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Respiratory motor training and neuromuscular plasticity in patients with chronic obstructive pulmonary disease: a pilot study

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Abstract

The objective of this study was to examine the feasibility of a full-scale investigation of the neurophysiological mechanisms of COPD-induced respiratory neuromuscular control deficits. Characterization of respiratory single- and multi-muscle activation patterns using surface electromyography (sEMG) were assessed along with functional measures at baseline and following 21 ± 2 (mean ± SD) sessions of respiratory motor training (RMT) performed during a one-month period in four patients with GOLD stage II or III COPD.

Pre-training, the individuals with COPD showed significantly increased ($p < .05$) overall respiratory muscle activity and disorganized multi-muscle activation patterns in association with lowered spirometrical measures and decreased fast- and slow-twitch fiber activity as compared to healthy controls (N=4). Following RMT, functional and respiratory sEMG activation outcomes during quite breathing and forced expiratory efforts were improved suggesting that functional improvements, induced by task-specific RMT, are evidence respiratory neuromuscular networks re-organization.

Keywords

Chronic obstructive pulmonary disease; Respiratory motor function; Respiratory muscles; Respiratory training; Electromyography; EMG

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Introduction

Chronic obstructive pulmonary disease (COPD) is currently the third leading cause of death and disability in the US (Heron, 2012) and, is projected to be ranked fifth worldwide in burden of disease by 2020 (Vestbo et al., 2013). While airflow limitations and parenchymal pulmonary destruction are the hallmarks of the disease, COPD is also associated with reduced respiratory muscle force and endurance leading to ventilatory insufficiency (Gea et al., 2012). In fact, respiratory failure remains a major cause of morbidity and mortality in COPD (Mannino and Martinez, 2011), which is in part attributed to respiratory muscle dysfunction (Gosselink et al., 2000). Consequences of decreased respiratory muscle performance include ineffective breathing and coughing, and changes in coordination of breathing and swallow (Clayton et al., 2014; Singh, 2011). In turn, these deficits may further contribute to dynamic hyperinflation and increased risk of COPD exacerbation (Vilaro et al., 2010). This explains why maintaining adequate respiratory motor function is critical for patients with COPD (McKenzie et al., 2009). Currently, there are no effective therapeutic strategies to improve respiratory motor function in those affected by COPD (Keating et al., 2011; Vestbo et al., 2013). A fundamental reason for this is that the pathophysiological mechanisms of respiratory motor dysfunction in COPD remain unclear (Gea et al., 2013). Although, these abnormalities can be linked to a variety of factors related to local and systemic insults affecting respiratory muscles (Vestbo et al., 2013). There is mounting evidence suggesting that the neural control of respiratory muscles is negatively affected in COPD resulting in altered neural drive (Duiverman et al., 2004; Jolley et al., 2009) and abnormal motor unit activation (Mantilla and Sieck, 2013). This suggests that respiratory motor dysfunction induced by COPD involves functional disorganization of the respiratory neuromuscular network (Duiverman et al., 2004).

As it now stands, pulmonary rehabilitation is an essential non-pharmacological therapeutic option for patients with COPD (Nici et al., 2006). This therapy is meant to accompany patients throughout the course of their disease with the primary goal of reducing disability (Ries et al., 2007). However, patients with COPD complain of dyspnea following physical exertion, often due to significantly reduced exercise capacities (Troosters, 2013) and progressive decline in lung function associated with a poor quality of life (Kim et al., 2008). Therefore, there is a great need for the development of effective physiologically-based rehabilitative techniques to restore the dysfunctional respiratory motor system induced by COPD (de Blasio and Polverino, 2012). There is growing evidence supporting the value of task-specific training based on evidence of significant use-dependent neural plasticity (Hubbard et al., 2009). However, this concept has never been tested in respiratory rehabilitation for patients with COPD. This pilot study was undertaken to determine the capacity of the respiratory neuromuscular networks for plasticity in order to develop effective rehabilitative strategies for patients with COPD.

2. Methods

2.1 Demographic and clinical characteristics

This study was conducted in the Neuroscience Collaborative Center at the Frazier Rehab Institute after informed consent was obtained as approved by the Institutional Review Board

for Human Research at the University of Louisville. Four individuals, two female and two males, with GOLD stage II or III COPD participated in this study. Data from four physically (age, sex, height, and weight) matched healthy controls with no history of respiratory dysfunction or smoking were used to calculate normative sEMG-based values (Bartuzi et al., 2007; Ovechkin et al., 2010).

2.2. Pulmonary function test

Standard spirometry testing was performed in the seated position before and after respiratory motor training (RMT) program obtaining Forced Vital Capacity (FVC), Forced Expiratory Volume in one second (FEV_1), and Maximum Forced Expiratory Flow (FEF_{max}) as measures of respiratory motor function (American Thoracic Society/European Respiratory Society, 2002; Hart et al., 2005). A Differential Pressure Transducer (MP45-36-871-350) with UPC 2100 PC card and software (Validyne Engineering, Northridge, CA) was used to measure Maximum Inspiratory Pressure (PI_{max}) and Maximum Expiratory Pressure (PE_{max}) (American Thoracic Society/European Respiratory Society, 2002) while subjects were blowing into the three-way valve system through a rubber tube used as a mouthpiece (Airlife 001504, Allegiance Healthcare Corp., McGaw Park, IL) from total lung capacity. The pressure meter incorporated a 1.5mm diameter leak to prevent glottic closure and to reduce buccal muscle contribution during measurements (Griffiths and McConnell, 2007; Smyth et al., 1984).

2.3 Respiratory motor control assessment

Respiratory muscle activation patterns were evaluated using surface electromyography (sEMG) of left and right sternocleidomastoid, scalene, upper trapezius (on midclavicular line), clavicular portion of pectoralis (on midclavicular line), diaphragm (on parasternal line), intercostal (at 6^{th} intercostal space on anterior axillary line), rectus abdominus (at umbilical level), obliquus abdominis (on midaxillary line), lower trapezius (paraspinally at midscapular level), and paraspinal (paraspinally on iliac intercrestal line) muscles using MA300 System (Motion Lab Systems, Baton Rouge, LA) (American Thoracic Society/ European Respiratory Society, 2002; Ovechkin et al., 2010). sEMG input was amplified with a gain of 2000, filtered at 4–1000 Hz and sampled at 2000 Hz. The overall amount of sEMG Magnitude (μV, Mag) and the Similarity Index (SI), that quantitate the multi-muscle distribution of activation during Maximum Expiratory Pressure Task (MEPT) in COPD subject compared to that of healthy subjects were calculated using vector-based analysis as previously described (Aslan et al., 2013; Ovechkin et al., 2010). In brief: multi-muscle activity parameters were calculated using averaged sEMG amplitudes using root mean squared (RMS) algorithm from each SCI subject for comparison to group values from NI subjects. The resulting Mag parameter was the amount of combined sEMG activity during MEPT calculated as a length of the resultant vector. The SI provides a value between 0 and 1.0 (most similar) equal to the cosine of the angle between the resultant multi-muscle distribution vectors in SCI subject to that of NI subjects. To perform MEPT, all subjects produced maximum expiratory efforts from total lung capacity for 5 seconds blowing into the Airlife 001504 circuit (Allegiance Healthcare Corp., McGaw Park, IL). Airway pressure; sEMG; breathing rate and chest wall kinematics monitored by using respiratory belt were recorded simultaneously using Powerlab acquisition system (ADInstruments, Colorado

Springs, CO). The amount of fast-twitching and slow-twitching muscle fiber activity of intercostal, rectus abdominis, and obliquus abdominis muscles were assessed using power spectrum analysis of sEMG frequency composition (Kamen and Gabriel, 2010) assessed during three trials of MEPT when respiratory muscles were either not-fatigued or fatigued. The fatigued condition was obtained using respiratory muscle endurance protocol with incremental resistant airway loading using MicroRMA100 respiratory muscle analyzer (MicroDirect, Lewiston, ME) by increasing the airflow resistance every 3 breathing cycles with an incremental step of 0.4 KPa/L/s until the subject could not continue (American Thoracic Society/European Respiratory Society, 2002; Keenan et al., 1995). The frequency outcomes have been calculated on the basis of the distribution of data into 1-sec intervals within a 5-sec window using a Fast Fourier Transform approach (Brigham, 1988). Percentage of the accumulated power of the spectrum within 4-60 Hz range, representing slow-twitch fiber activity; and 60-300 Hz range, representing fast-twitch fiber activity, were calculated (Bartuzi et al., 2007; Solomonow et al., 1990; Tkach et al., 2010).

2.4 Respiratory motor training

Research participants were seated during each training session with an approximately 45° head-up tilt. A threshold positive expiratory pressure device and inspiratory muscle trainer (Respironics Inc., Cedar Grove, NJ) were assembled using a three-way valve system (Airlife 001504, Allegiance Healthcare Corp., McGaw Park, IL) with flanged mouthpiece. The participants performed 6 work sets, 5 minutes in duration, separated by rest intervals lasting 3 minutes. Participants were trained 5 days/week, for 45 min/day during 1 month. The training was initiated at an intensity equal to 20% of their individual PI_{max} and PE_{max} with progressive increases as tolerated up to 40% of these values at the end of the training program (Griffiths and McConnell, 2007; Larson et al., 1999; Mueller et al., 2006).

2.6 Statistical analysis

Comparisons between unidentified data sets obtained before and after the RMT program were made using a paired t-test to detect the difference for each independent parametric variable (FVC, FEV_1, FEF_{max}, and SI) and Wilcoxon Signed-Rank Test for each non-parametric variable (PI_{max}, PE_{max} and Mag). All hypothesis tests were conducted at the $p < 0.05$ with the level of significance (α) being set at 0.05. All analyses were conducted using the open-source R software 3.0.2 package (R Development Core Team, 2013).

3. Results

3.1 Pulmonary function

Expiratory and inspiratory functional measures (FEF_{max}, PE_{max}, and PI_{max}) were significantly increased post-RMT as compared to the pre-RMT outcomes (Table 1).

3.2 Respiratory multi-muscle activation

During unloaded deep breathing, baseline muscle activation patterns in COPD patients were altered showing increased overall activity in upper trunk and neck muscles. It can be seen in Figure 1 that before the intervention, the unloaded deep breath provoked excessive co-activation in the muscles including those that are not normally involved in the task. This

abnormal activation pattern changed toward a more normative pattern after RMT as recorded in healthy controls (Figure 1). Similarly, sEMG over-activity that was observed during MEPT was associated with decreased airway pressure generation (Figure 2). When analyzed for the COPD group, this increased overall amount of sEMG activity during MEPT (Mag = 116 ± 8 μV, Mean ± SD) was significantly decreased (p=.02) post-RMT (Mag = 95 ± 9 μV) and have been associated with both significantly increased airway pressure generation (Table 1 and Figure 2) and not significantly (p=.09), but judged by eye, improved distribution of activity across the respiratory muscles (SI = 0.85 ± 0.03 vs. 0.91 ± 0.03) (Figure 2).

3.3 Respiratory muscle fiber activity

Frequency composition analysis of sEMG during MEPT in individuals with COPD revealed decreased activity representing fast-twitch fibers during forced respiratory efforts (Figures 3A and 3B) and failure of slow-twitch fibers during this task performed after long-term loaded breathing (Figures 4A and 4B) as compared to healthy subjects. Compared to pre-training values, all measures improved after RMT (Figures 3 and 4).

4. Discussion

The potential importance of respiratory motor dysfunction in COPD was initially described in the mid 1970's (Sharp et al., 1974), and since that time research has mainly focused on non-respiratory skeletal muscle dysfunction (Gea et al., 2012). As a consequence, non-specific general exercises have been recommended as a standard of care for individuals with COPD (de Blasio and Polverino, 2012). At the same time, there was limited therapeutic evidence of more specific respiratory rehabilitation for patients with COPD (Weiner and McConnell, 2005). Consequently, there has been no clinically-effective physiologically-based rehabilitative approach for COPD developed to date (Keating et al., 2011; Vestbo et al., 2013).

Respiratory dysfunction is a cardinal features of COPD pathogenesis, as it relates to increased airway resistance and increased ventilatory demands (McKenzie et al., 2009). Our current findings confirm what was shown by Duiverman and colleagues (2004), that individuals with COPD use different breathing strategies (Duiverman et al., 2004), and have abnormal respiratory muscle recruitment during eupneic and loaded breathing (Figures 1 and 2). Further, respiratory muscles demonstrate adaptive changes in response to the chronic mechanical load (Marchand and Decramer, 2000) demonstrating existence of a “fragile balance” between respiratory muscle overload and respiratory muscle adaptations (Orozco-Levi, 2003). As a result, neural respiratory drive is increased (De Troyer et al., 1994; Jolley et al., 2009) and redistributed (Gandevia et al., 1996). Our present findings demonstrate that these pathophysiological conditions are reversible by task-specific respiratory training (RMT) (Figures 1 and 2).

In the current study, the individuals with COPD demonstrated a reduction in respiratory force generating capacity due to a decrease in fast- and slow-twitch fibers activation, which lead to increased muscle fatigue and respiratory pump failure (Milner-Brown et al., 1975; Orozco-Levi, 2003). In comparison, the healthy subjects forced respiratory efforts resulted in continuously increased airway pressure, accompanied with increased recruitment of the

fast-twitch muscle fibers in non-fatigued expiratory muscles. This was revealed by 60 to 300 Hz frequency (fast-twitch fibers) predominance; with an effort-related decline in the lower-frequency domain (4 to 60 Hz; slow-twitch fibers) (Figure 3A). Interestingly, the control subjects increased slow-twitch muscle fibers recruitment to maintain the maximum airway pressure (Figure 4A), following the fatigue protocol. In contrast, the individuals with COPD, demonstrated compensatory activation of slow-twitch muscle fibers during pre-fatigue maximum effort tasks (Figure 3B), which was remediated with RMT (Table 1, Figure 3 and 4). These findings indicate that rehabilitative strategies to stimulate adaptive muscle activation are promising and warrant further clinical research. Valid and reliable tests of muscular function which can characterize an individual's fast- and slow-twitch muscle fibers composition, are important for demonstrating clinically-significant training response.

It is known that in stable COPD patients respiratory muscles can adapt in response to either inspiratory or expiratory exercise training (Crisafulli et al., 2007). However, our approach of using reciprocal inspiratory-expiratory training with adjustable threshold pressure load has never been previously used in a COPD population. This approach was chosen to affect not only the respiratory muscles, but to intervene the respiratory neuromuscular motor control through pulmonary and motor neural feedback initiated during cycles of reciprocal inspiratory-expiratory efforts. This choice was based on knowledge that corticospinal volitional activation (McKay et al., 2003), sensory feedback from stretched airways and alveoli (Coleridge and Coleridge, 1986), and muscles in order to modulate respiratory motor control (Aminoff and Sears, 1971; De Troyer et al., 1986; De Troyer et al., 2005; Decima et al., 1969; Murray et al., 2008). The results of this pilot study showing RMT-induced improvement in respiratory muscle activation patterns assessed during quiet (eupneic) (Figure 1) and loaded (Figure 2) breathing, confirmed the hypothesis that this therapeutic approach is a promising strategy to reverse maladaptive neuromuscular changes observed in patients with COPD.

Of note is the potential effect of RMT on the interaction of the respiratory pattern generator with other airway protective behaviors including swallow. Swallow, which uses inspiratory musculature, has a strong expiratory phase preference in animals and humans (Lefton-Greif and McGrath-Morrow, 2007; Pitts et al., 2013). It has been demonstrated clinically however, that patients with COPD switch from swallowing during expiration to inspiration (Leslie et al., 2002; Selley et al., 1989). It is not fully understood why this occurs, however it has been hypothesized by Pitts et al (2015) that alterations in biomechanics and thoracic-abdominal somatic and/or visceral mechanoreceptors lead changes in the central pattern generators (Pitts et al., 2015). This current work provides additional evidence that maladaptive neuromuscular changes from COPD could also be a potential mechanism.

Conclusion

The findings of this study demonstrate functional respiratory improvement, following a task specific respiratory training (RMT), results in adaptive re-organization of respiratory neuromuscular networks. These results indicate the need for future studies with test-re-test validation and expansion across related motor pattern generators such as swallow and cough.

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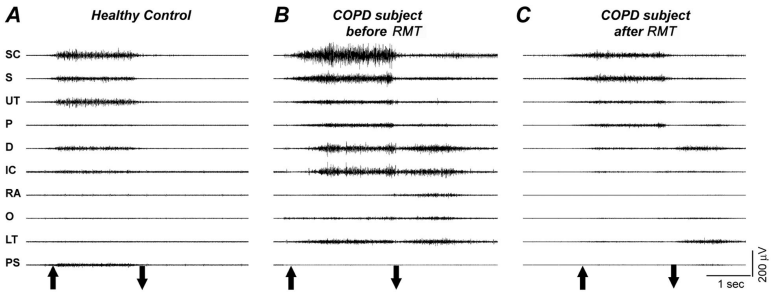

Figure 1.

Superimposed sEMG activity of left and right sternocleidomastoid (SC), scalene (S), upper trapezius (UT), pectoralis (P), diaphragm (D), intercostal (IC), rectus abdominis (RA), obliquus abdominis (O), lower trapezius (LT), and lumbar paraspinal (PS) muscles during unloaded deep breath recorded from Healthy Control and COPD individual before and after the Respiratory Motor Training (RMT). Start of inspiration is marked by the up arrow and expiration by the down arrow, down. Note that the abnormal pattern of increased activity of the respiratory muscles during unloaded breathing in COPD subject reverted towards normalization following RMT.

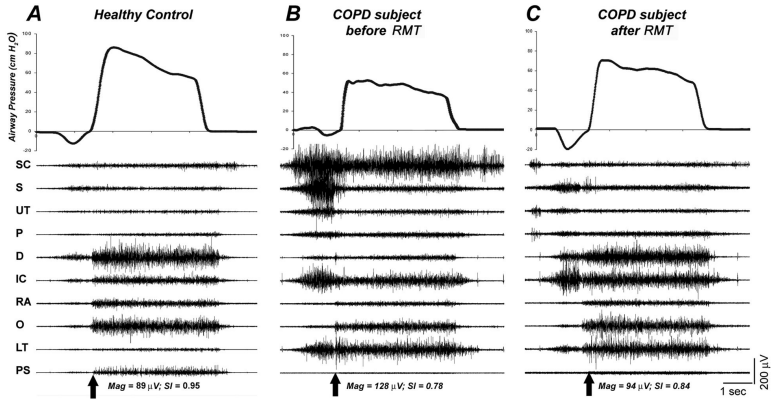

Figure 2.

Superimposed sEMG activity of left and right respiratory muscles (listed in Fig.1) and airway pressure during Maximum Expiratory Pressure Task (MEPT) recorded from a Healthy Control and COPD individual before and after the Respiratory Motor Training (RMT). Start of forced expiration is marked by arrow. Note inappropriate activation of inspiratory muscles (SC and S) during forced expiration and increase in overall sEMG activity (Mag = 128 μV) associated with lower airway pressure in COPD subject. Note that RMT brought improved respiratory muscle activation closer to the patterns recorded from the Healthy Control. Note also that this improvement was accompanied by higher airway pressure demonstrating improved respiratory muscle performance.

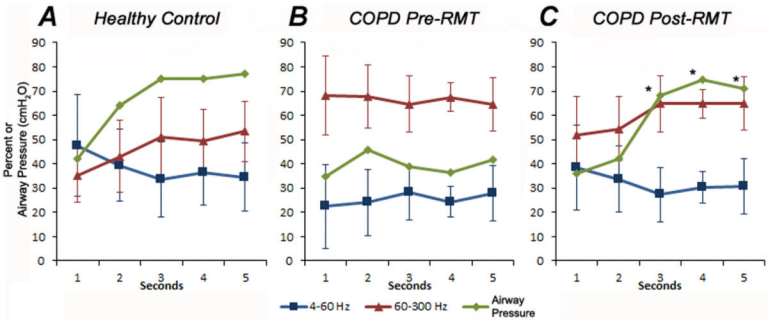

Figure 3.

The dynamics of airway pressure and sEMG frequency composition in non-fatigued expiratory muscles during Maximum Expiratory Pressure Task (MEPT) in Healthy Control subjects (n=4) and individuals with COPD (n=4) before and after Respiratory Motor Training (Pre- and Post-RMT). *Note a significant (P*<.05) post-RMT increase in airway pressure and that in contrast to Healthy Controls, in COPD subjects, fast-twitch muscle fibers (60-300 Hz) failed to be activated before training, and that this alteration was not the case after RMT. Note also trend to compensatory activation of slow-twitch muscle fibers (4-60 Hz) starting from 3s, observed in COPD subjects before RMT.

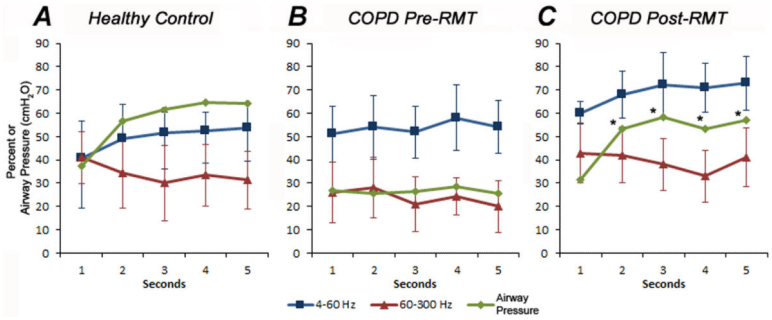

Figure 4.

The dynamics of airway pressure and sEMG frequency composition in fatigued expiratory muscles during Maximum Expiratory Pressure Task in Healthy Control subjects (n=4) and individuals with COPD (n=4) before and after Respiratory Motor Training (Pre- and Post-RMT). *Note a significant (P*<.05) post-RMT increase in airway pressure and that in contrast to Healthy Controls, in COPD subjects, slow-twitch muscle fibers (4-60 Hz) failed to be activated before training, and that this alteration was not the case after RMT. Note also that this improvement was associated with increased airway pressure.

Table 1

Summary of Pulmonary Function Test (PFT) values obtained before and after the Respiratory Motor Training (RMT)

Subjects (n = 4)	PFT									
	FVC (% predicted)		FEV_1 (% predicted)		FEF_{max} (% predicted)		PE_{max} (cmH_2O)		PI_{max} (cmH_2O)	
	Before RMT	After RMT	Before RMT	After RMT	Before RMT	After RMT	Before RMT	After RMT	Before RMT	After RMT
1	80	79	61	64	45	53	40	45	29	42
2	94	92	54	57	56	69	41	63	30	43
3	84	85	70	72	57	60	18	30	22	49
4	91	78	51	49	46	52	43	70	55	65
Mean ± SD	**87 ± 6**	**84 ± 6**	**59 ± 9**	**61 ± 10**	**51 ± 6**	**59 ± 8** *	**36 ± 12**	**52 ± 18** *	**34 ± 14**	**50 ± 11** *

* indicate significant increase ($p < 0.05$) after RMT