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Meta-analysis on the Physiological Benefits and Quality of Life of Muscle Training in Patients with Chronic Obstructive Pulmonary Disease

Enmanuel Jiménez Castro*, Luis Blanco Romero, Gerardo Araya Vargas and Luis Solano Mora

Faculty of Health Sciences, School of Human Movement Sciences and Quality of Life, National University, Brazil

Abstract

Justification: The existence of important peripheral muscular dysfunction contributes at very substantial manner to reduce the tolerance to exercise in a patient with chronic obstructive pulmonary disease.

Methods: this was an exhaustive research on benefits of exercise training for a group of patients, thirteen studies were found (n=351), from these four were excluded studies. The analysis was done using the SPSS v 15.0, and Excel 2007, p<0.05 was considered the significance value.

Results: the moderating variables that were meta-analysis were present in more than two experimental investigations. In total eight variables were found from which six variables showed significant effects (oxygen consumption, volume minute, heart rate, breathing rate, fatigue, dyspnea, emotional condition, six walking test).

Two control groups were compared; heart rate and breathing rate had a significant effect in the group that did exercise. Another analysis assessed the type of training: muscle strength, aerobic resistance, or combination of both, including body part involved, no significant difference was found.

In both comparisons the training type and the body part involved gives a significant effect.

Conclusion: the types of training should be combined for upper and low limbs.

Keywords: Chronic obstructive pulmonary disease; Meta-analysis; Physiological benefits

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; HR: Heart Rate; RR: Respiratory Rate; BMI: Body Mass Index; VE: Minute Volume; VO_2: Maximum Oxygen Consumption

Introduction

According to the Global Initiative for Chronic Obstructive Lung Disease, Chronic Obstructive Pulmonary Disease (COPD) is a disease that is characterized by airflow limitation and is not completely reversible. This airflow limitation becomes progressive and is associated with an abnormal inflammatory response of the lungs to the inhalation of particles or gases [1].

There is a classic conceptualization that exercise intolerance in the COPD patient is due exclusively to dyspnea caused by increased respiratory work but this issue has been questioned during the last decade, since it has been demonstrated that A great number of patients stop the exercise, due to discomforts that present in lower extremities and not dyspnea. It has also been demonstrated the existence of an important peripheral muscular dysfunction that contributes in a substantial way to reduce the tolerance to the exercise and in some studies realized that the intolerance to exercise in the COPD has a better correlation with the mass and the muscular function of Lower limbs than with the degree of bronchial obstruction [2,3].

As a result, they become forced to adopt sedentary lifestyles and become inserted into a vicious circle that leads to a significant deterioration of physical form [4]. The physical training becomes a therapeutic strategy that allows reversing some of the muscular alterations that must be attributed to muscular disuse in patients with COPD [2]. In addition, results in quality of life studies confirm that patients with COPD present, even at a stable stage of their disease, a significant deterioration of their quality of life that does not correlate with the magnitude of the commitment of the physiological indicators and demonstrate that the Physical training is capable of improving different aspects of quality of life in patients with advanced COPD [5].

At the present time, there are numerous studies (Table 1) that have helped improve and reinforce the physiological knowledge of COPD, Exercise and quality of life of these patients, however there are controversies in the management of rehabilitation in this group of patients and it is necessary to seek different conclusions from those already existing, which can be achieved with a meta-analysis.

Objective

To quantify relevant scientific literature on the effects of muscle training on physiological and affective variables indicative of quality of life in patients with chronic obstructive pulmonary disease.

Author	Year
Bernard et al. [2]	1999
Clark et al. [4]	2000
Conti et al. [5]	2003
López et al. [8]	2006
Mador et al. [9]	2004
Montes de Oca et al. [10,11]	2005
O´ Donnell et al. [12]	1998
Ortega et al. [13]	2002
Varga et al. [20]	2005

Table 1: List of articles included in the meta-analysis.

***Corresponding author:** Enmanuel Jiménez Castro, Master's Degree in Integral Health and Human Movement, Faculty of Health Sciences, School of Human Movement Sciences and Quality of Life, National University, Brazil, Tel: (506) 88601236; E-mail: melterapia@gmail.com

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Material and Methods

In order to carry out this study, we took into account the population of studies from 1990 on, on quality of life and physiological improvement of the patient with COPD who underwent a physical training program.

The selected studies were those that determined the effectiveness or improvements obtained from an exercise program or training for patients with COPD (i.e., only experimental studies) that included exercises in lower limbs (however, it was not thought to disregard studies that reported exercise in the upper limbs, but at the end of the selection process, no studies with this characteristic were found) and should have the characteristics of being complete reports of randomized clinical trials, in order to have the treatments randomly assigned to research subjects, this achieves a statistical equivalence between the treatment groups.

The search for the studies was carried out in the databases: Cochrane library, DARE, Pubmed Clinical Queries, Google academic, and search engines such as springer and ebscohost, the search that ended in September 2012, contains studies published between the years 1996 and 2009.

Included in the inclusion criteria are experimental studies, with no year limit and in which patients have at least six weeks of follow-up (Table 1). For the exclusion factors, incomplete studies were determined that did not have the complete or incomplete results (Table 2), that did not have complete data that allowed to calculate the effect sizes and that included subjects of whom the diagnosis was not certain EPOC.

Statistical Method

Of the nine studies selected, eight dependent variables were identified and subsequently meta-analyzed. These variables were: VO_2 (maximal oxygen consumption), HR (heart rate), FR (respiratory rate), VE (minute volume), dyspnea, emotion, fatigue and six-minute walk. Once the study variables were selected, the effect sizes for repeated measurements and the Hedges bias correction formula were calculated to finally calculate the overall effect size, 95% confidence intervals, and subsequently tests for heterogeneity were performed, and We analyzed categorical and continuous moderating factors through statistical tracking tests such as analysis of analog variance and linear regression weighted by inverse variance of effect sizes.

All the applied formulas were consulted in Cooper et al. [6], Botella and Gambara [3] for the fixed effects model. The analyzes were elaborated with the program SPSS V15.0 and Excel 2007 and considered as value of significance $p<0.05$.

Author	Year
Clark et al. [4]	1996
Lisboa et al. [7]	2001
Anoma et al. [14]	2009

Table 2: List of excluded articles in the meta-analysis.

Results

In the meta-analysis variables, in what corresponds to VO_2 exposed in L/min, it is evident that there is no significant effect of treatment with exercise on this variable. The average effect size of VO_2 is small with a value of -0.14 and was not different than 0. But despite not being a significant effect, a high heterogeneity was found. Observing the VE, indicates that the exercise causes a significant decrease in the VE, and this is clinically positive. In addition it was found that the heterogeneity is great. With regard to HR, there is a significant effect of exercise treatment on this variable, causing a significant decrease in heart rate and a large heterogeneity was found. Likewise, there is a significant ($p<0.05$) effect of improvement with the physical exercise treatment on the respiratory rate variable reflected in the effect size and a large heterogeneity is found. With regard to dyspnea, no significant improvement was found, with exercise treatment, however, heterogeneity is large. Subsequently, the fatigue variable, a significant improvement ($p<0.05$) was observed with the physical exercise treatment and has a large heterogeneity (Table 3).

In the emotion variable, a significant improvement with the exercise treatment is found, but with a very small heterogeneity, by examining the last variable corresponding to a six-minute walk, there is a significant improvement ($p<0.05$) with The treatment of physical exercise, demonstrated in its effect size and heterogeneity of 0%, since there is a heterogeneity in most of the results, there may be a mixture of moderating variables, which could be useful to examine for which the evidence to determine it.

Analyzing the VO_2 moderating variables, it was observed that there was a significant ($p<0.05$) relationship between two of the continuous moderating variables and the corrected effect sizes, which were the age and the weeks of exercise, with respect to the age, an inverse relationship was found, so that the older the age, the smaller the effect size of the exercise on VO_2 and in the case of the weeks of treatment with physical exercise, it was found, on the contrary, that there is a significant relation ($p<0.05$) but direct, which means that the greater the number of weeks of treatment, the greater the effect size on VO_2. Therefore, of the possible continuous moderating variables, only age and weeks of treatment with exercise may explain part of the heterogeneity observed in the effect size group of the VO_2 variable.

A statistically significant relationship ($p<0.05$) between three variables and the effect size of the exercise on minute volume was found on the minute volume; With regard to age, this was inversely related, therefore, to a lower age the effect of the exercise on the minute volume; In relation to the weeks of treatment, a statistically significant

Variables	Cantidad de Estudios	TEG Weighted	Error Stand	Z	Intervalos de 95% de Confianza		Qt	I^2
					IC-	IC+		
VO_2 L/min	7	-0.14	0.09	1.46	-0.34	0.04	34.98	82.85
VE	7	-0.26	0.1	2.4	-0.47	-0.04	43.64	86.25
HR	4	-0.61	0.13	4.71	-0.87	-0.35	23.44	87.2
BF	3	-0.77	0.15	4.85	-1.08	-0.46	9.47	78.88
Dyspnoea	9	0.07	0.08	0.86	-0.09	0.23	107.05	92.52
Fatigue	4	0.7	0.17	3.91	0.35	1.05	14.99	79.99
Emotion	4	0.55	0.16	3.3	0.22	0.88	2.72	0
6wt	7	0.47	0.09	5.02	0.29	0.66	3.88	0

OES: Overall effect size; VO_2: oxygen consumption; VE: Minute volume; HR: Heart rate; BF: Breathing frequency; 6 wt: six walking test

Table 3: Meta-analysed variables, with their respective results of weighted global effect size, standard error, confidence intervals (IC), Qt e I^2.

($p<0.05$) relationship of treatment weeks *vs.* minute volume was found directly, with the greater weeks of treatment being greater the effect of exercise on volume minute, and with respect to the number of sessions per week, it was found to be inversely related so that the fewer sessions, the greater the effect of the exercise on the minute volume.

Subsequently, a significant ($p<0.05$) relationship of the effect of physical exercise on the heart rate was found and three of these variables, among them is the age, inversely so that the older age is the effect of the treatment with exercise on heart rate; In relation to the weeks of treatment, a direct relationship was found, representing that the greater the number of weeks of treatment with physical exercise, the greater the effect of physical exercise on HR and the number of sessions per week, a significant and inverse relationship was found, therefore, the greater the number of sessions, the lower the HR.

With respect to RF, it is possible to estimate that there is a relationship between three variables and the effect of physical exercise on respiratory rate. Age is inversely related, so that the older age is the effect of physical exercise on respiratory rate. On the other hand, the weeks of treatment with physical exercise are related in a direct way, therefore the greater the number of weeks with physical exercise treatment, the greater the effect on the RF, and what corresponds to the frequency with which exercise, an inverse relationship with the effect of physical exercise on the respiratory rate was evidenced, which means that the greater the number of sessions, the lower the effect of exercise on the respiratory rate.

Examining the moderating variables to determine if there is a relationship to dyspnea, it is verified that there is this relationship between the four variables shown in the table and the effect of physical exercise on dyspnea. Age has a direct significant relationship ($p<0.05$), which means that the older the greater the effect size on dyspnea. On the other hand, in relation to the variable IMC, this one had direct relation, being that to greater BMI greater is the effect of the physical exercise on the dyspnea. And with regard to the variable frequency of sessions, it also presents a direct statistical relationship, being that the greater the frequency of sessions, the greater the effect of the treatment on dyspnea.

Finally, corresponding to the weeks of treatment, a statistically significant relationship ($p<0.05$) was evidenced but inversely, which means that the longer the treatment, the less the effect of exercise on dyspnea.

With respect to fatigue, only in the variable of weeks of treatment a significant relation ($p<0.05$) is obtained, this being inverse, so that the fewer weeks of treatment the greater the effect that is obtained with the treatment.

Continuing with the variable emotion, none of the variables with which it was possible to run the regression, had significant relation with the effect of the exercise on the emotion. Finishing the results of the analysis of moderating variables, none of the variables with which the regression was possible had a significant relation with the effect of the exercise on the result in the 6-minute walk (Figures 1 and 2).

The type of training that had the greatest effect on the variables was the combination, but this difference was not large enough to differ from the workouts, (resistance training and aerobic resistance training), in addition there are values that overlap from one type of exercise to another; It should be clarified that in the dyspnea variable, a significant difference ($p<0.05$) was found with aerobic endurance exercise.

The training in the lower train affected the variables of HR, fatigue, and 6-min walk, in the case of the HR, generated a negative effect which means that this intervention managed to decrease the heart rate, but not in the variables Of dyspnea and 6-min walk in which the effect was increased, which showed that the patients presented a greater degree of dyspnea, but a greater number of meters walked after the intervention (Table 4). When examining the information available from groups or control conditions, it was found that in those cases the subjects did not present changes in the variables of VE and FR, but not in the variable of CF in which a change was found that there could be an external factor to the treatment that could influence this variable (Table 5). When comparing the experimental group vs the control group, a significant effect was verified for the HR and Fr variables in which physical exercise causes a positive effect in contrast to the subjects who are not trained. Only in the LV variable did not find that effect (experimental subjects

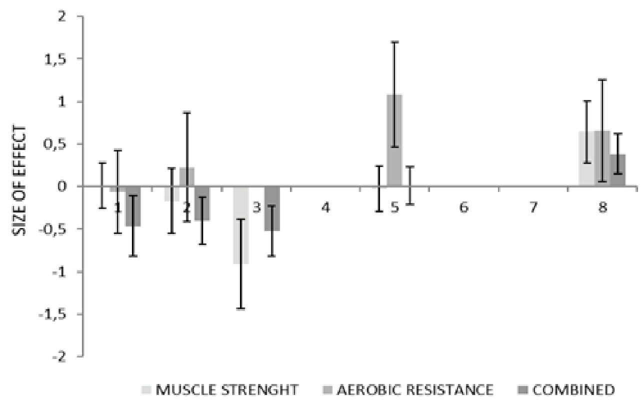

Figure 1: Effect sizes for categorical variables according to training type. 1: VO_2; 2: VE; 3: HR; 4: BF; 5: Dyspnoea; 6: Fatigue; 7: Emotion; y 8-6wt.

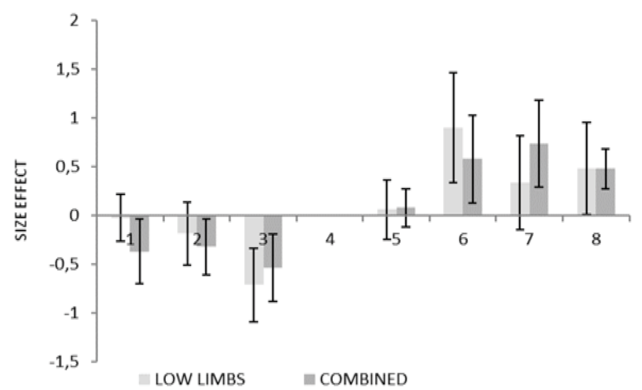

Figure 2: Sizes of effect for categorical variables, according to training only in lower limbs or combined. 1: VO2; 2: VE; 3: FC; 4: FR; 5: dypsnea: 6: fatigue; 7: Emotion; y 8-cam 6 min.

Variable	Trials	OES Weighted	Stand Error	Z	Confidence Intervals		QT	I^2
					IC-	IC+		
VE	2	-0.27	0.21	1.27	-0.7	0.15	0.01	0
HR	2	-0.62	0.21	2.89	-1.04	-0.2	3.17	68.53
BF	2	0.37	0.21	1.73	-0.04	0.8	2.04	51.18

Table 4: Meta-analysed variables, with their respective overall effect size (pre *vs.* post) weighted for group or control condition, standard error, confidence intervals, QT and I^2.

Variable	Trials	OES Weighed	Stand Error	Z	Confidence intervals		QT	I^2
					IC-	IC+		
VE	2	-0.47	0.25	1.87	-0.96	0.02	33.6	97.02
HR	2	-0.47	0.23	2	-0.94	-0.01	16.69	94
RF	2	-1.03	0.25	4.13	-1.53	-0.54	18.34	94.54
VE: Minute Volume; HR: Heart Rate; BF: Breath Frequency								

Table 5: Meta-analysed variables with their respective weighted overall effect size (control group *vs.* experimental group), standard error, confidence intervals, QT and I^2.

showed significant improvements in LV), although this variable showed a positive affectation in the meta-analysis, its effect does not manage to be strong enough to distinguish the results of subjects Trained vs. those of control

Discussion

These results shown above are novel, evidencing a tendency for new studies. It is clear that there is no consensus on the frequency, intensity, type of exercise and time (FITT) to approach an COPD patient in a cardiopulmonary rehabilitation program, so the present systematic review was performed.

Among the major revisions on the subject, we present a review that goes deeper and exposes essential aspects of muscular dysfunction in COPD patients and mechanisms responsible for these alterations, which eventually lead to a loss of body mass and a decrease in oxidative capacity. States that one of the main causes of muscle dysfunction are inflammatory factors such as TNFα and that the adaptation to oxidative stress is altered in the muscle of these patients, and may be another cause of the alteration in the mitochondrial chain [2]. Subsequently, other authors conclude that strength exercise should be present in any respiratory rehabilitation program, and even show results that strength training provides better results (related to health related quality of life) in contrast to training of Aerobic resistance, compare not only resistance training vs. resistance plus resistance, but also the intensities and whether they were intervals or continuous; However, at the end of the study, more resources are needed to ascertain the optimal intensities and whether the exercise should be continuous or at intervals [7].

Increasing findings related to physical exercise in COPD patients, a consensus fully supports the role of rehabilitation and finds interesting results, showing that in the walk test, they found significant improvements, but in respiratory muscle training, they did not find significant improvements between the the experimental group and the control group also highlight improvements in exercise capacity and less dyspnea in the experimental groups, and conclude that in addition to these improvements, patients benefit from programs that include lower limbs [8].

However, the mechanisms by which exercise, especially in lower limbs, increase resistance, are still unknown, but it shows that this increases the aerobic capacity of muscles, and also shares the theory that it increases the number of mitochondria in The fibers of type 1 and increases the concentration of aerobic enzymes [9]. Clarifying this improvement of muscular endurance relates to the integrity of the muscular functions of aerobic energy production and its functional integration with the muscle contractile apparatus, which explains the improvement of endurance and exercise tolerance associated with Muscle training in COPD patients leading to decreased fatigue [2] and it is exposed as the ventilatory response reflected in ventilation and lactic acid levels decrease, when patients are performing similar submaximal work after training at high intensities, the metabolism may be subject to modification by training in these Patients [10].

Among the effects that were found from the study, it is observed that although the VO_2 did not have a significant effect, there is a significant improvement in the distance of six minutes which was significant and there was no difference found between the improvement of This variable with the type of training, however it is noteworthy that this reflects that patients after the training period, improved the capacity to exercise.

The above result is intimately related by statements in recent publications where it is stated that the discomfort perceived by patients at the time of physical activity is related to muscle fatigue and for this reason they stop exercising and that this fatigue tends to improve significantly after including patients in a muscle training program, which explains why, although it does not improve its VO_2 condition, the distance of six minutes improves through muscle training, producing less fatigue [2]. This finding is contrary to that found by other investigators who found significant differences in the 6-minute walk only in the resistance training group [11].

In the case of the negative effect reflected in VO_2, an explanation can be found that in patients with COPD, oxidative capacity and oxidative enzymes are diminished, clearly becoming an influential factor to the detriment of VO_2 [12].

For its part, while it is true the VO_2 is the physiological capacity. However, although the effect is not significant between the types of exercise, when analyzing the moderating variables for this variable, it is found that there is a significant relationship with age but inversely, being that the older the effect of the training on the LV, another of the moderating variables that could affect are the weeks of treatment, in which it was found that the greater the duration of the program, the greater the effects of training, besides another variable that produces an affectation but in an inverse way, it is the number of sessions, that is, the greater the number of sessions, the lower the VE, the peripheral myopathy in COPD, shows a predominance of anaerobic metabolism in the muscle, involving more weeks of training, and more sessions We can reverse the detraining [4], and it is observed in studies that showed age ranges of the subjects less than the other studies and a response Significant in VE [11,13].

And in the relation of age to respiratory rate, we find its explanation that with aging, vital capacity, and expiratory volume decrease as age increases, this happens in turn, due to the loss of elasticity of lung tissue and the chest wall. On the other hand, with respect to the area of the body that was trained, neither a significant difference in the effect that was produced on the variable of VE was found, it is totally expected that as well as this chain of physiological improvements that are comparable with studies [14-17], in the same way the HR variable, also presented a compensation, in which it showed that when intervening to COPD patients with physical exercise a significant effect of decrease occurs, reflecting that it is independent of the type of training or Area of the body that was trained, where there were no differences when the comparison was made. This significant decrease in HR is reproducible with what is found in another article [18], while in its study it demonstrates a significant reduction in HR.

As for the results found in the significant decrease in HR, it is important to note that three variables were found to be affected, so that it can be affirmed that the older the lower the effect of training on the heart rate, It is reported that as the age increases, the systolic volume and the cardiac output decrease therefore a decrease of the HR can be given, which would explain a smaller effect on the HR by the physical training and with respect to the weeks of treatment It was observed that the greater the number of weeks of treatment with physical exercise, the greater the effect on the HR [19]. On the other hand, in what corresponds to the number of sessions, it is inversely related to a greater number of sessions, the lower the HR, when the training is 2 to 3 sessions per week but only for 4 weeks, the results a physiological levels are lower, unlike the 7-week programs [9].

With the improvement of the physiological variables such as VE, RR, HR and functional capacity to perform exercise translated by the 6-minute walk, it is evident that an improvement in measures related to quality of life was found.

Quality of life is a component that in several studies of the reviewed, it is shared that improvement is achieved [15] and concludes that exercise capacity, dyspnea to a lesser extent and quality of life improved after the rehabilitation program that They applied as a treatment to their patients and found significant differences after completing the rehabilitation program, also in another review [20] found significant differences, although they indicate that these can improve even more when the treatment is with combined exercise, these results do not Are reproducible in the results found in this study, because only a significant difference was found when applying treatment with physical exercise in the emotion variable, this improvement being positive for the patients, but not for the dyspnea and fatigue variables, in The case of dyspnea did not produce a significant effect, and in the case of fatigue, A significant effect but this was augmentation, which is undesirable in patients with COPD.

These variables that are strongly related to the quality of life of this patient population may not have been improved due to external factors that contaminated the results. For example, in the case of dyspnea, it is explained that it would be influenced by age, given that the greater the age of dyspnea, [18] with increasing age, HR max, systolic volume, and oxygen venous arteriovenous difference decrease and There is a loss of elasticity of the lung tissue and the rib cage, and as a result the dyspnea tends to increase and in the same way happens with the moderating variables of BMI and the frequency of sessions. In this regard, it was found that a higher BMI is greater dyspnea, this result contrasts with the results presented [2], which clarifies that low BMI is related to a high mortality and physical decomposition in the COPD patient and the last variable, at a higher frequency of greater session is the effect on dyspnea, it is affirmed that a minimum of 20 sessions and 3 times per week is necessary for beneficial physiological results [9].

In the case of fatigue only a statistically significant relationship was found and it was with the weeks of treatment and this relation was inverse. That is to say, the fewer weeks of treatment, the greater the effect on fatigue. This could be explained by accumulated tiredness in patients, interval training should be initiated to promote high intensity progressively, since there are patients who are more symptomatic and have greater fatigue [9].

And in the case of the emotion and the 6-minute walk there was no significant relationship that could suggest an affectation of part of the moderating variables, another study [15] found improvements at the 6-minute walking level and In quality of life, however, their subjects were at an optimal nutritional level (reflected by a body mass index of 24.5%). Other authors [14] found significant improvements in quality of life and walk of six minutes, but also their research subjects were at an optimal nutritional level, and the weeks of duration were 3 months and 6 weeks respectively, however [2,4] is exposed, that the better the muscle recruitment, the better the oxidative response, and therefore both variables would be influenced by presenting the patient physiological improvements and a better oxidative capacity in the muscle, the activity of the enzymes Oxidative, and acidosis is delayed, reducing patient fatigue and improving their functional capacity for physical exercise and activities in daily life.

Conclusion

It can be established after meta-analysis of nine studies (with a total of 351 subjects), that physical exercise produces positive effects on physiological variables such as HR, VE, FR, and on psycho-affective variables indicative of quality of life such as emotion and fatigue, while improving results in the 6-minute walk tests, but not in variables such as VO_2 and dyspnea in which it did not reflect a significant effect [21].

The significant effect was reflected in the analysis of the overall effect sizes in the subjects who were given physical exercise, as a treatment for their disease; however the results obtained were mostly with a large heterogeneity which warranted that tests were performed at moderating variables.

When comparing exercise programs, against resistance, aerobic and combined resistance, it was found that there is no significant difference between the different training modalities; however, it was possible to determine an effect caused by the type of training in each of the variables, in The case of the variable VO_2 only the combined training achieved a different effect although this was not an improvement, in the case of the Ve, the combined training was the one that obtained a greater effect of decrease of this variable, in the CF there was a Greater effect in those treatments with exercises against resistance. In the case of dyspnea, no type of training achieved a desired effect in the patients, and finally in the 6-minute walk variable all types of training were able to improve the results of this variable, the variables of fatigue and FR Could be compared.

Regarding the trained body area, whether it was only lower limbs, or combining lower and upper limbs, a significant difference was not found, however the combination had larger effect sizes in the variables of VE, emotion, and six-minute walk, while Training only in lower limbs, achieved a larger effect size, only in HR and in the 6-minute walk the effect size with both modalities was approximately the same. Variables such as VO_2, dyspnea and fatigue did not achieve a desired effect with any of the two modalities corresponding to the trained body area.

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