COPD (23♂, 37♀) 66.1 ± 6.4 years	COPD: all patients were clinically diagnosed (GOLD), FEV_1: 45.9 ± 17.4% predicted. Patients had no clinical signs or symptoms of acute exacerbations, hospital admissions preceding 6 weeks. And, they all had normal BMI. 20 patients randomly assigned to TG and CG	Controlled breathing I: TG; 4-week conventional PR + RFT, 30-min/sessions of controlled breathing using techniques of biofeedback with rapid shallow breathing, breath-to-breath irregularity in rate and depth and predominant thoracic breathing. II: CG; 4-week of conventional PR	HRV	NN mean= SDNN= RMSSD= LF/HF= LF= HF=	Adding RFT to conventional PR intervention did not have additional effect on cardiac autonomic function in patients with COPD.
Yazici et al.[5]	28 COPD 64 ± 10 years	COPD: the patients were clinically diagnosed using the ATS/ERS criteria. All patients had HRF. However, those with cardiovascular diseases, diabetes, hemodynamic instability, systemic disorders that can affect ANS were excluded. The HRF was defined by arterial blood gas criteria (partial pressure of CO_2: PaCO2 >45 mmHg (6kPa), and pH< 7.35).	NIMV BIPAP was administered at a level of 5 cmH_2O of EPAP and 15 cmH_2O of IPAP in a spontaneous/time mode as indicated for patients with HRF.	HRV	RMSSD= SDNN index = SDNN= SDANN= pNN50↑ HRVi↑ LF= HF↑ LF/HF=	The NIMV may improve HRV indices of parasympathetic modulation of heart rate in COPD cases with HRF and decrease arrhythmic potential.

CON: control; ↓: significantly lower; ↑: significantly higher; (=): no significant difference; ♂: male; ♀: female; vs: versus; GOLD: global initiative for obstructive lung disease; LF: lung function; $\%FEV_1$: percent forced expiratory volume in 1 s; FVC: forced vital capacity; BIPAP: bilevel positive airway pressure; BRS: baroreceptor sensitivity; CPAP; continuous positive air way pressure; HRV: heart rate variability; IPAP: inspiratory positive airway pressure; MSNA: muscle sympathetic nerve activity; EPAP: inspiratory positive airway pressure; TLC: total lung capacity; RV: residual volume; $SuppO_2$: supplemental oxygen; CA: compressed air; PBE: pranayama breathing exercise; HRF: hypercapnic respiratory failure; BMI: body mass index; RFT: respiratory feedback training; ATS: American Thoracic Society; ERS: European Respiratory Society; ANS: autonomic nervous system; R-SAM: respiratory sinusoidal arrhythmia maneuver; IRL: inspiratory resistive loading; PLB: pursed lip breathing; cmH_2O: centimeter of water (pressure); RRi: R-R waves interval; RMSSD: square root of the mean of the sum of the squares of differences between adjacent normal RRi within a given time minus one; pNN50: percentage of RRi that differs each other more than 50 ms; SDNN: standard deviations of all NN intervals; SDANN: standard deviation of the averages of NN intervals in all 5-min segments of the entire recording; TINN: triangular interpolation of RRi; NIMV: noninvasive mechanical ventilation; NNmean: average RRi; RMSSDNN: RMSSD between adjacent RRi; SDSD: standard deviations between adjacent NN intervals; SDRR: standard deviation of RRi for time domain analyses. For frequency domain analyses, these included TP (total power), HF (high-frequency power), VLF (very low-frequency power), LF (low-frequency power), and LF/HF (low frequency/high frequency ratio).

Table 2. Risk of bias and study quality.[a]

Reference	Design	1	2	3	4	5	6	7	8	9	10	Total	MQ 100%	LOE
Bartels et al.[35]	CC	+	+	+	+	−	−					4/6	66	B
Bartels et al.[36]	CC	+	+	+	+	−	+					5/6	83	B
Bernadi et al.[8]	CC	+	+	+	+	−	+					5/6	83	B
Borghi-Silva et al.[37]	CC	+	+	+	+	−	+					5/6	83	B
Haider et al.[20]	RCT	+	+	+	+	−	+	+	+	+		8/9	89	A2
Jaju et al.[6]	CC	+	+	−	+	−	+					5/6	83	B
Lewis et al.[19]	Cohort	+	+	+	+	−	−	+	+			6/8	75	B
Ramos et al.[27]	Cohort	+	+	+	+	−	−	−	+			5/8	63	B
Raupach et al.[10]	CC	+	+	+	+	−	+					5/6	83	B
Raupach et al.[15]	CC	+	+	+	+	−	+					5/6	83	B
Reis et al.[26]	CC	+	+	+	+	−	+					5/6	83	B
Reis et al.[22]	CC	+	+	+	+	−	−					4/6	66	B
Rossi et al.[38]	CC	+	+	+	+	−	+					5/6	83	B
Scalvini et al.[39]	CC	+	+	+	+	−	+					5/6	83	B
Sin et al.[23]	RCT	+	+	+	+	−	+	+	+	+		8/9	89	A2
Skyba et al.[40]	Cohort	+	−	+	+	−	−	+	+			6/8	75	B
van Gestel et al.[28]	RCT	+	+	+	−	−	+	+	+	+		7/9	77	A2
Yazici et al.[5]	Cohort	+	+	+	+	−	−	+	+			6/8	75	B

+: positive; −: negative or no adequate information; CC: case–control study; RCT: randomized control trial; LOE: level of evidence; MQ: methodological quality. [a]For cohort study: (1) Was the study population clearly defined? (2) Could selection bias be sufficiently excluded? (3) Was the exposure clearly defined and was the exposure-assessment method adequate? (4) Was the outcome clearly defined and outcome-assessment method adequate? (5) Was the outcome assessed blinded for the exposure status? (6) Was the follow-up period sufficiently long? (7) Could selective loss-to-follow-up be excluded? (8) Were the most important confounders or prognostic variables identified and adequately considered in the study design and analysis? For case–control study: (1): Was the study population clearly defined? (2) Was the control group clearly defined? (3) Well defined in/exclusion criteria? (4) Clearly defined and appropriate intervention? (5) Was the exposure (treatment) assessed blinded? (6) Identification of confounders in the design and analysis? For RCTs: (1) Was patient selection to group randomized? (2) Was randomization blinded (single or double blinded)? (3) Were patients blinded to treatment? (4) Were the health care professionals blinded to treatment? (5) Were the outcome assessors blinded to the treatment? (6) Were the groups comparable at baseline? (7) Could selective loss to follow-up be excluded? (8) Presence of intention to treat analysis, if all enrolled patients were analyzed in their randomized group? (9) Are the groups, with the exception of the intervention, treated the same?

633 articles remained. Of these, 613 articles were excluded for not fulfilling the eligibility criteria (during title and abstract screening). Six potential articles were also added following a search of the reference lists of the articles that fulfilled the eligibility criteria. Altogether, the full-text reports of 26 articles were retrieved and evaluated based on the inclusion and exclusion criteria. Eight articles were further excluded for failure to meet all the inclusion criteria. In the end, 18 studies comprising eleven case-controlled,[6,8,10,15,22,35–39,41] four cohort,[5,19,27,40] and three RCT[20,23,28] studies were included for evidence synthesis.

Study characteristics and outcome measures

A total of 322 (197 males) patients with COPD participated across the studies. However, two studies did not provide information on gender distribution.[5,35] The FEV_1 among the participants was generally <70% of predicted value (indicating a sign of obstructive lung disease). The participants across the reviewed studies varied from mild COPD (GOLD I–II),[8,20,22,41] to moderate-severe COPD (GOLD II–III),[27,36,37] to severe COPD (GOLD III–IV),[19,35] and a mixture of all stages (GOLD II–IV) in one study.[38] Generally, most study participants were clinically stable since those with chronic comorbidities and/or other active respiratory diseases were largely excluded.

The respiratory rehabilitation techniques reported in the studies included oxygen supplementation (six studies),[8,19,20,39,35,36] NIMV (five studies),[5,22,23,37,40] and controlled breathing techniques (eight studies) in form of slow breathing,[8,10] purse lip breathing,[27,38] resistive loading,[15] and breathing maneuvers.[6,28,41] Only three AF outcomes were reported in the included studies. Majority of the studies (14 of 18) reported on the HRV indices[5,6,19,20,22,23,27,28,35,37–40,41] followed by the BRS[8,20,35,36] in four studies and then the

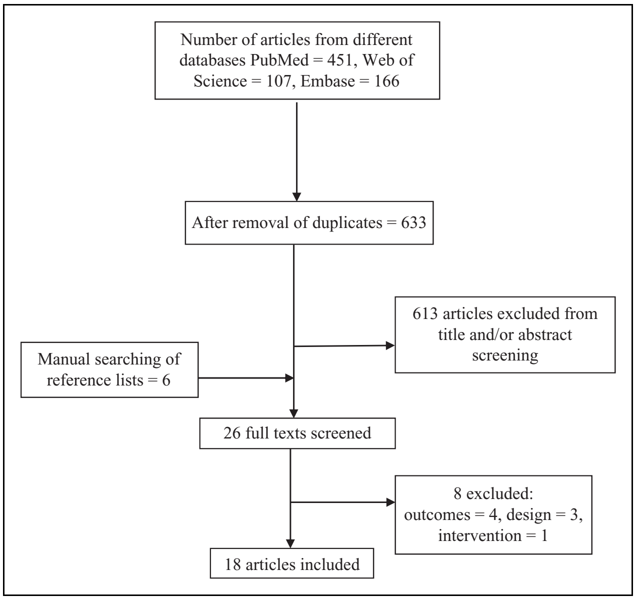

Figure 1. A flowchart of literature search used in the review.

MSNA in two studies.[10,15] Furthermore, the HRV parameters were represented in terms of time and frequency domain analyses. The time analyses of HRV reported in the included studies are R-R waves interval (RRi), square root of the mean of the sum of the squares of differences between adjacent normal RRi within a given time minus one (RMSSD), the percentage of RRi that differs each other more than 50 ms (pNN50), standard deviations of all NN intervals (SDNN), standard deviation of the averages of NN intervals in all 5-min segments of the entire recording (SDANN), triangular interpolation of RRi (TINN) average RRi (NNmean), RMSSD between adjacent RRi (RMSSDNN), standard deviation 1 (SD_1), standard deviation 2 (SD_2) from the Poincare plots, standard deviations between adjacent NN intervals (SDSD), and standard deviation of RRi for time domain analyses (SDRR). For frequency domain analyses, these included total power (TP), high-frequency power (HF), very low-frequency power (VLF), low-frequency power (LF), and low frequency/high frequency ratio (LF/HF). The frequency parameters were also expressed either in terms of absolute or normalized units (nu).

Methodological quality assessment

Initially, the assessors were in agreement regarding the evaluation of 116 of 125 question items. A consensus was only reached for the remaining nine question items after both assessors met to discuss initial points of disagreement. Table 2 shows the results of the methodological assessment. Generally, none of the studies fulfilled the criteria for blinding. However, the other question items (criteria) were mostly fulfilled. The overall methodological quality score in terms of percentages ranged from 63% to 83% across all the reviewed studies.

Synthesis of results

Controlled breathing techniques. Eight studies[6,8,10,15,27,28,38,41] reported on the effect of different controlled breathing techniques on three AF outcome parameters in the reviewed studies. The results from two of these studies that investigated the effect of pursed lip breathing (PLB) indicated that significant increases were recorded for some HRV indices including RMSSD,[27,38] SDNN,[38] SD_1,[38] SD_2,[38] LF,[38] and HF.[38] Simultaneously, no significant changes were reported for other HRV indices such as SD_1/SD_2 ratio,[38] Lfnu,[27] HFnu,[27] and LF/HF ratio.[27,38]

The results from the studies that utilized other fairly known controlled breathing maneuvers (pranayama breathing exercise, respiratory sinus arrhythmia maneuver, and resistance breathing) all reported that there were no significant changes for the HRV indices such as NNmean,[28] SDNN,[28,41] RMSSD,[28,41] LF,[6,28,41] HF,[6,28,41] LFnu,[6,41] HFnu,[6,41] and LF/HF.[6,28,41] Similarly, inspiratory resistive loading did not have any significant effect on the MSNA of patients with COPD.[15] On the other hand, however, slow breathing techniques (6 breaths per minute) were reported to positively influence both MSNA[10] and BRS[8,10] in patients with COPD in two studies.

Based on the results of these studies, the evidence to support the effects of controlled breathing techniques on the HRV and MSNA parameters of AF is inconsistent. A moderate-level evidence seems to support the effect of slow breathing on the BRS.

Noninvasive mechanical ventilation. Five studies[5,22,23,37,40] reported on the effect of NIMV application on the HRV indices in both time and frequency domain analyses in patients with COPD. Both significant and nonsignificant changes were reported in the results of the reviewed studies. Specifically, the results across the studies showed that just as no significant changes occurred for RMSSD,[5,23,37] SDNN,[5,22,23,37] SDNN index,[5,23] SDSD,[23] LF,[5,22] HF,[22,37] Lfnu,[22] Hfnu,[22] TP,[22] LF/HF,[5,22] and VLF[40] significant increases were seen for pNN50,[5] SDNN,[23] TINN,[23] SDANN,[23] HRVi,[5,23] RMSSD,[22] LF,[22,35,40] HF,[5,40] LFnu,[22,37] and LF/HF[37] indices. Furthermore, a significant decrease was also reported for HFnu.[22,37]

Based on the reviewed studies, the evidence to support the effect of NIMV application on the HRV indices is inconsistent.

Oxygen supplementation. Five studies[19,20,35,36,39] examined the effects of oxygen supplementation on the HRV and BRS parameters in patients with COPD. Of these, the results from four studies that reported on the effect of oxygen supplementation led to significant increase in the value of HRV indices such as Rri,[20] RMSSDNN,[19] SDNN,[19] and HF.[35] A significant decrease was also seen in for LF/HF in one study.[35] However, another results across three studies reported that HRV indices such as SDRR,[39] HF,[39] TP,[19] and LF[39] were not significantly influenced by oxygen supplementation.

Four studies assessing the effect of oxygen supplementation on the BRS of patients with COPD reported significant increases in the results of all four studies ($p < 0.05$).[8,20,35,36]

Based on the results of the reviewed studies, the evidence to support the effect of oxygen supplementation on HRV indices in patients with COPD is inconsistent. Second, a strong evidence was found to support the effect of oxygen supplementation on the BRS in these patients.

Discussion

This systematic review evaluated the existing evidence to support the effect of three respiratory rehabilitation techniques (controlled breathing, NIMV, and oxygen supplementation) on the AF indices in patients with COPD. The inclusion of different study designs provided an opportunity to include as much studies as possible with a view to answering our review objectives. Additionally, all the included studies had high methodological quality, despite the lack of blinding and follow-up in most of the studies.

The results of this review indicated that most of the evidence profile for the effect of respiratory rehabilitation techniques on the AF in patients with COPD was inconsistent, except for the evidence found to support the effect of controlled breathing and oxygen supplementation on the BRS values. This widespread inconsistency in the evidence validates the importance of our review. Hence, careful interpretation of AF parameters is warranted. Presently, it is known that lower values for BRS and time domain analyses of the HRV indices such as RMSSD, SDNN, and RRi are a sign of poor autonomic functioning. On the other hand, a high value for the MSNA variables signifies sympathetic activation, which causes an imbalance in the AF. Furthermore, the values for frequency domain parameters such as the LF, HF, and LF/HF ratio have variable interpretations, and they present robust information that can be utilized for monitoring patients prognosis. In a few occasions, however, differences may arise as a result of different laboratory assessment protocols or human error. However, the general output is reliable and indicative of the patients' autonomic status.

The positive effects of controlled breathing on the BRS have a potential for future application in clinical settings in addition to its current application for risk stratification. Moreover, the BRS is known for its protective role in regulating the blood pressure changes through its impact on the heart rate in individuals, as well as its role in monitoring the prognosis of patients with chronic diseases.[42] With these results, the mechanism by which BRS in particular responded to controlled breathing can be further brought to spotlight with a view to increasing its use for different purposes. Currently, it is known that these significant and consistent findings for the BRS values may have been as a result of increased oxygenation of the blood in the tissues independent of changing minute ventilation.[43] This implies that control breathing techniques may be of significant benefit for patients with COPD. Besides, reduced peripheral chemoreflex has been demonstrated in normal individuals who are instructed to slow down their ventilatory patterns.[44]

The HRV indices were mostly reported in the studies included in this review. However, the inconsistent evidence that were recorded for the HRV indices in both time and frequency domain analyses following respiratory rehabilitation techniques poses a challenge in postulating the actual effects of these techniques on the HRV, as well as their potential use for HRV modulation. Unfortunately, HRV indices provide a better and more robust information of the cardiovascular health, and it also acts as a powerful independent prognostic factor for risks stratification.[45] Nonetheless, there is a need for more studies focusing on separate control breathing techniques so as to re-enforce our findings. For instance, PLB showed a slight beneficial effect on a few important HRV indices.[27,38] However, the presence of other controlled breathing maneuvers such as pranayama, respiratory sinus arrhythmia maneuver, respiratory feedback training, and inspiratory resistance exercises,[6,15,28,41] all of which had no significant effect on the HRV in patients with COPD contributed to the inconsistent evidence.

Another result of this review revealed that an inconsistent evidence also supported the effect of NIMV application on the HRV.[5,22,37,40] This result is also corroborated by the findings of an earlier study that reported that NIMV has opposing influence on the HRV.[46] Three studies also reported significant increases in the values of LF HRV indices.[22,37,40] This is an indication of sympathetic activation, which is undesirable for patients with COPD. Second, a significant decrease in the HF indices, which is reflective of parasympathetic deactivation, was also recorded in two studies following NIMV application.[22,37] From this finding, it can be inferred that NIMV as a technique may have no potentially beneficial therapeutic effect on the AF of patients with COPD. However, this does not underestimate the role of NIMV in enhancing other clinical variables such as oxygen perfusion and breathing pattern that have been widely established for patients with COPD.[22,23,37]

One of the most important findings of our review was the strong evidence in support of oxygen supplementation on the BRS in patients with COPD. Oxygen supplementation showed a more potent and consistent effect on the BRS compared to other outcomes. This evidence clearly shows that oxygen supplementation has an unambiguous influence on the cardiovascular health of patients with COPD as represented by the BRS indices.[8,9,20,47] It is also known that oxygen supplementation could have enhanced the BRS through its action in reducing the levels of the pulmonary arterial tension and vasoconstriction, reduced right ventricular wall stress and also in improving the central venous oxygen saturation levels, all of which in turn causes a reduction in sympathetic tone.[35] Moreover, oxygen supplementation leads to an increase of the resting oxygen saturation and ventilation/perfusion (PO_2), which in turn causes a reduction in the sensation of dyspnea thereby activating the chemoreflex sensitivity.[42]

This review had a few limitations. First, the AF outcome parameters were mostly reported for the HRV indices. Fewer studies reported for BRS and MSNA, and there were no studies available for parameters like the HRR, chemoreflex sensitivity, and sympathetic skin responses, all of which are known to be significant markers of AF. Second, we observed the heterogeneity in some of the clinical characteristics of the study participants: stage of COPD disease, body mass index, degree of $\%FEV_1$ predicted values, age, and medication use across the included studies. Nevertheless, our findings remain relevant due to the multiplicity of studies and the need to shape the focus of future research in the topic area.

This review has showed that a variety of respiratory rehabilitation techniques may have a beneficial influence that can be clinically applied for the management of impairments of the sympathetic and parasympathetic systems, hence making important modifications in the cardiovascular health possible among patients with COPD. Finally, the findings from our systematic review will help to draw the attention of researchers in the field of rehabilitation of chronic respiratory disease to the impact of conservative treatment approaches on the extrapulmonary system.

Conclusion

It was concluded that oxygen supplementation and controlled breathing techniques had profound influence on the AF of patients with COPD, albeit mainly on the BRS indices. However, it is not yet clear whether this influence is of any therapeutic value in the long term. Hence, future studies may focus on specific long-term effects of these techniques on patients' important autonomic markers.

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