Literature Review

Optimal Intensity of Aerobic Exercise Training for Patient With Chronic Obstructive Pulmonary Disease (COPD): Systematic Review and Meta-Analysis

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Abstract

Background: Intensity for aerobic exercise is unclear in patient with COPD. Previous systematic review comparing effects of different levels of training intensity was done in 2011 and did not reach any conclusion. We conducted this systematic review to see the differences in aerobic training intensity on various aspects of health in COPD patients with updated information.

Method: We included RCTs, comparing the differences in intensity of aerobic training between groups. The primary search was done through Pubmed, Scopus, Science Direct, Proquest, and PEdro. The PEdro scale and Risk of Bias 2 tool was used to rate the studies. Lastly, we also rate the certainty of evidence using GRADE approach. The assessment was carried out by two reviewers independently. Data were extracted by one reviewer then evaluated by second reviewer.

Results: We found and analysed data from four studies with total of 472 patients. The primary outcomes extracted were Disease-specific Health-Related Quality of Life (HRQoL), Activities of Daily Living (ADL), Functional exercise capacity, Dyspnea symptoms. There was a significant difference only in St George's Respiratory Questionnaire (SGRQ) symptoms domain for HRQoL outcome (MD=5.53; 95% CI=1.08-9.97), favoured lower intensity group. No other significant results were found for any other outcomes/ outcome measures. According to GRADE, quality of the studies was very low to moderate.

Conclusion: The evidence we collected is very limited and difficult to evaluate. Further research comparing higher intensity with lower intensity of aerobic training is needed.

Keywords: chronic obstructive pulmonary disease; rehabilitation; exercise intensity; aerobic exercise

INTRODUCTION

Pulmonary rehabilitation (PR) is a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies designed to improve the physical and psychological condition of people with chronic respiratory disease and promote long-term adherence to health-enhancing behaviours.[1]

Exercise, which is the cornerstone of PR, is the best way to improve muscle function in chronic obstructive pulmonary

disease (COPD).[1] Certain levels of exercise result in less lactic acid release, leading to lowered ventilation and reduced dynamic hyperinflation[2]. In addition, exercise also has positive effects such as increased motivation during exercise, reduced mood disorders, reduced severity of symptoms, improved cardiovascular function, and quality of life.[1,3] Unfortunately, the exercise program features in PR for COPD patients have not been studied much.[4] In addition, many components of PR require further research, including ideal duration and location, level of supervision, frequency and intensity of training required, and how long the effects of treatment last.[5]

Currently, there is no consensus on the optimal intensity for aerobic training in people with COPD. Some guidelines suggest high intensity >60% peak work rate[1,6] and 60-80% peak work rate.[4] However, a previous systematic review has not reached any conclusions,[7] and to our knowledge, there have not been any updates ever since.

Therefore, we conducted this systematic review to analyze the differences of aerobic training intensity on various aspects of health in COPD patients with the updated information available. This review will focus on exercise-based intervention so we will not exclude studies that did not include education and psychosocial support component.

METHOD

The analysis and inclusion criteria were predetermined and documented in PROSPERO (ID: CRD42021247904).

The established inclusion and exclusion criteria are population of patients diagnosed with COPD defined by post-bronchodilator spirometry ratio of Forced expiratory volume in first second to forced vital capacity (FEV_1/FVC) <0.70 and %FEV_1 <0.80 who undergoes aerobic training.

The studies included are studies with the intervention of 12 sessions or more, which compared differences in intensity (with same mode (cycling/walking), same frequency, continuous, with same/different volume) consistent with previous review.[7] However, a flexible approach was used to prescribe intensity with expectation to gather more evidence comparing the differences of %peak working rate (%Wmax), %maximal oxygen uptake (%VO_2max), VO_2Reserve (%VO_2R), %Heart Rate Reserve (%HRR), %Maximum Heart Rate (%HRmax) between higher and lower intensities. The intensity used for incremental training type is its highest value. This study excluded studies that compares exercise training groups with no training groups and interval exercise.

The outcomes consists of primary outcomes (disease-specific health-related quality of life (HRQoL); Activities of Daily Living (ADL); functional exercise capacity; dyspnea symptoms) and secondary outcomes (peak exercise; isowork or isotime; endurance time of the exercise test with constant work rate; and muscle strength). This study uses primary outcome as inclusion criteria. Design of study that is the inclusion criterion is only randomised

controlled trials (RCTs) in English were included with no restrictions on the type of setting.

This systematic review was conducted under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[8] The search for articles was carried out through five electronic databases: Pubmed, Scopus, Science Direct, Proquest, and PEdro. Databases search the from beginning to February 2021. Also carried out additional searches on www.clinicaltrials.gov, the WHO ICTRP portal (www.who.int/ictrp/en/), and hands-on search of identified study reference lists and journals related to respiratory medicine. According to each electronic database, the search was compiled using boolean operations, which can be seen in the supplementary file.

One reviewer (CJI) screened each article based on inclusion criteria and determined its appropriateness to be included in the study, and evaluated by the second reviewer (AP). The selection process is reported in PRISMA flow diagram. Any disagreements were resolved by discussion between relevant reviewers, with a third reviewer (AP) consulted to arbitrate if necessary.

All data extraction was done by one reviewer (CJI). The second reviewer (AP) evaluated the extracted data, disagreements in extracted data collection were resolved by discussion. The third reviewer (YSS) was consulted to arbitrate where necessary. Data extraction included characteristics of the study (study design, inclusion criteria, number of samples, disease severity) and program components (Table 1).

Assessment of the quality of the studies was carried out by two reviewers (CJI and RA) independently. Any disagreements were resolved by discussion between relevant reviewers, and a third reviewer (AP) consulted to arbitrate where necessary. The PEdro scale was used to rate each study included.[9] The scale is a valid measure of the methodological quality of clinical trials.[10]

Risk of bias assessment was conducted using the 2nd version of the Cochrane tool to assess bias risk in randomised trials (RoB 2). This instrument provides a framework for evaluating the risk of bias of all types of RCT studies and an assessment specific for each trial outcome, that is, the relative effect of the two interventions.

We extracted the mean (the change score before and after the intervention) and the standard deviation of each measured outcome. We also confronted results obtained with the established MID. The unit equalisation from % VO_2max to Wmax performed using the formula % VO_2max=12.1+0.866 (%Wmax).[11]

The following are some of the MIDs that was used for the outcome of this study:

a. St George's Respiratory Questionnaire (SGRQ): -4 points of SGRQ total score.[12]
b. Chronic Respiratory Disease Questionnaire (CRQ): 0.5 points per item, so if we calculate per domain: dyspnea (5 items): 2.5 points, fatigue

(4 items): 2 points, emotional function (7 items): 3.5 points, mastery (4 items): 2 points.[13]

c. London Chest Activity of Daily Living scale (LCADL): 3 points.[14]
d. Six-Minute Walk Test (6MWT): Median 30 meters (25-33 meters).[15]
e. Modified Medical Research Council (mMRC) dyspnea scale: 1 unit.[16]
f. Mahler's Transition Dyspnea Index (TDI): 1 unit.[17]
g. Cycle endurance: 1.68 minutes (95% CI=1.43-1.93).[18]

The study was grouped per outcome measure. The meta-analysis used a forest plot, inverse variance statistical method, random-effect analysis model, and 95% Confidence Interval (CI) using Review Manager (Revman) 5.4.1 application[19].

To address missing data, we contacted the authors of the relevant studies. When the change score is not shown in the study, we calculated with these listed methods:

a. If the mean after intervention and baseline are available, Mean change score = $\text{Mean}_{\text{post}} - \text{Mean}_{\text{baseline}}$
b. If the mean score from the baseline and/or post-intervention is not available, We used data such as the median or the mean imputation from another similar study
c. If the standard deviation is not displayed, SD of mean change = $\sqrt{((\text{SD}^2\text{post} + \text{SD}^2\text{baseline})/2)}$,[20] or transform the data using CI and Standard Error, or impute the data from other studies.[21]

We examined statistical heterogeneity using the chi-squared test (Cochran's Q) dan I^2 test with P=0.10. I^2 test describes the percentage of variability in effect estimates due to heterogeneity rather than chance alone. Following are the I^2 test cutoffs that were used in this review:[22]

a. 0% to 40%: might not be important;
b. 30% to 60%: may represent moderate heterogeneity;
c. 50% to 90%: may represent substantial heterogeneity;
d. 75% to 100%: considerable heterogeneity.

As all meta-analyses included fewer than ten studies, we did not create the funnel plot because it can be very problematic when the number of studies is small, in which case they can appear spuriously wide or spuriously narrow.[22]

The quality of evidence was assessed using the GRADEpro Guideline Development Tool software.[23] We created a "Summary of findings" table using the seven most important outcomes. Finally, we justified all decisions to derive the quality of the evidence using footnotes and comments if needed.

Sensitivity analysis is performed on the important outcomes listed in the Summary of Findings table, which can be seen in the supplementary file. In this review this analysis performed if these one of these conditions are met:

a. High risk of bias
b. The intensity in the intervention/control group is only an estimate

c. Substantial methodological heterogeneity

Subgroup analysis can be performed to investigate mixed results or answer specific questions about a particular patient group, type of intervention, or type of study.[22] In this review, the analysis was carried out as the difference in work volume per session. The work volume of the session is an essential determinant of training response and is often calculated as the intensity multiplied by the duration of the exercise.

RESULTS

From the search results of five primary databases, we found 6039 articles, 414 articles from Pubmed, 2509 articles from Proquest, 2407 articles from Scopus, 963 articles from ScienceDirect, 45 articles from the PEDro database, and five articles from hands-on search. After eliminating the duplicates, 5091 remaining articles went through title and abstract screening. We excluded 5042 articles that were not an RCT study/irrelevant to the topic discussed. Of the remaining 36 articles, a full-text screening was carried out, where 32 articles were excluded for several reasons, which can be seen in a schematic diagram illustrating this process (Figure 1).

There were four studies with 472 patients whose data were synthesised, with 404 included in primary analyses suffering from moderate-severe COPD, 204 of whom received higher-intensity interventions, and 200 others received lower-intensity interventions[24–27]. Two studies compared the intensity of 80% Wmax with 60% Wmax[25,26], one study compared 80% Wmax with 50% Wmax[24], and one study compared >70% VO2max (>72.7% Wmax) with 50-70% VO2max (55.4%-72.7% Wmax)[27]. A complete description of each study can be seen in Table 1.

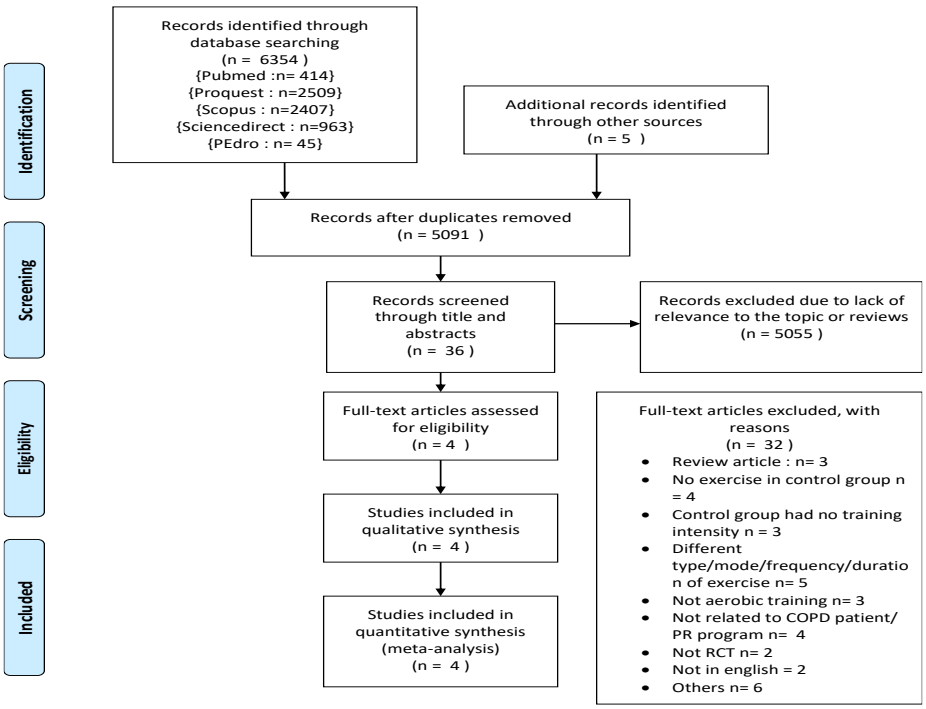

Figure 1. Flowchart of Literature Search and Study Selection

Table 1. Study Characteristics

Study	Participants	Setting, Frequency, Length	High Intensity(HI)	Low intensity(LI)	Outcomes	Withdrawals	Comments
Casaburi et al[24] (RCT)	Total: 34 patients(17 patients each group) with COPD (mean age 52 y; FEV_1 56% predicted)	Outpatient, five days/week for eight weeks	Continuous constant cycle ergometry at 60% difference between anaerobic threshold(AT) and VO_2 max work rate / 80% Wmax, 45 minutes/ session	Continuous constant cycle ergometry at 90% AT and VO_2 max work rate/ 50% peak work rate, 72 minutes/ sessions	Endurance, Lactate threshold	-	-
Maltais et al[25] (RCT)	Total: 252 patients (126 patients each group) with COPD (mean age 66y; FEV_1 45% predicted)	Higher intensity: outpatient Lower intensity: home Three days/week for eight weeks	Continuous constant cycle ergometry at 80% Wmax for 25-30 minutes	Continuous constant cycle ergometry at 60% Wmax for 40 minutes	CRQ, SGRQ, 6MWD, Endurance	36 patients 17 in HI group: 14 withdrew, two lost to follow up, one died 19 in LI group: 16 withdrew, two lost to follow up, one died	Additional strength training for 30 minutes per session
Santos et al[26] (RCT)	Total: 34 patients (17 patients each group) with COPD (mean age 67y; FEV_1 55% predicted)	Outpatient, 3 days/week for 8 weeks (atleast 20 sessions)	Continuous (94%)/interval (6%) threadmill (74%)/ cycle (24%) ergometry at 80% Wmax for 30 minutes per session	Continuous (94%)/interval (6%) threadmill (74%)/ cycle (24%) ergometry at 60% Wmax for 30 minutes per session	SGRQ, LCADL, TDI, 6MWD, Peak exercise capacity, Endurance	Six patients: loss to follow up (2 in HI group 4 in LI group)	Additional strength training for two days/weeks, flexibility training three days/weeks, and five educational skills training
He et al[27] (RCT)	Total: 217 patients (73 patients each for high and moderate intensity group), 71 patients for low intensity group) with COPD (mean age 65y; FEV_1 48% predicted)	Outpatient, 5days/week for 20 weeks	Continuous incremental cycling starting at 50% W peak progressively increased by 10W until >70% VO_2max reached for 20 minutes per session	Continuous incremental cycling starting at 50% W peak progressively increased by 10W until 50-70% VO_2max reached for 20 minutes per session (moderate-intensity group)	mMRC, 6MWD	14 patients(6 in HI group, 5 in moderate intensity group, 3 in low intensity group) HI: three poor cooperation Moderate: four poor cooperation, one death with AE	Three-arm study, the low intensity group used in the primary analysis in our review is the moderate intensity group in the trial, Low-intensity group: Continuous incremental

Study	Participants	Setting, Frequency, Length	High Intensity(HI)	Low intensity(LI)	Outcomes	Withdrawals	Comments
						Low intensity: five poor cooperation, one death with AE	cycling starting at 50% W peak progressively increased by 10W until <50% VO_2max reached for 20 minutes per session (low-intensity group) Additional ten minutes of warm-up before training and ten minutes of relaxation after training, ten education session in all the groups

The sensitivity test was carried out in the study by He et al due to the intensity level used is only an estimation.[27] We also removed the study by Maltais et al due to differences in supervision between groups.[25] Subgroup analysis was performed by dividing the studies into two groups. The first group compared intensity with different exercise volumes (duration x intensity), while the second group compared intensity with the same exercise volume.

The risk of bias within included studies and across studies assessed with the assessment of study quality based on the PEdro scale can be seen in Table 2. The average score obtained was 6.5, with a score range of 6-7. The evaluation of each outcome using the RoB2 tools can be seen in Figure 2.

For the intervention effect, we did not analyse the results on several outcomes, including isowork, isotime, and peak exercise, because no new studies discuss these outcomes in relation to the last systematic review.[7] We also did not analyse muscle strength outcomes because no studies addressed this topic.

1. HRQoL

This assessment uses two different questionnaires (SGRQ and CRQ). Two studies reported HRQoL using the SGRQ questionnaire, where 112 patients were trained at a higher intensity and 106 patients at a lower intensity.[25,26]

On the SGRQ, higher scores indicate poorer quality of life; therefore, a positive effect favours the lower-intensity group.

Table 2. Quality Assessment Using the PEdro Scale

Study	Random allocation	Concealed allocation	Similarity at baseline	Subject blinding	Therapist blinding	Assessor blinding	Completeness of follow up	Intention-to-treat analysis	Between-group statistical comparison	Variability estimates	Total
Casaburi et al[24]	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6
Maltais et al[25]	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7
Santos et al[26]	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	6
He et al[27]	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	7

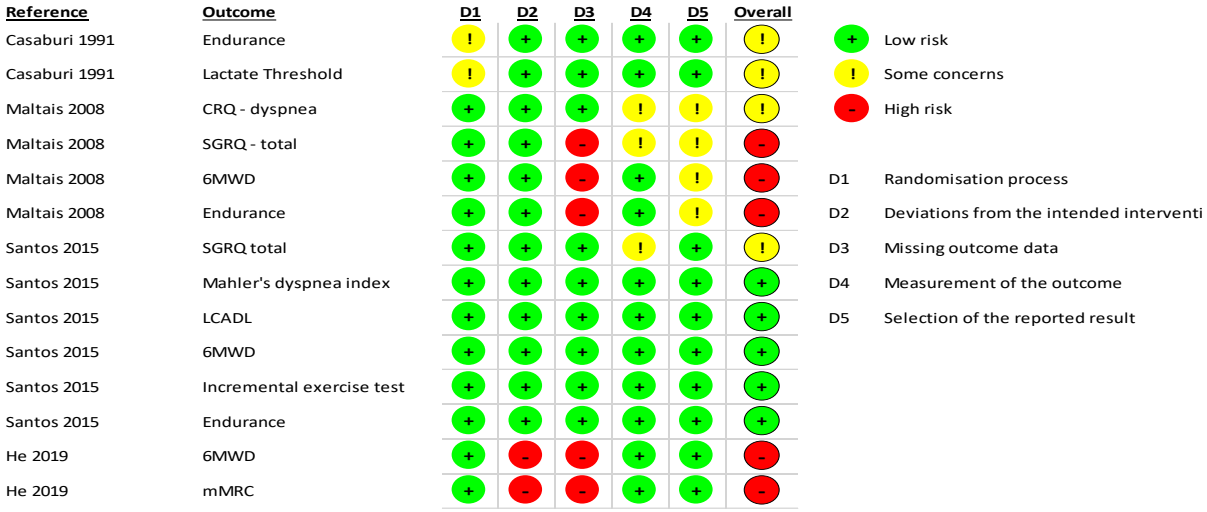

Figure 2. Risk of Bias Assessment using Version 2 of the Cochrane tool for assessing risk of bias in randomised trials (RoB 2)

There was a significant difference in symptoms domain (MD=5.53; 95% CI=1.08-9.97), favouring the lower-intensity group (Supplementary Figure S1). The common effect size exceeds the MID limit of 4 points, but the lower limit of the confidence interval does not exceed the MID. The total score (MD=1.79; 95% CI= -0.90 - 4.48; Low quality evidence), activity domain (MD=1.77; 95% CI= -3.51 - 7.05) and impact domain (MD=0.60 ; 95% CI= -2.52 - 3.71) on the SGRQ also favored the lower intensity, but there was no significant difference (Supplementary Figure S2-4). There was no heterogeneity in all domains, except in the activity domain (I^2 test = 27%), which suggests that the existing heterogeneity may not be important. Subgroup analysis showed no significant differences between subgroups (based on exercise volume) from all domains and total scores.

One study reported HRQoL using the CRQ questionnaire in which the total number of patients in the higher-intensity group was 109 people, and the lower intensity was 107.[25] On CRQ, higher scores indicate better quality of life; therefore, positive effect favours higher intensity group. There were no significant differences in all CRQ domains between the two groups (dyspnea (MD= -0.04; 95% CI= -0.30 - 0.22; Low quality evidence), mastery (MD=0.02; 95% CI= -0.21 - 0.25), fatigue (MD=0.10;95% CI= -0.17 - 0.37),

emotion (MD=0.03; 95% CI= -0.18 - 0.24) (Supplementary Figure S5-8).

2. Activities of Daily Living

ADL was only reported in one study where the total number of patients at a higher intensity and a lower intensity each of 17 people.[26] In LCADL, higher scores indicate poorer quality of life; therefore positive score favours the lower-intensity group. The effect obtained favoured lower intensity, but there was no significant difference between the two groups (MD=0.8; 95% CI= -1.24 - 1.84; Moderate quality evidence) (Supplementary Figure S9).

3. Functional exercise capacity

Comparison of functional exercise capacity was assessed by three studies using the 6MWT test.[25–27] The total number of participants was 179 people in the higher-intensity group and 174 people in the lower-intensity group. The effect favours higher intensity, but there were no significant differences (MD=6.20; 95% CI= -4.80 - 17.20; Very low quality of evidence) (Supplementary S10). Heterogeneity was not found in either the chi-squared test (P=0.54) or the I^2 test (0%).

We performed a secondary analysis on the study by He et al because there were three different groups.[27] This analysis compares a high-intensity (>70% VO_2max) group with a low intensity (<50% VO_2max) group (Supplementary Figure S19). The effect favours the high-intensity group where significant results were obtained (MD=28.60; 95% CI=4.82-52.38), and the effect crossed the MID limit. However, the lower limit of the confidence interval does not exceed the MID limit. The second analysis compared the moderate intensity (50-70% VO_2max) with the low-intensity group (<50% VO_2max) (Supplementary Figure S20). The effect obtained was favourable to moderate intensity but showed no significant results (MD=11.50; 95% CI= -11.20 - 34.20).

4. Dyspnea symptom

There were a total of two studies comparing dyspnea symptoms in patients with higher and lower intensity, each using a different questionnaire (mMRC and Mahler's dyspnea index).[26,27] mMRC is used to evaluate the intensity of dyspnea in daily activities. One study reported dyspnea symptoms using mMRC, where the total number of patients at the higher intensity was 67 people, and at the lower intensity was 68 people.[27] A higher score indicates more severe dyspnea symptoms; therefore positive score favours the lower-intensity group. Effect favours the higher intensity groups, but no significant differences were found (MD= -0.30; 95% CI= -0.73 - 0.13; Low-quality evidence) (Supplementary Figure S11).

We performed two secondary analyses on the study by He et al because there were three different groups[27]. The first analysis compares the highest intensity (>70% VO_2max) group with the lowest intensity (<50% VO_2max) group (Supplementary Figure S21). The effect favours the high-intensity group, and there were significant differences between

groups (MD= -0.60; 95% CI= -0.87 – -0.33) but did not exceed the MID threshold. Another analysis compared the moderate intensity (50% -70% VO_2max) with the low-intensity group (<50% VO_2max), where the effect favours moderate-intensity groups, but there were no significant differences (MD= -0.30; 95% CI= -0.73 - 0.13) (Supplementary Figure S22).

One study assessed dyspnea symptoms using the Mahler's Transitional Dyspnea Index (TDI) instrument.[26] Higher scores indicate less severe dyspnea symptoms; therefore, a positive effect favours the higher-intensity group. Effect favours higher intensity groups but showed no significant differences (MD=0.50; 95% CI= -1.63 - 2.63; Moderate quality evidence) (Supplementary Figure S12).

5. Endurance

There were a total of 3 studies comparing endurance in patients with higher and lower intensity exercise.[24–26] The total number of patients at the higher intensity was 123 people, and at the lower intensity was 114 people. Effect favours the higher intensity groups but showed no significant differences (MD=1.22; 95% CI= -1.61 - 4,05; Very low quality of evidence) (Supplementary Figure S13). Heterogeneity between studies was found from the chi-squared test results (P=0.03) dan 70% in the I^2 test, which showed the possibility of substantial heterogeneity. There was no significant heterogeneity between subgroups based on exercise volume, but there was significant heterogeneity in the subgroup with the same training volume (chi-squared test P=0.01; I^2 test = 84%). We also performed a secondary analysis on the study by Casaburi et al, which used the anaerobic threshold as a boundary in choosing the work rate[24] (Supplementary Figure S23). A significant effect was found (MD=4.20; 95% CI=1.30-7.10), favouring intensity above the anaerobic threshold.

6. Peak exercise

Two studies assessed a comparison of peak exercise.[24,26] One study measured peak aerobic capacity, where the total number of patients at higher and lower intensities was 17 each.[26] The effect favours higher intensity but showed no significant difference (MD=0.40; 95% CI= -0.28 - 1.08) (Supplementary Figure S14).

One other study measured comparison of the lactate threshold on the incremental exercise test.[24] The total number of patients at higher intensity was 11 people, and at lower intensity was eight people. A higher lactate threshold indicates better exercise tolerance. The effect favours higher intensity but showed no significant difference (MD=0.10; 95% CI= -0.02 - 0.22) (Supplementary Figure S15).

7. Sensitivity analysis

We removed two studies in the sensitivity analysis.[25,27] We excluded the study by Maltais et al because it had a high risk of bias and differences in supervision which could become a confounding variable.[25] Meanwhile, the study by He et al was excluded because of the high risk of

bias, and the intensity used was only an estimation.[27]

The sensitivity analysis of the SGRQ total score omits the study from Maltais et al,[25] leaving only the study by Santos et al[26] (Supplementary Figure S16). Effect favours lower-intensity group, but showed no significant difference between the two groups (MD=4.10; 95% CI= -3.01 - 11.21), which is consistent with the primary analysis. In the sensitivity analysis of 6MWT, we removed the study by He et al and Maltais et al,[25,27] leaving only Santos et al.[26]

The effect favours the lower-intensity group, but there was no significant difference (MD= -3.50; 95% CI= -64.32 - 57.32) (Supplementary Figure S17). In the endurance test sensitivity analysis, we removed the study by Maltais et al,[25] leaving two studies by Casaburi et al and Santos et al.[24,26] (Supplementary Figure S18). The pooled effect favours lower intensity, but the difference is not significant (P=0.35), and there was substantial heterogeneity (I^2 test = 72%). The differences between subgroups were significant (P=0.06) with the I^2 test = 72.3%

DISCUSSION

This review aims to describe the available evidence for interventions that compare aerobic exercise intensity in COPD patients. Previous systematic reviews and meta-analyses comparing the intensity of PR were done in 2011.[7] The criteria used are more flexible, comparing the difference between %peak working rate (%Wmax), %maximal oxygen uptake (%VO_2max), %VO_2Reserve (%VO_2R), %Heart Rate Reserve (%HRR), and %Maximum Heart Rate (%HRmax) between higher and lower intensities. The calculated intensity is the highest number, so studies using incremental training can be compared with constant training. We used these criteria due to the lack of evidence found in the previous review. One new study was included,[27] and a study from Santos et al, which was referred to in this study, showed slight data differences from the last review because the article had not been published.[26]

The primary analysis results using HRQoL tools (SGRQ and CRQ) showed a beneficial effect at lower intensities. However, the differences were not significant, except for the symptoms domain of the SGRQ instrument. However, these results are unclear because the confounding variables from the study of Maltais et al may affect the pooled effect.[25]

In this study, the group with higher intensity undertook an outpatient program at the hospital and received direct supervision. The group with lower intensity was put in a self-monitored rehabilitation program at home so that there was a possibility of inadequate supervision. The sensitivity analysis was carried out on the SGRQ total score leaving only one small study,[26] favouring the lower-intensity group but showed no significant result. The ADL outcome also favoured a lower intensity in the primary analysis, but no significant effect was found.[26] The results

of this analysis should be interpreted with caution because there were only 17 people in each group.

The 6MWT is often used to perform functional capacity assessments in COPD because of its simplicity. There were three studies comparing 6MWT between higher and lower intensities.[25–27] The pooled effect favoured higher intensity but showed no significant difference between the two groups. Similar to HRQoL, the largest proportion of this pooled effect comes from the study of Maltais et al, where the effects obtained are possibly unclear due to differences in supervision.[25]

In addition, most of the patients exercised by cycling were different from the outcome test, where patients exercised by walking according to the 6MWT method. Therefore, the effect may not be accurate. Finally, the sensitivity analysis performed on a small study favoured lower-intensity but not significant[26].

Dyspnea is one of the most prominent symptoms in COPD patients.[1,4,28] Tools for measuring dyspnea are divided into three main categories: short-term intensity measurements, situational measurements, and the measurement of the impact of dyspnea. There are two questionnaires obtained from the included studies in measuring dyspnea, namely Modified British Medical Research Council Questionnaire (mMRC) and transition dyspnea index (TDI). Both are situational measurements that quantify dyspnea. In addition, two other tools measure dyspnea in this review, namely the dyspnea domain of CRQ and the dyspnea domain of SGRQ, which measures the impact of dyspnea, but both are discussed in the outcome quality of life. The pooled effect in the primary analysis of the two tools favours higher intensity, but this effect is not significant. However, these results are still unclear because each questionnaire was only reported by one study.[26,27]

In three studies that carried out the endurance test, subjects performed the test according to their training mode. The therapeutic effect favoured higher intensity but insignificant with substantial heterogeneity. Substantial heterogeneity could also be found in the subgroups with the same exercise volume. Heterogeneity may be due to the study by Casaburi et al,[24] which used lactate threshold as the basis for the prescription while Maltais et al did not.[25]

When a sensitivity test was performed, omitting the study by Maltais et al,[25] substantial heterogeneity between subgroups by volume was found. However, it seems the heterogeneity is not due to the difference in volume because the effect shown in the subgroups with different volumes of work favoured the lower-intensity group. Instead, this may be due to the study by Casaburi et al,[24] which used the lactate threshold as the basis for the prescription. Further research is needed to conclude this effect, as the two studies we used showed opposite effects.

In peak exercise capacity assessment, the effect is also unclear because only two studies were included.[24,26] Two different outcome tests were used: peak aerobic capacity and

lactate threshold, each of which came from one study, and both favoured higher intensity but not significant. However, a previous analysis showed that a higher-intensity exercise program produced significantly lower lactate in iso-work and ventilation at iso-time than a low-intensity training program. These results are based on one study comparing higher intensity which induces a lactate threshold, and lower intensity which does not induce a lactate threshold.[7,24]

With all the limitations, there are no significant results between groups of higher intensity with lower intensity in this review for the patient-centred outcome, except for analysis of the SGRQ symptoms domain.

However, the secondary analysis which was carried out in the He et al study comparing high intensity (>70% VO_2max) and lowest intensity (<50% VO_2max) in the 6MWT and dyspnea, found favourable result for the high intensity and was significant. On the other hand, comparison analysis of moderate (50-70% VO_2max) and low intensity (<50% VO_2max) found favourable results for moderate-intensity but showed no significant difference.[27]

This could support a theory that in normal people, exercise at the anaerobic threshold level has a more beneficial effect than exercise below the anaerobic threshold. This seems to be also true for patients with COPD.[4,29] If we assume the lactate threshold in normal people is the same as in COPD patients (around 60% Wmax/VO_2max), then maybe comparisons made in the two studies between 80% Wmax and 60% Wmax had no significant effect because both groups trained above the lactate threshold.[25,26] Conversely, one study comparing 80% Wmax with 50% Wmax obtained significant results because the lower intensity has not crossed the lactate threshold.[24] Also, studies comparing >70% VO_2max with 50-70% VO_2max do not obtain significant results because the intensity described is only an estimate, some of which cross the lactate threshold and some do not.[27] We cannot confirm this hypothesis because the lactate threshold was not measured in these studies (except the study by Casaburi et al[24]).

Based on the studies included in this review, it was found that higher intensity is not always better, especially after 60% Wmax. However, this cannot be confirmed and requires further study.

This review has several strengths, including a more in-depth analysis and discussion than the previous review, which can be done because of the inclusion of new studies. In addition, all data used in the meta-analysis were uniformly using a change score.

The main limitation is that the evidence we had collected is scanty and difficult to evaluate, although the criteria are more flexible. In addition, we suggest carefully interpreting the data in this review because based on the assessment of evidence using GRADE, the quality of several primary outcomes was very low-moderate (the quality of the evidence is low for HRQoL, moderate for ADL, very low for exercise tolerance, low-moderate for dyspnea symptoms and very low for

endurances). The decline in the quality of evidence is primarily due to the imprecision where the sample size is too small for each meta-analysis, high risk of bias, and indirectness because there are studies with confounding variables. See the Summary of Findings to see in full the reasons for the deduction in study quality.

CONCLUSION

The evidence we collected is scanty and difficult to evaluate. This review is still inconclusive and indicates there is still a gap of knowledge in this topic. Further research comparing higher intensity with lower intensity of PR in COPD patients is still needed, especially studies with the same setting, mode, type, total sessions, time, and frequency so that there are no confounding variables.

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