

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE:
CARDIOLOGIA E CIÊNCIAS CARDIOVASCULARES

**NOVAS EVIDÊNCIAS PARA DOENÇA PULMONAR OBSTRUTIVA
CRÔNICA: EFEITO DO TREINAMENTO DE FORÇA, MUSCULAR
RESPIRATÓRIO E DA ELETROESTIMULAÇÃO NEUROMUSCULAR**

TESE DE DOUTORADO

PAULO J. C. VIEIRA

Universidade Federal do Rio Grande do Sul

Programa de Pós-Graduação em Ciências da Saúde:

Cardiologia e Ciências Cardiovasculares

**NOVAS EVIDÊNCIAS PARA DOENÇA PULMONAR OBSTRUTIVA
CRÔNICA: EFEITO DO TREINAMENTO DE FORÇA, MUSCULAR
RESPIRATÓRIO E DA ELETROESTIMULAÇÃO NEUROMUSCULAR**

Paulo J. C. Vieira

*Tese de doutorado apresentada como
requisito parcial para obtenção do título de
Doutor em Ciências Cardiovasculares, à
Universidade Federal do Rio Grande do
Sul, Programa de Pós-Graduação em
Ciências da Saúde: Cardiologia e Ciências
Cardiovasculares.*

Orientador: Dr. Gaspar R. Chiappa

Porto Alegre

2015

CIP - Catalogação na Publicação

Cardoso Vieira, Paulo José

NOVAS EVIDÊNCIAS PARA DOENÇA PULMONAR OBSTRUTIVA
CRÔNICA: EFEITO DO TREINAMENTO DE FORÇA, MUSCULAR
RESPIRATÓRIO E DA ELETROESTIMULAÇÃO NEUROMUSCULAR /
Paulo José Cardoso Vieira. -- 2015.

119 f.

Orientador: Gaspar Rogério da Silva Chiappa.

Tese (Doutorado) -- Universidade Federal do Rio
Grande do Sul, Faculdade de Medicina, Programa de Pós-
Graduação em Ciências da Saúde: Cardiologia e
Ciências Cardiovasculares, Porto Alegre, BR-RS, 2015.

1. Doença Pulmonar Obstrutiva Crônica - DPOC . 2.
Força. 3. Eletroestimulação. 4. Treinamento
Respiratório. 5. Capacidade Funcional. I. da Silva
Chiappa, Gaspar Rogério, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os
dados fornecidos pelo(a) autor(a).

DEDICO ESTE TRABALHO

A meus pais, Wilmar Carvalho Vieira (*in memorian*) e Maria Beatriz Cardoso Vieira,
exemplos de dedicação, carinho e amor.

Por todos os momentos em que me acompanharam sempre me incentivando.

A toda minha família pelo apoio constante, carinho e atenção.

A meu grande amigo, irmão e professor orientador Gaspar R. Chiappa por toda atenção,
incentivo e disponibilidade.

À minha esposa e melhor amiga, Fernanda e meu filho Davi.

Pelos momentos que vivemos durante esta trajetória.

AGRADECIMENTOS

A realização deste trabalho, e, mais do que isso, esta etapa da minha vida, não estaria sendo concluída, não fosse a importância das pessoas a quem aqui devo minha gratidão.

Agradeço ao meu orientador prof. Gaspar R. Chiappa, pelo entusiasmo, trabalho e responsabilidade com que me conduziu nesta trajetória acadêmica, por me mostrar que é possível ser homem de ciência, e ser humano. Sem sua presença constante e incentivo esse trabalho jamais seria possível, além da amizade e irmandade ímpar que temos, levo hoje um exemplo de excelência profissional a ser seguido e respeitado sempre.

Ao Prof. Jorge Pinto Ribeiro (*in memoriam*), por ter me recebido, acima de tudo, ter ouvido minhas idéias, sendo com certeza uma das grandes personalidades que proporcionou o início da minha formação acadêmica.

A todos os professores deste programa de pós-graduação, pelos ensinamentos, solidariedade e amizade.

Aos colegas do LaFiEx, especialmente ao Prof. Daniel Umpierre, exemplo de colega, que sempre me incentivou e ensinou quando possível.

Ao Prof. Gerson Cipriano, pelas discussões, auxílio material e intelectual.

Ao serviço de Eng^a Biomédica do Hospital de Clínicas de Porto Alegre, pela importante contribuição técnica e ensinamentos na área.

As Professoras Andréia Biolo e Carisi Polanczyk, coordenadoras deste programa de pós-graduação, pela ética de ambas, cobrança e incentivo.

À Sirlei, secretária do Pós-Graduação em Cardiologia, pelo carinho, atenção e constante disposição em sempre ajudar os alunos.

Agradeço com muito amor a toda minha família, pelo carinho e atenção que sempre disponibilizaram.

Aos meus pais, em especial a memória de pai, pelo exemplo de honestidade, dedicação, empenho e humildade, eu gostaria de expressar minha eterna gratidão pelo seu amor. Aos momentos que não estávamos juntos, mas mesmo sem a presença de vocês, sempre serei agradecido pelo que sou e pelos ensinamentos, sempre amarei vocês.

Agradeço à minha esposa e amiga, Fernanda, pela paciência, dedicação, carinho e amor durante toda esta jornada, em especial pelo maior de todos os presentes em nossas vidas, nosso filho Davi, amo muito vocês.

À Deus pela oportunidade de nos deixar evoluir constantemente.

Muito obrigado.

*“O atrativo do conhecimento seria pequeno se, no caminho que a ele conduz,
não houvesse que vencer tanto pudor.”*

Friedrich Nietzsche

(1844 - 1900)

SUMÁRIO

LISTA DE ABREVIATURAS.....	9
RESUMO.....	12
INTRODUÇÃO	13
REFERÊNCIAS	16
2. REVISÃO DA LITERATURA	19
2.1 DPOC	19
2.1.1 <i>DEFINIÇÃO E PRINCIPAIS ACHADOS CLÍNICOS.....</i>	<i>19</i>
2.1.2 <i>DADOS EPIDEMIOLÓGICOS</i>	<i>23</i>
2.1.3 <i>DPOC E COMORBIDADES</i>	<i>24</i>
2.2 DPOC E ATIVIDADE FÍSICA	25
2.3 DISFUNÇÃO MUSCULAR ESQUELÉTICA NA DPOC.....	26
2.4 DISTRIBUIÇÃO DA FORÇA E RESISTÊNCIA MUSCULAR NA DPOC	28
2.5 INTOLERÂNCIA AO EXERCÍCIO NA DPOC.....	29
2.6 IMPACTO DA DPOC SOBRE AS AVD'S	31
3 INTERVENÇÕES TERAPÊUTICAS EM REABILITAÇÃO NA DPOC.....	34
3.1 TREINAMENTO DE FORÇA.....	34
3.2 TREINAMENTO MUSCULAR RESPIRATÓRIO	35
3.3 ESTIMULAÇÃO ELÉTRICA NEUROMUSCULAR E FORTALECIMENTO MUSCULAR.....	36
3.4 MECANISMOS RESPONSÁVEIS PELAS ALTERAÇÕES NA CAPACIDADE DE PRODUÇÃO DE FORÇA POR MEIO DA EEN	37
4 JUSTIFICATIVA	41
5 OBJETIVOS	43
REFERÊNCIAS	44
ARTIGO I	52
COMPARISON OF THE EFFECTS OF RESPIRATORY MUSCLE TRAINING AND RESISTANCE TRAINING ON RESPIRATORY AND SKELETAL MUSCLE STRENGTH IN PATIENTS WITH COPD	52

ARTIGO II.....	77
NEUROMUSCULAR ELECTRICAL STIMULATION IMPROVES CLINICAL AND PHYSIOLOGICAL FUNCTION IN COPD PATIENTS	77
CONCLUSÕES.....	114
ANEXOS	115
PRODUÇÃO DURANTE A PÓS-GRADUAÇÃO	115
<i>ARTIGOS PUBLICADOS.....</i>	<i>116</i>

LISTA DE ABREVIATURAS

DPOC	Doença Pulmonar Obstrutiva Crônica
EEN	Estimulação Elétrica Neuromuscular
HD	Hiperinsuflação Dinâmica
TMR	Treinamento Muscular Respiratório
TF	Treinamento de Força
P _I max	Pressão Inspiratória Máxima
P _E max	Pressão Expiratória Máxima
VO ₂ pico	Consumo Máximo de Oxigênio
TC6'	Teste e Caminhada 6 Minutos
TMQ	Torque do Músculo Quadríceps
RMQ	Resistência do Músculo Quadríceps
TNF- α	Fator de Necrose Tumoral
VEF ₁	Volume Expiratório Forçado no 1'
CVF	Capacidade Vital Funcional
T _{lim}	Tempo de Tolerância Ao Exercício
FMI	Fraqueza Muscular Inspiratória
GOLD	Global Initiative for Chronic Obstructive Lung Disease
LLN	Limite Inferior do Normal
VO ₂ max	Consumo Máximo de Oxigênio
AVD's	Atividades de Vida Diária
CI	Capacidade Inspiratória
CRF	Capacidade Residual Funcional
1-RM	Uma Repetição Máxima
TMI	Treinamento Muscular Inspiratório
COPD	Chronic Obstructive Pulmonary Disease
RMT	Respiratory Muscle Training
RT	Resistan

P _I max	Maximum Inspiratory Pressure
P _E max	Maximum Expiratory Pressure
1-RM	One-Repetition Maximum
PFT	Pulmonary Function Test
FVC	Functional Vital Capacity
FEV ₁	Forced Expiratory Volume (one second)
FEV ₁ /FVC	FEV ₁ to FVC Ratio
IC	Inspiratory Capacity
TLC	Total Lung Capacity
IC/TLC	Inspiratory Fraction
SpO ₂	Arterial Oxyhemoglobin Saturation
VO ₂	Oxygen Consumption
IF	Inspiratory Fraction
DH	Dynamic Hyperinflation
6-MWT	Six-Minute Walk Test
QMT	Quadriceps Muscle Torque
QME	Quadriceps Muscle Endurance
NMES	Neuromuscular Electrical Stimulation
<i>T_{lim}</i>	Time T=to Exercise Tolerance
6-MWTD	Six-Minute Walk Test Distance
SGRQ	St. Georges Respiratory Questionnaire Score
BDS and BLS	<i>Borg</i> Dyspnea and Leg Score
TNF- α	Tumor Necrosis Factor
CWT	Constant Work Rate Test
BMI	Body Mass Index
FFM	Fat Free Mass
VO _{2peak}	Peak Oxygen Uptake
HR	Heart Rate
EELV	End Expiratory Lung Volume

ME	Mechanical Efficiency
RER	Respiratory Exchange Ratio
HRQOL	Health-Related Quality Of Life
MVV	Maximal Ventilatory Voluntary
RV	Residual Volume
D_{LCO}	Lung Diffusing Capacity for Carbono Monoxide
Pa	Arterial Partial Pressure
Sa	Arterial Saturation
VCO_2	Carbon Dioxide Output
VE	Minute Ventilation
VE/MVV	Maximal Voluntary Ventilation
VT	Tidal Volume
MM	Muscle Mass
RMS	Root Mean Square

RESUMO

Pacientes com doença pulmonar obstrutiva crônica (DPOC) apresentam uma função muscular alterada com prejuízo na capacidade de exercício. Na tentativa de reverter esse quadro, tem-se recomendado o uso de treinamento de força, de musculatura respiratória e mais recentemente da utilização de estimulação elétrica neuromuscular (EEN). No entanto, os estudos não demonstraram, o efeito sobre a hiperinsuflação dinâmica (HD) e qual a relação entre a presença do componente de fraqueza muscular respiratória e periférica na intolerância ao exercício.

Métodos: Um programa de treinamento muscular respiratório (TMR, n = 51), treinamento de força (TF, n = 53) ou controle (n = 50), foi instituído. Função pulmonar, força muscular respiratória (P_{Imax} e P_{E_{max}}), consumo de oxigênio (VO_{2pico}), teste de caminhada de 6 minutos (TC6'), torque do músculo quadríceps (TMQ) e resistência (RMQ) foram avaliados. Em outro estudo com EEN (n = 11) e controles (n = 9). Foram avaliados, tolerância ao exercício (T_{lim}), função pulmonar, fator de necrose tumoral (TNF- α) e níveis de β -endorfina. **Principais achados:** O VEF₁, CVF e VEF₁/CVF aumentaram significativamente no TF. P_{Imax} (P <0,001) e TC6' (P <0,01) aumentaram nos grupos TMR e TF. P_{E_{max}} (P <0,001) foi maior no grupo TF vs. TMR. VO_{2pico} (P <0,001) aumentou nos 2 grupos (TMR e TF) vs. controles. TMQ e RMQ (P <0,01) aumentou significativamente no grupo TF vs. TMR. O grupo EEN aumentou o VEF₁, VEF₁ /CVF, TC6' e T_{lim} (P <0,01) e reduziu os valores na escala de *Borg* (P <0,01). Além disso, o T_{lim} foi positivamente correlacionado com melhorias no VEF₁ ($\rho = 0,48$; P <0,01), reduzindo os níveis de TNF- α e aumentando β -endorfina, em comparação com o grupo controle (P <0,001) **Conclusão:** O TMR e TF melhoram o desempenho do músculo esquelético periférico e respiratório em pacientes com DPOC. A EEN reduziu a dispnéia durante o exercício, acompanhado por melhorias no VEF₁, tolerância ao exercício e HD.

INTRODUÇÃO

Pacientes com doença pulmonar obstrutiva crônica (DPOC) caracterizam-se por apresentarem limitação do fluxo aéreo limitando a capacidade de exercício [1-5]. Embora a tolerância ao exercício reduzida na DPOC tem uma origem multifatorial [2], o aumento progressivo dos volumes pulmonares, secundário à limitação do fluxo expiratório, a hiperinsuflação dinâmica (HD), e consequente dispnéia, assume um papel importante, especialmente em pacientes com doença pulmonar avançada [3]. A dispnéia é um fator crítico na restrição ao exercício, associado com aumentos dos níveis de citocinas pró-inflamatórias, desequilíbrio antioxidante, hiperinsuflação dinâmica e intensiva [6], colaborando com as alterações no músculo esquelético, o que está intimamente associado com a fisiopatologia da DPOC, e reduções acentuadas no transporte de oxigênio para os músculos [1]. Aparentemente, o transporte de oxigênio pode ser prejudicado devido a alterações nas trocas gasosas pulmonares, resultando em diminuição da saturação de hemoglobina [4], a hiperinsuflação induzida pela limitação do fluxo expiratório e maior trabalho muscular respiratório, contribuem para a fadiga muscular inspiratória e/ou expiratória [7]. Apesar das deficiências de função pulmonar, que tradicionalmente têm sido identificadas como um fator-chave na gênese da baixa tolerância ao exercício nestes pacientes [2], considerável atenção tem sido dada ao papel das mudanças sistêmicas, principalmente a disfunção muscular esquelética, como um elemento importante neste processo [8, 9]. Essa disfunção do músculo esquelético na DPOC indica uma série de mudanças na estrutura e função, levando à diminuição da força e anormalidades no metabolismo energético durante o exercício [5].

Em estudos sobre condicionamento muscular em DPOC, demonstrou-se que os pacientes se beneficiam muito com o treinamento de força (TF) em sua musculatura periférica [10, 11], também existem relatos de melhora no desempenho cardiovascular e na captação de

oxigênio pelo músculo [12]. Na área de reabilitação pulmonar, porém os estudos do componente de força e resistência ainda não definem muito bem a melhor forma de treinar os pacientes com DPOC [13]. Por outro lado, a inclusão do TF na reabilitação pulmonar tem sido recomendada como um meio para melhorar o desempenho do exercício [13-15]. A literatura atual sugere que o TF em pacientes com DPOC melhora a força muscular [5, 16], apesar de poucas evidências avaliarem o possível efeito adicional sobre a força muscular respiratória e a hiperinsuflação dinâmica (HD) em pacientes com DPOC [17].

Semelhante à musculatura esquelética, a disfunção também pode afetar a musculatura inspiratória. Um grande número de pacientes com DPOC podem apresentar fraqueza muscular inspiratória (FMI) com pressão inspiratória máxima (P_Imax <60-70%) do valor previsto [18], além da hiperinsuflação que contribuem de forma sinérgica para tolerância prejudicada ao exercício e dispnéia [18, 19]. No entanto, as evidências que demonstram fraqueza e fadiga muscular inspiratória crônica não são muito robustas em pacientes com DPOC [20]. Vários estudos têm demonstrado uma melhora na P_Imax após o treinamento muscular respiratório (TMR) em pacientes com DPOC [21, 22]. Outros estudos mostraram resultados inconsistentes sobre melhorias na dispnéia e capacidade de exercício [23, 24]. Uma recente meta-análise [18] demonstrou um aumento da capacidade funcional, dispnéia e qualidade de vida após TMR quando comparado com os controles. Além disso, os autores sugerem a combinação de TMR com um programa geral exercícios, o que resulta em melhorias significativas da P_Imax e tolerância ao exercício em pacientes com FMI. Ainda nesse contexto, há um interesse substancial em modalidades de reabilitação muscular que não evocam dispnéia, tais como a estimulação elétrica neuromuscular (EEN). A EEN envolve a aplicação de uma corrente elétrica em um nível que induz contrações do músculo esquelético [25]. A aplicação de EEN têm sido associada ao aumento da força muscular, capacidade funcional e estado geral de saúde em pacientes com DPOC [6, 26]. Embora os benefícios clínicos tenham sido mostrados após

intervenções com a EEN em populações com doenças crônicas [6, 27, 28] análises, ainda mais detalhadas sobre as melhorias fisiológicas associadas com a EEN são necessárias. Além disso, é particularmente relevante para pacientes com DPOC, uma avaliação mais aprofundada sobre a aplicação da EEN nos músculos periféricos e seus impactos na função pulmonar. Dessa forma, desenvolvemos um estudo tendo como objetivo comparar a eficácia do TMR e TF na função pulmonar, hiperinsuflação dinâmica, capacidade de exercício, força muscular respiratória e força muscular periférica em pacientes com DPOC. Já no segundo estudo apresentado o objetivo é avaliar de forma abrangente os efeitos da EEN na DPOC, fundamentando-se que a EEN pode melhorar medidas clínicas relacionadas com vários processos fisiopatológicos associados com a doença.

REFERÊNCIAS

1. Amann, M., et al., *Impact of pulmonary system limitations on locomotor muscle fatigue in patients with COPD*. Am J Physiol Regul Integr Comp Physiol, 2010. **299**(1): p. R314-24.
2. O'Donnell, D.E. and K.A. Webb, *The major limitation to exercise performance in COPD is dynamic hyperinflation*. J Appl Physiol (1985), 2008. **105**(2): p. 753-5; discussion 755-7.
3. Cordoni, P.K., et al., *Dynamic hyperinflation during treadmill exercise testing in patients with moderate to severe COPD*. J Bras Pneumol, 2012. **38**(1): p. 13-23.
4. Maltais, F., et al., *Effects of oxygen on lower limb blood flow and O₂ uptake during exercise in COPD*. Med Sci Sports Exerc, 2001. **33**(6): p. 916-22.
5. Gosselink, R., T. Troosters, and M. Decramer, *Peripheral muscle weakness contributes to exercise limitation in COPD*. Am J Respir Crit Care Med, 1996. **153**(3): p. 976-80.
6. Neder, J.A., et al., *Home based neuromuscular electrical stimulation as a new rehabilitative strategy for severely disabled patients with chronic obstructive pulmonary disease (COPD)*. Thorax, 2002. **57**(4): p. 333-7.
7. Polkey, M.I., et al., *Inspiratory pressure support reduces slowing of inspiratory muscle relaxation rate during exhaustive treadmill walking in severe COPD*. Am J Respir Crit Care Med, 1996. **154**(4 Pt 1): p. 1146-50.
8. Vestbo, J., et al., *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary*. Am J Respir Crit Care Med, 2013. **187**(4): p. 347-65.
9. Petrovic, M., et al., *Effects of inspiratory muscle training on dynamic hyperinflation in patients with COPD*. Int J Chron Obstruct Pulmon Dis, 2012. **7**: p. 797-805.
10. Clark, C.J., et al., *Skeletal muscle strength and endurance in patients with mild COPD and the effects of weight training*. Eur Respir J, 2000. **15**(1): p. 92-7.
11. Storer, T.W., *Exercise in chronic pulmonary disease: resistance exercise prescription*. Med Sci Sports Exerc, 2001. **33**(7 Suppl): p. S680-92.

12. Steiner, M.C. and M.D. Morgan, *Enhancing physical performance in chronic obstructive pulmonary disease*. Thorax, 2001. **56**(1): p. 73-7.
13. Troosters, T., et al., *Pulmonary rehabilitation in chronic obstructive pulmonary disease*. Am J Respir Crit Care Med, 2005. **172**(1): p. 19-38.
14. O'Shea, S.D., N.F. Taylor, and J.D. Paratz, *A predominantly home-based progressive resistance exercise program increases knee extensor strength in the short-term in people with chronic obstructive pulmonary disease: a randomised controlled trial*. Aust J Physiother, 2007. **53**(4): p. 229-37.
15. Spruit, M.A., et al., *Resistance versus endurance training in patients with COPD and peripheral muscle weakness*. Eur Respir J, 2002. **19**(6): p. 1072-8.
16. Troosters, T., et al., *Resistance training prevents deterioration in quadriceps muscle function during acute exacerbations of chronic obstructive pulmonary disease*. Am J Respir Crit Care Med, 2010. **181**(10): p. 1072-7.
17. O'Donnell, D.E., *Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease*. Proc Am Thorac Soc, 2006. **3**(2): p. 180-4.
18. Gosselink, R., et al., *Impact of inspiratory muscle training in patients with COPD: what is the evidence?* Eur Respir J, 2011. **37**(2): p. 416-25.
19. Koppers, R.J., et al., *Exercise performance improves in patients with COPD due to respiratory muscle endurance training*. Chest, 2006. **129**(4): p. 886-92.
20. Polkey, M.I., et al., *Diaphragm strength in chronic obstructive pulmonary disease*. Am J Respir Crit Care Med, 1996. **154**(5): p. 1310-7.
21. Crowe, J., et al., *Inspiratory muscle training compared with other rehabilitation interventions in adults with chronic obstructive pulmonary disease: a systematic literature review and meta-analysis*. COPD, 2005. **2**(3): p. 319-29.
22. Geddes, E.L., et al., *Inspiratory muscle training in adults with chronic obstructive pulmonary disease: a systematic review*. Respir Med, 2005. **99**(11): p. 1440-58.
23. Weiner, P., et al., *Comparison of specific expiratory, inspiratory, and combined muscle training programs in COPD*. Chest, 2003. **124**(4): p. 1357-64.

24. Lisboa, C., et al., *Inspiratory muscle training in chronic airflow limitation: effect on exercise performance*. Eur Respir J, 1997. **10**(3): p. 537-42.
25. Sillen, M.J., et al., *Effects of neuromuscular electrical stimulation of muscles of ambulation in patients with chronic heart failure or COPD: a systematic review of the English-language literature*. Chest, 2009. **136**(1): p. 44-61.
26. Dal Corso, S., et al., *Skeletal muscle structure and function in response to electrical stimulation in moderately impaired COPD patients*. Respir Med, 2007. **101**(6): p. 1236-43.
27. Vivodtzev, I., et al., *Functional and muscular effects of neuromuscular electrical stimulation in patients with severe COPD: a randomized clinical trial*. Chest, 2012. **141**(3): p. 716-25.
28. Karatzanos, E., et al., *Electrical muscle stimulation: an effective form of exercise and early mobilization to preserve muscle strength in critically ill patients*. Crit Care Res Pract, 2012. **2012**: p. 432752.

2. REVISÃO DA LITERATURA

2.1 DPOC

2.1.1 DEFINIÇÃO E PRINCIPAIS ACHADOS CLÍNICOS

A DPOC é uma doença caracterizada pela presença de limitação ao fluxo aéreo decorrente de bronquite crônica ou enfisema. Essa obstrução, geralmente, evolui de maneira lenta e progressiva, é irreversível ou parcialmente reversível e está associada à resposta inflamatória do pulmão a partículas ou gases nocivos [1-3].

O padrão ouro no diagnóstico da DPOC é a espirometria. A relação fixa pós broncodilatador entre o volume expiratório forçado no primeiro segundo (VEF_1) e a capacidade vital forçada (CVF) de 0,7 é usada para definir a presença de limitação do fluxo aéreo [4]. A gravidade da doença, com base no VEF_1 , é estratificada em quatro estágios: doença leve ou estágio 1 ($VEF_1 \geq 80\%$), moderada ou estágio 2 ($VEF_1 \geq 50$ e menor que 80%), grave ou estágio 3 ($VEF_1 \geq 30$ e menor que 80%,) e muito grave ou estágio 4 ($VEF_1 < 30\%$) [1]. Entretanto, ainda existe divergência entre os diferentes autores sobre o melhor critério para identificar a obstrução ao fluxo aéreo na DPOC [5]. Como o valor do VEF_1 diminui mais rapidamente com a idade do que a capacidade vital, a definição do consenso GOLD tende a superdiagnosticar a DPOC em idosos. Em função disso alguns autores sugerem a utilização do Limite Inferior do Normal (LLN) como critério diagnóstico para a doença [5].

Tabela 1 – Classificação da Gravidade da DPOC

Estágio	VEF₁/ CVF	VEF₁% previsto
Estágio I: Leve	$\leq 0,70$	VEF ₁ ≥ 80
Estágio II: Moderado	$\leq 0,70$	VEF ₁ ≥ 50 e < 80
Estágio III: Grave	$\leq 0,70$	VEF ₁ ≥ 30 e < 50
Estágio IV: Muito Grave	$\leq 0,70$	VEF ₁ < 30

*Fonte: *GOLD 2011[4]*

Em um estudo de Coorte, Guder *et al.* [5] acompanharam durante 4,5 anos 405 pacientes, cujo diagnóstico de DPOC foi realizado segundo os dois critérios - o preconizado pelo consenso GOLD e o LLN, sendo a resposta ao tratamento e o prognóstico levados em consideração. Em suas conclusões os autores observaram que os dois métodos ainda apresentam falhas para diagnosticar a DPOC. A discussão teórica sobre o critério utilizado para detectar a doença em países desenvolvidos esbarra na situação “real” do acesso aos serviços de saúde e da disponibilidade da espirometria nos setores de atendimento primário nos países em desenvolvimento e subdesenvolvidos. Como a progressão da doença é usualmente insidiosa e lenta, podendo demorar algumas décadas antes que os principais sintomas apareçam, o mais frequente é que o diagnóstico seja feito em estádios avançados da doença [6].

Com a segunda revisão do consenso GOLD em 2011 [1], as exacerbações e comorbidades foram introduzidas para a definição da DPOC de acordo com a contribuição para a gravidade da doença nos pacientes. Um novo sistema multidimensional para a avaliação e gestão da doença foi introduzido. Pela primeira vez, foi recomendado que fatores além do FEV₁ devem ser incluídos na avaliação da DPOC. A abordagem proposta, consiste em uma combinação do grau de limitação do fluxo aéreo, o impacto da doença percebido pelo paciente e a frequência de exacerbação, refletindo melhor a complexidade da DPOC do que a análise unidimensional até então proposta. Desde a introdução desta nova avaliação, profissionais de

saúde e investigadores vêm discutindo ativamente os potenciais pontos fortes e limitações deste sistema e suas implicações para a prática clínica. Agusti *et al.* [4] reviram os resultados de vários estudos recentes que aplicaram o sistema de estadiamento multidimensional para coortes existentes da DPOC. Embora alguns estudos [4, 7, 8] incluídos nesta revisão não foram concebidos para esse fim, essas análises têm aumentado significativamente a nossa compreensão da distribuição, característica, estabilidade ao longo do tempo e relacionamento com resultados para o novo GOLD em categorias A, B, C e D [9].

Tornou-se claro que a distribuição das diferentes categorias depende da população estudada e que a classificação pode realmente mudar ao longo do tempo, assim como as comorbidades são predominantemente presentes nos grupos com altos sintomas B e D [4]. Além disso, os resultados destes estudos recentes indicam claramente que a nova categorização A-D não reflete necessariamente um aumento linear na gravidade da doença, e que o risco de hospitalização e de mortalidade é semelhante nos grupos B (altos sintomas e baixo risco) e C (baixos sintomas e alto risco) [4]. Portanto, os grupos não diferiram na taxa de declínio da função pulmonar, o que sugere que este sistema não prevê a atividade da doença. Vale ressaltar que nenhum dos grupos com DPOC analisados usou o Teste de Avaliação da DPOC [10] para medir sintomas atuais. No entanto, uma discrepância nos resultados relacionados com o paciente entre as duas medidas propostas para os sintomas (pontuação modificada para dispneia do *Medical Research Council* e o Teste de Avaliação da DPOC) foi relatado anteriormente [9, 10].

Baseado no conhecimento atual sobre a avaliação da DPOC, é provavelmente seguro concluir que a apresentação clínica e o curso da DPOC são muito heterogêneos de serem capturados por um número limitado de variáveis em duas dimensões. De fato, foi demonstrado recentemente que existe uma considerável heterogeneidade dentro de uma população de pacientes do grupo D [11]. Uma explicação possível para esta observação é o fato de que a

grande maioria dos pacientes classificados como "alto risco" (grupos C e D) são desses grupos em função de um FEV₁ reduzido severamente e não devido a um elevado número de exacerbações [9]. Na verdade, o fenótipo "exacerbador frequente" [11] dos pacientes nos grupos C e D pode exigir uma classificação separada [4, 9]. Do ponto de vista de uma avaliação ótima do estado de saúde integrado na DPOC, a lista de variáveis a serem incluídas é provavelmente infinita, incluindo não só os resultados adicionais clínicas (como hiperinsuflação, capacidade de exercício, índice de massa corporal e comorbidades), mas também fatores de estilo de vida (incluindo o tabagismo, nível de atividade física e dieta), e marcadores biológicos e genéticos suplementares [9]. No entanto, deve ser considerado que o GOLD é de fato uma iniciativa global e que as regiões menos desenvolvidas do mundo não podem se beneficiar de abordagens de estadiamento da doença mais complexas. Assim, qualquer sistema de estadiamento da DPOC deve encontrar um equilíbrio entre a facilidade de implementação e captura adequada da complexidade da doença [9].

A dispnéia é uma das manifestações clínicas importantes da doença, que costuma se apresentar aos grandes esforços quando o VEF₁ se reduz para cerca de 50% do previsto [12]. Com a evolução da doença a dispnéia aumenta progressivamente, estando presente durante pequenos esforços, comprometendo as AVD's e posteriormente se manifestando até no repouso. Apesar do comprometimento no sistema respiratório predominar, a DPOC é considerada uma doença de ordem sistêmica, com alterações do humor, alterações nutricionais e perda de peso, depleção dos tecidos orgânicos e perda de massa muscular. Essas alterações comprometem a função muscular periférica, diminuem a tolerância ao exercício e estão associadas a um pior prognóstico [13, 14].

2.1.2 DADOS EPIDEMIOLÓGICOS

A prevalência da DPOC ainda está em ascensão e os custos de saúde pública relacionados à doença são substanciais. A DPOC está entre as doenças com maior índice de morbidade e mortalidade no mundo. Nos Estados Unidos a DPOC, em 2012, foi considerada a quarta causa de morte, ainda é a única doença que continua em expansão entre as 10 maiores causas de mortalidade. No mesmo ano, o número de óbitos em mulheres excedeu o número de homens [14]. Entretanto, acredita-se que estes dados possam estar subestimados, pois a DPOC muitas vezes está entre as comorbidades ao invés de ser a causa subjacente do óbito dos pacientes portadores da doença [6].

A prevalência mundial da DPOC apresenta índices com grande variabilidade. O estudo PLATINO teve como objetivo descrever a epidemiologia da DPOC em cinco grandes cidades da América Latina: São Paulo (Brasil), Santiago (Chile), Cidade do México (México), Montevideu (Uruguai) e Caracas (Venezuela). Informações completas, incluindo espirometria, foram obtidas de 963 pessoas em São Paulo, 1173 em Santiago, 1000 na Cidade do México, 885 em Montevideu, e 1294 em Caracas. Taxas brutas de DPOC variaram de 7,8% (78 de 1000, 95% IC 5,9-9,7) na Cidade do México para 19,7% (174 de 885; 95% IC 17,2-22,2), em Montevideu. Estes resultados sugerem que a DPOC é um grande problema de saúde na América Latina, principalmente pelas altas taxas de consumo de tabaco nestes países [15].

No Brasil, a análise de um subgrupo do estudo PLATINO, demonstrou a prevalência da DPOC em indivíduos com 40 ou mais anos de idade residentes na área metropolitana da Grande São Paulo. Nesse estudo a prevalência total da DPOC foi de 15,8%, sendo 18% nos homens e 14% nas mulheres. A distribuição de DPOC pela faixa etária foi: 40-49 anos, 8,4%; 50-59 anos, 16,2%; e acima de 60 anos, 25,7% [15]. No nosso país ainda temos dificuldades de levantamentos como esse em função da falta de registros epidemiológicos e recursos que possam disponibilizar exames de maior complexidade para essa população [15].

2.1.3 DPOC E COMORBIDADES

Além do comprometimento respiratório a DPOC apresenta alterações “extrapulmonares” conhecidas como manifestações sistêmicas. Entre estas, destacam-se as mudanças nos níveis de estresse oxidativo, ativação de células inflamatórias, alterações nutricionais e na composição corporal, assim como, comprometimentos osteoarticulares, cardiovasculares e no sistema nervoso. A limitação ao exercício não está condicionada somente as alterações respiratórias, dispnéia e hiperinsuflação dinâmica, mas também com a disfunção muscular esquelética [16-18].

A inflamação sistêmica e o estresse oxidativo participam na patogênese da DPOC [19, 20]. Foram descritas alterações no número de neutrófilos, aumento na carga oxidante e redução da capacidade antioxidante, aumento no número de moléculas de adesão dos neutrófilos circulantes em pacientes com DPOC estável e aumento no número de mediadores pró-inflamatórios, tais como, o fator de necrose tumoral e interleucinas [17, 20, 21].

O sedentarismo, a hipóxia tecidual, o uso crônico de corticosteróide, a depleção nutricional e principalmente, a inflamação sistêmica contribuem para a piora do prognóstico destes pacientes [3, 12]. A doença cardiovascular é uma causa frequente de morte em indivíduos com DPOC, ocasionada muitas vezes por doença arterial coronariana. A insuficiência ventricular esquerda e arritmias são relatadas com frequência na DPOC [22]. A inflamação sistêmica contribui ainda para o aparecimento de osteoporose e distúrbios do SNC, incluindo a depressão [23].

Os pacientes com DPOC apresentam alterações relacionadas com a arquitetura e função do sistema musculoesquelético [18]. A atrofia pela inatividade física pode estar presente na DPOC, sendo os músculos dos membros inferiores os mais acometidos. No estudo realizado por HajGhanbari *et al.* [24] foram investigados, através de ressonância magnética tridimensional, a medição do tamanho e forma do trofismo da musculatura da coxa em 20

pacientes com DPOC e 20 indivíduos saudáveis. Os resultados permitiram observar anormalidades nos músculos extensores e flexores do joelho em pacientes com DPOC, quando comparados com indivíduos normais. Adicionalmente, a constituição da musculatura esquelética de acordo com o tipo de fibras musculares foi avaliada previamente em portadores de DPOC. Em pacientes com a doença, independentemente da perda de massa muscular, foi relatada uma diminuição nas fibras de contração lenta do tipo 1 e aumento relativo das fibras do tipo 2, indicando um desvio relativo da capacidade oxidativa para a via glicolítica [17].

2.2 DPOC E ATIVIDADE FÍSICA

A obstrução ao fluxo aéreo, a inatividade e o descondicionamento físico são importantes fatores que contribuem para a piora do prognóstico na DPOC [25]. Em função dos fatores pulmonares e extrapulmonares e da intensidade dos sintomas, os indivíduos com DPOC evitam o esforço físico e, conseqüentemente, acentuam o descondicionamento físico, gerando um ciclo vicioso de dispnéia e inatividade [25, 26].

O conceito de atividade física é diferente do conceito de tolerância ao exercício, ou seja, atividade física é definida como qualquer movimento produzido pelo sistema músculo esquelético onde haja consumo de oxigênio. Em pessoas saudáveis a atividade física é condição relacionada com a expectativa de vida, já no grupo de pessoas que apresentam comprometimentos na sua saúde, baixo nível de atividade física e intolerância ao exercício são também considerados marcadores de gravidade da doença [27].

Pacientes com DPOC moderada a grave, em comparação com indivíduos saudáveis, apresentam redução importante das atividades físicas, um gasto energético maior no desempenho das atividades e um menor consumo máximo de oxigênio (VO_{2max}) [28]. Esta redução do VO_{2max} ocorre devido a três fatores: limitação cardiovascular, limitação respiratória,

incluindo fatores de mecânica ventilatória e troca de gases e fatores periféricos, referentes ao descondicionamento muscular [29, 30].

O estudo de Garcia-Aymerich *et al.* [29], demonstrou que a atividade física reduz internações hospitalares e até mesmo a mortalidade em pacientes com DPOC. Em outro trabalho realizado pelo mesmo autor, foram avaliados 41 pacientes com DPOC na sua primeira internação devido a episódio de exacerbação em nove hospitais de ensino da Espanha. O objetivo foi avaliar a relação entre atividade física regular e as características clínicas e funcionais da DPOC. Os autores observaram que pacientes fisicamente mais ativos apresentam melhor estado funcional em termos de capacidade de difusão do monóxido de carbono, pressão expiratória máxima, teste de caminhada de seis minutos, consumo máximo de oxigênio e a inflamação sistêmica. Do mesmo modo, a capacidade de realizar exercícios está diretamente ligada com a capacidade de resistência dos músculos ventilatórios [31].

Um grande número de estratégias como oxigenioterapia [32], heliox [30], suplementação de esteróides anabolizantes [33], creatina monohidratada [34], estimulação neuromuscular [35] e técnicas de conservação de energia [34] foram estudadas no contexto da reabilitação de pacientes com DPOC. No entanto, entre todas estas estratégias, a recuperação do condicionamento muscular, parece ser a medida com maior impacto sobre a qualidade de vida, já que a intolerância ao exercício é comum em pacientes com DPOC [36].

2.3 DISFUNÇÃO MUSCULAR ESQUELÉTICA NA DPOC

A disfunção muscular esquelética é um dos principais efeitos extrapulmonares da DPOC apresentando impacto negativo sobre o estado de saúde [37] e capacidade funcional destes pacientes [38]. A perda de massa muscular esquelética ocorre em aproximadamente 30% dos portadores de DPOC e é responsável pela redução na força muscular devido à diminuição

de unidades funcionais disponíveis para a contração muscular com consequente instalação de fraqueza muscular [18, 39].

Fatores como descondicionamento muscular por desuso, desnutrição, miopatia pelo uso de corticoesteróides sistêmicos, hipoxemia, inflamação sistêmica (com aumento dos níveis circulantes de citocinas pró-inflamatórias) e alterações hormonais têm sido sugeridos como potenciais contribuintes para o desenvolvimento da disfunção muscular esquelética em pacientes com DPOC [40-42], com evidências apontando para o descondicionamento por desuso como uma das causas mais comuns [43]. Portadores de DPOC tendem a diminuir seu nível de atividade física por medo da dispneia, o que pode resultar em um ciclo vicioso com reduções da atividade física gerando descondicionamento com consequente aumento do comprometimento muscular esquelético, levando à percepção de sintomas em níveis de trabalho cada vez mais baixos [43].

As anormalidades musculoesqueléticas em portadores de DPOC ocorrem tanto na musculatura ventilatória quanto na musculatura periférica, porém com padrões de carga diferentes. Enquanto os músculos respiratórios, particularmente o diafragma, estão expostos a uma carga de trabalho aumentada devido à alta resistência das vias aéreas e hiperinsuflação (o que os torna cronicamente sobrecarregados e mais propensos à fadiga), os músculos periféricos, principalmente de membros inferiores, tornam-se subutilizados devido ao estilo de vida sedentário adotado por estes pacientes (inatividade crônica), levando ao descondicionamento muscular e/ou à atrofia por desuso e reduzindo sua massa muscular e sua capacidade oxidativa, tornando-os também mais suscetíveis à fadiga [44].

Estudos mostram que pacientes com DPOC apresentam diminuição significativa de força em membros superiores e inferiores, quando comparados com indivíduos saudáveis [18, 43]. A diminuição da força muscular é mais acentuada nos membros inferiores, com o músculo quadríceps apresentando menos força do que os músculos da cintura escapular. Esta

distribuição desigual de força apoia o conceito de descondição por desuso, sugerindo que enquanto os músculos dos membros inferiores são menos utilizados, os músculos da cintura escapular estão mais envolvidos nas atividades de vida diária, além de participarem concomitantemente da respiração acessória [43, 45].

Em indivíduos com DPOC, a disfunção muscular esquelética está associada à perda de força muscular, que é um importante determinante da capacidade de exercício independente da gravidade da doença, é um importante preditor de mortalidade em pacientes com DPOC, independente da função pulmonar, idade e índice de massa corporal [46].

Tabela 2 – Alterações musculares na DPOC

Fatores Etiológicos	Mecanismos Biológicos
Fumaça do cigarro	↓ Mioglobina muscular
Hipercapnia	↑ Autofagia
Acidose	↓ Densidade mitocondrial
Hipoxia	↓ Rede de capilares
Medicamentos	↑ Apoptose
Genética	↑ Atrofia da fibra muscular
Nutrição	↑ Stress oxidativo
Envelhecimento	↑ Proteólise
Metabolismo	↓ Anabolismo
Inflamação Sistêmica	↓ Capacidade oxidativa
Comorbidades	↓ Porcentagem de fibras do tipo I
Exacerbações	
Inatividade	

Fonte: Adaptado de Barreiro *et al.* Guidelines for the Evaluation and Treatment of Muscle Dysfunction in Patients With Chronic Obstructive Pulmonary Disease [47].

2.4 DISTRIBUIÇÃO DA FORÇA E RESISTÊNCIA MUSCULAR NA DPOC

O treinamento com exercícios físicos para a recuperação da força e resistência dos músculos periféricos tem sido usado como terapia coadjuvante na DPOC desde o início da

década de 1960, e tem se mostrado altamente benéfico [48]. O prejuízo da função muscular esquelética em pacientes com DPOC não é homogêneo e sua distribuição entre membros superiores e inferiores ainda não está clara, embora estudos sugiram que a disfunção muscular seja predominante em membros inferiores [13].

Regueiro *et al.* [49], em estudo comparando a força máxima de 52 indivíduos sedentários e 43 pacientes com DPOC, por meio de avaliação isocinética, demonstraram que os pacientes com DPOC apresentaram redução da atividade muscular. Porém, após o treinamento de força e resistência, a função muscular e a resistência no teste de caminhada melhoraram sem nenhuma mudança no consumo máximo de oxigênio. Os resultados propõem que má nutrição, hipoxemia e envelhecimento, dentre outros fatores, possam contribuir para a fraqueza e anormalidades funcionais e morfológicas, porém não justifica o déficit da função muscular esquelética na DPOC, o qual está diretamente ligada ao descondicionamento periférico geral [36].

Embora a musculatura dos membros inferiores seja a grande responsável pela limitação em atividades como andar e subir ladeiras ou escadas, é reconhecido que as AVD's realizadas com os membros superiores, especialmente de maneira não sustentada (na altura dos ombros sem apoio), também são pouco toleradas pelos pacientes com DPOC [49].

Quando comparadas as atividades de membros superiores e membros inferiores, os exercícios com os membros superiores resultam em maior demanda metabólica e ventilatória com sensação de dispnéia e fadiga mais intensas [50].

2.5 INTOLERÂNCIA AO EXERCÍCIO NA DPOC

A intolerância ao exercício é uma das queixas mais frequentes entre portadores de DPOC [51]. Além do comprometimento pulmonar, outros fatores estão envolvidos na limitação ao exercício nestes indivíduos, tais como: 1) a limitação ventilatória devido ao comprometimento da mecânica respiratória e disfunção dos músculos ventilatórios; 2) as anormalidades

metabólicas e nas trocas gasosas; 3) a disfunção muscular periférica; 4) o comprometimento cardíaco; 5) os sintomas relacionados ao esforço, e 6) as combinações de alguns destes fatores interdependentes [3]. Entre os fatores citados acima a limitação ventilatória e a muscular periférica tem um papel importante no comprometimento da capacidade de exercício nestes pacientes.

A hiperinsuflação pulmonar ocorre nos estágios mais avançados da DPOC e é definida como um aumento na capacidade pulmonar total, onde uma maior quantidade de ar permanece nos pulmões no final da expiração espontânea em decorrência da complacência pulmonar aumentada e da limitação ao fluxo aéreo, causadas pelo enfisema [52]. A hiperinsuflação reduz a capacidade inspiratória (CI) e aumenta a capacidade residual funcional (CRF), principalmente durante o exercício (hiperinsuflação dinâmica) [3, 52]. O aumento da demanda ventilatória durante o exercício em pacientes fluxo-limitados aumenta o alçapamento de ar, aumentando ainda mais os volumes pulmonares já aumentados em repouso, resultando em dispneia e limitação da capacidade de exercício [3]. Os músculos respiratórios também são afetados pela hiperinsuflação. À medida que a hiperinsuflação aumenta, o diafragma é empurrado para baixo tornando-se retificado, isto reduz o seu comprimento em repouso, produzindo uma desvantagem mecânica substancial e perda da geração da capacidade de tensão, tornando-o sobrecarregado e mais suscetível a fadiga, especialmente durante o exercício [52]. A dispneia é o principal sintoma limitante do exercício em pacientes com DPOC avançada e muitas vezes leva o indivíduo a evitar a atividade física, com conseqüente descondicionamento muscular esquelético [3, 12], o que somado a hipoxemia, um achado bastante comum em portadores de DPOC, resulta em menor conteúdo de oxigênio sanguíneo podendo elevar a resistência vascular pulmonar e gerar hipertensão arterial pulmonar e conseqüente insuficiência cardíaca direita. A conseqüente redução do débito cardíaco, juntamente com o baixo teor de oxigênio, reduz o fornecimento de oxigênio a todos os órgãos do corpo, incluindo os músculos esqueléticos [3].

Associado a isto, o descondicionamento físico gerado pela subutilização dos músculos periféricos (principalmente membros inferiores) devido ao estilo de vida sedentário destes pacientes, pode levar à atrofia por desuso, com conseqüente limitação ao exercício [3].

Estudos [31, 44, 47], mostram que pacientes com DPOC apresentam fadiga nos membros inferiores durante atividades físicas, indicando que a disfunção muscular periférica, com conseqüente desconforto de membros inferiores durante o exercício, pode contribuir para a limitação da capacidade de exercício nestes pacientes [53]. Além disso, fatores com a anemia e caquexia também podem contribuir para o agravamento da dispneia e para o comprometimento da capacidade de exercício, porém o mecanismo pelo qual interferem na capacidade de exercício ainda não está bem estabelecido [54].

2.6 IMPACTO DA DPOC SOBRE AS AVD'S

As AVD's são definidas como tarefas de desempenho ocupacional, realizadas todos os dias, na preparação ou como adjuntas às tarefas que são conferidas aos indivíduos. Fazem parte das AVD's a capacidade do indivíduo de vestir-se, alimentar-se, tomar banho, pentear-se, habilidades como atender telefone, comunicar-se pela escrita, manipular correspondências, dinheiro, livros e jornais, além da própria mobilidade corporal, como a capacidade de virar-se na cama, sentar-se, mover-se ou transferir-se de um lugar para outro [49].

As AVD's podem ser subdivididas em: AVD's básicas, que são todas aquelas feitas no cotidiano de forma automática e que todo ser humano realiza no decorrer do seu dia, como higiene pessoal, tomar banho, vestir-se, calçar-se e deambular; e AVD's instrumentais, que são aquelas atividades mais complexas de trabalho que necessitam maior independência funcional, como cozinhar, guardar utensílios em armários, arrumar a cozinha, lavar roupas [55]. Os sintomas e as complicações resultantes da DPOC interferem na execução das AVD's e tem

repercussões sobre a qualidade de vida, o que acarreta em quadros de afastamento social, depressão e ansiedade [28].

Uma redução significativa do nível de atividade física em pacientes com DPOC foi demonstrada previamente por Pitta *et al.* [28], os autores compararam atividade física e intensidade de movimento em 50 pacientes com DPOC (64 anos \pm 7 anos) e 25 idosos saudáveis (66 anos \pm 5 anos) e observaram valores menores no tempo de caminhada, tempo de pé e na intensidade de movimento nos pacientes com DPOC.

O gasto energético despendido na execução das AVD's é alto em pacientes com DPOC. Os sintomas e o próprio descondicionalamento físico tornam uma tarefa simples em extremamente difícil e extenuante. Regueiro *et al.* [49] realizaram uma análise da demanda metabólica e ventilatória durante a execução de AVD's em indivíduos com DPOC e indivíduos saudáveis. Nas atividades de trocar a lâmpada, elevar peso, varrer, subir degrau e caminhar na rua, os indivíduos com doença pulmonar apresentaram diminuição na reserva metabólica e na reserva ventilatória [49].

O grau de dificuldade para a realização das AVD's varia de acordo com a tarefa e com as características próprias do paciente. Em atividades como "amarrar os sapatos" e "pentear os cabelos" os pacientes podem desenvolver um padrão respiratório irregular, superficial e rápido durante sua realização e, após as mesmas, respiram rápida e profundamente. A realização de tarefas aparentemente simples, tais como varrer, apagar a lousa, elevar potes e trocar lâmpadas, representa um consumo de oxigênio em torno de 50% a 60% do consumo máximo de oxigênio, além de aumentar também a ventilação minuto, com o uso em torno de 60% a 70% da ventilação voluntária máxima [55].

Pacientes com DPOC podem depender de auxílio na execução de suas AVD's. Alterações de coordenação e equilíbrio também foram observadas em pacientes com DPOC.

Estas alterações tornam os pacientes suscetíveis a quedas, e podem dificultar a realização das AVD's [56].

3 INTERVENÇÕES TERAPÊUTICAS EM REABILITAÇÃO NA DPOC

3.1 TREINAMENTO DE FORÇA

A DPOC progride com a diminuição da força muscular que é predominante nos membros inferiores e isso contribui na intolerância ao exercício, portanto o exercício de força é opção racional no processo de reabilitação [57]. Conforme Clark *et al.* [36], podem ser utilizados aparelhos de musculação comercialmente disponíveis para treinar força, tanto nos membros inferiores quanto nos membros superiores. Os treinamentos com o objetivo de hipertrofia muscular não resultam em aumentos de *endurance*, ou seja, em ganho aeróbio, tendo em vista que as variáveis como $VO_{2máx}$ e limiar anaeróbio não se alteram significativamente [1, 58]. Os treinamentos de força com pesos ainda não estão bem definidos para os pacientes com DPOC [36, 57]. Entretanto, Storer *et al.* [59] relatam: dois a três dias de treino por semana, uma a três séries de repetições para cada grupo muscular escolhido, oito a doze repetições, intervalo de dois a três minutos entre as séries, intensidade de 50 a 85% de 1RM e ajuste da intensidade a cada três ou quatro semanas.

Alguns estudos demonstraram que os escores de força nos pacientes com doença pulmonar obstrutiva crônica eram em média 81% daqueles de uma população controle [58, 59]. Em um outro estudo feito por Bernard *et al.* [45] constatou-se que as medidas de força voluntária das extremidades inferiores com uma repetição máxima para os pacientes com DPOC eram em média de 73% daquelas de um grupo controle equivalente, enquanto o tamanho em corte transversal dos músculos da coxa era em média 76% do grupo controle. Neste mesmo estudo foi mostrado que o treinamento de resistência aprimora a função muscular e o desempenho das atividades funcionais nos pacientes com DPOC. Os princípios de progressão de exercícios sugerem que para maximizar a resposta duas ou três séries podem ser mais vantajosas à medida que o paciente progride. Para o paciente com DPOC, um menor número

de repetições parece ser mais bem tolerado que um número maior, com o ideal parecendo ser oito a dez repetições [57]. Uma introdução gradual ao treinamento com exercícios de resistência, talvez com uma série de oito a dez repetições utilizando 50 a 60% de 1- RM para os principais grupos musculares, evita a fadiga muscular e permite ao participante estabelecer uma base de treinamento a partir da qual poderá avançar o programa de exercício [57, 60]. Além disso, Casaburi *et al.* sugerem que o treinamento seja realizado de duas a três vezes por semana com duas a três séries de oito a dez repetições utilizando cargas de 50 a 85% de uma avaliação atual de 1-RM, com intervalo de repouso entre as séries difícil de ser estabelecido para os pacientes com DPOC, principalmente por causa da dispnéia e ou desaturação de oxigênio, que devem ser acompanhadas constantemente [60].

3.2 TREINAMENTO MUSCULAR RESPIRATÓRIO

O TMR tem sido muito utilizado como uma intervenção isolada ou como integrante da reabilitação pulmonar em pacientes com DPOC. Interessantemente, o TMR é largamente difundido na literatura em várias situações em função de seus benefícios sobre a função da musculatura ventilatória e tolerância ao exercício. No entanto, têm-se discutido o real benefício do aumento da força muscular inspiratória em pacientes com DPOC. Muitos estudos não têm mostrado esse benefício ao paciente, onde o mesmo deve possuir fraqueza da musculatura inspiratória ($P_{I\max} < 60\%$ do previsto) [61]. Parte dos pacientes com DPOC apresentam fraqueza muscular inspiratória (FMI) [62], o que contribui para o surgimento da hipercapnia e dispneia, desaturação noturna [63] e redução da distância caminhada [18].

Estudos prévios [6, 51] e meta-análises [64, 65] não são indiscutivelmente positivos sobre a aplicação do TMR. Os efeitos do TMR são bem definidos, especialmente o seu efeito sobre a força da musculatura inspiratória e redução da dispneia. Gosselink *et al.* [61] publicaram uma importante metanálise de TMR em pacientes com DPOC, onde incluíram 32 estudos. Os

autores encontraram melhora significativa na força muscular inspiratória (13cm H₂O) e resistência (261segundos), capacidade funcional avaliada através do teste de caminhada de 6 minutos (aumento de 32m), dispneia (2,8 pontos) e qualidade de vida (3,8 pontos). Os autores relatam que pacientes com fraqueza muscular inspiratória e baixos valores para PaO₂ ou elevado PaCO₂ são os que melhor respondem ao programa de TMR sobre os desfechos de força muscular inspiratória e capacidade funcional do que aqueles com força preservada.

Recentemente, Petrovic *et al.* [66] avaliaram a eficácia do TMR sobre a hiperinsuflação dinâmica em pacientes com DPOC. Como de acordo com a literatura, os autores encontraram um significativo aumento da P_Imax (14cm H₂O) e aumento da tolerância ao exercício (119 segundos) em comparação com o grupo controle. Interessantemente, os autores identificaram um aumento da fração inspirada, que é a relação entre a capacidade inspiratória e a capacidade pulmonar total, indicativo de redução da hiperinsuflação dinâmica. O grande problema dos estudos com TMR em DPOC é que poucos são os pacientes que desenvolvem fraqueza muscular respiratória, em torno de 20% [61] e que realmente se beneficiarão com essa intervenção de treinamento, além disso, muitas vezes o diafragma se adapta rapidamente ao estímulo [66]. Outro problema está em incluir pacientes classe GOLD IV em função das constantes exacerbações sintomáticas, o que gera dificuldade de aderência e seguimento nos estudos [67].

3.3 ESTIMULAÇÃO ELÉTRICA NEUROMUSCULAR E FORTALECIMENTO MUSCULAR

A estimulação elétrica neuromuscular (EEN) é uma forma alternativa de intervenção que vem sendo proposta para o fortalecimento muscular [68, 69]. Já havia sido demonstrado que adultos jovens obtêm melhoras importantes na força dos músculos extensores do joelho após cinco semanas de treinamento com EEN realizados diariamente [68]. Além disso, a efetividade da EEN foi ainda maior para as contrações dinâmicas em maiores velocidades, quando o joelho era treinado isometricamente em posições fletidas [70], embora isso não tenha

sido observado anteriormente por outros autores, que encontraram apenas um aumento da força isométrica [71]. Porém, em pessoas saudáveis, tem sido sugerido que a EEN não seria tão efetiva para o fortalecimento quanto o treinamento por meio de contrações voluntárias [72]. Já em indivíduos acima de 65 anos, observou-se que o fortalecimento por meio da EEN dependia diretamente do nível de atividade física antes do início da sua aplicação, havendo a necessidade do ajuste adequado da carga para gerar o estresse necessário e garantir os ganhos de força. A EEN quando realizada de forma progressiva passou então a ser indicada para a recuperação da força também em pessoas idosas, e em pacientes com doenças crônicas que geram alguma incapacidade da musculatura esquelética periférica [69].

Atualmente, evidências propõem que a EEN pode ser uma modalidade mais efetiva do que exercícios voluntários no fortalecimento da musculatura dos membros inferiores, especialmente para aqueles indivíduos que sofrem de algum nível de hipotrofia muscular [73]. Como qualquer outra forma de tratamento, a intensidade da EEN deve ser estritamente dosada e aplicada em função do estado funcional inicial do paciente, sendo ajustada gradativamente às mudanças adaptativas musculares ocorridas no decorrer do programa de treinamento [74].

Na DPOC uma das questões fundamentais levantadas por alguns estudos é o fenótipo de pacientes, ou seja, nem todos beneficiam-se com a EEN [75, 76]. Em recente metanálise de Pan *et al.* (2014) não houve evidência de melhora sobre a função respiratória, apenas acréscimos substanciais sobre a musculatura esquelética periférica [77].

3.4 MECANISMOS RESPONSÁVEIS PELAS ALTERAÇÕES NA CAPACIDADE DE PRODUÇÃO DE FORÇA POR MEIO DA EEN

Ainda não estão bem definidos os mecanismos responsáveis pelas alterações na capacidade de produção de força por efeito da EEN. Sabe-se que as alterações nos níveis de força ocorrem tanto em função de alterações neurais quanto musculares, e que a arquitetura

muscular é um fator determinante de 50% da capacidade funcional dos músculos [78, 79]. Contudo, Gondin *et al.* demonstraram que homens jovens saudáveis aumentam em 27% o torque de extensão de joelho após oito semanas de treinamento com EEN em função de adaptações musculares e neurais. Utilizando-se a técnica de interpolação, encontrou-se um aumento de 6% da ativação após o treinamento, indicando que a EEN aumenta a ativação em todo o músculo [76, 80].

Observou-se, também, aumento de 5 a 8% das áreas de secção transversa dos músculos vasto lateral, vasto medial e vasto intermédio, sem alterações na área de secção transversa do músculo reto femoral, acompanhado de um aumento de 14% do ângulo de penação do vasto lateral. Curiosamente, o aumento da ativação dos músculos vasto lateral e vasto medial, observado ao final da quarta semana, não foi acompanhado de alterações significativas dos parâmetros de arquitetura muscular, sugerindo que os fatores neurais são responsáveis pelos ganhos de força iniciais, enquanto as alterações musculares participariam do aumento na força posteriormente [76]. Os mesmos autores avaliaram ainda os efeitos do destreino após quatro semanas do término do treinamento com EEN. Demonstraram que uma diminuição da contração voluntária máxima foi acompanhada de uma queda tanto da ativação muscular, quanto de uma diminuição das áreas de secção transversa. Também foi demonstrado que a área de secção transversa foi responsável pelos valores mais altos da contração voluntária máxima após o destreino, quando comparados com níveis antes do início dos treinos, confirmando que mudanças no nível muscular ocorrem mais lentamente que alterações neurais [80].

Dentre os diversos fatores musculares responsáveis pela geração de força, foi observado que as propriedades intrínsecas das fibras musculares têm papel importante sobre a força específica e sofrem alterações em função do treinamento voluntário [78, 79]. No entanto, pouco se sabe sobre os efeitos da EEN sobre estas propriedades musculares e é provável que seu padrão de recrutamento característico gere adaptações distintas das observadas por efeito de

contrações voluntárias. Em contrações geradas pela EEN, o recrutamento é não-seletivo e randômico, sendo que as unidades motoras não são recrutadas com uma ordem relacionada ao seu tipo (tipo I: fibras de contração lenta resistentes à fadiga; tipo II: de contração rápida menos resistentes à fadiga). Isso implicaria na ativação conjunta de unidades motoras rápidas e lentas, mesmo em níveis baixos de carga elétrica [81]. Por esta razão, a EEN traria benefícios para pessoas com atrofia seletiva das fibras do tipo II ou até pessoas que não conseguem realizar contrações voluntárias com alta intensidade em função de lesão. Mesmo em baixas intensidades de contração, seria possível treinar ao menos parte das fibras rápidas, que voluntariamente são recrutadas apenas em contrações intensas [82].

O treinamento por meio da EEN em adultos saudáveis, Maffiuletti *et al.* mostraram haver uma mudança na distribuição das quantidades de isoformas de cadeias pesadas de miosina na direção IIx \rightarrow IIa. Os autores atribuíram a mudança das isoformas de cadeias pesadas de miosina no sentido IIx \rightarrow IIa à solicitação contínua dessas fibras com o padrão de recrutamento imposto pela EEN. Contudo, também foi observada uma maior hipertrofia das fibras lentas, mostrando que adaptações em função da EEN não são limitadas às fibras rápidas. Por fim, o aumento da força específica observado neste estudo, indica que, de fato, a EEN é capaz de aumentar a força muscular em função de alterações nas propriedades intrínsecas do músculo [83]. Ainda que não se saibam quais seriam os efeitos da EEN no tipo de fibras, estas mudanças sugerem que a EEN é uma modalidade que apresenta vantagens para a reabilitação de indivíduos com atrofia dos músculos.

As contrações provocadas por EEN impõem um padrão randômico de recrutamento das unidades motoras que gera uma demanda metabólica exagerada sobre regiões superficiais dos músculos. Tal efeito está relacionado à ativação celular sincronizada e espacialmente fixa tanto de fibras rápidas quanto lentas. Quando se compararam exercícios voluntários com a EEN, Jubeau *et al.* observaram que, para uma mesma intensidade, a EEN gerou uma maior resposta

de marcadores sanguíneos de dano muscular (aumento da liberação de hormônio de crescimento e atividade da creatinoquinase), além de um aumento da concentração de lactato sanguíneo e da sensibilidade da musculatura, os quais estariam diretamente associados com o nível de lesão muscular gerado [84]. Contudo, outro estudo observou que após a sessão inicial de EEN, adaptações protetoras foram geradas resultando em um menor grau de lesão muscular a partir da segunda sessão [85]. Muito provavelmente, no estudo de Jubeau *et al.* a EEN gerou uma sobrecarga excessiva em função do estado físico inicial dos indivíduos. Tal comportamento corrobora com o pressuposto de que as adaptações em função da EEN são dose-dependentes [74], havendo também a necessidade de aumento da sobrecarga ao longo do tratamento para gerar um nível mínimo de dano muscular, assim como no treinamento voluntário. Levando-se em conta esses achados, a aplicação da EEN sobre o ponto motor é vantajosa ao passo que estimula inclusive fibras mais profundas, quando em comparação com a estimulação elétrica aplicada diretamente sobre o músculo. A aplicação sobre o ponto motor permite um aumento da demanda metabólica também em regiões mais profundas, contribuindo para o processo adaptativo em todo o músculo.

4 JUSTIFICATIVA

A DPOC é uma doença respiratória crônica, que apresenta importantes manifestações extrapulmonares [86] e comorbidades, as quais podem influenciar o quadro clínico, o prognóstico e a qualidade de vida dos portadores da doença. Entre estas manifestações, a disfunção muscular esquelética tem despertado particular interesse devido a sua contribuição para a limitação ao exercício nestes pacientes.

Em conjunto com a dispneia [16], a baixa tolerância ao exercício é a queixa mais comum entre portadores de DPOC [51]. A intolerância ao exercício já foi atribuída exclusivamente ao comprometimento respiratório e à hiperinsuflação que esses pacientes apresentam [52], porém, outros estudos mostraram que a redução da força muscular ventilatória e periférica em portadores de DPOC é um fator que contribui adicionalmente para a limitação da capacidade de exercício [18].

Killian *et al.* [53] relataram a fadiga de membros inferiores como um sintoma limitante ao exercício em indivíduos com DPOC, demonstrando a importância da disfunção muscular periférica sobre a capacidade de exercício nestes pacientes. Este achado foi confirmado por outros estudos [50], sendo que a fadiga de membros inferiores pode ser um fator independente do grau de obstrução ao fluxo aéreo [38]. Além de contribuir para a baixa tolerância ao exercício, a fraqueza muscular esquelética está associada a maior utilização dos serviços de saúde [37]. Swallow *et al.* [46] demonstraram que, a fraqueza muscular periférica avaliada através da força muscular de quadríceps, é um preditor de mortalidade melhor do que índices tradicionalmente aceitos na DPOC, como o índice de massa corporal, idade e o VEF₁.

Portanto, diante das evidências da importância da função muscular esquelética em portadores de DPOC, torna-se extremamente útil comparar intervenções que propiciem melhorias sobre as medidas clínicas envolvidas nos processos fisiopatológicos da doença, assim

como determinar o impacto das mesmas sobre o desempenho, capacidade funcional e qualidade de vida desses pacientes.

5 OBJETIVOS

A partir desse contexto temos como objetivos no primeiro estudo, comparar a eficácia do treinamento muscular respiratório e treinamento de força na função pulmonar, hiperinsuflação dinâmica, capacidade de exercício, força muscular respiratória e periférica em pacientes com DPOC. Já no segundo estudo, avaliaremos de forma abrangente os efeitos clínicos e fisiológicos da estimulação elétrica neuromuscular em pacientes com DPOC, fundamentado sobre as melhorias nas medidas clínicas relacionadas com os vários processos fisiopatológicos.

REFERÊNCIAS

1. Vestbo, J., et al., *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary*. Am J Respir Crit Care Med, 2013. **187**(4): p. 347-65.
2. O'Donnell, D.E. and K.A. Webb, *The major limitation to exercise performance in COPD is dynamic hyperinflation*. J Appl Physiol (1985), 2008. **105**(2): p. 753-5; discussion 755-7.
3. O'Donnell, D.E., *Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease*. Proc Am Thorac Soc, 2006. **3**(2): p. 180-4.
4. Agustí, A., et al., *FAQs about the GOLD 2011 assessment proposal of COPD: a comparative analysis of four different cohorts*. Eur Respir J, 2013. **42**(5): p. 1391-401.
5. Guder, G., et al., *"GOLD or lower limit of normal definition? A comparison with expert-based diagnosis of chronic obstructive pulmonary disease in a prospective cohort-study"*. Respir Res, 2012. **13**(1): p. 13.
6. Ries, A.L., et al., *Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines*. Chest, 2007. **131**(5 Suppl): p. 4S-42S.
7. Lange, P., et al., *Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification: a study of the general population*. Am J Respir Crit Care Med, 2012. **186**(10): p. 975-81.
8. Soriano, J.B., et al., *Distribution and prognostic validity of the new Global Initiative for Chronic Obstructive Lung Disease grading classification*. Chest, 2013. **143**(3): p. 694-702.
9. Franssen, F.M. and M.K. Han, *"The ABC of GOLD A-B-C-D"*. Eur Respir J, 2013. **42**(5): p. 1166-8.
10. Jones, P.W., et al., *Comparisons of health status scores with MRC grades in COPD: implications for the GOLD 2011 classification*. Eur Respir J, 2013. **42**(3): p. 647-54.

11. Sillen, M.J., et al., *Heterogeneity in clinical characteristics and co-morbidities in dyspneic individuals with COPD GOLD D: findings of the DICES trial*. *Respir Med*, 2013. **107**(8): p. 1186-94.
12. O'Donnell, D.E., D.J. Bain, and K.A. Webb, *Factors contributing to relief of exertional breathlessness during hyperoxia in chronic airflow limitation*. *Am J Respir Crit Care Med*, 1997. **155**(2): p. 530-5.
13. Castagna, O., et al., *Is impairment similar between arm and leg cranking exercise in COPD patients?* *Respir Med*, 2007. **101**(3): p. 547-53.
14. Pauwels, R.A., et al., *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary*. *Am J Respir Crit Care Med*, 2001. **163**(5): p. 1256-76.
15. Menezes, A.M., et al., *Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study*. *Lancet*, 2005. **366**(9500): p. 1875-81.
16. Agustí, A.G., et al., *Systemic effects of chronic obstructive pulmonary disease*. *Eur Respir J*, 2003. **21**(2): p. 347-60.
17. Wouters, E.F., *Chronic obstructive pulmonary disease. 5: systemic effects of COPD*. *Thorax*, 2002. **57**(12): p. 1067-70.
18. Gosselink, R., T. Troosters, and M. Decramer, *Peripheral muscle weakness contributes to exercise limitation in COPD*. *Am J Respir Crit Care Med*, 1996. **153**(3): p. 976-80.
19. Wagner, P.D., *Possible mechanisms underlying the development of cachexia in COPD*. *Eur Respir J*, 2008. **31**(3): p. 492-501.
20. Barreiro, E., et al., *Cytokine profile in quadriceps muscles of patients with severe COPD*. *Thorax*, 2008. **63**(2): p. 100-7.
21. Barreiro, E. and J.I. Sznajder, *Epigenetic regulation of muscle phenotype and adaptation: a potential role in COPD muscle dysfunction*. *J Appl Physiol* (1985), 2013. **114**(9): p. 1263-72.

22. Mannino, D.M., et al., *Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD*. Eur Respir J, 2008. **32**(4): p. 962-9.
23. Halpin, D.M., *Systemic effects of chronic obstructive pulmonary disease*. Expert Rev Respir Med, 2007. **1**(1): p. 75-84.
24. HajGhanbari, B., et al., *MRI-based 3D shape analysis of thigh muscles patients with chronic obstructive pulmonary disease versus healthy adults*. Acad Radiol, 2011. **18**(2): p. 155-66.
25. Oga, T., et al., *Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status*. Am J Respir Crit Care Med, 2003. **167**(4): p. 544-9.
26. Celli, B.R., *Chronic obstructive pulmonary disease: from unjustified nihilism to evidence-based optimism*. Proc Am Thorac Soc, 2006. **3**(1): p. 58-65.
27. Thompson, P.D., et al., *Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity)*. Circulation, 2003. **107**(24): p. 3109-16.
28. Pitta, F., et al., *Characteristics of physical activities in daily life in chronic obstructive pulmonary disease*. Am J Respir Crit Care Med, 2005. **171**(9): p. 972-7.
29. Garcia-Aymerich, J., et al., *Physical activity and clinical and functional status in COPD*. Chest, 2009. **136**(1): p. 62-70.
30. Chiappa, G.R., et al., *Heliox improves oxygen delivery and utilization during dynamic exercise in patients with chronic obstructive pulmonary disease*. Am J Respir Crit Care Med, 2009. **179**(11): p. 1004-10.
31. Bachasson, D., et al., *Quadriceps and respiratory muscle fatigue following high-intensity cycling in COPD patients*. PLoS One, 2013. **8**(12): p. e83432.
32. Hardinge, M., et al., *Guideline update: The British Thoracic Society Guidelines on home oxygen use in adults*. Thorax, 2015. **70**(6): p. 589-91.

33. Pan, L., et al., *Effects of anabolic steroids on chronic obstructive pulmonary disease: a meta-analysis of randomised controlled trials*. PLoS One, 2014. **9**(1): p. e84855.
34. van de Bool, C., M.C. Steiner, and A.M. Schols, *Nutritional targets to enhance exercise performance in chronic obstructive pulmonary disease*. Curr Opin Clin Nutr Metab Care, 2012. **15**(6): p. 553-60.
35. Sillen, M.J., et al., *Effects of neuromuscular electrical stimulation of muscles of ambulation in patients with chronic heart failure or COPD: a systematic review of the English-language literature*. Chest, 2009. **136**(1): p. 44-61.
36. Clark, C.J., et al., *Skeletal muscle strength and endurance in patients with mild COPD and the effects of weight training*. Eur Respir J, 2000. **15**(1): p. 92-7.
37. Decramer, M., et al., *Muscle weakness is related to utilization of health care resources in COPD patients*. Eur Respir J, 1997. **10**(2): p. 417-23.
38. Saey, D., et al., *Contractile leg fatigue after cycle exercise: a factor limiting exercise in patients with chronic obstructive pulmonary disease*. Am J Respir Crit Care Med, 2003. **168**(4): p. 425-30.
39. Rabinovich, R.A. and J. Vilaro, *Structural and functional changes of peripheral muscles in chronic obstructive pulmonary disease patients*. Curr Opin Pulm Med, 2010. **16**(2): p. 123-33.
40. Decramer, M., et al., *Corticosteroids contribute to muscle weakness in chronic airflow obstruction*. Am J Respir Crit Care Med, 1994. **150**(1): p. 11-6.
41. Jakobsson, P., L. Jorfeldt, and A. Brundin, *Skeletal muscle metabolites and fibre types in patients with advanced chronic obstructive pulmonary disease (COPD), with and without chronic respiratory failure*. Eur Respir J, 1990. **3**(2): p. 192-6.
42. Schols, A.M., et al., *Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease*. Thorax, 1996. **51**(8): p. 819-24.
43. Bernard, S., et al., *Peripheral muscle weakness in patients with chronic obstructive pulmonary disease*. Am J Respir Crit Care Med, 1998. **158**(2): p. 629-34.

44. Kim, H.C., M. Mofarrahi, and S.N. Hussain, *Skeletal muscle dysfunction in patients with chronic obstructive pulmonary disease*. Int J Chron Obstruct Pulmon Dis, 2008. **3**(4): p. 637-58.
45. Bernard, S., et al., *Aerobic and strength training in patients with chronic obstructive pulmonary disease*. Am J Respir Crit Care Med, 1999. **159**(3): p. 896-901.
46. Swallow, E.B., et al., *Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease*. Thorax, 2007. **62**(2): p. 115-20.
47. Barreiro, E., et al., *Guidelines for the Evaluation and Treatment of Muscle Dysfunction in Patients With Chronic Obstructive Pulmonary Disease*. Arch Bronconeumol, 2015. **51**(8): p. 384-395.
48. Bourjeily, G. and C.L. Rochester, *Exercise training in chronic obstructive pulmonary disease*. Clin Chest Med, 2000. **21**(4): p. 763-81.
49. Regueiro, E.M., et al., *[Analysis of metabolic and ventilatory demand during the execution of daily life activities in individuals with chronic obstructive pulmonary disease]*. Rev Lat Am Enfermagem, 2006. **14**(1): p. 41-7.
50. Miranda, E.F., C. Malaguti, and S.D. Corso, *Peripheral muscle dysfunction in COPD: lower limbs versus upper limbs*. J Bras Pneumol, 2011. **37**(3): p. 380-8.
51. Nici, L., et al., *American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation*. Am J Respir Crit Care Med, 2006. **173**(12): p. 1390-413.
52. O'Donnell, D.E. and P. Laveneziana, *The clinical importance of dynamic lung hyperinflation in COPD*. COPD, 2006. **3**(4): p. 219-32.
53. Killian, K.J., et al., *Dyspnea and leg effort during incremental cycle ergometry*. Am Rev Respir Dis, 1992. **145**(6): p. 1339-45.
54. Cote, C., et al., *Haemoglobin level and its clinical impact in a cohort of patients with COPD*. Eur Respir J, 2007. **29**(5): p. 923-9.
55. Velloso, M. and J.R. Jardim, *Functionality of patients with chronic obstructive pulmonary disease: energy conservation techniques*. J Bras Pneumol, 2006. **32**(6): p. 580-6.

56. Beauchamp, M.K., et al., *Impairments in balance discriminate fallers from non-fallers in COPD*. *Respir Med*, 2009. **103**(12): p. 1885-91.
57. Strasser, B., U. Siebert, and W. Schobersberger, *Effects of resistance training on respiratory function in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis*. *Sleep Breath*, 2013. **17**(1): p. 217-26.
58. Steiner, M.C. and M.D. Morgan, *Enhancing physical performance in chronic obstructive pulmonary disease*. *Thorax*, 2001. **56**(1): p. 73-7.
59. Storer, T.W., *Exercise in chronic pulmonary disease: resistance exercise prescription*. *Med Sci Sports Exerc*, 2001. **33**(7 Suppl): p. S680-92.
60. Casaburi, R., *Limitation to exercise tolerance in chronic obstructive pulmonary disease: look to the muscles of ambulation*. *Am J Respir Crit Care Med*, 2003. **168**(4): p. 409-10.
61. Gosselink, R., et al., *Impact of inspiratory muscle training in patients with COPD: what is the evidence?* *Eur Respir J*, 2011. **37**(2): p. 416-25.
62. Polkey, M.I., et al., *Diaphragm strength in chronic obstructive pulmonary disease*. *Am J Respir Crit Care Med*, 1996. **154**(5): p. 1310-7.
63. Heijdra, Y.F., et al., *Nocturnal saturation and respiratory muscle function in patients with chronic obstructive pulmonary disease*. *Thorax*, 1995. **50**(6): p. 610-2.
64. Smith, K., et al., *Respiratory muscle training in chronic airflow limitation: a meta-analysis*. *Am Rev Respir Dis*, 1992. **145**(3): p. 533-9.
65. Lotters, F., et al., *Effects of controlled inspiratory muscle training in patients with COPD: a meta-analysis*. *Eur Respir J*, 2002. **20**(3): p. 570-6.
66. Petrovic, M., et al., *Effects of inspiratory muscle training on dynamic hyperinflation in patients with COPD*. *Int J Chron Obstruct Pulmon Dis*, 2012. **7**: p. 797-805.
67. Weiner, P., et al., *Comparison of specific expiratory, inspiratory, and combined muscle training programs in COPD*. *Chest*, 2003. **124**(4): p. 1357-64.

68. Laughman, R.K., et al., *Strength changes in the normal quadriceps femoris muscle as a result of electrical stimulation*. Phys Ther, 1983. **63**(4): p. 494-9.
69. Caggiano, E., et al., *Effects of electrical stimulation or voluntary contraction for strengthening the quadriceps femoris muscles in an aged male population*. J Orthop Sports Phys Ther, 1994. **20**(1): p. 22-8.
70. Fahey, T.D., et al., *Influence of sex differences and knee joint position on electrical stimulation-modulated strength increases*. Med Sci Sports Exerc, 1985. **17**(1): p. 144-7.
71. Currier, D.P. and R. Mann, *Muscular strength development by electrical stimulation in healthy individuals*. Phys Ther, 1983. **63**(6): p. 915-21.
72. Mohr, T., et al., *Comparison of isometric exercise and high volt galvanic stimulation on quadriceps femoris muscle strength*. Phys Ther, 1985. **65**(5): p. 606-12.
73. Bax, L., F. Staes, and A. Verhagen, *Does neuromuscular electrical stimulation strengthen the quadriceps femoris? A systematic review of randomised controlled trials*. Sports Med, 2005. **35**(3): p. 191-212.
74. Arkov, V.V., et al., *New aspects of the influence of quadriceps femoris muscle stimulation course on functional capabilities of the organism*. Bull Exp Biol Med, 2010. **149**(2): p. 177-9.
75. Gerovasili, V., *Neuromuscular electrical stimulation appears to be useful in people with severe chronic obstructive pulmonary disease*. J Physiother, 2012. **58**(4): p. 270.
76. Gondin, J., et al., *Electromyostimulation training effects on neural drive and muscle architecture*. Med Sci Sports Exerc, 2005. **37**(8): p. 1291-9.
77. Pan, L., et al., *Lack of efficacy of neuromuscular electrical stimulation of the lower limbs in chronic obstructive pulmonary disease patients: a meta-analysis*. Respiriology, 2014. **19**(1): p. 22-9.
78. Narici, M.V., C. Maganaris, and N. Reeves, *Myotendinous alterations and effects of resistive loading in old age*. Scand J Med Sci Sports, 2005. **15**(6): p. 392-401.

79. Narici, M.V. and C.N. Maganaris, *Adaptability of elderly human muscles and tendons to increased loading*. J Anat, 2006. **208**(4): p. 433-43.
80. Gondin, J., et al., *Neural and muscular changes to detraining after electrostimulation training*. Eur J Appl Physiol, 2006. **97**(2): p. 165-73.
81. Gregory, C.M. and C.S. Bickel, *Recruitment patterns in human skeletal muscle during electrical stimulation*. Phys Ther, 2005. **85**(4): p. 358-64.
82. Maffiuletti, N.A., *Physiological and methodological considerations for the use of neuromuscular electrical stimulation*. Eur J Appl Physiol, 2010. **110**(2): p. 223-34.
83. Maffiuletti, N.A., et al., *Neuromuscular adaptations to electrostimulation resistance training*. Am J Phys Med Rehabil, 2006. **85**(2): p. 167-75.
84. Jubeau, M., et al., *Comparison between voluntary and stimulated contractions of the quadriceps femoris for growth hormone response and muscle damage*. J Appl Physiol (1985), 2008. **104**(1): p. 75-81.
85. Aldayel, A., et al., *Less indication of muscle damage in the second than initial electrical muscle stimulation bout consisting of isometric contractions of the knee extensors*. Eur J Appl Physiol, 2010. **108**(4): p. 709-17.
86. van Eeden, S.F. and D.D. Sin, *Chronic obstructive pulmonary disease: a chronic systemic inflammatory disease*. Respiration, 2008. **75**(2): p. 224-38.

ARTIGO I

COMPARISON OF THE EFFECTS OF RESPIRATORY MUSCLE TRAINING AND RESISTANCE TRAINING ON RESPIRATORY AND SKELETAL MUSCLE STRENGTH IN PATIENTS WITH COPD

Comparison of the Effects of Respiratory Muscle Training and Resistance Training on Respiratory and Skeletal Muscle Strength in Patients with COPD

Paulo J. C. Vieira^a, Adriana M. Guntzel Chiappa^b, Vinicius Z. Maldaner da Silva^c, Gerson Cipriano Jr^c, Sergio R. M. Mateus^c, Paulo Mueller^d, Gaspar R. Chiappa^a

^aExercise Pathophysiology Research Laboratory and Cardiology Division, Porto Alegre Hospital, Porto Alegre, Brazil; ^bPhysical Therapy Service, Porto Alegre Hospital, Porto Alegre, Brazil; ^cHealth Sciences and Technologies, University of Brasilia, Brazil; ^dProfessor of Respiratory Medicine and Pneumology, Federal University of Mato Grosso do Sul; ^eSerra Gaucha College, Physical Therapy and Nurse Division, Public Health Research Group, Caxias do Sul, Brazil

Running Title: **Inspiratory and Resistance Muscle Training in COPD**

Sources of financial support: Brazilian fostering agencies CNPq and FIFE

Potential conflict of interest: None of the authors have any potential conflict of interest related to the contents of this paper.

Address for Correspondence:

Gaspar R. Chiappa, PT, ScD

Exercise Pathophysiology Research Laboratory

Hospital de Clínicas de Porto Alegre,

Rua Ramiro Barcelos 2350, 90035-007 Porto Alegre, RS, Brazil

Phone: +55 51 91177267, Fax: +55 51 3359 6332

E-mail: gaspar.chiappa@gmail.com

ABSTRACT

Introduction: Inspiratory and peripheral muscle weakness is commonly found in chronic obstructive pulmonary disease (COPD) and may play a role in the lack of tolerance to exercise among such patients. The aim of the present study was to investigate the effects of respiratory muscle training (RMT) in comparison with resistance training (RT) in patients with moderate to severe COPD.

Methods: Patients were assigned to a six-month program of RMT (n=51), RT (n=53) or control (usual care, n=50). Pulmonary function, maximum inspiratory and expiratory pressure (P_Imax and P_Emax, respectively), exercise capacity based on oxygen uptake (peak VO₂) and the Six-Minute Walk test (6MWT) as well as quadriceps muscle torque and endurance were evaluated.

Results: FEV₁, FVC and FEV₁/FVC did not change with RMT, while RT resulted in significant increases in these variables. P_Imax (p < 0.001) and the distance travelled on the 6MWT (p < 0.01) increased in both the RMT and RT groups in comparison to the control group. P_Emax (p < 0.001) was higher in the RT group than the RMT group. VO_{2peak} (p < 0.001) increased in both the RMT and RT groups in comparison to the control group. Peak quadriceps muscle torque and endurance (p < 0.01) increased in the RT group in comparison to the RMT and control groups.

Conclusions: This study demonstrated that respiratory muscle training and resistance training led to a significant increase in respiratory and peripheral skeletal muscle performance in patients with COPD.

Keywords: Exercise, Functional Capacity, Maximum Inspiratory Pressure, Respiratory Muscle Strength.

INTRODUCTION

Pulmonary abnormalities and a diminished capacity for functional exercise are important clinical manifestations of chronic obstructive pulmonary disease (COPD) (1). Airflow obstruction leads to altered ventilation/perfusion matching and hyperinflation, decreasing effective alveolar ventilation and reducing ventilatory efficiency (2), which are associated with dyspnea, de-conditioning and muscle weakness.

Although pulmonary function impairment has been traditionally identified as a key factor in the genesis of low tolerance to exercise in these patients (3), considerable attention has been given to the role of systemic changes, mainly skeletal muscle dysfunction, as an important element in this process (1, 4). Skeletal muscle dysfunction in patients with COPD indicates a set of changes in structure and function, leading to decreased strength and abnormalities in energy metabolism during exercise (5). This dysfunction may also affect the respiratory muscles. A number of patients with COPD exhibit inspiratory muscle weakness, maximum inspiratory pressure (P_Imax) < 60 to 70% of the predicted value (6) and hyperinflation, which synergistically contribute to impaired exercise tolerance and dyspnea (2, 6). However, the evidence demonstrating inspiratory muscle weakness and chronic inspiratory muscle fatigue is not very robust in patients with COPD (7). Several studies have demonstrated an improvement in P_Imax after respiratory muscle training (RMT) in such patients (8, 9). Other studies have demonstrated inconsistent results regarding improvements in dyspnea and exercise capacity (10, 11). A meta-analysis (6) found improvements in functional capacity, dyspnea and quality of life after RMT in comparison to a control group. Furthermore, the authors suggested the combination of RMT with a general exercise training program results in significant improvements in P_Imax and exercise tolerance in patients with inspiratory muscle weakness. These findings are consistent with a previous meta-analysis on this topic (12).

On the other hand, the inclusion of progressive resistance training (RT) in pulmonary rehabilitation has been recommended as a means to improve exercise performance (13-15). The current body of literature suggests that RT in patients with COPD improves muscle strength (5, 16), although no study has assessed the possible additional effect on respiratory muscle strength and dynamic hyperinflation in patients with COPD.

The aim of the present study was to compare the effectiveness of RMT and RT on pulmonary function, dynamic hyperinflation, exercise capacity, respiratory muscle strength and peripheral muscle force in patients with COPD.

METHODS

Patient Population

Patients with mild to severe COPD (forced expiratory volume in one second/forced vital capacity [FEV_1/FVC] < 70%) (3) were included in this study. The following were the inclusion criteria: 1) a diagnosis of COPD with an FEV_1 < 80% predicted as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines and 2) dyspnea and/or fatigue during at least one activity of daily living that requires arm exercise. The following were the exclusion criteria: 1) musculoskeletal or neurologic conditions that may affect exercise performance, symptomatic cardiac disease, or previous lung surgery; 2) acute exacerbation of COPD that required a change in pharmacological management within the preceding two months; and 3) the use of oral corticosteroids. All subjects gave written informed consent (79/2010) as approved by the Institutional Medical Ethics Committee. This study was conducted in compliance with the Declaration of Helsinki.

Study Design

The effects of RMT and RT were investigated in a non-randomized parallel study design. Patients were screened at a physical therapy clinic. Subjects were allocated to the RMT group (n = 51), RT group (n = 53) or control group (usual care, n = 50). All measurements were performed before the RMT or RT programs as well as within one week after completion. After familiarization with testing procedures, the subjects underwent pulmonary function testing.

Intervention

Eligible patients were initially evaluated based on medical history, a physical examination, lung function, maximum respiratory pressure, maximum and sub-maximum functional exercise capacity as well as quadriceps muscle strength and endurance. The interventions were conducted for 24 weeks (three times per week). All groups received usual care for respiratory physical therapy (stimulus of cough, bronchial hygiene and pulmonary expansion), when necessary. The control group did not receive sham training sessions. The subjects exercised individually and all sessions were fully supervised. If necessary, the subjects were allowed to use a short-acting bronchodilator (salbutamol of 120 mg/ipratropium of 20 mg; Combivent, Boehringer Ingelheim GmbH, Ingelheim, Germany). The patients were separated into three groups: a) **Respiratory Muscle Training**: The patients were submitted to RMT using the *POWERbreathe* Inspiratory Muscle Training program (Northfield Road, Southam, Warwickshire, UK) and expiratory muscle training using the Threshold PEP-EMT (Philips Respironics, Inc., Philips Healthcare, The Netherlands) for 40 min, three times a week, with a respiratory load set at 30% of P_Imax and P_Emax, as described elsewhere (17). Each week, the training loads were adjusted to maintain 30% (18); b) **Resistance Training**: The patients underwent RT targeting the quadriceps using a leg press exercise, pectoral and triceps muscle groups on a multi-station apparatus (MG 525, Cybex Internacional UK, LTD, Derbyshire, UK).

The deltoids, biceps and hamstrings were trained on a pulley apparatus (Steens Industries AS, Oslo, Norway). The patients started at 70% of the initial one-repetition maximum (1-RM) established during the first week of the study for three sets of eight repetitions per exercise maneuver. Every week the load was increased by 5% of the 1-RM (15). Before and after each exercise, the patients were asked to rate their dyspnea and arm fatigue using a visual analog scale (scored from 0 to 10) (19); and c) **Control Group:** The patients in the control group underwent training that consisted of usual care, as prescribed by the respiratory physiotherapist (stimulus of cough, bronchial hygiene and pulmonary expansion) and upper limb flexibility and stretching exercises. The duration of the control group training sessions was the same as the sessions of the intervention groups.

Measurements

Pulmonary function tests: Spirometric tests were performed using the PFT System (Medical Graphics-MGC, St. Paul, MN< USA) with air flow measured using a three-liter syringe calibrated with a Pitot tube (PreVent, Pneumotach). The subjects completed at least three acceptable maximum forced and slow expiratory maneuvers before and after the inhalation of 400 mcg of salbutamol via a metered-dose inhaler. FVC (liters), FEV₁ (liters), FEV₁/FVC, inspiratory capacity (IC, liters) and total lung capacity (TLC, liters) were recorded using a plethysmograph. IC was measured based on the protocol described by O'Donnell and Webb (1993) (20), and the IC/TLC (inspiratory fraction) was used as a measure of resting hyperinflation (21).

Respiratory muscle function: Inspiratory and expiratory muscle function testing was performed using a pressure transducer (MVD-500 V.1.1 Microhard System, Globalmed, Porto Alegre, Brazil). Maximum inspiratory (P_Imax) and maximum expiratory pressure (P_Emax) were measured as described elsewhere (17). P_Imax and P_Emax were obtained from three valid

and reproducible maneuvers (difference < 5%) and expressed in relation to the reference values for the Brazilian population (22).

Cardiopulmonary exercise testing: Patients performed cardiopulmonary exercise testing to evaluate their aerobic capacity on an electronically braked cycle ergometer (Inbrasport, Porto Alegre, Brazil) at 60 rpm. Standard metabolic and ventilatory responses were measured breath-by-breath using a calibrated, computer-based system (K4b², Cosmed, Rome, Italy). Arterial oxyhemoglobin saturation (SpO₂) was determined by pulse oximetry (POX 010-340, Medaid, Torrance, USA). The incremental exercise test started with two minutes of unloaded cycling and increments of 5 to 10 watts per min were added until exhaustion. Gas exchange variables were averaged every five seconds and peak oxygen consumption (VO₂) was defined as the highest value achieved during the test. IC and (inspiratory fraction) IF were measured immediately after cardiopulmonary exercise testing, serving as parameters for dynamic hyperinflation. It is assumed that total lung capacity (TLC) remains constant during exercise (23).

Submaximum functional capacity: The maximum distance covered during the Six-Minute Walk Test (6MWT) was used to assess sub-maximum functional capacity and was performed following the guidelines of the European Respiratory Society (24).

Lower limb muscle function: Quadriceps muscle strength was evaluated by peak quadriceps muscle torque (QMT) and 1-RM, as described by Laoutaris (25). Peak quadriceps muscle torque as calculated as the peak measured force (N) multiplied by the distance (m) between a rotation axis (knee joint) and a point where lifted weights were attached and expressed as (N.m). 1-RM was calculated as the highest weight lifted by the quadriceps throughout a complete range of motion. Quadriceps muscle endurance (QME) was calculated as the product of the 50% of 1-RM with the number of maximum repetitions.

Statistical analysis

Baseline data were evaluated with descriptive statistics to characterize differences among the groups. The SPSS version 19.0 statistical software was used for data analysis (SPSS, Chicago, IL, USA). Changes after interventions and in relation to the control group were evaluated using two-way repeated-measures ANOVA for the comparison of the variables. The level of statistical significance was set at $p < 0.05$.

RESULTS

Flow of participants

One hundred eighty patients with COPD referred to the physical therapy clinic and who met the inclusion criteria were selected for non-randomization to the RMT, RT or control groups (**Figure 1**). Ten patients were excluded due to exacerbation ($n = 8$) and other reasons ($n = 2$). Therefore, a total of 170 patients were included in the study. During the follow-up period, 16 patients were excluded from the analysis of the database for not having completed the 24-week protocol (RMT, $n = 4$; RT, $n = 4$; and control, $n = 8$). Thus, 154 patients completed the study (RMT, $n = 51$; RT, $n = 53$; and control, $n = 50$). As shown in **Table 1**, the clinical characteristics and baseline values for all groups were similar, except for maximum inspiratory pressure. No differences were found regarding baseline peak VO_2 , 6MWT, Borg score and quadriceps strength among all groups. There were no changes in the medical regimen throughout the study protocol.

Table 2 displays the effects of RMT and RT on the pulmonary and respiratory variables. FEV_1 , FVC and FEV_1/FVC remained unchanged with RMT, whereas RT resulted in a significant increase in all variables. Both RMT and RT resulted in an additional gain in IC and IF, with no statistically significant differences, indicating a reduction in dynamic hyperinflation. PI_{max}

significantly increased in both the RMT and RT groups compared to the control group (RMT pre: 56 ± 22 and post: 126 ± 23 cm H₂O; RT pre: 67 ± 22 and post: 101 ± 26 cm H₂O; control pre: 75 ± 33 and post: 78 ± 35 cm H₂O, ANOVA, $p < 0.001$), but RMT differed significantly from the RT intervention. The increase in PEmax was higher in the RT group than the RMT group (RMT pre: 69 ± 24 and post: 103 ± 28 cm H₂O; RT pre: 63 ± 14 and post: 127 ± 31 cm H₂O; ANOVA, $p < 0.001$). VO_{2peak} was significantly increased in the RMT group (pre: 18.5 ± 4.5 ; post: 21.1 ± 3.8 ml·kg⁻¹·min⁻¹; ANOVA, $p < 0.001$) and RT group (pre: 18.7 ± 5.6 ; post: 20.5 ± 4.3 ml·kg⁻¹·min⁻¹) in comparison to the control group (pre: 19.1 ± 5.2 ; post: 19.7 ± 3.9 ml·kg⁻¹·min⁻¹) (**Figure 2, upper panel**). The distance travelled on the 6MWT increased significantly in both RMT and RT groups in comparison to the control group (RMT – pre: 387 ± 98 and post: 461 ± 96 m; RT – pre: 391 ± 79 and post: 460 ± 91 m; control – pre: 425 ± 97 and post: 427 ± 88 m, ANOVA, $p < 0.01$), with no statistically significant differences among the groups (**Figure 2, under panel**). Peak QMT and QME increased significantly only in the RT group (**Figure 3, upper panel**). Interestingly, RMT significantly increased quadriceps muscle endurance in comparison to the control group (**Figure 3, under panel**).

DISCUSSION

The present study confirms that a six-month supervised program of RMT or RT significantly improved a number of clinically important measures, including pulmonary and respiratory muscle function, maximum and sub-maximum exercise capacity and lower limb muscle strength production in patients with COPD. To the best of our knowledge, this is the first study to evaluate the efficacy of the RMT versus RT compared with controls on clinical and functional parameters in patients with COPD.

Lung and Respiratory Function

In accordance with previous literature, RMT (6, 8, 11, 12) and RT (26-29) do not affect resting pulmonary function test results. Although RT did not involve any respiratory exercise, the effect on the respiratory muscles was found to improve pulmonary function in patients with COPD. Recently, a meta-analysis by Strasser et al. (30) showed that RT improves pulmonary function (increased FVC and a borderline improvement in ventilation without any changes in FEV₁). The authors reported that this effect may be associated with an improvement in expiratory muscle function, which may lead to gain in FVC. However, we believe that the differences in the present findings and previous studies may be related to the improvement in inspiratory and expiratory muscle strength, which may have lead to improved FVC (31) and IC/TLC through the increased recruitment of abdominal muscles, thereby facilitating expiratory muscle strength (32). Patients with COPD have with expiratory flow limitations that may over-activate expiratory muscles and aggravate the competition for blood flow between the locomotor and respiratory musculature, thereby increasing dynamic hyperinflation (33). A plausible explanation for the improved dynamic hyperinflation is observed with the increase in P_Imax, which is influenced by residual volume and the viscoelastic properties of the respiratory system (34).

Interestingly, changes in FEV₁ > 1 L (n = 25) were detected after RT, suggesting important benefits with this form of training, reducing the severity of the disease from severe to moderate, as demonstrated previously (30). Therefore, these factors together may be expected to diminish the resistive component and reduce the severity of lung hyperinflation, as evidenced by an increased IF.

On the other hand, studies have demonstrated that RMT results in an improvement in breathing frequency in relation to tidal volume, indicating an improved breathing pattern and IF (4, 35). Petrovic et al. (4) attributed this increased IF after RMT to the improvement in breathing

patterns during exercise. The authors demonstrated that RMT results in a significant decrease in the fraction between breathing frequency to minute ventilation and an increase in mean IF both during incremental and constant load exercises. This response facilitates lung emptying, which may reduce dynamic hyperinflation, the effect of which may also be related to an increase in respiratory frequency, which is one of air trapping mechanisms, known as auto-PEEP. However, it seems that RT may result in an improvement in lung mechanics. In the present study, RT increased expiratory muscle strength, which may contribute to the greater use of the abdominal muscles, placing the diaphragm higher in the chest and reducing the competition for blood flow between the locomotor and the respiratory muscles.

Exercise Capacity

The subjects who participated in the RMT and RT programs experienced a significant increase in functional capacity, as measured by peak VO_2 . This was accompanied by an increase of 19.0% and 17.6% in the 6MWT distance in the RMT and RT groups, respectively, which is consistent with previous investigations (6). This response may be attributed to improvements in respiratory muscle function with both protocols. Previous studies have indicated that the increase in respiratory muscle strength through RMT may reduce end expiratory lung volume and increase inspiratory capacity during exercise, which contributes to improved exercise performance. Likewise, some studies have shown that RT may increase mechanical efficiency through a reduction in ventilatory equivalents for oxygen and carbon dioxide (36), which may lead to increased efficiency of peripheral muscle oxygen extraction (37) and exercise tolerance. Moreover, we believe that this effect may be linked to the longer program duration, but the effects of exercise among patients with COPD is influenced by duration, training frequency and intensity (38).

Lower Limb Performance

As expected, RT increased quadriceps strength and endurance, which is consistent with data reported in previous studies (26, 28, 30). In the present investigation, RMT and RT increased quadriceps muscle endurance. Interestingly, RT improved respiratory muscle strength, which may be related to the higher oxygen availability in the periphery, increasing skeletal muscle performance. Recently, Singer et al. (39) have suggested that leg and inspiratory muscle weakness are considered independent factors for poorer exercise capacity and lower extremity function in patients with COPD. Studies have evaluated the relationship between leg muscle weakness and exercise capacity (5, 40). In the present study, the subjects in the RT group demonstrated a significant increase in leg muscle strength and functional capacity, which clearly has clinical benefits.

We did not confirm our hypothesis that RMT significantly added benefits to RT during a pulmonary rehabilitation program. RT has been shown to be more effective in increasing significantly FVC, PEmax, peak quadriceps muscle torque and quadriceps muscle endurance in comparison to RMT. Therefore, RMT differed with RT only with regard to PImax and IF. To the best of our knowledge, no previous study has evaluated differences in outcomes between RMT and RT. Thus, we believe that improvements in lower limb and expiratory muscle indices may have contributed to the incremental benefits shown in exercise performance in the RT group.

A potential limitation of the present study resides in its open-labeled design with a non-randomized study involving selection bias. However, the impact on the results is very important and reflects that the number of participants in each group can be a positive contributor. Random sampling would be ideal and should be employed in upcoming designs. The 6MWT is also known to be less sensitive to interventions, particularly in patients with higher exercise capacity, but studies have previously shown that RMT improves performance during this

functional assessment in patients with COPD (10, 41). The load during RT program was controlled by a 1-RM test can underestimate maximum strength in older patients (42). However, this is a safe method to determine higher loads of training (43), which were used in this study. Furthermore, we did not evaluate the combination of RMT and RT, which may have an added synergistic effect.

Clinical Implications: The present study may help define the importance of integrating RMT plus RT therapeutic interventions in the management of patients with COPD. Previous studies have demonstrated success in enhancing exercise tolerance using RMT and RT on patients with COPD (44-46).

Future randomized clinical trials should be conducted with the goal of investigating the combination of the interventions, respiratory muscle training associated with resistance training affects with increase in the effect size and the effectiveness of these rehabilitation interventions. However, the results obtained in this study encourage the use of both respiratory muscle training, as resistance should be recommended in patients with COPD in rehabilitation programs.

In conclusion, this trial demonstrates that RT and RMT both significantly improve a number of clinically relevant variables. Therefore, large-scale clinical trials are warranted to additionally evaluate the long-term effects of these interventions on clinical outcomes.

Potential conflict of interest

None of the authors have any potential conflict of interest related to the contents of this paper.

Disclosure: Paulo J. C. Vieira is supported by a Doctoral Scholarship.

Acknowledgments: The authors thank Dr. Jorge P. Ribeiro (*IN MEMORIAM*) for the clinical coordination and clinical database management.

REFERENCES

1. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. American journal of respiratory and critical care medicine. 1995 Nov;152(5 Pt 2):S77-121. PubMed PMID: 7582322.
2. Koppers RJ, Vos PJ, Boot CR, Folgering HT. Exercise performance improves in patients with COPD due to respiratory muscle endurance training. Chest. 2006 Apr;129(4):886-92. PubMed PMID: 16608934.
3. O'Donnell DE, Revall SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 2001 Sep 1;164(5):770-7. PubMed PMID: 11549531.
4. Petrovic M, Reiter M, Zipko H, Pohl W, Wanke T. Effects of inspiratory muscle training on dynamic hyperinflation in patients with COPD. International journal of chronic obstructive pulmonary disease. 2012;7:797-805. PubMed PMID: 23233798. Pubmed Central PMCID: 3516469.
5. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. American journal of respiratory and critical care medicine. 1996 Mar;153(3):976-80. PubMed PMID: 8630582.
6. Gosselink R, De Vos J, van den Heuvel SP, Segers J, Decramer M, Kwakkel G. Impact of inspiratory muscle training in patients with COPD: what is the evidence? The European respiratory journal. 2011 Feb;37(2):416-25. PubMed PMID: 21282809.
7. Polkey MI, Kyroussis D, Hamnegard CH, Mills GH, Green M, Moxham J. Diaphragm strength in chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 1996 Nov;154(5):1310-7. PubMed PMID: 8912741.
8. Crowe J, Reid WD, Geddes EL, O'Brien K, Brooks D. Inspiratory muscle training compared with other rehabilitation interventions in adults with chronic obstructive pulmonary disease: a systematic literature review and meta-analysis. Copd. 2005 Sep;2(3):319-29. PubMed PMID: 17146997.
9. Geddes EL, Reid WD, Crowe J, O'Brien K, Brooks D. Inspiratory muscle training in adults with chronic obstructive pulmonary disease: a systematic review. Respiratory medicine. 2005 Nov;99(11):1440-58. PubMed PMID: 15894478.

10. Weiner P, Magadle R, Beckerman M, Weiner M, Berar-Yanay N. Comparison of specific expiratory, inspiratory, and combined muscle training programs in COPD. *Chest*. 2003 Oct;124(4):1357-64. PubMed PMID: 14555566.
11. Lisboa C, Villafranca C, Leiva A, Cruz E, Pertuze J, Borzone G. Inspiratory muscle training in chronic airflow limitation: effect on exercise performance. *The European respiratory journal*. 1997 Mar;10(3):537-42. PubMed PMID: 9072981.
12. Geddes EL, O'Brien K, Reid WD, Brooks D, Crowe J. Inspiratory muscle training in adults with chronic obstructive pulmonary disease: an update of a systematic review. *Respiratory medicine*. 2008 Dec;102(12):1715-29. PubMed PMID: 18708282.
13. Troosters T, Casaburi R, Gosselink R, Decramer M. Pulmonary rehabilitation in chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine*. 2005 Jul 1;172(1):19-38. PubMed PMID: 15778487.
14. O'Shea SD, Taylor NF, Paratz JD. A predominantly home-based progressive resistance exercise program increases knee extensor strength in the short-term in people with chronic obstructive pulmonary disease: a randomised controlled trial. *The Australian journal of physiotherapy*. 2007;53(4):229-37. PubMed PMID: 18047457.
15. Spruit MA, Gosselink R, Troosters T, De Paepe K, Decramer M. Resistance versus endurance training in patients with COPD and peripheral muscle weakness. *The European respiratory journal*. 2002 Jun;19(6):1072-8. PubMed PMID: 12108859.
16. Troosters T, Probst VS, Crul T, Pitta F, Gayan-Ramirez G, Decramer M, et al. Resistance training prevents deterioration in quadriceps muscle function during acute exacerbations of chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine*. 2010 May 15;181(10):1072-7. PubMed PMID: 20133927.
17. Dall'Ago P, Chiappa GR, Guths H, Stein R, Ribeiro JP. Inspiratory muscle training in patients with heart failure and inspiratory muscle weakness: a randomized trial. *Journal of the American College of Cardiology*. 2006 Feb 21;47(4):757-63. PubMed PMID: 16487841.
18. Cahalin LP, Arena R, Guazzi M, Myers J, Cipriano G, Chiappa G, et al. Inspiratory muscle training in heart disease and heart failure: a review of the literature with a focus on method of training and outcomes. *Expert review of cardiovascular therapy*. 2013 Feb;11(2):161-77. PubMed PMID: 23405838.

19. Borg GA. Psychophysical bases of perceived exertion. *Medicine and science in sports and exercise*. 1982;14(5):377-81. PubMed PMID: 7154893.
20. O'Donnell DE, Webb KA. Exertional breathlessness in patients with chronic airflow limitation. The role of lung hyperinflation. *The American review of respiratory disease*. 1993 Nov;148(5):1351-7. PubMed PMID: 8239175.
21. Zhang Y, Sun X-g, Yang W-l, Tan X-y, Liu J-m. Inspiratory Fraction is Correlated with Exercise Capacity of Patients with Stable Moderate to Severe Chronic Obstructive Pulmonary Disease. *Respiratory Care*. 2013 April 16, 2013.
22. Neder JA, Andreoni S, Lerario MC, Nery LE. Reference values for lung function tests. II. Maximum respiratory pressures and voluntary ventilation. *Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas / Sociedade Brasileira de Biofisica [et al]*. 1999 Jun;32(6):719-27. PubMed PMID: 10412550.
23. O'Donnell DE. Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. *Proceedings of the American Thoracic Society*. 2006 Apr;3(2):180-4. PubMed PMID: 16565429.
24. Hernandez NA, Wouters EF, Meijer K, Annegarn J, Pitta F, Spruit MA. Reproducibility of 6-minute walking test in patients with COPD. *Eur Respir J*. 2010 Dec 22. PubMed PMID: 21177838. Epub 2010/12/24. Eng.
25. Laoutaris ID, Adamopoulos S, Manginas A, Panagiotakos DB, Kallistratos MS, Doulaptsis C, et al. Benefits of combined aerobic/resistance/inspiratory training in patients with chronic heart failure. A complete exercise model? A prospective randomised study. *Int J Cardiol*. 2012 May 31. PubMed PMID: 22658571. Epub 2012/06/05. Eng.
26. Arnardottir RH, Sorensen S, Ringqvist I, Larsson K. Two different training programmes for patients with COPD: a randomised study with 1-year follow-up. *Respiratory medicine*. 2006 Jan;100(1):130-9. PubMed PMID: 15885996.
27. Casaburi R, Bhasin S, Cosentino L, Porszasz J, Somfay A, Lewis MI, et al. Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine*. 2004 Oct 15;170(8):870-8. PubMed PMID: 15271690.

28. Kongsgaard M, Backer V, Jorgensen K, Kjaer M, Beyer N. Heavy resistance training increases muscle size, strength and physical function in elderly male COPD-patients--a pilot study. *Respiratory medicine*. 2004 Oct;98(10):1000-7. PubMed PMID: 15481277.
29. Skumlien S, Aure Skogedal E, Skrede Ryg M, Bjortuft O. Endurance or resistance training in primary care after in-patient rehabilitation for COPD? *Respiratory medicine*. 2008 Mar;102(3):422-9. PubMed PMID: 18037283.
30. Strasser B, Siebert U, Schobersberger W. Effects of resistance training on respiratory function in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Sleep & breathing = Schlaf & Atmung*. 2013 Mar 7;17:217-26. PubMed PMID: 22395963. Epub 2012/03/08. Eng.
31. Skumlien S, Skogedal EA, Bjortuft O, Ryg MS. Four weeks' intensive rehabilitation generates significant health effects in COPD patients. *Chronic respiratory disease*. 2007;4(1):5-13. PubMed PMID: 17416147.
32. Abe T, Kusuhara N, Yoshimura N, Tomita T, Easton PA. Differential respiratory activity of four abdominal muscles in humans. *J Appl Physiol*. 1996 Apr;80(4):1379-89. PubMed PMID: 8926270. Epub 1996/04/01. eng.
33. Athanasopoulos D, Louvaris Z, Cherouveim E, Andrianopoulos V, Roussos C, Zakynthinos S, et al. Expiratory muscle loading increases intercostal muscle blood flow during leg exercise in healthy humans. *J Appl Physiol*. 2010 Aug;109(2):388-95. PubMed PMID: 20507965. Pubmed Central PMCID: 2928598. Epub 2010/05/29. eng.
34. Rochester DF. Tests of respiratory muscle function. *Clinics in chest medicine*. 1988 Jun;9(2):249-61. PubMed PMID: 3292126.
35. Weiner P, Man A, Weiner M, Rabner M, Waizman J, Magadle R, et al. The effect of incentive spirometry and inspiratory muscle training on pulmonary function after lung resection. *J Thorac Cardiovasc Surg*. 1997 Mar;113(3):552-7. PubMed PMID: 9081102. Epub 1997/03/01. eng.
36. Clark CJ, Cochrane L, Mackay E. Low intensity peripheral muscle conditioning improves exercise tolerance and breathlessness in COPD. *The European respiratory journal*. 1996 Dec;9(12):2590-6. PubMed PMID: 8980974.
37. Taylor R, Jones NL. The reduction by training of CO2 output during exercise. *European journal of cardiology*. 1979 Jan;9(1):53-62. PubMed PMID: 759188.

38. American College of Sports Medicine Position Stand. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. *Medicine and science in sports and exercise*. 1998 Jun;30(6):975-91. PubMed PMID: 9624661.
39. Singer J, Yelin EH, Katz PP, Sanchez G, Iribarren C, Eisner MD, et al. Respiratory and skeletal muscle strength in chronic obstructive pulmonary disease: impact on exercise capacity and lower extremity function. *Journal of cardiopulmonary rehabilitation and prevention*. 2011 Mar-Apr;31(2):111-9. PubMed PMID: 21240003. Pubmed Central PMCID: 3085880.
40. Hamilton AL, Killian KJ, Summers E, Jones NL. Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. *Am J Respir Crit Care Med*. 1995 Dec;152(6 Pt 1):2021-31. PubMed PMID: 8520771. Epub 1995/12/01. eng.
41. Weiner P, Magadle R, Beckerman M, Weiner M, Berar-Yanay N. Specific expiratory muscle training in COPD. *Chest*. 2003 Aug;124(2):468-73. PubMed PMID: 12907530.
42. Shaw CE, McCully KK, Posner JD. Injuries during the one repetition maximum assessment in the elderly. *Journal of cardiopulmonary rehabilitation*. 1995 Jul-Aug;15(4):283-7. PubMed PMID: 8542534.
43. Yamada M, Arai H, Uemura K, Mori S, Nagai K, Tanaka B, et al. Effect of resistance training on physical performance and fear of falling in elderly with different levels of physical well-being. *Age and ageing*. 2011 Sep;40(5):637-41. PubMed PMID: 21729926.
44. Berton DC, Reis M, Siqueira AC, Barroco AC, Takara LS, Bravo DM, et al. Effects of tiotropium and formoterol on dynamic hyperinflation and exercise endurance in COPD. *Respiratory medicine*. 2010 Sep;104(9):1288-96. PubMed PMID: 20580216.
45. Troosters T, Weisman I, Dobbels F, Giardino N, Valluri SR. Assessing the Impact of Tiotropium on Lung Function and Physical Activity in GOLD Stage II COPD Patients who are Naive to Maintenance Respiratory Therapy: A Study Protocol. *The open respiratory medicine journal*. 2011;5:1-9. PubMed PMID: 21503263. Pubmed Central PMCID: 3078679.
46. Ambrosino N, Foglio K, Balzano G, Paggiaro PL, Lessi P, Kesten S, et al. Tiotropium and exercise training in COPD patients: effects on dyspnea and exercise tolerance. *International journal of chronic obstructive pulmonary disease*. 2008;3(4):771-80. PubMed PMID: 19281092. Pubmed Central PMCID: 2650608.

Figure Legends

Fig. 1. Design and flow of participants through the trial. RMT, respiratory muscle training; RT, resistance training; P_Imax, inspiratory muscle pressure; 1-RM, one repetition maximum; VO₂ = oxygen consumption; 6MWT, 6 min walk test; quadriceps muscle torque and quadriceps muscle endurance = quadriceps muscle torque and quadriceps muscle endurance, respectively.

Fig. 2. Peak oxygen uptake (peak VO₂, upper panel) and 6-minute walk test (6MWT, under panel) before (black) and after (white) RMT, RT and controls. * comparison between RMT versus control ($P < 0.001$) and † RT and control ($P < 0.01$).

Fig. 3. Peak quadriceps muscle torque (QMT), upper panel and quadriceps muscle endurance (QME), under panel before (black) and after (white) RMT, RT and controls. * comparison between RMT versus control ($P < 0.001$), † RT and control ($P < 0.01$) and ‡ from RMT, RT and controls ($P < 0.001$).

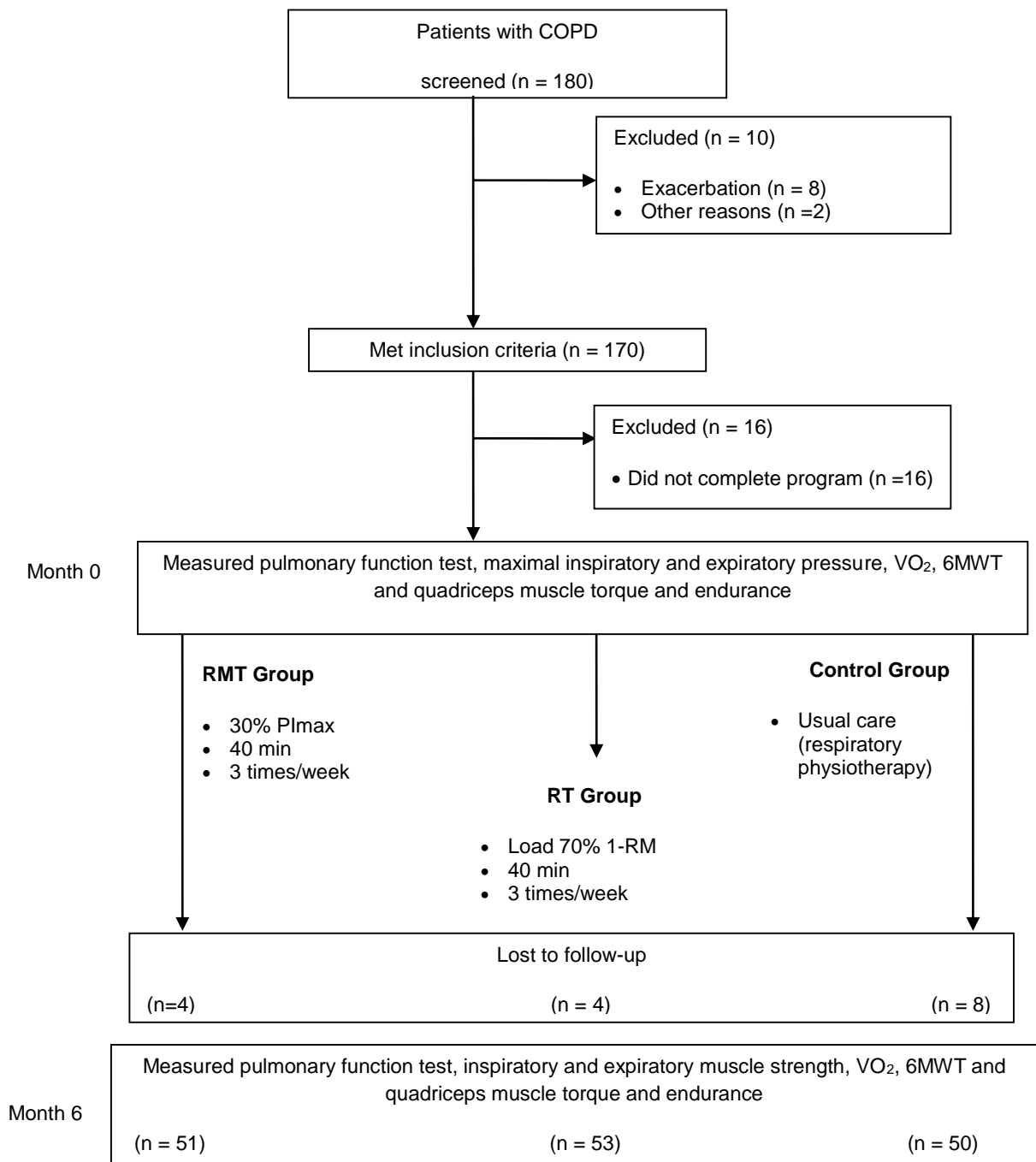


Figure 1. Design and flow of participants through the trial.

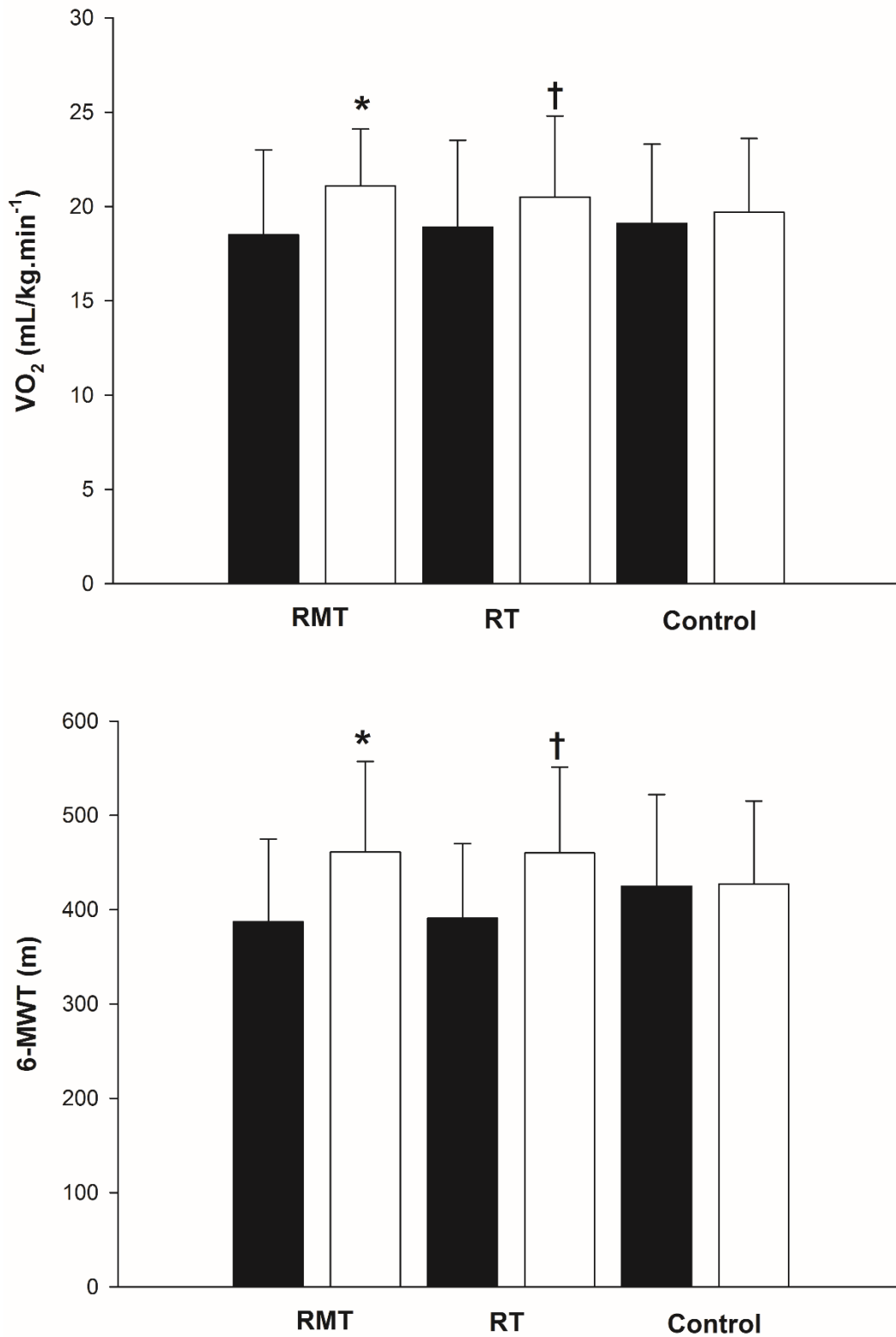


Fig. 2. Peak oxygen uptake (peak VO₂, upper pannel) and 6-minute walk test (6MWT, under pannel) before (black) and after (white) RMT, RT and controls. * comparison between RMT versus control ($P < 0.001$) and † RT and control ($P < 0.01$).

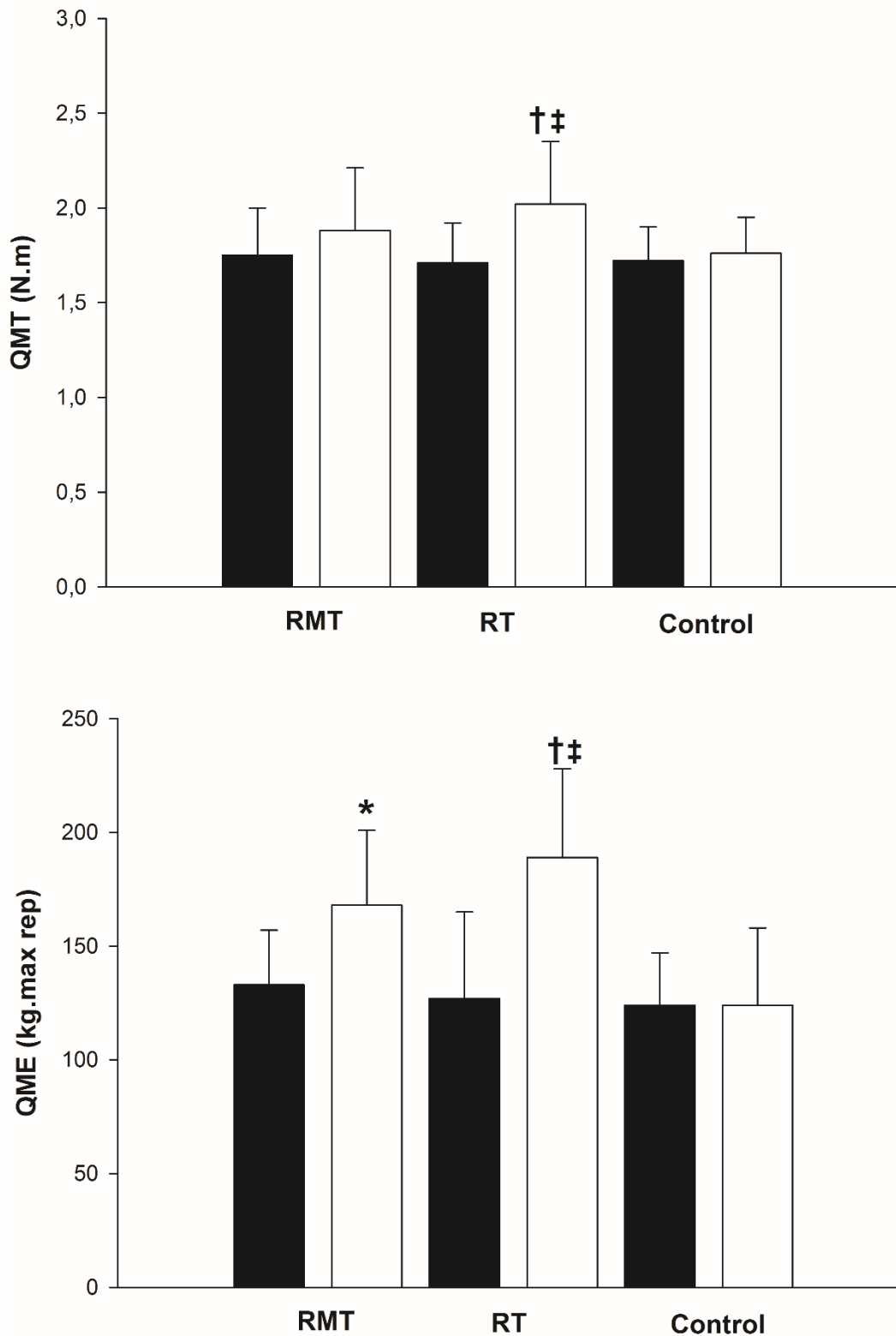


Fig. 3. Peak quadriceps muscle torque (quadriceps muscle torquepeak, upper pannel) and quadriceps muscle endurance (quadriceps muscle endurance, under pannel) before (black) and after (white) RMT, RT and controls. * comparison between RMT versus control ($P < 0.001$), † RT and control ($P < 0.01$) and ‡ from RMT, RT and controls ($P < 0.001$).

Table 1. Clinical characteristics of study participants

	Patients (n=154)		
	RMT (n=51)	RT (n=53)	Control (n=50)
Demographic/anthropometric			
Age, years	62 ± 12	60 ± 13	61 ± 18
Male/Female	26/25	25/28	25/25
BMI, kg/m ²	30 ± 5	29 ± 6	30 ± 4
Current smoker	17 (33)	14 (26)	15 (30)
Pulmonary Function			
FEV ₁ , L (% pred)	1.20 ± 0.33 (48 ± 9)	1.18 ± 0.36 (46 ± 7)	1.23 ± 0.44 (46 ± 15)
FVC, % pred	66 ± 12	65 ± 10	62 ± 12
FEV ₁ /FVC	72 ± 7.8	70 ± 8.8	74 ± 10
IC, L (% pred)	2.02 ± 0.34 (78 ± 18)	2.01 ± 0.74 (76 ± 12)	2.05 ± 0.54 (78 ± 11)
IF, % pred	30.5 ± 10	28.7 ± 9.6	29.3 ± 9.3
Cardiopulmonary Test			
VO _{2peak} (ml.kg ⁻¹ . min ⁻¹)	18.5 ± 4.5	19.7 ± 5.6	19.1 ± 5.2
Respiratory Muscle Function			
PImax, cm H ₂ O	56 ± 22*	67 ± 22	75 ± 33
PImax (% pred)	57 ± 12*	69 ± 24	73 ± 18
PEmax, cm H ₂ O	69 ± 24	63 ± 14	78 ± 28
PEmax (% pred)	67 ± 13	66 ± 12	75 ± 15
Peak Flow, mL	257 ± 97	265 ± 95	254 ± 88
Performance on Walk Test			
6-MWT, m	387 ± 98	391 ± 79	425 ± 97
Borg dyspnoea scores	4 (1-5)	4 (1-6)	4 (1-6)
Borg leg effort scores	4 (3-8)	4 (3-9)	4 (3-7)
Strength Test			
1-RM, Kg	21.3 ± 3.5	19.5 ± 2.8	20.4 ± 1.8

Data expressed in mean ± SD. Abbreviations: RMT, respiratory muscle training; RT, resistance training; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; FEV₁= forced expiratory volume in 1 s (pred); FVC= forced vital capacity (pred); IC= inspiratory capacity; IF = inspiratory fraction (IC/TLC); peak VO₂ = peak oxygen consumption; PImax and PEmax= maximal inspiratory and expiratory muscle pressure (pred); 6MWT = 6 min walk test; 1-RM = 1 repetition maximum. **p*-value represents the overall comparison among the 3 study groups.

Table 2. Pulmonary and respiratory muscle function tests before and after intervention for patients in RMT, RT and control groups

	RMT (n = 51)		RT (n = 53)		Control (n = 50)	
	Before	After	Before	After	Before	After
FEV ₁ (% pred)	48 ± 9	49 ± 11	46 ± 7	54 ± 8*‡	46 ± 15	45 ± 27
FVC (% pred)	66 ± 12	68 ± 8	65 ± 10	71 ± 9*‡	62 ± 12	60 ± 10
FEV ₁ /FVC	72 ± 7.8	72 ± 9.6	70 ± 8.8	76 ± 9.3*‡	74 ± 10	75 ± 8
TLC (L)	6.98 ± 0.35	6.89 ± 0.17	7.01 ± 0.64	7.0 ± 0.38	6.97 ± 0.73	6.95 ± 0.56
IC (L)	2.85 ± 0.17	3.01 ± 0.24†	2.71 ± 0.28	2.95 ± 0.29*	2.71 ± 0.19	2.68 ± 0.24
IF (% pred)	0.40 ± 0.11	0.43 ± 0.19†	0.38 ± 0.07	0.42 ± 0.13*	0.39 ± 0.09	0.38 ± 0.12
PImax (cm H ₂ O)	56 ± 22	126 ± 23‡	67 ± 22	97 ± 16*	75 ± 33	78 ± 35
PEmax (cm H ₂ O)	69 ± 24	86 ± 28†	63 ± 14	127 ± 31*‡	78 ± 28	81 ± 31

Data expressed in mean ± SD. Abbreviations: RMT, respiratory muscle training; RT, resistance training; FEV₁ = forced expired volume in 1 s; FVC = forced vital capacity; FEV₁/FVC = FEV₁ to FVC ratio; PImax, PEmax = maximal inspiratory and expiratory pressure, respectively. * RT compared to control; † RMT compared to control; ‡ RMT compares to RT.

ARTIGO II

**NEUROMUSCULAR ELECTRICAL STIMULATION IMPROVES CLINICAL AND
PHYSIOLOGICAL FUNCTION IN COPD PATIENTS**

Neuromuscular Electrical Stimulation Improves Clinical and Physiological Function in COPD Patients

Paulo J. C. Vieira^a, Adriana M. Güntzel Chiappa^b, Gerson Cipriano Jr^c, Daniel Umpierre^a, Ross Arena^d, Gaspar R. Chiappa^{a,e}

^aExercise Pathophysiology Research Laboratory and Cardiology Division, Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, Brazil; ^bPhysical Therapy Division and Intensive Care Unit from Hospital de Clínicas de Porto Alegre; ^cPhysical Therapy Division, University of Brasilia, Brasília, Brazil; ^dDepartment of Physical Therapy, College of Applied Health Sciences, University of Illinois Chicago, Chicago, IL, USA; ^eSerra Gaucha College, Physical Therapy Division, Brazil

Running Title: NMES in COPD patients

Correspondence to:

*Gaspar R. Chiappa, PT, ScD

Exercise Pathophysiology Research Laboratory

Hospital de Clínicas de Porto Alegre,

Rua Ramiro Barcelos 2350,

90035-007 Porto Alegre, RS, Brazil

Phone: +55 51 91177267

Fax: +55 51 3359 6332

E-mail: gchiappa@hcpa.ufrgs.br

Abstract

Background. Neuromuscular electrical stimulation (NMES) improves muscle performance and exercise tolerance in chronic obstructive pulmonary disease (COPD) patients. In contrast, no study has assessed the effect of NMES on dynamic hyperinflation (DH) in COPD. This study investigated the effect of short-term, high-frequency NMES on DH in patients with COPD.

Methods. Twenty patients were randomly allocated to either a NMES applied bilaterally to the quadriceps muscles (n=11: 8 weeks, 5 days/week, twice/day, 45 min/session) or a control group (n=09). All patients received respiratory physical therapy and stretching exercises. Free fat mass, pulmonary function, time to exercise tolerance (*Tlim*), 6-min walk test distance (6-MWTD), tumour necrosis factor (TNF- α) and β -endorphin levels, Borg dyspnea and leg score (BDS and BLS) and quality of life by the St. George's Respiratory Questionnaire score (SGRQ) were examined before and after the intervention.

Results. Compared with the control group, NMES increased FEV₁ and FEV₁/FVC, 6-MWD and *Tlim* ($P<0.01$) and reduced BDS and SGRQ ($P<0.01$). Additionally, changes in the *Tlim* were positively correlated with respiratory improvements in FEV₁ ($\rho = 0.48$, $P<0.01$). Also, NMES reduced TNF- α and increased β -endorphin levels, compared with the control group ($P<0.001$).

Conclusion. In summary, 8 weeks of NMES promotes reduction of the perceived sensation of dyspnea during exercise in patients with COPD. This finding is accompanied by improvements in FEV₁, exercise tolerance and quality of life, and DH. Interestingly, these findings may be associated with enhanced vasodilatory function and a reduction in inflammatory responses.

Clinical Trial Registration: NCT01695421.

Keywords: Electrical stimulation; dynamic hyperinflation; dyspnea; body composition; exertion; pulmonary rehabilitation.

Introduction

Patients with chronic obstructive pulmonary disease (COPD) are characterized by airflow limitation during exercise, oftentimes resulting in significant exercise intolerance (1). Although the reduced exercise tolerance in COPD has a multifactorial origin (2), the progressive increase in operating lung volumes, secondary to the expiratory flow limitation, dynamic hyperinflation (DH), and consequent dyspnea, takes on a major role, especially in patients with advanced disease (3). Dyspnea is a critical factor in restricting exercise associated with increased level of plasma pro-inflammatory cytokines, antioxidant imbalance and intensive dynamic hyperinflation (4). In addition, most patients with COPD present peripheral muscle fatigue (5) and limited exercise performance (6). Alterations in skeletal muscle are associated with the pathophysiology of COPD, and linked to marked reductions in oxygen (O₂) transport to limb locomotor muscles (1). Apparently, O₂ transport may be impaired due to deleterious changes in pulmonary gas exchange resulting in decreased hemoglobin saturation (7), hyperinflation induced by expiratory flow limitation and greater respiratory muscle work, all of which contributing to inspiratory and/or expiratory muscle fatigue (8).

In this context, there is substantial interest in physical training modalities that do not evoke dyspnea, such as neuromuscular transcutaneous electrical stimulation (NMES). NMES involves the application of an electrical current at a level that induces skeletal muscle contractions (9). Application of NMES has been linked to increased muscle strength, function capacity and health status in COPD patients (4, 10). Although clinical benefits have been shown after NMES interventions in chronic disease populations (4, 11-13), further detailed analyses into the physiological improvements associated with NMES are needed. Moreover, and particularly relevant to patients with COPD, further

assessment of whether application of NMES to peripheral muscles impacts pulmonary function. Therefore, the present study aimed to evaluate comprehensively the clinical and physiological effects of NMES in a COPD cohort. We reasoned that the NMES could improve clinical measures linked to the improvement in several pathophysiological processes associated with COPD.

Methods

Patient Population

Twenty-one men patients with stable COPD, not engaged in pulmonary rehabilitation, and who met the criteria defined by the GOLD (14), were recruited in this study. Patients included in our study did not present cough and sputum production for most days in three consecutive months in the last two years or more successive years (chronic bronchitis diagnosis) (15), presenting moderate to severe airflow limitation ($FEV_1 < 40\%$ predicted) and a previous history of exercise intolerance (walked distance by 6-minute walk test [6-MWT] < 350 m) (16). Inclusion criteria were the following: (1) a diagnosis of COPD with $FEV_1 < 50\%$ predicted as per the GOLD guidelines and (2) self-reported dyspnea and/or arm fatigue during at least one activity of daily living that required arm exercise. Dyspnea and/or physical activity fatigue were self-reported by the Borg Scale. Exclusion criteria were as follows: (1) musculoskeletal or neurologic conditions that might affect exercise performance, symptomatic cardiac disease, or previous lung surgery; (2) an acute exacerbation of COPD that required a change in pharmacological management within the preceding 2 months; (3) use of oral corticosteroids; (4) a change in medication dosage or exacerbation of symptoms in the preceding 12 weeks., (5) implantable electrical devices. Before entering in the study, all patients had their pulmonary function optimized with long-acting bronchodilators and corticosteroids. If necessary patients could also use a

short-acting bronchodilator (salbutamol 120 mg/ipratropium 20 mg, Combivent, Boehringer Ingelheim GmbH, Ingelheim, Germany). Procedures and potential risks were clarified in details to the subjects. This study was conducted in accordance with the amended Declaration of Helsinki. All participants gave written, informed consent as approved by the Institutional Review Board.

Study Design

A prospective double-blind, randomized, pilot study was conducted to compare the use of NMES to a control intervention. The design of the study is shown in **Figure 1**. The patients were referred from a Private Physical Therapy Clinic by two investigators who were blind to the order of patient allocation. Patients were randomly assigned to either the NMES group (n = 11) or the control group (n = 9). All patients received respiratory physical therapy (bronchial hygiene techniques such as huffing and assisted coughing) when indicated by the pulmonary auscultation, as well as regular stretching exercises (upper limbs, lower limbs, and back region, during 30 min). Randomization was performed by the Graphpad StatMate computerized program (version 1.01i, San Diego, California, EUA). The NMES intervention period lasted 60 minutes, being consistent with previous investigations (17, 18). Each evaluation consisted of a two-day protocol including: (1) a quality of life questionnaire, body composition assessment, pulmonary function tests and an incremental exercise test (day 1); (2) constant work rate test (CWT) to the limit of tolerance with electromyography of left *vastus lateralis* muscle.

NMES Intervention

NMES was applied to the bilateral quadriceps with surface electrodes as previously described (4). A portable, user friendly, dual channel NMES stimulator was used (Multicurrent Device, EndoMed 686, Enraf-Nonius B.V., Rotterdam, Netherlands, GB

3004). The following training protocol was chosen in order to minimize the effects of muscular fatigue: a) symmetrical biphasic square pulsed current at 50 Hz, b) duty cycle: 2 s on and 18 s off (10%) during the first week, 5 s on and 25 s off (20%) during the second week, and 10 s on and 30 s off (33%) thereafter; and c) pulses of 300 to 400 μ s wide using the highest tolerable amplitude (15-20 mA at the start of the training session increasing up to 100 mA). The intensity was increased until a visible strong muscle contraction occurred or to the maximum level of toleration. The same instruction and electrode positions were provided to the control, although the equipment did not provide any stimulation current. Patients underwent a series of evaluations before and after the 8 week intervention period. Each evaluation comprised measurements of body composition, respiratory and exercise variables, as well as blood draws.

NMES was applied in each thigh 5 times per week, twice a day for 8 weeks, lasting 60 minutes per session. The electrodes were positioned over the motor-point in order to produce skeletal muscle contractions as a result of intramuscular nerve branch activation (19).

Outcomes

Body composition, thigh circumference, pulmonary and respiratory muscle function tests, cardiopulmonary exercise testing, the 6-MWT, TNF- α and β -endorphin level, and quality of life assessments were obtained. Baseline demographic data including age, gender, body mass index (BMI), medical history, exercise habits and smoking history were recorded. Subjects were then asked to rest for 30 min in the sitting position to achieve a steady cardiopulmonary status for the following assessments.

Measurements

Body composition and thigh circumference. Fat-free mass (FFM) was measured by bioelectrical impedance (Bodystat-500, Bodystat Ltd, Douglas, UK). Impedance measurements were performed on the right side with subjects supine and with their limbs slightly apart from the trunk. FFM was calculated by specific regression equation (20), using height squared divided by resistance (Ht^2/Res) and total body mass and expressed as a percentage of ideal body weight (4). All measurements of the thigh circumference were performed at 14 (C14), 21 (C21) and 28 (C28) cm below the iliac crest while subjects were in a resting state (21). All anthropometric measurements were taken in accordance with WHO standards (22).

Pulmonary and respiratory muscle function tests. Spirometric tests were performed using the CPF System (Medical Graphics-MGC, St. Paul, MN) with airflow being measured by a calibrated Pitot tube (PreVent, Pneumotach). The subjects completed at least three acceptable maximal forced and slow expiratory maneuvers after 15 min the inhalation of 400 μ g of salbutamol via a metered-dose inhaler (23). Forced vital capacity (FVC, L), forced expiratory volume in one second (FEV_1 , L), FEV_1/FVC , and inspiratory capacity (IC) were measured according to American Thoracic Society standards (2, 24). Maximal voluntary ventilation was estimated by multiplying FEV_1 by 37.5 (25). The patients completed at least three slow, forced expiratory maneuvers, considered acceptable and reproducible. The predicted values were derived from those for the Brazilian population (26). Respiratory muscle function assessment was performed using a pressure transducer (MVD-500 V.1.1 Microhard System, Globalmed, Porto Alegre, Brazil), connected to a system with two unidirectional valves (DHD Inspiratory Muscle Trainer, Chicago, Illinois). Maximal static inspiratory ($P_{I_{max}}$) and expiratory ($P_{E_{max}}$) pressure were determined as described elsewhere (27). The highest pressure of six

measurements was used for analysis. Arterial partial pressures for O₂ and CO₂ were obtained during visit 1 from samples taken by radial artery puncture, and analyzed in the ABL 330 system (Radiometer, Copenhagen, Denmark).

Cardiopulmonary exercise testing. Cardiopulmonary exercise tests were performed on an electronically braked cycle ergometer (Inbrasport, Porto Alegre, Brazil) at 60 rpm. The Standard metabolic and ventilatory responses were measured breath-by-breath using a calibrated, computer-based system (K4b², Cosmed, Rome, Italy). Pulse oximetry (SpO₂) was also assessed during testing (POX 010-340, Mediasid, Torrance, USA). An incremental exercise test was carried out at baseline by all subjects to establish individualized workloads for the subsequent constant work test (CWT). The incremental ramp exercise test started with 2-min unloaded cycling followed by incremental workload adjustments of 5 to 10 watts per min until exhaustion. Gas exchange variables were averaged every 10 s and peak oxygen uptake ($\dot{V}O_{2\text{peak}}$) was defined as the highest value achieved during the test. $\dot{V}O_2$ at the first ventilatory threshold was estimated by the V-slope method as previously described (28). Heart rate (HR) was determined using the R-R intervals from a 12-lead electrocardiogram. Subjects were also asked to rate their 'shortness of breath' at exercise cessation using the 0-10 Borg's category-ratio scale (29). A CWT test was performed at baseline and after 8 weeks in all subjects. The CWT to exercise tolerance (*Tlim*) was performed without the administration of long- or short-acting bronchodilators. The constant power output was chosen to elicit an $\dot{V}O_2$ that exceeded the first ventilatory threshold by a value of 60% of the difference between $\dot{V}O_{2\text{peak}}$ and ventilatory threshold $\dot{V}O_2$ (~80% peak work rate) (30). *Tlim* was defined as the point in time when patients signaled to stop exercising or could not maintain the required pedaling rate for 10 s, despite being encouraged by the investigators. Serial inspiratory capacity (IC) maneuvers were performed every 2 min during the CWT. Assuming that

total lung capacity (TLC) remains constant during exercise, IC maneuvers provide an estimate of end-expiratory lung volume ($EELV = TLC - IC$) (31) .

Electromyography. A four-channel surface electromyography system (Miotool, Miotec Biomedical Device, Porto Alegre, Brazil) was used to measure muscle activity from the left *vastus lateralis* muscle as previously described (32). Root mean square values normalized by a previously obtained maximal voluntary contraction were calculated by a mathematical routine using Matlab 7.1 software (Math Works Inc., Natick, MA).

Mechanical efficiency. Gross mechanical efficiency (ME) was calculated as the ratio of work accomplished $\cdot\text{min}^{-1}$ (watts converted to $\text{kcal}\cdot\text{min}^{-1}$) to energy expended $\cdot\text{min}^{-1}$ ($\text{kcal}\cdot\text{min}^{-1}$). Energy expenditure $\cdot\text{min}^{-1}$ ($\text{kcal}\cdot\text{min}^{-1}$) was calculated from $\dot{V}O_2$ and the respiratory exchange ratio (RER) as described by Fornusek and Davis (33).

Six-minute walk test. The maximum distance covered during the 6-MWT was used to assess submaximal functional capacity (34). The 6-MWT was conducted according to ATS guidelines (16). Dyspnea and leg effort (Borg scale) as well as SpO_2 were assessed at the beginning and end of the test. Following completion of the 6-MWT, subjects were asked if they experienced any of the following symptoms: dyspnea, chest pain, lightheadedness or leg pain.

TNF- α and β -Endorphin analysis A total of ten milliliters of venous blood was taken by the phlebotomist, 3 ml of which was stored in ethylenediaminetetraacetic acid (EDTA) for analysis of a differential white cell count. Seven ml of blood was divided between an EDTA tube and a lithium heparin (LH) gel tube. These blood samples were centrifuged and frozen until assayed. Serum tumour necrosis factor (TNF- α) and β -endorphin were measured by sandwich enzyme immunoassay (ELISA) kit (Phoenix Pharmaceuticals, Inc., USA).

Quality of life questionnaire. The Saint Georges's Respiratory Questionnaire (SGRQ) (35) was used to assess the health-related quality of life (HRQOL). The SGRQ is a self-administered HRQOL measure containing 50 items and 76 weighted responses divided into three components: symptoms, activity, and impacts. The symptoms component contains items addressing the symptomatology, frequency of cough, sputum production, wheeze, breathlessness, and the duration and frequency of breathlessness or wheeze. The activity component addresses physical activities that either cause or are limited by breathlessness. The impacts component assesses factors such as employment, being in control of health, panic, stigmatization, the need for medication and its side effects, expectations for health and disturbance of daily life. Scores ranging from 0 to 100 were calculated for each component, as well as a total score that summarizes the responses to all items. A zero score indicates no impairment of HRQOL. The questionnaire takes approximately 10 min to be filled out and has been shown to be reproducible, valid and responsive in both COPD and asthmatic populations (36).

Statistical Analysis

Based on the results of Ngai et al (37), which examined the long-term effects of a different electrical stimulation (Acu-TENS) on FEV₁ in COPD patients, with an effect size of 1.51, power of 0.8 and α value of 0.05, 9 participants per group were required. Differences between groups at baseline were assessed by an unpaired Student's *t* test; mean differences and their 95% confidence intervals are reported for the main outcomes. In addition, the data following NMES in patients on group 2 were compared with baseline values using a two-way, mixed model ANOVA assessing within (pre vs. post) and between-groups (control vs. NMES) effects. Product-moment correlation (Spearman) was used to define the associations between FEV₁ and *Tlim*. A p-value <0.05 was

considered statistically significant. Statistical analyses were conducted by using SPSS version 19.0. All data are presented as mean \pm SD values.

Results

Flow of participants

Figure 1 illustrates the flow diagram of patients in the study. Thirty patients were screened for eligibility. Four patients did not meet inclusion criteria and 2 declined to participate. Therefore, 24 patients were randomized. Twelve patients were randomized to NMES, but 1 patient had an exacerbation during the first week of intervention period. Twelve patients were randomized to control, but 3 patients had an exacerbation during the intervention period. Therefore, 20 patients completed the study.

At baseline, no significant differences were found between the groups in anthropometric, pulmonary variables as well as in respiratory muscle function (**Table 1**). There were also no differences in the incremental cardiopulmonary exercise testing results between the groups. Medical regimen was unchanged throughout the experiments.

Pulmonary and respiratory muscle function

Table 2 shows the results of pulmonary function and respiratory muscle function before and after 8 weeks of treatment. The NMES intervention resulted in significant improvements in FEV₁ (NMES 0.98 ± 0.33 vs. 1.12 ± 0.36 ; Control 0.96 ± 0.17 vs. 0.93 ± 0.27 L; ANOVA, $P < 0.001$), FEV₁/FVC (NMES 44.1 ± 11.4 vs. 53.1 ± 10.8 ; Control 39.4 ± 9.6 vs. 42.1 ± 11.5 ; ANOVA, $P < 0.001$), and peak flow (NMES 191.8 ± 79.8 vs. 245.6 ± 86.1 ; Control 204.4 ± 106.3 vs. 212 ± 93.3 mL; ANOVA, $P < 0.001$). Inspiratory and expiratory muscle strength increased after the intervention, but there was not a significant interaction effect.

Anthropometric measures

As shown in **Table 3**, body composition was affected by NMES program. Fat-free mass (FFM) increased only NMES (NMES, 32.01 ± 4.75 vs 34.01 ± 4.67 %; control, 32.3 ± 5.87 vs 33.1 ± 4.34 %; *P* *intra-group* < 0.01, with no interaction). Muscle mass (MM) increased by ~8 % only in the NMES group (NMES, 49.1 ± 4.55 vs 52.9 ± 5.88 kg; control, 50.2 ± 4.78 vs 50.4 ± 4.88 kg; *P* *intra-group* < 0.01, with no interaction). Interestingly, thigh circumference significantly increased of 51.8 ± 7.7 to 53.3 ± 6.9 cm with NMES, without changes in the control group.

Constant work exercise test and the 6-minute walk test

Table 3 shows data from the CWT. The $\dot{V}O_2$ (NMES, 989 ± 245 vs 1089 ± 233 ; control, 977 ± 189 vs 969 ± 1918 mL/min; ANOVA, *P* < 0.01) and \dot{V}_E (NMES, 38.3 ± 9.7 vs 46.5 ± 9.2 ; control, 34.5 ± 8.5 vs 36.9 ± 6.1 L; ANOVA, *P* < 0.01) at *T*_{lim} increased significantly in the NMES group compared with control group. $\dot{V}CO_2$ and RER only augmented when compared with baseline values in the NMES group. *T*_{lim} increased significantly by 32% only in the NMES group (NMES, 6.9 ± 1.5 vs 9.11 ± 2.4 ; control, 8.2 ± 3.1 vs 8.4 ± 3.4 min; ANOVA, *P* < 0.01). Borg leg effort (NMES, 8.6 ± 1.1 vs 7.3 ± 1.6 ; control, 7.8 ± 1.6 vs 8.1 ± 1.2 ; ANOVA, *P* < 0.01) and Borg dyspnea score (NMES, 8.0 ± 1.7 vs 6.2 ± 1.4 ; control, 7.3 ± 1.5 vs 7.7 ± 1.4 ; ANOVA, *P* < 0.01) assessed at the end of exercise reduced significantly following NMES with no change in the control group. Similarly, mechanical efficiency improved by 24.6% only in the NMES group (NMES, 19.5 ± 3.5 vs 24.3 ± 4.5 ; control, 20.5 ± 5 vs 20.1 ± 4.1 ; ANOVA, *P* < 0.01). The 6-MWT distance significantly increased by nearly 76 m in the NMES group but not in the control group (NMES, 359.6 ± 71.3 vs 435.3 ± 36.5 ; control, 349.8 ± 95.2 vs 350.6 ± 95.6 ; ANOVA, *P* < 0.01).

Association between FEV₁ and *Tlim*

In the NMES group, the improvement in *Tlim* was significantly associated with the increase in FEV₁ adjusted for post-training changes in exercise duration (CWT and 6-MWT) ($\rho = 0.48$; $P < 0.001$) (**Figure 2**).

Dynamic hyperinflation responses during exercise

At the 8-week follow-up, inspiratory capacity significantly increased at 4, 6, 8 and 10 min during the CWT in the NMES group with no change in the control group (**Figure 3**).

Electromyography

Subjects in the NMES group demonstrated a lower submaximal root mean square (RMS) at 8-week follow-up during the CWT compared to no change in the control group (**Figure 4**).

TNF- α and β -endorphin levels

NMES resulted in a significant decrease in TNF- α levels (Figure 5A, NMES 1.45 ± 0.39 vs. 1.05 ± 0.23 ; Control 1.55 ± 0.33 vs. 1.48 ± 0.43 pg/ml; ANOVA, $P < 0.001$) as well as a significant increase in β -endorphin levels (Figure 5B, NMES, 356 ± 27 vs. and 489 ± 34 ; Control 333 ± 16 vs. 345 ± 33 ; ANOVA, $P < 0.001$).

Quality of life

The SGRQ domain (NMES, 60 ± 12 vs. 44 ± 11 ; control, 54 ± 9 vs. 52 ± 8 after: ANOVA, $P < 0.05$) and total score (NMES, 48 ± 10 vs. 37 ± 11 ; control, 52 ± 7 vs. 50 ± 9 : ANOVA, $P < 0.05$) improved in the NMES group only (**Figure 6**).

Discussion

The primary findings of the present study were that NMES promoted increases in exercise performance, QOL and peripheral muscle function, and such changes were accompanied by improvements in pulmonary function, markers of systemic inflammation and pain modulation in COPD patients. Thus, this study supports clinical benefits of NMES and extends the knowledge in the NMES-mediated improvements in function and QOL in patients with COPD.

Using a different NMES protocol on the stellate ganglion region, Lau et al have demonstrated a significant improvement in FEV₁ (38). In our study, we found similar effects on FEV₁, comparable to bronchodilators therapy (FEV₁ gain \geq 10-15%) (39), with benefits to DH. Other studies have suggested an association between FEV₁ and reduced residual volume (40). The effect of NMES on FEV₁ does not seem to be directly chemical (i.e. bronchodilators mechanism) or neural with stimulation in hypothalamic region reducing airway constriction (41). In the present study, the increase of FEV₁ may be the result of improvements in peripheral muscle dysfunction, which in turn contribute to improve FEV₁ (42).

There is evidence that NMES attenuates the production of cardiovascular inflammatory mediators and improves peripheral endothelium-dependent vasodilatation in chronic heart failure (43). In our study, NMES resulted in decreased TNF- α and increased β -endorphin levels. TNF- α is considered as an important systemic inflammatory marker associated with the disease progression in COPD patients (44). Therefore, the changes in β -endorphin levels in patients with COPD after 8 weeks of NMES intervention may be linked to more systemic benefits. Previous study has demonstrated that NMES reduces TNF- α and improves peripheral endothelium-dependent vasodilatation in chronic heart

failure, which could facilitate the blood supply to active muscles (43). Although this latter suggested mechanism needs to be evaluated in COPD, the hypothesis of enhanced blood delivery mediated by improved vasodilation could be a possible explanation for the increased exercise tolerance. Additionally, the increased β -endorphin levels in COPD patients after NMES intervention have contributed to the rhythm-generating component of the respiratory centre (45), therefore impacting the respiratory control.

The FVC reflects the integrity of all components involved with pulmonary function and is an important surrogate of cough effectiveness because the peak flow during the cough is comparable with the mean peak flow during a FVC maneuver (46). In our study, NMES increased FVC and FEV₁. Apparently, FEV₁ is linked to increased strength of the expiratory musculature and the diameter of upper airways (47), which helps to reinforce the increase of peak flow and expiratory muscle strength in our study. This concept is not novel, especially in the context of demonstrated changes in respiratory muscle function during traditional exercise training. In a recent study (48), we showed that aerobic training results in significant activation of the inspiratory musculature, similar to the expected effects of inspiratory muscle training. In part, we believe that these effects might be due to initial inspiratory muscle weakness, which is afforded the opportunity to improve once expiratory flow limitations are lessened.

The effect of NMES on peripheral muscle strength has been described previously (4, 21). In our study, muscle mass and fat-free mass were changed with NMES. Conversely, Dal Corso et al. (10) showed no significant changes in muscle strength with NMES, but an increase in type II and decrease in type I muscle fibers. However, these changes were not sufficient to increase muscle strength, which is accordance with other findings (4). In our study, we found a significant increase in thigh circumference with NMES as found by Vivodtzev et al. (21). This investigation found an increase of corrected thigh

circumference during application NMES, suggesting an improvement to neural remodeling because of the relatively short duration of the interventions (4-6 weeks). However, other investigations did not find changes in thigh mass evaluated by DEXA (10). The disparities between studies may be attributed to differences in disease severity and variations in NMES protocols. Apparently, a difference in parameters of stimulation could influence the potential for a hypertrophic response. Studies demonstrating an increase in muscle mass with NMES (21) used higher intensities (15-90 mA) and lower frequencies (5-35 Hz) while other studies (10) demonstrating no change used lower intensities (10-45 mA) and higher frequencies (50 Hz).

We can only speculate on possible mechanisms related to the improved exercise tolerance and lung function. In this regard, NMES has shown to improve cycling mechanical efficiency as indicated by in our study. Previous studies have shown a reduced mechanical efficiency seemed to be associated with an increased work of breathing in COPD patients (49, 50), therefore suggesting the muscle adaption induced by NMES could at least partially reduce the breathing demand during exercise.

Apparently, our data are consistent with growing evidence that NMES can be safe and effective in patients with skeletal muscle dysfunction and exercise intolerance secondary to systemic chronic diseases. Quittan et al. (18) have described substantial gains in muscle strength and exercise tolerance after NMES in patients with congestive heart failure, which have been confirmed by others (9, 51). These positive effects of NMES are likely to be similar to those morphological changes described by Maltais et al. (52) in patients with COPD who were submitted to conventional endurance training. Using a comprehensive range of outcome measures, our study showed a reduction in leg effort for a submaximal of exercise after NMES training, which would be consistent with this view. Finally, Vivodtzev et al. (11) showed that muscle function is associated with a more

favorable muscle anabolic to catabolic balance. Further morphological studies after NMES training, however, will be required to test this hypothesis.

Previous studies (4) have demonstrated significant increases in 6-MWT distance after NMES in COPD patients. Likewise, our results indicate clinically relevant changes in 6-MWT after NMES. We observed an increase of 87 m (95% CI, 13.16 to 172.5 m; $P < 0.01$), which is greater than the 47 m improvement recommended for an intervention to be of credible clinical significance by ATS (16). Furthermore, the increase of 6-MWT was accompanied by changes in SpO₂ (mean increase of 2.3%) and reduction in Borg dyspnea scores after the NMES intervention, which has been also shown previously.(38) In contrast, Ngai et al. (53) could not find reduction in dyspnea score with application of transcutaneous electrical nerve stimulation. It is possible that the difference between findings may be due to the fact that COPD patients were in a more stable condition in the study by Ngai et al. (53), while in other studies (37, 38), such as the current analysis, subjects were considered to have a higher disease severity.

Some limitations should be addressed in our study. First, the use of a non-perceptible stimulus as the control intervention, without a real sham intervention, may have resulted in ascertainment bias. In order to reduce underreporting of clinical improvements in control group, subjects were managed as a group of conventional physiotherapy, rather than a group non-intervention group. Second, the limited sample size did not allow us to perform sub-group analysis that could clarify characteristics possibly associated with clinical changes. In this regard, we encourage future research with different sets of patients in order to clarify those who can derive larger gains with a NMES program. Third, the lack of post-intervention measurements such as cardiopulmonary exercise testing or pulmonary tests limited our interpretation of direct indicators of lung hyperinflation and air trapping.

Clinical Implications

Electrical stimulation has been shown to produce benefits in the muscle function of COPD patients (54, 55), which indicates that NMES is a potential adjunctive technique especially for patients who may sustain low metabolic and ventilatory demands (56). The present study provides evidence that NMES may improve the exercise tolerance in COPD non-bronchitic patients. Interestingly, these benefits may be associated with reduction in dynamic hyperinflation, inflammatory responses, with concomitant increases in vasodilatory function.

In summary, the present study shows that a short term, high frequency, NMES program improves a variety of measures associated with function, symptomatology, QOL, and physiological function in COPD patients. As such, this interventional approach may be a efficacious and feasible complimentary rehabilitation technique in this chronic disease population. Future studies should extend the present analysis, perhaps testing whether the primary NMES effects are local (muscular adaptation) or systemic (blood supply, inflammation, etc).

Potential conflict of interest

None of the authors have any potential conflict of interest related to the contents of this paper.

Disclosure: This study was supported by a research grant from the Hospital de Clínicas de Porto Alegre, FIPE/HCPA, Porto Alegre Brazil. Dr. Gaspar R. Chiappa receives a Post-doctoral Fellowship from the Coordination for the Improvement of Higher Education Personnel (CAPES), Brasilia, Brazil.

Acknowledgements: Paulo J. C. Vieira and Gaspar R. Chiappa designed the study. Gaspar R. Chiappa coordinated the study. Adriana M. Guntzel and Paulo J. C. Vieira were responsible for patient screening, and enrolment. Gaspar R. Chiappa performed statistical analysis. A Gerson Cipriano Jr, Daniel Umpierre, Ross Arena, Paulo J. C. Vieira and Gaspar R. Chiappa analysed the data and wrote the manuscript. All authors contributed to interpretation of the data and provided comments on the report at various stages of development. We thank Dr. Jorge P. Ribeiro (IN MEMORIAN) for clinical coordination and clinical database management.

Figure Legends

Fig.1. The CONSORT, Flow diagram of patients in the study.

Fig. 2. Scatterplot of the association between changes (post-pre) of FEV₁ and *Tlim* during NMES (closed circles) and Control group (open squares).

Fig. 3. Inspiratory capacity at rest and during exercise (until the 10th minute) in COPD patients during pre and post NMES compared with control group. *Differences between the groups at a given time point. †Differences related to the previous time point in a given group.

Fig. 4. Significant decreases in peripheral muscle fiber activation during constant work rate exercise in response to NMES (closed circles) compared with Control group (open circles) in patients with chronic obstructive pulmonary disease. RMS = root mean square. * $P < 0.05$.

Fig. 5. TNF- α (A) and β -endorphin (B) levels in two groups before and after the intervention period, (NMES, black bar, and Control, gray bar). * Two-way repeated-measures ANOVA ($P < 0.001$) for group, training and interaction effects.

Fig. 6. SGRQ categorical and total score measured at pre and post NMES and Control. (A) Symptom score; (B) activity score; (C) impact score; (D) total score. SGRQ = St. George's Respiratory Questionnaire. * $P < 0.05$ within-group comparison and † $P < 0.05$ between-group comparison.

REFERENCES

1. Amann M, Regan MS, Kobitary M, Eldridge MW, Boutellier U, Pegelow DF, et al. Impact of pulmonary system limitations on locomotor muscle fatigue in patients with COPD. *Am J Physiol Regul Integr Comp Physiol*. 2010;299(1):R314-24.
2. O'Donnell DE, Webb KA. The major limitation to exercise performance in COPD is dynamic hyperinflation. *J Appl Physiol*. 2008;105(2):753-5; discussion 5-7.
3. Cordoni PK, Berton DC, Squassoni SD, Scuarcialupi ME, Neder JA, Fiss E. Dynamic hyperinflation during treadmill exercise testing in patients with moderate to severe COPD. *J Bras Pneumol*. 2012;38(1):13-23.
4. Neder JA, Sword D, Ward SA, Mackay E, Cochrane LM, Clark CJ. Home based neuromuscular electrical stimulation as a new rehabilitative strategy for severely disabled patients with chronic obstructive pulmonary disease (COPD). *Thorax*. 2002;57(4):333-7.
5. Mador MJ, Deniz O, Aggarwal A, Kufel TJ. Quadriceps fatigability after single muscle exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2003;168(1):102-8.
6. Gagnon P, Saey D, Vivodtzev I, Laviolette L, Mainguy V, Milot J, et al. Impact of preinduced quadriceps fatigue on exercise response in chronic obstructive pulmonary disease and healthy subjects. *J Appl Physiol*. 2009;107(3):832-40.
7. Maltais F, Simon M, Jobin J, Desmeules M, Sullivan MJ, Belanger M, et al. Effects of oxygen on lower limb blood flow and O₂ uptake during exercise in COPD. *Med Sci Sports Exerc*. 2001;33(6):916-22.
8. Polkey MI, Kyroussis D, Mills GH, Hamnegard CH, Keilty SE, Green M, et al. Inspiratory pressure support reduces slowing of inspiratory muscle relaxation rate during exhaustive treadmill walking in severe COPD. *Am J Respir Crit Care Med*. 1996;154(4 Pt 1):1146-50.
9. Sillen MJ, Speksnijder CM, Eterman RM, Janssen PP, Wagers SS, Wouters EF, et al. Effects of neuromuscular electrical stimulation of muscles of ambulation in patients with chronic heart failure or COPD: a systematic review of the English-language literature. *Chest*. 2009;136(1):44-61.
10. Dal Corso S, Napolis L, Malaguti C, Gimenes AC, Albuquerque A, Nogueira CR, et al. Skeletal muscle structure and function in response to electrical stimulation in moderately impaired COPD patients. *Respir Med*. 2007;101(6):1236-43.
11. Vivodtzev I, Debigare R, Gagnon P, Mainguy V, Saey D, Dube A, et al. Functional and muscular effects of neuromuscular electrical stimulation in patients with severe COPD: a randomized clinical trial. *Chest*. 2012;141(3):716-25.
12. Gerovasili V. Neuromuscular electrical stimulation appears to be useful in people with severe chronic obstructive pulmonary disease. *Journal of physiotherapy*. 2012;58(4):270.

13. Karatzanos E, Gerovasili V, Zervakis D, Tripodaki ES, Apostolou K, Vasileiadis I, et al. Electrical muscle stimulation: an effective form of exercise and early mobilization to preserve muscle strength in critically ill patients. *Critical care research and practice*. 2012;2012:432752.
14. Fabbri LM, Hurd SS. Global Strategy for the Diagnosis, Management and Prevention of COPD: 2003 update. *Eur Respir J*. 2003;22(1):1-2.
15. Menezes AM, Victora CG, Rigatto M. Prevalence and risk factors for chronic bronchitis in Pelotas, RS, Brazil: a population-based study. *Thorax*. 1994;49(12):1217-21.
16. ATS Statement: Guidelines for the Six-Minute Walk Test. *Am J Respir Crit Care Med*. 2002;166(1):111-7.
17. Hainaut K, Duchateau J. Neuromuscular electrical stimulation and voluntary exercise. *Sports Med*. 1992;14(2):100-13.
18. Quittan M, Wiesinger GF, Sturm B, Puig S, Mayr W, Sochor A, et al. Improvement of thigh muscles by neuromuscular electrical stimulation in patients with refractory heart failure: a single-blind, randomized, controlled trial. *Am J Phys Med Rehabil*. 2001;80(3):206-14; quiz 15-6, 24.
19. Hultman E, Sjöholm H, Jäderholm-Ek I, Krynicki J. Evaluation of methods for electrical stimulation of human skeletal muscle in situ. *Pflugers Arch*. 1983;398(2):139-41.
20. Schols AM, Wouters EF, Soeters PB, Westerterp KR. Body composition by bioelectrical-impedance analysis compared with deuterium dilution and skinfold anthropometry in patients with chronic obstructive pulmonary disease. *Am J Clin Nutr*. 1991;53(2):421-4.
21. Vivodtzev I, Pepin JL, Vottero G, Mayer V, Porsin B, Levy P, et al. Improvement in quadriceps strength and dyspnea in daily tasks after 1 month of electrical stimulation in severely deconditioned and malnourished COPD. *Chest*. 2006;129(6):1540-8.
22. Seidell JC, Deurenberg P, Hautvast JG. Obesity and fat distribution in relation to health--current insights and recommendations. *World Rev Nutr Diet*. 1987;50:57-91.
23. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319-38.
24. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319-38.
25. Neder JA, Andreoni S, Lerario MC, Nery LE. Reference values for lung function tests. II. Maximal respiratory pressures and voluntary ventilation. *Braz J Med Biol Res*. 1999;32(6):719-27.

26. Pereira CA, Sato T, Rodrigues SC. New reference values for forced spirometry in white adults in Brazil. *J Bras Pneumol*. 2007;33(4):397-406
27. Dall'Ago P, Chiappa CRS, Guths H, Stein R, Ribeiro JP. Inspiratory muscle training in patients with heart failure and inspiratory muscle weakness - A randomized trial. *Journal of the American College of Cardiology*. 2006;47(4):757-63.
28. Neder JA, Nery LE, Castelo A, Andreoni S, Lerario MC, Sachs A, et al. Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomised study. *Eur Respir J*. 1999;14(6):1304-13.
29. Hamilton AL, Killian KJ, Summers E, Jones NL. Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. *Am J Respir Crit Care Med*. 1995;152(6 Pt 1):2021-31.
30. Chiappa GR, Borghi-Silva A, Ferreira LF, Carrascosa C, Oliveira CC, Maia J, et al. Kinetics of muscle deoxygenation are accelerated at the onset of heavy-intensity exercise in patients with COPD: relationship to central cardiovascular dynamics. *J Appl Physiol*. 2008;104(5):1341-50.
31. O'Donnell DE. Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. *Proceedings of the American Thoracic Society*. 2006;3(2):180-4.
32. Chiappa GR, Queiroga F, Jr., Meda E, Ferreira LF, Diefenthaler F, Nunes M, et al. Heliox improves oxygen delivery and utilization during dynamic exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2009;179(11):1004-10.
33. Fornusek C, Davis GM. Cardiovascular and metabolic responses during functional electric stimulation cycling at different cadences. *Arch Phys Med Rehabil*. 2008;89(4):719-25.
34. Hernandez NA, Wouters EF, Meijer K, Annegarn J, Pitta F, Spruit MA. Reproducibility of 6-minute walking test in patients with COPD. *Eur Respir J*. 2010.
35. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Koyama H, Izumi T. Analysis of clinical methods used to evaluate dyspnea in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1998;158(4):1185-9.
36. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis*. 1992;145(6):1321-7.
37. Ngai SP, Jones AY, Hui-Chan CW, Ko FW, Hui DS. Effect of Acu-TENS on post-exercise expiratory lung volume in subjects with asthma-A randomized controlled trial. *Respir Physiol Neurobiol*. 2009;167(3):348-53.

38. Lau KS, Jones AY. A single session of Acu-TENS increases FEV1 and reduces dyspnoea in patients with chronic obstructive pulmonary disease: a randomised, placebo-controlled trial. *Aust J Physiother.* 2008;54(3):179-84.
39. Tashkin DP, Celli B, Decramer M, Liu D, Burkhart D, Cassino C, et al. Bronchodilator responsiveness in patients with COPD. *Eur Respir J.* 2008;31(4):742-50.
40. Aliverti A, Rodger K, Dellaca RL, Stevenson N, Lo Mauro A, Pedotti A, et al. Effect of salbutamol on lung function and chest wall volumes at rest and during exercise in COPD. *Thorax.* 2005;60(11):916-24.
41. Takeshige C, Oka K, Mizuno T, Hisamitsu T, Luo CP, Kobori M, et al. The Acupuncture Point and Its Connecting Central Pathway for Producing Acupuncture Analgesia. *Brain Res Bull.* 1993;30(1-2):53-67.
42. Couillard A, Prefaut C. From muscle disuse to myopathy in COPD: potential contribution of oxidative stress. *Eur Respir J.* 2005;26(4):703-19.
43. Karavidas AI, Raisakis KG, Parissis JT, Tsekoura DK, Adamopoulos S, Korres DA, et al. Functional electrical stimulation improves endothelial function and reduces peripheral immune responses in patients with chronic heart failure. *Eur J Cardiovasc Prev Rehabil.* 2006;13(4):592-7.
44. Eagan TM, Gabazza EC, C DA-G, Gil-Bernabe P, Aoki S, Hardie JA, et al. TNF-alpha is associated with loss of lean body mass only in already cachectic COPD patients. *Respir Res.* 2012;13(1):48.
45. Takita K, Herlenius EA, Lindahl SG, Yamamoto Y. Actions of opioids on respiratory activity via activation of brainstem mu-, delta- and kappa-receptors; an in vitro study. *Brain Res.* 1997;778(1):233-41.
46. Braun SR, Giovannoni R, O'Connor M. Improving the cough in patients with spinal cord injury. *Am J Phys Med.* 1984;63(1):1-10.
47. Cheng PT, Chen CL, Wang CM, Chung CY. Effect of neuromuscular electrical stimulation on cough capacity and pulmonary function in patients with acute cervical cord injury. *J Rehabil Med.* 2006;38(1):32-6.
48. Winkelmann ER, Chiappa GR, Lima CO, Vecili PR, Stein R, Ribeiro JP. Addition of inspiratory muscle training to aerobic training improves cardiorespiratory responses to exercise in patients with heart failure and inspiratory muscle weakness. *Am Heart J.* 2009;158(5):768 e1-7.
49. Baarends EM, Schols AM, Akkermans MA, Wouters EF. Decreased mechanical efficiency in clinically stable patients with COPD. *Thorax.* 1997;52(11):981-6.
50. Franssen FM, Wouters EF, Baarends EM, Akkermans MA, Schols AM. Arm mechanical efficiency and arm exercise capacity are relatively preserved in chronic obstructive pulmonary disease. *Med Sci Sports Exerc.* 2002;34(10):1570-6.

51. Roig M, Reid WD. Electrical stimulation and peripheral muscle function in COPD: a systematic review. *Respir Med.* 2009;103(4):485-95.
52. Jones DT, Thomson RJ, Sears MR. Physical exercise and resistive breathing training in severe chronic airways obstruction--are they effective? *Eur J Respir Dis.* 1985;67(3):159-66.
53. Ngai SP, Jones AY, Hui-Chan CW, Ko FW, Hui DS. Effect of 4 weeks of Acu-TENS on functional capacity and beta-endorphin level in subjects with chronic obstructive pulmonary disease: a randomized controlled trial. *Respir Physiol Neurobiol.* 2010;173(1):29-36.
54. Bausewein C, Booth S, Gysels M, Higginson I. Non-pharmacological interventions for breathlessness in advanced stages of malignant and non-malignant diseases. *Cochrane Database Syst Rev.* 2008(2):CD005623.
55. Sillen MJ, Janssen PP, Akkermans MA, Wouters EF, Spruit MA. The metabolic response during resistance training and neuromuscular electrical stimulation (NMES) in patients with COPD, a pilot study. *Respir Med.* 2008;102(5):786-9.
56. Napolis LM, Dal Corso S, Neder JA, Malaguti C, Gimenes AC, Nery LE. Neuromuscular electrical stimulation improves exercise tolerance in chronic obstructive pulmonary disease patients with better preserved fat-free mass. *Clinics (Sao Paulo).* 2011;66(3):401-6.

Figure 1 The CONSORT. Flow diagramo of patients in the study

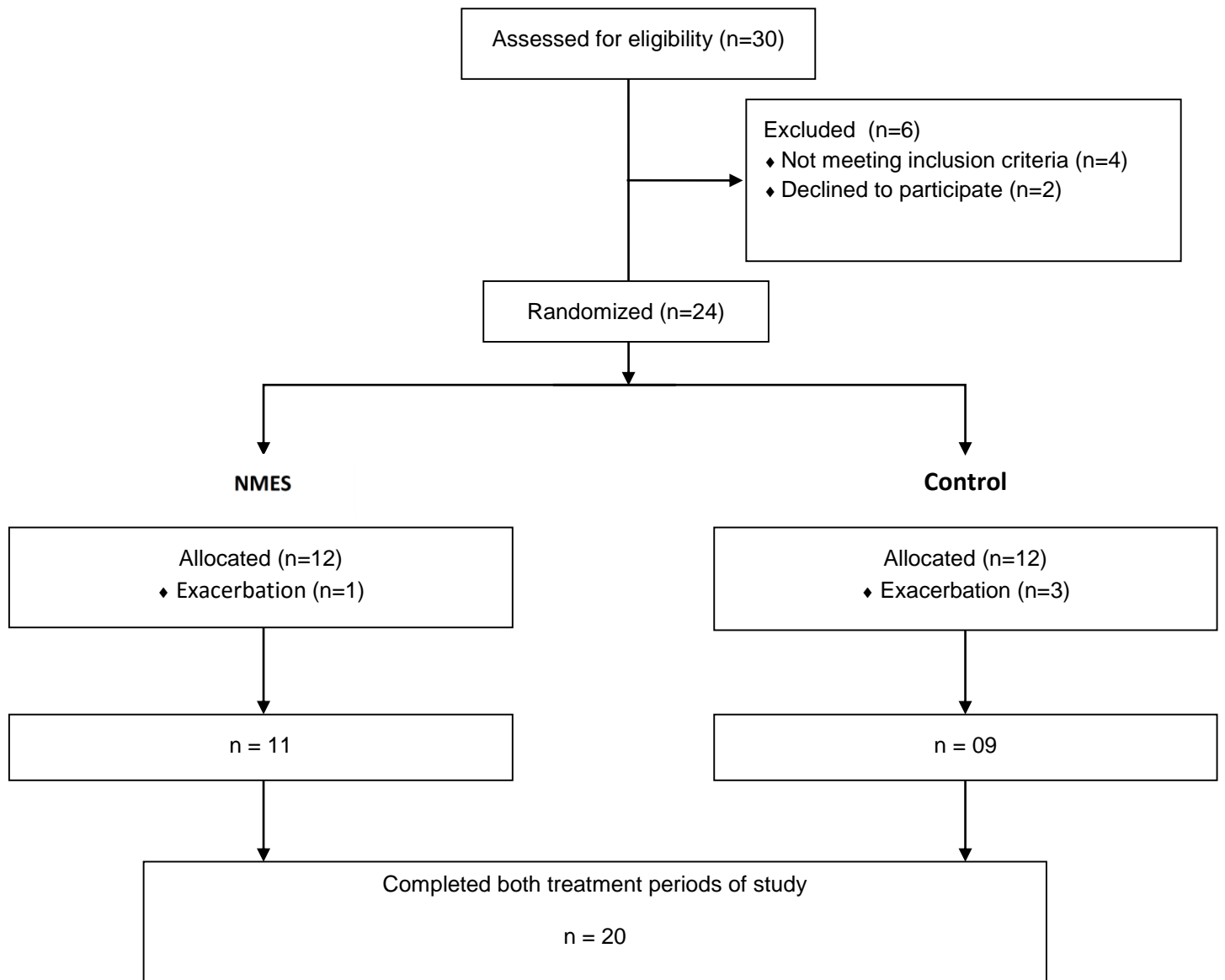


Table 1. Clinical characteristics of the study population

	NMES (n=11)	Control (n=09)	<i>P</i> Value
Demographic/anthropometric			
Age, years	56.3 ± 11	56.4 ± 13	0.98
Height (cm)	164.4 ± 89.3	160.5 ± 48.7	0.25
Weight (kg)	75.1 ± 14.1	70.2 ± 14.5	0.46
BMI	27.4 ± 4.3	27.6 ± 6.4	0.74
Fat-free mass (% ideal weight)	49.14 ± 9.41	51.87 ± 10.92	0.55
COPD disease years	8.2 ± 1.4	8.5 ± 1.8	0.68
Pulmonary function			
FEV ₁ , L	0.91 ± 0.33	0.88 ± 0.17	0.11
FEV ₁ , % pred	36.5 ± 10.5	39.6 ± 14.4	0.24
FVC, L	2.13 ± 0.63	2.19 ± 0.63	0.83
FVC, % pred	61.9 ± 20.1	69.7 ± 20.2	0.39
FEV ₁ /FVC	47.5 ± 12.8	56.7 ± 13.6	0.13
FEV ₁ /FVC, % pred	58.6 ± 16.4	68.9 ± 15.6	0.17
MVV, L	38.9 ± 19.8	52.5 ± 24.7	0.18
IC, L	1.99 ± 0.23	2.01 ± 0.32	0.56
IC, % pred	76 ± 12	78 ± 22	0.87
TLC, L	5.88 ± 0.66	5.93 ± 0.43	0.51
TLC, % pred	104 ± 23	106 ± 29	0.52
RV, L	2.88 ± 0.34	2.99 ± 0.49	0.42
RV, % pred	164 ± 34	169 ± 0.44	0.61
D _L CO, % pred	50 ± 12	52 ± 17	0.34
Arterial blood gases			
PaO ₂ , mm Hg	66 ± 5	68 ± 9	0.77
SaO ₂ , %	92 ± 1.5	93 ± 2.5	0.44
PaCO ₂ , mm Hg	39 ± 3	39.5 ± 6	0.66
Respiratory muscle function			
P _I max, cm H ₂ O	77.9 ± 24.3	72.2 ± 22.5	0.78
P _E max, cm H ₂ O	60.8 ± 25.8	67.2 ± 28.6	0.66
Peak Flow, mL	191.8 ± 79.8	224.4 ± 106.3	0.78
Incremental ramp exercise test			
\dot{V} O ₂ peak, ml.min ⁻¹	989 ± 245	977 ± 189	0.88
\dot{V} CO ₂ peak, ml.min ⁻¹	997 ± 187	981 ± 202	0.63
RER peak	1.01 ± 0.03	1.02 ± 0.01	0.69
\dot{V} _E peak, L	38.3 ± 9.7	34.5 ± 8.5	0.81
\dot{V} _E peak/MVV, %	101.5 ± 22	103.6 ± 31	0.91
V _T peak, L	1.01 ± 0.12	0.98 ± 0.21	0.45
SpO ₂ peak (%)	92 ± 3	94 ± 2	0.66
Power (watts)	75.5 ± 7.8	70.6 ± 10.7	0.71
Borg dyspnea scores	8 (5-10)	8 (4-9)	0.61
Borg leg effort scores	8 (4-8)	7 (4-8)	0.74
Performance walk test			
6-MWT, m	334.1 ± 89.8	349.9 ± 95.3	0.71

Values are means ± standard deviation, except for symptoms (median and range). Definition of abbreviations: NMES, neuromuscular electrical stimulation; BMI, body mass index; FEV₁, forced expiratory volume in 1s; FVC, forced vital capacity;

FEV₁/FVC, FEV₁ to FVC ratio; MVV, maximal ventilatory voluntary; IC, inspiratory capacity; TLC, total lung capacity; RV, residual volume; D_LCO, lung diffusing capacity for carbon monoxide; Pa, arterial partial pressure; Sa, arterial saturation; P_Imax and P_Emax, maximal inspiratory and expiratory muscle pressure; $\dot{V}O_2$ = oxygen uptake; $\dot{V}CO_2$ = carbon dioxide output; RER = ratio exchange ratio; $\dot{V}E$ = minute ventilation; $\dot{V}E$ /MVV= maximal voluntary ventilation; VT= tidal volume; SpO₂= oxyhemoglobin saturation by pulse oximetry; 6-MWT, 6-minute walk test. *P* value represents the overall comparison between the groups.

Table 2. Pulmonary and respiratory muscle function responses

	NMES		Control	
	Before	After	Before	After
FEV ₁ , L	0.98 ± 0.33	1.12 ± 0.36*†‡	0.96 ± 0.17	0.93 ± 0.27
FVC, L	2.10 ± 0.63	2.16 ± 0.62*	2.08 ± 0.66	2.12 ± 0.56
FEV ₁ /FVC, %	44.1 ± 11.4	53.1 ± 10.8*†‡	39.4 ± 9.6	42.1 ± 11.5
Peak Flow, mL	191.8 ± 79.8	245.6 ± 86.1*†‡	204.4 ± 106.3	212 ± 93.3
P _I max, cm H ₂ O	69.9 ± 18.4	77.9 ± 24.3*	72.2 ± 22.5	71.9 ± 18.8
P _E max, cm H ₂ O	52.2 ± 17.4	66.8 ± 15.8*	57.2 ± 18.2	64.1 ± 23.4

Values are means ± SD. Definition of abbreviations: NMES, neuromuscular electrical stimulation; FEV₁= forced expiratory volume in 1 s; FVC= forced vital capacity; IC= inspiratory capacity; EELV= end-expiratory lung volume; P_Imax = maximal inspiratory muscle pressure; P_Emax = maximal expiratory muscle pressure; * p< 0.05 from before within a given intervention; † p<0.05 from trough within a given intervention; ‡p<0.05 between-intervention comparison.

Table 3. Measurements at the time to the limit of tolerance in the constant work tests

	NMES		Control	
	Before	After	Before	After
Body composition				
FFM, %	32.01 ± 4.75	34.01 ± 4.67*	32.3 ± 5.87	33.1 ± 4.34
MM, Kg	49.1 ± 4.55	52.9 ± 5.88*	50.2 ± 4.78	50.4 ± 4.88
Thigh circumference				
C14, cm	43.1 ± 7.2	44.3 ± 6.7	42.7 ± 7.1	42.7 ± 6.8
C21, cm	48.5 ± 6.8	49.7 ± 7.1	47.1 ± 8.9	47.4 ± 8.2
C28, cm	51.8 ± 7.7	53.3 ± 6.9*†	50.1 ± 8.1	50.0 ± 7.8
Constant work test				
$\dot{V}O_{2Tlim}$, ml.min ⁻¹	989 ± 245	1089 ± 233*†	977 ± 189	969 ± 191
$\dot{V}CO_{2Tlim}$, ml.min ⁻¹	997 ± 187	1125 ± 289*	981 ± 202	1003 ± 154
RER _{Tlim}	1.01 ± 0.03	1.03 ± 0.02*	1.02 ± 0.01	1.03 ± 0.01
$\dot{V}E_{Tlim}$, L	38.3 ± 9.7	46.5 ± 9.2*†	34.5 ± 8.5	36.9 ± 6.1
T _{lim} , min	6.9 ± 1.5	9.11 ± 2.4*†	8.2 ± 3.1	8.4 ± 3.4
SpO _{2Tlim}	93.2 ± 2.8	97.1 ± 1.2*†	94.6 ± 2.3	94.1 ± 1.8
BLE _{Tlim}	8.6 ± 1.1	7.3 ± 1.6*†	7.8 ± 1.6	8.1 ± 1.2
BDS _{Tlim}	8.0 ± 1.7	6.2 ± 1.4*†	7.3 ± 1.5	7.7 ± 1.4
Mechanical efficiency				
Gross ME (%)	19.5 ± 3.5	24.3 ± 4.5*†	20.5 ± 5	20.1 ± 4.1
6-MWT	359.6 ± 71.3	435.3 ± 36.5*†	349.8 ± 95.2	350.6 ± 95.6

Abbreviations: FFM, fat-free mass; MM, muscle mass; thigh circumference at 14 cm (C14), 21 cm (C21) and 28 cm (C28); $\dot{V}O_2$ = oxygen uptake; $\dot{V}CO_2$ = carbon dioxide output; RER = ratio exchange ratio; $\dot{V}E$ = minute ventilation; T_{lim}, exercise tolerance; SpO₂, pulse oximetry (oxyhemoglobin saturation); BLES, Borg leg effort; BDS, Borg dyspnea sensation; Gross ME, mechanical efficiency; 6-MWT, 6-minute walk test. *P* value represents the overall comparison between the groups. Data presented as mean ± SD.* *p*< 0.01 from before within a given treatment; †*p*<0.01 between-treatment comparison.

Fig. 2. Scatterplot of the association between changes (post-pre) of FEV₁ and T_{lim} during NMES (closed circles) and Control group (open squares).

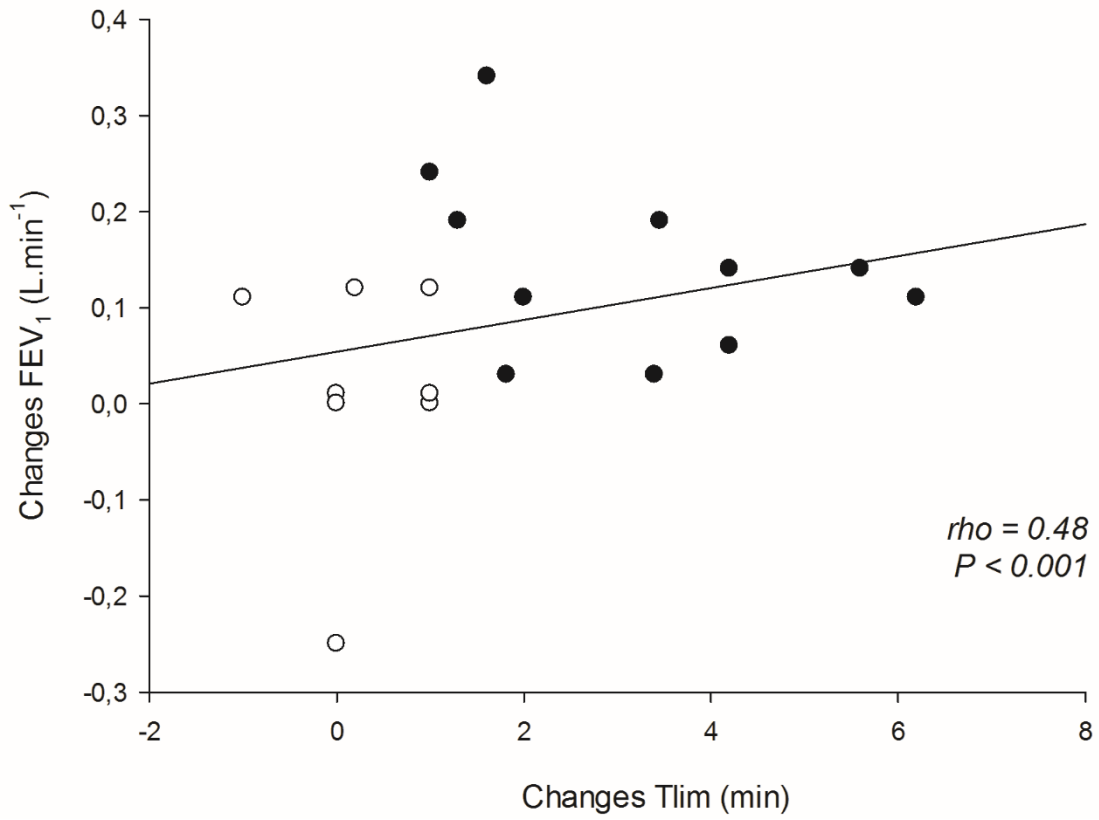


Fig. 3. Inspiratory capacity at rest and during exercise (until the 10th minute) in COPD patients during pre and post NMES compared with control group. *Differences between the groups at a given time point. †Differences related to the previous time point in a given group.

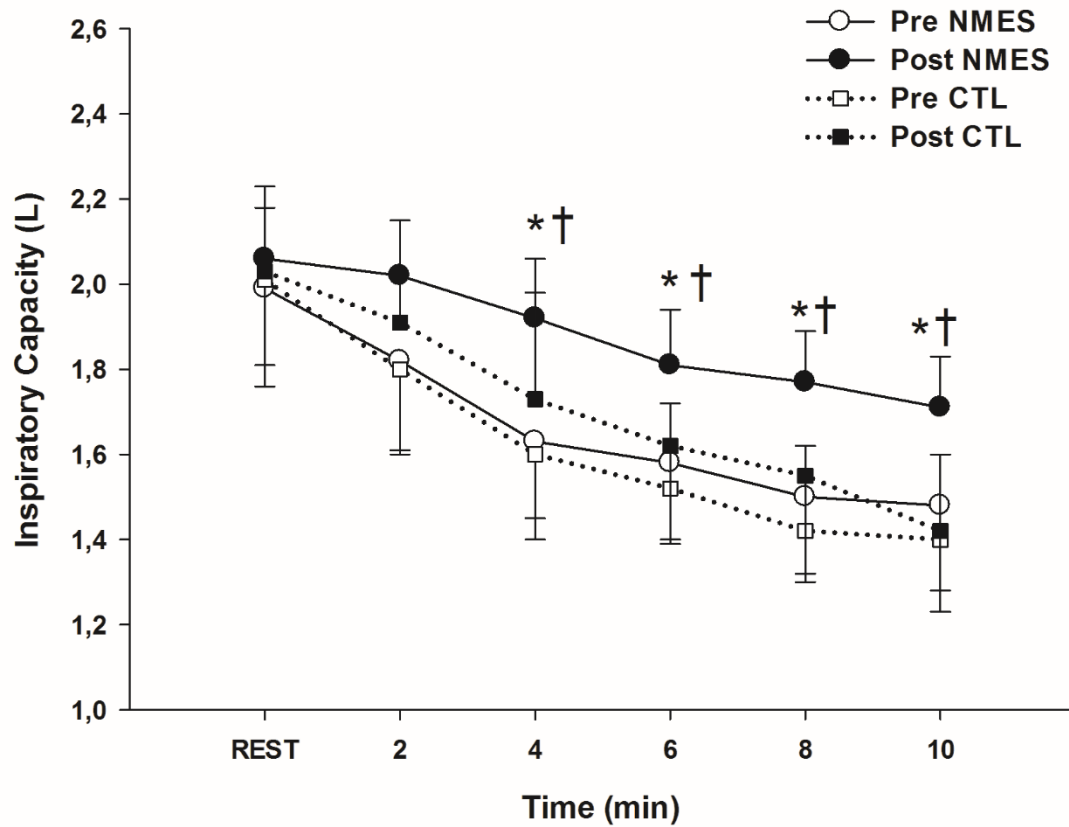


Fig. 4. Significant decreases in peripheral muscle fiber activation during constant work rate exercise in response to NMES (closed circles) compared with Control group (open circles) in patients with chronic obstructive pulmonary disease. RMS = root mean square.

* $P < 0.05$.

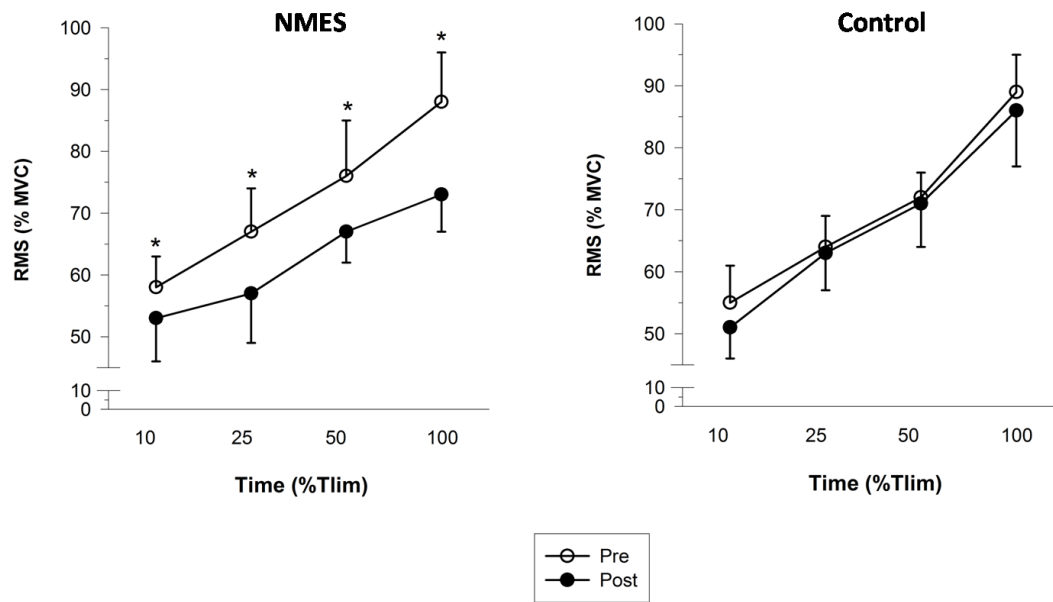


Fig. 5. TNF- α (A) and β -endorphin (B) levels in two groups before and after the intervention period, (NMES, black bar, and Control, gray bar). * Two-way repeated-measures ANOVA ($P < 0.001$) for group, training and interaction effects.

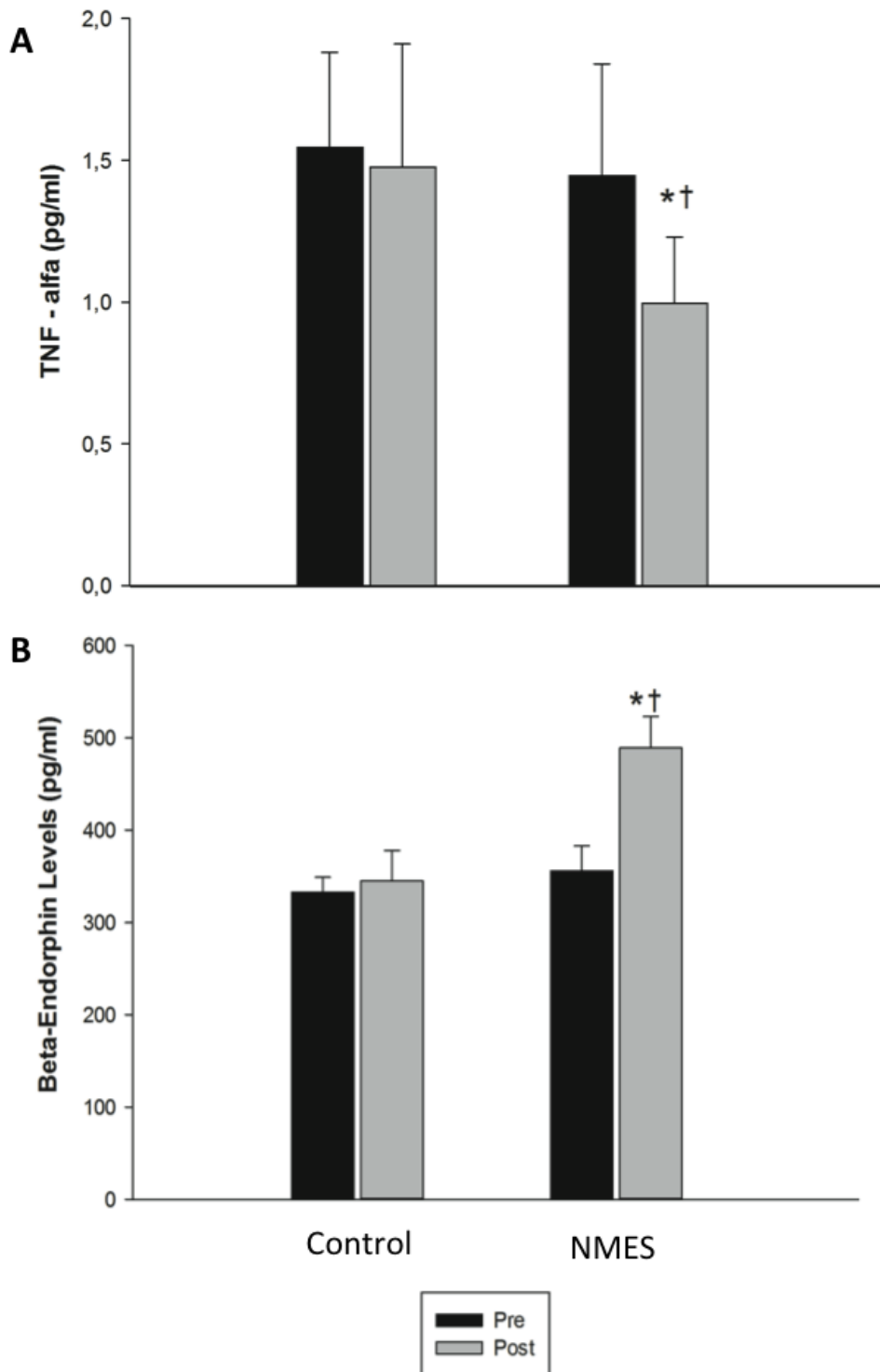
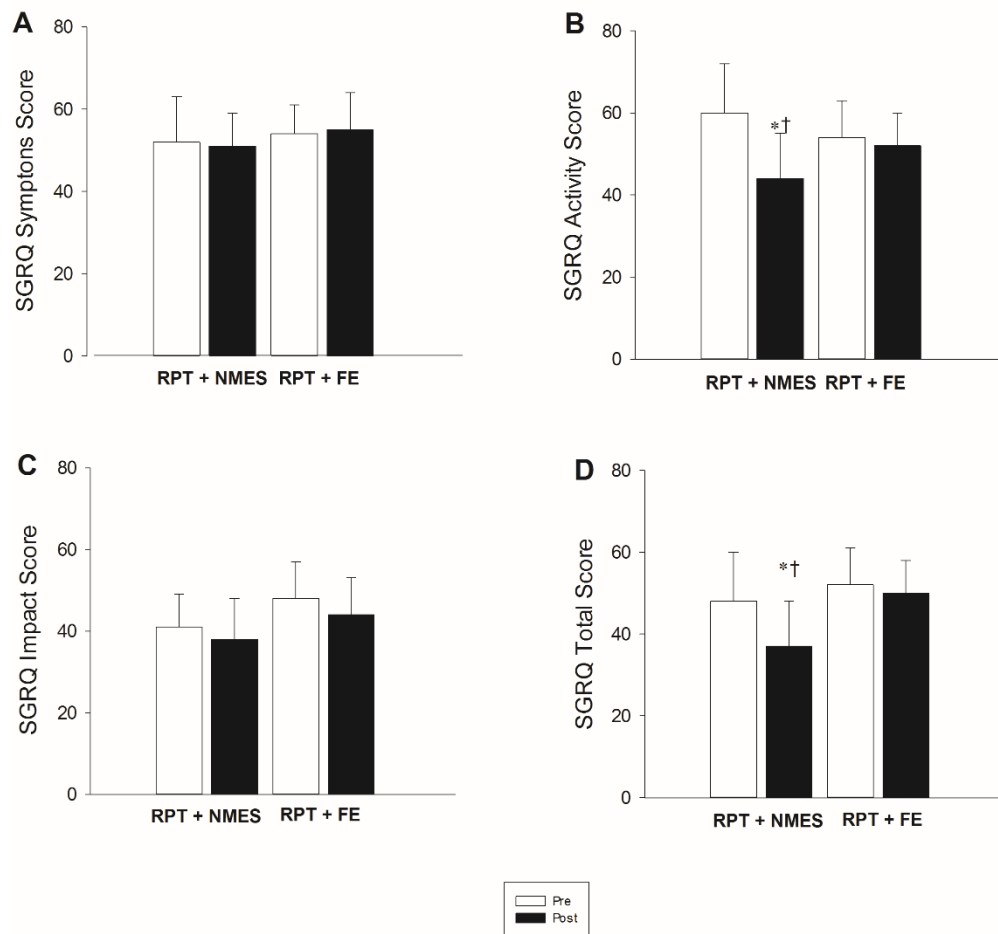


Fig. 6. SGRQ categorical and total score measured at pre and post NMES and Control. (A) Symptom score; (B) activity score; (C) impact score; (D) total score. SGRQ = St. George's Respiratory Questionnaire. * $P < 0.05$ within-group comparison and † $P < 0.05$ between-group comparison.



CONCLUSÕES

1. O treinamento muscular respiratório e de força melhoraram significativamente uma série de variáveis clinicamente relevantes. Entretanto mais ensaios são necessários para avaliar, adicionalmente, os efeitos a longo prazo destas intervenções.
2. A estimulação elétrica neuromuscular de alta frequência melhora uma variedade de medidas relacionadas com a função fisiológica, sintomatologia e qualidade de vida em pacientes com DPOC. Esta abordagem de intervenção pode ser uma técnica eficaz e viável de reabilitação nessa população.

ANEXOS

PRODUÇÃO DURANTE A PÓS-GRADUAÇÃO

Fonte: <http://www.ncbi.nlm.nih.gov/pubmed/?term=Vieira+PJ>

1 Skeletal muscle metaboreflex in patients with chronic renal failure.

Vieira PJ, Silva LR, Maldamer VZ, Cipriano G Jr, Chiappa AM, Schuster R, Boni VH, Grandi T, Wolpat A, Roseguini BT, Chiappa GR.

Clin Physiol Funct Imaging. 2015. doi: 10.1111/cpf.12293.

2 Factors associated with inspiratory muscle weakness in patients with HIV-1.

Jerônimo FS, Alves GN, Cipriano G Jr, **Vieira PJ**, Chiappa AM, Chiappa GR. Braz J

Infect Dis. 2015;19(1):1-7. doi: 10.1016/j.bjid.2014.07.003.

3 Sympathetic ganglion transcutaneous electrical nerve stimulation after coronary artery bypass graft surgery improves femoral blood flow and exercise tolerance.

Cipriano G Jr, Neder JA, Umpierre D, Arena R, **Vieira PJ**, Chiappa AM, Ribeiro JP, Chiappa GR.

J Appl Physiol (1985). 2014;117(6):633-8. doi:10.1152/jappphysiol.00993.2013.

4 Neuromuscular electrical stimulation improves clinical and physiological function in COPD patients.

Vieira PJ, Chiappa AM, Cipriano G Jr, Umpierre D, Arena R, Chiappa GR.

Respir Med. 2014;108(4):609-20. doi: 10.1016/j.rmed.2013.12.013.

5 Exercise capacity in adolescent and adult patients with post infectious bronchiolitis obliterans.

Frohlich LF, **Vieira PJ**, Teixeira PJ, Silva FA, Ribeiro JP, Berton DC.

Pediatr Pulmonol. 2014;49(9):911-8. doi: 10.1002/ppul.22929.

6 Inspiratory resistance decreases limb blood flow in COPD patients with heart failure.

Chiappa GR, **Vieira PJ**, Umpierre D, Corrêa AP, Berton DC, Ribeiro JP, Neder JA.

Eur Respir J. 2014;43(5):1507-10. doi: 10.1183/09031936.00166013.

7 Oral L-arginine modulates blood lactate and interleukin-6 after exercise in HIV-infected men.

Alves GN, Tavares AM, **Vieira PJ**, Sprinz E, Ribeiro JP.

Int J Sports Med. 2014;35(4):339-43. doi: 10.1055/s-0032-1331740.

8 Interferential electrical stimulation improves peripheral vasodilatation in healthy individuals.

Santos FV, Chiappa GR, **Vieira PJ**, Umpierre D, Ribeiro JP, Cipriano G Jr.

Braz J Phys Ther. 2013;17(3):281-8.

9 TP53 p.R337H is a conditional cancer-predisposing mutation: further evidence from a homozygous patient.

Giacomazzi J, Selistre S, Duarte J, Ribeiro JP, **Vieira PJ**, de Souza Macedo G, Rossi C, Czepielewski M, Netto CB, Hainaut P, Ashton-Prolla P.

BMC Cancer. 2013;13:187. doi: 10.1186/1471-2407-13-187.

10 Hemodynamic responses to resistance exercise with restricted blood flow in young and older men.

Vieira PJ, Chiappa GR, Umpierre D, Stein R, Ribeiro JP.

J Strength Cond Res. 2013;27(8):2288-94. doi: 10.1519/JSC.0b013e318278f21f.

11 Effect of transcutaneous electrical nerve stimulation on muscle metaboreflex in healthy young and older subjects.

Vieira PJ, Ribeiro JP, Cipriano G Jr, Umpierre D, Cahalin LP, Moraes RS, Chiappa GR.

Eur J Appl Physiol. 2012;112(4):1327-34. doi: 10.1007/s00421-011-2084-z.

12 Inspiratory resistive loading after all-out exercise improves subsequent performance.

Chiappa GR, Ribeiro JP, Alves CN, **Vieira PJ**, Dubas J, Queiroga F Jr, Batista LD, Silva AC, Neder JA.

Eur J Appl Physiol. 2009;106(2):297-303. doi: 10.1007/s00421-009-1022-9.

13 Blunted vascular responses but preserved endothelial vasodilation after submaximal exercise in chronic heart failure.

Umpierre D, Stein R, **Vieira PJ**, Ribeiro JP.

Eur J Cardiovasc Prev Rehabil. 2009;16(1):53-9. doi: 10.1097/HJR.0b013e32831c8489

14 Inspiratory muscle training improves blood flow to resting and exercising limbs in patients with chronic heart failure.

Chiappa GR, Roseguini BT, **Vieira PJ**, Alves CN, Tavares A, Winkelmann ER, Ferlin EL, Stein R, Ribeiro JP.

J Am Coll Cardiol. 2008;51(17):1663-71. doi: 10.1016/j.jacc.2007.12.045.