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Systematic review

Respiratory training improved ventilatory function and respiratory muscle strength in patients with multiple sclerosis and lateral amyotrophic sclerosis: systematic review and meta-analysis[☆]

Gustavo D. Ferreira^{a,b}, Ana Cecília C. Costa^b, Rodrigo D.M. Plentz^{b,c},
Christian C. Coronel^b, Graciele Sbruzzi^{b,d,*}

^a Universidade Federal de Pelotas, Brazil

^b Instituto de Cardiologia do Rio Grande do Sul, Brazil

^c Universidade Federal de Ciências da Saúde de Porto Alegre, Brazil

^d Universidade Federal do Rio Grande do Sul, Brazil

Abstract

Background Among neurodegenerative diseases, multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) have a high rate of respiratory disability.

Objectives To analyze the effects of respiratory muscle training (RMT) on ventilatory function, muscle strength and functional capacity in patients with MS or ALS.

Data sources A systematic review and meta-analysis of randomized controlled trials (RCTs) was performed. The sources were MEDLINE, PEDro, Cochrane CENTRAL, EMBASE, and LILACS, from inception to January 2015.

Study selection/eligibility criteria The following were included: RCTs of patients with neurodegenerative diseases (MS or lateral ALS) who used the intervention as RMT (inspiratory/expiratory), comparison with controls who had not received RMT full time or were receiving training without load, and evaluations of ventilatory function (forced vital capacity – FVC, forced expiratory volume in one second – FEV₁, maximum voluntary ventilation – MVV), respiratory muscle strength (maximal expiratory pressure/maximum inspiratory pressure – MEP/MIP) and functional capacity (6-minute walk test – 6MWT).

Results The review included nine papers, and a total of 194 patients. It was observed that RMT significantly increased at MIP (23.50 cmH₂O; 95% CI: 7.82 to 39.19), MEP (12.03 cmH₂O; 95% CI: 5.50 to 18.57) and FEV₁ (0.27 L; 95% CI: 0.12 to 0.42) compared to the control group, but did not differ in FVC (0.48 L; 95% CI: –0.15 to 1.10) and distance in 6MWT (17.95 m; 95% CI: –4.54 to 40.44).

Conclusion RMT can be an adjunctive therapy in the rehabilitation of neurodegenerative diseases improving ventilatory function and respiratory strength.

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Keywords: Multiple sclerosis; Amyotrophic lateral sclerosis; Breathing exercises; Systematic review; Meta-analysis

Introduction

Among neurodegenerative diseases, multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) have a high incidence and high rate of disability [1]. Although they have different causes, these diseases affect the skeletal muscles, including the respiratory ones [1]. MS is a demyelinating,

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* Correspondence: Physiotherapy Course, Universidade Federal do Rio Grande do Sul, Street Felizardo, 750, 90690-200 Porto Alegre, Brazil.
Tel.: +55 51 33085758.

E-mail address: graciele.sbruzzi@ufrgs.br (G. Sbruzzi).

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chronic, neurological disease with progressive degeneration in the nervous system. It is the second leading cause of disability in young adults [2,3]. ALS is also characterized by the degeneration of motor neurons, causing atrophy and loss of muscle mass with progressive difficulty in movements, including ventilatory ones [4,5].

The weakness of respiratory muscles, predominantly expiratory, is a characteristic of individuals with advanced neurodegenerative diseases and may result in pulmonary dysfunction, such as difficulty in clearing secretions, to repeated episodes of pneumonia, which is the main cause of death in this population [6,7]. Furthermore, the ventilatory function is diminished, leading to a restrictive feature [1], and possibly, these aspects also relate to lower functional capacity in this group of patients. Thus, training of respiratory muscles gives these patients a better quality of life [8–11].

In this way, physiotherapy appears to have an important role in multidisciplinary care of these patients. A well-structured exercise-training program may improve autonomic control, blood pressure, cardiorespiratory capacity and musculoskeletal function in patients with neurodegenerative diseases [3,12]. Additionally, physiotherapy also uses breathing exercise techniques to maintain adequate ventilatory function in people with impaired lung function, and to prevent pulmonary complications. Interventions with breathing exercises have already been reported as a possible benefit in neurological and cardiopulmonary diseases [13,14].

Studies linking respiratory muscle training (RMT) (inspiratory/expiratory muscle training – IMT/EMT) and neurodegenerative diseases are still scarce in the literature and have not confirmed the existing results, but offer hypotheses that RMT may be effective in increasing ventilatory muscle strength, decreasing pulmonary complications and hospitalizations in these patients [5,6,8]. Reyes *et al.* performed a systematic review of RMT in patients with MS and Parkinson's disease and concluded that there is evidence that training can improve respiratory muscle in patients with these disorders, but did not analyze the functional capacity of these patients [1]. Eidenberger *et al.* [15] and Martín-Valero *et al.* [16] reviewed RMT in ALS and MS, respectively, showing increased respiratory muscle strength in these populations, but they were not included under randomized controlled trials (RCTs).

Therefore, this systematic review aims to analyze the effects of RMT compared to controls, on ventilatory function, respiratory muscle strength and functional capacity in patients with neurodegenerative diseases such as MS and ALS.

Method

Design and search strategy

This systematic review was reported according to PRISMA Statement and the Cochrane Collaboration [17].

The search for papers was conducted in the following electronic databases: MEDLINE (PubMed), Cochrane Central Register of Controlled Trials (Cochrane CENTRAL), Physiotherapy Evidence Database (PEDro), EMBASE, LILACS and SciELO, from beginning of the bases until January 2015. The MeSH terms (“Multiple Sclerosis”; “Amyotrophic Lateral Sclerosis”; “Breathing Exercises”) and their synonyms were used, as well as a list of sensitive terms to search for RCTs. The search strategy used in PubMed may be observed in Appendix.

Eligibility criteria, intervention and participants

RCTs that evaluated RMT (EMT or IMT or a combination of both types) in patients with neurodegenerative diseases (MS and ALS) compared to control group, who did not receive RMT full time or were receiving training without load were included in the study. Exclusion criteria were those RCTs in which there was addition of another intervention to RMT and data of variables were not informed.

Outcome measures

Ventilatory function (forced vital capacity – FVC, forced expiratory volume in one second – FEV₁, maximum voluntary ventilation – MVV); respiratory muscle strength (maximal expiratory pressure – MEP and maximum inspiratory pressure–MIP); and functional capacity (6-minute walk test – 6MWT).

Study selection and data extraction

Two independent reviewers assessed the titles and abstracts of all articles identified by the search strategy. Abstracts that did not provide sufficient information were selected for evaluation of full texts. Then, the same reviewers independently assessed the full text to perform the selection according to pre-specified eligibility criteria. Data extraction was done using a standardized form by two reviewers independently. Extracted outcomes were related to lung function and functional capacity.

Assessment of risk of bias

The assessment of methodological quality was analyzed descriptively, according to the method proposed by the Cochrane Collaboration [17], considering the following characteristics of the studies including generation of the random sequence, concealed allocation, blinding of investigators (professional who administered the training), blinding of outcome assessors, intention to treat analysis, and description of losses and exclusions. Intention to treat analysis was considered as all randomized patients were analyzed at the end of the study.

Data analysis

The meta-analysis was performed using the random effects model. Effect size was calculated using the difference between the mean and the standard deviation of the difference between the mean, comparing the RMT and control group. Statistical heterogeneity was assessed using the Cochran's Q test and the inconsistency test (I^2), where values above 25% and 50% were considered indicative of moderate and high heterogeneity, respectively. An alpha value ≤ 0.05 and a confidence interval of 95% (95% CI) were considered statistically significant. All analyses used Review Manager 5.1 software. Sensitivity analyses were performed considering the characteristics of patients (MS or ALS) and intervention characteristics (IMT or EMT and intensity of training).

Results

Flow of studies

In the search strategy 41 papers were found, but seven were duplicates. After reviewing titles and abstracts, 15 papers were selected for full-text evaluation. Of these, nine papers were included in the systematic review and meta-analysis (Fig. S1).

Descriptions of studies

Table 1 shows the characteristics of the included studies. Six studies were performed with MS patients [6,18–22] vs. three studies with ALS [4,5,23]. Six studies performed IMT [4–6,19,20,23], two EMT [20,22] and one combination of both [24]. Furthermore, the MIP outcome was assessed in eight studies and MEP in seven. The FVC was evaluated in six papers, the FEV₁ in three and MVV in four. The distance walked in 6MWT was evaluated just in two studies.

Protocol characteristics and intensity of training are also described in Table 1. The reviewed papers covered training protocols that were carried out for 8 weeks to 3 months at a frequency of 7 days/week with 2 daily sessions consisting of 3 sets of 15 repetitions or 10 minutes at an intensity of 30 to 40 or 60% of the subject's maximum pressure. The utilization of three sets has duration of a few minutes and we considered it equivalent to the training for 10 minutes.

Risk of bias

All included studies presented adequate sequence generation (all studies reported an appropriate method used to generate the randomization sequence). In 89% (eight studies) of the articles losses and exclusions were described and intention to treat analysis was performed, with a low risk of bias for these analyses. The allocation was concealed in 78% (seven studies) of these articles. In 56% (five studies) of these

articles, the investigator and outcome assessors were blinded. These data are present in Supplementary online information.

Effects of interventions

Maximal expiratory pressure

Seven studies evaluated MEP, totaling 175 patients. It was observed that the RMT increased the MEP at 12.0 cmH₂O (95% CI: 5.5 to 18.6, I^2 : 68%) (Fig. 1). Because of the high heterogeneity, the sensitivity analysis was performed in relation to the type of training and disease, and training intensity. Analyzing only those studies that used IMT [6,19,20,22], there was no change in the overall results and the high heterogeneity remained (12.1 cmH₂O, 95% CI: 1.8 to 22.5, I^2 : 74%). Analyzing studies that used EMT [18,22], there was no change in the overall result, but there was no heterogeneity (4.4 cmH₂O, 95% CI: 0.1 to 8.6, I^2 : 0%). Analyzing studies with MS patients [6,18–22], there was no change in the overall outcome and the heterogeneity was moderate (8.4 cmH₂O, 95% CI: 3.6 to 13.2, I^2 : 44%).

In studies using high intensity training [18,19], 60% of maximum, MEP showed an increase compared to control (14.7 cmH₂O, 95% CI: 5.4 to 24.1, I^2 : 0%), whereas studies using a lower intensity [6,20,23], 30 to 40% of maximum, showed no difference (11.0 cmH₂O, 95% CI: -1.7 to 23.7, I^2 : 83%).

Maximal inspiratory pressure

Eight studies evaluated the MIP, totaling 194 patients. The studies showed that the RMT increased MIP at 23.5 cmH₂O (95% CI: 7.8 to 39.2, I^2 : 87%) (Fig. 2). Because of the high heterogeneity, the sensitivity analysis looked at the type of disease of the participants. Analyzing studies with participants who had MS [6,18–22], there was no change in the overall result and high heterogeneity remained (22.5 cmH₂O, 95% CI: 3.4 to 41.5, I^2 : 90%). When analyzing studies with ALS patients [4,5], there was no change in the overall result, but there was no heterogeneity (18.9 cmH₂O; 95% CI: 8.9 to 29.0, I^2 : 0%). The same occurred in the analysis of studies that used IMT (19.2 cmH₂O; 95% CI: 2.3 to 36.2, I^2 : 84%) and EMT (20.4 cmH₂O; 95% CI: 17.1 to 33.6, I^2 : 0%). In this outcome, the high intensity training was not the determining factor, because the studies that trained at 60% MIP [5,18,19] did not differ from the control group (7.4 cmH₂O, 95% CI: -2.1 to 16.8, I^2 : 0%); however, the low intensity training (30 to 40%) [4,6,20] increased MIP in intervention group (39.1 cmH₂O, 95% CI: 9.2 to 68.9), but with high heterogeneity (I^2 : 93%).

Forced expiratory volume in one second

Three studies evaluated the FEV₁, a total of 101 patients. It was observed that the RMT increased FEV₁ at 0.27 L (95% CI: 0.12 to 0.42, I^2 : 0%) (Fig. 3). The analysis of the two studies that used only IMT intervention and cited the training intensity (30% MIP) [6,20] maintained the overall result (0.32 L; 95% CI: 0.15 to 0.45, I^2 : 0%). For this outcome

Table 1
Characteristics of the included studies.

Author, year	Patients (n)	Training protocol	Training intensity	Measured outcomes	Features
Cheah <i>et al.</i> 2009 [5]	19 patients with ALS. Intervention: 9 Control: 10	Intervention: IMT: 10 minutes training 3 times/day 7 days/week, 12 weeks. Control: the same protocol, but without intensity.	Intervention: 15% of MIP, 30% in the second week, 45% in the third week, 60% at 4 to 12 weeks Control: no intensity.	FVC MIP	Intervention: There was no significant difference in pre- and post-training outcome in FVC and MIP. Control: no significant difference in pre- and post-training outcome in FVC and MIP.
Pinto <i>et al.</i> 2013 [23]	18 patients with ALS. Intervention: 11 Control: 7	Intervention: IMT: 10 minutes training twice a day 8 weeks. Control: 50% of training volume and lower intensity than RMT (4 weeks).	Intervention: 30 to 40% MIP.	FVC	Longer survival in the intervention group compared to controls. No difference in FVC.
Pinto <i>et al.</i> 2012 [4]	26 patients with ALS. Intervention: 11 Control: 9	Intervention: IMT: 10 minutes training twice a day 8 weeks. Control: 50% of training volume and lower intensity than RMT (4 weeks).	Intervention: 30 to 40% MIP.	MIP MEP MVV	The intervention group had improved MEP, MIP and MVV compared to the control group.
Gosselink <i>et al.</i> 2000 [18]	18 patients with MS. Intervention: 9 Control: 9	Intervention: EMT: 3 sets 15 repetitions 7 days/week, 3 months. Control: deep breathing exercises.	Intervention: 60% MEP.	FVC MIP MEP	Cough efficacy significantly better compared to the control group. FVC, MEP and MIP with no difference between groups.
Fry <i>et al.</i> 2007 [6]	41 patients with MS. Intervention: 20 Control: 21	Intervention: IMT: 3 sets 15 repetitions 7 days/week, 10 weeks. Control: no exercise.	Intervention: 30% MIP and Borg scale.	FVC FEV1 MIP MEP MVV	Intervention: improvement in FEV1 and FVC between the pre- and post-treatment. Control: no significant changes.
Klefbeck <i>et al.</i> 2003 [19]	16 patients with MS. Intervention: 8 Control: 8	Intervention: IMT: 3 sets 10 repetitions 7 days/week, 10 weeks. Control: deep breathing exercises.	Intervention: 40 to 60% MIP	FVC FEV1 MIP MEP	Intervention: increased MIP and MEP between pre- and post-treatment. Control: no significant changes.
Ray <i>et al.</i> 2013 [21]	21 patients with MS. Intervention: 11 Control: 10	Intervention: RMT combined: 30 minutes 3 days/week, 5 weeks. Control: no exercise.	Intervention: Progressive resistance. Does not describe intensity.	MIP MEP MVV FEV1 FVC 6MWT	The intervention group improved MIP and MEP compared to the control. No difference in 6MWT.
Smeltzer <i>et al.</i> 1996 [22]	15 patients with MS. Intervention: 10 Control: 5	Intervention: EMT: 3 sets 15 repetitions 7 days/week, 3 months. Control: same protocol, no intensity.	Intervention: not reported.	MIP MEP	Intervention: increased MEP in pre- and post-treatment. Control: no significant changes.
Pfalzer <i>et al.</i> 2011 [20]	39 patients with MS. Intervention: 20 Control: 19	Intervention: IMT: 3 sets 15 repetitions 10 weeks. Control: no exercise	Intervention: 30% MIP and Borg scale.	MIP MEP MVV FVC FEV1 6MWT	Intervention had improved MIP compared to the control. No difference between groups in other outcomes.

ALS: amyotrophic lateral sclerosis, EMT: expiratory muscle training, FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity, IMT: inspiratory muscle training, MEP: maximal expiratory pressure, MIP: maximal inspiratory pressure, MS: multiple sclerosis, MVV: maximal voluntary ventilation, RMT: respiratory muscle training, 6MWT: the 6-minute walk test.

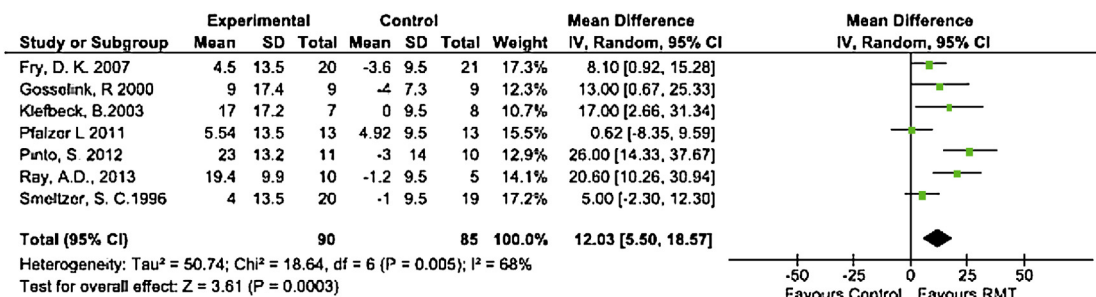


Fig. 1. Analysis of maximal expiratory pressure comparing the respiratory muscle training group and control group. SD: standard deviation, CI: confidence interval, I²: inconsistency test.

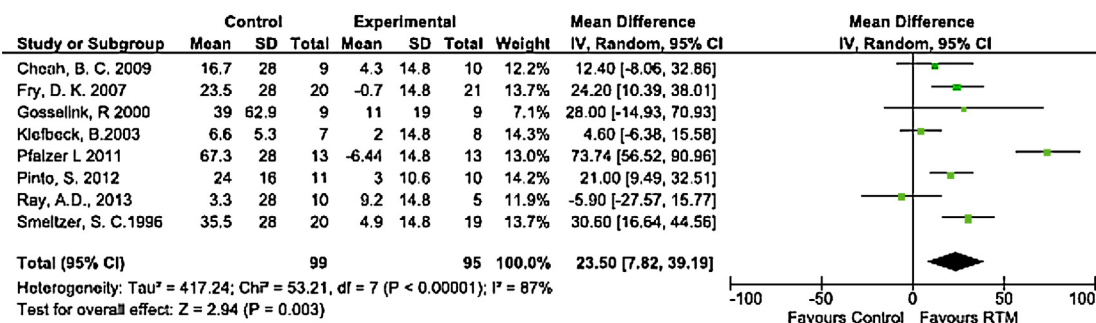


Fig. 2. Analysis of maximal inspiratory pressure comparing the respiratory muscle training group and control group. SD: standard deviation, CI: confidence interval, I²: inconsistency test.

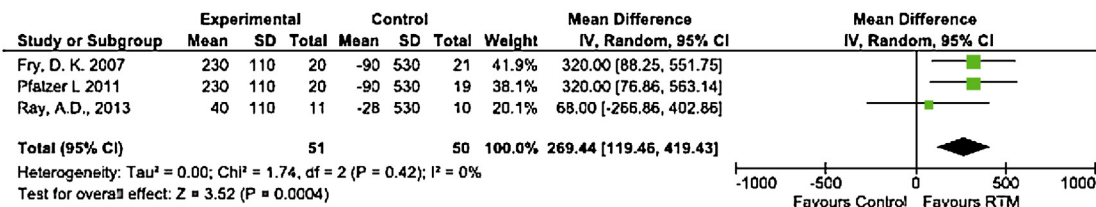


Fig. 3. Analysis of forced expiratory volume in one second comparing the respiratory muscle training group and control group. SD: standard deviation, CI: confidence interval, I²: inconsistency test.

sensitivity analyses were not performed according to disease (three studies were performed with MS).

Forced vital capacity

Six studies assessed FVC, totaling 172 patients. There was no difference between the groups using RMT (0.48 L; 95% CI: -0.15 to 1.10; I²: 0%) (Fig. 4). Sensitivity analysis

was performed and evaluating studies with participants with MS [6,18,20,21] and ALS [5,23], there was no change in the overall result (0.40 L, 95% CI: -0.27 to 1.07, I²: 0% and 0.46 L, 95% CI: -0.46 to 1.37, I²: 0%). The analysis of studies that used the intervention as IMT [5,6,20,21,23] also showed no difference between groups (0.32 L, 95% CI: -0.29 to 0.92, I²: 0%). Furthermore, the intensity of the training to

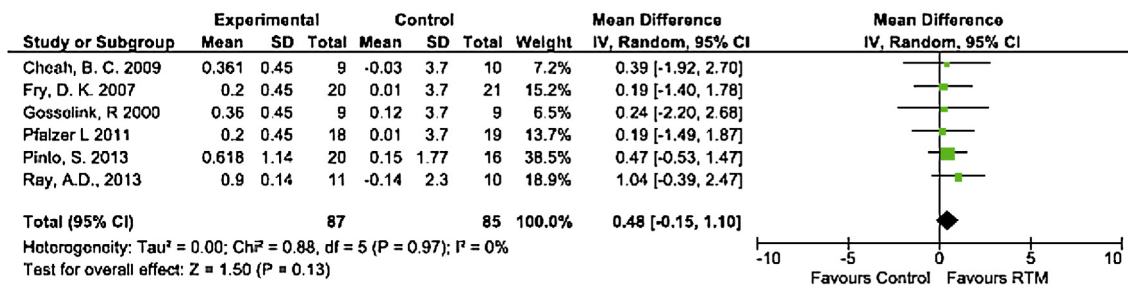


Fig. 4. Analysis of forced vital capacity comparing the respiratory muscle training group and control group. SD: standard deviation, CI: confidence interval, I²: inconsistency test.

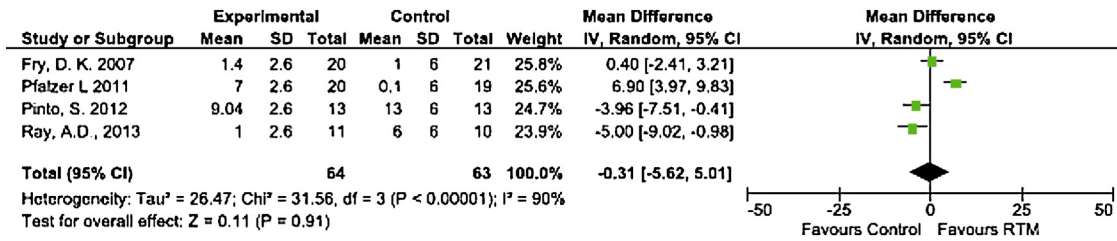


Fig. 5. Analysis of maximum voluntary ventilation comparing the respiratory muscle training group and control group. SD: standard deviation, CI: confidence interval, I²: inconsistency test.

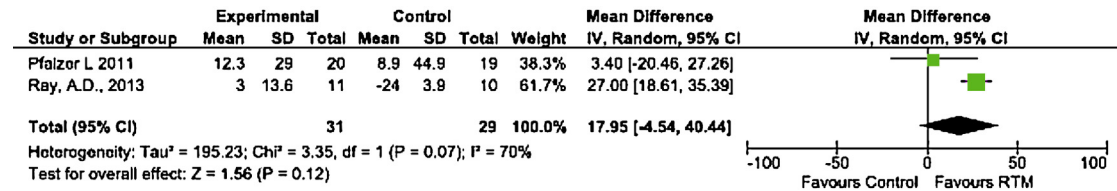


Fig. 6. Analysis of the 6-minute walk test comparing the respiratory muscle training group and control group. SD: standard deviation, CI: confidence interval, I²: inconsistency test.

60% [5,16] or 30 to 40% MIP [6,20,23] did not change the result (0.32 L, 95% CI: -1.36 to 2.00, I²: 0% and 0.35 L, 95% CI: -0.41 to 1.11, I²: 0%).

Maximum voluntary ventilation

Four studies evaluated MVV, a total of 127 participants. In the overall analysis, there was no difference between groups (-0.31 L/min; 95% CI: -5.62 to 5.01, I²: 90%) (Fig. 5). Sensitivity analysis was performed and evaluated the two studies that used only the intervention as IMT [6,20]. It also showed no difference between groups (3.64 L/min; 95% CI: -2.73 to 10.01, I²: 90%). Analyzing the three studies of MS [6,20,21], the overall result was maintained (0.88 L/min; 95% CI: -5.47 to 7.24 L, I²: 92%). The studies used 30 to 40% MIP.

6-minute walk test

Two studies assessed the 6MWT, totaling 60 patients. It was observed that RMT increased the distance by approximately 18 meters, however with no significant difference (95% CI: -4.54 to 40.44, I²: 70%) (Fig. 6). No sensitivity analysis was performed, because the two studies were performed with MS patients and had IMT intervention.

Discussion

Summary of evidence

In this systematic review with a meta-analysis of RCTs, it was observed that the RMT improved ventilator function, by increasing FEV₁, and respiratory muscle strength, increasing MEP and MIP, in patients with MS and ALS, although there was no change in the FVC, MVV and 6MWT.

RMT helped improve respiratory muscle strength in the intervention group compared to control. This result is

expected, since the objective of the training is to increase strength. Generally, ventilation was performed against constant linear load, both inspiratory and expiratory, and results in hypertrophy of skeletal muscle, improving strength and stability of the chest, preparing the ventilatory muscle, and preventing respiratory fatigue [21]. Even in patients who already had dyspnea and muscle weakness, RMT has proved effective to relieve this condition [24,25], and possibly this may happen in patients with neurodegenerative diseases. Studies show that RMT helps improve respiratory muscle strength in healthy individuals and athletes [26,27]. A recent meta-analysis showed that the RMT also has a positive influence on patients with neurological diseases, in which the intervention increased respiratory muscle strength in tetraplegic patients [28].

The training, inspiratory or expiratory, affects the chest muscles. However, based on the principle of the specificity, this effect was more evident in the inspiratory muscle strength (MIP) because most of the studies just used the threshold (IMT) as intervention. For this reason, it is possible that in this meta-analysis the MIP has improved almost two times compared to the MEP [1,29,30].

In this meta-analysis, ventilatory function improved with the increase in FEV₁; however, FVC did not change. Studies report that although RMT achieved its goal of increasing muscle strength, it had little influence on lung capacity, not changing the FVC [13,30]. Although the RMT did not change other measures in spirometry, the increasing MEP increases peak flow, and this may be associated with improvement in FEV₁ [31]. In general, neurodegenerative diseases restrict lung volume and thus cause a decrease in vital capacity [32]; thereby, RMT can slow the decline in respiratory function [5]. Therefore, respiratory muscle must be trained with specific stimulus for maintenance of the quality of ventilation [11,15]. Probably, improving ventilation quality improves quality of

life in this population. Pozza [11] mentions in his review that respiratory exercises improved quality of life, especially in ALS.

In addition, the RMT did not change functional capacity. Despite an improvement of 17% in the 6MWT, this was not statistically significant. In general, physical exercise has already been shown for many years to improve the physical capacity and independence in patients with neurodegenerative diseases [12,33]. Recently, there has been a specific interest to associate respiratory training with improved physical capacity, related with increase of ventilator strength and organism capacity to consume oxygen and improve cardiorespiratory endurance [21]. Although there are only a few studies, results are positive, in which groups with RMT achieve a greater distance walked in the 6-minute walk test, developing the independence that is essential for these patients [21]. Gain of 17% of distance in 6MWT can be important for clinic this patient, and maybe not have the statistically significant result by the low number and the lack of follow-up studies and patients. We expected that the training was to improve functional capacity, since the RMT is associated with improvement in ventilator function, as well as reduction of peripheral and respiratory muscle fatigue and perceived dyspnea [20,34,35], and with increased efficiency of ventilation and a higher oxygen uptake period after RMT [15,36]. We need more studies evaluating this variable.

Furthermore, a lower physical ability is associated to a poorer quality of life in neurodegenerative diseases [37]. Studies have shown that patients receiving RMT have improved activities of daily living, such as feeding, and have lower scores on the Expanded Disability Status Scale test [EDSS], becoming more independent [16,20,35].

Cheah *et al.* [5] followed up patients after the training period and observed that the gains in MIP were partially reversed during a period of training cessation. Most of these studies did not report the follow-up of patients; therefore, we are not sure of preservation of the gains. A study in patients with heart failure showed that the RMT gains were maintained for up to 1 year [30]. This factor should be more investigated in neurodegenerative diseases; however, we suggest that a continuation is important to maintain the benefits of treatment because it is a chronic disease, and constantly, there is muscle deterioration.

Strengths and limitations of the review

In some cases, the analyses showed a high heterogeneity between studies, and this possibly happened by joint evaluation of MS and ALS and types of muscle training, which was necessary because of the scarcity of randomized controlled trials on this subject. In addition, another factor that could have contributed was little indication of the stage of disease in most studies, and there was absence of detail in the papers about the number of assessment test attempts before and after RMT. Analyses were performed by isolating the kind of training and disease and the results remained unchanged,

but decreased heterogeneity. Positively, there is the methodological quality of studies, most of which had low or moderate risk of bias for the characteristics analyzed.

Comparison with other studies

A systematic review that was similar is of Reyes *et al.*, which evaluated the effects of RMT in patients with MS and Parkinson. Although no statistical analysis has been performed, it was concluded that there is evidence that the training can improve respiratory muscle strength in these patients [1]. Eidenberger *et al.* showed that there is evidence that IMT leads to strengthening of inspiratory muscles in ALS; however, there were included just two RCTs, one pre-experimental study and one with a historical control group [15]. Recently, Martín-Valero *et al.*, after reviewing 15 studies, including RCTs, non-RCTs, case studies and reviews, have described that RMT improves MIP and MEP in MS [16]. Our review corroborates with findings and adds a meta-analysis.

In summary, RMT improved the strength of respiratory muscles and ventilatory function, and should be an adjunct to rehabilitation of patients with neurodegenerative diseases.

Ethical approval: The Instituto de Cardiologia do Rio Grande do Sul Ethics Committee: number 4924/13.

Conflict of interest: The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.physio.2016.01.002>.

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