RESPIRATORY CARE Paper in Press. Published on October 22, 2013 as DOI: 10.4187/respcare.02626

Physical training and non-invasive ventilation in stable chronic obstructive pulmonary disease patients: a meta-analysis and meta-regression.

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Key words: physical rehabilitation, chronic obstructive pulmonary disease, non-invasive ventilation

Abstract

Background: Exercise training improves both exercise tolerance and Quality of Life in patients with chronic obstructive pulmonary disease (COPD). The intensity of exercise training is crucial to achieve a true physiological effect. However, in COPD patients, exertional dyspnea and leg fatigue mean that the patient cannot maintain intensity of training for enough time to yield a physiological training effect. The use of non-invasive ventilation support (NIV) has been proposed as an alternative strategy to improve exercise tolerance, respiratory and cardiovascular performances. The first aim of our meta-analysis was to evaluate exercise training with NIV in terms of physiological effects after the completion of a pulmonary rehabilitation programme. A

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second aim was to investigate the dose-response relationship between physical improvement and training intensity.

Methods: Literature research was performed using MEDLINE, EMBASE and CINAHL. Meta-analysis and meta-regressions were performed using random effect models.

Results. Eight studies provided a proper description of a training schedule in stable COPD patients. A similar effect between NIV and placebo was observed for the outcomes considered despite differences between studies. However, subjects experienced a relevant and statistically significant improvement after rehabilitation for almost all of the outcomes considered. Heart rate (6 beats min-1 [0.98; 11.01] P = 0.02), workload (9.73 Watt [3.78; 15.67] P = 0.0001), and VO2 (242.11 ml min-1 [154.93; 329.9] P < 0.0001) significantly improved after training. Improvements in heart rate and workload were significantly correlated to training intensity.

Conclusion: Given the small number of available papers, the small sample sizes and the complete absence of power calculation we think that this topic deserves a more in-depth investigation. Randomised clinical trials, with larger sample sizes based on statistical power calculations, and designed to investigate the effect of training duration and intensity on rehabilitation, are needed to confirm results in this important field.

Introduction

Exercise training is a key component of pulmonary rehabilitation. It significantly improves both exercise tolerance and Quality of Life in patients with chronic obstructive pulmonary disease (COPD).[1-3] The intensity of exercise training is crucial to achieve a true physiological effect. However, in patients with severe COPD, exertional dyspnea and leg fatigue mean that the patient cannot maintain intensity of training for enough time to yield a physiological training effect.[4] The use of non-invasive ventilation support (NIV) during training sessions has been proposed as an alternative strategy to improve exercise tolerance[5-9] and respiratory and cardiovascular

performances[10, 11] in patients with mild to severe COPD. Previous studies have suggested that the application of NIV delivered by different devices (continuous positive airway pressure device, proportional assisted ventilation, pressure support) during exercise in patients with COPD results in an immediate improvement in exertional dyspnea and exercise endurance.[9] Few studies up to now have compared the effect of using NIV during a pulmonary rehabilitation programme in COPD patients with a control group. The studies from Hawkins *et al.*[13] and Bianchi *et al.*[12] used proportional assisted ventilation (PAV) among these studies, Bianchi *et al.*[12] did not observe any significant post-rehabilitation differences in exercise tolerance or cardiorespiratory response to an incremental test between an NIV group and a control group. Hawkins *et al.*[13] reported a significant increase in the maximal incremental cycle exercise and greater training intensities in the NIV group compared to controls, but not in the constant work rate test. During the constant work rate test, there was no difference in the physiological response in terms of exercise duration, heart rate and lactate concentration between the groups. When considering studies using pressure support ventilation (PSV) it could be noticed that Costes *et al*.[14] observed a greater improvement in peak VO_2 and reduced ventilatory requirements for maximal exercise in the NIV group when compared with the control group. After training, the change in the work rate exercise duration and isotime decrease in blood lactate was similar in both groups. A small but significant difference in the NIV group after six weeks of training in terms of walking endurance, maximum workload metabolic equivalents and heart rate was observed by Johnson *et al*.[15] Borghi-Silva *et al.*[16] showed that, at peak exercise in the incremental exercise test, after six week of training only the NIV group patients showed significant changes in walking speed, heart rate, VCO_2 and VO_2 peak, and respiratory rate. Moreover, there was a significant reduction in lactate/speed ratio only in the NIV group. In the paper by Reuveny *et al.,*[17] eight weeks of training with NIV produced significant physiological changes in terms of VO_2 max, anaerobic threshold, tidal volume, minute ventilation,

and oxygen pulse. No physiological improvement was found in any of the cardiorespiratory parameters in the control group patients. The authors did not observe any change in the maximal workload at the incremental test performed after training in either group.

Van't Hul *et al*.[18] observed a statistically significant difference in favour of the group that trained with an inspiratory pressure of 10 cmH_2O in terms of improvement in exercise tolerance (shuttle test), intensity of training, cycle endurance, and reduction in minute ventilation isotime. After 12 weeks of training, Toledo *et al.*[19] observed that, compared to the control group, the group which trained with NIV had a significant improvement in heart rate, systolic blood pressure and oxygen consumption after training. A significant reduction in blood lactate was observed at identical levels of exercise in the NIV group when compared to control patients.

For the moment, it is difficult to draw any firm conclusions about the potential physiological effects of the use of NIV during exercise training for many reasons: small size of the studies, differences in the pathophysiological characteristics of the enrolled patients, differences in the devices used, and outcome measures assessed. In this context, the first aim of our meta-analysis was to evaluate the effectiveness of supporting exercise training with NIV in terms of physiological effects after the completion of a pulmonary rehabilitation programme in patients with COPD. A second aim was to investigate the dose-response relationship between physical improvement and total training time in the NIV arm.

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Materials and Methods

Data source

Papers to be included in the study were identified through a search of electronic databases and by scanning reference lists of articles. This search was applied to MEDLINE, EMBASE and CINAHL using "non-invasive ventilation", "training exercise" and "chronic obstructive pulmonary disease" as key words. In addition, we made a manual search of reference lists of included studies, reviews, meta-analyses and guidelines on non-invasive ventilation and pulmonary disease.

Study selection

The literature search was conducted independently and in duplicate by 2 investigators (MG and CR). The same authors independently selected potentially eligible studies for inclusion. Disagreements between reviewers were resolved by consensus; if no agreement could be reached, the opinion of a third senior author (FG) was requested and his decision was considered final.

Data extraction and quality assessment

Study papers were included if they: 1) provided comparative data investigating the effect of NIV and exercise training in stable COPD patients; 2) reported one or more of the following outcomes: lactate production, heart rate, walking or physical exercise performance, respiratory outcomes and training characteristics (number of training session, training duration per session, and for the overall rehabilitation schedule); 3) were published in English. Methodological quality was independently assessed by 2 investigators (MG and AS) using the PEDro (Physiotherapy Evidence Database) scale. This scale has eleven dichotomous items concerning the study design,

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statistical analysis and intention to treat. The PEDro score was calculated by counting the number of checklist criteria that were satisfied in the trial report.

Data synthesis and analysis

We developed a data extraction sheet. This was pilot-tested on three randomly selected papers and modified accordingly. The following data were extracted from selected studies and entered into a data extraction form by one investigator (ST): author, study year, participants, country, outcomes, training schedule characteristics, and number of dropouts. A second investigator (CR) checked the extracted data to ensure accurate reporting. Disagreements were resolved by discussion between the 2 investigators; if no agreement could be reached, it was planned that a third investigator would make the final decision (AD). Baseline characteristics (Age, gender and FEV_1) were compared by means of random effect comparison, then the comparisons between non-invasive ventilation and placebo at isotime were reported. To account for ventilation setting this analysis was also performed comparing results between PAV and PSV ventilation. Afterwards, we investigated variable modification at isotime after training in the NIV arm. A meta-analytical approach was used for both analyses. If the heterogeneity evaluated by the I^2 was greater than 50%, the random effects model described by DerSimonian and Laird[20] was selected over the fixed effects model. Small study and publication bias effect was assessed by funnel plot visual inspection. Both Harbord and Egger[21] tests were applied if at least 5 studies were included. Finally, to investigate to what extent training duration influenced changes in outcome in the NIV arm, a random effect meta-regression approach was used. The random effect meta-regression model used evaluated training duration as explanatory covariate. Study weight resulting from meta-analysis was used in the regression analysis as weight variable. Alpha 0.05 was considered statistically significant and all statistical tests were 2-tailed. Funnel plots were obtained by

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RevMan5[22] (*data not shown*). Meta-analysis, meta-regressions, and Harbord and Egger asymmetry tests were performed using the SAS[23] software package v9.2.

Results

A total of 107 results were selected after examining titles and abstracts; of these, 53 were excluded because they were duplicates or were not designed as comparative studies. Of the 54 papers remaining, 33 were excluded because they did not concern stable COPD patients. Among the 21 papers remaining, only 8 used and properly described a physical training schedule. Figure I shows the flow chart of paper selection. Tables I-II summarises study characteristics. Among the 8 studies considered, the UK and Brazil provided 2 studies each, while France, Italy, Israel and the Netherlands provided one study each. All selected studies were controlled trials. The studies by Costes *et al*.[14] enrolled consecutive patients while the others were randomised controlled trials. At the end of the training protocol, the sample size in each study varied between 7 and 15 patients, and the number of dropouts varied between zero and the 50% reported by Bianchi *et al*.[12] Mean age was similar between studies, whereas FEV_1 could be considered heterogeneous even if not statistically significant. Women were included in all of the studies considered except in that by Bianchi *et al*.[12] When considering the study quality, we noticed that all studies obtained a satisfactory score on the PEDro scale and the agreement between the two people evaluating this was satisfactory, being higher than 95%. The duration of training protocols was homogeneous, ranging from six to eight weeks. Whereas, session duration could be considered heterogeneous, ranging from 20 to 60 minutes. Training exercises consisted of treadmill training, endurance walking or cycling using a cycle ergometer. Finally, ventilation protocols in the NIV arm followed different approaches. Funnel plot visual inspection and Harbord and Egger asymmetry test results did not exclude the hypothesis of a small study or publication bias effect.

Non-invasive ventilation versus *placebo*

When considering the comparison between non-invasive ventilation and placebo, some slight and not statistically significant differences between groups were found. In particular, when looking at the heart rate as an outcome, we noticed that the studies from Costes *et al.*[14] and Toledo *et al.*[19] observed a similar difference between NIV and placebo, showing a slightly better outcome in the NIV group (respectively a reduction of 5.0 [-16; 25] and 5.8 beat min^{-1}). This effect was not confirmed in the study by Hawkins *et al*.[13] regarding workload and lactate as outcome variable so firm conclusions could not be drawn. On the other hand, and as expected, the difference of VO_2 as outcome is clearer (167 [-15 ; 350] P = 0.07) even if this was not statistically significant. Two studies Hawkins *et al*.[13] and Bianchi *et al*.[12] used PAV while other studies employed PSV. Sub-analysis considering stratification by ventilation protocol did not result in any statistically significant difference from the pooled analysis.

Post-training evaluation in the non-invasive ventilation arms

After the training schedule, clear improvements in performance were observed. The prevalence of the variable considered resulted in a clinically relevant modification after training. Heart rate at isotime improved by approximately 6 beats min^{-1} [0.98; 11.01] P = 0.02) after training, as did workload (fixed effect mean change 9.73 [3.78; 15.67] P = 0.0001) and VO_2 (fixed effect mean change 242.11 [154.93; 329.9] P < 0.0001). Even if not statistically significant, there was also a big change in lactate production after training (0.21 [-0.1; 0.54] P = 0.2).

Effect of training intensity on patient performance

The meta-regressions reported in figure II showed a positive relationship between variable modification and total training time for all of the outcomes considered. A statistically significant effect on slope was found when considering heart rate and workload as response variable; the

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random effect estimates of these slopes were 0.015 [0.008; 0.22] and 0.01 [0.0002; 0.0215] for heart rate and workload, respectively.

Discussion

In the papers selected, patients were trained with treadmill exercises (Reuveny *et al.,*[17] Toledo *et al.,*[19] Borghi-Silva *et al.*[16]) or cycle ergometer (Costes *et al.*,[14] Hawkins *et al.,*[13] Bianchi *et al.,*[12]) with comparable outcome variables and measurement methods. Therefore, the characteristics of the rehabilitation programmes were almost similar and no evidence of biases due to any relevant difference in training method was considered as a potential confounder. On the other hand, ventilation protocol used were objectively not homogeneous, only the studies from Hawkins *et al.*[13] and Bianchi *et al.*[12] used proportional assisted ventilation while other studies used pressure support ventilation. In the studies included in our meta-analysis, the dropout rate was heterogeneous ranging from 7.1% for Borghi-Silva *et al.*[16] (4 patients of 28, 14 completed the study) to 50% for Bianchi *et al.*[12] (9 patients of 18) and 33% (5 patients of 15) for NIV patients and controls, respectively. Nevertheless, within study dropout rates were comparable according to treatment group and no effect due to drop out bias could be assumed as relevant. Baseline clinical and demographic variables were considered to be comparable despite a heterogeneous FEV_1 at baseline. Even if the effect of these confounders was not found to be relevant from a statistically view point between studies heterogeneity could affect our results showing a distorted effect on estimates. As regards the comparison between NIV and controls, the analysis showed no clear superiority of the NIV treatment. In fact, whereas NIV showed beneficial effects on heart rate and oxygen consumption, these effects were not statistically significant. On the other hand, NIV treatment seems to be equivalent to control only in terms of effects on workload and production of lactate. However, it seems that training duration could positively influence the effect of physical

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rehabilitation and so lead to better results. This finding is in line with previous results suggesting that longer duration of pulmonary rehabilitation programmes have a more favourable effect on exercise capacity.[24-27] These last results seems to be in contrast to the general idea that NIV could improve the ability of a patient to endure an intensive exercise training session. Moreover, since no differences was found between NIV and placebo controls it could be speculated that training could produce benefits regardless NIV. On the other hand, the effect of NIV on VO_2 and heart rate leads us to suppose that ventilation is in some way useful. In the NIV arm of our meta-analysis, patients had lower heart rates, higher workload, and improved oxygen consumption after rehabilitation when compared to initial values. No firm conclusion could be drawn from our results regarding the production of lactate and CO_2 volume. In particular, when considering lactate, a clinical improvement was observed in all studies except in that by Borghi-Silva *et al*.[16]

In the conclusions of their papers, most authors were favourable towards the use of NIV during rehabilitation whereas only one study[12] concluded that non-invasive ventilation gave no additional physiological benefit in comparison with exercise training alone. In the NIV arm of that study, the result regarding workload had the broadest confidence interval when compared to those found in the other papers; however, this study does not have an appreciable weight in the analysis (3.0%) and only had a marginal effect on the overall result. Moreover, the study from Bianchi *et al.* included less severe patients considering the baseline FEV_1. An interesting finding regards the effect of NIV on heart rate and workload; this seems to increase parallel to the duration of training. This trend did not emerge in the analysis regarding the number of sessions per week or the number of weeks in the training schedule. Some limitations regarding ventilation approaches arise from our work. First, it remains unclear how to define the best technique for NIV to be used in order to enhance exercise capability in COPD patients since different ventilation modes were used. Second, the ventilators used in the selected studies are not specifically designed to be used

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during physical exercise when ventilation demand is increased indeed. In fact, it can be assumed that the problem of patient-ventilator synchronization is more marked during exercise. In the 8 studies retained, patients were ventilated with low inspiratory pressures, which cannot produce important effects, especially during exercise, a higher inspiratory pressure may allow to draw more firm conclusions in a field that appears to be of primary importance from both a clinical and an epidemiological point of view.[28-33]

Moreover, Positive End Expiratory Pressure (PEEP) is an important question for reducing the work of breathing. PEEP was not tested in a few studies and PEEP adjustment was never adapted to PEEPi, which has never been correctly determined. It is well known that using patient sensation for setting PEEP is not adequate[34], this also could be considered as a limit.

Two more limitations could be hypothesized. First, most studies where NIV was applied during exercise COPD patients had no indication for long-term NIV. Second, patients with hypercapnia are more likely to benefit from NIV during nighttime and probably also during other different physiological/real life conditions such as exercise. It is to be hoped that future studies could define which subgroups of patients may benefit from NIV in view of its effects on exercise. Further studies should also be aimed at clarifying which mode and ventilator settings are most beneficial in improving exercise capability in COPD patients. In parallel, ventilator technological breakthrough should target the ability to detect the initiation of inspiratory effort while the patient continues to expire, which is almost a constant situation in the COPD population.Some methodological limitations regarding study design arise from this work . In all the papers considered, the number of patients who completed the study protocols was generally small and some papers drew conclusions from extremely small samples. For example, in the study by Costes *et al.*,[14] the 7 patients enrolled in each group were assigned consecutively to one group or the other, thus generating a possible bias. Moreover, none of the papers included took into

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consideration the power of statistical tests performed. Furthermore, the most commonly used outcome for evaluating exercise performance in COPD patients is the six mininute walk distance. Unfortunately only one study[12] considered this test as outcome variable.

Conclusions

Considering the small number of available papers and the technical heterogeneity regarding the ventilation protocols and the small sample sizes, we believe this topic deserves further investigation. Randomised clinical trials with larger sample sizes based on statistical power calculations should be especially designed to investigate also the effect of training duration and intensity. In conclusion, our meta-analysis suggests that, for the moment, there is no clear evidence of superiority for the use of non-invasive ventilation. On the other hand, it seems that training duration could positively influence the effect of physical rehabilitation, leading to better results as previously reported.[2]

Author´s contributions: CR and FG conceived the study design and method. AD, AS, ST and FG revised the paper from a medical viewpoint. CR and MG revised study methodology.

Figures legends:

Figure I. Flow chart of paper selection.

Figure II. Random effects meta-regressions and paired comparison effect estimate in the non-invasive ventilation arm. Evaluation of the relationship between the random effect estimate of

outcome modification after training and the overall training time. Bubble diameters show study weights from meta-analysis. Heart rate meta-regression considered references 13, 14, 16 and 19. Workload meta-regression considered references 12, 13, 14, 16 and 17. Lactate meta-regressions considered references 13, 14, 16, 17 and 19. VO_2 meta-regression considered references 12, 14, 16 and 17.

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Table I. General characteristics of examined studies.

Author (Year)	*Groups*	*Subjects by group*	*Mean age (SD)[range]*	*Mean % FEV_1 (SD)*	*Training protocol*	*Quality score*
[16]Borghi-Silva (2010)	NIV OXY	12 12	68 (9) 67 (7)	34(10) 33(7)	18 sess. (30 min.) 6 weeks	7
[19]Toledo (2007)	BiPAP control	9 9	68 (9) 67 (11)	33(10) 34(8)	36 sess. (30 min.) 12 weeks	8
[18]van't Hul (2006)	NIVS control	14 15	70 (5) 71 (4)	41(10) 38(9)	24 sess. (45 min.) 8 weeks	8
[17]Reuveny (2005)	BiPAP, control	9 10	64 (9) 63 (9)	32(4) 33(9)	16 sess. (45 min.) 8 weeks	6
[14]Costes (2003)	NIV control	7 7	60 (7) 67 (6)	31(12) 32(7)	24 sess. (30 min.) 8 weeks	6
[15]Johnson (2002)	NIPPV HT UT	11 10 11	69 (9) 72 (9) 67 (8)	32(9) 34(13) 31(11)	12 sess. (20 min.) 6 weeks	6
[13]Hawkins (2002)	PAV control	10 9	68 (9) 66 (7)	26(7) 28(7)	18 sess. (30 min.) 6 weeks	7
[12]Bianchi (2002)	PAV control	9 10	64 [61-67] 65 [61-69]	48(19) 40(12)	18 sess. (60 min) 6 weeks	7

NIV: noninvasive ventilation; **OXY**: supplemental oxygen; **NIPPV**: noninvasive positive pressure ventilation; **NIVS**: noninvasive ventilatory support; **PAV**: proportional assist ventilation; **BiPAP**: bi-level positive pressure ventilation; **HT-UT**: unassisted heliox breath.

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Table II. Comparisons groups and ventilation technical details.

Author (Year)	*Groups ventilation technical specifications*	*Outcomes considered*
[16]Borghi-Silva (2010)	IPAP(12 ±1 cmH_2O)+EPAP (4±2 cmH_2O) Oxygen	Maximum inspiratory and expiratory pressure, 6 Min Walk Distance, Peak torque, Workload, Total Power, Fatigue Index, SGRQ Scores, Walk Speed, Heart Rate, Respiratory Rate, VT, VCO_2 , VO_2 , Lactate, Lactate/Speed, SpO_2 , Systolic Blood Pressure, Dyspnea (Borg Score)
[19]Toledo (2007)	IPAP (10-15 cmH_2O)+ EPAP (4-6 cmH_2O) control	Speed, SpO_2, Heart Rate, Systolic Blood Pressure Diastolic Blood Pressure, Dyspnea (Borg Score), Lactate, VO_2, VCO_2
[18]Van't Hul (2006)	EPAP (10 cmH_2O) control (PSV 5 cmH_2O)	Exercise Time, Heart rate, SpO_2 , VE, VT, VO_2, VCO_2, Respiratory Exchange Ratio, SGRQ Scores
[17]Reuveny (2005)	IPAP (7-10 cmH_2O) + EPAP (2 cmH_2O) control	Workload, VO_2, Anaerobic Threshold, VE, VT, Lactate, SpO_2, End Tidal PCO_2
[14]Costes (2003)	IPAP + EPAP (4-8 cmH_2O) control	Workload, VO_2,VCO_2, Respiratory Quotient, Heart Rate, VE, VE/VO_2, VE/VCO_2, Respiratory Rate, Vd/Vt, SpO_2, PO_2, PCO_2, Lactate
[15]Johnson (2002)	IPAP (8-12 cmH_2O)+ EPAP (2 cmH_2O) HT UT	Exercise Time, Workload, Heart Rate, Systolic Blood Pressure, Dyspnea (Borg score), PO_2, VO_2
[13]Hawkins (2002)	PAV (FA 3.6±0.7 cmH_2O, VA 12.7±1.5cmH_2O) control	FEV_1, FEV_1 (% pred), RV/TLC, KCO (% pred), PO_2, PCO_2, Workload, VE, lactate, Heart Rate, Heart Rate (% maximum)
[12]Bianchi (2002)	PAV(FA 3.5±1.6 cmH_2O, VA 6.6±2.2 cmH_2O) control	Work Rate, 6 min walk distance, VE, VO_2, Dyspnea (Borg score), SGRQ Scores

IPAP: inspiratory positive airway pressure; **EPAP:** expiratory positive airway pressure; **PSV:** pressure support ventilation; **PAV:** proportional assist ventilation; **FA:** flow assist; **VA:** volume assist; **HT:** unassisted heliox breathing training; **UT:** unassisted breathing training ;

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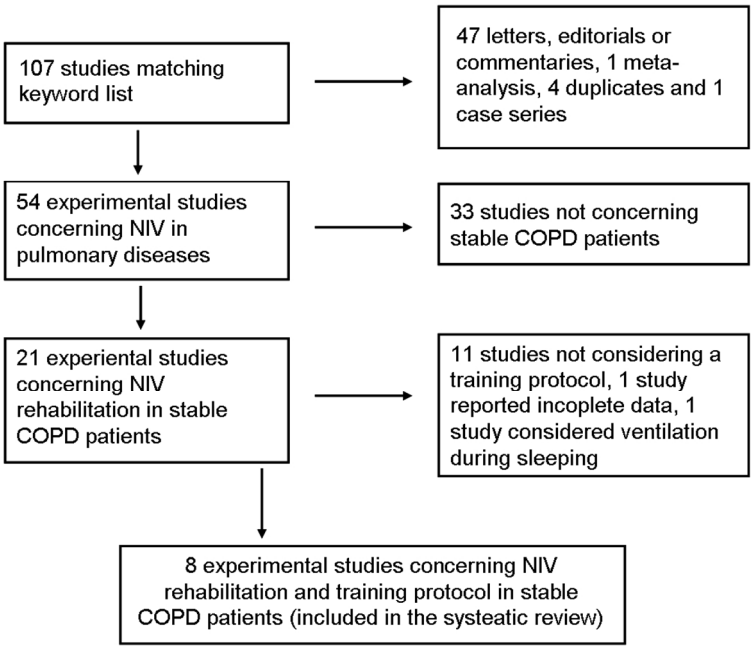

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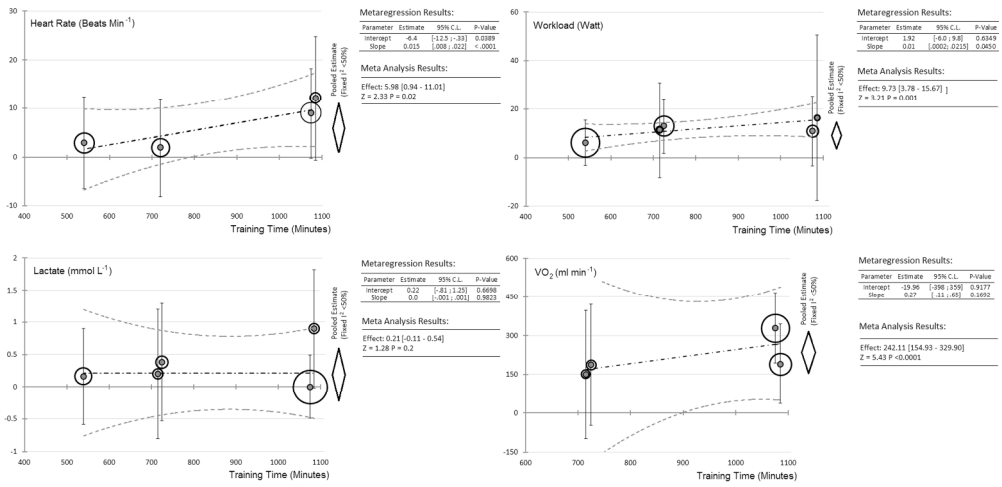

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