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Original Article

Effect of Exercise on Respiratory Drive in Chronic Obstructive Pulmonary Disease Patients: A Systematic Review and Meta-Analysis

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Abstract

Background and objectives: Chronic obstructive pulmonary disease (COPD) dyspnea intensity is strongly correlated with respiratory drive, when assessed in relation to EMGdi activity expressed as a percentage of maximum (EMGdi%max). There is growing evidence that respiratory drive can be improved by exercise. The present systematic review investigates the effects and clinical significance of exercise interventions on respiratory drive in COPD patients.

Methods: With the application of PRISMA guidelines, Pubmed, PEDro, Science direct, and the Cochrane Central Register of Controlled Trials were searched from inception until 25 January 2022.

Results: A total of 14 studies (n = 238) were identified, and 12 studies were included in the meta-analysis. The meta-analysis revealed that EMGdi%max was higher during intense exercise, when compared to at rest, with significant heterogeneity (I^2 = 89%). However, EMGdi%max significantly decreased after eight weeks of inspiratory muscle training (IMT). Three studies that examined the acute exercise effects revealed that breathlessness is highly correlated to EMGdi%max during aerobic exercise. During constant work rate exercise, EMGdi%max initially increased, and subsequently reached a plateau, while during incremental exercises, this gradually increased without reaching a plateau. This was associated with low ventilatory and neuromuscular efficiency.

Conclusions: Intense (≥75% of peak work rate) exercise induces a higher EMGdi%max, when compared to at rest, in COPD patients, and is highly correlated to dyspnea intensity during exercise. Eight weeks of IMT can reduce the dyspnea intensity and improve exercise tolerance. Measuring EMGdi%max during exercise is a useful clinical approach. This is associated with dyspnea severity, and reduced ventilatory and neuromuscular efficiency, and is sensitive to exercise interventions.

Keywords: COPD; Diaphragm; EMG; Exercise; Dyspnea.

Abbreviations: COPD, chronic obstructive pulmonary disease; EMGdi, diaphragm electromyogram; EMGdi%max, percentage of maximum diaphragm electromyogram; IMT, inspiratory muscle training; PEDro, physiotherapy evidence database; PRISMA, preferred reporting items for systematic reviews and meta-analyses; RCT, randomized control trial.

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Introduction

According to a systematic analysis for the Global Burden of Disease, chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death on the global scale.[1] The Global Initiative for Chronic

Obstructive Lung Disease guidelines categorize the comprehensive management of COPD into four main objectives: assessment and monitoring of the disease, reduction of risk factors, management of stable COPD, and prevention and management of exacerbations.[2] Management plans are not limited to pharmacological interventions, and should be supplemented by proper non-pharmacological treatments, in which exercise interventions are included.[3]

The respiratory control center, through complex physiological mechanisms, adjusts signal(s) that command the respiratory pump to produce specific alveolar ventilation. The command signal is called, "respiratory drive," and various outcomes have been used to measure this physiological parameter.[4] In particular, since the diaphragm is one of the most significant respiratory muscles, it has been considered that the quantification of its activation can reflect commanding signals to the respiratory pump. Thus, this can be a measure of the respiratory drive. Indeed, diaphragm activation can be accurately measured at rest with the diaphragm electromyogram (EMGdi) using a multipair esophageal electrode positioned at the diaphragm crus.[5–7] Through the utilization of this technique, it was found that the amplitude of EMGdi is greater in patients with COPD, when compared to healthy subjects, after this is normalized to each subject's volitional maximum, that is, when the EMGdi activity is expressed as a percentage of maximum (EMGdi%max).[8,9]

To the best of the authors' knowledge, no systematic review has been conducted to assess the effects of exercise on respiratory drive, as evaluated using EMGdi%max, in patients with COPD. The overall accumulation of present scientific evidence has a direct impact on clinical practice. This not only provides conclusive findings regarding the potentially beneficial physiological effect of exercise on respiratory drive, but also further supports the notion that COPD specialists should include exercise in the rehabilitation routine for the management of this disease. Therefore, the present systematic review and meta-analysis aimed to investigate the effects and clinical significance of exercise interventions on respiratory drive (EMGdi%max) in patients with COPD.

Materials and methods

This systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (Supplemental File 1),[10] and was registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY, Registration no.: INPLASY202070021).

Search strategy

The eligibility assessment of the titles, abstracts and full texts of the retrieved articles was performed in a 3-step process, based on the Bettany-Saltikov model.[11,12] The literature search was independently performed by two investigators (AD and AP). The Pubmed, PEDro, Science direct, and Cochrane Central Register of Controlled Trials databases were searched from inception up to 25 January 2022. Any inconsistencies in the search procedure were resolved by consensus. The search algorithms used for the selected databases are listed in the Supplementary File 2.

Selection process

The selection process was independently performed by two investigators (AD and PD), and any conflict was resolved by a referee investigator (AP).

Inclusion and exclusion criteria

Studies that met the following criteria were included: (1) human subject studies; (2) the participants were patients with COPD; (3) studies presented in the English language; (4) no limit was set for the time of publication; (5) both acute and chronic interventions were investigated; (6) randomized and non-randomized controlled trials; (7) studies that included exercise interventions, including aerobic and/or resistance exercise, and/or respiratory muscle training. Review articles, and grey literature and trials with pharmacological or surgical, or "mechanical ventilation" intervention were excluded.

Data extraction

Two authors (AD and CC) independently extracted the data, and entered the data in an appropriate table. The extracted data included the first author's name, year of publication, type of clinical trial, number of participants assessed at the end of the trial, and exercise interventions.

Study quality (risk of bias assessment)

The evaluation of study quality was independently performed by two investigators (AD and CC), and inconsistencies were resolved by consensus. The quality of the included studies was assessed using the PEDro methodological quality scale (Table 1).[9,13–26] This 11-item scale evaluates (internal and external) the validity and interpretability of studies, and identifies the potential bias with good reliability.[13,27] The score was calculated as the sum of scores for each item, except for the first item. Studies with scores of <4 were considered to be of low methodological quality, studies with scores within 4–6 were considered to be of moderate methodological quality, and studies with scores of ≥7 were considered to be of high methodological quality.[28]

Data analysis

A random-effect model inverse variance continuous meta-analysis was conducted using the RevMan 5.3[29] software, based on the calculated mean differences. The means and standard deviations (SDs) of EMGdi%max at rest, and during constant intense exercise (≥75% of peak work rate) or incremental exercise to subjective exhaustion were used. In the study conducted by Luo *et al*.,[14] EMGdi%max was calculated, as follows: EMGdi × 100 / EMGdimax. When the data was not available in the tables or text,[15,16] this was extracted from the figures using a web digitizer (automeris.io/Web Plot Digitizer), or the corresponding authors were conducted by E-mail to request for the data. The 95% confidence interval (CI) and heterogeneity between studies were calculated using the I^2 statistic. A significant result for heterogeneity was considered when $p<0.10$, and the interpretation of the I^2 index was made based on previous guidelines.[30] Publication bias was assessed using the asymmetry identification of the funnel plot.[30] Trial sequential analysis was performed using the TSA software 0.9.5.10 beta version to determine whether the available sample size for the meta-analysis is optimal to reach a statistical significance.[31]

Table 1. Classification of studies using the PEDro scale.

Study	1*	2	3	4	5	6	7	8	9	10	11	Total
Langer *et al*.[16] (2018)	–	1	1	1	1	0	1	1	1	1	1	9a
Frazão *et al*.[20] (2021)	–	1	0	0	0	0	0	1	1	1	1	5b
James *et al*.[19] (2021)	–	0	0	1	0	0	0	1	1	1	1	5b
Louvaris *et al*.[21] (2021)	–	0	0	1	0	0	0	0	1	1	1	4b
Luo *et al*.[22] (2020)	–	0	0	0	0	0	0	1	1	1	1	4b
Faisal *et al*.[9] (2016)	–	0	0	0	0	0	0	1	1	1	1	4b
Ciavaglia *et al*.[18] (2014)	–	1	0	1	0	0	0	0	0	1	1	4b
Sinderby *et al*.[26] (2001)	–	0	0	0	0	0	0	1	1	1	1	4b
Dacha *et al*.[15] (2019)	–	0	0	0	0	0	0	1	1	0	1	3c
Wu *et al*.[17] (2017)	–	0	0	1	0	0	0	0	0	1	1	3c
Jolley *et al*.[23] (2015)	–	0	0	1	0	0	0	0	0	1	1	3c
Luo *et al*.[14] (2011)	–	0	0	1	0	0	0	0	0	1	1	3c
Guenette *et al*.[24] (2014)	–	0	0	0	0	0	0	0	0	1	1	2c
Qin *et al*.[25] (2010)	–	0	0	0	0	0	0	0	0	1	1	2c

PEDro scale items: (1) eligibility criteria were specified (*this item was not used to calculate the PEDro score); (2) the subjects were randomly allocated to groups; (3) the allocation was concealed; (4) the groups were similar at baseline, in terms of the most important prognostic indicators; (5) there was blinding for all subjects; (6) there was blinding for all therapists who administered the therapy; (7) there was blinding for all assessors who measured at least one key outcome; (8) the measurement of at least one key outcome was obtained from more than 85% of subjects that were initially allocated to groups; (9) all subjects with available outcome measures received the treatment or control condition, as allocated, or when this was not the case, the data for at least one key outcome was analyzed by "intention to treat"; (10) the results for the between-group statistical comparisons were reported for at least one key outcome; (11) the study provides both the point measures and measures of variability for at least one key outcome. 1 = item satisfied, 0 = item not satisfied; a = high methodological quality, b = intermediate methodological quality, c = low methodological quality.

Sensitivity analysis

For the acute effect of exercise, the study conducted by Wu *et al*.[17] presented data on the effects of exercise using two different respiratory devices (a respiratory resistance device and a respiratory threshold load device) on EMGdi%max in 12 patients with COPD. Ciavaglia *et al*.[18] examined the effects of incremental cycle and treadmill exercise tests on EMGdi%max in 12 patients with COPD. Similarly, Luo *et al*.[14] investigated the effects of incremental and constant treadmill exercise on EMGdi%max in 16 patients with COPD. Furthermore, Langer *et al*.[16] presented the baseline data on EMGdi activity in two groups of patients, with 10 participants in each group, at rest and during cycling at a constant work rate. These studies had one control group and one intervention group, and the later underwent inspiratory muscle training (IMT). Each of the above four studies was split into two separate "sub-studies" for the subsequent meta-analysis. Specifically, for the first sub-study conducted by Wu *et al*.,[17] data on the effects of exercise with the respiratory resistance device was included, while for the second sub-study, data on the effects of exercise with the respiratory threshold load device was included. Similarly, for the first sub-study conducted by Ciavaglia *et al*.,[18] data on the effects of incremental cycle exercise was included, while for the second sub-study, data on the effects of incremental treadmill exercise was included. Furthermore, for the first sub-study conducted by Luo *et al*.,[14] data on the effects of incremental treadmill exercise was included, while for the second sub-study, data on the effects of constant treadmill exercise was included. Moreover, for the first sub-group study conducted by Langer *et al*.,[16] the baseline (i.e. before IMT intervention) data for the control group was included, while for the second sub-study, the corresponding data of the intervention group was included. In addition, James *et al*.[19] examined two groups of COPD patients during the symptom-limited incremental cycle exercise test: one group had a normal lower limit resting diffusing capacity for carbon monoxide (DLCO), and the other group had less than the lower limit of normal (DLCO-LLN).

Results

Search results

The search retrieved a total of 196 articles. After removing duplicate records, 169 articles remained, while 148 articles were subsequently excluded based on the titles and abstracts. After screening the full texts, 14 articles satisfied the eligibility criteria, and were included in the systematic review. Furthermore, among these 14 articles, 12 articles were included in the quantitative analysis (meta-analysis). The search process is presented in the PRISMA flow diagram (Fig. 1).

Characteristics of the included studies

The characteristics of studies included in the present review are presented in Table 2.[9,14–26] The overall sample size was 238 participants, while the sample size of each study ranged within 7–32 subjects. For the 14 eligible selected studies, one study (approximately 7%) was a randomized control trial (RCT), 12 studies (86%) were cross-sectional studies, and one study (approximately 7%) was a case-control study. All studies included COPD patients, except for one study[22] that reported the EMGdi data in µV and presented data on the effects of exercise interven-

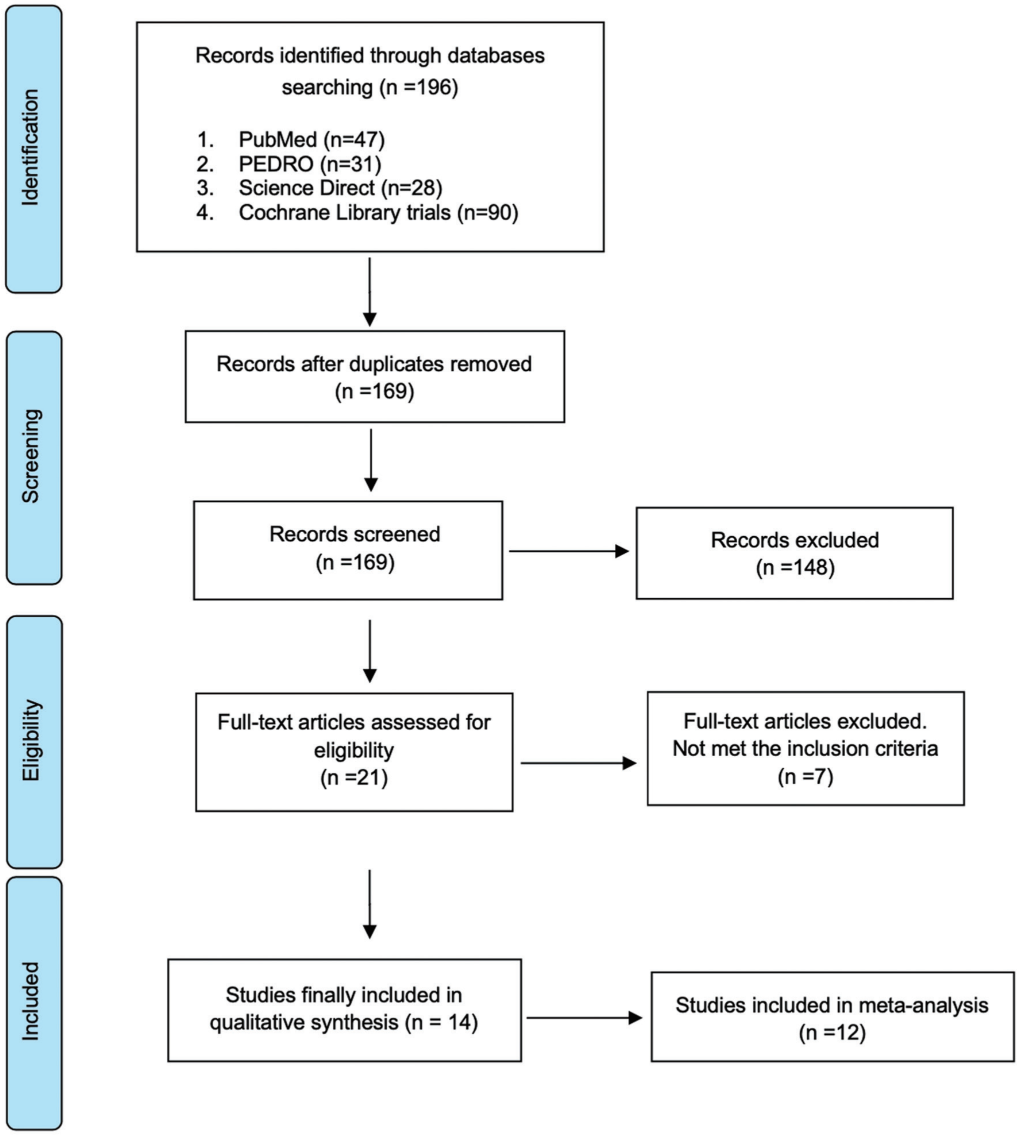

Fig. 1. The PRISMA flow diagram showing the search results.

tions on EMGdi%max, which was used as an index of respiratory drive.[9,14–21,23–26] Furthermore, two of the included studies presented data on both acute and chronic (training) effects,[15,16] while the remaining 12 studies examined the acute effects of exercise on EMGdi%max.[9,14,18–26] Specifically, one of the 12 studies investigated the acute effects of respiratory training,[17] while the other studies investigated the acute effects of cycle or treadmill exercise.

Risk of bias of the included studies

The risk of bias of the included studies is presented in Table 1. According to the PEDro methodological quality scale,[13] among the 14 studies, six[14,15,17,23–25] studies were considered to be of low methodological quality, seven studies[9,18–22,26] were considered to be of intermediate methodological quality, and one[16] study was considered to be of high methodological quality.

Quantitative data synthesis

For the effects of acute exercise, 12 articles were included in the quantitative analysis.[9,14–21,24–26] However, since five of these studies[14,16–19] were split into two separate "sub-studies" each (refer to the Sensitivity analysis section), a total of 17 studies were used for the subsequent meta-analysis (Fig. 2). Significant heterogeneity was found (I^2 = 89%), and the meta-analysis results revealed a significant difference between EMGdi%max during intense exercise and EMGdi%max at rest, in patients with COPD (p<0.00001, Fig. 2).

Qualitative data synthesis

Chronic effects

Merely two studies examined the training effects of exercise on the

Table 2. Characteristics of the included studies

Study	Type of clinical trial	Number of assessed subjects	Exercise interventions	Main outcomes
Faisal *et al.*[9] (2016)	Cross-sectional study	16	Incremental cycle test to subjective exhaustion	EMGdi%max gradually increased without a plateau during incremental exercise
Frazão *et al.*[20] (2021)	Cross-sectional study	12	Incremental cycle test up to the tolerance limit	Healthy subjects presented higher respiratory neuromuscular efficiency during exercise, when compared to COPD
James *et al.*[19] (2021)	Cross-sectional study	28	Symptom-limited incremental cycle ergometer test	EMGdi%max was higher during exercise in COPD patients with low resting diffusing capacity for carbon monoxide (DLCO), when compared to COPD patients with normal DLCO
Louvaris *et al.*[21] (2021)	Cross-sectional study	11	Cycle at 80% WRpeak to symptom limitation	EMGdi%max was similar between exercise and hyperpnoea, with similar ventilatory responses to exercise, but the dyspnoea was higher during exercise due to the impairment of extra diaphragmatic respiratory muscle perfusion
Luo *et al.*[22] (2020)	Cross-sectional study	26	Incremental cycle test to symptom limitation	EMGdi in inspiratory capacity maneuver gradually increased from rest to the end of exercise
Dacha *et al.*[15] (2019)	Cross-sectional/ Longitudinal study	7	Cycle at 75% WRpeak to symptom limitation; Eight weeks of inspiratory muscle training in four patients	EMGdi%max initially increased and reached a plateau during constant work rate exercise; EMGdi%max decreased after inspiratory muscle training in four patients
Langer *et al.*[16] (2018)	Randomized control trial	20	Cycling at constant work rate (75% WRpeak) to symptom limitation; Eight weeks of controlled inspiratory muscle training	EMGdi%max significantly decreased before vs. after inspiratory muscle training
Wu *et al.*[17] (2017)	Cross-sectional study	12	Exercise using respiratory resistance device and respiratory threshold load device	EMGdi%max measured using the respiratory resistance device was significantly lower than the EMGdi%max measured using the respiratory threshold load device in all exercise intensity levels.
Jolley *et al.*[23] (2015)	Cross-sectional study	12	Incremental cycle and treadmill exercise	Dyspnea intensity during exercise correlated best with EMGdi%max
Guenette *et al.*[24] (2014)	Cross-sectional study	32	A symptom limited cycle test	Dyspnea intensity during exercise correlated best with EMGdi%max
Ciavaglia *et al.*[18] (2014)	Cross-sectional study	12	Incremental cycle and treadmill exercise tests	Dyspnea intensity during exercise correlated best with EMGdi%max
Luo *et al.*[14] (2011)	Cross-sectional study	16	Incremental and constant (80% of maximal oxygen consumption) treadmill exercise.	EMGdi%max initially increased and reached a plateau during constant work rate exercise, while EMGdi%max gradually increased without a plateau during incremental exercise
Qin *et al.*[25] (2010)	Case-control study	24	Constant work treadmill exercise at 80% of maximal oxygen consumption	EMGdi%max initially increased and reached a plateau during constant work rate exercise
Sinderby *et al.*[26] (2001)	Cross-sectional study	10	Incremental cycle test to subjective exhaustion	EMGdi%max gradually increased without a plateau during incremental exercise

EMGdi%max: The amplitude of diaphragm electromyogram (EMGdi) in volitional maximum, that is, the EMGdi activity expressed as a percentage of maximum; WRpeak: Peak work rate.

main outcome of the systematic review, which was EMGdi%max. Langer *et al.*[16] investigated the effects of eight weeks of IMT on EMGdi%max during constant work rate cycle exercise in COPD patients with activity-related dyspnea. The subjects were randomized into the IMT or sham training (control) group, and it was revealed that EMGdi%max significantly decreased after IMT, when compared to control conditions, and when compared to pre-IMT levels in the exercise training group. Similarly, Dacha *et al.*[15] employed a semi-automated method to analyze the EMGdi data, and reported a reduction in EMGdi%max after eight weeks of IMT

Study or Subgroup	Rest Mean	Rest SD	Rest Total	Intense exercise Mean	Intense exercise SD	Intense exercise Total	Weight	Std. Mean Difference IV, Random, 95% CI
Dacha 2019	17	3	7	77	6	7	2.5%	−11.84 [−17.12, −6.56]
Sinderby 2001	24	6	10	81	7	10	4.4%	−8.37 [−11.40, −5.35]
Faisal 2016	18.2	4.4	16	67.1	8.8	16	5.7%	−6.85 [−8.77, −4.93]
Qin 2010	18.9	9.8	12	75.8	8.4	12	5.5%	−6.02 [−8.05, −3.99]
Luo_Constant 2011	17	6	16	73.6	15.6	16	6.2%	−4.67 [−6.07, −3.26]
Ciavaglia_Treadmill 2014	19	9	12	72	13	12	6.0%	−4.58 [−6.20, −2.95]
Langer 2018 (control)	18	12	10	72	11	10	5.8%	−4.49 [−6.28, −2.71]
Louvaris 2021	26.4	9.8	11	72.9	11.5	11	6.0%	−4.19 [−5.79, −2.59]
Luo_Incremental 2011	17	6	16	70.4	16.8	16	6.4%	−4.13 [−5.41, −2.84]
Langer 2018 (intervention)	21	6	10	91	23	10	6.0%	−3.99 [−5.62, −2.35]
Ciavaglia_Cycle 2014	18	10	12	64	14	12	6.3%	−3.65 [−5.04, −2.27]
Guenette 2014	12.8	3.4	16	59.5	17.5	16	6.5%	−3.61 [−4.78, −2.44]
James_DLCO 2021	13.3	7.9	13	49.5	11.5	13	6.3%	−3.55 [−4.85, −2.25]
James_DLCO-LLN 2021	13	1.05	15	61.7	21.7	15	6.5%	−3.08 [−4.19, −1.98]
Wu_Threshold 2017	22.12	18.32	12	69.98	16.78	12	6.5%	−2.63 [−3.77, −1.49]
Frazao 2021	15.67	5.6	12	27.17	12.4	12	6.7%	−1.15 [−2.03, −0.28]
Wu_Resistive 2017	22.12	18.32	12	17.26	14.65	12	6.7%	0.28 [−0.52, 1.09]
Total (95% CI)			**212**			**212**	**100.0%**	**−4.08 [−5.12, −3.04]**

Heterogeneity: $Tau^2 = 3.98$; $Chi^2 = 148.92$, df = 16 ($P < 0.00001$); $I^2 = 89\%$
Test for overall effect: Z = 7.71 ($P < 0.00001$)

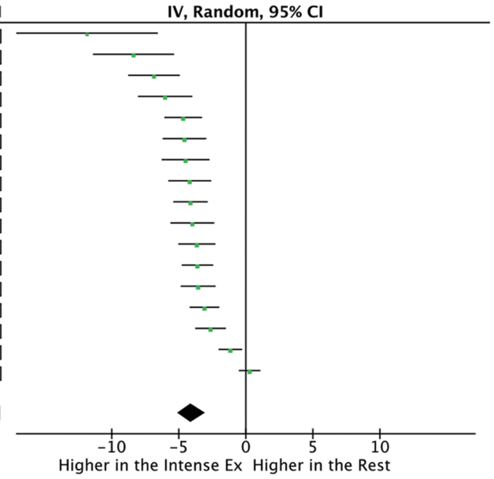

Fig. 2. The meta-analysis for the effect of acute exercise interventions on EMGdi%max.

in four COPD patients. Interestingly, in both studies, the reduction was accompanied by the improvement in exercise tolerance after the IMT program.

Acute effects of respiratory exercise training

Wu *et al*.[17] compared two different respiratory devices: a respiratory resistance device (PFLEX; Respironics Inc., Pittsburgh, PA, USA), which provides a constant and predetermined inspiratory load preserved during inspiration, and a respiratory threshold load device (Threshold Inspiration Muscle Trainer; Respironics Inc., Pittsburgh, PA, USA), which does not provide a constant inspiratory load to maintain the attainment of inspiratory exercise intensity.[32] The present study reported that the EMGdi%max measured using the respiratory resistance device was significantly lower, when compared to the EMGdi%max measured using the respiratory threshold load device, in all exercise intensities (low, moderate and high).

Acute effects of the cycle or treadmill exercise

Thirteen studies[9,14–16,18–26] investigated the effects of the cycle or treadmill exercise on EMGdi%max in patients with COPD. It was revealed that EMGdi%max initially increased, and reached a plateau during constant work rate exercise,[14,15,25] while EMGdi%max gradually increased without reaching a plateau during incremental exercise.[14,23,26] A similar gradual increase in EMGdi data, which was expressed in μV, was recently reported by Luo *et al*.[22] during the cycling incremental exercise to volitional fatigue. Furthermore, Ciavaglia *et al*.[18] reported that EMGdi%max at the peak of the cycle exercise was significantly lower, when compared to EMGdi%max at the peak of the treadmill exercise. Nevertheless, for the given ventilation (VE) during exercise, both exercise modalities had a similar EMGdi%max. In addition, Guenette *et al*.[24] reported that at rest, EMGdi%max was significantly lower in the control group, when compared to the COPD group. Similarly, at the highest equivalent work rate (60 W), EMGdi%max was significantly lower in the control group, when compared to the COPD group. It is noteworthy that the dyspnea intensity during exercise was found to correlate best with EMGdi%max.[9,18,23,24] Specifically, Faisal *et al*.[9] examined the effects of incremental cycle exercise on EMGdi%max in patients with COPD and healthy controls, revealing that EMGdi%max was higher in patients with the most severe airflow obstruction and hyperinflation, and that this was attributed to the neuromechanical uncoupling in patients with COPD.

Discussion

The present study conducted a systematic review with meta-analysis to investigate the effects of various exercise interventions on the important functional and clinical outcome in patients with COPD, the neural respiratory drive, which was assessed using EMGdi%max. The analysis revealed that exercise increased the EMGdi%max, when compared to that at rest, in patients with COPD. Furthermore, the increase in EMGdi%max was highly correlated with the intensity of dyspnea during exercise. Specifically, the meta-analysis for the included studies in the quantitative analysis revealed that EMGdi%max was higher during intense exercise, when compared to that at rest ($I^2 = 89\%$, Fig. 2), while breathlessness during exercise correlated best with EMGdi%max in patients with COPD.[18,23,24] These findings may indicate the value of EMGdi%max as an indirect measure of the key component of respiratory function, which can be utilized as a complementary index of exercise intolerance in COPD patients with different severities. Since the monitoring of EMGdi%max gives a breath-by-breath measure of the load on the respiratory system,[33] this can be a useful tool in research, and this may also be used in clinical practice to provide continuous measurements during exercise,[14,25,26] given that the use of esophageal catheters needed for this technique has been reported to be acceptable in 95% of patients, and are usually well-tolerated.[33]

Twelve studies were included in the qualitative analysis of the present systematic review.[9,14–21,24–26] Among these, two studies presented data on the chronic effects of exercise intervention on EMGdi%max.[15,16] Specifically, these studies revealed that EMGdi%max significantly decreased after IMT, when compared to both the control group and pre-IMT levels,[16] or when compared to the pre-IMT values in the small sample of four patients.[15] Furthermore, despite the reduction in EMGdi%max, the patents presented with improved exercise tolerance, and were able to exercise longer at a constant load equivalent to 75–80% of the peak work rate. The positive training effect of exercise on the respiratory drive is in accordance with the exercise training-induced changes reported by similar research approaches in patients with chronic heart failure.[34] Therefore, EMGdi%max may be used as a measure to assess the respiratory adaptations of COPD patients to exercise, both at rest and during exercise.

On the other hand, 13 studies[9,14–16,18–26] investigated the acute effects of cycle or treadmill exercise on EMGdi%max in patients with COPD. Specifically, it was revealed that EMGdi%max initially increased and reached a plateau during constant work rate exercise,[14,15,25] while EMGdi%max gradually increased without reaching a plateau during incremental exercise.[14,23,26] The different EMGdi%max responses induced during constant work rate vs. incremental exercise might suggest the use of EMGdi%max as an alternative monitoring index for the ventilatory response of COPD patients to steady-state vs. incremental exercise. Furthermore, it was observed that EMGdi%max was higher in COPD patients with the most severe airflow obstruction and hyperinflation,[9] suggesting that EMGdi%max can be an outcome for the evaluation of the severity of COPD.[33]

In addition, merely one study investigated the acute effects of respiratory exercise on respiratory drive,[17] and reported that the EMGdi%max measured when using the respiratory resistance device was significantly lower, when compared to the EMGdi%max measured when using the respiratory threshold load device, in all assessed exercise intensities.

Strengths, limitations and future directions

The present systematic review has limitations. The main limitation is the limited number of existing studies that examined the effects of exercise interventions on EMGdi%max in patients with COPD. Furthermore, six[14,15,17,23–25] of the 11 included studies were assessed to be of low methodological quality.[13] In addition, the studies analyzed in the present review had a relatively small sample size. Hence, the extrapolation of these findings should be undertaken with caution. Moreover, merely one[16] of the included studies was a RCT that investigated the chronic effects of exercise, and another study reported the training exercise effects in only four patients.[15] Thus, more RCTs are needed, and future studies should follow the CONSORT guidelines for reporting RCTs,[35] in order to improve key methodological features, such as the comprehensive reporting of participant adherence rates, since these are essential for appraising the efficacy of exercise interventions in this clinical population. Another limitation of the present systematic review was that this merely utilized published literature, since the grey literature was excluded. In light of this fact, there was potential publication bias in the present review, and the inclusion of the grey literature could itself introduce bias.[30] Furthermore, the investigators were unable to compare the present results with other similar systematic reviews or meta-analyses, since, to the best of our knowledge, this is the first systematic review and meta-analysis that evaluated the effects of exercise on neural respiratory drive (EMGdi%max).

Nevertheless, the present review has some strengths. First, the appropriate algorithm with standardized indexing terms was used for the PubMed database.[30] Second, a systematic method was applied to identify articles,[10] and a well-established tool[13] was used to evaluate the included studies. Overall, more research is warranted on both the acute and chronic effects of exercise interventions on EMGdi%max in patients with COPD. In particular, future high-quality RCTs are necessary to determine the type of exercise and its specific characteristics for optimum effectiveness in EMGdi%max adaptations. This would reduce the dyspnea symptoms, both at rest and during physical activity, and improve the quality of life of patients with COPD. Furthermore, the trial sequential analysis in the present meta-analysis indicated the optimal sample size of the meta-analysis to reach statistical significance (Supplementary File 2, Fig. 2). Finally, publication bias was not detected in the meta-analysis.

Conclusions

The respiratory drive, expressed in EMGi%max, was higher during intense exercise, when compared to at rest, in patients with COPD. This was significantly correlated with the dyspnea intensity during exercise. Furthermore, the eight-week IMT reduced the EMGdi%max and improved the exercise tolerance of patients with activity-related dyspnea. Moreover, different EMGdi%max responses were induced during constant work rate exercise, when compared to incremental exercise, in patients with COPD. However, more studies, especially RCT studies, with better methodological quality should be performed to further investigate the EMGdi activity in response to exercise in COPD patients. The EMGdi%max measured during exercise in this population is a useful clinical tool for health professionals, because this is associated with dyspnea severity, and is sensitive to exercise interventions. Hence, the practical importance of EMGdi%max can be its utilization as a complementary index of exercise intolerance in COPD patients with different severities. This can provide continuous measurements during exercise and be applied as a useful tool in both clinical practice and research.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/ERHM.2021.00077.

Supplemental File 1. PRISMA checklist.

Supplemental File 2. Search algorithms.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Author contributions

Conceptualization (AD, AP and SN); Analysis and interpretation of data (AD, PD and CC); Manuscript writing (AD, PD and CC); Critical revision (AP, SN and CC); Statistical analysis (PD, AD and CC); Technical support (PD). All authors have made a significant contribution to the study and have approved the final manuscript.

Data sharing statement

The search strategy (algorithms) used in the three databases, the Funnel Plot figure of the meta-analysis, and the trial sequential analysis graph used to support the findings of the study are included in the supplementary information file.

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