MECHANISMS BY WHICH EXERCISE TRAINING BENEFITS PATIENTS WITH COPD MECANISMOS PELO QUAL O TREINAMENTO DE EXERCÍCIO BENEFICIA PACIENTES COM DPOC RUNNING TITLE: EXERCISE TRAINING

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GALLO-SILVA, B.; KEL-SOUZA, L. D. Mechanisms by which exercise training benefits patients with COPD mecanismos pelo qual o treinamento de exercício beneficia pacientes com DPOC running title: exercise training. **Arquivos de Ciências da Saúde da UNIPAR**. Umuarama. v. 26, n. 3, p. 1343-1359, set./dez. 2022.

ABSTRACT: The clinical consequences of chronic obstructive pulmonary disease (COPD) include fatigue, dyspnea and progressive impairment of exercise capacity. It also produces significant systemic consequences such as nutritional depletion, physical deconditioning, systemic inflammation, and structural and functional changes in the respiratory and locomotor muscles. Regular exercise provides improvements in the health of patients with stable COPD and can relieve the symptoms, increasing the exercise capacity and improving the quality of life, while also reducing hospitalization and, to some extent, the risk of morbidity and mortality. Training with progressive exercises is associated with metabolic and neurohumoral adaptations, heart rate variability, with adaptations in the pulmonary and skeletal muscles, as well as the inflammatory, cardiovascular and respiratory systems. This review will focus on current knowledge of the mechanisms by which physical training can provide beneficial effects in COPD patients. Results: After analyzing the titles, abstracts and content, out of 500 articles found, 489 were excluded, leaving 11 articles. Studies have shown the beneficial effect of aerobic training on COPD. Conclusion: Physical training should be considered a therapeutic option in patients with COPD, regardless of being terrestrial or aquatic, as it can have beneficial effects on the systems.
KEYWORD: COPD; exercise training.

MECANISMOS PELOS QUAIS O TREINAMENTO DE EXERCÍCIO BENEFICIA PACIENTES COM O TÍTULO DPOC RUNNING: TREINAMENTO DE EXERCÍCIO

RESUMO: As consequências clínicas da doença pulmonar obstrutiva crônica (DPOC) são: fadiga, dispnéia e comprometimento progressivo da capacidade do exercício, além disso, também produz consequências sistêmicas significativas como depleção nutricional, descondicionamento físico, inflamação sistêmica, mudanças estruturais e funcionais de músculos respiratórios e locomotores. O treinamento físico regular traz como benefícios efeitos da melhoria da saúde em pacientes com DPOC estável e pode aliviar os sintomas, melhorar a capacidade de exercício e a qualidade de vida, reduzir a hospitalização e, em certa medida, o risco de morbi-mortalidade. Já o treinamento com exercícios progressivos está associado a adaptações metabólicas, neurohumorais, variabilidade da frequência cardíaca, inflamatórias, dos músculos pulmonares e esqueléticos, cardiovasculares e respiratórias. Esta revisão enfocará o conhecimento atual dos mecanismos pelos quais o treinamento físico pode ter efeitos benéficos em pacientes com DPOC. Resultados: Após análise dos títulos, resumos e conteúdo, dos 500 artigos encontrados, 489 foram excluídos, restando 11 artigos. Estudos têm demonstrado o efeito benéfico do treinamento aeróbico na DPOC. Conclusão: O treinamento físico deve ser considerado uma opção terapêutica em pacientes com DPOC, independente de ser terrestre

DOI: 10.25110/arqsaude.v26i3.20228989
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ou aquático, pois pode ter efeitos benéficos nos sistemas.
PALAVRAS-CHAVE: DPOC; treinamento de exercício.

MECANISMOS POR LOS QUE EL ENTRENAMIENTO DE EJERCICIO BENEFICIA A LOS PACIENTES CON EPOC MECANISMOS POR LOS QUE EL ENTRENAMIENTO DE EJERCICIO BENEFICIA A LOS PACIENTES CON EPOC RUNNING TITLE: EXERCISE TRAINING

RESUMEN: Las consecuencias clínicas de la enfermedad pulmonar obstructiva crónica (EPOC) incluyen fatiga, disnea y deterioro progresivo de la capacidad de ejercicio. También produce importantes consecuencias sistémicas como el agotamiento nutricional, el desacondicionamiento físico, la inflamación sistémica y los cambios estructurales y funcionales en los músculos respiratorios y locomotores. El ejercicio regular proporciona mejoras en la salud de los pacientes con EPOC estable y puede aliviar los síntomas, aumentando la capacidad de ejercicio y mejorando la calidad de vida, al tiempo que reduce la hospitalización y, en cierta medida, el riesgo de morbilidad y mortalidad. El entrenamiento con ejercicios progresivos se asocia a adaptaciones metabólicas y neurohumorales, a la variabilidad de la frecuencia cardíaca, con adaptaciones en los músculos pulmonares y esqueléticos, así como en los sistemas inflamatorio, cardiovascular y respiratorio. Esta revisión se centrará en el conocimiento actual de los mecanismos por los que el entrenamiento físico puede proporcionar efectos beneficiosos en los pacientes con EPOC. Resultados: Tras analizar los títulos, resúmenes y contenido, de los 500 artículos encontrados se excluyeron 489, quedando 11 artículos. Los estudios han demostrado el efecto beneficioso del entrenamiento aeróbico en la EPOC. Conclusiones: El entrenamiento físico debe considerarse una opción terapéutica en pacientes con EPOC, independientemente de que sea terrestre o acuático, ya que puede tener efectos beneficiosos sobre los sistemas.
PALABRAS CLAVE: EPOC; entrenamiento con ejercicios.

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1. INTRODUCTION

The incidence and prevalence of chronic obstructive pulmonary disease (COPD) has increased (GOLD, 2018). According to GOLD (GOLD, 2018), COPD can be defined as a preventable and treatable disease characterized by the presence of chronic airflow obstruction, which is not fully reversible, is progressive and is associated with an abnormal inflammatory response of the lungs to particle inhalation or Toxic gases, primarily caused by smoking, in brief it is the association of chronic bronchitis and pulmonary emphysema. The most common is breathlessness under physical exertion, with others including cough, wheezing, secretion production and recurrent respiratory infections (DOURADO *et al*., 2006). In addition, it also has significant systemic consequences (BARNES; CELLI, 2009).

Exercise therapy has increased the survival of COPD patients (GARVEY *et* al., 2016). The functional capacity of the exercise is used to verify the patient's response to the treatment (HERNANDES *et* al., 2011). Exercise intolerance in patients with COPD is classically attributed to ventilatory limitations, however, skeletal muscle dysfunction is a common manifestation in these patients (RABINOVICH; VILARO, 2010).

Decreased exercise capacity negatively affects the individual's ability to adequately perform activities necessary for normal daily life (SIEVI *et al*., 2018) and quality of life (HAVLUCU *et* al., 2019). In patients with stable COPD, physical training can relieve symptoms, increase the exercise capacity and improve the quality of life (GARVEY *et* al., 2016). Based on the above, this review will discuss the knowledge of the mechanisms by which physical training relieves symptoms in COPD patients.

2. NEUROHUMORAL EFFECTS OF EXERCISE

Neurohumoral activation is present in COPD and may provide a link between pulmonary and systemic effects, especially regarding cardiovascular disease (HAARMAN *et* al., 2015). Persistent neurohumoral excitement results in the deterioration of myocardial function (FERRARA *et* al., 2002). Patients with COPD exhibit sympathetic hyperactivity and reduced parasympathetic activity (GESTEL; KOHLER; CLARENBACH, 2012), presenting reduced heart rate variability (CALISKAN; POLATTI; BILGIN, 2018), with elevated levels of circulating catecholamine (PEPPER; LEE, 1999). SAKAMAKI *et al* .,1999 investigated the plasma noradrenalin concentration in the COPD patients was significantly higher than in the control subjects. Furthermore, COPD patients present decreased baroreflex sensitivity, as studied by COSTES *et al*., 2004, in this study, the baroreflex sensitivity was found to be significantly lower in the COPD patients.

Physical training can reduce sympathetic arousal for peripheral and central effects. Physical training is associated with improved autonomic dysfunction (ZUPANIC *et* al., 2014).

Different physical training protocols are associated with reduced sympathetic activity and increased parasympathetic activity, as demonstrated by BORGHI-SILVA *et al*., 2009, who studied heart rate variability before and after physical training in 40 patients with COPD, the training group and control group, for a period of 6 weeks. It was found that there was a positive change in the neural control of the heart rate. This is in agreement with CAMILLO *et al*., 2011, who evaluated 40 patients with COPD randomized into two groups, high- or low-intensity exercise groups. It was found that the high-intensity exercise training improved heart rate variability at rest and during orthostatic stimulation in COPD patients. In the aquatic environment, GALLO-SILVA *et al*., 2019 investigated the effects of aerobic aquatic interval training on heart rate variability in 19 patients randomized into aquatic training and control groups. It was found that aquatic training promoted beneficial adaptations in cardiac autonomic modulation, with significant changes in heart rate variability, observed through increased parasympathetic modulation. An interesting feature of aerobic exercise training performed in an aquatic environment is the physical properties of water and the physiological characteristics and effects of immersion, which should be considered as plausible mechanisms for improving heart rate variability, as hydrostatic pressure increases peripheral blood flow and stimulates parasympathetic activity, promoting increased venous return as a result of baroreflex control (GABRIELSEN *et* al., 2000).

3. ENDOTHELIAL EFFECTS OF EXERCISE

Endothelium-dependent vasodilation, a clinical marker of endothelial function, is decreased in patients with COPD (KEYMEL *et* al., 2018). Several studies have shown that COPD causes endothelial dysfunction. EICKHOFF *et al*., 2008 evaluated endothelial function in 60 COPD patients. Patients with COPD showed significantly lower endothelial function.

Regular exercise improves endothelium-dependent vasodilation and decreases vascular injury (NAPOLI *et* al., 2006). Evidence suggests that improved endothelial function and neoangiogenesis may be related mechanisms by which physical training can exert its beneficial effects regarding COPD (SZUCS; PETREKANITS; VARGAS, 2018). In addition, physical training promotes increased nitric oxide (NO) synthesis, increased levels of nitric oxide synthase enzyme (eNOS), superoxide dismutase (SOD) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, increased endothelial progenitor cells and decreased NO inactivation, increasing endothelial function (NEGRAO; BARRETO, 2010).

Decreased production of reactive oxygen species (ROSs) should also be considered. Aerobic training decreases the expression of subunits of NADPH oxidase (gp91phox and p22phox) (ADAMS *et* al., 2005), an enzyme corresponding to the elementary source that generates these reactive species in the blood vessels (CAI; GRIENDLING; HARRISON, 2003).

4. ANTI-INFLAMMATORY EFFECTS OF EXERCISE

The increased inflammatory response has been recognized as an important factor in the pathophysiology of COPD, which is associated with chronic airway inflammation, which increases further during exacerbations and is also associated with systemic inflammation that has been linked to a 2 to 4-fold increased risk in cardiovascular disease (BARNES, 2016).

Physical training may have an anti-inflammatory effect in COPD patients. SILVA *et al*., 2018, studied the metabolic and inflammatory responses to resistance of different COPD training, 3 groups were randomized, the elastic group, elastic tube group and weight training group, with inflammatory markes levels being evaluated. After 12 weeks of training, acute exercise response showed improved inflammation compared to the baseline. Regarding chronic effects, a decrease in all cytokines except IL-10 was observed. EL-KADER; JIIFRI; 2016 analyzed the response of plasma inflammatory biomarkers to aerobic versus resistance exercise training in COPD patients, with 100, one group with 12 weeks of resistance training and the other with the same amount of aerobic training. The TNF-α, IL-2, IL-4, IL-6 and C-reactive protein were evaluated. It was found that after 12 weeks of training the mean values of the above mentioned biomarkers were significantly reduced in both groups, in addition, there was a significant reduction in the intergroup comparison. Physical training increases plasma levels of anti-inflammatory cytokines (NUNES *et* al., 2008) and can modulate the innate immune system, influencing macrophage and lymphocyte function (BATISTA *et* al., 2008).

5. EFFECTS OF EXERCISE ON SKELETAL MUSCLE

Skeletal muscle dysfunction is a common manifestation in COPD patients, characterized by reduced muscle strength and endurance, contributing to limited functional capacity and reduced quality of life (DOURADO *et* al., 2006; BARNES; CELLI, 2009; RABINOVICH; VILARO, 2010). In addition, skeletal muscle dysfunction is associated with early activation of anaerobic glycolysis, lactic acidosis, and premature onset of muscle fatigue during exercise[33].

The plausible pathophysiological mechanisms that trigger skeletal muscle dysfunction are multifactorial, including nutritional abnormalities, protein synthesis/degradation, tissue hypoxia and hypercapnia, corticosteroid use, physical inactivity (muscle disuse), oxidative stress, systemic inflammation, abnormalities. mitochondrial disorders, ventilatory limitation and functional, morphological and biochemical abnormalities of the peripheral muscles (DOURADO *et* al., 2006; BARNES; CELLI, 2009; RABINOVICH; VILARO, 2010; MCINTYRE, 2006). Elevated levels of C-reactive protein in COPD patients are associated with reduced strength and lean mass of the quadriceps (REMELS *et* al., 2007).

Physical exercise plays a fundamental role in reducing ventilatory demand, dyspnea and dynamic hyperinflation, reflecting in the improvement of the locomotor muscles, and providing balance in the oxygen supply between the respiratory and locomotor muscles, thus avoiding tissue ischemia. When this oxygen supply is sufficient for the locomotor muscles, it is possible to proportionally increase the intensity of the exercises (ALIVERT; MACKLEM, 2008; DEBIGARE; MALTAIS, 2008; AMANN *et* al., 2010).

Exercise training also provides increased stimulation of the production of mitochondrial oxidative enzymes, increased capillarization of the trained muscles (BROMANN *et* al., 2006), increased VO2 peak and anaerobic threshold, reduced lactic acid production during exercise, normalization of creatine phosphate decline, and decreased creatine phosphate recovery time and oxidative stress (ALCAZAR *et* al., 2019).

Additionally, exercise training promotes morphological changes such as the transformation of fatigable fast-twitch type II muscle fibers to fatigue-resistant slow-twitch type I fibers (DOURADO *et* al., 2006; MAN *et* al., 2009). Another point to consider about interval exercise training is the increase in the muscle cross-sectional area in COPD patients (VOGIATZIS *et al* ., 2005).

ALCAZAR *et al*., 2019 studied the effects of physical training on muscle dysfunction and systemic oxidative stress in older adults with COPD. A total of 20 outpatients with COPD were randomly assigned to a 12-week training exercise program. The cross-sectional area of the thigh muscle and systemic oxidative stress were evaluated. It was found that in the training group there was a 4% increase in the cross-sectional area of the thigh muscle and a 27% reduction in oxidative stress.

In the aquatic environment, FELCAR *et al*., 2018 studied the comparison of the effects of two similar protocols of six-month high-intensity physical training in water and on land in COPD patients. A total of 36 patients were randomized in to the land group or water group. Peripheral muscle strength and the maximal and submaximal exercise capacity were evaluated. Statistically significant improvements in peripheral muscle strength and exercise capacity were found in both groups.

6. RESPIRATORY EFFECTS OF EXERCISE

Physical training can also have beneficial effects on respiratory performance in COPD patients. In COPD, the loss of the pulmonary elastic capacity and progressive expiratory limitation promote air trapping, consequently increasing the functional residual capacity and decreasing the inspiratory capacity. Static hyperinflation and its increase during exercise (dynamic hyperinflation) are associated with exercise limitations in COPD patients (O'DONELL; REVILL; WEBB, 2001; MARIN *et al* ., 2001). In addition, COPD patients present exertional dyspnea and, according to GIGLIOTTI *et al*., 2003, exercise training contributes to the relief of this symptom, although according to BARREIRO *et al*., 2015 it does not promote changes in pulmonary function parameters.

In COPD patients there is also a reduction in the maximum inspiratory and expiratory pressures of the respiratory muscles (GEA; AUGUSTI; ROCA, 2013; POLKEY *et al* ., 1996).

According to O'DONELL *et al*., 1998 the strength of the expiratory muscles increases in parallel to the inspiratory musculature. Although the expiratory muscles use a smaller fragment of their maximum capacity to produce strength relative to the inspiratory muscles, the effect of the exercise suggests that repetitive expiratory muscle activity during exercise may increase the strength of these muscles after a period of training.

In the aquatic environment, ARAUJO *et al*., 2012 investigated the efficacy of low intensity aquatic exercise in COPD patients, with 42 individuals with COPD being divided into three groups, control, land and water. Spirometry, respiratory muscle strength, exercise capacity and quality of life were evaluated. The authors found significant improvements in FEV1 for both the land and water intervention groups. They also observed statistically significant differences for maximal respiratory pressures (inspiratory and expiratory) in the intragroup assessment.

7. TYPES OF EXERCISE TRAINING

The majority of the evidence for the benefits of physical training in COPD patients is with stable patients regardless of the disease stage, i.e. GOLD I/II/III/IV, with physical training now being generally accepted as safe in these patients (GOLD, 2018; GARVEY *et* al., 2016). In studies of patients with stable COPD, the exercise intervention varies in mode, intensity and duration. The type and intensity of the physical training may determine the level of benefit, with strength and endurance training and moderate continuous training appearing to be less effective than high intensity interval training (GARVEY *et* al., 2016).

Current guidelines for physical training in COPD patients recognize the benefits of aerobic training, however, the precise protocol must be individually tailored to the patient’s clinical and functional status. Aerobic training can be performed at high or low intensity. The recommended exercise intensity is 30% to 80% peak work rate, with high intensity training of at least 60% to 80% peak work rate being associated with improved aerobic fitness, endurance, ventilation and submaximal work rate. Options for progression include titration for a subjective perception level of selected exertion or dyspnea intensity (GARVEY *et* al., 2016; CASABURI *et al*., 1997).

According to the American College of Sports Medicine (ACSM, 2013) the duration is usually longer than 30 minutes based on the severity of the COPD. Four to twelve weeks are recommended, with at least eight weeks to promote clinically important physiological changes (GARVEY *et* al., 2016).

Typical modes of aerobic exercise are walking or cycling (GARVEY *et* al., 2016). Currently another way to perform aerobic exercise is in the aquatic environment, which combines hydrostatic pressure to promote physiological effects during training of both high/moderate and low intensity aerobic exercises (GALLO-SILVA *et al*., 2019; FELCAR *et al*., 2018; ARAUJO *et al*., 2012; WADELL *et al*., 2004). Patients with COPD present increased functional residual capacity and residual volume due to pulmonary pathological changes. This increases breathing work, contributing to increased dyspnea. During immersion, these respiratory variables decrease, causing a decrease in the sensation of dyspnea, and facilitating the performance of physical exercises in the aquatic environment (WADELL *et al*., 2004).

Endurance training is another option, as its goals are to condition the walking muscles and improve cardiorespiratory function. High intensity exercise at more than 60% of peak work rate in an incremental test, performed for 20 to 60 minutes, is required to achieve these goals (GARVEY *et* al., 2016). The training intensity can also be titrated according to the Borg dyspnea scores (4-6, moderate to very severe) or subjective exertion perception scale (12-14 of 20) (HOROWITZ; LITTENBERG; MAHLER, 1996). A frequency of 3 to 5 sessions per week is recommended and walking is considered the best training modality (ACSM, 2013). Interval training is proposed as an alternative to continuous training, especially for individuals who are unable to tolerate high intensity continuous endurance training due to their symptoms. Interval and continuous training results are no different when the same total work is performed (BEAUCHAMP *et al*., 2010).

Resistance training does not have specific guidelines for this type of training for COPD patients. The recommended format for resistance training exercises includes the use of resistance equal to 40% to 50% of 1-repetition maximum (1RM) for 1 to 4 sets with 10 to 15 repetitions per set on ≥2 days per week. Some patients may be able to progress to moderate intensity resistance training using 60% to 70% of 1RM. Resistance exercises should involve the large muscle groups (GARVEY *et* al., 2016).

8. METHOD

Literature review performed in five electronic databases: PubMed/Medline, Lilacs, PEDro, SciELO and Cochrane library, using the descriptors "COPD" and "exercise training", in English, Spanish and Portuguese.

To select the article, the databases were accessed by a researcher, who performed a selection of articles related to the research topic. A later selection was made by another researcher, based on the inclusion and exclusion criteria pre-established. Studies that met the inclusion criteria were then selected.

The following were excluded: letters to the editor, editorials, comments, presentations poster and oral, literature reviews. Included were trials controlled (randomized or quasi-randomized) and observational studies (cohort, case-control, and case reports) that addressed aerobic training in COPD patients.

9. RESULTS

After excluding the articles, analysis of titles, abstracts and content. Of the 500 articles screened, only 11 were included in this literature review (Figure 1).

Figure 1: Flowchart describing the study selection process.

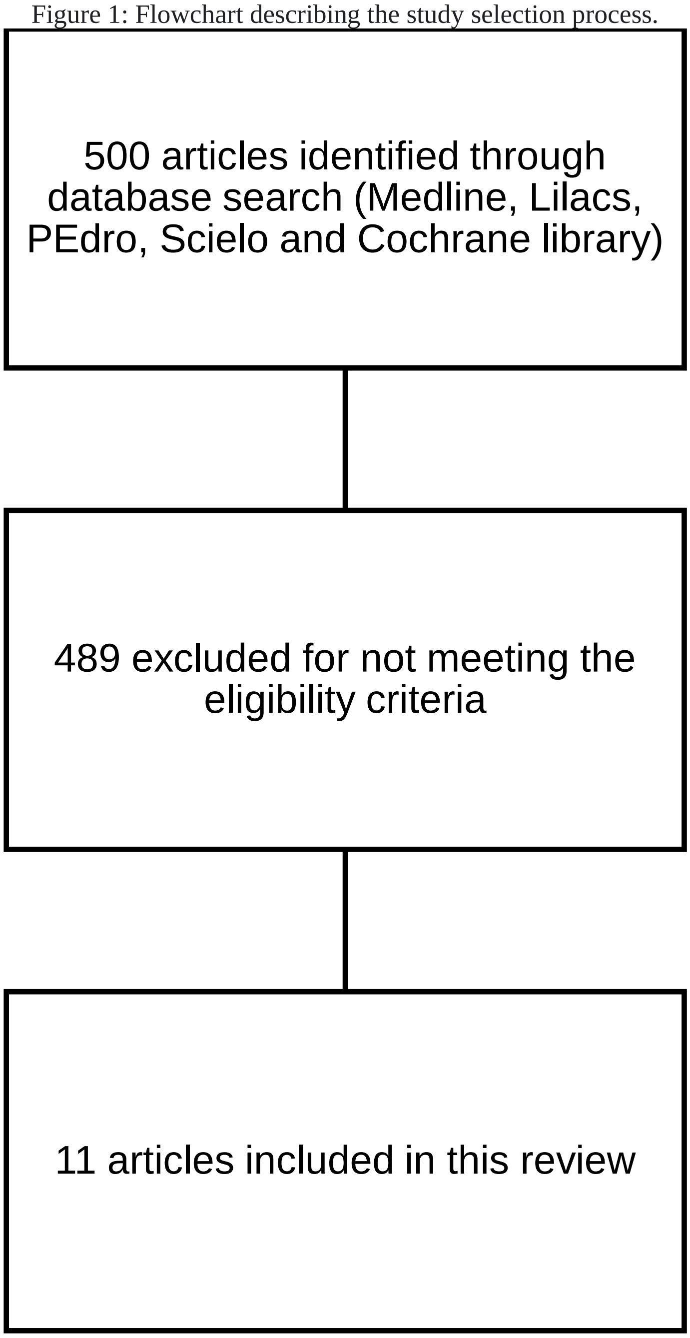

Table 1: Main randomized controlled trials related to physical training in COPD.

Study	Number of COPD patients	Study design	Intervention
(VOGIATIZIS et al., 2002)	36	Randomized clinical trial	Continuous training at 50% of peak work rate from baseline or interval training at 100% peak work rate alternating with 30 seconds rest.
(WADELL et al., 2004)	30	Randomized clinical trial	Aerobic endurance exercise in water or on land for 45 min. For 12 weeks, three times a week.
(MARQUIS et al., 2008)	21	Randomized clinical trial	Aerobic exercise with cycle ergometer, for 30 minutes, three times a week.
(PROBST et al., 2011)	40	Randomized clinical trial	Endurance and strength training or training in breathing and calisthenic exercises. For 12 weeks, three times a week.
(CHENG et al., 2014)	64	Prospective	Aerobic exercise on the cycle ergometer consisting of warm-up (4 min), 60-100% of peak VO2 (40 min) and cool-down (4 min), for 12 weeks, twice a week.
(BORGHI-SILVA et al., 2015)	20	Prospective randomized clinical trial	Aerobic exercise on the treadmill at 70% of the peak rate of cardiopulmonary exercise test for 30 minutes. Performed three times a week for a period of 6 and 12 weeks.
(WADA et al., 2016)	30	Randomized clinical trial	Aerobic treadmill exercise at 60% and reaching 85% of the mean speed attained in the 6-min walk test, associated with respiratory muscle training. Over a 12 week period, twice a week.
(YAZDANI et al., 2018)	22	Randomized clinical trial	Aerobic exercise performed on bikes and treadmills, carried out over eight weeks, three 30-40 minute sessions.
(VARAS et al., 2018)	33	Randomized clinical trial	Aerobic exercise through walking, performed over eight weeks, five times a week, lasting 30-60 minutes.
(WU et al., 2018)	45	Randomized clinical trial	Aerobic exercise through water and land-based Liuzijue exercises, performed over three months, twice a week for 60 minutes.
(ROOS et al., 2018)	52	Randomized clinical trial	Aerobic exercise on treadmill (10min), bicycle (10min) and extremity resistance exercises. For 10 weeks, twice a week for 1 hour.

10. DISCUSSION

This study has shown that physical training programs are widely recommended as part of treatment of patients with COPD, both on the land and in water, being capable of producing representative physiological changes on the neural-humoral activation, endothelial vasodilation, inflammatory response in the skeletal muscle and in respiratory pattern. In this way, it is relevant that sedentarism associated with autonomic control disorders are related with the development of arrhythmia and sudden death (PANTONI *et al*., 2007). Patients with COPD exhibit sympathetic hyperactivity (GESTEL; KOHLER; CLARENBACH, 2012), presenting reduced heart rate variability (CALISKAN; POLATTI; BILGIN, 2018) and, in this investigation, it was observed that physical training both on the land and in water promote an increase in vagal tone, which improves survival, decreases the amount of work and oxygen consumed by the heart, through the decrease of heart rate and contractibility of the myocardium at rest, reducing the susceptibility of lethal arrhythmias. Training with exercises improves the endothelial function and nitric oxide, since nitric oxide increases the vagal tone and indirectly inhibits the sympathetic influence (CRIMI, *et al*. 2009).

Physical training performed preventively or as adjuvant therapy improves sympathovagal balance, expressed by increased heart rate variability (ZUPANIC et al., 2014; BORGHI-SILVA et al., 2009; CAMILLO et al., 2011; GALLO-SILVA et al., 2019),

There is a correlation indicating an association between the heart rate variability indexes at rest with aerobic physiological variables. Indexes that express the vagal modulation action (RMSSD, SD1, and HF), as well as those representing global modulation (SDNN, LF, and SD2) are correlated with the velocity corresponding to VO2peak, with the vagal values being interlinked with a physiological transition threshold indicator. In summary, patients with COPD, with higher vagal component values at rest tend to reach higher exercise intensities (LEITE, *et al.* 2015).

In an aquatic environment, there are the physical properties of water and the physiological characteristics and effects of immersion, which should be considered as mechanisms for improving heart rate variability, since the hydrostatic pressure increases peripheral blood flow and stimulates parasympathetic activity, promoting increased venous return as a result of baroreflex control (GABRIELSEN *et* al., 2000).

Furthermore, the reduction of the distance of the six-minute walk test is related with the mortality and reduction of quality of life in patients with COPD (DOURADO *et al*., 2004; CELLI, 2010). It can also be noted that the 6MWT, as well as a mortality predictor, is also used as a tool for prescribing exercises in patients with COPD, providing both precision and reliability. In the absence of maximum tests, the 6MWT can be a tool for prescribing high-intensity exercises, improving the capacity of exercises in the same magnitude (RODRIGUES *et al.,* 2016). Patients with COPD present a reduction in the quality of life demonstrated by SGRQ, and there is a relationship between the iR-R and SGRQ. A reduced quality of life is related with the reduction of iR-R, indicating that a higher cardiac rate is related to a worsening of the quality of life in patients with COPD. Moreover, it is known that patients with COPD present elevated levels of anxiety, which in turn is translated in a decreased quality of life, resulting in an increase in the heart rate (CAMILLO *et al.,* 2008).

The blood flow in the skeletal muscle is regulated to correspond to the demand for oxygen, and its deregulation contributes to the intolerance to exercise in patients with COPD (IEPSEN *et al.,* 2017). The vascular function can be negatively affected in COPD (MACLAY; MCNEE, 2013). The response of the blood flow of lower limbs to the muscular mass exercise is negatively affected in COPD, observing that the endotelin-1 vasoconstrictor is increased in plasma, and the interstitial formation of the prostacyclin vasodilator was reduced during the exercise, while the formation of nitric oxide in plasma and in the muscular interstice remained intact. Therefore, the disbalance between locally formed vasoconstrictors and vasodilators explain the blood flow observed in lower limbs in patients with COPD (IEPSEN *et al.,* 2017). Exercise training improves endothelium-dependent vasodilation and decreases vascular injury (NAPOLI et al., 2006), increases plasma levels of anti-inflammatory cytokines (NUNES *et al*., 2008), provides increased stimulation of the production of mitochondrial oxidative enzymes, increases capillarization of the trained muscles (BROMANN *et al*., 2006) and promotes increased strength of respiratory muscles (ARAUJO *et al*., 2012). With regard to the respiratory muscles, it is known that the gain in diaphragm strength improves the perfusion of the muscles of the lower limbs, through the metaboreflex mechanism (WITT *et al*., 2007). The strength of the expiratory muscles increases in parallel to the inspiratory musculature with exercise training (O'DONELL *et al*., 1998). In a study performed on the effect of the physical training on inflammatory cytokine, a greater expression of the TC4+ lymphocyte and in interleukin 13 (IL-13) could be verified after a training period (UZELOTTO *et al*., 2022), and IL-13 demonstrates it plays an important role in biogenesis and mitochondrial respiration, as well as in the increase in the resistance capacity, in the number of muscular oxidative fibers and glucose tolerance in resistive training (KNUDSEN *et al.*, 2020).

As mentioned above, the exercise training, whether resistive, aerobic, on the land or aquatic, promotes benefic effects in all the systems in patients with chronic obstructive pulmonary diseases (GOLD, 2018). Additionally, high-intensity training programs are associated with physiological improvement, including the increase in the exercise capacity and the decrease in the ventilatory demand during the effort (SPRUIT *et al.*, 2013).

Study limitations: this is a literature review, being limited to the results of original studies, being recommended to carry out original articles with the evaluation of each outcome highlighted in this review.

11. CONCLUSION

Exercise training should be considered a therapeutic choice in COPD patients, regardless of whether on land or in water, as it may have beneficial effects on neurohumoral and inflammatory responses, as well as skeletal muscle, endothelial function and respiratory function, leading to improvements in functional capacity and quality of life. All of these training-induced changes can effectively counteract the progression of the deleterious compensatory mechanisms of COPD. In the literature review demonstrated the beneficial effects of exercise for patients with COPD, being essential as a basis for clinical practice and for future studies.

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Recebido em: 04/11/2022
Aceito em: 05/12/2022