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CASE SERIES

EFFECTS OF RESPIRATORY MUSCLE TRAINING ON RESPIRATORY MUSCLE STRENGTH AND HEART RATE VARIABILITY IN MYOTONIC DYSTROPHY PATIENTS TYPE 1

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KEYWORDS

Respiratory muscle training; Myotonic Dystrophy; Respiratory muscles; Heart rate variability

Introduction: Myotonic dystrophy (MD) is a multisystemic neuromuscular disease responsible for causing progressive respiratory muscle weakness. Respiratory muscle training (MRT) has been shown to be effective in several diseases; however, its effects on respiratory and cardiac functions in MD are still inconsistent.

Objective: Assess the effects of MRT on respiratory muscle strength and heart rate variability in patients with type 1 myotonic dystrophy. **Methods:** The sample was composed of 6 individuals of both sexes. The following was assessed: respiratory muscle strength, before and after training (sessions 1-4) and heart rate variability before and after sessions 2 and 3. The group submitted to MRT used the Threshold IMT device, adapted for inspiratory and expiratory training, three times a week, once at an outpatient facility and twice at home. Results were expressed as median and interquartile ranges for pulmonary function variables, and the Friedman and Wilcoxon tests were applied to compare heart rate variability.

Results: respiratory muscle strength significantly improved expiratory and inspiratory muscles (33% and 20%, respectively), considering training sessions 1-4. With respect to variability, there was a 102% increase in sympathetic activity, reflected by low frequency and 194% increase in vagal tonus, represented by high frequency.

Conclusions: Preliminary study results demonstrate that a partial home-based respiratory muscle-training program is feasible, in addition to improving strength and heart rate variability in patients with MD.

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INTRODUCTION

Myotonic dystrophy (MD) is a multi-system neuromuscular disease, autosomal dominant disorder that develops slowly. Pathogenesis is varied, involving cataracts, endocrine deficiencies, cardiovascular manifestations and central nervous system¹. In addition to several symptoms, as a syndrome, the respiratory failure involves both the central and peripheral nervous systems, resulting in varying degrees of respiratory muscle weakness². This progressive respiratory muscle weakness is responsible for inefficiency of ventilation and cough. Ineffective cough leads to the most deleterious consequences as lung infections that could result in pneumonias and respiratory insufficiency³. Furthermore, the involvement of respiratory and cardiac system is responsible for half of MD related mortality⁴.

Respiratory muscles, as other skeletal muscles can be trained. Both the structure and the functional characteristics of respiratory muscles may be modified in response to increased by imposing loads or decrease follow inactivity⁵. The structural, functional and metabolic changes of the respiratory muscles in response to training have proven to be effective in increasing the cross-sectional area of fibers and power generation with a clear increase in contractile proteins⁶. Clinically, the respiratory muscle training (RMT) demonstrated to be effective in increasing strength and endurance of respiratory muscle in numerous diseases, including myotonic dystrophy⁷, however, its effects on the respiratory and cardiac function are inconsistent. The propose of this case series are to assess the effects of respiratory muscle training on respiratory muscle strength and heart rate variability in Myotonic Dystrophy type 1 patients.

MATERIALS AND METHODS

The sample consisted of 6 individuals of both sexes. Were including in the study patients diagnosed with MD by the neurologist. Patients with a history of chronic respiratory or heart disease, hypertension, diabetes mellitus, thromboembolic disease, thyroid disease, stroke, depression, tobacco use or alcoholism were excluded. Any patients took medication that could affect the autonomic control of Heart. The study was approved by the University Hospital's Ethics Committee (number 151/07) and all the

patients gave written consent to participate in the study. In an crossover study following an A-B-A design, phase A control time, phase B training time and phase A control time, patients with Myotonic Dystrophy were enrolled in an inspiratory and expiratory muscle training program. Respiratory muscle strengths were assessed before and after three study phases (moment 1 to 4) and heart rate variability were evaluated before and after phase B (moment 2 and 3).

Participants were evaluated in the morning to avoid differences caused by circadian changes. Laboratory temperature was maintained between 22°C and 24°C and relative air humidity between 50 and 60%. Patients were informed about the protocol, instructed to abstain from stimulants or alcoholic beverages during the 24 hours preceding the test and to ingest a light meal at least 2h before assessment. On the day of the test, patients were questioned and examined in relation to their overall well being, a good night's sleep (7-8 hours) and instruction compliance. After a 20-minutes rest period, systemic blood pressure (Missouri-Mikato, SP, Brazil) and radial pulse (Nonin Medical, MN, USA) were measured to determine if basal conditions were adequate for the test. To obtain HR data, volunteers were monitored in the supine position for 15 minutes using a Polar S810i® monitor (Polar Electro Oy®, Finland) after 5-minutes of signal stabilization. The Polar S810i® monitor is a practical and reliable device to monitor beat-by-beat HR for HRV analysis; the equipment captures R-R intervals through 2 adhesive electrodes. Electrodes were placed on the skin, on top of the xiphoid process and on the middle axillary line at the level of the xiphoid process. Data obtained by the Polar monitor were transferred to the computer using an interface with an infrared device for signal emission. This system detects ventricular depolarization, corresponding to the R wave on the ECG, with a sampling rate of 500 Hz and a temporal resolution of 1 millisecond⁸, validated by Loimaala *et al.*⁹. The infrared interface was placed at a maximum distance of 8 inches and at a 15° angle to the Polar S810i®²⁰. HR signals were processed to calculate HRV values using a specific MatLab® program (Math Works, USA), which calculates HRV values based on the R-R intervals obtained on the device. HRV was evaluated in both time and frequency domains, using the region of greatest stability in tracing R-R intervals, provided it exhibited at least 256 consecutive beats. Frequency domains were analyzed by

fast Fourier transform applied in a single window after linear subtraction of tendency in previously selected R-R intervals. Analysis in the frequency domain was carried out using total power, low (LF: 0.04 to 0.15 Hz) and high (HF: 0.15 to 0.4 Hz) frequency bands in normalized units (*nu*) and an LF/HF ratio. The LF band is modulated by both sympathetic and parasympathetic nervous systems and the HF band is related to cardiac vagal control¹⁰.

The technical procedure, acceptability and reproducibility criteria, as well as standardization for measure were in accordance with the Brazilian Thoracic Association¹¹. The DATOSPIR 120 spirometer (Sibelmed®, Barcelona, Spain) was used to measure forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC). Three reproducible maneuvers were performed and the one with the best curve was considered for the study. Predicted values were those described from pre-established equations¹². Respiratory muscle strength: maximal respiratory pressures were measured in accordance with Black and Hyatt and the Brazilian Thoracic Association, using reference values obtained from the Brazilian population. Maximal inspiratory pressure (P_Imáx) was measured with the subjects in a seated position and the nostrils occluded, at residual volume (RV) and maximal expiratory pressure (P_Emáx) at total lung capacity (TLC). Between five and eight maneuvers were carried out until two maximal values were reproducible. The sniff test was measured in an occluded nostril during a maximal sniff through the contralateral nostril. A plug with an orifice of around 1 mm coupled to a catheter was connected to a hand-held MicroRPM® (MICRO Medical®, Rochester, Kent, UK) pressure meter. Ten measures were taken and the result with the highest value was selected¹³. Reference values were obtained from equations described previously¹⁴.

The RMT group achieved inspiratory and expiratory muscle training, using the Threshold® IMT and adapted Threshold® IMT respectively to training inspiratory and expiratory muscles¹⁵. The program consisted of training 3 times for weekdays, once at the outpatient and twice at home. The training was progressive as the loads in both muscle groups using a protocol adapted to the previously published¹⁶. The load has increased gradually from 25% to 70% of P_Imáx and P_Emáx with an increase of 5% every week until the maximum of 70% of P_Imáx and P_Emáx that were maintained until the end of training. The training

program consisted of two series of 15 breathing in the first week, two series of 20 breathing in the second week, three series of 20 breathing in the third week and four series of 20 breathing in the fourth until eighth week. The results were analyzed using descriptive nonparametric statistical were used analysis due to the small sample size. Results are expressed as median (interquartile range [IQR]), for respiratory muscle strength variables, P_Imáx/P_Emáx and SNIP, *Friedman* test was used and *Wilcoxon* signed-rank test was used to compare HRV. Data were analyzed using GraphPad Prism 5 for Mac (GraphPad Software Inc.) software's. The level of significance was set at $p < 0.05$ with a two-tailed approach.

RESULTS

The sample presented a median age 35.5 (26.7 - 51.0) years and body mass index 25.7 (18.6 -32.9) Kg/m². The values found for spirometric data were FVC (L) 2.7 (2.1-3.4), FVC % 72 (58-79.2), VEF₁ (L) 2.5 (1.8-2.8), VEF₁ % 70.5 (58.7-81.5), VEF₁/FVC% 86.1 (80.6-89.5). The results presented in Table 1 show no changes were found in lung function. Respiratory muscle strength improves significantly in average 33% for expiratory muscle and 20% for inspiratory muscle when considered the hole period for 1 - 4 moment, was also observed that SNIP significantly increase after phase B or training phase. The effects of RMT on HRV are present in Table 2. We found that RMT increase activity of sympathetic tone represented by low frequency in 102% and increase vagal modulation of the heart represented by High Frequency domain in 194%. We also observed a decrease in sympathetic/vagal index that means the patient improve your HRV and near to normal ranges.

DISCUSSION

The propose of this case series was to assess the effects of inspiratory and expiratory muscles training on respiratory muscle strength and heart rate variability in Myotonic Dystrophy type 1 patients. Dystrophy Myotonic is a well-characterized cause of muscle weakness, this phenomenon implies in loss of cough effectiveness. Impairment of cough is the major responsible for secretion accumulation that leads a respiratory tract infection. Furthermore respiratory tract infections are related with respiratory failure, which

is the most important cause of death in neuromuscular patients³.

Table 1. Patient's characteristics of respiratory function

	Moment 1	Moment 2	Moment 3	Moment 4
PEmáx (cmH₂O)	62 (54-67.7)	62.5 (55.5-69.5)	89 (57.5-97.7)	75 (57.2-98)
PImáx (cmH₂O)	54 (42.7- 64.7)	52.0 (44-68)	64.5 (53.7-74.2)	67.5 (59.7-77) *
PEmáx %	50.5 (38.5-77)	53.5 (45.5-71)	78.5 (43.5-103)	76.5 (42.5-89.5)
PImáx %	50 (35.5-63.5)	48 (41.5-61.5)	58 (47-78.5)	58 (51.5-78) *
SNIP	67 (55.5-73)	58 (46.2-73.2)	77.5 (60.2-87)	69 (57.7-79.7) *
SNIP %	66.5 (55.5-78)	61.5 (46-70)	75 (65.5-87)	67.5 (58.5-81) *

PEmáx (maximal expiratory pressure); PImáx (maximal inspiratory pressure); SNIP (Sniff Nasal Inspiratory Pressure). Friedman test * $p < 0, 05$.

Table 2. Heart Rate Variability

	Before MRT	After MRT	<i>p</i>
LF (ms²)	495.2 (145.9-944.4)	252.6 (154-371.5)	<i>ns</i>
HF (ms²)	260.1 (71.21-790.1)	99.7 (63.3-238.6)	<i>ns</i>
LF/HF	2 (0.9-3.1)	2.8 (1-4.1)	<i>ns</i>

LF (Low Frequency); HF (High Frequency); LF/HF (Low/High Frequency Ratio). Wilcoxon test * $p < 0, 05$.

In the current study, the respiratory muscle training showed a significant increase in respiratory muscle strength, inspiratory and expiratory pressures and nasal inspiratory pressure (SNIP), nevertheless any changes were observed in spirometric values as a FVC and VEF₁. This result is not surprising; previously, Koessler *et al.*¹⁷ studied 27 patients, eighteen diagnosed with Duchenne's muscular dystrophy and 9 diagnosed with spinal muscular atrophy, which underwent a domiciliary IMT program conducted over a period of two years. These authors found a significant increase in respiratory muscle strength and endurance measure by PImáx, PEmáx and maximum voluntary ventilation (MVV), but the program was not able to minimize the impairment of FVC over the

period of 2 years. Although the increase in strength has been documented in the two studies, this question still controversial in respect to training time and the load intensity used.

Previous study as a published by Smith *et al.* states that training of inspiratory muscle possibly will accelerate the fatigue and damage of respiratory muscles¹⁸. These authors also found a stabilization of the vital capacity, which can be an important predictor of need for mechanical ventilation¹⁹. In another study⁷ described a case of a subject aged 42, with myotonic dystrophy that underwent a domiciliary training program targeting to inspiratory and expiratory muscles for 12 weeks. They found on improvement in 36% of inspiratory muscle strength, which may mean allowed slower progression to inspiratory muscle weakness. Nevertheless these authors related the difficult to training expiratory muscles due Heart rate variability is relatively simple toll to assess the control of autonomic nervous on heart. A decrease on heart rate variability is a predictor of morbidity and mortality²⁰. Previous data has suggested that the sympathetic drive in middle-aged male MD patients who are not severely impaired seems to be greater than in healthy matched subjects²¹. The present study showed that RMT applied during 8 weeks with low to moderated

loads decrease not only sympathetic and parasympathetic drive but also cardiac vagal tone in Myotonic Dystrophy type 1 patients. Nevertheless the sympathetic vagal balance tend to increase after RMT the results suggest that respiratory muscle training can modulate the autonomic control of the heart. Despite of large number of the study focus on effects of breathing or paced breathing on heart rate variability, we not found previous studies that emphasized the RMT and heart rate variability. Therefore we can just speculate the mechanism of the results found in this matter. Its well documented that RMT can modulate the respiratory pattern determine a more physiological breathing patter during the training with linear threshold load. Previous data has been demonstrated that Threshold loading improves velocity of inspiratory muscle shortening that was related to shorten inspiratory time²² and increase in expiratory time²³.

CONCLUSIONS

The preliminary results of this study demonstrate that a partial home program of RMT is feasible and improves respiratory strength and HRV in MD patients.

DISCLOSURES

G Fregonezi and V Resqueti have applied for patents for the use of adapted Threshold[®] IMT respectively to training inspiratory and expiratory muscles with loads until 85 cm H₂O". Patent deposit number: PI1102391-0 - INPI. "Device to training inspiratory and expiratory muscle with load until de 85 cm H₂O".

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