Universidade Estadual de Londrina

ANTENOR LUIZ LIMA RODRIGUES

TESTE DE CAMINHADA DE SEIS MINUTOS COMO RECURSO PARA PRESCRIÇÃO DE TREINAMENTO FÍSICO DE ALTA INTENSIDADE PARA PACIENTES COM DOENÇA PULMONAR OBSTRUTIVA CRÔNICA

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Dissertação apresentada ao Programa de Pós-Graduação em Ciências da Reabilitação (Programa Associado entre Universidade Estadual de Londrina [UEL] e Universidade Norte do Paraná [UNOPAR]), como requisito parcial à obtenção do título de Mestre em Ciências da Reabilitação.

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Londrina, 04 de Fevereiro de 2016.

Dedico este trabalho à minha familia

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A todos meu muito obrigado!

“*If you close your eyes*

Because the house is on fire

And think you couldn't move

Until the fire dies

The things you never did

Cause you might die trying...

...You will be as good as a dead”

Dave Matthews Band / Mark Batson

RODRIGUES, Antenor. **Teste de Caminhada de Seis Minutos como Recurso para Prescrição de Treinamento Físico de Alta Intensidade em Pacientes com Doença Pulmonar Obstrutiva Crônica**. 2016. 100 f. Dissertação (Mestrado em Ciencia da Reabilitação) – Universidade Estadual de Londrina, Londrina, 2016.

RESUMO

Objetivo: Avaliar a aplicabilidade do Teste de Caminhada de Seis Minutos (6MWTmin) para a prescrição de intensidade de exercício de acordo com recomendações internacionais para pacientes com Doença Pulmonar Obstrutiva Crônica (DPOC). **Métodos:** Pacientes com DPOC (n= 27) foram avaliados quanto à função pulmonar (espirometria), capacidade de exercício (TC6min e *Incremental Shuttle Walking* Test [ISWT]), sensação de dispneia na vida diária (*Medical Research Council scale* [MRC]), composição corporal (bioimpedância elétrica), e força muscular inspiratória (pressão inspiratória máxima [PImax]) pré e pós um programa de treinamento físico (TF) com duração de 12 semanas e frequência de 3 vezes por semana. Os critérios adotados no estudo foram os seguintes: critério baseado no TC6min ($TC6min_C$): ≥ 75% da velocidade média do TC6min ($TC6min_{VM}$); critério baseado nas recomendações da ATS/ERS ($ISWT_C$): ≥ 60% da velocidade do último estágio atingido no ISWT ($ISWT_V$). **Resultados:** Treze (48%) pacientes cumpriram o $TC6min_C$ e o $ISWT_C$, e dez (40%) cumpriram o $Borg_C$ na primeira semana do TF. O TC6min mostrou boa performance diagnóstica (valores preditivos positivos e negativos de 0,69 e 0,71, respectivamente, e acurácia de 0,70), boa reprodutibilidade (CCI 0,70, 95%IC 0,45-0,85) e moderada concordância (k 0,41, 95%CI 0,13-0,67) para determinar treinamento físico de alta intensidade de acordo com recomendações internacionais ($ISWT_C$). Comparações entre os pacientes nos quais o $TC6min_C$ e o $ISWT_C$ concordaram (GC) *versus* pacientes nos quais os critérios não concordaram (GNC) na primeira semana de TF revelaram que o GC apresentou maior velocidade (3,9 ± 2,1 *vs*. 3,0 ± 0,74 km/h; *P*= 0,01), maior $\%TC6min_{VM}$ (77 [76 - 86] *vs*. 74 [62 - 75]; *P*< 0,001), maior $\%ISWT_V$ (70 ± 4 *vs*. 52 ± 10; *P*< 0,001) e maior relação $6MWT_{VM}/ISWT_V$ (0,87 ± 0,08 *vs*. 0,70 ± 0,09; *P*=0,04). Adicionalmente, pacientes nos quais 75% da $TC6min_{vm}$ era maior ou igual que 60% da $ISWT_v$ foram comparados com os casos que 75% da $TC6min_{VM}$ era menor que 60% da $ISWT_V$. Esses resultados mostraram pior função pulmonar (CVF 65 ± 13 *vs*. 82 ± 20; VEF_1 45 [31 - 55] *vs.* 61 [44 - 69] %predito, *P*< 0.05 para todos), maior sensação de dispneia na vida diária (4 [3-4] *vs*. 2,5 [2-4], pontos na escala MRC; *P*= 0,04), menor ISWT (379 ± 100 *vs.* 516 ± 207, m, *P*= 0.03) e maior relação $6MWT_{VM}/ISWT_V$ (0.89 ± 0.6 *vs*. 0.72 ± 0.05 *P*< 0,001) para o grupo no qual 75% da $TC6min_{VM}$ era igual ou maior que 60% da $ISWT_V$. Após TF os pacientes apresentaram aumento da capacidade de exercício (6MWT pré vs pós TF: 464 ± 70,4 *vs*. 506 ± 85 m; *P*= 0,003; e 86 ± 14 *vs*. 94 ± 17 %predito; *P*= 0.003). Após TF, o grupo GNC teve maior aumento na velocidade em km/h do que o GC (66 [46 - 79] vs. 28 [21 - 40] %Δ, *P*= 0.02), e em $\%ISWT_V$ pós TF (63 [46 - 67] *vs*. 27 [14 - 30] %Δ; *P*= 0,01). **Conclusão:** O TC6min se mostrou uma ferramenta útil para a prescrição de treinamento de alta intensidade em pacientes com DPOC.

Palavras-chave: Doença Pulmonar Obstrutiva Crônica. Exercício. Tolerância ao Exercício. Estudos de Validação.

RODRIGUES, Antenor. **Is the Six-Minute Walking test a tool to prescribe high-intensity exercise in Chronic Obstructive Pulmonary Disease?**2016. 100 p. Dissertação (Mestrado em Ciencia da Reabilitação) – Universidade Estadual de Londrina, Londrina, 2016.

ABSTRACT

Objective: To evaluate the applicability of the Six-Minute Walking Test (6MWT) to prescribe exercise intensity in accordance with international guidelines in patients with chronic obstructive pulmonary disease (COPD). **Methods:** Patients with COPD (n=27) were evaluated concerning lung function (spirometry), exercise capacity (6MWT and Incremental Shuttle Walking Test [ISWT]), dyspnea sensation in daily life (Medical Research Council Scale [MRC]), body composition (bioelectrical impedance), and inspiratory muscle strength (maximal inspiratory pressure [MIP]) before and after a 12-week, 3 times/week, high-intensity exercise training program (ET). High-intensity criteria were: 6MWT criteria ($6MWT_C$): ≥75% of the 6MWT average speed ($6MWT_{AS}$); ATS/ERS criteria ($ISWT_C$): ≥60% of the speed achieved in the ISWT last stage ($ISWT_S$). **Results:** According to $6MWT_C$ and $ISWT_C$, 13 (48%) patients achieved the desired training intensity in the first week of the ET whereas ten (40%) patients achieved $Borg_C$. The 6MWT showed good diagnostic performance (positive and negative predictive values of 0.69 and 0.71, respectively, and accuracy of 0.70), good reliability (ICC 0.703, 95%CI 0.447-0.853) and moderate agreement (k 0.41, 95%CI 0.13-0.67) when used to determine high-intensity exercise according to the ATS/ERS guidelines. When comparing patients in which the $6MWT_C$ and $ISWT_C$ agreed (GA_{week1}) *versus* the cases in which they did not agree (GNA_{week1}) in the first week of ET, results revealed that GA_{week1} had higher speed (3.9 ± 2.1 vs. 3 ± 0.74, km/h, *P*= 0.01), $\%6MWT_{AS}$ (77 [76 - 86] *vs*. 74 [62 – 75], *P*< 0.001), $\%ISWT_S$ (70.4 ± 3.7 vs. 51.8 ± 10.3, *P* <0.001), and $6MWT_{AS}/ISWT_S$(0.87 ± 0.08 *vs*. 0.70 ± 0.09, *P*= 0.04). Patients in whom 75% of the $6MWT_{AS}$ was higher or equal to 60% of $ISWT_S$ were compared with the cases in which it was lower. In this analysis, worse pulmonary function (FVC 65 ± 13 *vs*. 82 ± 20; FEV_1 45 [31 - 55] *vs.* 61 [44 - 69], %pred, *P*< 0.05 for all), higher dyspnea sensation in daily life (4 [3-4] vs. 2.5 [2-4], MRC 1-5, *P*= 0.04), lower ISWT (379 ± 100 *vs.* 516 ± 207, m *P*= 0.03) and higher $6MWT_{AS}/ISWT_S$ ratio (0.87 [0.84-0.90] vs. 0.72 [0.67-0.78], *P*= <0.001) were found in favor of the cases which 75% of the 6MWT speed was equal or higher than 60% of the ISWT speed. As expected, improvements in exercise capacity were found after the ET program (6MWT 464 ± 70 vs. 506 ± 85m, pre vs. post-ET *P*= 0.003; and 6MWT (%pred) 86 ± 14 vs. 94 ±17, *P*= 0.003). After ET, larger increase in the speed in km/h was observed in GNA_{week1} than in GA_{week1} (66 [46-79] vs.28 [21-40] $\%\Delta$, respectively; *P*= 0.02), as well as concerning the post-ET $ISWT_S$ (63 [46 - 67] vs.27 [14 - 30] ,$\%\Delta$, respectively: *P*=0.01). **Conclusion:** The 6MWT was shown to be useful as a tool to prescribe high-intensity exercise for patients with COPD.

Key words: Pulmonary Disease. Chronic Obstructive. Exercise. Exercise Test. Validation Studies.

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LISTA DE ABREVIATURAS E SIGLAS

[LA]: concentração de lactato

ACSM: American College of Sports Medicine

AFVD: nível de atividade física na vidadiaria

ATS: *American Thoracic Society*

AVD: atividades de vida diária

CO_2: dióxido de carbono

CPT: capacidade pulmonar total

CS: *critical speed*

CVF: capacidade vital forçada

DPOC: Doença Pulmonar Obstrutiva Crônica

EADPOC: exacerbação aguda da DPOC

EENM: eletro-estimulação neuromuscular

ERS: *European Respiratory Society*

GOLD: *Global Initiative for Chronic Obstructive Pulmonary Disease*

H^+: hidrogênio

ISO-V_E: volume minuto no isotempo

ISO-VO_2: consumo de oxigênio no isotempo

LA: limiar de lactato

MDCI: minima diferença clinicamente importante

O_2: oxigênio

$PaCO_2$: pressão arterial de monóxido de carbono

RER: quociente respiratório

RP: reabilitação pulmonar

sRaw: Resistência específica das vias aéreas

TC6min: Teste de caminhada de seis minutos

$TC6min_{VM}$: velocidade média do TC6min

TCPE: Teste cardiopulmonar de esforço

T_I/T_{TOT}: relação entre tempo inspiratório e tempo total do ciclo respiratório

TLCO: fator de transferência do monóxido de carbono

V_A: ventilação alveolar

VCO_2: volume expirado de dióxido de carbono

VD: espaço morto

VE: volume minuto

VEF_1: volume expiratório forçado no primeiro segundo

VEF_1/CVF: relação entre volume expiratório forçado no primeiro segundo e capacidade vital forçada

VO_2: consumo de oxigênio

VO_2max-VO_2LA: diferença entre consumo máximo de oxigênio e consumo de oxigênio no limiar de lactato

VO_2max: Consumo máximo de oxigênio

$VO_2TC6min$: consumo de oxigênio do TC6min

VO_2TCPE: consumo máximo de oxigênio durante um TCPE

VR: volume residual

VRE: volume de reserve expiratório

V_T: volume corrente

SUMÁRIO

1 INTRODUÇÃO

O Teste de Caminhada de Seis minutos (TC6min) é um teste reprodutível, confiável e responsivo à intervenções em pacientes com Doença Pulmonar Obstrutiva Crônica (DPOC). Trata-se de um dos testes de campo mais utilizados para essa população[1]. No entanto, o uso de TC6min como recurso para prescrição da intensidade de treinamento físico (TF) em alguns estudos[2-5] tem recentemente aumentado o interesse sobre o estudo deste tópico[6].

A prescrição da intensidade de exercício de programas de TF deve ser realizada de maneira personalizada e baseada na capacidade máxima de exercício (Wmax) de cada indivíduo, indiferentemente se no caso de estados de saúde ou de doença[7,8]. Apesar do fato do Teste Cardiopulmonar de Esforço (TCPE) ser considerado o teste padrão ouro para avaliação da Wmax[9], o uso do TC6min para prescrição da intensidade de exercício baseia-se em respostas similares de consumo máximo de oxigênio (VO_2max) durante o TC6min e o TCPE em pacientes com DPOC[10]. No entanto, vieses metodológicos (*e.g.*, TCPE realizado em bicicleta e pista não-padronizada para realização do TC6min) podem ter induzido resultados cientificamente questionáveis[6].

Paradoxalmente, alguns estudos tem encontrado que a velocidade média do TC6min ($TC6min_{VM}$) é similar ou menor que a velocidade máxima que um individuo é capaz de sustentar enquanto mantem respostas integradas dos sistemas envolvidos na oferta e no consumo de oxigênio, ou *critical speed* (CS)[11,12]. Em pacientes com DPOC a CS foi encontrada como sendo abaixo de 85% da Wmax, indicando o perfil do TC6min como um teste de avaliação da capacidade funcional[13,14] (ou sub–máxima) de exercício que é o perfil de resposta para o qual o teste foi desenvolvido[1].

Apesar dos resultados contraditórios na literatura sobre o TC6min ser um teste que avalia a capacidade máxima ou sub máxima de exercício em pacientes com DPOC[6,10-12,15,16], diferentes porcentagens da $TC6min_{VM}$ tem sido utilizadas para prescrição da intensidade de programas de TF em pacientes com DPOC[2-5]. Estes programas se mostraram comprovadamente eficazes na promoção do aumento da capacidade de exercício e da qualidade de vida, ultrapassando os valores de mínima diferença clinicamente importante (MDCI) para esta população.

Com a finalidade de testar se o TC6min poderia ser utilizado como

recurso para prescrição de TF de alta intensidade em paciente com DPOC, um estudo recente demostrou uma ampla variabilidade na resposta do consumo de oxigênio (VO_2) quando pacientes caminharam por dez minutos em velocidade correspondente a 80% da $TC6min_{VM}$[6]. Sendo assim, apesar do TC6min ser atualmente utilizado para prescrição de TF, algumas questões permanecem sem respostas, como por exemplo: 1) o TC6min é um recurso válido para a prescrição de TF em DPOC?; 2) caso ele seja válido, qual é o melhor método para estimar intensidade do TC6min que deveria ser utilizada para prescrição de TF?; 3) existe concordância entre a prescrição de TF realizada por meio do TC6min e aquela realizada de acordo com as recomendações internacionais?; 4) programas que prescrevem exercício por meio do TC6min podem ser comparados a programas com prescrição baseada em um TCPE, em estudos de revisão sistemática e/ou meta-analise?

De tal modo, ainda não se sabe se o TC6min pode ou não ser utilizado como recurso para prescrição da intensidade de TF para pacientes com DPOC, e essa questão continua um campo aberto a discussões. Portanto, o objetivo principal deste estudo foi o de avaliar a aplicabilidade do TC6min como recurso para prescrição de TF de alta intensidade, de acordo com critérios internacionalmente recomendados para pacientes com DPOC.

2 REVISÃO DE LITERATURA – CONTEXTUALIZAÇÃO

2.1 DOENÇA PULMONAR OBSTRUTIVA CRÔNICA (DPOC)

Apesar de ter os primeiros relatos de alterações anatômicas compatíveis com a doença (*i.e.* volume pulmonar aumentado e alvéolos dilatados) datados do ano de 1793, a doença que viria a se tornar, aproximadamente 200 anos depois reconhecida mundialmente pela sigla DPOC foi descrita pela primeira vez como enfisema (do grego, *en*= dentro; *physan*= soprar) por Laennec no ano de 1824. O emprego deste termo foi utilizado para descrever um pulmão com quantidades excessivas de ar[17]. No entanto, o termo doença pulmonar obstrutiva crônica (DPOC) foi uniformizado em todo o mundo somente no ano de 2000, quando a Organização Mundial de Saúde organizou a iniciativa GOLD, do inglês *Global Initiative for Chronic Obstructive Pulmonary Disease*[17].

Após a criação da iniciativa GOLD, o termo DPOC englobou o enfisema e a bronquite crônica, doenças que eram anteriormente tratadas como patologias distintas. Desde então, achados característicos de enfisema e de bronquite crônica tornaram-se fenótipos dentro de uma mesma doença, a DPOC[18].

De acordo com o ultimo documento publicado pela GOLD[19], a DPOC é definida como uma doença prevenível e tratável, caracterizada por obstrução persistente, geralmente progressiva e associada a uma resposta inflamatória crônica nas vias aéreas e no pulmão, causada por partículas e gases nocivos. Exacerbações e comorbidades contribuem para a piora do estado geral do portador de DPOC de maneira particular à cada individuo.

O diagnóstico da DPOC é feito por meio de prova de função pulmonar, baseando-se na relação VEF_1/CVF (volume expiratório forçado no primeiro segundo [VEF_1]/Capacidade vital forçada [CVF]) após o uso de broncodilatador[19]. No caso de presença de obstrução ao fluxo aéreo (VEF_1/CVF <0.70) o paciente é diagnosticado como portador de DPOC, e então classificado em um dos quatro estágios da doença (GOLD I: VEF_1 ≥80% predito; GOLD II: VEF_1 ≥50 e <80% predito; GOLD III: VEF_1 ≥30 e <50% predito; GOLD IV: VEF_1<30% predito)[19].

Apesar de ter o diagnóstico baseado em índices de função pulmonar (relação VEF_1/CVF e VEF_1 % predito), outras alterações como inatividade física[20],

inflamação sistêmica, frequência de exacerbações[19], hiperinsuflação[21], maior estresse oxidativo[22], fraqueza muscular respiratória[23] e periférica[24], e sintomas de ansiedade e depressão[25], por exemplo, também tem papel importante no impacto da doença sobre seus portadores. Dentre estes, fatores que tem relação importante com o tema desta dissertação serão discutidos nos próximos capítulos.

2.2 Limitação ao Exercício Em Pacientes com DPOC

Apesar de ser indiscutivelmente multifatorial[8], a limitação ao exercício em pacientes com DPOC tem fomentado discussões científicas importantes[26-30]. Nesta sessão, serão discutidos os focos muscular, ventilatório e cardíaco e seus papéis na limitação ao exercício em pacientes com DPOC. Isso tem o intuito de esclarecer como e por que os mecanismos responsáveis pela manutenção da homeostase corporal durante o exercício falham na execução desta tarefa em pacientes com DPOC, levando-os ao desenvolvimento de maior sintomatologia (sensação de dispneia e fadiga) e interrupção precoce de atividades e/ou exercício físico.

2.2.1 Limitação Ventilatória

A limitação ao fluxo expiratório (VEF_1/CVF <0,7) presente em pacientes com DPOC é a expressão final de varias alterações da mecânica respiratória destes indivíduos. No entanto, ela não é completamente adequada para representar toda a heterogeneidade das anormalidades fisiológicas presentes nesses pacientes[31]. Estudos tem mostrado uma ampla variabilidade no comprometimento da capacidade de difusão pulmonar (TLCO), da resistência especifica das vias aéreas (sRaw), e do grau de aprisionamento aéreo ao repouso (maior volume residual [VR] em % do predito) em grupos de pacientes com valores semelhantes de VEF_1%predito[32]. Contudo, quando esses pacientes são submetidos a atividades com maior carga metabólica, o aumento da exigência ventilatória que visa suprir as demandas impostas por esta atividade faz com que fatores imperceptíveis ao repouso se manifestem (ou se ampliem), permitindo assim uma avaliação mais completa dos mecanismos responsáveis pela limitação ventilatória durante o exercício em pacientes com DPOC[33].

O aumento da ventilação alveolar (V_A) durante o exercício (na ausência de acidose metabólica) é diretamente proporcional ao aumento dos níveis de dióxido de carbono (CO_2) ventilado pelos pulmões, e pela quantidade de ar ventilada através do espaço morto do indivíduo (V_E= 863 $VCO_2/PaCO_2[1-V_D/V_t]$)[34]. Sendo assim, durante atividades com maior carga metabólica (*i.e.* exercício físico ou atividades de vida diária [AVD]) a maior liberação de CO_2 pelos grupos musculares responsáveis pela realização de uma determinada atividade atinge os pulmões e desencadeia uma maior demanda ventilatória com o intuito de eliminar o CO_2 dos pulmões. A maior relação V_D/V_T (maior espaço morto, tanto anatômico [aprisionamento aéreo e hiperinsuflação dinâmica] quanto fisiológico) que pode estar presente ao repouso e/ou se manifestar/ampliar durante atividades físicas também contribui para o aumento da demanda ventilatória (V_E) dessa população[31,33]. O V_E aumentado também proporciona maior capacidade pulmonar de captação de oxigênio (O_2), aumentando também a oferta de O_2 aos músculos responsáveis por realizar trabalho. No entanto, limitações mecânicas (*i.e.* hiperinsulflação dinâmica)[35] e fisiológicas (*i.e.* menor fluxo sanguíneo pulmonar)[36-38] interferem de maneira prejudicial no ajuste fino entre a produção de CO_2 e o aumento da ventilação ([in]eficiência ventilatória) durante o exercício em pacientes com DPOC[39-41]

Durante o exercício o aumento da ventilação (V_E) é obtido às custas de um aumento da frequência respiratória[33], fato esse que cursa com uma alteração da relação T_I/T_{TOT}, causando uma diminuição do tempo expiratório. Apesar de ser uma alteração necessária para atingir as demandas metabólicas impostas por determinada atividade, o aumento da frequência respiratória nos pacientes com DPOC (*i.e.* com obstrução ao fluxo expiratório) faz com que eles tenham menos tempo para eliminar todo o ar inspirado previamente. Consequentemente, isso ocasiona o aumento do aprisionamento aéreo durante a execução de determinada atividade, conhecido como hiperinsuflação dinâmica, que somado à hiperinsuflação estática pulmonar já existente ao repouso, aumenta ainda mais a demanda ventilatória[31,33,42,43].

Devido ao aumento da hiperinsuflação pulmonar destes pacientes, de uma maneira tempo-dependente, eles são colocados em desvantagem mecânica, por estarem respirando cada vez mais próximos à capacidade pulmonar total (CPT). Isso aumenta ainda mais o já aumentado trabalho respiratório desses indivíduos[42]. Ainda como efeito deletério da hiperinsuflação dinâmica e da necessidade de

respirar em volumes próximos a CPT, ocorre uma redução do volume de reserva inspiratório (VRI) a níveis críticos (O'Donnell *threshold*[44]), o que eleva o nível de sensação de dispneia desses indivíduos, fazendo com que o exercício e/ou atividade seja interrompido[31,33,35,41,42,44].

2.2.2 Limitação Muscular

A importância da disfunção muscular periférica (perda de uma ou das duas principais propriedades do tecido muscular, força e *endurance*[43]) na limitação ao exercício em pacientes com DPOC fica clara quando mesmo um ano após a restauração da capacidade ventilatória (transplante pulmonar) de pacientes com DPOC, estes ainda apresentam baixa tolerância ao exercício. Isso indica que outros fatores, além da função pulmonar, influenciam a tolerância ao exercício nessa população[45].

Atualmente, é sabido que um terço dos pacientes com DPOC apresentam limitação funcional da musculatura periférica[46]. Além disso, o decréscimo de força e/ou *endurance* muscular pode ser até quatro vezes mais rápido nesses pacientes quando comparados a indivíduos saudáveis pareados[47]. Alterações musculares como a mudança de fibras do tipo oxidativas (tipo I) para fibras com maior atividade glicolitica (tipo II)[48], diminuição da densidade capilar[49], diminuição da eficiência e do volume mitocondrial[50,51] e aumento da inflamação local[52,53] são achados comuns em pacientes com DPOC.

Recentemente, o desequilibrio entre oferta e consumo de oxigênio aos músculos envolvidos na realização de trabalho durante uma determinada atividade tem se mostrado como outro fator importante relacionado à disfunção muscular na limitação ao exercício em pacientes com DPOC[39,40,54-58]. Além disso, intervenções que proporcionam um melhor equilibrio entre a oferta e o consumo de oxigênio muscular durante o exercício tem refletido também em aumento da capacidade de exercício de maneira aguda[39,54-56,58]. Os efeitos da maior oferta de oxigênio aos músculos durante o exercício a longo prazo ainda não foram descritos.

Aparentemente, a menor oferta de oxigênio aos músculos envolvidos na realização do trabalho, somado a menor eficiência muscular e as alterações histopatológicas descritas anteriormente causam liberação precoce de metabólitos derivados do metabolismo energético anaeróbio (*e.g.* H^+ e Lactato) alterando o pH e

perturbando a homeostase corporal durante o exercício, levando ao aumento da sensação de fadiga muscular local e ao término do exercício/atividade[24,30,46].

2.2.3 Limitação Cardíaca.

Disfunções cardíacas crônicas estão comumente presentes em pacientes com DPOC devido ao aumento da sobrecarga imposta ao ventrículo direito, que pode ser desencadeada pelo aumento da resistência vascular pulmonar[59], da vasoconstrição hipóxia[60] ou pelo acúmulo de eritrócitos[61] decorrentes da patofisiologia da doença. Devido a mudanças estruturais relacionadas às alterações do ventrículo direito (*i.e.* deslocamento do septo cardíaco), o ventrículo esquerdo também pode ter sua função comprometida, limitando sua capacidade de suprir as demandas impostas por atividades com maior carga metabólica (*i.e.* exercício/atividade física e/ou AVD)[62]. De maneira aguda, o aparecimento da hiperinsuflação dinâmica durante o exercício também pode limitar a função cardíaca devido à restrições mecânicas[63,64].

2.2.4 Em Resumo

De maneira geral, pacientes com DPOC apresentam uma captação prejudicada de O_2 e menor eficiência na eliminação de CO_2 pelos pulmões, entrega deteriorada de O_2 aos músculos devido à função cardíaca prejudicada, e menor eficiência muscular periférica. Em conjunto, essas alterações desencadeariam uma perturbação da homeostase corporal de magnitude maior que a capacidade de respostas destes sistemas, causando o termino do exercício/atividade realizada devido a manifestações clínicas como aumento da sensação de dispneia e fadiga.

Devido à sintomatologia desencadeada pelo conjunto de limitações presente nesses pacientes durante a realização de AVD com maior demanda metabólica, os mesmos passam a adotar um estilo de vida menos ativo (*i.e.* evitar realização de atividades que desencadeiam sintomas). O menor nível de atividades física, por sua vez, acarreta uma piora da capacidade de exercício, e por conseguinte, maior sintomatologia durante a realização das mesmas AVD, caracterizando o ciclo vicioso ou espiral negativo da DPOC[19,65].

2.3 Efeitos e Prescrição de Programas de Treinamento Físico de Alta Intensidade em Pacientes Com Dpoc

"*The Cochrane Airways editorial board made the unusual decision that this review is now closed. Therefore, it will no longer be updated*"[66].

A frase acima citada, de autoria do grupo Cochrane, foi publicada recentemente após a última atualização de revisão sistemática sobre Reabilitação Pulmonar (RP) desenvolvida pelo mesmo grupo[67]. Ela elimina qualquer dúvida restante sobre a eficácia dos programas de RP na melhora da qualidade de vida e capacidade de exercício de pacientes com DPOC, e indica que novas revisões sistemáticas sobre esse tema não são mais necessárias. No entanto, o TF é o componente principal dos programas de RP, e portanto a prescrição da intensidade de exercício tem papel fundamental nos comprovados efeitos benéficos da RP. Visto que este é o tema principal deste trabalho, uma breve revisão sobre esses efeitos será realizada. Além disso, recomendações internacionais para prescrição da intensidade dos programas de TF e estudos que fundamentam o uso do TC6min na prescrição da intensidade de TF também serão expostos e confrontados de forma a elucidar a importância da questão sob investigação nesta dissertação.

2.3.1 Efeitos dos Programas de Treinamento Físico em Pacientes com Dpoc

Após alguns resultados iniciais controversos[68] os efeitos do exercício de *endurance* em pacientes com DPOC foram comprovados em um estudo realizado por Casaburi *et al*. no ano de 1991. Neste estudo, um programa de TF com exercícios de alta intensidade foi altamente eficiente na promoção da melhora da capacidade submáxima de exercício de pacientes com DPOC, e sua superioridade em comparação a um programa realizado com intensidade moderada foi comprovada[69]. A partir de então, diversos outros estudos corroboraram esses achados, além de expandirem a eficácia desses programas para desfechos como o aumento do número e da proporção das fibras tipo I em relação à fibras tipo II, a melhora da função cardíaca, a diminuição da sensação de dispneia na vida diária, o aumento da capacidade funcional e máxima de exercício, aumento da força muscular respiratória e periférica, melhora dos sintomas de ansiedade e depressão e

melhora da qualidade de vida em pacientes com DPOC, independentemente da gravidade da doença[2-5,8,11,13,24,66,67,70-81].

Dentre os mecanismos responsáveis pelos efeitos dos programas de TF, a melhora da eficiência muscular, o aumento da capacidade muscular oxidativa, e a diminuição da hiperinsuflação dinâmica são responsáveis por promover a diminuição da demanda ventilatória (V_E), e por conseguinte a diminuição da sensação de dispneia durante a realização de uma atividade com mesma demanda ventilatória (*Iso*-V_E) e/ou metabólica (*Iso*-VO_2) após um programa de treinamento[24,31,49,66,67,69,75,76,80].

Os exercícios de fortalecimento muscular periférico também tem sido aplicados em pacientes com DPOC com o intuito de reverter ou amenizar a disfunção muscular presente nesses pacientes[4,82-87]. O treinamento de força muscular realizado isoladamente é eficaz para promover a melhora da força muscular, capacidade de exercício e qualidade de vida em pacientes com DPOC. No entanto, a associação do treinamento de força com exercício de *endurance* é considerada indispensável, pois promove resultados mais completos quando comparada a qualquer um dos dois protocolos de treinamento aplicados de forma isolada[4,83,84,88].

2.3.2 Prescrição de Treinamento Físico de Alta Intensidade em Pacientes com DPOC

Atualmente diferentes associações (*e.g. American Thoracic Society* [ATS], *European Respiratory Society* [ERS], *American Colege of Sports Medicine* [ACSM]) possuem recomendações específicas para a prescrição de intensidade de exercício. No entanto, cada associação propõe limites específicos para determinar a faixa de intensidade que compreende cada domínio de intensidade de exercício (*e.g*. baixa, modera e alta intensidade)[7,8]. Porém, todas as associações concordam que cada domínio deve ser delimitado sempre baseando-se na capacidade máxima de exercício do individuo[7,8]. Além disso, é proposto por alguns autores que a intensidade de exercício deveria ser determinada de acordo com respostas fisiológicas intrínsecas individuais (*e.g.* exercício de alta intensidade seriam os exercícios realizados entre o limiar de lactato e a CP [do inglês *critical power,* ou trabalho critico], que corresponde à velocidade máxima que um individuo

é capaz de sustentar enquanto mantem respostas integradas dos sistemas envolvidos na oferta e no consumo de oxigênio)[89].

Além de recomendações pautadas em respostas fisiológicas, que necessitam de testes máximos (*e.g.* TCPE e ISWT) para prescrição da intensidade do exercício[7,8,89] o exercício também pode ser prescrito com base na sensação de esforço percebida pelo paciente[7,8]. Nesse caso a mensuração pode ser realizada por meio da escala de Borg modificada (0-10), objetivando uma sensação de esforço entre 4-6,[8,90,91] ou entre 14-17 para a escala de Borg original (6-20)[7].

No entanto, recomendações especificas para pacientes com doenças pulmonares crônicas são fornecidas por duas das mais importantes associações de medicina respiratória do mundo, ATS e ERS[8]. Devido à grande aceitabilidade das recomendações relacionadas a doenças pulmonares conforme proposto por essas duas entidades no campo clínico e científico, o critério sugerido pelas mesmas foi adotado neste estudo. Sendo assim, exercício de alta intensidade foi considerado como todo exercício realizado acima de 60% da capacidade máxima de exercício individual[8].

2.3.3 O Teste de Caminhada de Seis Minutos (Tc6min) e seu uso como Recurso para Prescrição de Treinamento Físico de Alta Intensidade em DPOC

O TC6min é um teste reprodutível, confiável e responsivo a intervenções em pacientes DPOC, e um dos testes de campo mais utilizados para essa população[1]. Trata-se de um teste de velocidade auto-ditada pelo paciente, no qual os pacientes são orientados a caminhar a maior distância possível em seis minutos, em um corredor de exatos 30 metros. O principal desfecho do teste é a distância percorrida pelos indivíduos em metros. Como o incentivo verbal pode influenciar no resultado do teste, instruções padronizadas de incentivo devem ser oferecidas a cada minuto durante o teste[1].

O uso do TC6min para prescrição da intensidade de exercício teve inicio após um estudo no qual pacientes com DPOC foram submetidos a realização de um TC6min e um TCPE em ciclo ergômetro de membros inferiores. Os resultados demonstraram a comparação dos valores de VO_2, VCO_2, RER (quociente respiratório), V_E, e [LA] (concentração de lactato) ao final do TC6min (VO_2TC6min) com os valores obtidos ao final do TCPE (VO_2TCPE)[10]. Apesar da ausência de

diferença estatística entre o VO_2TC6min e o VO_2maxTCPE, o TCPE apresentou valores estatisticamente maiores de VCO_2, RER, V_E, e [LA].

De fato, o uso do TC6min para prescrição da intensidade de exercício não seria equivocado, já que algumas recomendações são baseadas apenas em valores de porcentagem do VO_2max para prescrição de intensidade de exercício[7]. Contudo, limitações metodológicas do estudo, como o uso do ciclo ergômetro de membros inferiores para a realização do TCPE e a pista não-padronizada para realização do TC6min, podem ter gerado resultados questionáveis[6].

O ciclo ergômetro de membros inferiores é o ergômetro mais comumente utilizado para a realização do TCPE devido à menor complexidade na realização de procedimentos intra-teste[9,92]. No entanto, esta preferência pela realização do TCPE no ciclo ergômetro de membros inferiores não considera respostas fisiológicas e perceptuais específicas a cada atividade (andar e pedalar)[9,92-96].

Já é consenso que, quando realizado em esteira, maiores valores de VO_2max são atingidos em comparação ao ciclo ergômetro de membros inferiores, tanto para indivíduos saudáveis como para pacientes com DPOC[9,92-96]. Isso ocorre devido à maior massa muscular envolvida na realização de trabalho e maior trabalho muscular realizado contra a ação da gravidade (*e.g.* aumento da inclinação da esteira). Sendo assim, o achado de que o VO_2TC6min é similar ao VO_2max de um TCPE em ciclo ergômetro de membros inferiores[10] não significa que o VO_2TC6min é igual ao VO_2max do individuo, mas sim que o VO_2TC6min pode ser menor que o VO_2max de um teste realizado em esteira. De acordo com estas informações parece que uma adaptação dos resultados advindos do TC6min seria necessária para a correta prescrição de exercício baseada na capacidade máxima do individuo (*i.e.* VO_2max).

Após estudos se basearem nos resultados do TC6min para prescrição de exercício[2-5], outros estudos tem procurado responder à mesma questão abordada neste documento, ou seja, a aplicabilidade do TC6min para a prescrição de exercício. No entanto, hiatos metodológicos também tem impactado de forma negativa na validade desses resultados.

Com o intuito de testar a eficiência de 80% da velocidade média do TC6min ($TC6min_{VM}$) para a prescrição de exercício, Zainuidin *et al.*[6] submeteram

pacientes com DPOC à realização de três atividades: 1) TC6min; 2) TCPE em ciclo ergômetro de membros inferiores; e 3) caminhada de dez minutos a 80% da $TC6min_{VM}$. Como resultado, uma grande variabilidade na resposta do VO_2 durante a caminhada a 80% da $TC6min_{VM}$ foi encontrada, com valores de VO_2 entre 52% e 100% do VO_2max. Além da grande variabilidade na resposta do VO_2, a realização do TC6min fora das recomendações internacionais (*i.e.* corredor de 30 metros) e a realização do TCPE em ciclo ergômetro de membros inferiores comprometeram a validade externa dos resultados. Em outro estudo realizado por Ciftci *et al*.[15] novamente as já mencionadas falhas metodológicas podem ser observadas (*i.e.* TCPE em cicloergômetro de membros inferiores e TC6min realizado em corredor de 20 metros). Sendo assim, a aplicabilidade do TC6min como ferramenta para a prescrição de exercício continua um campo aberto de investigação.

Por fim, como o trabalho muscular se mostrou importante para a magnitude de melhora após treinamento físico[97,98], o uso do TC6min para prescrição de TF em relação à capacidade de máxima de trabalho seria de suma importância para esta população. Ao menos ao conhecimento dos autores, isso ainda não foi estudado. Sendo assim, este estudo extende os achados da literatura atual sobre a aplicabilidade do TC6min na prescrição de exercício em relação à porcentagem do trabalho máximo do paciente. Com isso, evita-se repetir o objetivo dos estudos citados anteriormente, que foi avaliar o uso do TC6min na prescrição de exercício baseado no VO_2max do indivíduo.

3. ARTIGO

Submetido ao periódico Heart and Lung

Title: **Is the Six-Minute Walking test a useful tool to prescribe high-intensity exercise in patients with Chronic Obstructive Pulmonary Disease?**

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Abstract

Objective: To evaluate the applicability of the Six-Minute Walking Test (6MWT) to prescribe exercise intensity for patients with chronic obstructive pulmonary disease (COPD) in accordance with international guidelines

Background: It is not yet solidly known whether the 6MWT can be used to prescribe high-intensity exercise for patients with COPD.

Methods: Patients with COPD (n=27) were evaluated before and after a 12-week high-intensity exercise program. Criteria for high-intensity training were ≥75% of the 6MWT average speed; and ATS/ERS criteria (≥60% of the maximal speed achieved in the Incremental Shuttle Walking test).

Results: The 6MWT showed good diagnostic performance (positive and negative predictive values of 0.69 and 0.71, respectively, and accuracy of 0.70), good reliability (ICC 0.70 [95%CI 0.45-0.85]) and moderate agreement (k 0.41 [95%CI 0.13-0.67]) when used to determine high-intensity exercise according to the ATS/ERS guidelines.

Conclusion: The 6MWT is a useful tool to prescribe high-intensity exercise for patients with COPD.

Keywords: Pulmonary Disease, Chronic Obstructive; Exercise; Exercise Test; Validation Studies.

Abbreviations:

6MWT: Six-minute walking test;

$6MWT_{AS}/ISWT_{S}$: ratio between average speed during the 6MWT and speed achieved in the last stage of the ISWT;

$6MWT_{C}$: 6MWT criteria;

$6MWT_{AS}$: average speed during the 6MWT;

$Borg_{C}$: Borg criteria;

COPD: Chronic Obstructive Pulmonary Disease;

CPET: cardiopulmonary exercise test;

ET: Exercise training;

GOLD: Global initiative for Chronic Obstructive Pulmonary Disease;

ICC: intra class correlation coefficient;

$ISWT_{C}$: ISWT criteria;

$ISWT_{S}$: speed achieved in the last stage of the ISWT;

K: Cohen's kappa value;

NPV: negative predictive value;

PPV: positive predictive value;

UEL: Universidade Estadual de Londrina;

VO_2: oxygen consumption.

VO_2max: maximum oxygen consumption;

Introduction

The six-minute walking test (6MWT) has proved to be reproducible, reliable, and responsive to interventions in patients with Chronic Obstructive Pulmonary Disease (COPD) and is possibly the most used field test in this population[1]. Guidelines[2] do not specifically recommend the 6MWT as a tool to prescribe high-intensity exercise training (ET). However, this test has been used by many in order to prescribe exercise intensity during ET programs[3-6], and this has generated recent interest in this topic[7].

The prescription of exercise intensity in ET programs must be individually tailored and based on the maximal exercise capacity both in healthy subjects and patients[2,8]. The cardiopulmonary exercise test (CPET) is considered the gold standard method to measure maximal exercise capacity[9]. At the same time, the use of the 6MWT to prescribe ET intensity for patients with COPD has been based on the similarity of responses concerning maximal oxygen consumption (VO_{2max}) during the 6MWT and during the CPET in COPD[10]. However, methodological gaps (*e.g.*, CPET performed on cycle-ergometer [instead of treadmill/walking] and non-standardized track for the 6MWT) could have led the authors to misleading conclusions on this matter[7]. Some studies have found that the 6MWT average speed ($6MWT_{AS}$) is lower or similar to the maximal sustainable speed that a person is able to deal while maintaining an integrated response of the systems involved in O_2 transport and utilization, the critical speed[11,12]. In patients with COPD, the critical speed has been indicated to be at intensities bellow 85% of maximal exercise capacity[13,14], supporting the sub-maximal (or functional) profile in which the 6MWT has been commonly suggested.

Despite the conflicting results in the literature, different percentages of the $6MWT_{AS}$ have been used to prescribe exercise intensity for patients with COPD[3-6], and indeed these programs have improved exercise capacity and quality of life exceeding the minimal important difference for this population. However, a recent study has investigated whether or not 80% $6MWT_{AS}$ could be adequately used for exercise prescription[7], and in this case a wide variability in the VO_{2max} response was found.

Therefore, the issue of whether or not the performance in the 6MWT can be adequately applied to prescribe ET intensity for patients with COPD remains unsolved. The aim of this study was to evaluate the applicability of the 6MWT to prescribe exercise intensity for patients with chronic obstructive pulmonary disease (COPD) in accordance with international guidelines. This will be done by investigating the agreement between high-intensity exercise prescribed based on the 6MWT and based on international recommendations[2].

Material and Methods

The study was approved by the Research Ethics Committee of the University Hospital, State University of Londrina, Londrina, Brazil (N 123/09).

Study Design

In this longitudinal study, anthropometric data, lung function (spirometry), functional and maximal exercise capacity (6MWT and Incremental Shuttle Walking Test [ISWT], respectively), dyspnea sensation in daily life (Medical Research Council

Scale, MRC), body composition (bioelectrical impedance) and inspiratory muscle strength (maximal inspiratory pressure, MIP) were assessed before and after a 12-week high-intensity ET program. At the first and the 12th week of the ET program, data concerning dyspnea and fatigue sensation (modified Borg scale), speed (km/h), and intensity relative to the $6MWT_{AS}$ and speed achieved in the last stage of the ISWT ($ISWT_S$) were also collected.

Subjects

Patients with diagnosis of COPD according to GOLD[15] who satisfied the following inclusion criteria took part in the study: 1) Stable condition for at least three months before entering the program; 2) absence of severe and/or unstable cardiovascular disease; 3) ability to perform the proposed assessments and activities; 4) not having attended to any formal ET program in the preceding year. Exclusion criteria were: physical or cognitive inability to perform the proposed activities; development or diagnose of other conditions/diseases that could influence the proposed activities and/or the results of the study. Patients who dropped out of the ET program due to severe acute exacerbation of COPD, hospitalization for any cause, severe unrelated health problems, lack of motivation and/or adherence, transportation difficulties or any personal reason were excluded from the post-ET statistical analysis.

Assessments

Patients were evaluated concerning their lung function by spirometry[16] (Spirobank spirometer, version 3.6 MIR, Rome, Italy), inspiratory muscle strength by MIP[17] (Makil®, Brasil), functional exercise capacity by the 6MWT and maximum exercise capacity by the ISWT, both tests performed according to international guidelines[1]. National reference values were used for calculating the predicted values of these tests[18-21].

Dyspnea sensation in daily life was measured by the MRC scale[22] and body composition by bioelectrical impedance[23] (Biodynamics, EUA). Furthermore, in the first and last week of the ET program the following measurements were also performed at the end of the exercise on treadmill: dyspnea and lower limb fatigue sensation by the modified 10-point Borg scale[24]; and speed performed by the patient during the ET (in km/h).

Details regarding the ET program have been previously described[3], including the fact that this program was shown to be beneficial for improving exercise capacity in patients with COPD[3]. In brief, it was a high-intensity ET program composed by whole-body endurance exercise performed on cycle-ergometer and treadmill plus upper and lower-limbs strengthening exercises. For the cycle ergometry training the intensity was initially set at 60% of the maximal estimated work rate[25], whereas for the treadmill walking it was initially set at 75% of the average walking speed during the baseline 6MWT. The strength training intensity was initially set at 70% of the baseline one-repetition maximum test. There was increase in training intensity every week, guided by a pre-determined schedule and also driven by the patient's perception of symptoms (modified Borg score between four and six as target).

Criteria for high-intensity exercise

According to international pulmonary rehabilitation guidelines[2] the threshold for high-intensity exercise for patients with pulmonary diseases is 60% of the maximal exercise capacity. Despite the fact that other criteria are described in the literature[8,26], this criterion was followed in this study based on its high acceptance in the COPD research field[2,4,27,28]. Exercise above 60% of the $ISWT_S$ was therefore used as cut off value for the ISWT criterion ($ISWT_C$).

The cutoff value of 75% $6MWT_{AS}$, as applied in previous studies[3-6], was used as the 6MWT criterion ($6MWT_C$) in the present analysis. The agreement and reliability of this criterion in comparison to $ISWT_C$ were the main focus of this study.

Since another recommendation to guide high-intensity ET prescription is a value in the Borg scale between four and six[2] ($Borg_C$), the agreement of this criterion was also compared with the $ISWT_C$ and the $6MWT_C$ as secondary results. $Borg_C$ had two variants: $Borg_C$ D “OR” F concerned achieving one of the two criteria (dyspnea or fatigue, any of them), whereas $Borg_C$ D “AND” F concerned achieving both criteria.

Statistical analysis

Statistical analysis was performed with the Statistical Package of Social Science (SPSS) 17.0 (SPSS Inc., Chicago, IL, USA). Normality in data distribution was checked with the Shapiro-Wilk test. Accordingly, continuous variables normally distributed were expressed as mean ± standard deviation (SD), non-normally distributed continuous variables as median (interquartile range, IQR), and categorical variables as number of cases and percentages (n, [%]).

Comparisons between changes due to intervention were done using the paired T-test. Since 12 patients dropped out during the ET program, they were not considered for the post-ET statistical analysis. The unpaired T-test or Mann-Whitney test were used for comparisons between patients in which the $6MWT_C$ and $ISWT_C$ agreed (GA_{week1}) *versus* the cases in which they did not agree (GNA_{week1}) and between patients in whom 75% of the $6MWT_{AS}$ was higher or equal to 60% of $ISWT_S$ with the cases in which it was lower. The Pearson product-moment correlation coefficient was used to analyze correlations between two continuous, normally distributed variables. Correlations involving one categorical and one continuous variable were investigated with the point-biserial correlation coefficient.

Positive predictive values (PPV), negative predictive values (NPV) and accuracy were calculated for each of the criteria according to recommended equations[29]. The Cohen's kappa (k) test was used to determine whether there was agreement between each criterion at the first and last weeks of the ET program and how strong this agreement eventually was. For the k statistics patients who exercised above the criteria (*e.g.* >60% $ISWT_S$) were represented by the number one and those who exercised below the criteria (*e.g.* ≤60% $ISWT_S$) by the number zero. Classification of the k value was done according to Landis *et al.*[30] as poor agreement (k lower than zero); slight agreement (k= 0-20); fair agreement (k= 0.21-0.40); moderate agreement (k= 0.41-0.60); substantial agreement (k= 0.61-0.80); and almost perfect agreement (0.81-1). Finally, reliability between 75% $6MWT_{AS}$ and 60% $ISWT_S$ was analyzed with the intra-class correlation coefficient (ICC) at the first and last week of the program.

Results derived from analyses of week one and week 12 were considered as evaluation of the clinical applicability of the test (*e.g.* agreement between criterias).

The psychometric propretie of the test to prescribe ET was evaluated by the ICC and Bland-Altman plots.

Results

Baseline sample characteristics

Twenty-seven patients were included in the high-intensity ET program and had full available data on the speed performed in the first and last week of the program. Two out of the 27 patients did not have Borg scale data, and baseline data of the MRC was not obtained in one patient due to technical issues.

The sample was composed by patients with moderate to very-severe airflow obstruction, mean age of 67 years and classified as ranging from underweight to obese according to their BMI (table 1). In general, they exhibited a relatively preserved functional exercise capacity as measured by the 6MWT and impaired maximal exercise capacity according to the ISWT (table 1). Most patients were symptomatic in terms of breathlessness and women had decreased average fat-free mass index (14 ± 1.7 Kg/m2), which was better preserved in men (17.4 ± 1.4 Kg/m2)[31]. The average MIP was above the absolute cutoff values considered for the diagnosis of inspiratory muscle weakness[32] (table 1).

During the first week of ET more than a half of the patients failed to achieve the cutoff for high-intensity exercise regardless of the criterion (figures 1 and 2).

Baseline predictive values and accuracy

The $6MWT_C$ demonstrated a PPV of 0.69, a NPV of 0.71, and an accuracy of 0.70 to identify patients who achieve the $ISWT_C$. $6MWT_C$ also showed a PPV of 0.38, a NPV of 0.60, and an accuracy of 0.50 to identify patients who achieve the $Borg_C$. Between $ISWT_C$ and $Borg_C$, values were 0.60 for PPV, 0.59 for NPV, and 0.59 for accuracy.

Baseline agreement between criteria

According to $6MWT_C$ and $ISWT_C$, 13 (48%) patients achieved the desired training intensity in the first week of the ET (figure 1); whereas ten (40%) patients achieved $Borg_C$ (figure 2).

As analyzed by the Cohen's kappa test, agreement of $6MWT_C$ with $ISWT_C$, $Borg_C$ D "OR" F and $Borg_C$ D "AND" F was 0.41 ± 0.18, -0.02 ± 0.19 and 0.10 ± 0.15, respectively. Agreement of $ISWT_C$ with $Borg_C$ D "OR" F and $Borg_C$ D "AND" F was 0.18 ± 0.19 and 0.09 ± 0.15, respectively. Finally, agreement between $Borg_C$ D "OR" F with $Borg_C$ D "AND" F was 0.50 ± 0.16.

Baseline reliability of the 75% $6MWT_C$

An ICC of 0.70 (95% CI 0.45-0.85) was found between 75% $6MWT_{AS}$ and the 60% $ISWT_S$, and this respective Bland & Altman analysis is depicted in figure 3, upper plot.

The 6MWT 75% cutoff point.

In the first week, comparisons between patients in which the $6MWT_C$ and $ISWT_C$ agreed (GA_{week1}) *versus* the cases in which they did not agree (GNA_{week1}) revealed higher speed, $\%6MWT_{AS}$, $\%ISWT_S$ and $6MWT_{AS}/ISWT_S$ during the first week of ET in favor of the GA_{week1} (table 2).

Patients in whom 75% of the $6MWT_{AS}$ was higher or equal to 60% of $ISWT_S$ were compared with the cases in which it was lower. In this analysis, lower pulmonary function and maximal exercise capacity, higher dyspnea sensation in daily life, and higher $6MWT_{AS}/ISWT_S$ ratio were found in those cases which 75% of 6MWT speed was equal or higher than 60% of ISWT speed (table 3). A large variability in the percentage of $6MWT_{AS}$ representing 60% of $ISWT_S$ occurred, with values ranging from 58% to 92% of the $6MWT_{AS}$ found to be equal to 60% of $ISWT_S$.

A strong correlation was found between the intensity of the 6MWT representing 60% of $ISWT_S$ and the $6MWT_{AS}/ISWT_S$ ratio (r= -0.991, P<0.001)

Improvements post-ET program

Fifteen out of 27 patients finished the program. The reasons for dropping out of the program were: severe acute exacerbation of COPD (n=1); severe unrelated health problems (n= 4); lack of adherence (n=3) and personal reasons (n= 4).

At the last week of the ET program patients increased the speed in km/h and also relatively to the 6MWT and ISWT. As expected, improvements in exercise capacity were also found after the ET program (table 4).

Additionally, larger increase in the speed in km/h was observed in GNA_{week1} when compared to GA_{week1} (66 [46 - 79] vs. 28 [21 - 40] $\%\Delta$, respectively; P= 0.02),

as well as concerning the increase in the intensity of exercise in %$ISWT_S$ (63 [46 - 67] vs. 27 [14 - 30], %Δ, respectively: *P*= 0.01).

Despite the fact that not all patients achieved the high-intensity criteria at the first week of ET, all patients were exercising above $6MWT_C$ and $ISWT_C$ at the last week of ET (figure 1).

Post-ET predictive values, agreement and accuracy

Due to the fact that all patients were exercising above the $6MWT_C$ and $ISWT_C$ at the end of the ET program (figure 1), calculation of PPV, NPV and accuracy, as well as the Cohen's k value, were mathematically limited.

Post-ET reliability of the 75% $6MWT_C$

After the ET program, ICC between 75% $6MWT_{MS}$ and 60% $ISWT_{MS}$ in the 15 completers was 0.68 (95% CI 0.28-0.88), and this respective Bland & Altman analysis is depicted in figure 3, lower plot.

Discussion

The main findings of this study were the good performance of the $6MWT_C$ to detect high-intensity exercise in patients with COPD according to international recommendations[2], represented in the present study by the $ISWT_C$. This was indicated by its good PPV, NPV, accuracy and reliability, as well as its moderate agreement. Secondary findings included 1) the lower exercise tolerance (*i.e.*, lower

training intensity) in those patients in which $6MWT_C$ and $ISWT_C$ did not agree in the beginning of the program (GNA_{week1} *vs.* GA_{week1}); 2) the higher increase in exercise tolerance (*i.e.*, higher increase in training intensity from week one to week 12) in the GNA_{week1}; and 3) similar exercise training intensities at the last week of exercise training in both groups.

The use of the 6MWT to prescribe ET intensity seemed justified due to previous research showing no statistical difference when the VO_2 of the 6MWT was compared with the VO_{2max} achieved in a CPET in COPD[10]. More recently, increasing interest in this theme has risen[7,33]. Noteworthy, methodological gaps are present in the current literature such as the CPET performed on cycle-ergometer[7,10], the use of only one variable to guide conclusions[10], the use of a non-standardized track to perform the 6MWT[7], and even the comparison with expected results[33]. In fact, these limitations could have contributed to the misconception of the 6MWT being considered by some as a maximal test for patients with COPD.

A number of studies have used the 6MWT as a tool to prescribe high-intensity ET, and beyond doubt, they had achieved improvements in exercise capacity and quality of life above the minimal clinical important difference in patients with COPD[3-6]. The present results indicated a good performance of the $6MWT_C$ in reflecting the $ISWT_C$. All things considered, it seems reasonable to recommend the 6MWT as a tool to prescribe ET intensity, in the absence of a CPET, since it showed a good ICC, PPV, NPV and accuracy, besides proving to generate improvements in exercise capacity and quality of life[3-6]. However, further studies are needed to determine the exact range of the $6MWT_{AS}$ which is able to represent 60% of maximal exercise capacity in patients with COPD.

Despite GNA_{week1} having lower exercise tolerance in the first week of ET, there were no baseline differences in resting pulmonary function and exercise capacity between the two groups (table 2). This indicates that other factors not evaluated in this study, such as muscle dysfunction and fatigue[34], dynamic ventilatory and lung mechanics constraints[35], and metabolic factors[36] may be responsible for the lower exercise tolerance in GNA_{week1}.

In spite of the larger increase in exercise intensity from week one to week 12 in GNA_{week1}, improvements in functional and maximal exercise capacity were similar between the groups. The larger increase in ET intensity in favor of the GNA_{week1} is in accordance with previous literature findings[37,38], showing larger improvements in patients with worse exercise tolerance at the beginning of ET programs.

The moderate (or relatively modest) agreement between $6MWT_C$ and $ISWT_C$ is the statistical portrait of the high variability (from 58% to 92%) of $\%6MWT_{AS}$ representing 60% of $ISWT_S$ revealed in the present results. This variability is represented by the ratio between $6MWT_{AS}/ISWT_S$, which represents how much of the maximal exercise capacity the patient is able to use in his/her functionality[1]. As this ratio showed a strong correlation with the intensity of the 6MWT representing 60% of $ISWT_S$ (see results), this points out to this variability as the main responsible factor for this modest agreement between $6MWT_C$ and $ISWT_C$. Moreover, a higher $6MWT_{AS}/ISWT_S$ ratio was found in patients whose $6MWT_C$ agrees with the $ISWT_C$ (table 3), confirming the relevance of this relationship.

In accordance with the variability of the $\%6MWT_{AS}$ representing 60% $ISWT_S$ and the higher variability in $6MWT_{AS}/ISWT_S$ ratio found in this study (mean 0.81, range 0.65-1.03), a higher variability in the $\%VO_2$ has also been previously shown when patients were asked to walk at 80% $6MWT_{AS}$ (mean 77, range 52-100

%VO_2max)[7]. Altogether these results indicate that some, but not all patients use their maximal exercise capacity in functional activities, and in this subgroup of patients maximal and submaximal exercise capacity are comparable. However, the clinical importance of this variability, represented by the $6MWT_{AS}/ISWT_S$ ratio is not clear.

Even though recommended as a tool to guide ET intensity for patients with chronic lung diseases, including COPD, $Borg_C$ showed slightly (lower) agreement with international recommendations[2]. A long time has passed since studies set out the use of dyspnea and fatigue sensation (Borg scale) to determine high-intensity exercise for patients with COPD, firstly based on percentage of maximal heart rate[24], and afterwards based on oxygen consumption[39]. However, a key point must be accounted for to justify the more modest agreement between $ISWT_C$ and $Borg_C$: studies found a Borg scale value between 4-6 (out of Borg scale 0-10) to represent an intensity of 80% of maximal exercise capacity[24,39], a divergent intensity from the recommended in the same guideline (*i.e.* 60% maximal exercise capacity)[2]. On the other hand, $Borg_C$ showed an acceptable diagnostic performance (PPV, NPV and AC), which provides some basis for its use in the absence of a CPET and a 6MWT.

Limitations

The fact all patients were exercising above the $6MWT_C$ and $ISWT_C$ at the last week of training made unfeasible the calculation of agreement, PPV, NPV, and accuracy at week 12 due to limitations in the test equations. This may limit the present results, affecting the decision to use or not the $6MWT_C$ to prescribe exercise intensity for patients who have had already finished an ET program. However, as shown in this study, patients were exercising at an average of 101.7% (range, 89.1 -

114.4) of $6MWT_{AS}$ after three months of ET; therefore, the $6MWT_{AS}$ could be used accordingly as target intensity in programs in which the intensity is adjusted from time to time.

Conclusion

In conclusion, the 6MWT can be used as a tool to prescribe ET at high intensity for patients with COPD, since it showed good PPV, NPV, accuracy, reliability and moderate agreement in prescribing high-intensity exercise according to international guidelines[2] (*i.e.*, 60% of the maximal speed achieved in a maximal exercise test, the ISWT). Moreover, patients who exercised according to one or both of these criteria improved exercise capacity in the same magnitude, and most importantly, exceeding the values of minimal important difference for this population.

References

1. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44(6):1428-1446.
2. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med. 2013;188(8):e13-64.
3. Probst VS, Kovelis D, Hernandes NA, Camillo CA, Cavalheri V, Pitta F. Effects of 2 exercise training programs on physical activity in daily life in patients with COPD. Respir Care. 2011;56(11):1799-1807.
4. Pitta F, Troosters T, Probst VS, Langer D, Decramer M, Gosselink R. Are patients with COPD more active after pulmonary rehabilitation? Chest. 2008;134(2):273-280.
5. Troosters T, Gosselink R, Decramer M. Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. Am J Medicine. 2000;109(3):207-212.
6. Spruit MA, Gosselink R, Troosters T, De Paepe K, Decramer M. Resistance versus endurance training in patients with COPD and peripheral muscle weakness. Eur Respir J. 2002;19(6):1072-1078.
7. Zainuldin R, Mackey MG, Alison JA. Prescription of walking exercise intensity from the 6-minute walk test in people with chronic obstructive pulmonary disease. J Cardiopulm Rehabil Prev. 2015;35(1):65-69.
8. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in

apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011;43(7):1334-1359.

9. American Thoracic S, American College of Chest P. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003;167(2):211-277.

10. Troosters T, Vilaro J, Rabinovich R, et al. Physiological responses to the 6-min walk test in patients with chronic obstructive pulmonary disease. Eur Respir J. 2002;20(3):564-569.

11. Dolmage TE, Evans RA, Hill K, Blouin M, Brooks D, Goldstein RS. The effect of pulmonary rehabilitation on critical walk speed in patients with COPD: a comparison with self-paced walks. Chest. 2012;141(2):413-419.

12. Casas A, Vilaro J, Rabinovich R, et al. Encouraged 6-min walking test indicates maximum sustainable exercise in COPD patients. Chest. 2005;128(1):55-61.

13. Puente-Maestu L, Sanz ML, Sanz P, Ruiz de Ona JM, Rodriguez-Hermosa JL, Whipp BJ. Effects of two types of training on pulmonary and cardiac responses to moderate exercise in patients with COPD. Eur Respir J. 2000;15(6):1026-1032.

14. Neder JA, Jones PW, Nery LE, Whipp BJ. Determinants of the exercise endurance capacity in patients with chronic obstructive pulmonary disease. The power-duration relationship. Am J Respir Crit Care Med. 2000;162(2 Pt 1):497-504.

15. Vestbo J, Hurd SS, Agusti AG, 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):347-365.

16. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-338.

17. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. Am Rev Respir Dis. 1969;99(5):696-702.

18. Pereira CA, Sato T, Rodrigues SC. New reference values for forced spirometry in white adults in Brazil. Braz J Pneumol. 2007;33(4):397-406.

19. 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):719-727.

20. Britto RR, Probst VS, de Andrade AF, et al. Reference equations for the six-minute walk distance based on a Brazilian multicenter study. Braz J Phys Ther. 2013;17(6):556-563.

21. Probst VS, Hernandes NA, Teixeira DC, et al. Reference values for the incremental shuttle walking test. Respir Med. 2012;106(2):243-248.

22. Kovelis D, Segretti NO, Probst VS, Lareau SC, Brunetto AF, Pitta F. Validation of the Modified Pulmonary Functional Status and Dyspnea Questionnaire and the Medical Research Council scale for use in Brazilian patients with chronic obstructive pulmonary disease. J Bras Pneumol. 2008;34(12):1008-1018.

23. Kyle UG, Pichard C, Rochat T, Slosman DO, Fitting JW, Thiebaud D. New bioelectrical impedance formula for patients with respiratory insufficiency: comparison to dual-energy X-ray absorptiometry. Eur Respir J. 1998;12(4):960-966.

24. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377-381.

25. Cavalheri V, Hernandes NA, Camillo CA, Probst VS, Ramos D, Pitta F. Estimation of maximal work rate based on the 6-minute walk test and fat-free mass in chronic obstructive pulmonary disease. Arch Phys Med Rehabil. 2010;91(10):1626-1628.

26. Mark Burnley and Andrew M. Jones. Oxygen uptake kinetics as a determinant of sports performance. Eur J Sport Sci. 2007;7(2):63-79.

27. Gloeckl R, Marinov B, Pitta F. Practical recommendations for exercise training in patients with COPD. Eur Respir Rev. 2013;22(128):178-186.

28. Maltais F, LeBlanc P, Jobin J, et al. Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1997;155(2):555-561.

29. Altman DG, Bland JM. Diagnostic tests 2: Predictive values. BMJ. 1994;309(6947):102.

30. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-174.

31. Schols AM, Ferreira IM, Franssen FM, et al. Nutritional assessment and therapy in COPD: a European Respiratory Society statement. Eur Respir J. 2014;44(6):1504-1520.

32. Lotters F, van Tol B, Kwakkel G, Gosselink R. Effects of controlled inspiratory muscle training in patients with COPD: a meta-analysis. Eur Respir J. 2002;20(3):570-576.

33. van Gestel AJ, Baty F, Rausch-Osthof AK, Brutsche MH. Cardiopulmonary and gas-exchange responses during the six-minute walk test in patients with chronic obstructive pulmonary disease. Respiration. 2014;88(4):307-314.

34. Maltais F, Decramer M, Casaburi R, et al. An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2014;189(9):e15-62.

35. O'Donnell DE, Neder JA, Elbehairy AF. Physiological impairment in mild COPD. Respirology. 2015.

36. Vogiatzis I, Zakynthinos S. The physiological basis of rehabilitation in chronic heart and lung disease. J Appl Physiol. 2013;115(1):16-21.

37. Troosters T, Gosselink R, Decramer M. Exercise training in COPD: how to distinguish responders from nonresponders. J Cardiopul Rehabil. 2001;21(1):10-17.

38. Spruit MA, Augustin IM, Vanfleteren L, et al. Differential response to pulmonary rehabilitation in COPD: multidimensional profiling. Eur Respir J. 2015.

39. Horowitz MB, Littenberg B, Mahler DA. Dyspnea ratings for prescribing exercise intensity in patients with COPD. Chest. 1996;109(5):1169-1175.

Table 1. General characteristics of the included patients with COPD before exercise training.

	Baseline
Anthropometrics	
Male/Female, n^{o}	17/10
Age, yrs	67 ± 8.5
Height, cm	162 ± 8
BMI, kg/cm^2	25.8 ± 5
Função Pulmonar	
FVC, l	2.5 ± 0.75
FVC, %pred	73 ± 18
FEV_1, l/min	1.3 ± 0.53
FEV_1, %pred	52 [32 - 62]
FEV_1/FVC, %	51 ± 13
FEV_1/FVC, %pred	65 ± 18
Exercise capacity	
6MWT, m	464 ± 70
6MWT, %pred	86 ± 14
ISWT, m	440 ± 168
ISWT, %pred	65 ± 22
$6MWT_{AS}$/$ISWT_S$	0.81 ± 0.10
Dyspnea in daily life	
MRC, 1-5	4 [2 - 4]
Body composition	
FFMI, kg/m^2	16.5 ± 1.9

Maximal inspiratory strenght	
MIP, cmH_20	64 ± 25
MIP, %pred	70 ± 25
Exercise Training variables	
Speed, km/h	3.3 ± 0.86
Borg D, 0-10	3 [2 - 4]
Borg F, 0-10	3 [0.75 - 5]
$\%6MWT_{AS}$	75 [69 - 77]
% $ISWT_S$	58 ± 12

ET: exercise training program; BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; 6MWT: six-minute walking test; ISWT: incremental shuttle walking test; $6MWT_{AS}/ISWT_S$: ratio between average speed during the 6MWT and speed achieved in the last stage of the ISWT; MRC: Medical Research Council scale; FFMI: fat free mass index; MIP: maximum inspiratory pressure; Speed: speed performed by the patients at the first week of ET; Borg D: Dyspnea sensation in the first week of ET; Borg F: lower limb fatigue sensation in the first week of ET; %6MWT: percentage of $6MWT_{AS}$ performed by the patients in the first week of ET; %ISWT: percentage of $ISWT_S$ performed by the patient in the first week of ET.

Table 2. Comparison between patients whose $6MWT_C$ and $ISWT_C$ agree vs. patients in whom these criteria did not agree at the first week of the exercise training program.

	GNAweek1	**GAweek1**	***P***
Anthropometrics			
Male/Female, n°	11/7	6/3	0.88
Age, yrs	69 ± 8	64 ± 8	0.15
Height, cm	160 ± 8	164 ± 7	0.25
BMI, kg/cm^2	26 ± 5	25 ± 5	0.59
Função Pulmonar			
FVC, l	2.5 ± 0.79	2.4 ± 0.69	0.58
FVC, %pred	77 ± 18	65 ± 16	0.11
FEV_1, l/min	1.29 ± 0.55	1.33 ± 0.52	0.85
FEV_1, %pred			0.59
FEV_1/FVC, %	49 ± 13	55 ± 15	0.31
FEV_1/FVC, %pred	63 ± 17	70 ± 19	0.34
Exercise capacity			
6MWT, m	457 ± 72	481 ± 67	0.41
6MWT, %pred	85 ± 15	87 ± 12	0.76
ISWT, m	442 ± 150	437 ± 209	0.94
ISWT, %pred	68 ± 20	61 ± 28	0.47
$6MWT_{AS}/ISWT_S$	0.78 ± 0.09	0.87 ± 0.08	0.04
Dyspnea in daily life			
MRC, 1-5	3 [2 - 4]	4 [2.5 - 4]	0.41
Body composition			
FFMI, kg/m^2	16.6 ± 1.9	16.4 ± 2.1	0.85

Maximal inspiratory strenght			
MIP, cmH_20	65 ± 25	62 ± 26	0.75
MIP, %pred	72 ± 25	65 ± 26	0.48
Exercise Training variables			
Speed, km/h	3 ± 0.74	3.9 ± 0.79	0.007
Borg D, 0-10	2 [1.25 - 3.75]	3 [2.5 - 6]	0.12
Borg F, 0-10	2 [0.25 - 4.75]	4 [0.25 - 4.75]	0.27
$\%6MWT_{AS}$	74 [62 - 75]	77 [76 - 86]	<0.001
% $ISWT_S$	52 ± 10	70 ± 4	<0.001

GA_{week1}: patients whose $6MWT_C$ and $ISWT_C$ agreed in the first week of ET; GNA_{week1}: patients whose $6MWT_C$ and $ISWT_C$ did not agree in the first week of ET. BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; 6MWT: six-minute walking test; ISWT: incremental shuttle walking test; $6MWT_{AS}/ISWT_S$: ratio between average speed during the 6MWT and speed achieved in the last stage of the ISWT; MRC: Medical Research Council scale; FFMI: fat free mass index; MIP: maximum inspiratory pressure; Speed: speed performed by the patients at the first week of ET; Borg D: Dyspnea sensation in the first week of ET; Borg F: lower limb fatigue sensation in the first week of ET; %6MWT: percentage of $6MWT_{AS}$ performed by the patients in the first week of ET; %ISWT: percentage of $ISWT_S$ performed by the patient in the first week of ET

Table 3. Differences between patients in whom 75% $6MWT_{AS}$ was equal to or higher than 60% $ISWT_S$

	6MWTC not-OK (n=12)	**6MWTC OK (n=15)**	***P***
Função Pulmonar			
FVC, %pred	82 ± 20	65 ± 13	0.015
FEV1, %pred	61 [44 - 69]	45 [31 - 55]	0.016
Exercise capacity			
ISWT, m	516 ± 207	379 ± 100	0.033
$6MWT_{AS}/ISWT_S$	0.72 ± 0.05	0.89 ± 0.6	<0.001
Dyspnea in daily life			
MRC, 1-5	2.5 [2 - 4]	4 [3 - 4]	0.04

6MWTC OK: $6MWT_C \geq 60\%ISWT$, i.e., 75% of $6MWT_{AS}$ was higher than 60% of $ISWT_S$; 6MWTC not-OK: $6MWT_C < 60\%ISWT$, i.e., 75% of $6MWT_{AS}$ was lower than $60\%ISWT_S$. FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; ISWT: incremental shuttle walking test; $6MWT_{AS}/ISWT_S$: ratio between functional and maximal exercise capacity (average speed during the 6MWT divided by the maximum speed achieved in the ISWT); MRC: Medical Research Council scale.

Table 4. Baseline and post-exercise training characteristics of patients with COPD who finished the program.

Variavel	Baseline	Post-ET	*P*
Anthropometrics			
Male/Female, n°	10/5		
Age, yrs	64 [60 - 75]		
Height, cm	162 [157 - 167]		
BMI, kg/cm^2	28 ± 5	28 ± 5.3	0.65
Função Pulmonar			
FVC, l	2.6 ± 0.83	2.6 ± 0.87	0.69
FVC, %pred	74 ± 19	73 ± 22	0.9
FEV_1, l/min	1.4 ± 0.61	1.48 ± 0.74	0.37
FEV_1, %pred	57 [31 - 68]	52 [30 - 64]	0.73
FEV_1/FVC, %	59 [38 - 63]	60 [36 - 64]	0.02
FEV_1/FVC, %pred	65 ± 19	69 ± 21	0.16
Exercise capacity			
6MWT, m	466 ± 71	506 ± 85	0.003
6MWT, %pred	87 ± 15	94 ± 17	0.003
ISWT, m	483 ± 179	509 ± 208	0.21
ISWT, %pred	70 ± 22	76 ±	0.14
$6MWT_{AS}$/$ISWT_S$	0.78 ± 0.10	0.82 ± 0.06	0.95
Dyspnea in daily life			
MRC, 1-5	3.5 [2 - 4]	4 [2 - 4]	0.5
Body composition			
FFMI, kg/m^2	17.2 ± 1.8	17.4 ± 1.9	0.5

Maximal inspiratory strenght			
MIP, cmH_20	69 ± 28	75 ± 28	0.41
MIP, %pred	74 ± 28	81 ± 29	0.34
Exercise Training variables			
Speed, km/h	3.3 ± 0.8	5.1 ± 0.76	<0.001
Borg D, 0-10			
Borg F, 0-10			
$\%6MWT_{AS}$	75 [73 - 76]	101 [96 - 110]	0.001
% $ISWT_S$	57 ± 10	84 ± 8	<0.001

ET: exercise training program; BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; 6MWT: six-minute walking test; ISWT: incremental shuttle walking test; $6MWT_{AS}/ISWT_S$: ratio between average speed during the 6MWT and speed achieved in the last stage of the ISWT; MRC: Medical Research Council scale; FFMI: fat free mass index; MIP: maximum inspiratory pressure; Speed: speed performed by the patients at the first week of ET; Borg D: Dyspnea sensation in the first week of ET; Borg F: lower limb fatigue sensation in the first week of ET; %6MWT: percentage of $6MWT_{AS}$ performed by the patients in the first week of ET; %ISWT: percentage of $ISWT_S$ performed by the patient in the first week of ET.

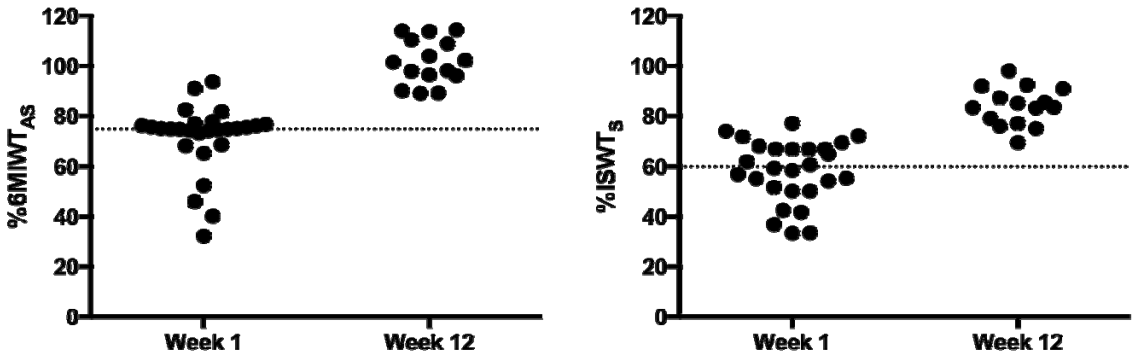

Fig 1. Intensity of training at the first and 12th week of the exercise training program. Left: % of the $6MWT_{AS}$. Right: % $ISWT_S$. Lines are the cutoff for high-intensity exercise training according to each criteria

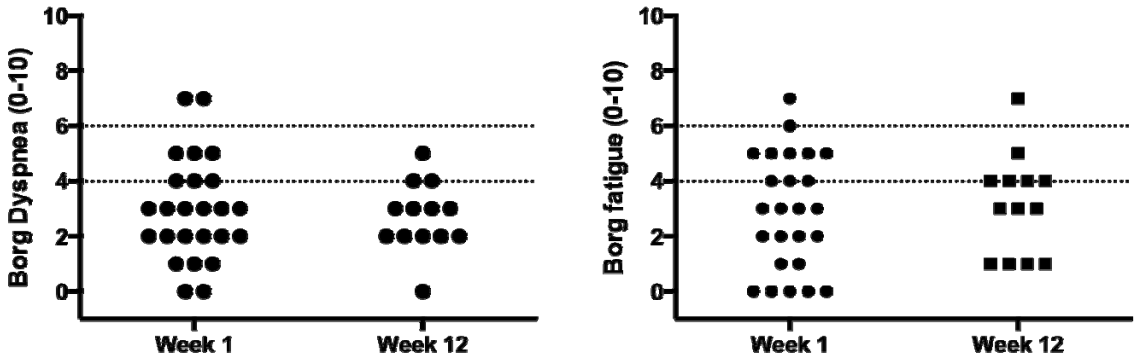

Fig 2. Dyspnea (left) and fatigue (right) sensation during the first and 12th week of the exercise training program. Lines are the cutoff for high-intensity exercise training according to each criteria

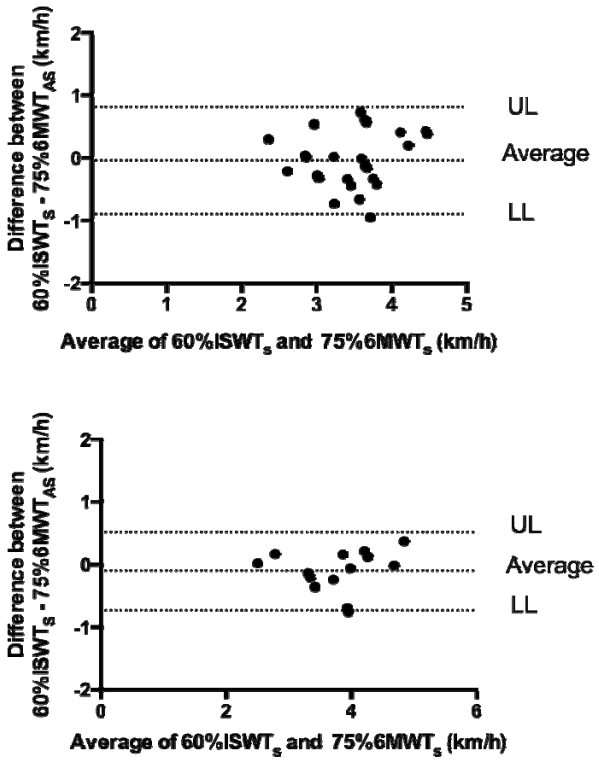

Fig 3. Bland-Altman plots of 60%ISWT – 75%6MWT at baseline (upper plot) and post-exercise training (lower plot). UL: upper limit; LL: lower limit.
Upper plot: UL: 0.81; average: -0.04; LL: -0.81. Lower plot: UL:0.51; average: -0.1; LL: -0.73.

4 CONCLUSÃO GERAL

Com base nos resultados deste estudo e dos achados de literatura descritos na revisão realizada nesta dissertação, pode-se concluir que o TC6min é um teste útil para a prescrição de TF para pacientes com DPOC na ausência de TCPE. Os resultados indicaram sua boa performance diagnóstica, indicada pelos valores preditivos positivos e negativos e acurácia, boa confiabilidade e aceitável concordância na prescrição de TF de alta intensidade de acordo com critérios internacionais para esa população. Somado a isso, pacientes com DPOC submetidos a um protocolo de TF prescrito com base no TC6min experienciam melhoras após TF que ultrapassam a mínima melhora clinicamente importante para essa população. No entanto, estudos desenhados com o intuito de desenvolver uma adaptação dos resultados do TC6min para prescrição de exercício são necessários. Isso poderia diminuir a variabilidade (em relação à intensidade máxima) da intensidade de exercício que acontece quando a intensidade é prescrita com base no TC6min.

REFERÊNCIAS

1. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44(6):1428-1446.
2. Probst VS, Kovelis D, Hernandes NA, Camillo CA, Cavalheri V, Pitta F. Effects of 2 exercise training programs on physical activity in daily life in patients with COPD. Respir Care. 2011;56(11):1799-1807.
3. Troosters T, Gosselink R, Decramer M. Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. Am J Respir Crit Care Med. 2000;109(3):207-212.
4. Spruit MA, Gosselink R, Troosters T, De Paepe K, Decramer M. Resistance versus endurance training in patients with COPD and peripheral muscle weakness. Eur Respir J. 2002;19(6):1072-1078.
5. Pitta F, Troosters T, Probst VS, Langer D, Decramer M, Gosselink R. Are patients with COPD more active after pulmonary rehabilitation? Chest. 2008;134(2):273-280.
6. Zainuldin R, Mackey MG, Alison JA. Prescription of walking exercise intensity from the 6-minute walk test in people with chronic obstructive pulmonary disease. J Cardiopul Rehabil Prev. 2015;35(1):65-69.
7. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exer. 2011;43(7):1334-1359.

8. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med. 2013;188(8):e13-64.

9. American Thoracic S, American College of Chest P. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003;167(2):211-277.

10. Troosters T, Vilaro J, Rabinovich R, et al. Physiological responses to the 6-min walk test in patients with chronic obstructive pulmonary disease. Eur Respir J. 2002;20(3):564-569.

11. Dolmage TE, Evans RA, Hill K, Blouin M, Brooks D, Goldstein RS. The effect of pulmonary rehabilitation on critical walk speed in patients with COPD: a comparison with self-paced walks. Chest. 2012;141(2):413-419.

12. Casas A, Vilaro J, Rabinovich R, et al. Encouraged 6-min walking test indicates maximum sustainable exercise in COPD patients. Chest. 2005;128(1):55-61.

13. Puente-Maestu L, Sanz ML, Sanz P, Ruiz de Ona JM, Rodriguez-Hermosa JL, Whipp BJ. Effects of two types of training on pulmonary and cardiac responses to moderate exercise in patients with COPD. Eur Respir J. 2000;15(6):1026-1032.

14. Neder JA, Jones PW, Nery LE, Whipp BJ. Determinants of the exercise endurance capacity in patients with chronic obstructive pulmonary disease. The power-duration relationship. Am J Respir Crit Care Med. 2000;162(2 Pt 1):497-504.

15. Ciftci F, Sen E, Akkoca Yildiz O, Saryal S. A comparison of cardiopulmonary exercise test and 6 minute walking test in determination of exercise capacity in chronic obstructive pulmonary disease. Tuberk Toraks. 2014;62(4):259-266.

16. van Gestel AJ, Baty F, Rausch-Osthof AK, Brutsche MH. Cardiopulmonary and gas-exchange responses during the six-minute walk test in patients with chronic obstructive pulmonary disease. Respiration. 2014;88(4):307-314.

17. Tarantino AB. *Doenças Pulmonares.* Vol. Sixth ed: Guanabara Koogan; 2007.

18. Marsh SE, Travers J, Weatherall M, et al. Proportional classifications of COPD phenotypes. Thorax. 2008;63(9):761-767.

19. Vestbo J, Hurd SS, Agusti AG, 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):347-365.

20. Watz H, Pitta F, Rochester CL, et al. An official European Respiratory Society statement on physical activity in COPD. Eur Respir J. 2014;44(6):1521-1537.

21. Ramon MA, Ferrer J, Gimeno-Santos E, et al. Inspiratory capacity-to-total lung capacity ratio and dyspnoea predict exercise capacity decline in COPD. Respirology. 2015.

22. Kirkham PA, Barnes PJ. Oxidative stress in COPD. Chest. 2013;144(1):266-273.

23. Barreiro E, Gea J. Respiratory and Limb Muscle Dysfunction in COPD. COPD. 2015;12(4):413-426.

24. Maltais F, Decramer M, Casaburi R, et al. An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2014;189(9):e15-62.

25. Panagioti M, Scott C, Blakemore A, Coventry PA. Overview of the prevalence, impact, and management of depression and anxiety in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2014;9:1289-1306.

26. O'Donnell DE, Webb KA. The major limitation to exercise performance in COPD is dynamic hyperinflation. J Appl Physiol. 2008;105(2):753-755; discussion 755-757.

27. Nici L. The major limitation to exercise performance in COPD is inadequate energy supply to the respiratory and locomotor muscles vs. lower limb muscle dysfunction vs. dynamic hyperinflation. Difficulties in determining the primary physiological abnormality that limits exercise performance in COPD. J Appl Physiol. 2008;105(2):760-761.

28. Neder JA. The major limitation to exercise performance in COPD is inadequate energy supply to the respiratory and locomotor muscles vs. lower limb muscle dysfunction vs. dynamic hyperinflation. Interpretation of exercise intolerance in COPD requires an integrated, multisystemic approach. J Appl Physiol. 2008;105(2):758-759.

29. Debigare R, Maltais F. The major limitation to exercise performance in COPD is lower limb muscle dysfunction. J Appl Physiol. 2008;105(2):751-753; discussion 755-757.

30. Aliverti A, Macklem PT. The major limitation to exercise performance in COPD is inadequate energy supply to the respiratory and locomotor muscles. J Appl Physiol. 2008;105(2):749-751; discussion 755-747.

31. O'Donnell DE, Laveneziana P, Webb K, Neder JA. Chronic obstructive pulmonary disease: clinical integrative physiology. Clin Chest Med. 2014;35(1):51-69.

32. Deesomchok A, Webb KA, Forkert L, et al. Lung hyperinflation and its reversibility in patients with airway obstruction of varying severity. COPD. 2010;7(6):428-437.

33. Guenette JA, Chin RC, Cheng S, et al. Mechanisms of exercise intolerance in global initiative for chronic obstructive lung disease grade 1 COPD. Eur Respir J. 2014;44(5):1177-1187.

34. Whipp BJ. Ventilatory control during exercise in humans. Ann Rev Physiol. 1983;45:393-413.

35. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;164(5):770-777.

36. Rodriguez-Roisin R, Drakulovic M, Rodriguez DA, Roca J, Barbera JA, Wagner PD. Ventilation-perfusion imbalance and chronic obstructive pulmonary disease staging severity. J Appl Physiol. 2009;106(6):1902-1908.

37. O'Donnell DE, Neder JA, Webb KA, Elbehairy AF. Reply: Effects of Mild Chronic Obstructive Pulmonary Disease on Gas Exchange during Cycling and Walking. Am J Respir Crit Care Med. 2015;192(9):1138-1139.

38. Neder JA, O'Donnell CD, Cory J, et al. Ventilation Distribution Heterogeneity at Rest as a Marker of Exercise Impairment in Mild-to-Advanced COPD. COPD. 2015;12(3):249-256.

39. Chiappa GR, Queiroga F, Jr., Meda E, 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):1004-1010.

40. Chiappa GR, Borghi-Silva A, Ferreira LF, 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):1341-1350.

41. Neder JA, Arbex FF, Alencar MC, et al. Exercise ventilatory inefficiency in mild to end-stage COPD. Eur Respir J. 2015;45(2):377-387.

42. Faisal A, Alghamdi BJ, Ciavaglia CE, et al. Common Mechanisms of Dyspnea in Chronic Interstitial and Obstructive Lung Disorders. Am J Respir Crit Care Med. 2015.

43. Gea J, Orozco-Levi M, Barreiro E, Ferrer A, Broquetas J. Structural and functional changes in the skeletal muscles of COPD patients: the "compartments" theory. Monaldi Arch Chest Dis. 2001;56(3):214-224.

44. Casaburi R, Rennard SI. Exercise limitation in chronic obstructive pulmonary disease. The O'Donnell threshold. Am J Respir Crit Care Med. 2015;191(8):873-875.

45. Williams TJ, Patterson GA, McClean PA, Zamel N, Maurer JR. Maximal exercise testing in single and double lung transplant recipients. Am Rev Respir Dis. 1992;145(1):101-105.

46. Gea J, Agusti A, Roca J. Pathophysiology of muscle dysfunction in COPD. J Appl Physiol. 2013;114(9):1222-1234.

47. Hopkinson NS, Tennant RC, Dayer MJ, et al. A prospective study of decline in fat free mass and skeletal muscle strength in chronic obstructive pulmonary disease. Respir Res. 2007;8:25.

48. Gosker HR, van Mameren H, van Dijk PJ, et al. Skeletal muscle fibre-type shifting and metabolic profile in patients with chronic obstructive pulmonary disease. Eur Respir J. 2002;19(4):617-625.

49. Jobin J, Maltais F, Doyon JF, et al. Chronic obstructive pulmonary disease: capillarity and fiber-type characteristics of skeletal muscle. J Cardiopul Rehabil. 1998;18(6):432-437.

50. Jakobsson P, Jorfeldt L, Henriksson J. Metabolic enzyme activity in the quadriceps femoris muscle in patients with severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1995;151(2 Pt 1):374-377.

51. Gosker HR, Hesselink MK, Duimel H, Ward KA, Schols AM. Reduced mitochondrial density in the vastus lateralis muscle of patients with COPD. Eur Respir J. 2007;30(1):73-79.

52. Wouters EF. Local and systemic inflammation in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2005;2(1):26-33.

53. Montes de Oca M, Torres SH, De Sanctis J, Mata A, Hernandez N, Talamo C. Skeletal muscle inflammation and nitric oxide in patients with COPD. Eur Respir J. 2005;26(3):390-397.

54. Sperandio PA, Oliveira MF, Rodrigues MK, et al. Sildenafil improves microvascular O2 delivery-to-utilization matching and accelerates exercise O2 uptake kinetics in chronic heart failure. Am J Physiol Heart Circ Physiol. 2012;303(12):H1474-1480.

55. Siqueira AC, Borghi-Silva A, Bravo DM, Ferreira EM, Chiappa GR, Neder JA. Effects of hyperoxia on the dynamics of skeletal muscle oxygenation at the onset of heavy-intensity exercise in patients with COPD. Respir Physiol Neurobiol. 2010;172(1-2):8-14.

56. Roseguini BT, Hirai DM, Alencar MC, et al. Sildenafil improves skeletal muscle oxygenation during exercise in men with intermittent claudication. Am J Physiol Regul Integr Comp Physiol. 2014;307(4):R396-404.

57. Medeiros WM, Fernandes MC, Azevedo DP, et al. Oxygen delivery-utilization mismatch in contracting locomotor muscle in COPD: peripheral factors. Am J Physiol Regul Integr Comp Physiol.. 2015;308(2):R105-111.

58. Berton DC, Barbosa PB, Takara LS, et al. Bronchodilators accelerate the dynamics of muscle O2 delivery and utilisation during exercise in COPD. Thorax. 2010;65(7):588-593.

59. Santos S, Peinado VI, Ramirez J, et al. Characterization of pulmonary vascular remodelling in smokers and patients with mild COPD. Eur Respir J. 2002;19(4):632-638.

60. Voelkel NF, Tuder RM. Hypoxia-induced pulmonary vascular remodeling: a model for what human disease? J Clin Invest. 2000;106(6):733-738.

61. Chetty KG, Brown SE, Light RW. Improved exercise tolerance of the polycythemic lung patient following phlebotomy. Am J Med. 1983;74(3):415-420.

62. MacNee W. Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. Part One. Am J Respir Crit Care Med. 1994;150(3):833-852.

63. Visca D, Aiello M, Chetta A. Cardiovascular function in pulmonary emphysema. Biomed Res Int. 2013;2013:184678.

64. Tzani P, Aiello M, Elia D, et al. Dynamic hyperinflation is associated with a poor cardiovascular response to exercise in COPD patients. Respir Res. 2011;12:150.

65. Folgering H, von Herwaarden C. Exercise limitations in patients with pulmonary diseases. Int J Sports Med. 1994;15(3):107-111.

66. Lacasse Y, Cates CJ, McCarthy B, Welsh EJ. This Cochrane Review is closed: deciding what constitutes enough research and where next for pulmonary rehabilitation in COPD. Cochrane Database Syst Rev. 2015;11:ED000107.

67. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev.. 2015;2:CD003793.

68. Belman MJ, Kendregan BA. Exercise training fails to increase skeletal muscle enzymes in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis. 1981;123(3):256-261.

69. Casaburi R, Patessio A, Ioli F, Zanaboni S, Donner CF, Wasserman K. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. Am Rev Respir Dis. 1991;143(1):9-18.

70. Rodriguez DA, Arbillaga A, Barberan-Garcia A, et al. Effects of interval and continuous exercise training on autonomic cardiac function in COPD patients. Clin Respir J. 2014.

71. Nasis I, Kortianou E, Vasilopoulou M, et al. Hemodynamic effects of high intensity interval training in COPD patients exhibiting exercise-induced dynamic hyperinflation. Respir Physiol Neurobiol. 2015;217:8-16.

72. Gimeno-Santos E, Rodriguez DA, Barberan-Garcia A, et al. Endurance exercise training improves heart rate recovery in patients with COPD. COPD. 2014;11(2):190-196.

73. Georgiopoulou VV, Dimopoulos S, Sakellariou D, et al. Cardiopulmonary rehabilitation enhances heart rate recovery in patients with COPD. Respir Care. 2012;57(12):2095-2103.

74. Bronstad E, Tjonna AE, Rognmo O, et al. Aerobic exercise training improves right- and left ventricular systolic function in patients with COPD. COPD. 2013;10(3):300-306.

75. Whittom F, Jobin J, Simard PM, et al. Histochemical and morphological characteristics of the vastus lateralis muscle in patients with chronic obstructive pulmonary disease. Med Sci Sports Exer. 1998;30(10):1467-1474.

76. Vogiatzis I, Terzis G, Stratakos G, et al. Effect of pulmonary rehabilitation on peripheral muscle fiber remodeling in patients with COPD in GOLD stages II to IV. Chest. 2011;140(3):744-752.

77. Vogiatzis I, Terzis G, Nanas S, et al. Skeletal muscle adaptations to interval training in patients with advanced COPD. Chest. 2005;128(6):3838-3845.

78. Troosters T, Gosselink R, Decramer M. Exercise training in COPD: how to distinguish responders from nonresponders. J Cardiopul Rehabil. 2001;21(1):10-17.

79. Spruit MA, Augustin IM, Vanfleteren L, et al. Differential response to pulmonary rehabilitation in COPD: multidimensional profiling. Eur Respir J. 2015.

80. Vogiatzis I, Zakynthinos S. The physiological basis of rehabilitation in chronic heart and lung disease. J Appl Physiol. 2013;115(1):16-21.

81. Maltais F, LeBlanc P, Jobin J, et al. Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1997;155(2):555-561.

82. Panton LB, Golden J, Broeder CE, Browder KD, Cestaro-Seifer DJ, Seifer FD. The effects of resistance training on functional outcomes in patients with chronic obstructive pulmonary disease. Eur J Appl Physiol. 2004;91(4):443-449.

83. Ortega F, Toral J, Cejudo P, et al. Comparison of effects of strength and endurance training in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2002;166(5):669-674.

84. Mador MJ, Bozkanat E, Aggarwal A, Shaffer M, Kufel TJ. Endurance and strength training in patients with COPD. Chest. 2004;125(6):2036-2045.

85. 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. Respir Med. 2004;98(10):1000-1007.

86. Hoff J, Tjonna AE, Steinshamn S, Hoydal M, Richardson RS, Helgerud J. Maximal strength training of the legs in COPD: a therapy for mechanical inefficiency. Med Sci Sports Exerc. 2007;39(2):220-226.

87. Clark CJ, Cochrane LM, Mackay E, Paton B. Skeletal muscle strength and endurance in patients with mild COPD and the effects of weight training. Eur Respir J. 2000;15(1):92-97.

88. Bernard S, Whittom F, Leblanc P, et al. Aerobic and strength training in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1999;159(3):896-901.

89. Mark Brunley and Andew M. Jones. Oxygen uptake kinetics as a determinant of sports performance. Eur J Sport Sci. 2007;7(2):63-79.

90. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377-381.

91. Horowitz MB, Littenberg B, Mahler DA. Dyspnea ratings for prescribing exercise intensity in patients with COPD. Chest. 1996;109(5):1169-1175.

92. Hsia D, Casaburi R, Pradhan A, Torres E, Porszasz J. Physiological responses to linear treadmill and cycle ergometer exercise in COPD. Eur Respir J. 2009;34(3):605-615.

93. Palange P, Forte S, Onorati P, Manfredi F, Serra P, Carlone S. Ventilatory and metabolic adaptations to walking and cycling in patients with COPD. J Appl Physiol. 2000;88(5):1715-1720.

94. Murray JA, Waterman LA, Ward J, Baird JC, Mahler DA. Perceptual and physiologic responses during treadmill and cycle exercise in patients with COPD. Chest. 2009;135(2):384-390.

95. Mathur RS, Revill SM, Vara DD, Walton R, Morgan MD. Comparison of peak oxygen consumption during cycle and treadmill exercise in severe chronic obstructive pulmonary disease. Thorax. 1995;50(8):829-833.

96. Mahler DA, Gifford AH, Waterman LA, Ward J, Machala S, Baird JC. Mechanism of greater oxygen desaturation during walking compared with cycling in patients with COPD. Chest. 2011;140(2):351-358.

97. Mador MJ. Exercise training in patients with COPD: one leg is better than two? Chest. 2008;133(2):337-339.

98. Bjorgen S, Hoff J, Husby VS, et al. Aerobic high intensity one and two legs interval cycling in chronic obstructive pulmonary disease: the sum of the parts is greater than the whole. Eur J Appl Physiol. 2009;106(4):501-507.

APÊNDICES

APÊNDICE A

Termo de cosentimento livre e esclarecido

Prezado(a) Senhor(a):

O(A) Sr(a) está sendo convidado para participar de um projeto de pesquisa chamado “Efeitos de um programa de exercício físico de longa duração sobre aspectos pulmonares e sistêmicos em pacientes com Doença Pulmonar Obstrutiva Crônica (DPOC)”, cujos pesquisadores responsáveis são Prof. Dr. Fábio de Oliveira Pitta e Nidia A. Hernandes, do Departamento de Fisioterapia da Universidade Estadual de Londrina (UEL). O estudo analisará principalmente as melhoras obtidas após 6 meses de treinamento utilizando-se dois tipos diferentes de exercício físico.

Justificativa: O presente estudo contribuirá para solucionar uma questão não resolvida e que tem sido alvo de grande debate: levando em conta que a longa duração do programa de treinamento físico é fundamental no processo de conscientizar pacientes com DPOC a aumentar sua atividade física diária, será necessário que o treinamento físico realizado durante esse programa de longa duração seja feito em alta intensidade, ou um programa de baixa intensidade de treinamento já atingiria o objetivo? Se programas de longa duração, porém com baixa intensidade de treinamento, trouxerem benefícios importantes no aumento da atividade física diária, isso poderá trazer mudança no entendimento atual sobre protocolos de exercício em pacientes com DPOC, que hoje são realizados sob alta intensidade de treinamento.

Objetivo: Comparar os efeitos de dois protocolos de treinamento físico em um programa de reabilitação de longa duração (6 meses) em pacientes com DPOC: um

protocolo de alta intensidade (baseado em treinamento de endurance e força) e um protocolo de baixa intensidade (baseado em exercícios respiratórios e de readequação do complexo tóraco-pulmonar).

Procedimentos: Os pacientes incluídos realizarão uma série de testes que incluirá avaliação da função pulmonar, capacidade máxima e funcional de exercício, força muscular periférica e respiratória, atividade física na vida diária, composição corporal, função autonômica cardíaca, qualidade de vida, estado funcional e sensação de dispnéia. A realização dos testes requer uma visita de aproximadamente 2 horas ao Hospital Universitário Regional Norte do Paraná, em Londrina, além do uso do pequeno aparelho na cintura durante dois dias (12 horas por dia, apenas durante o dia e não de noite).Após a avaliação inicial, os pacientes serão divididos em dois grupos: um grupo realizará um programa de exercícios físicos direcionado ao aumento da mobilidade torácica realizado 3 vezes por semana, durante 24 semanas ; e outro grupo realizará um programa de treinamento de endurance e força de membros superiores e inferiores realizado 3 vezes por semana, durante 24 semanas. Ao final do programa de treinamento, os participantes serão reavaliados seguindo os mesmos testes realizados na avaliação inicial.

Custos: A pesquisa é gratuita e portanto não envolve qualquer custo por parte dos indivíduos. Não haverá qualquer gratificação financeira pela participação. No entanto, em caso de eventuais danos ocorridos exclusivamente por causa deste estudo, o Sr(a) terá direito a tratamento médico completo oferecido pela instituição.

Riscos: Nenhum dos procedimentos utilizados constitui risco direto para a integridade física ou moral dos participantes. Além disso, os participantes poderão

abandonar o estudo a qualquer momento que se achar conveniente, sem qualquer prejuízo em nenhum sentido.

Sigilo: Embora os resultados da pesquisa possam ser divulgados em publicações e eventos científicos, a identidade dos participantes será sempre preservada de maneira sigilosa, ou seja, em segredo.

Caso o(a) Sr(a) aceite esse convite e concorde voluntariamente em participar do estudo assinando este termo de consentimento, consideramos que o Sr(a) acredita que foi suficientemente informada pela pesquisadora Nidia Aparecida Hernandes sobre a pesquisa, os procedimentos envolvidos nela, assim como os possíveis riscos e benefícios decorrentes dessa participação. Ressaltamos novamente que o Sr(a) pode retirar seu consentimento a qualquer momento, sem que isto leve a qualquer prejuízo em nenhum sentido.

Local e data: _____

Nome do participante: _____

Assinatura do participante ou responsável:_____

Assinatura do pesquisador: _____

Colocamo-nos à disposição para qualquer esclarecimento que se fizer necessário nos telefones (43) 3371-2477 ou pessoalmente no Ambulatório de Fisioterapia Respiratória do Hospital Universitário Regional Norte do Paraná: Av. Robert Koch, 60 – Vila Operária – Londrina – PR (perguntar pelo Professor Fábio de Oliveira Pitta).

Atenciosamente,

Prof. Fábio de Oliveira Pitta

Coordenador do Projeto

ANEXOS

ANEXO A

Normas de formatação da revista *Heart and Lung*.

Heart and Lung: The Journal of Acute and Critical Care, the official publication of The American Association of Heart Failure Nurses, presents original, peer-reviewed articles on techniques, advances, investigations, and observations related to the care of patients with acute and critical illness and patients with chronic cardiac or pulmonary disorders.

The Journal's **acute care** articles focus on the care of hospitalized patients, including those in the critical and **acute care** settings. Because most patients who are hospitalized in acute and critical care settings have chronic conditions, we are also interested in the chronically critically ill, the care of patients with **chronic cardiopulmonary disorders**, their rehabilitation, and disease prevention. The Journal's heart failure articles focus on all aspects of the care of patients with this condition. Manuscripts that are relevant to populations across the human lifespan are welcome.

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Editor:

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Registro CONEP 268

Parecer Nº 123/09 **CAAE Nº 0093.0.268.000-09** **FOLHA DE ROSTO Nº 257672**	Londrina, 14 de setembro de 2009.

PESQUISADOR: **FABIO DE OLIVEIRA PITTA**
PROPPG (Processo 12955/09)

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O "**Comitê de Ética em Pesquisa Envolvendo Seres Humanos da Universidade Estadual de Londrina/ Hospital Universitário Regional Norte do Paraná**" de acordo com as orientações da Resolução 196/96 do Conselho Nacional de Saúde/MS e Resoluções Complementares, avaliou o projeto:

"EFEITOS DE UM PROGRAMA DE EXERCÍCIO FÍSICO DE LONGA DURAÇÃO SOBRE ASPECTOS PULMONARES E SISTÊMICOS EM PACIENTES COM DOENÇA PULMONAR OBSTRUTIVA CRÔNICA (DPOC)"

Informamos que deverá ser comunicada, por escrito, qualquer modificação que ocorra no desenvolvimento da pesquisa, bem como deverá apresentar ao CEP/UEL relatório final da pesquisa.

Situação do Projeto: **APROVADO**

Atenciosamente,

Profª. Dra. Ester M. O. Dalla Costa
Coordenadora
Comitê de Ética em Pesquisa - CEP/UEL

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Form. Código 11.764 – Formato A4 (210x297mm)