Universidade Estadual de Londrina

KARINA COUTO FURLANETTO

ATIVIDADE FÍSICA NA VIDA DIÁRIA E COMPORTAMENTO SEDENTÁRIO DE PACIENTES COM DPOC:

MORTALIDADE, PERFIL DOS PACIENTES E IMPACTO DA VARIAÇÃO SAZONAL E DO USO DE EQUIPAMENTOS PORTÁTEIS

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Orientador: Prof. Dr. Fabio de Oliveira Pitta.

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Londrina, 06 de maio de 2016.

Dedico este trabalho aos queridos familiares e amigos que acreditaram junto comigo na conquista do doutorado.

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“Ninguém é tão grande que não possa aprender, e nem tão pequeno que não possa ensinar.”

(Blaise Pascal)

FURLANETTO, Karina Couto. **Atividade física na vida diária e comportamento sedentário de pacientes com DPOC:** mortalidade, perfil dos pacientes e impacto da variação sazonal e do uso de equipamentos portáteis. 2016. 210 f. Tese (Doutorado em Ciências da Reabilitação) – Universidade Estadual de Londrina, Londrina, 2016.

RESUMO

Introdução: A quantificação detalhada, objetiva e padronizada do nível de atividade física na vida diária (AFVD) de pacientes com doença pulmonar obstrutiva crônica (DPOC) permitiu identificar que desfechos clínicos relevantes estão associados com o padrão de comportamento inativo desses pacientes. Apesar da crescente relevância de diferentes aspectos da AFVD no mundo científico e na rotina clínica, muitas lacunas sobre este tema ainda existem na literatura atual. Questões importantes precisam ser melhor elucidadas em pacientes com DPOC com base em evidências sólidas, como a associação entre inatividade e mortalidade, uma melhor definição do perfil da população, e o grau de influência de variações sazonais e do uso de equipamentos portáteis. Adicionalmente, os termos “sedentarismo” e “inatividade física” são comumente e erroneamente considerados como sinônimos. A presente tese de doutorado foi desenvolvida com o intuito de contribuir com evidências científicas envolvendo questões relativas à mortalidade, perfil dos pacientes e impacto da variação sazonal e do uso de equipamentos portáteis sobre a AFVD de pacientes com DPOC. **Métodos:** Quatro estudos foram desenvolvidos, sendo 3 artigos originais e 1 artigo de revisão de literatura. Os dois primeiros estudos abordam as formas e pontos de corte para identificar os pacientes com DPOC que apresentam padrão de comportamento sedentário, inativo ou ativo. Os outros dois estudos abordam o impacto de dois fatores sobre a AFVD que ainda não estão bem estabelecidos, como a sazonalidade e o uso de equipamentos portáteis. Foram desenvolvidos: (1) um estudo retrospectivo de coorte (n=101) para identificar um ponto de corte de comportamento sedentário em pacientes com DPOC e investigar sua associação com a mortalidade em um *follow-up* de 5 anos; (2) um estudo transversal (n=104) para comparar o perfil de pacientes com DPOC considerados fisicamente ativos ou inativos de acordo com diferentes classificações do nível de AFVD; (3) um estudo prospectivo de coorte para investigar a variabilidade da AFVD causada pela sazonalidade (verão e inverno) em pacientes com DPOC que vivem em regiões do mundo com diferentes características climáticas (Londrina, Brasil [n=19] e Leuven, Belgica [n=18]); e (4) um estudo de revisão de literatura que investiga se a utilização de equipamentos portáteis, como a oxigenoterapia domiciliar ou a ventilação não-invasiva (VNI) influenciam no aumento ou redução do nível de AFVD, e neste caso, de pacientes mais graves. **Resultados:** O estudo (1) concluiu que 8:30 horas/dia em atividades que requerem <1,5 equivalente metabólico (MET) é um ponto de corte capaz de identificar pacientes com DPOC sedentários e que apresentam maior risco de mortalidade. Este estudo também mostrou que cada hora/dia gasta em atividades <1,5 MET aumenta o risco de mortalidade em 42%. O estudo (2) identificou que, independente do método de classificação utilizado, pacientes com DPOC fisicamente ativos são caracterizados por melhor capacidade de exercício, função pulmonar, composição corporal e estado funcional quando comparados a pacientes fisicamente inativos. Adicionalmente, pacientes fisicamente ativos são possivelmente também caracterizados por melhor força muscular periférica e expiratória e qualidade de vida, além de menor prevalência de doença cardíaca estável e risco de mortalidade. O estudo (3) mostrou que a AFVD dos pacientes com DPOC reduz no período do inverno em ambas as regiões do mundo, e de forma mais acentuada em pacientes brasileiros. Além disso, identificou que pacientes brasileiros são mais ativos que pacientes belgas mesmo após o ajuste para as variáveis climáticas. Por fim, o estudo de revisão de literatura (4) identificou que pacientes com DPOC que utilizam oxigenoterapia ou VNI domiciliar apresentam a AFVD ainda mais comprometida do que pacientes que não se utilizam desses equipamentos. Possivelmente, fornecer equipamentos mais leves de oxigenoterapia não seja suficiente para reverter o comportamento sedentário. Adicionalmente, diferentes estudos mostraram que intervenções com implementação de 3 meses de VNI noturna parecem aumentar a AFVD de pacientes com hipercapnia. **Conclusões:** Os quatro artigos científicos desenvolvidos apresentam conclusões clinicamente relevantes e mostram que os fatores pesquisados nesta tese impactam na AFVD dos pacientes com DPOC. A associação entre mortalidade e o ponto de corte para sedentarismo proposto sugere que estratégias para reduzir o comportamento sedentário podem aumentar a sobrevida desses pacientes. Além disso, estratégias que encorajam o paciente com DPOC a se tornar fisicamente mais ativo são fortalecidas com as evidências encontradas por meio da comparação entre os pacientes fisicamente inativos ou ativos. Por fim, as variações no clima e o uso de equipamentos portáteis como a oxigenoterapia domiciliar e a ventilação não invasiva noturna devem ser considerados nas avaliações futuras dos pacientes com DPOC pois são fatores que influenciam a atividade física diária. Novas pesquisas em pacientes com DPOC são incentivadas, de forma que no futuro seja possível determinar quais formas de intervenção que objetivam o aumento da atividade física e a redução do sedentarismo podem resultar em benefícios reais para a saúde desses pacientes.

Palavras-chave: Doença Pulmonar Obstrutiva Crônica. Atividade Motora. Mortalidade. Estilo de Vida Sedentário. Equipamentos e Provisões.

FURLANETTO, Karina Couto. **Physical activity in daily life and sedentary behavior in patients with COPD:** mortality, profile of patients and impact of seasonal variation e portable devices. 2016. 209 p. Thesis (Doctoral Degree in Rehabilitation Sciences) – Universidade Estadual de Londrina, Londrina, 2016.

ABSTRACT

Background: The detailed, objective and standardized quantification of physical activity in daily life (PADL) in patients with chronic obstructive pulmonary disease (COPD) allow identifying that relevant clinical outcomes are associated with the inactive pattern of these patients. Despite the growing relevance of different aspects related to PADL in the scientific world and clinical settings, there are many gaps in the current literature regarding this issue. Important questions should be better elucidated in patients with COPD based on solid evidences, such as the association between inactivity and mortality, a better definition of the population profile, and the degree of influence of seasonal variations and the use of portable devices. Additionally, the terms "sedentary behaviour" and "physical inactivity" have been commonly and confusingly mixed. The present thesis was developed to contribute with scientific evidences related to mortality, patients' profile and the impact on PADL of seasonal variations and the use of portable devices in patients with COPD. **Methods:** Four studies were developed, being 3 original articles and 1 literature review. The two former studies investigated the methods and cut-off points to identify patients with COPD who present sedentary, inactive or active behaviour pattern. The two later studies investigated the impact of given factors on PADL which are not totally elucidated, such as seasonality and the use of portable devices. The studies were: (1) a retrospective cohort study (n=101) aimed at proposing a cut-off point for sedentarism in patients with COPD and investigating its association with mortality in a 5-year follow-up period; (2) a cross-sectional study (n=104) with the objective of comparing the profile of patients with COPD considered physically active or inactive according to different classifications of PADL level; (3) a prospective cohort study aimed at investigating the variability of PADL caused by summer-winter seasonality in patients with COPD who live in regions of the world with different climatic characteristics (Londrina, Brazil [n=19] and Leuven, Belgium [n=18]); and (4) a literature review study aiming to investigate if the use of portable devices, such as home oxygen therapy or non-invasive ventilation (NIV) have influence on the improvement or reduction of PADL, and in this case, involving more severe patients. **Results:** Study (1) concluded that 8:30 hours/day in activities requiring <1.5 metabolic equivalent of task (MET) is a useful cut-off to identify patients with COPD who present sedentary behaviour and higher mortality risk. It also found that each hour/day spent <1.5MET increases mortality risk by 42%. Study (2) identified that, regardless of the classification method used to define a patient as active or inactive, physically active patients with COPD are characterized by better exercise capacity, lung function, body composition and functional status compared to physically inactive patients. Additionally, physically active patients are possibly also characterized by better peripheral and expiratory muscle strength and quality of life (activity domain), in addition to lower prevalence of stable heart disease and mortality risk. Study (3) showed that PADL of patients with COPD from the abovementioned two regions of the world decrease their PADL in winter, and more markedly in Brazilian patients.

Furthermore, the study identified that Brazilian patients are more active than Belgian patients, even when adjusting for weather variables. Finally, the review study (4) identified that patients with COPD receiving long-term oxygen therapy or domiciliary NIV present impaired PADL level compared to patients who do not use these devices. It is possible that providing lightweight oxygen devices may not be enough in itself to change sedentary behaviour. On the other hand, different studies have shown that interventions involving 3 months of nocturnal NIV implementation seem to improve PADL in hypercapnic patients. **Conclusions:** The four studies present clinical relevant conclusions as well as show that the investigated factors in the present thesis impact on PADL of patients with COPD. The association between mortality and the proposed sedentarism cut-off point suggests that strategies aiming at reducing sedentary behaviour might improve survival among these patients. Moreover, strategies encouraging the patient with COPD to became physically more active are strengthened with the evidences found with the comparison between physically inactive or active patients. Finally, weather variations and the use of portable devices such as home oxygen therapy and nocturnal NIV should be considered in future assessments of patients with COPD since these are factors which influence daily physical activity. Novel researches in patients with COPD may be undertaken, so that in the future it may be possible to determine which interventions aiming at increasing physical activity and decreasing sedentarism will be able to generate real health benefits to these patients.

Keywords: Pulmonary Disease. Chronic Obstructive. Motor activity. Mortality. Sedentary Lifestyle. Medical devices.

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LISTA DE ABREVIATURAS E SIGLAS

1RM	*One repetition maximum*
6MWT	*Six-minute walking test*
ACSM	*American College of Sports Medicine*
ADL	*Activities of daily living*
AFVD	Atividade física na vida diária
AHA	*American Heart Association*
AUC	*Area under the curve*
AVAPS	*Average volume-assured pressure support*
BMI	*Body mass index*
CI	*Confidence intervals*
COPD	*Chronic obstructive pulmonary disease*
CPET	*Cardiopulmonary exercise testing*
CRF	*Chronic respiratory disease*
CRF	*Chronic respiratory failure*
CVF	Capacidade vital forçada
DPOC	Doença Pulmonar Obstrutiva Crônica
ERS	*European Respiratory Society*
GOLD	*Global Initiative for Obstructive Lung Disease*
FFM	*Fat-free mass*
FFMI	*Fat-free mass index*
FEV_1	*Forced expiratory volume in the first second*
FVC	*Forced vital capacity*
HR	*Hazard ratio*
HRQL	*Heath related quality of life*
LCADL	*London Chest Activity of Daily Living questionnaire*
LO	*Liquid oxygen*
LTOT	*Long Term Oxygen Therapy*
MEP	*Maximum expiratory pressures*
MET	Equivalente Metabólico
MET	*Metabolic Equivalent of Task*
MIP	*Maximum inspiratory pressures*
MRC	*Medical Research Council (MRC)*

MVPA	*Moderate-vigorous physical activity*
NIV	*Non-invasive ventilation*
OC	*Oxygen concentrator*
OMS	Organização Mundial da Saúde
PAL	*Physical Activity Level*
PaO_2	*Partial pressure of arterial oxygen*
$PaCO_2$	*Partial pressure of arterial carbon dioxide*
PFSDQ-M	*Pulmonary Functional Status and Dyspnea Questionnaire-Modified*
PS	*Pressure support*
Q	Quartis
RCT	*Randomized clinical trial*
SGRQ	*Saint George Respiratory Questionnaire*
ST	*Sedentary Time*
TC6min	Teste da Caminhada de 6 minutos
UMV	Unidades de magnitude de vetor
VEF_1	Volume expiratório forçado no primeiro segundo
VNI	Ventilação não invasiva
VMU	*Vetor magnitude units*

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1 INTRODUÇÃO

Estima-se que a população mundial atingiu um recorde de 7,3 bilhões no ano de 2015, e com isso, o aumento das doenças crônicas associadas à idade e ao tabaco aumentaram ainda mais[1]. O tabagismo é o principal fator de risco para desenvolver a doença pulmonar obstrutiva crônica (DPOC)[2,3], e mais do que previamente reconhecido, atualmente sabe-se que até 50% dos tabagistas de longa data desenvolvem a doença[4].

De acordo com estimativas da Organização Mundial da Saúde (OMS), atualmente a DPOC é considerada a quarta principal causa de morte no mundo, e provavelmente ocupará a terceira posição dentro dos próximos anos[5]. Cerca de 65 milhões de pessoas apresentam DPOC de moderada a grave no mundo. No entanto, acredita-se que existe uma subestimação nesses dados, visto que a maioria das informações sobre a prevalência, morbidade e mortalidade da DPOC são provenientes de países de alta renda e sabe-se que quase 90% das mortes por DPOC ocorrem em países de baixa e média renda[5].

A DPOC é uma doença usualmente progressiva, na qual os sintomas frequentemente relatados pelos pacientes são dispneia e/ou fadiga[2]. Esses pacientes apresentam limitação para realizar exercício físico, e muitas vezes a realização das simples atividades de vida diária também são comprometidas. O nível de atividade física na vida diária (AFVD) dos pacientes com DPOC é marcadamente reduzido quando comparado com idosos sem a doença[6,7], e, além disso, a função muscular e a qualidade de vida desses pacientes também são reconhecidamente prejudicadas[8].

Embora a DPOC ainda não tenha cura, estratégias de tratamento para esses pacientes tem sido amplamente estudadas. Atualmente sabe-se que a reabilitação pulmonar, uma intervenção abrangente baseada em cuidadosa avaliação e terapias direcionadas ao paciente, incluindo treinamento físico, é amplamente indicada como opção terapêutica por aumentar a capacidade de exercício, força muscular, qualidade de vida e reduzir a sensação de dispneia dos portadores da doença[9,10]. No entanto, o padrão de comportamento inativo desses pacientes sofre pouca ou nenhuma alteração com a reabilitação pulmonar tradicional, ou seja, como aplicada na maioria dos centros de tratamento[10,11].

Em 2011, constatou-se que o nível de AFVD dos pacientes com DPOC é o principal preditor independente de mortalidade por todas as causas[12]. Desde então, um tópico de discussão crescente na literatura é a atividade física realizada na vida diária e o comportmento sedentário que estes pacientes apresentam. Instalou-se no mundo científico uma busca incessante por métodos acurados capazes de identificar os pacientes fisicamente inativos, e, consequentemente, com maior risco de morte. Além disso, pesquisas sobre os diversos fatores que impactam na AFVD dos pacientes com DPOC são amplamente visadas, visto que as estratégias para aumentar a AFVD desses pacientes não estão bem estabelecidas.

Em 2014, a *European Respiratory Society* (ERS) publicou um importante documento que reúne as principais evidências até o momento sobre a AFVD de pacientes com DPOC[13]. Apesar da crescente relevância de aspectos da AFVD no mundo científico e na rotina clínica, muitas lacunas sobre este tema são vigentes na literatura atual e perguntas importantes precisam ser respondidas com base em evidências sólidas.

A presente tese de doutorado foi desenvolvida com o intuito de contribuir com evidências científicas relacionadas à AFVD em pacientes com DPOC. Quatro estudos foram desenvolvidos, sendo 3 artigos originais e um artigo de revisão de literatura.

2 REVISÃO DE LITERATURA – CONTEXTUALIZAÇÃO

2.1 DOENÇA PULMONAR OBSTRUTIVA CRÔNICA (DPOC)

A DPOC é caracterizada por uma limitação persistente ao fluxo aéreo que é usualmente progressiva e associada a um aumento crônico da resposta inflamatória das vias aéreas e dos pulmões às partículas nocivas ou aos gases[2]. De acordo com estimativas da OMS, atualmente a DPOC é considerada a quarta principal causa de morte no mundo, e provavelmente ocupará a terceira posição dentro dos próximos anos[5].

O tabagismo é a principal causa da DPOC e cerca de 80% dos pacientes que são diagnosticados com a doença já foram ou ainda são fumantes de forma ativa ou passiva. Uma pequena porcentagem de não-fumantes também são acometidos pela DPOC por diversas outras causas como deficiência da alfa-1 antitripsina, poluição do ar, exposição ocupacional a poeiras, asma ou infecções respiratórias na infância, entre outras[14]. Dispneia, tosse e acúmulo de secreção nas vias aéreas são sintomas característicos na vida diária dos pacientes com DPOC[2] e o diagnóstico clínico é comumente realizado em conjunto com a história clínica do paciente. No entanto, a realização de espirometria é atualmente recomendada para confirmar o diagnóstico, devendo os pacientes apresentarem uma relação entre o Volume Expiratório Forçado no Primeiro Segundo e a Capacidade Vital Forçada (VEF_1 / CVF) menor que 0,70 após o uso de medicação broncodilatadora, de acordo com diretrizes internacionais [2,15,16].

Apesar da definição da doença estar associada ao acometimento das vias aéreas e dos pacientes apresentarem limitações na ventilação pulmonar e nas trocas gasosas, a DPOC apresenta importantes manifestações sistêmicas[3,17]. Sabe-se, por exemplo, que os pacientes com DPOC podem apresentar disfunção cardíaca, especialmente sobrecarga do ventrículo direito[18]. Outra manifestação extrapulmonar comum é a disfunção muscular periférica, que pode ser atribuída à inflamação sistêmica, ao uso de corticosteróides, ao estresse oxidativo e à redução da massa muscular[19]. O nível de AFVD dos pacientes com DPOC é marcadamente reduzido quando comparado com idosos sem a doença[6,7]. Além disso, pacientes com DPOC também costumam apresentar anormalidades na composição corporal, como perda de peso e depleção de massa magra[20].

Todas essas manifestações sistêmicas da doença em conjunto com o comprometimento respiratório contribuem para a sensação de dispneia e de fadiga, que são os sintomas frequentemente relatados pelos pacientes durante a realização de atividades físicas, ou mesmo em repouso, nos casos mais graves[2,21]. Esses sintomas são limitantes do exercício físico nesses pacientes e quando associados à inatividade física, caracteriza-se o espiral negativo da doença[6].

2.2 SEDENTARISMO E ATIVIDADE FÍSICA NA VIDA DIÁRIA

Atualmente, diversas evidências científicas indicam que o comportamento sedentário resulta em efeitos deletérios na saúde da população em geral, o que se difere daqueles efeitos negativos atribuídos à falta da realização de atividade física moderada a vigorosa[22,23]. Evidências científicas sugerem que indivíduos sedentários apresentam redução da densidade mineral óssea, maior risco de doenças cardiovasculares e metabólicas com aumento dos triglicerídios, redução do colesterol HDL (*high-density lipoprotein)* e redução da sensibilidade à insulina. Além disso, o comportamento sedentário está associado à obesidade e, consequentemente, à menor satisfação corporal[22]. Está cientificamente comprovado que a realização de atividade física regular reduz o risco de doenças cardiovasculares, diabetes tipo II, acidente vascular encefálico e algumas formas de câncer. Adicionalmente, evidências sugerem que ocorre uma redução da pressão arterial e do risco de quedas em indivíduos que atingem as recomendações de atividade física, o que também previne o ganho de peso e a instalação de desordens psicológicas leves e moderadas[23].

De fato, os termos "sedentarismo" e "inatividade física" são comumente e erroneamente considerados como sinônimos. No entanto, esses termos possuem significados diferentes, visto que indivíduos podem atingir altos níveis de atividade física moderada a vigorosa e ainda exibirem um padrão de comportamento sedentário[22,24-26]. Um tipo de comportamento não necessariamente substitui o outro. Por isso, alguns termos chave estão definidos abaixo.

2.2.1 Definições

O quadro 1 descreve os principais termos relacionados ao sedentarismo e à atividade física, bem como suas subcategorias.

Quadro 1: Definições de termos chave relacionados à atividade física e ao sedentarismo

Atividade Física	Qualquer movimento corporal gerado pelos músculos esqueléticos que resultam em gasto energético acima dos níveis de repouso[27].
Exercício Físico	Uma subcategoria de atividade física que é planejada, estruturada e repetitiva. É realizada de forma proposital e relaciona-se com o desempenho físico e sua melhora[27].
Atividade Física na Vida Diária (AFVD)	Totalidade de movimentos voluntários (*i.e* atividade física) realizados pelos músculos esqueléticos no dia a dia[28].
Atividade de Vida Diária (AVD)	Outra subcategoria de atividade física. Refere-se às atividades rotineiras do indivíduo e são geralmente relacionadas às atividades domésticas, de cuidados pessoais, lazer ou trabalho[13,29].
Sedentarismo	Conjunto de atividades realizadas em intensidade menor que 1,5 equivalente metabólico (MET) em posturas sentadas ou reclinadas[25,30,31].
Indivíduo Fisicamente Ativo / Suficientemente Ativo	Indivíduo que atinge as recomendações estabelecidas de realização de atividade física[23] (geralmente acima de um ponto de corte pautado em tempo mínimo de atividade física moderada a vigorosa)[22].
Indivíduo Fisicamente Inativo / Insuficientemente Ativo	Indivíduo que não atinge as recomendações estabelecidas de realização de atividade física[23] (geralmente abaixo de um ponto de corte pautado em tempo mínimo de atividade física moderada a vigorosa)[22].
Indivíduo sedentário	Indivíduo que apresenta pouco movimento físico e baixo gasto energético no dia-a-dia (i.e., <1,5 MET) com comportamentos caracterizados por movimento mínimo, baixo gasto energético e descanso[22].

Existe um espectro de gasto energético associado com o comportamento sedentário ou com os diferentes tipos de atividade física de acordo com a intensidade. Neste contexto, o equivalente metabólico (MET) é utilizado para quantificar o gasto energético das atividades, e 1 MET corresponde à taxa metabólica basal, ou seja, 1 MET equivale ao consumo de oxigênio de 3,5 $ml.kg^{-1}.min^{-1}$. que corresponde ao gasto de energético de repouso do indivíduo[25]. Uma corrida em alta velocidade pode requerer pelo menos 8 METs, e esta atividade é classificada, portanto, como atividade de intensidade vigorosa. A figura 1 exemplifica algumas atividades de acordo com o gasto energético requerido. De outro modo, os comportamentos ou atividades que são realizados sentados ou em postura reclinada (com exceção de dormir) e requerem baixo gasto energético (≤1,5 MET) são comumente classificados como comportamento sedentário[25,30,31].

Figura 1: Exemplos de atividades para cada equivalente metabólico (MET) de acordo com o compêndio de atividade física[32]

2.2.2 Sedentarismo, Atividade Física na Vida Diária e Mortalidade na DPOC

Sabe-se que o comportamento sedentário e a não realização de atividade física regular de acordo com as recomentações propostas pelo *American College of Sports Medicine* (ACSM) geram efeitos deletérios para a saúde da população em geral[22,23]. Pacientes com DPOC tipicamente realizam pouca atividade física de intensidade moderada a vigorosa na vida diária[6,25]; além disso, o comportamento sedentário é característico nesses pacientes[25,33]. Recentemente, estudos identificaram que o reduzido nível de AFVD é preditor independente de mortalidade nos pacientes com DPOC[12,34-36]. Em um estudo de coorte, Waschki e colaboradores[12] quantificaram a AFVD por meio de uma variável conhecida como *Physical Activity Level* (PAL) *index*, que corresponde ao gasto energético total dividido pela taxa metabólica basal. Eles concluíram que a avaliação objetiva da atividade física, nesse caso representada pelo PAL, é o preditor independente mais forte de mortalidade por todas as causas em pacientes com DPOC. Adicionalmente, Garcia-Rio e colaboradores[35] classificaram os pacientes com DPOC de acordo com os quartis (Q) de unidades de magnitude de vetor (UMV) (i.e. Q1: <130 UMV; Q2: 130-200 UMV; Q3: 200-270 UMV; Q4 >270 UMV) e concluíram que a redução da atividade física também estava associada com o maior risco de mortalidade. Embora ambos estudos sejam indiscutivelmente relevantes para a literatura científica, a diferenciação do comportamento sedentário do comportamento inativo é importante.

De fato, indivíduos podem atingir altos níveis de atividade física moderada a vigorosa e ainda exibirem um padrão de comportamento sedentário[22,24-26] e a investigação do sedentarismo avaliado objetivamente com a mortalidade dos pacientes com DPOC ainda não foi realizada. Até o presente momento, apenas um estudo realizado no Japão, que avaliou o tempo assistindo televisão por dia de forma auto-relatada, investigou se havia associação do comportamento sedentário com a mortalidade de pacientes com DPOC[37]. Após um seguimento de 19 anos, o estudo mostrou que os homens que assistiam televisão por tempo maior que quatro horas por dia apresentavam maior chance de morrer do que aqueles que assistiam televisão por tempo menor que 2 horas por dia[37]. Portanto, apesar de estar bem estabelecido que existe uma associação entre AFVD e mortalidade nos pacientes com DPOC e entre sedentarismo e mortalidade na população em geral[24,38], uma associação semelhante entre sedentarismo e mortalidade ainda não foi descrita especificamente em pacientes com DPOC.

2.2.3 Formas de Avaliar Sedentarismo e Atividade Física na Vida Diária

Devido à estreita associação entre o nível reduzido de atividade física dos pacientes com DPOC com desfechos negativos da doença[12,39-41], muitos estudos foram desenvolvidos para determinar como quantificar de forma acurada o nível de AFVD nessa população, identificando monitores de atividade física acurados e métodos de avaliação confiáveis, assim como padronizando as análises[42-44].

A quantificação do sedentarismo e da AFVD pode ser realizada por meio de questionários, medidas do gasto energético, observação direta e utilização de sensores de movimento[22,25,45]. O uso de questionários, apesar de ser o método mais simples, barato e fácil, não é tão acurado em nível individual, e por isso outras formas de quantificar objetivamente o perfil de atividade física tem sido recomendadas[45]. A mensuração de gasto energético pode ser realizada por meio da água duplamente marcada[46,47] e calorimetria (direta ou indireta)[47,48], que apesar de serem métodos “padrão ouro”, são relativamente caros e exigem treinamento específico devido à sua manipulação complexa, dificultando sua aplicabilidade. A observação direta é a que reflete da maneira mais próxima do real o comportamento sedentário e o nível de AFVD dos indivíduos; porém, este método exige longo tempo para sua realização e invade a privacidade do paciente, o que também dificulta sua aplicação prática[45]. Portanto, é cada vez maior o interesse dos pesquisadores em sensores de movimento, que são instrumentos capazes de detectar os movimentos corporais, e quantificar objetivamente o nível de AFVD.

Atualmente, existem várias opções de sensores de movimentos no mercado, e eles são classificados basicamente em dois tipos: acelerômetros ou pedômetros. Os acelerômetros são instrumentos tecnologicamente mais avançados que os pedômetros por serem capazes de registrar além da quantidade (*e.g.* número de passos), a intensidade dos movimentos durante longos períodos de tempo (*e.g.* gasto energético de cada atividade)[28]. Acelerômetros são preferíveis para a avaliação de pacientes com doenças crônicas que caminham mais lentamente, pois pedômetros podem ser inacurados nessa população[44].

Alguns monitores de atividade física são validados em pacientes com DPOC[42,49-51]. Os dispositivos tecnologicamente mais avançados normalmente possuem um acelerômetro triaxial interno. Dentre as diversas opções disponíveis no mercado, dois exemplos de monitores de atividade física amplamente utilizados e mais acurados para avaliar pacientes com DPOC são o *Dynaport MoveMonitor* (McRoberts, Holanda) e o *SenseWear Armband* (Body Media, EUA)[51]. A correta utilização do *Dynaport* posicionado na região posterior da cintura do paciente (Figura 2A), viabiliza a detecção de cada movimento realizado durante o dia de avaliação e possibilita estimar, como principal variável, o tempo gasto em diferentes posturas e atividades, por exemplo o tempo deitado, sentado, em pé e andando, entre outros. Desta forma, identifica-se o tempo sedentário ou o tempo em atividade de acordo com as posturas adotadas pelos indivíduos. Também é possível identificar qual a intensidade e/ou aceleração dos movimentos realizados durante o dia. Esse método de avaliação é validado e normalmente bem aceito pelos pacientes com DPOC[42].

De outro modo, o *SenseWear Armband* é um monitor de atividade física utilizado no braço esquerdo do indivíduo (Figura 2B). Este dispositivo possui sensores fisiológicos que detectam a resistência galvânica da pele e, em conjunto com as medidas de um acelerômetro triaxial, estimam de forma acurada o gasto energético e o tempo gasto em atividades de diferentes intensidades (i.e. MET) nos pacientes com DPOC[49,50,52], dentre outras variáveis. Por exemplo, é possível identificar o tempo gasto pelo indivíduo em atividade de intensidade no mínimo moderada ao longo do dia. Normalmente, solicita-se que o paciente utilize o monitor de atividade física durante todo o período acordado de pelo menos 2 dias rotineiros da semana[6,13].

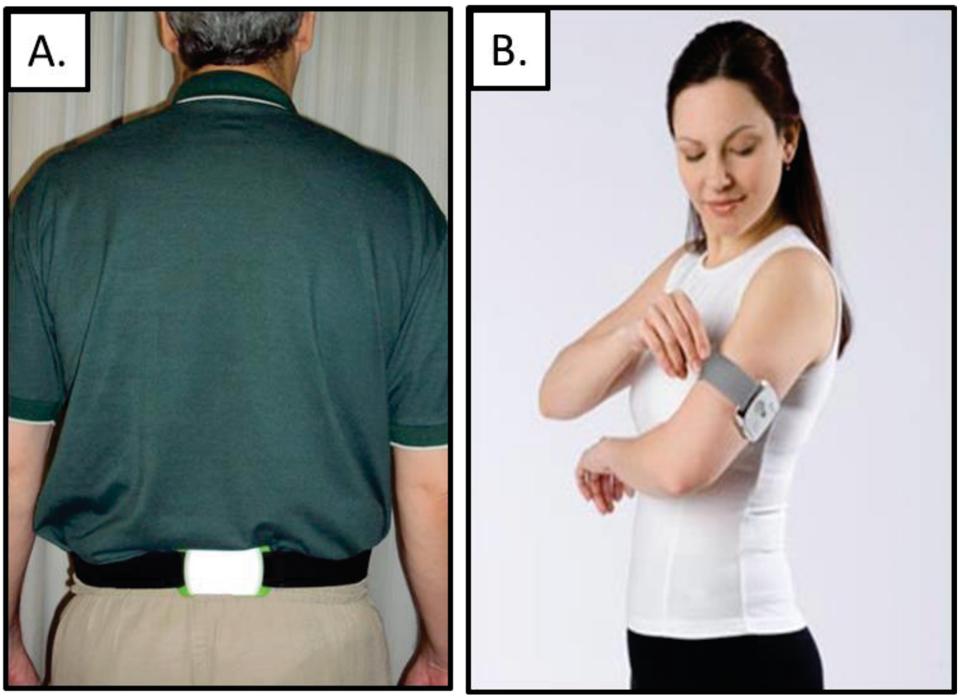

Figura 2: Monitores de atividade física: A) *Dynaport MoveMonitor*; B) *SenseWear Armband*.

2.2.4 Como identificar pacientes com DPOC sedentários, ativos e inativos?

Apesar de estarem disponíveis no mercado monitores de atividade física tecnologicamente avançados que são capazes de mensurar detalhadamente a quantidade e a intensidade de atividade física realizada pelo indivíduo, os pontos de corte utilizados para identificar atividade leve, moderada ou vigorosa não estão bem estabelecidos. O mesmo ocorre para o comportamento sedentário. Muitos autores utilizam valores fixos para definir a intensidade da atividade (Figura 3). No entanto esses valores são amplamente questionados, principalmente na população com diagnóstico de DPOC que sabidamente apresenta um padrão de comportamento inativo e que, em casos mais graves, pode apresentar um gasto energético aumentado devido à maior demanda de oxigênio durante a respiração e à ineficiência da mecânica ventilatória[53].

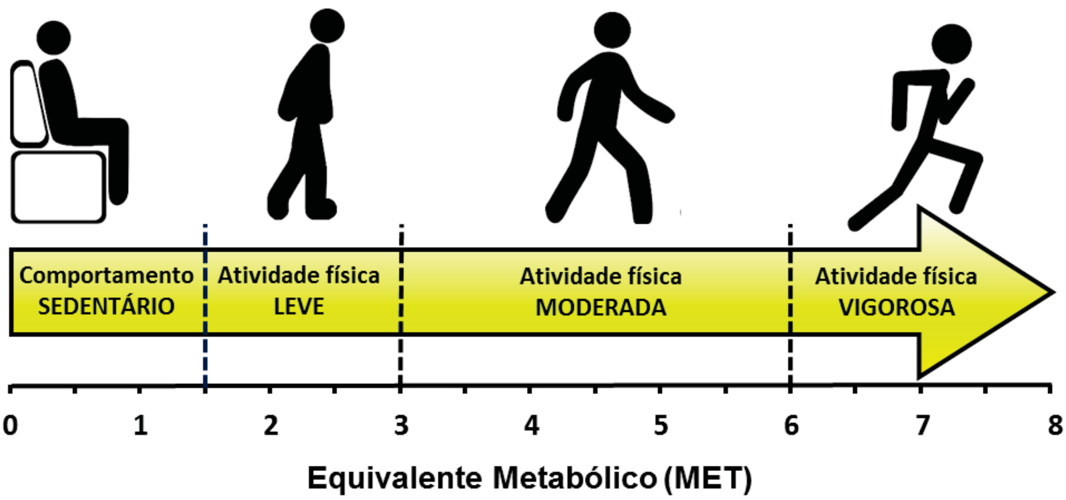

Figura 3. Pontos de corte fixos de equivalente metabólico (MET)**.** Adaptado de http://www.sedentarybehaviour.org/what-is-sedentary-behaviour.

Apesar de algumas referências sugerirem que 1,5 MET deve ser o ponto de corte para identificar comportamento sedentário[25,30,31], alguns autores questionam esse valor. Um estudo realizado com adultos saudáveis que examinou o ponto de corte de 1,5 MET como definição de comportamento sedentário em contraste com a calorimetria indireta, concluiu que algumas atividades comuns realizadas na posição sentada requeriam um gasto energético, em MET, acima deste ponto de corte[54]. Estes achados questionam a atual definição de sedentarismo e sugerem que atividades comuns realizadas na posição sentada são definidas como não sedentárias em uma grande proporção da população. Da mesma forma, um estudo prévio realizado na Austrália com pacientes com DPOC[55], utilizou 2 METs como limite inferior do ponto de corte para identificar atividades leves visto que 2 METs já é considerado o mínimo de intensidade nas atividades realizadas na postura em pé, como estender roupas e preparar refeições[32]. Portanto, é possível questionar se o uso do ponto de corte <1,5 MET reflete comportamento sedentário em pacientes com DPOC ou se um ponto de corte mais alto (*i.e* 2 METs) é mais indicado.

Essa falta de padronização também ocorre com relação a identificação dos pacientes fisicamente ativos ou inativos. De acordo com a ACSM para ser considerado fisicamente ativo, um indivíduo deve realizar no mínimo 30 minutos de atividade física moderada a vigorosa em cinco ou mais dias na semana, sendo que esses 30 minutos devem ser realizados continuamente ou em blocos de pelo menos 10 minutos[23]. Mais recentemente, um estudo realizado por van Remoortel e colaboradores[56] considerou apenas os blocos de atividade física de no mínimo 10 minutos sem intervalos para detectar se o indivíduo atinge a recomendação de 30 minutos de atividade física de intensidade no mínimo moderada[23], e constatou que os indivíduos fisicamente ativos são os que realizam pelo menos 80 minutos de atividade física com intensidade ≥ 3 METs sem considerar os intervalos de 10 minutos contínuos.

Além disso, o ponto de corte em METs para identificar atividade física de intensidade no mínimo moderada também pode variar. Algumas definições de pontos de corte de gasto energético (em METs) para identificar atividade física de intensidade no mínimo moderada divergem na literatura, e alguns exemplos estão descritos abaixo de acordo com cada recomendação.

- ≥ 3,0 METs (para todas as idades) → *American College of Sports Medicine and American Heart Association* (2007)[57]
- ≥ 3,0 METs (≤ 65 anos); e ≥ 50% VO_2 de reserva (METs) (>65 anos) → *American College of Sports Medicine and American Heart Association reccomendation* (para idosos) (2007)[58]
- ≥ 4,0 METs (≤65 anos); e ≥ 3,2 METs (>65 anos) → *American College of Sports Medicine* (2011)[23]

Adicionalmente, Demeyer e colaboradores identificaram que o ponto de corte de 2 METs é mais sensível do que o ponto de corte de 3 METs para avaliar atividade física moderada nos pacientes com DPOC[43]. Os autores não sugerem a mudança da definição, mas sim a utilização desse ponto de corte intermediário (2 METs) para detectar o tempo ativo quando os estudos forem realizados com pacientes com DPOC. Devido ao comprometimento dos pacientes, o ponto de corte de 3 METs pode ser muito rigoroso e dificilmente atingido na vida diária. Essa falta de padronização dificulta o entendimento dos estudos já realizados e prejudica a reprodutibilidade dos resultados em estudos futuros.

2.3 Fatores que Impactam na Atividade Física na Vida Diária de Pacientes com DPOC

A quantidade de atividade física que o paciente com DPOC realiza na vida diária está associada com diversos fatores[59]. O fato de ser mais ativo fisicamente pode estar relacionado, por exemplo, com uma maior capacidade de exercício; no entanto, não é possível afirmar que os indivíduos com maior capacidade de exercício serão necessariamente mais ativos na vida diária[6]. O mesmo acontece com todos os outros fatores associados com a AFVD dos pacientes com DPOC. Ainda não existe uma característica, ou nem mesmo um conjunto delas, que explica completamente o padrão de atividade física desses pacientes.

Sabe-se que fatores físicos, ambientais, psicológicos e sociais podem influenciar o padrão de atividade física de um indivíduo[60]. Considerando que a inatividade física apresenta efeitos deletérios sobre a saúde da população em geral, e que isso se acentua nos pacientes com DPOC, uma ampla investigação sobre os fatores que impactam na AFVD desses pacientes se instalou no mundo científico desse campo de pesquisa[13,34]. Uma revisão sistemática recente que investigou os fatores determinantes e os desfechos associados com a AFVD de pacientes com DPOC incluiu 86 estudos com diversas variáveis[34]. A figura 4 exemplifica os principais fatores que já foram identificados como associados com a AFVD de pacientes com DPOC.

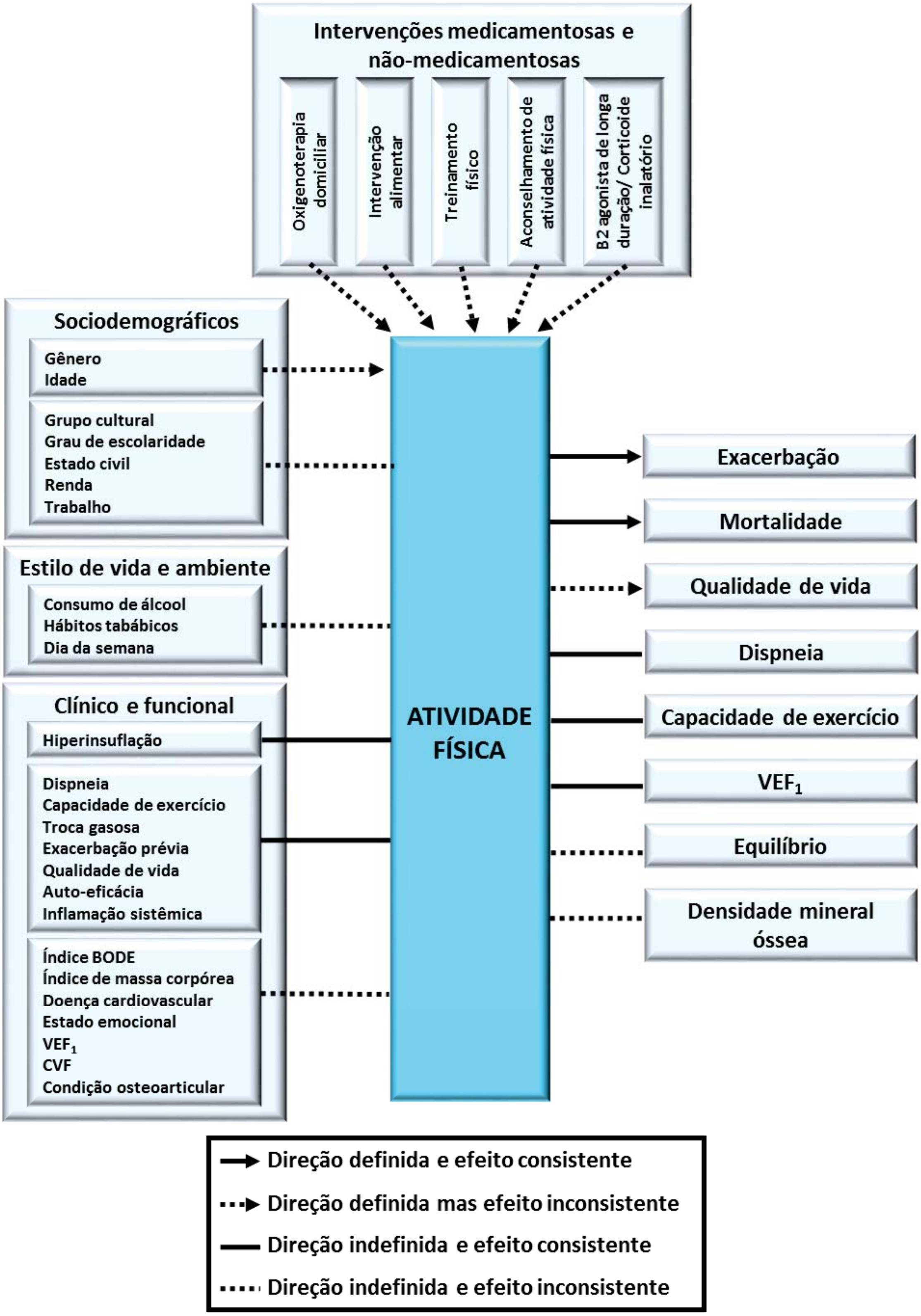

Figura 4. Mapa conceitual da atividade física na vida diária de pacientes com DPOC (adaptado com autorização dos autores)[34]. VEF_1: volume expiratório forçado no primeiro segundo; CVF: capacidade vital forçada.

No entanto, o impacto de alguns fatores sobre a AFVD de pacientes com DPOC ainda não está bem estabelecido. Um dos fatores é a influência das condições climáticas. A literatura sugere que a sazonalidade influencia na AFVD de pacientes com DPOC[59,61-63]; no entanto, poucas evidências levam em consideração as variações naturais do nível de atividade física decorrentes das diferentes situações climáticas enfrentadas pelos pacientes ao longo do ano[63,64]. Outro tópico de interesse no tema que também não foi estudado em profundidade, é se a utilização de equipamentos portáteis, como a oxigenoterapia domiciliar ou a ventilação não-invasiva (VNI) influencia no aumento ou redução do nível de AFVD, e neste caso, de pacientes mais graves. Desta forma, o impacto da sazonalidade e da utilização de equipamentos portáteis na AFVD merecem atenção especial da literatura científica.

2.3.1 Atividade Física na Vida Diária e Sazonalidade

Atualmente, apesar dos diversos monitores de atividade física disponíveis no mercado para quantificar de forma acurada a AFVD, a influência das condições climáticas na atividade física realizada na vida diária dos pacientes com DPOC ainda não foi investigada objetivamente com a profundidade necessária. Até o presente momento, a grande maioria dos estudos que avaliam o nível de AFVD em pacientes com DPOC se restringe a uma avaliação transversal[59,61], que não leva em consideração as variações naturais do nível de atividade física decorrentes das diferentes situações climáticas enfrentadas pelos pacientes ao longo do ano. Apesar de estudos prévios com indivíduos adultos e saudáveis sugerirem que na maioria dos casos existe uma redução da atividade física no inverno, resultados conflitantes ainda são encontrados[65-68], especialmente em regiões com menor variação climática ao longo do ano, onde as variações sazonais apresentam magnitude insuficiente para impactar na AFVD.

Um estudo em indivíduos adultos saudáveis realizado em uma cidade com pouca variação de condições climáticas ao longo do ano (Perth, Austrália) mostrou que a discreta variação climática observada naquela região não teve impacto significativo na atividade física diária dos indivíduos ao longo do ano, gerando apenas pequenas variações no seu nível de atividade física[65]. Hipotetiza-se, portanto, que as características geográficas e meteorológicas específicas de cada região podem influenciar no padrão de atividade física dos indivíduos.

Até o presente momento, os dois únicos estudos que avaliaram os efeitos da sazonalidade (i.e. relativo a uma época do ano) e/ou variáveis climáticas (i.e. condições atmosféricas que caracterizam uma região) na AFVD dos pacientes com DPOC foram realizados na Inglaterra onde o contraste climático entre as estações do ano é mais acentuado[63,64]. O estudo de Sewell e colaboradores[63] realizado em Leicester, aponta para o fato de que o nível de atividade física de pacientes com DPOC é diretamente afetado pela estação do ano em que esse nível é avaliado. O estudo incluiu diferentes grupos de pacientes com DPOC avaliados nas quatro estações do ano, e mostrou que pacientes avaliados no inverno são significativamente menos ativos na vida diária do que pacientes com a mesma gravidade da doença porém avaliados em qualquer uma das outras três estações. Posteriormente, o estudo de Alahmari e colaboradores realizado em Londres[64], acrescentou a informação de que a inatividade física dos pacientes com DPOC sofre influências da baixa temperatura, umidade e quantidade de luz durante o dia ao longo do ano. No entanto, com as informações disponíveis na literatura atual, é impossível saber se as variações climáticas decorrentes da mudança de estações do ano geram diferenças no nível de atividade física diária em pacientes com DPOC de cidades e países com situações climatológicas contrastantes.

2.3.2 Atividade Física na Vida Diária e Equipamentos Portáteis

Outro tópico pouco investigado e que também abrange aspectos relacionados à atividade física dos pacientes com DPOC é a utilização de equipamentos portáteis para assistência ventilatória. O crescente avanço tecnológico disponibilizou no mercado alguns equipamentos portáteis capazes de fornecer oxigênio ou até mesmo ventilação não invasiva (VNI) domiciliar.

Sabe-se que alguns pacientes com indicação de oxigenoterapia domiciliar apresentam um padrão de atividade física prejudicado quando comparado com pacientes não hipoxêmicos[69,70]. Acredita-se que além da gravidade da doença, esta redução do nível de AFVD deve-se ao peso e ao tamanho do equipamento que fornece oxigênio ao paciente, prejudicando a sua mobilidade em casa. O documento oficial da ERS[13] que reúne as principais evidências sobre a AFVD nos pacientes com DPOC, constata que a "oxigenoterapia aumenta a tolerância ao exercício nos pacientes hipoxêmicos com DPOC, mas não está claro se o nível de atividade física desses pacientes também aumenta".

Um ensaio clínico aleatorizado que substituiu equipamentos pesados que forneciam oxigênio domiciliar por equipamentos mais leves para pacientes com DPOC não detectou aumento no nível de AFVD em um *follow-up* de 6 meses[71]. No entanto, este estudo foi realizado com uma amostra relativamente pequena e, portanto, novos estudos são necessários para identificar quais os reais benefícios da utilização de equipamentos portáteis sobre a AFVD desses pacientes.

A mesma dúvida persiste com relação à utilização de VNI domiciliar. Até o presente momento, não foi realizado nenhum estudo de revisão de literatura considerando os efeitos da VNI sobre a AFVD dos pacientes com falência ventilatória crônica. Poucos estudos utilizaram a AFVD como desfecho da utilização de VNI.

No *statement* de atividade física para pacientes com DPOC[13], bem como na revisão sistemática mais recente disponível sobre os fatores determinantes e desfechos que impactam na AFVD de pacientes com DPOC[34], a utilização de VNI não foi considerada como desfecho. Portanto, pesquisas precisam ser realizadas nessa área para investigar quais os efeitos da utilização de equipamentos portáteis sobre a AFVD.

A presente tese de doutorado hipotetiza encontrar associação entre mortalidade e sedentarismo nos pacientes com DPOC bem como evidenciar que indivíduos fisicamente inativos apresentam maior comprometimento da saúde independente do ponto de corte utilizado para esta classificação. Além disso, hipotetiza-se encontrar que fatores como as variações no clima e o uso de equipamentos portáteis como a oxigenoterapia domiciliar e a ventilação não invasiva noturna influenciam a atividade física diária. Como previamente mencionado, esta tese de doutorado tem o objetivo de contribuir com evidências científicas relacionadas à AFVD em pacientes com DPOC nas diversas lacunas identificadas nesta revisão da literatura. Questões relativas à mortalidade, perfil dos pacientes e impacto da variação sazonal e do uso de equipamentos portáteis sobre a AFVD de pacientes com DPOC foram investigadas nesta tese. Para isso, quatro estudos foram desenvolvidos, sendo 3 artigos originais e um artigo de revisão de literatura, que são incluídos a seguir.

3 ARTIGO 1

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HOW MUCH TIME SPENT PER DAY IN SEDENTARY BEHAVIOR INCREASES MORTALITY RISK IN PATIENTS WITH COPD?

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ABSTRACT

Purpose: The terms "sedentary behaviour" and "physical inactivity" have been confusingly mixed. Although the association between physical inactivity and mortality has been previously shown in patients with chronic obstructive pulmonary disease (COPD), this association was not yet investigated concerning sedentarism. This study aims to propose a cut-off point for sedentarism in patients with COPD and to investigate its association with mortality.

Methods: In this retrospective cohort study, sedentary behaviour was assessed with two activity monitors (DynaPort and Sensewear armband) in 101 patients with COPD from 2006 to 2011. Vital status was then ascertained in 2015. Cut-off points for sedentarism and their respective prognostic values were investigated for the following six variables: average of metabolic equivalent task [MET]/day and time spent/day lying, sitting, lying+sitting and in activities requiring <1.5MET and <2MET.

Results: Forty-one patients (41%) died over a median (25-75%IQR) follow-up period of 62(43-88) months. After adjusting for potential confounders in the Cox regression model, the strongest independent cut off for predicting mortality was ≥8:30 hours/day spent in sedentary activities <1.5MET (Area Under the Curve: 0.76; Hazard Ratio [HR] 4.09; 95%CI 1.90-8.78); *P*<0.0001). Each hour/day spent <1.5MET increases mortality risk by 42% (HR 1.42; 95%CI 1.15-1.76; *P*=0.001).

Conclusions: Mortality is higher in patients with COPD who spend more than 8:30 hours/day in activities requiring <1.5MET. Each hour/day spent <1.5MET increases mortality risk by 42%. These findings may open room for future studies aiming at decreasing sedentary time as a promising strategy to reduce mortality risk in patients with COPD.

Key words: Pulmonary Disease, Chronic Obstructive; Sedentary Lifestyle; Motor Activity; Mortality; Longitudinal Studies; Survival Analysis.

CONDENSED ABSTRACT

Sedentary behaviour was assessed with two activity monitors in 101 patients with COPD in this retrospective cohort study. It was found that mortality risk was 3.54 times higher in those patients who spent more than 8:30 hours/day in activities requiring <1.5MET, and each hour/day spent <1.5MET increases mortality risk by 42%.

INTRODUCTION

Reduced level of physical activity in daily life (PADL) is an important predictor of mortality in patients with chronic obstructive pulmonary disease (COPD)(1-4). Increased sedentary behaviour is also associated with deleterious health effects, which differ from those that can be attributed to reduced PADL (or lack of moderate-to-vigorous physical activity [MVPA])(5). In fact, the terms "sedentary behaviour" and "physical inactivity" have been confusingly mixed. However, these are different outcomes, since it is possible for an individual to accumulate large amounts of both MVPA and sedentary behaviour throughout the same day(5-8).

The differentiation between these terms has recently gain interest(5, 7, 9, 10). The two most common definitions of sedentarism are as follows: one based solely on low intensity (activities performed at an intensity <1.5 metabolic equivalents [MET]); and another which combines low intensity (≤1.5 METs) with a large proportion of the day spent in the seated or reclined posture(11). In contrast, “inactive” term should be used “to describe those who are performing insufficient amounts of MVPA (i.e., not meeting specified physical activity guidelines)”(5, 7, 9).

Patients with COPD typically do very little activity at moderate or vigorous intensities(7, 12), and sedentary behaviour is predominant in their daily lives(7, 13). Previous studies have shown the association between physical activity profile with mortality among many other outcomes in these patients(1, 14-16). However, up to this moment there is no study in COPD which investigated the association between mortality and variables of sedentary behaviour (instead of variables of physical activity), according to the above mentioned definitions. In addition, there is no available cut-off points of objectively assessed variables of sedentarism which classify patients as sedentary or not, and investigating whether this classification impacts on mortality. Therefore, despite the well-known links between PADL and mortality in COPD and between sedentarism and mortality in the general population(6, 17), a similar link between sedentarism and mortality has not yet been clearly described in patients with COPD. Based on this, it was hypothesized that patients with COPD classified as sedentary would also present higher risk of mortality than non-sedentary patients. In order to investigate this hypothesis, the aims of this study were to propose a cut-off point for sedentarism in patients with COPD and to investigate its association with mortality.

METHODS

Sample and study design

This is a cohort retrospective study which used baseline data from a study previously published elsewhere by the present group(18). From May 2006 to July 2011, 102 patients with diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD)(19) gave written informed consent and were assessed at the Laboratory of Research in Respiratory Physiotherapy, State University of Londrina (Brazil). After baseline assessment, all patients were enrolled in a prospective interventional study(18) which investigated the effects of two different exercise programs performed during three months. However, in that study, no significant improvement in PADL was observed after these three months of rehabilitation, which indicates that this cohort was not strongly influenced by the effects of pulmonary rehabilitation on PADL, as previously shown(20). Furthermore, the groups of patients included in the two different exercise programs presented similar time to death when compared to each other and also with the group of drop-outs ($P>0.05$, data not shown), indicating that the recruitment method did not impact on the results.

Inclusion criteria for the present study were the same as those previously published(18) and the exclusion criterion was the absence of available baseline data. The analysis of mortality or survival for each subject included in the previous study was performed *a posteriori* on August 2015, as described below. The study was approved by the institutional research ethics committee (996.413).

Measurements

Sedentary Behaviour

Sedentarism variables and time spent in MVPA (i.e. >3METs) were assessed at the study entry, when all patients wore two activity monitors simultaneously over 2 weekdays (Tuesday and Wednesday) during 12 hours a day. The 2-day average was used for the analysis. Reliability of this assessment period (i.e., 2 days) was previously shown to be good in patients with COPD(12, 21). The two activity monitors were the multisensor *SenseWear armband* (BodyMedia; Pittsburgh, USA) which is worn on the upper-posterior region of the right arm and the triaxial *DynaPort MoveMonitor* (McRoberts, The Hague, The Netherlands) which is worn on the patient's waist. Both activity monitors have been validated for COPD(12, 22-24).

Six sedentarism variables were used in this study and they may be divided in three types: 1) three variables reflecting time spent/day in sedentary postures (lying time/day, sitting time/day and the sum of lying and sitting time (lying+sitting time/day)(5); 2) one variable reflecting intensity of performed activities during the day (average of MET/day)(25); and 3) two variables reflecting the combination of time and intensity (sedentary time spent/day in activities requiring <1.5 MET [ST/day<1.5MET] and <2 MET [ST/day<2MET] [since it has been suggested that the range of sedentarism could be extended to activities below 2.0 MET instead of 1.5 MET])(26)).

Mortality

Vital status was ascertained by telephone contact and officially confirmed by checking the dataset of the Center for Information on Mortality, which is the responsible organ for registering all death events in the municipality. These data were collected after formal authorization from the city's Health Secretary. Date of death was recorded (if it was the case), and survival time was defined as the time from the baseline assessment to the date of death or the last contact. The last day of follow-up was August 07, 2015. The outcome of this study was all-cause mortality.

Secondary outcomes

Lung function was assessed by spirometry according to international recommendations(27) and Brazilian reference values from Pereira et al(28) were used. Exercise capacity was evaluated by the 6-minute walking test (6MWT)(29), also considering the reference values from the Brazilian population(30). Dyspnea during activities of daily living was assessed with the modified Medical Research Council scale(31, 32). Antropometric characteristics such as height, weight and subsequent calculation of the body mass index (BMI) were objectively assessed and educational level was referred by all patients.

Statistical analysis

Shapiro-Wilk test was performed to analyse normality in data distribution. Results are shown as median (interquartile range 25-75%) or absolute and relative frequency (%). Patients were classified as survivors or non-survivors according to their vital status at the end of the follow-up period and differences between groups were investigated using unpaired T-test, Mann Whitney test or Chi-square test, as appropriate.

Receiver operating characteristics (ROC) curves were used to determine threshold values with the best sensitivity and specificity to predict mortality. Kaplan-Meier curves with the Log-Rank tests were performed to analyze the differences of survival over time according to the cut-off value of each sedentarism variable. Cox's proportional-hazard regressions estimated the survival probability of each sedentarism variable (univariate) and were adjusted (multivariate) for gender, age, BMI, educational level, FEV_1 (%predicted), 6MWT (%predicted) and time spend in MVPA, in accordance with univariate regressions and previous studies in COPD(15, 33). Estimated hazard-ratio (HR) and 95% confidence intervals (CI) were calculated after stratifying for each sedentarism threshold. Skewed variables were log-transformed to normalize their distribution. Statistical analyses were carried out using SPSS v.21 and GraphPad Prism 6.0, and significance level was set at $P<0.05$.

RESULTS

Baseline Characteristics

One subject was excluded from the study at baseline due to incomplete daily physical activity assessment, and therefore 101 patients with COPD were analyzed. Patient characteristics at baseline are shown in table 1. No patient classified as GOLD I (i.e. $FEV_1>80\%$ predicted) was included while 26% were GOLD II, 50% GOLD III and 24% GOLD IV.

Survivors and non-survivors

There was no loss concerning data from any patient in the follow-up analysis. Forty one (41%) of the patients died over a median (IQR25-75%)

follow-up period of 62(43-88) months. Table 1 also compares the characteristics of survivors and non-survivors. Patients who died were predominantly men, older and presented worse lung function and exercise capacity, although with similar educational level and dyspnea sensation during daily life. In addition, patients who died spent more time in sedentary activities than survivors as identified by four variables: lying+sitting time/day, ST/day<1.5MET; ST/day<2MET and the average of MET/day ($P<0.05$ for all). The same variables were associated with mortality in the univariate cox regression model ($P<0.05$ for all). The percentage of patients who reported at least one comorbidity was similar in both groups (80% from group survivors and 74% from group non-survivors; p=0.60). Furthermore, there was no difference in the number of comorbidities per patient between survivors (1 [1-2]) and non-survivors (2 [0-4], $P=0.35$) (median [Q1-Q3]).

Sedentarism cut-off points and mortality

Table 2 presents the best threshold values of the six sedentarism variables to predict mortality in patients with COPD over the follow-up period. The highest value of area under the curve (AUC) was found for ST/day <1.5MET (0.76). Five of those six variables present the range within no or poor discrimination, with low sensitivity and specificity, which means only ST/day <1.5MET presented acceptable discrimination.

Figure 1 shows the Kaplan-Meier curves with each Log-Rank test comparison. The negative impact of sedentarism was presented in five of the survival curves according to the identified cut-off points. Time to death (or time of survival) was shorter in more sedentary patients (≥5:20 hours of sitting time/day; ≥8 hours of lying+sitting time/day; ≥8:30 hours of ST/day<1.5MET; ≥9 hours of ST/day<2MET; and average of MET ≤1.5 MET/day (*P*<0.05 for all).

Cox's regression models according to the proposed cut-off values showed that significant HR in the univariate survival analysis (table 3) were observed for the same five variables with shorter time to death (Figure 1) (*P*<0.05 for all). After adjusting for all relevant confounders, only two threshold values of sedentarism variables were significant (table 2). The strongest independent cut off for predicting mortality was ≥8:30 hours/day spent in sedentary activities <1.5MET. Furthermore, univariate analysis showed that each hour/day spent <1.5MET increases mortality risk by 42% (HR 1.42; 95%CI 1.15-1.76; *P*=0.001).

DISCUSSION

The present study was the first to propose a cut-off point of objectively measured time spent in sedentary behaviour in patients with COPD and to investigate its association with mortality. It was found that mortality risk in patients with COPD was 4.09 times higher in those patients who spent more than 8:30 hours/day in activities requiring <1.5MET, and each hour/day spent <1.5MET increases mortality risk by 42%. It should be highlighted that there are available cut-off values to identify sedentary behaviour in the general population which are based on subjective variables, such as self-reported time spent watching TV(5, 26). However, objective measures allow for more robust assessments of sedentarism variables in comparison to self-reported methods(7, 10).

Waschki and colleagues(2) found that objectively measured physical activity is the strongest predictor of all-cause mortality in patients with COPD using the Physical Activity Level (PAL) of >1.70 to define an active person, between 1.40 and 1.69 a sedentary person, and <1.40 a very inactive person. Additionally, Garcia-Rio and colleagues(3) classified patients with COPD according to the quartiles (Q) of Vector Magnitude Units (VMU) (i.e. Q1: <130 VMU; Q2: 130-200 VMU; Q3: 200-270 VMU; Q4 >270 VMU) and concluded that daily physical activity reduction was also associated with a higher mortality risk. Although these studies present undisputed relevance, conceptualizing sedentary behaviour as distinct from lack of physical activity is important to avoid confusion and differentiate deleterious effects from patients physically inactive from those with sedentary lifestyle. In fact, individuals can achieve high levels of moderate-to-vigorous physical activity and still present high levels of sedentary behaviour(5).

A recent study(34) examined the association between self-reported average time of TV viewing duration/day and COPD-related mortality. After a follow-up of 19 years the study found that men who watched TV for more than 4 hours/day were more likely to die of COPD than those who watched TV for less than 2 hours/day (HR 1.63; 95%CI, 1.04-2.55)(34). By providing objective measurement instead of self-reported methods, the present study confirmed that time to death is shorter in those patients who spent more time in sedentary postures (i.e., sitting or lying+sitting) despite the poor discriminative power of these cut off points. Furthermore, also by using objective assessment, Hartman and colleagues showed that longer sitting time in daily life is associated with a higher number of COPD exacerbations(16). The adjusted predictive value of sitting time/day for mortality in the present study was not significant as it was for ST/day<1.5MET or <2MET. This indicates that activity intensity is also a key point for higher risk of death in COPD. The present results point out that the combination of time (duration) of sedentarism and very low intensity of activities (as in ST/day<1.5 MET or <2MET) may be a more relevant outcome as prognostic factor than only time spent sitting/day by itself. This is in line with Donaire-Gonzalez and colleagues who recently suggested that benefits of physical activity on COPD hospitalization also depend on intensity(35). Future studies with larger samples may provide a more in-depth investigation on the role of sitting time/day by itself as a prognostic factor for mortality in patients with COPD, as observed in the general population(5, 6, 8, 26).

Despite the low AUC value, the cut-off point of average MET/day with the best sensitivity and specificity values for mortality in the present study was 1.5 MET/day, exactly the same threshold of intensity present in the definition of the term “sedentarism”(11). The threshold of 2 MET as the lower limit for light activity has been previously used in patients with COPD(36) since 2 MET is the minimum intensity associated with activities performed in the upright posture such as folding clothes or preparing a meal(25). Moreover, a study examining the use of 1.5 MET threshold in the definition of sedentary behaviour in adults against indirect calorimetry concluded that some common sitting behaviours appeared to have a MET level above this threshold(37). These findings have specific relevance to the current definition of sedentary behaviour and suggest that common sitting activities, such as typing (e.g., working in a computer), are actually defined as non-sedentary in a large proportion of the population(37). Although it has been shown that there is influence of the use of different activity thresholds in patients with COPD(21), this issue was not yet investigated in depth.

A previous study has shown that sedentary time of patients with COPD was significantly and positively associated with metabolic risk factors such as waist circumference and glucose levels(38). Surprisingly, we could not find any study investigating the prognostic value of mortality using 1.5 MET intensity as threshold for sedentarism. This might have happened because the focus of the studies has been rather on physical activity/inactivity and not on sedentarism. Future research may focus on confirming this for different stages of disease severity.

In the present study, lying time had no influence on mortality when analyzed solely (table 3). This was not surprising since there was no difference in lying time/day between survivors and non-survivors (table 1). A recent review about the use of time in daily life by patients with COPD(13) found a median of time spent lying of 88 $min.day^{-1}$, therefore very close to our cut-off point of 80 $min.day^{-1}$. Perhaps a discriminative cut-off point for lying time was not detected in the present sample. Additionally, it might be that this variable is not capable of discriminating its influence on mortality when analysed separately, and this hypothesis is reinforced by its low specificity value (i.e. 52%, Table 2), the lowest among the six studied variables.

Despite this study presenting some strengths such as the clinical relevance and the addition of novel information to the literature, it also shows some limitations such as the lack of assessment of bouts of sedentary time. Various studies in the general population have emphasized the importance of interrupting continuous periods of sedentary time(8, 26, 39) and this analysis would certainly be interesting also for patients with COPD. Further, the applicability of the proposed cut-off points of sedentarism must be tested in other populations with different wearing times of the activity monitors.

In conclusion, cut-off points from variables which combine duration of sedentary time and intensity <1.5 MET or <2 MET were associated with the increased risk of mortality in patients with COPD. Sedentary patients can be identified by spending ≥8h30 hours/day in sedentary activities requiring <1.5 MET, and each hour/day spent <1.5MET increases mortality risk by 42%. These findings may open room for future studies aiming at decreasing sedentary time as a promising strategy to reduce mortality risk in patients with COPD.

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DECLARATION OF INTEREST

The authors report no conflicts of interest.

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TABLE 1: Baseline characteristic of the study population according to vital status.

Variable	All patients (n=101)	Survivors(n = 60)	Non-survivors(n = 41)	*P* value
Gender, M(%)	58 (57)	27(45)	31(76)	0.004
Age (years)	66[60-72]	64[59-71]	69[61-74]	0.03
Weight (kg)	69[55-79]	67[57-78]	71[52-80]	0.94
Height (m)	1.59[1.53-1.67]	1.58[1.53-1.66]	1.63[1.53-1.68]	0.38
BMI (kg*m^{-2})	26[21-31]	27[22-31]	25[19-31]	0.42
FEV_1 (l)	0.99[0.77-1.35]	1.11[0.81-1.47]	0.88[0.69-1.14]	0.02
FEV_1 (%pred)	41[30-50]	43[34-58]	34[26-46]	0.001
FEV_1/FVC	51[41-65]	56[43-68]	46[35-57]	0.009
6MWT (m)	434[385-495]	455[397-510]	404[334-455]	0.001
6MWT (%pred)	81[70-88]	85[77-95]	74[61-82]	<0.0001
mMRC (0-4)	3[2-3]	3[1-3]	3[2-3]	0.18
Educational level, L/H (%)[a]	36/64 (36/64)	21/39(35/65)	15/24(38/62)	0.83
MVPA (hours/day)	0.48[0.14-1.24]	0.78[0.29-1.31]	0.25[0.07-0.77]	0.006
Sitting time (hours/day)	5.28[3.95-6.52]	5.00[3.80-6.44]	5.82[4.29-6.44]	0.15
Lying time (hours/day)	1.72[0.56-2.97]	1.29[0.41-2.97]	1.96[0.81-3.05]	0.21
Lying+Sitting time(hours/day)	7.52[5.63-8.65]	7.10[5.12-8.35]	8.02[5.98-9.19]	0.04
ST/day < 1.5 MET (hours/day)	8.21[6.39-10.49]	7.21[5.69-8.35]	8.99[8.04-10.18]	<0.0001
ST/day < 2MET (hours/day)	9.33[7.90-10.49]	8.94[7.41-9.94]	10.28[8.80-11.40]	0.003
Average of MET (MET/day)	1.45[1.2-1.8]	1.3[1.1-1.6]	1.6[1.3-2.0]	0.003

BMI: Body Mass Index; FEV_1: Forced Expiratory Volume in the first second; 6MWT: 6-minute walking test; mMRC: modified Medical Research Council scale; Educational level, L: Lower educational level (i.e., illiterate or only primary school); H: Higher educational level (i.e., complete high school); MVPA: time spent/day in moderate-to-vigorous physical activity (> 3 METs); MET: Metabolic Equivalent of Task; ST/day < 1.5 MET: time spent/day in sedentary activities requiring less than 1.5 MET; ST/day < 2 MET: time spent/day in sedentary activities requiring less than 2 MET.Mann-Whitney test or T independent test according to distribution of the data were used.[a]Two patients with missing data.

TABLE 2: Sedentarism cut-off points for the prediction of mortality during a median (IQR25-75%) of 62 (43-88) months of follow-up.

Sedentarism variable	AUC	Sensitivity (%)	Especificity (%)	Likelihood ratio	Best cut-off
Sitting time/day	0.58	61	62	1.69	≥5:20 hours
Lying time/day	0.57	66	52	1.36	≥ 1:20 hours
Lying+Sitting time/day	0.63	54	72	1.89	≥ 8 hours
ST/day < 1.5 MET	0.76	84	65	2.39	≥ 8:30 hours
ST/day< 2MET	0.69	74	61	1.88	≥ 9 hours
Average of MET/day	0.67	64	73	2.40	≤ 1.5 MET

ST/day < 1.5 MET: time spent/day in sedentary activities requiring less than 1.5 MET; ST/day < 2 MET: time spent/day in sedentary activities requiring less than 2 MET; MET: Metabolic Equivalent of Task; AUC: Area Under the Curve. Receiver Operating Characteristic (ROC) curve analysis.

TABLE 3: Prognostic values for mortality of six sedentarism cut-off points by Cox's proportional models.

Sedentarism variables	Unadjusted HR (95%CI)	*P* value	Adjusted HR (95%CI)	*P* value
Sitting time (≥ 5:20 hours/day)	2.21 (1.15-4.25)	0.02	1.82 (0.80-4.17)	0.16
Lying time/day (≥ 1:20 hours/day)	1.72 (0.89-3.32)	0.10	1.48 (0.62-3.53)	0.38
Lying+Sitting time/day (≥ 8 hours/day)	2.37 (1.26-4.47)	0.008	1.92 (0.86-4.28)	0.11
ST/day <1.5 MET (≥ 8:30 hours/day)	3.66 (1.76-7.61)	0.001	4.09 (1.90-8.78)	<0.0001
ST/day< 2 MET (≥ 9 hours/day)	2.74 (1.25-6.01)	0.01	3.11 (1.38-7.01)	0.006
Average of MET (≤ 1.5 MET/day)	2.61 (1.28-5.31)	0.008	1.74 (0.53-5.68)	0.36

MET: Metabolic Equivalent of Task; ST/day < 1.5 MET: time spent/day in sedentary activities requiring less than 1.5 MET; ST/day < 2 MET: time spent/day in sedentary activities requiring less than 2 MET; HR: Hazard Ratio; CI: Confidence Interval. Univariate analysis (Unadjusted) and Multivariate analyses (Adjusted). Cox regressions were adjusted for gender, age, body mass index, educational level, lung function, functional exercise capacity and moderate-to-vigorous physical activity [MVPA].

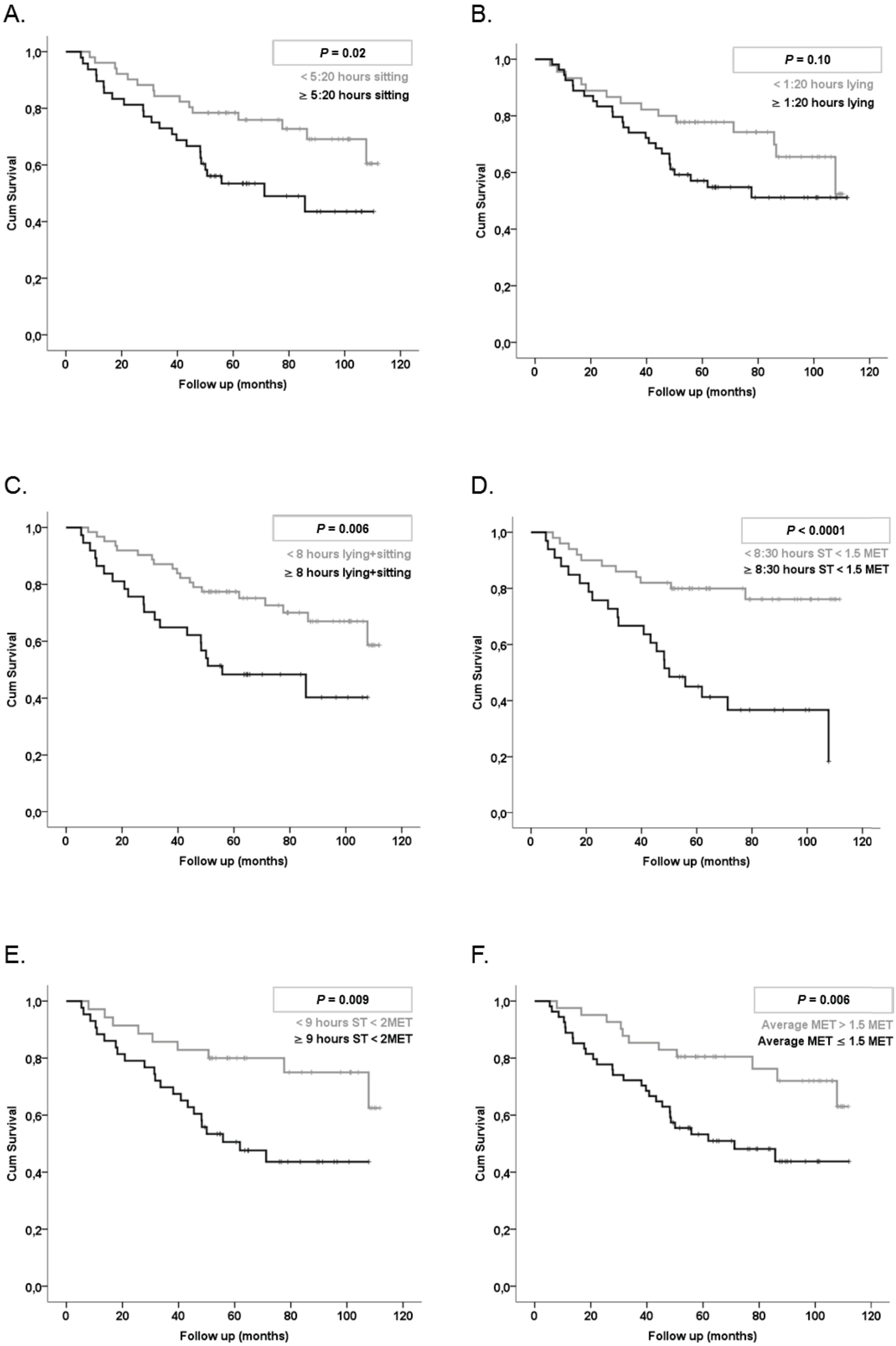
A.
P = 0.02
< 5:20 hours sitting
≥ 5:20 hours sitting
Cum Survival
Follow up (months)
B.
P = 0.10
< 1:20 hours lying
≥ 1:20 hours lying
Cum Survival
Follow up (months)
C.
P = 0.006
< 8 hours lying+sitting
≥ 8 hours lying+sitting
Cum Survival
Follow up (months)
D.
P < 0.0001
< 8:30 hours ST < 1.5 MET
≥ 8:30 hours ST < 1.5 MET
Cum Survival
Follow up (months)
E.
P = 0.009
< 9 hours ST < 2MET
≥ 9 hours ST < 2MET
Cum Survival
Follow up (months)
F.
P = 0.006
Average MET > 1.5 MET
Average MET ≤ 1.5 MET
Cum Survival
Follow up (months)

FIGURE 1: Kaplan-Meier figure of cumulative survival with the Log-Rank test of the variables separated according to the sedentarism cut-off points. **A:** ≥5:20 hours/day of sitting time; **B:** ≥1:20 hours/day of lying time; **C:** ≥8 hours/day of lying+sitting time; **D:** ≥9 hours/day of time spent in sedentary activities < 2 MET; **E:** ≥8:30 hours/day of time spent in sedentary activities< 1.5 MET; **F:** Average of MET ≤ 1.5 MET/day. Log Rank Tests were performed to compare time to death.

4 ARTIGO 2

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TITLE*: *Profile of patients with chronic obstructive pulmonary disease classified as physically active and inactive according to different thresholds of physical activity in daily life.

TÍTULO: Perfil de pacientes com doença pulmonar obstrutiva crônica fisicamente ativos e inativos classificados de acordo com diferentes pontos de corte para nível de atividade física na vida diária.

ABREVIATED TITLE: Profile of active and inactive COPD patients.

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Keywords: Motor Activity; Pulmonary Disease, Chronic Obstructive; Energy Metabolism, Exercise, Movement
Palavras Chave: Atividade Motora; Doença Pulmonar Obstrutiva Crônica (DPOC); Metabolismo Energético; Exercício; Movimento

Abstract

Objective: To compare the profile of patients with chronic obstructive pulmonary disease (COPD) considered physically active or inactive according to different classifications of the level of physical activity in daily life (PADL). **Methods:** Pulmonary function, dyspnea, functional status, body composition, exercise capacity, respiratory and peripheral muscle strength and presence of comorbidities were assessed in 104 patients with COPD. The level of PADL was quantified by the SenseWear Armband activity monitor. Three classifications were used to classify the patients in physically active or inactive: 30 minutes of activity/day with intensity >3.2 METs, if age ≥65 years and >4 METs, if age<65 years; 30 minutes of activity/day with intensity >3.0 METs, regardless the patient age; and 80 minutes of activity/day with intensity >3.0 METs, regardless the patient age. **Results:** In all classifications, when compared with the inactive group, the physically active group had better values of anthropometric variables (higher fat-free mass, lower body weight, body mass index and fat percentage), exercise capacity (6-minute walking distance), lung function (forced vital capacity) and functional status (personal care domain of the London Chest Activity of Daily Living). Furthermore, patients classified as physically active in two classifications also had better peripheral and expiratory muscle strength, airflow obstruction, functional status and quality of life, as well as lower prevalence of heart disease and mortality risk. **Conclusion:** In all classification methods, physically active patients with COPD have better exercise capacity, lung function, body composition and functional status compared to physically inactive patients.

Resumo

Objetivo: Comparar o perfil de pacientes com Doença Pulmonar Obstrutiva Crônica (DPOC) considerados fisicamente ativos ou inativos de acordo com diferentes classificações do nível de atividade física na vida diária (AFVD). **Métodos:** Função pulmonar, dispneia, estado funcional, composição corporal, capacidade de exercício, força muscular respiratória e periférica e presença de comorbidades foram avaliadas em 104 pacientes. O nível de AFVD foi quantificado pelo monitor de atividade física SenseWear Armband. Foram utilizadas três classificações para categorizar os pacientes em fisicamente inativos ou ativos: 30 minutos/dia de atividade física com intensidade >3,2 METs se ≥65 anos e >4 METs se <65 anos; 30 minutos/dia de atividade física com intensidade >3,0 METs independente da idade do paciente; e 80 minutos/dia de atividade física com intensidade >3,0 METs independente da idade do paciente. **Resultados:** Nas três diferentes classificações, quando comparados aos inativos, os pacientes fisicamente ativos apresentaram valores significativamente melhores nas variáveis antropométricas (menor peso, índice de massa corpórea e percentual de gordura e maior percentual de massa livre de gordura), capacidade de exercício (distância percorrida no teste da caminhada de 6 minutos), função pulmonar (capacidade vital forçada) e funcionalidade (pontuação no domínio cuidado pessoal na escala *London Chest Activity of Daily Living*). Pacientes classificados como fisicamente ativos em duas classificações apresentaram também melhores valores de força muscular periférica e expiratória, obstrução de vias aéreas, pontuação total de funcionalidade e qualidade de vida, além de menor prevalência de doenças cardíacas estáveis e risco de mortalidade. **Conclusão:** Independente do método de classificação utilizado, pacientes com DPOC fisicamente ativos são caracterizados por melhor capacidade de exercício, função pulmonar, composição corporal e estado funcional quando comparados aos pacientes fisicamente inativos.

Bullet points:

- There are different cut-offs to identify (i.e. classify) physical (in) activity.
- The profile of COPD patients according to different cut-offs has never been investigated
- Profile of active patients is similar regardless of the classification used.
- Active patients have clear health benefits compared to inactive patients.
- Interventions to modify sedentary behavior in COPD should be encouraged.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation, not fully reversible, and consequent dyspnea[1]. In addition, patients with COPD present systemic manifestations of the disease, such as skeletal muscle dysfunction that leads to restrictions on exercise capacity, resulting in reduced level of physical activity in daily life (PADL)[2]. Scientific evidence has clearly shown that patients with COPD are less active than healthy elderly[2,3]. Additionally, PADL is known to be closely related to a higher incidence of exacerbations and a higher mortality rate in this population[4-6].

The detailed and accurate assessment of the PADL in these patients, therefore, has generated scientific interest. Therefore, for an objective and accurate evaluation of the level of PADL, it is recommended the use of motion sensors, which are portable devices, which quantify the amount (and sometimes intensity) of physical activity performed by an individual in a given period of time[7]. This evaluation allows determining whether patients are considered physically active or inactive in accordance with the minimum recommendations of physical activity practice[8,9].

The physical activity recommendations published by the American College of Sports Medicine (ACSM) and American Heart Association (AHA)[8] suggest that physically active individuals are those who reach a minimum of 30 minutes per day of physical activity performed, at least, at moderate intensity, i.e., ≥3 Metabolic Equivalent of Task (METs), for all ages. However, in 2011 there was an update of the recommendations for physical activity by the ACSM[9], and the moderate intensity during physical activity was determined according to age (>4 METs for individuals between 40 and 64 years, >3.2 METs for individuals ≥65 years). More recently, a study by van Remoortel et al.[10] considered only the bouts of physical activity of at least 10 minutes, without intervals, to detect if a patient with COPD reaches the recommendation of 30 minutes of physical activity of at least moderate intensity. These results suggested that physically active individuals are those who perform, at least, 80 minutes of physical activity, with intensity ≥3 METs, without necessarily including the-10 minute bouts characterizing as continuous physical activity[8,10]. Therefore, there are different options to classify a patient as physically active or inactive, and the comparison between these different classifications has been little explored to date.

Taking into consideration the clinical relevance of correctly quantifying the level of physical activity of patients with COPD and knowing the different ways to classify the patient as physically active or inactive, this study aimed to compare the profile of patients with COPD who are considered physically active or inactive according to different classifications available in the literature.

Method

Study Design and Sample

In this cross-sectional study, 127 patients diagnosed with COPD according to the Global Initiative for Obstructive Lung Disease (GOLD)[1] were initially included. In addition to the diagnosis of COPD, the inclusion criteria of the study were: absence of osteo-neuro-muscular dysfunctions that could constrain PADL and other assessments; absence of severe or unstable heart disease; clinical stability (without occurrence of infections or exacerbations in the last three months); and not having practiced any kind of regular exercise program over the past year. The study was approved by the Ethics Research Committee from State University of Londrina, Londrina, Paraná, Brazil (061/06) and all subjects involved have been included only after obtaining formal written consent. Those patients who do not perform full PADL assessment (see below) were excluded.

Physical activity assessment and classifications

PADL was objectively evaluated by a physical activity monitor (SenseWear Armband [SWA], BodyMedia, USA), which was validated for patients with COPD[11,12]. Patients were evaluated during two routine days of the week, 12 hours/day starting at waking up, and the average of the two days was used for statistical analysis. The SWA is a biaxial accelerometer combined with physiological sensors, which offers as main outcomes the energy expenditure estimation and the time spent in physical activities stratified by intensity ('active time'). The limits to determine if physical activity was performed in at least moderate intensity were determined according to the chosen recommendation as described below.

Three physical activity cut-offs based on previous literature were used in the same group of patients to classify patients as physically inactive or active: (1) Classification of 30 minutes based on age: the minimum recommendation is to achieve 30 minutes/day of physical activity with an intensity of at least 3.2 METs in patients <65 years and 4 METs in patients <65 years according to the ACSM[9]; (2) Classification of 30 minutes regardless of age: the minimum recommendation is to achieve 30 minutes/day of physical activity with an intensity of at least 3 METs for all subjects according to the ACSM and AHA[8,9]; and (3) Classification of 80 minutes regardless of age: the minimum recommendation is to achieve 80 minutes/day of physical activity with an intensity of at least 3 METs. In the latter, the blocks of 10 minutes of physical activity without intervals (>3 METs) were considered based on the study by van Remoortel et al.[10]. The groups of physically active subjects were composed by patients who reached the minimum recommendation of physical activity for each respective classification. Patients who did not reach the recommendations for each respective classification were classified as physically inactive.

Secondary outcomes

Pulmonary function assessment was performed using the Spiropalm spirometer (Cosmed, Italy). The technique was carried out according to the guidelines of the American Thoracic Society[13] and reference values used were those proposed for the Brazilian population by Pereira et al.[14] Assessment of respiratory muscle strength was performed by measuring the maximum inspiratory and expiratory pressures (MIP and MEP, respectively) using a manometer, according to the technique described by Black and Hyatt[15] and following reference values for the Brazilian population described by Neder et al.[16].

Functional exercise capacity was assessed using the six-minute walk test (6MWT), carried out in accordance with the standards recommended internationally in a corridor of 30 meters[17]. The normal values used were those proposed for the Brazilian population by Britto et al.[18].

Body composition was assessed by bioelectrical impedance (Biodynamics © model 310, USA). This device provides through patient data (gender, age, height and weight) the following variables: fat mass (percentage of fat mass and fat mass in kg); body mass index (BMI); percentage of fat-free mass (FFM); fat-free mass index (FFMI); percentage of the ideal fat mass; body water; and the weight to lose/gain. The assessment was performed according to the technique described by Lukaski et al.[19], using the reference values described by Kyle et al.[20] for fat mass and fat-free mass.

Assessment of peripheral muscle strength was performed with the one repetition maximum test (1RM) of knee extensors (i.e., essentially the quadriceps femoralis muscle), elbow flexors and extensors. This test involves a trial and error procedure in which progressively heavier loads are raised until they exceed the capacity of the individual, determining, this way, the greater load which the individual is able to lift for one complete movement[21].

Quality of life was assessed using a specific questionnaire for patients with COPD and validated in Portuguese, the Saint George Respiratory Questionnaire (SGRQ)[22]. This questionnaire has three domains which evaluate symptoms, activity and psychosocial impact of the disease. Each domain has a maximum possible score; the scores of each answer are added up and the total is referred as a percentage of this maximum. A total score is also calculated based on the results of the three domains.

Functional status (limitations and ability to perform daily activities) was evaluated with two different tools: by the application of the London Chest Activity of Daily Living (LCADL)[23] scale and the modified version of the Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ-M, Questionnaire on Dyspnea and Pulmonary Functional Status)[24], both validated for the Portuguese language[23]. The LCADL is divided into four domains: personal care, household care, physical activity and leisure. The score for each domain is calculated and the total score is the sum of all domains[23]. The PFSDQ-M questionnaire consists of three components: activity, dyspnea and fatigue. In both instruments, higher values indicate worse functional status[24].
The Medical Research Council (MRC) scale, also validated in Portuguese[24], was used to evaluate the limitation by dyspnea in daily life. The scale consists of only five items, in which the patient chooses the item which corresponds to his/her limitation by breathlessness.

Comorbidities were assessed by a self-report questionnaire in which the patient indicates the presence or absence of medical diagnosis for a number of diseases (e.g. arthritis/osteoarthritis, hypertension, diabetes, osteoporosis, thyroid disease in, vascular disease and allergies).

The index known as BODE (BMI+Obstruction+Dyspnea+Exercise) was calculated from four variables: BMI ($kg.m^{-2}$); degree of airway obstruction assessed with the forced expiratory volume in the first second (FEV_1) in % of predicted values; dyspnea by the MRC scale (modified with the range from 0 to 4); and exercise capacity quantified by the 6MWT distance in meters[25]. The total score ranges from zero to ten points, and higher values indicate higher risk of mortality.

Statistical Analysis

The Shapiro-Wilk test was used to analyze data normality. In case of normal distribution, results were reported as mean ± standard deviation; otherwise, data were expressed as median [interquartile range 25-75%]. To compare numerical variables of the two groups of patients (active and inactive, according to each cut-off), the Student t test or the unpaired Mann-Whitney test were used and statistical significance was determined as $P<0.05$. Categorical data were described as frequency and percentages and compared using the Chi-square test. Finally, one-way ANOVA was used to compare the characteristics of the three groups of patients classified as physically active according to those criteria, and the same was performed with the three groups classified as physically inactive. Statistical analysis was performed with the 6.0 version GraphPad Prism software.

Results

Sample

This convenience sample was initially composed of 127 patients; 23 of them were excluded for lack of full PADL data (patient did not use physical activity monitor properly or there were technical problems in the assessment). The final sample (n=104) had mean age of 66±8 years, FEV_1 42±16 % predicted and BMI 26±6 kg.m^{-2}. There was no statistical difference when the sample (n=104) was compared with the 23 excluded patients (P>0.05 for all variables). Out of the analyzed patients, 63% were men, 72% were literate, 80% were ex-smokers and 3% used home (i.e. long term) oxygen therapy. The demographic and anthropometric characteristics of the patients included in the study are described in table 1. Eight one percent reported at least one comorbidity while the median [IQR25-75%] of comorbidities per patient was 1[2-3]. Additionally, 31% presented arthritis, 19% heart disease, 54% hypertension, 18% diabetes, 9% osteoporosis, 10% thyroid-related diseases, 38% vascular disorders and 38% allergies.

Profile of physically active vs inactive patients

In the classification of 30 minutes based on age, the proportion of active versus inactive patients was 35% vs 65%, while this proportion was 56% vs 44% in the classification of 30 minutes regardless of age and 27% vs 73% in the classification of 80 minutes regardless of age. There was statistical difference between the proportion of individuals considered active and inactive in all 3 forms of classification (P<0.0001).

The active group, when compared to the inactive group in three different classifications, showed lower weight, BMI, percentage of fat mass and score in the personal care domain of LCADL scale, besides presenting a higher percentage of fat-free mass, forced vital capacity and distance walked in the 6MWT (Table 2). Additionally, if we take into consideration a statistical difference in one or two classifications, physically inactive patients also had more pronounced higher physical impairment regarding many other characteristics (Table 3).

There were no differences in any characteristic among the groups of patients classified as physically active according to the three criteria (*P*>0.05 for all), and the same was observed among the groups of patients classified as physically inactive.

Discussion

This study showed that patients with COPD classified as physically active, regardless of classification (i.e., cut-off) used, have lower weight, BMI, percentage of fat mass and score in the personal care domain of LCADL scale, as well as have a higher percentage of fat-free mass, forced vital capacity and 6MWT distance compared to physically inactive patients. In addition, physically active patients are possibly those with higher values of peripheral and expiratory muscle strength, better (i.e. lower) functional status total score and quality of life in the activity domain of SGRQ, and lower airway obstruction, prevalence of stable heart disease and mortality risk.

The comparison between active and inactive patients was previously investigated by Pitta et al.[7]. That study showed that COPD patients considered physically inactive were characterized by having worse exercise capacity, pulmonary function and highest score in the BODE index. The same differences were found in the present study, even by using different ways to classify physically inactive from active patients. In the study by Pitta et al.[7], the walking time above 30 minutes was used as the cut-off point, regardless of the intensity of physical activity, whereas a novelty of the present study is that it was possible to characterize and identify the differences between physically active and inactive patients with COPD taking into consideration three different classifications described in the scientific literature which consider activities of at least moderate intensity.

The observed differences in body composition between physically active and inactive patients were demonstrated in a previous study of Monteiro et al.[26]. The relationship of obesity with physical activity in daily life in this population showed that physically inactive patients had higher body weight and lower fat-free mass. Results of the present study confirmed that physically inactive patients had worse body composition when compared with active patients, and again add new information since the results are independent of the classification used to determine if a patient is physically active or inactive.

In a previous study about the profile of Brazilian patients with COPD[3], the movement intensity in daily life was positively correlated with the 6MWT (r=0.42) and negatively with the personal care domain and total score of the LCADL scale, MRC, BODE index and age (-0.32<r<-0.58 for all). Additionally, walking time was negatively correlated with the MRC scale (r=-0.31), BODE index (r=-0.30) and age (r=-0.43)[3]. In the present study, physically inactive patients also had worse scores in the personal care domain of the LCADL scale and BODE index, which respectively confirm the more limited functionality in activities of daily living and higher risk of mortality. On the other hand, limitation by dyspnea assessed by the MRC scale was higher in most physically inactive patients when using classification of 30 minutes regardless of age but not the classifications of 30 minutes based on age and 80 minutes regardless of age.. These results support the concept that dyspnea assessed by a scale with a small range (i.e: from 0 to 4) is not highly associated with PADL outcomes in patients with COPD, as previously shown[3,27].

Among the evaluated comorbidities, patients classified as physically inactive showed higher presence of self-reported heart disease compared with physically active patients in two classifications. This was not a surprising result since Watz et al.[28] concluded that cardiac dysfunction is associated with physical inactivity in patients with COPD. Therefore, due to this combination, patients with heart disease associated with chronic lung disease should be priority targets in the search for interventions that aim to reverse the physical inactivity.

In addition to the differences observed between the three ways to classify physical activity (table 2), other differences were found in the comparison between physically active and inactive patients considering only one or two of the recommendations (table 3). Factors such as the degree of obstruction (FEV_1% predicted), peripheral muscle strength of knee and elbow extensors, expiratory muscle strength (MEP), functionality (LCADL) and quality of life (SGRQ activity domain) were better in physically active patients in two classifications, and may also be considered as indicators of profile differences between active and inactive patients.

A limitation of the study is the fact that there are other ways of classifying individuals as physically active or inactive in the scientific literature. Hartman et al.[29] showed that the application of seven different physical activity recommendations in the same population led to large differences in the classification of patients with COPD as sufficiently physically active or not; however that study aimed to compare the different classifications of physical activity and not the characteristics of physically active or inactive patients, as aimed in the present study. The choice of the three classifications proposed in this study was due to the fact that these are very commonly used in the recent literature which aims at quantifying objectively the level of PADL in COPD. Moreover, the proportion of patients classified as physically active or inactive in this study was not similar in the three classifications, and although other options are available in the literature[29], the chosen classifications were sensitive to detect these differences. Another limitation is the self-report assessment of comorbidities, since this may under/overestimate the proportion of patients with stable heart disease and other diseases. However, the authors did not have access to other diagnostic methods for these comorbidities, and this self-reported evaluation is commonly used in studies in the scientific literature to investigate the profile of patients with COPD[3,26]. Finally, despite the fact that at least two days of physical activity assessment has shown acceptable reliability in patients with COPD[2,30], it has been recommended that at least 5 days of physical activity assessment are necessary for patients with mild disease[31]. Although only two days of assessment can be seen as a limitation, the present sample was composed in its vast majority by severe patients, and therefore the results were unlikely influenced by this methodological characteristic. Future studies including more patients with mild disease are encouraged, so that the assessment of physical activity in daily life comprises at least five assessment days.

Conclusion

Regardless of the classification used to identify and classify patients with COPD as physically active or inactive, physically active patients are characterized by better exercise capacity, body composition, lung function and functional status compared to physically inactive patients. This indicates clear health benefits for physically active patients with COPD compared to those inactive, and further motivates us to seek interventions to modify the sedentary behavior observed in a large number of patients with COPD.

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TABLE 1: Characteristics of patients with COPD enrolled in the study.

Variable	(n=104)
Gender, M/F (%)	66/38 (63/37)
Age (years)	66±8
Weight (kg)	67±16
Height (m)	1.60±0.09
BMI ($kg.m^{-2}$)	26±6
FEV_1 (L)	0.98 [0.70 -1.34]
FEV_1 (% pred)	42±16
6MWT (m)	544±42
6MWT (%pred)	82 [72 - 94]
MIP (cmH_2O)	70 [50 - 80]
MIP (% pred)	69±26
MEP (cmH_2O)	100 [77 - 120]
MEP (% pred)	96 [81 - 122]
MF – QF (kg)	15±6
MF – TB (kg)	10±4
MF – BB (kg)	12±4
GOLD, I/II/III/IV (%)	1/30/42/30 (1/29/41/29)
BODE, I/II/III/IV (%)	27/34/33/10 (26/33/32/9)
mMRC (pts)	3 [2 - 3]
LCADL total (pts)	21 [16 - 28]
SGRQ total (pts)	52 [40 - 64]
PFSDQ-M[a] (pts)	18 [8 -31]
PFSDQ-M[b] (pts)	16 [7 - 30]
PFSDQ-M[c] (pts)	22 [10 - 37]

Values are described as mean± standard deviation or median [interquartile range 25-75%] or absolute frequency (relative). M: male; F: female; BMI: body mass index; FEV_1: forced expiratory volume in the first second; 6MWT: six-minute walking test; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; MF: muscle force; QF: quadriceps femoris; TB: triceps brachii; BB: biceps brachii; GOLD: Global Initiative for Chronic Obstructive Lung Disease;

BODE (BMI; Obstruction; Dyspnea; Exercise): patients classified in quartile of grouped BODE I, II, III, and IV[25]. mMRC: modified version of Medical Research Council; LCADL: London Chest Activity of Daily Living scale; SGRQ: Saint George Respiratory Questionnaire; PFSDQ-M: modified version of the Pulmonary Functional Status and Dyspnea questionnaire.

[a] Dyspnea Domain PFSDQ-M.

[b] Fatigue Domain PFSDQ-M.

[c] Activity Domain PFSDQ-M.

TABLE 2: Differences among patients with COPD classified as physically active or inactive according to all 3 cut-off points of physical activity/inactivity.

Variable	30 min based on age		30 min regardless of age[a]		80 min regardless of age [a]	
	Active (n=36)	Inactive (n=68)	Active (n=58)	Inactive (n=44)	Active (n=28)	Inactive (n=74)
Weight (kg)	60±12	71±16*	63±15	72±16*	57[48-64]	71[58-80]*
BMI (kg.m^{-2})	23±4	28±6*	24±15	28±6*	23±4	27±6*
FFM (%)	68[62-76]	60[55-69]*	65[58-75]	60[54-68]*	71[62-78]	61[56-69]*
FM (%)	28[23-36]	35[29-39]*	29[24-35]	35[29-41]*	28[22-32]	35[28-390]*
6MWT (m)	567[536-590]	535[509-557]*	555±38	530±43*	569±36	535±41*
6MWT (%)	88[81-95]	79[70-91]*	87[79-98]	75[68-83]*	87[80-97]	82[71-93]*
FVC (L)	2.6±0,8	2.0±0,6*	2.5±0,8	1.9±0,6*	2.7±0,9	2.0±0,6*
FVC (%)	60[0-71]	59[48-71]*	69[55-84]	59[46-68]*	76[62-86]	60[48-72]*
LCADL – Personal care (pts)	5[4-6]	6[5-9]*	5[4-7]	7[5-9]*	5[4-6]	6[5-8]*

Values are described as mean± standard deviation or median [interquartile range 25-75%]. 30 min based on age: 30 min/day of physical activity with intensity 3.2 METs if ≥65 years and 4 METs if <65 years; 30 min regardless of age: 30 min/day of physical activity with intensity >3.0 METs regardless of age; 80 min regardless of age: 80 min/day of physical activity with intensity >3.0 METs regardless of age. BMI: Body Mass Index; FFM: fat-free mass; FM: fat mass; 6MWT: six-minute walking test; FVC: Forced Vital Capacity. * *P*≤0,05 vs active. [a] Two patients had missing data of physical activity in daily life with an intensity of at least 3 METs.

TABLE 3: Differences among patients with COPD classified as physically active or inactive which reached statistically significant difference in just one or two cut-off points of physical activity/inactivity.

Variable	30 min based on age		30 min regardless of age[a]		80 min regardless of age [a]	
	Active (n=36)	Inactive (n=68)	Active (n=58)	Inactive (n=44)	Active (n=28)	Inactive (n=74)
Age (years)	65±9	66±8	64±8	68±8*	63±9	66±8
FFMI (kg/m^2)	16±2	17±2*	16±2	17±2	16±1	16±2
FEV_1 (L)	1.2[0,8-1,6]	0.9[0.6-1.2]	1.2[0.8-1.5]	0.8[0.6-1.0]*	1.8[1.2-2.8]	0.9[0.7-1.3]
FEV_1(% pred)	45[35-55]	39[26-50]*	43[33-55]	34[25-49]*	45[30-55]	40[26-53]
MF – QF (kg)	17±6	14±6*	16±6	13±7*	17±6	14±6
MF – TF (kg)	12[10-15]	11[8-14]	13[10-16]	10[7-13]*	13±5	11±4*
MF – BF (kg)	11±4	9±4	8[5-11]	8[6-12]*	10[8-14]	10[6-13]
MEP (% pred)	89[72-112]	105[85-132]*	93[77-118]	104[84-125]	87[67-103]	106[85-130]*
MRC (pts)	3[1-3]	3[2-3]	2[1-3]	3[2-3]*	3[1-3]	3[2-3]
LCADL (pts)	18[15-26]	23[16-29]*	20[17-28]	17[16-29]	18[15-26]	23[16-29]*
SGRQ-Activity (pts)	60[48-74]	70[53-81]*	61±19	66±22	60[48-73]	68[49-81]*
PFSDQ-M Dyspnea(pts)	16[6-27]	20[10-33]	16[8-28]	19[10-34]	11[6-20]	20[12-33]*
PFSDQ-M Fatigue(pts)	12[6-25]	18[8-32]	14[8-28]	18[7-32]	9[5-17]	19[8-31]*
BODE, I+II/III+IV (%)	27/9 (75/25)	34/34(50/50)*	43/15(74/26)	17/27(39/61)*	21/7(75/25)	39/35(53/47)
Heart disease, Y (%)	3(8)	15(25)	7(10)	12(28)*	1(3)	16(24)*

Values are described as mean± standard deviation or median [interquartile range 25-75%].

Categorical variables expressed in absolute frequency (relative): BODE I+II/III+IV: patients classified in quartile of grouped BODE I and II (≤4 points) compared with BODE III and IV (≥ 5 points); Heart Disease, Yes: Presence of self-referred stable heart disease.

30 min based on age: 30 min/day of physical activity with intensity 3.2 METs if ≥65 years and 4 METs if <65 years; 30 min regardless of age: 30 min/day of physical activity with intensity >3.0 METs regardless of age; 80 min regardless of age: 80 min/day of physical activity with intensity >3.0 METs regardless of age.

FFMI: fat-free mass index; FEV_1= Forced expired volume in the first second; MF: Muscle force; MEP: maximal expiratory pressure; QF: quadriceps force; TF: Triceps force; BF: Biceps Force; MRC: Medical Research Council; LCADL: London Chest Activity of Daily Living scale; SGRQ: Saint George Respiratory Questionnaire; PFSDQ-M: modified version of the Pulmonary Functional Status and Dyspnea questionnaire. * $P \leq 0.05$ vs active. [a] Two patients had missing data of physical activity in daily life with an intensity of at least 3 METs.

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5 ARTIGO 3

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SUMMER-WINTER VARIABILITY OF PHYSICAL ACTIVITY IN DAILY LIFE: COMPARISON BETWEEN BRAZILIAN AND BELGIAN PATIENTS WITH COPD

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ABSTRACT

Background: Seasonal changes in physical activity in daily life (PADL) of patients with Chronic Obstructive Pulmonary Disease (COPD) living in regions of the world with contrasting (i.e., mild or marked) weather variations have not been yet investigated.

Aims: To quantify PADL and compare its variability caused by seasonality in patients with COPD who live in world regions with different summer-winter climatic variation (i.e. Londrina, Brazil and Leuven, Belgium), when adjusted for climate.

Methods: In a longitudinal, prospective and observational study, patients with COPD from Brazil and Belgium wore the Sensewear Armband for 7 days in summer and 7 days in winter. Active time (≥2METs) was the primary outcome. PADL data were matched day-by-day with weather information.

Results: Taking into account the two assessment moments, median (min;max) temperatures were 11(-5.5;27.2)°C in Leuven and 21 (7;27)°C in Londrina. Patients in Brazil (n=19, 69±7years, $FEV_1$47±15%$_{pred}$) and Belgium (n=18, 69±6years, $FEV_1$50±15%pred) decreased their active time in winter compared to summer ($p<0.05$) and this reduction was more pronounced in Londrina ($p=0.01$, between group). Mean, minimum and maximum temperature, daylight duration and relative humidity were significantly related to active time. Patients in Brazil had higher active time independently of the season and adjusted for weather differences (286±116 vs 201±116 min.day^{-1}; $p<0.01$).

Conclusion: Patients with COPD decrease their PADL in winter regardless of living in Brazil or Belgium. Patients in Brazil are more active compared to those in Belgium, independent of season and adjusted for weather variables.

INTRODUCTION

Physical activity level in patients with Chronic Obstructive Pulmonary Disease (COPD) is closely related to worse disease outcomes, higher exacerbation rate and morbi-mortality risk[1-4].Various studies have been developed to accurately quantify the level of physical activity in daily life (PADL) in this population by using validated activity monitors and reliable assessment methods, as well as suggesting analysis standardization[5-7]. However, the influence of changes in climatic conditions on the level of PADL in patients with COPD has not been investigated with the necessary depth.

Up to this moment, the only two available studies investigating the effects of weather and/or seasonal variations on PADL in patients with COPD were performed in the United Kingdom[8, 9]. Inactivity in British patients was more pronounced in winter[8], on cold, wet and overcast days[9]. However, physical activity patterns may be influenced by specific geographical and meteorological characteristics from each region. Overall, a decreased activity due to climatic variations was also seen in healthy and much younger populations, however these studies present contrasting results[10-13]. For example, in a region with less marked climatic changes throughout the year (e.g. Perth, Australia), weather variations were of insufficient magnitude to impact PADL level in healthy subjects[10].

Compared to regions distant from the Equator, equatorial regions present less marked climatic variation throughout the year, with lower variations in temperature and daylight time (i.e. hours between sunrise and sunset). It is not yet clear whether these less pronounced climatic variations are translated into proportionally smaller variations in PADL compared to regions with more pronounced climatic changes. Moreover, regardless of these climatic changes in a specific region, when patients with COPD from different continents and geographical situations are assessed under similar climatic conditions, they can also present different levels of physical activity[14].This discrepancy in physical activity behavior observed between patients from different world regions still deserves further investigations.

The objective and longitudinal quantification of PADL patterns in patients with COPD in cities and countries with contrasting climatic variations allows to identify potential climatic influences on the level of PADL in these patients. Therefore, the aim of this study was to quantify PADL and compare its variability caused by seasonality in patients with COPD who live in world regions with different summer-winter climatic variation (i.e., Londrina, Brazil and Leuven, Belgium), when adjusted for climate. The initial hypothesis was that there would be no (or very little) change in PADL due to seasonality in the center with less marked weather variation (Londrina) in contrast to a larger change in the center with more marked weather variation (Leuven).

METHODS

Sample and design

The sample was initially composed by 24 patients with COPD from Belgium and 27 from Brazil recruited ineach of the two sites involved in this study: University Hospital Gasthuisberg (Leuven, Belgium) or Laboratory of Research in Respiratory Physiotherapy from the State University of Londrina (Londrina, southern Brazil). In this longitudinal, prospective and observational study conducted from January to September 2013, patients were included if fulfilling the following criteria: diagnosis of COPD based on internationally accepted criteria[15]; clinically stable (i.e., absence of an hospitalization due to an exacerbation) for at least 3 months before inclusion in the study; absence of severe orthopedic comorbidities which could hinder the performance in the proposed assessments; not participating in a pulmonary rehabilitation program or any high intensity physical exercise training at the time of inclusion in the study. Patients were excluded if they did not demonstrate physical or cognitive conditions to complete the proposed assessments, in case of technical problems with the activity monitoring assessment, or in case of exacerbation with consequent hospitalization in the period between the two assessment moments. The two involved centers purposefully composed the groups with similar gender distribution and disease severity in order to achieve the best possible matching.

The study design is depicted in Figure 1. Both groups of patients were objectively evaluated during two different moments: (1) simultaneous assessment during winter in Belgium and summer in Brazil, and (2) simultaneous re-assessment during summer in Belgium and winter in Brazil. Officially available and detailed climatic data from each region were taken into account in order to choose the best assessment period, focusing on the weeks with more markedly extreme temperatures in both seasons and centers.The months of January and February have similar average temperatures in southern Brazil, hence PADL collection was avoided in January since it has historically high rainfall indexes, potentially influencing the comparison[16]. The study was approved by the Ethics Research Committee from both centers and all patients provided informed consent to participate in the study.

Measurements – Primary outcomes

Objective assessment of physical activity in daily life

Patients' PADL level was objectively and similarly assessed in both centers through the use of a multisensory activity monitor (SenseWear Pro, Body Media, Pittsburgh, United States of America). Patients were instructed to wear the device during 7 days, to remove it only when bathing and not to change their daily routine while wearing the device. This activity monitor was previously validated in patients with COPD[17,18]. Active time (i.e., time spent per day in activities of intensity above 2 Metabolic Equivalents of Task [METs], in $min.day^{-1}$) was used as primary outcome. Time spent per day in moderate-to-vigorous intensity physical activity (MVPA time, in $min.day^{-1}$) (i.e. time spent per day in activities of intensity above 3 METs) was also analyzed[19]. A valid day was defined as at least 8 hours of wearing time between 7AM and 8PM and weekend days were excluded, in accordance with recent recommendations[6]. It was determined that at least 4 weekdays were required for patients to be maintained in the analysis[6]. Each valid day was included in a day-by-day analysis. Minute-by-minute exports were created with the software SenseWear Professional 6.1 at both centers and further analyzed with the SAS 9.4 statistical software.

Weather variables

Daily weather data for the assessment moments were gathered from each national meteorological institutes[16,20]. Variables measured across 24h-periods included: mean temperature (^{o}C), minimum temperature (°C), maximum temperature (°C), precipitation (rainfall, in millimeters), relative humidity (%) and the duration of daylight (in minutes). Calculation of daylight time was standardized for both centers and is described in detail elsewhere[6]. Data concerning weather characteristics were day-by-day matched with the SenseWear PADL data.

Measurements – Secondary outcomes

All patients performed spirometry following the American Thoracic Society / European Respiratory Society (ATS/ERS) standardized protocol[21] and expressed according to reference values from Pereira et al. for Brazilian patients[22] and Quanjer et al. for Belgian patients[23]. Exercise capacity was assessed with the 6-minute walking test (6MWT) according to international standards[24], using the longest distance of two tests. Impact of the disease on functional status and health status were assessed with the COPD Assessment Test (CAT)[25] and the degree of limitation due to dyspnea in daily life was assessed with the modified Medical Research Council scale (mMRC)[26]. Personal data, socio-demographic aspects, smoking habits, comorbidities, medical history and exercise training history were all self-reported in a questionnaire which was translated to the two languages (Portuguese and Dutch).

Statistical analysis

Data distribution was analyzed by the Shapiro-Wilk test. All analyses were performed with the SAS 9.4 statistical software using repeated measures mixed model analyses including day-by-day data, adjusting for center and season factors and controlling for within patient variability. The difference in PADL between summer and winter ('season') and the difference between the two centers ('center') and the season*center interaction effect were retrieved from the model. Similar bivariate and multivariate analyses were performed to investigate the influence of different weather variables on active time. Precipitation was converted to a binary outcome ('rain') and therefore treated as a categorical variable (i.e., rain was defined as a precipitation >0 mm); other weather data were analyzed as continuous variables. Scatter plots were created to visually investigate linearity, whereas multicollinearity of the weather variables was analyzed prior to the multivariate analyses. Since mean, minimum and maximum temperature induced collinearity, the one providing the best fit and highest explained variance (maximum temperature) was kept in the multivariate analyses. The models were judged based on goodness of fit. Age, lung function, gender, functional exercise capacity and level of education were considered as confounders. For all analysis, statistical significance was set at 5%. Sample size calculation found that at least 18 patients should be included in each group, as described in the supplementary material.

RESULTS

Patients' characteristics

Fifty-one patients were recruited, and 37 successfully completed the two assessment moments (Figure2). The characteristics of the 37 analyzed patients are presented in Table 1. Seventeen (89%) patients from Brazil and 14 (78%) from Belgium had previously participated in a pulmonary rehabilitation (PR) program (with a median [25%-75% interquartile range] of 3 [1-3] years vs 3 [1-6] years before inclusion, respectively; p = 0.19). Similar proportion of patients in

Brazil (n=13, 68%) and Belgium (n=12,67%) reported participation on regular exercise (supervised or not) with a median [interquartile range] frequency of 2 [2-3] and 2 [1-3] times per week, respectively (p>0.91 between centers). Patients who dropped out or were excluded from the study (n=8 in Brazil; n=6 in Belgium) did not differ from patients included in the final analysis in each respective center concerning age, gender, smoking history, lung function, dyspnea in daily life, body mass index and functional exercise capacity.

There were no changes in patients' disease characteristics between the two assessment moments (Supplementary Material, Table S1). Nineteen patients experienced at least 1 episode of mild exacerbation (more information in the Supplementary Material). The majority of patients in both centers (n=19, 100% in Brazil and n=15, 83% in Belgium) reported at least one comorbidity (p = 0.11). The median [Q1-Q3] number of comorbidities per patient was similar in the two centers (2 [1-3] comorbidities for both; p=0.54).

Table 1: Patient characteristics presented as the mean of the two assessment moments.

	Belgium	**Brazil**	**p-value***
N	18	19	
Age (years)	69±6	69±7	0.93
Gender (male, %)	67	53	0.38
BMI($kg*m^{-2}$)	27±6	26±5	0.36
FEV_1 (l)	1.25±0.38	1.23±0.42	0.85
FEV_1(%pred)	50±15	47±15	0.47
6MWD (m)	464±109	465±62	0.99
GOLD (A/B/C/D, %)	28/11/17/44	16/26/26/32	0.47
mMRC (0/1/2/3/4, %)	0/50/33/17/0	0/47/32/11/10	0.54
CAT (0-40)	15±6	16±6	0.55
Smoking history (pack/years)	61±39	59±37	0.93
Current smoker (%)	0	11	0.18
Living alove (%)	17	16	0.94

Marital status (%)			0.25
Single	6	5	
Married/partner	72	47	
Widower/widow	22	32	
Divorced	0	16	
Educational level completed (%)			0.001
No primary school	6	42	
Primary school	33	26	
Secondary school	61	11	
University level	0	21	
Work status (%)			0.34
Employed	6	21	
Not employed	11	5	
Retired	83	74	

Data are presented as mean±SD or as percentage. BMI = body mass index; FEV1 = forced expiratory volume in the first second; 6MWD: distance achieved in the 6-mnute walking test; mMRC = modified Medical Research Council scale; CAT = COPD assessment test; GOLD = quadrants of the Global Initiative for Chronic Obstructive Lung Disease using mMRC to classify symptoms. *Unpaired T tests and chi-square tests were performed.

Weather variables and PADL

In a total of 365 patient-days, PADL was matched with the corresponding weather variables (i.e. mean, minimum and maximum temperature, humidity, precipitation, duration of daylight), see Figure 3. Valid days collected in Belgium (n=176) showed a median (min–max) of 11 (-5.5–27.2)°C for mean temperature, 14 (-4.5-34)°C for maximum temperature, 8 (-10-21)°C for minimum temperature, 705 (507–982) minutes of daylight, 0.35 (0–20)mm precipitation, 78 (55–93)% relative humidity and it rained on 56% of the days. Valid days collected in Londrina (n=189) showed a median (min–max) of 21 (7–27) °C mean temperature, 29 (12-35) °C for maximum temperature, 17 (1-22) for minimum temperature, 736 (642–786) minutes of daylight, 0 (0–52) mm precipitation, 79 (63–99) % relative humidity and it rained on 40% of the days. There was no snow on any day during the assessment period.

There were no differences in wearing time of activity monitors between different seasons or centers (median[interquartile range] wearing time per day of all patients in all assessment moments:1408[1363-1429] min.day^{-1}). Patients from both Belgium and Brazil decreased their active time in winter compared to summer [mean (standard error)]: Belgium: 214(28) vs 188(28) minutes.day^{-1}during summer and winter, respectively; Brazil: 317(27) vs 254(27) minutes.day^{-1}during summer and winter, respectively) (see Figure 4). Additionally, decrease in active time in winter compared to summer was more pronounced in patients from Brazil compared to Belgium (p=0.01). There were no significant summer-winter differences in the two centers for MVPA time [mean (standard error)]: Belgium: 70(16) vs 62(16) minutes.day^{-1} during summer and winter, respectively; Brazil: 89(15) vs 84(15) minutes.day^{-1} during summer and winter, respectively).

In the model with bivariate analyses including the two centers, mean temperature (p<0.001), minimum temperature (p<0.001), maximum temperature (<0.001), duration of daylight (p<0.001) and relative humidity (p=0.002) were significantly related to active time. Physical activity on days with rain was not significantly different from days without rain when considering all data.

Humidity had a comparable effect on physical activity in the two centers, i.e., for every percentage increase in humidity, active time decreased with mean (standard error) 1.03(0.7) minutes. The influence of duration of daylight and temperature (maximum) differed between centers (p<0.01). Patients from Belgium increased 1.4(0.5) minutes of active time per °C increase in maximum temperature (p=0.002) and 0.09(0.03) minutes of active time per minute increase in daylight (p=0.002), respectively. Patients from Brazil increased

6.0(1.1) (p<0.001) and 0.6(0.1) (p<0.001) minutes of active time per °C increase in maximum temperature and per minute increase in daylight, respectively. Patients from Belgium decreased their active time by 22(11) minutes on days with rain compared to days without rain (p=0.04). Only patients from Brazil did not change their active time when comparing days with or without rain (p=0.98); this, however, did not generate a statistically significant different influence in PADL between centers.

Differences in PADL pattern between patients from Londrina (Brazil) and Leuven (Belgium)

Overall, patients from Brazil were more active than patients from Belgium[mean (standard error): 286(26) vs 201(27) minutes of active time; p=0.03)]. This difference remained statistically significant after adjusting for season (model 2), and showed similar results (albeit non-significant) after adjusting just for weather variables (model 3) but also when combining functional exercise capacity with weather variables (model 4), as shown in Table 2. Age, gender, rain, education and lung function did not remain in the final model.

Figure 5 illustrates minute-by-minute PADL of patients in Brazil and in Belgium at both summer and winter time. In addition to the different amount of PADL in the two centers (see figure 4), a different within-day pattern can be seen when physical activity is analyzed minute-by-minute throughout the day. Patients in Belgium seem to behave similarly in both seasons whereas patients in Brazil markedly reduce their physical activity in the morning period during winter in comparison to summer (see figure 5).

Table 2: Multivariate analyses to investigate differences in physical activity in daily life between patients from Leuven (Belgium) and Londrina (Brazil) (model 1) and after adjusting for season of assessment (model 2), season and weather variables (model 3) and functional exercise capacity (model 4).

	Estimate	**SE**	**p-value***
Model 1			
Intercept	286	27	
Center	-85	38	0.03
Model 2			
Intercept	263	27	
Center	-84	38	0.03
Season	45	7.5	<0.001
Model 3			
Intercept	247	28	
Center	-72	41	0.08
Season	65	17	<0.01
Max temp (°C)	0.74	1.1	0.5
RH (%)	-1.0	0.5	0.05
DL (min)	-0.17	0.07	0.03
Model 4			
Intercept	267	27	
Center	-72	39	0.07
Season	64	17	<0.01
Max temp (°C)	0.72	1.1	0.5
RH (%)	-1.0	0.5	<0.05
DL (min)	-0.16	0.07	0.03
6MWD (m)	0.48	0.21	0.02

Max temp = (centered) maximum temperature, RH = (centered) relative humidity, DL = (centered) daylight, 6MWD = (centered) 6-minute walking distance Age, educational level, gender, rain and $FEV_1\%_{pred}$ were not significant in a bivariate analysis and hence not considered in the multivariate model. The reference is a physical activity measurement of a patient with a 6MWD of 463 m, living in Londrina as measured during winter (season), on a day with 21°C maximum temperature (max temp), 77% relative humidity (RH) and a daylight of 721 minutes (DL). *Repeated measures mixed model analyses including day-by-day data was performed controlling for within patient variability.

DISCUSSION

This study shows that physical activity levels in patients with COPD vary considerably according to the season, even when climate differences between winter and summer are less pronounced. Therefore, the hypothesis that regions with less pronounced summer-winter variation in climatic conditions would present lower variability in PADL was rejected. Patients with COPD living in Brazil spend more time actively than patients in Belgium regardless the season and adjusted for functional capacity. This result corroborates previous findings that Brazilian patients are more active than matched Austrian patients, although in that study patients were assessed under similar climatic conditions[14].

This is the first cohort study comparing summer-winter variability of physical activity in the same group of patients with COPD. Previous cross-sectional studies have already shown an association between season and physical activity in this population[27, 28]. Moy et al. showed that patients with COPD from Boston (USA) walked on average 645 steps/day less in a median follow-up period of 3.9 months, which was partly explained by the season of monitoring[29]. Moreover, Sewell et al. showed that patients from Leicester (UK) who started a pulmonary rehabilitation program in winter had greater improvement in physical activity compared to those who started the program in summer[8]. The present results provide further evidence that in the absence of an intervention, patients with COPD presented a mean reduction of active time of 26±55 minutes.day^{-1} between summer and winter in Belgium (12% decrease from summer) and 63±73 minutes.day^{-1} in Brazil (20% decrease from summer).

More recently, meteorological conditions and atmospheric pollution have been associated with physical activity in patients with COPD[9]. Alahmari et al.

suggested that patients were less active on cold, wet and overcast days in a London (UK) cohort. In the present multicenter trial, these results were confirmed by showing that temperature, duration of daylight and humidity were predictors of time spent in physical activity assessed with a valid tool. In general, a 1°C. rise in (maximum) temperature increased the time spent active by 1 minute in patients in Belgium and 6 minutes in patients in Brazil.

In general, weather variables and subsequently season, have influence on physical activity behaviors of adults and healthy elderly[11, 13, 30]. A similar reduction of steps/day from summer to winter was observed in healthy adults from the UK (13%)[31] and from the USA (10%)[32], despite the differences both in latitude and climatic conditions. The present study shows that summer-winter changes in PADL were more pronounced in patients from Brazil compared to Belgium, reflecting a smaller influence of the more marked climatic variation (i.e. in Belgium) in the summer-winter reduction in physical activity, which is in opposition to the initial hypothesis. It can be speculated that the higher variability may be due to the higher PADL level in Brazilian patients, or that perhaps there are other factors, different from climatic variables, which are associated with PADL and may have an influence on this variability, although this certainly requires further investigation. Interestingly, a review study from eight different countries (Canada, USA, Australia, Cyprus, Scotland, The Netherlands, France and Guatemala) showed a systematic decrease in physical activity during cold months in the general population that was similar among all countries, regardless the fact that weather varies by geographical region[13]. Moreover, weak correlations between weather variables and physical activity in older functionally impaired people from Dundee (UK) have been reported[30].

Therefore, it is reasonable to believe that patients' perception of climatic variation is not proportional to the actual magnitude of climatic changes between summer and winter. In general, subjects who were less likely to perceive the weather as a barrier were more likely to be high-volume walkers[33]. It has also been suggested that sufficiently motivated individuals are less affected by weather conditions[34]. Perhaps the pronounced differences in weather conditions did not translate into substantial differences in physical activity variability among patients with COPD from different regions, as observed in the present study. Other explanations why patients in Brazil are more physically active than patients from Central-Europe may be related to socio-economic status, culture and environmental aspects, such as occupational, housework and transport-related activity[14]. In general, occupational physical activity is usually higher in people with low income while leisure-time exercise is more common in people with high income[35]. Furthermore, physical inactivity is more common in countries of high income than in those of low income[36].

In both regions the physical activity level of patients with COPD was higher during morning with a marked reduction during the evening, as previously stated in the literature[6, 37]. The same is observed in a population of healthy elderly men[38]. The present study, however, identified a different pattern of physical activity between summer and winter in Brazilian patients. It seems that patients from Brazil modify their physical activity habits in the morning by being more active in summer and less active in winter. This was not observed in Belgian patients. Two hypotheses may arise. First, the higher temperatures during the afternoon hours in summer in Brazil may have forced patients to adapt their physical activity pattern during this period of the year by doing more activities in the morning and less in the afternoon. This hypothesis is in line with the previous investigation from Alahmari et al.[9] that identified a cut off of temperature (22.5°C) above which patients start decreasing their physical activity level. Second, the perception of cold during the winter mornings for Brazilian patients may have forced them to do less activities in this period and more in the afternoon, when temperatures have risen. A combination of these two hypothesis is also possible. Regardless the explanation, it is likely that Brazilian patients adapt their daily physical activity planning throughout the day since they are forced to keep up a higher level of PADL due to socio-economic factors, for example. This finding stresses the fact that information of PADL based on one center cannot be generalized to the entire COPD population. In fact, data from general population suggests that a different social pattern of inactivity becomes apparent when countries with different incomes are compared[39]. Therefore, these region-related different social patterns provide insight on how we can build up physical activity interventions in patients with COPD.

As study limitations, besides the lack of a control healthy group, it can be discussed that a relatively small number of patients was included, although the sample size was sufficient to yield contrasts between winter and summer in the two centers involved. On the other hand, differences in physical activity between summer and winter were not detectable using moderate intensity of physical activity as a threshold, although time spent above 2 MET seems a more sensitive outcome compared to 3 MET in patients with COPD[6] due to the physically inactive profile of the patients. The study may not have enough power to detect changes in this more stringent outcome (i.e.MVPA). Finally, the lack of data on air pollution could also be seen as a limitation.

CONCLUSION

Weather variables influence physical activity behavior of patients with COPD living both in Brazil and Belgium since there is significant reduction of the time spent actively in winter when compared to summer in both groups of patients, although more markedly in patients from Brazil. Patients in Brazil are more active compared to those in Belgium, independent of season and adjusted for weather variables.

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CONFLICTS OF INTEREST

None declared

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Figure 1.

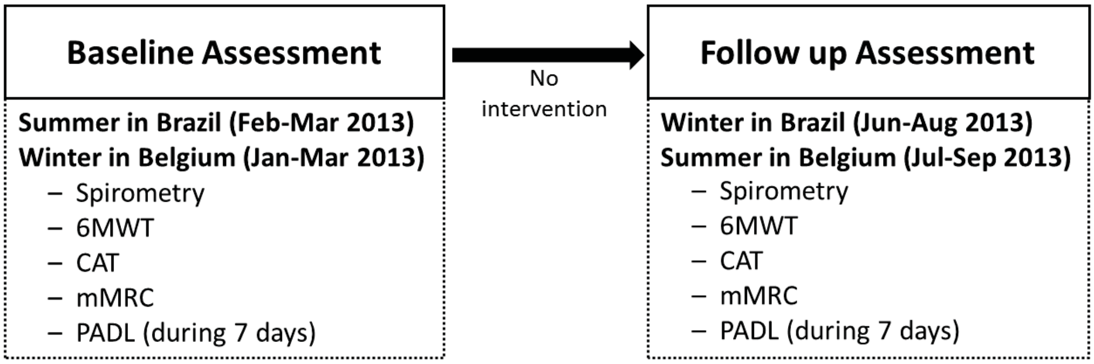

Figure 1. *Study design. 6MWT: 6-minute walking test; CAT: COPD Assessment Test; mMRC: modified Medical Research Council scale; PADL: physical activity in daily life.*

Figure 2.

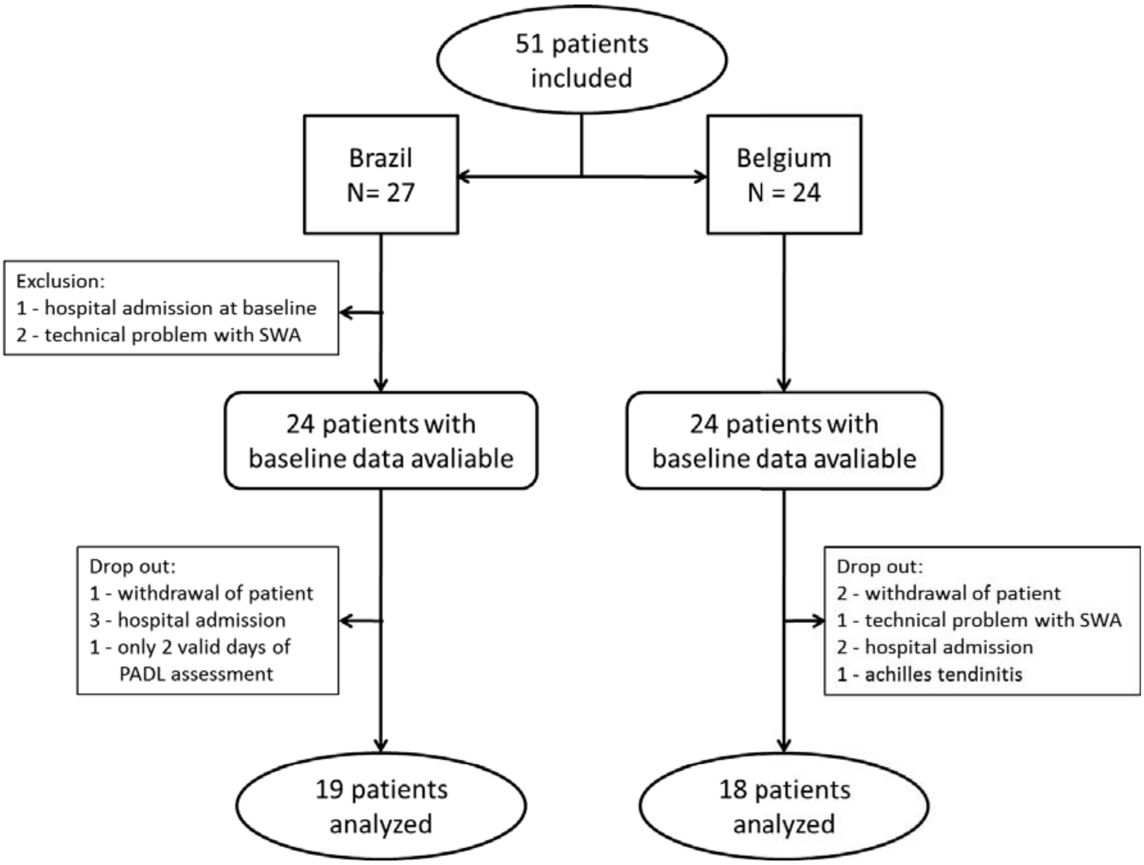

Figure 2: *Flowchart of the study. SWA: SenseWear Pro armband activity monitor; PADL: physical activity in daily life.*

Figure 3.

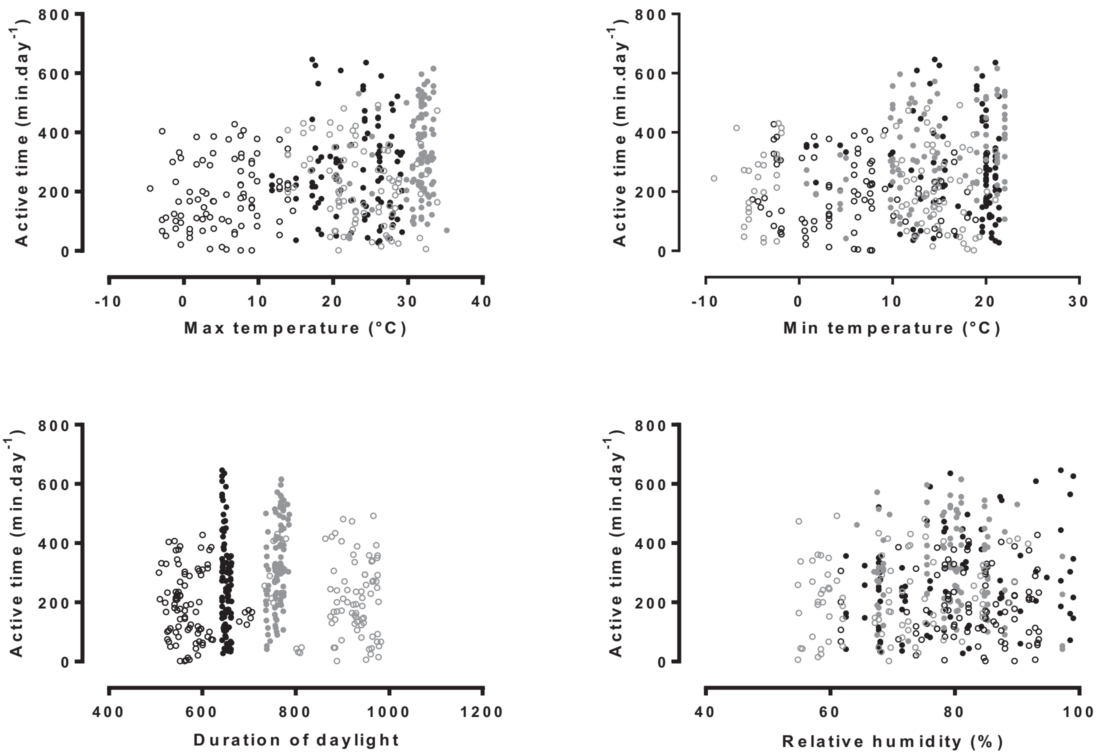

Figure 3: *Relationship between physical activity in daily life and weather variables in 365 patient-days. Solid circles represent patients from Londrina (Brazil), whereas open circles represent patients from Leuven (Belgium). Data collected during summer are presented in grey, whereas data collected during winter are presented in black. Active time: minutes per day of activity with an intensity of at least 2 MET.*

Figure 4.

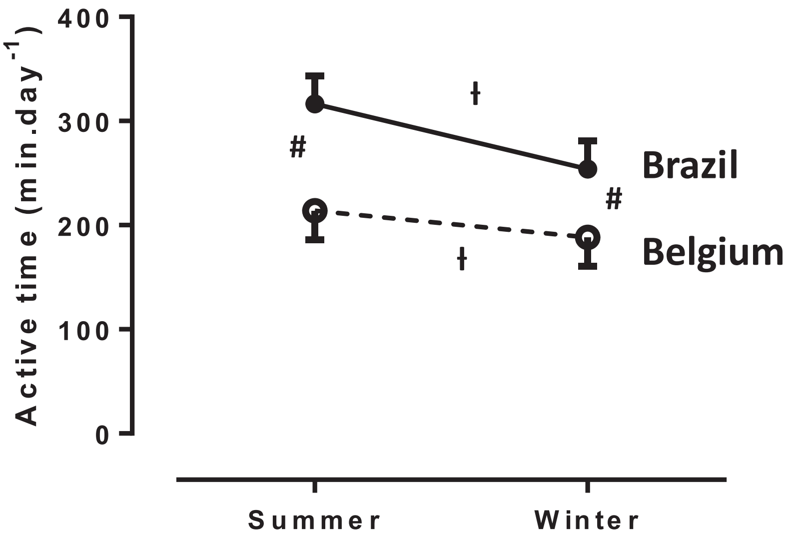

Figure 4: *Comparison of active time (minutes per day in activities of intensity ≥ 2 metabolic equivalents), depicted within and between centers. Patients from Brazil are depicted in solid circles and solid lines; patients from Belgium in open circles and dotted lines. Values are shown as mean and standard error. [#]Center main effect: p=0.03; [ƚ] seasonal change: p<0.01; center*season interaction effect: p=0.01. Repeated measures mixed model analyses including day-by-day data controlling for within patient variability was used.*

Figure 5.

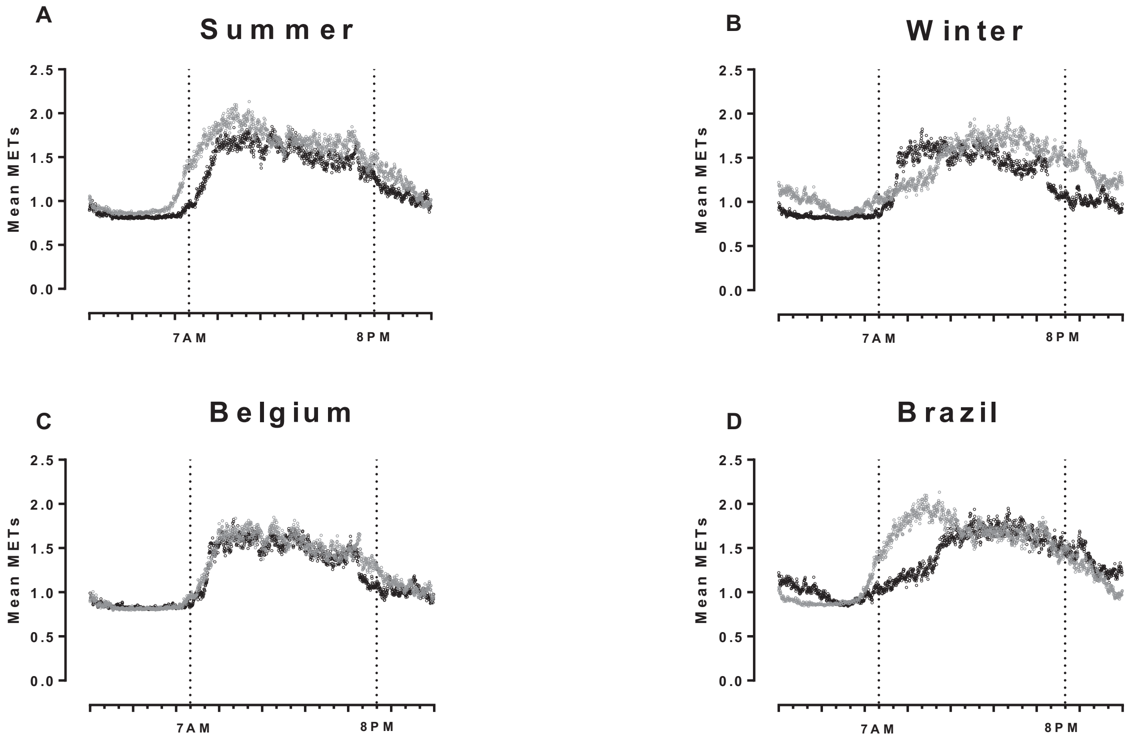

Figure 5: *Minute-by-minute mean physical activity pattern (A) of patient-days measured during summer, (B) of patient-days measured during winter, (C) patients in Leuven (Belgium) and (D) patients in Londrina (Brazil). In the upper panels (A and B) patients from Leuven are depicted in black and patients from Londrina in grey; in the lower panels (C and D) days in summer are depicted in grey, days in winter in black. METs = metabolic equivalent of task.*

5.1 SUPPLEMENTARY MATERIAL

SUMMER-WINTER VARIABILITY OF PHYSICAL ACTIVITY IN DAILY LIFE: COMPARISON BETWEEN BRAZILIAN AND BELGIAN PATIENTS WITH COPD

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Keywords: Chronic Obstructive Pulmonary Disease; Physical Activity; Weather, Seasonal variation.

Supplementary material

Methods

Sample size calculation

The sample size of the study was calculated according to the assumption of a mean (and standard deviation) difference of counts*day^{-1} between two groups of patients with COPD, namely one in Europe and another in Brazil. The first group was assessed in summer and winter, as found in the study by Sewell et al. performed in England[1]. This study presented a mean difference of 5656 counts (8857 in summer and 3201 in winter), with standard deviation of 7497 and 2629 counts, respectively. The second group was based on the initial hypothesis that there will be no (or very little) change in PADL due to seasonal variation in Londrina (Brazil), and taking into account a similar standard deviation of 5063 counts/day. At least 18 patients in each group were necessary to be able to reject the null hypothesis that the population means of the two centers are equal with probability (power) 90% and alfa coefficient of 0.05. Taking into account a drop-out rate of 25%, a minimum of 24 patients were calculated to be recruited and included to compose each group (Londrina and Leuven), adding up to the inclusion of at least 48 patients.

Results

Patients did not change their characteristics between the two assessment moments (Table S1). Furthermore, during the study period, patients from both centers reported no changes on marital status, work status and housing. Mild exacerbations without hospitalizations occurred in both centers throughout the study period. In Brazil, 5 (26%) patients had one mild exacerbation and 3 patients (15%) 2 or more; in Belgium, 10 (56%) patients had one mild exacerbation and 1 (6%) presented 2 or more ($p = 0.17$).

Table S1. Lung function, exercise capacity, quality of life and degree of dyspnea in daily life among patients in the two centers (Londrina, Brazil and Leuven, Belgium).

	Brazil (n = 19) [a]		**Belgium (n = 18)** [b]	
	Summer	**Winter**	**Summer**	**Winter**
FEV_1, l	1.28±0.46	1.18±0.40	1.31±0.40	1.28±0.43
FEV_1, %	48±16	45±14	51±12	50±15
6MWT, m	472±66	457±70	450±133	473±97
CAT, 0-40	14[11;22]	14[10;22]	16[9;21]	15[10;19]
mMRC, 0-4	1[1;3]	2[1;3]	1[1;2]	1.5[1;2]

Data described as mean±standard deviation or median [interquartile range] according to the normality in data distribution. FEV_1: forced expiratory volume in the first second, liters; 6MWT, m: 6-Minute Walking Test, meters; CAT: COPD Assessment Test; mMRC: modified Medical Research Council.
[a.] Missing data of Brazilian winter assessment: 2 patients for CAT and mMRC.
[b.] Missing data of Belgian summer assessment: 3 patients for 6MWT and 1 patient for spirometry.
There were no significant differences in within-group or between-group comparisons.

Reference

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6 ARTIGO 4

Artigo formatado de acordo com as normas do periódico Expert Review of Medical Devices; Fator de Impacto: 1,683; Qualis: B1

Oxygen therapy devices and portable ventilators for improved physical activity in daily life in patients with chronic respiratory disease

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Abstract

Patients with chronic respiratory failure (CRF) and hypoxemia may have to use oxygen therapy to correct hypoxaemia or ventilatory support to augment alveolar ventilation, reverse abnormalities in blood gases (in particular hypercapnia) and reduce the work of breathing. Moreover, patients with chronic respiratory disease (CRD), hypoxemia and CRF benefit from physical activity; however, physical impairment due to dyspnoea in addition to the dependence of devices in day-by-day life can aggravate the reduced mobility and physical inactivity. Advances in technology led to the development of portable devices for home oxygen therapy or ventilatory support. This is the first review about the use of oxygen therapy devices or portable ventilators for improved physical activity in daily life in patients with CRD.

Keywords: Medical devices; Oxygen Inhalation Therapy; Mechanical Ventilator; Non-Invasive Ventilation; Motor activity; Walking; Mobility limitation; Respiration Disorders; Pulmonary Disease, Chronic Obstructive.

INTRODUCTION

Definitions

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure[1]. Physical activity is a complex behaviour that can be characterised by type, intensity, duration, patterns and symptom experience[2].There are subsets of physical activity with different concepts and each term definition and applicability are described below.

The term "exercise" has been used interchangeably with "physical activity", and, in fact, both have a number of common elements (e.g., both physical activity and exercise involve bodily movement produced by skeletal muscles that expends energy). Exercise, however, is not synonymous with physical activity: it is a subcategory of physical activity. Exercise means a planned, structured, repetitive and purposeful way of performing physical activity related to physical fitness which is commonly assessed by tests of exercise capacity[1]. Examples of widespread used exercise tests for these purpose are the cardiopulmonary exercise testing (CPET)[3] and the 6-minute walk test (6MWT)[4].

Activities of daily living (ADL) are another category of physical activity. This term refers to activities related to the subject’s routine and are generally linked to domestic tasks, personal self-care, leisure and work-related activities[2, 5]. ADL can either be those essentially required for daily life (i.e. basic ADL), such as personal hygiene, toileting, dressing, eating and physical mobility, or can be optional (i.e. instrumental ADL), which are those which depend on the social/family arrangements and financial condition, such as housework, driving a car, cooking, gardening and doing the laundry[6]. A term often used to describe the level of ADL impairment and performance is “functional status”[7]. The most common instruments available to evaluate ADL and functional status are questionnaires. Examples of validated used questionnaires for patients with chronic respiratory pulmonary disease (COPD), are the Pulmonary Functional Status and Dyspnea Questionnaire-Modified version (PFSDQ-M)[8] and the London Chest Activity of Daily Living questionnaire (LCADL)[9].

Finally, the term “physical activity in daily life" (or PADL), which is the main focus of the present manuscript, means the totality of voluntary movement produced by skeletal muscles during everyday functioning[10]. In other words, it can be understood as the quantification of all movements performed in day-by-day life, or the total amount of physical activity performed by someone in real life by someone. It is assessed with physical activity monitors (e.g. Actigraph GT3X and DynaPort MoveMonitor[11], among others) and/or questionnaires[12]. Despite the importance of exercise and ADL, this manuscript focuses mainly on PADL and the impact of oxygen therapy and portable ventilators on its level.

Physical activity in daily life and chronic respiratory disease

PADL is the strongest predictor of all-cause mortality in patients with chronic obstructive pulmonary disease (COPD)[13]. Overall, it is widely accepted that patients with chronic respiratory disease (CRD) benefit from physical activity.

In recent years, the scientific literature showed a markedly and growing research interest in investigating aspects related to physical activity and CRD. Consensus documents are now available regarding PADL[2]. To exemplify, it is known that the assessment of physical activity should be preferably performed objectively, such as by using activity monitor devices to accurately quantify the amount and intensity of physical activity performed in a routine day[12]. Subjects often over or underestimate their own physical activity level when self-reported methods are used; thus, valid activity monitors are an excellent option to accurately assess PADL[2].

Despite the current variety of available studies about PADL, some crucial points remain unknown, especially those regarding strategies for improving and maintaining physical activity. Another issue, which has been recently explored but requires further investigation, is the study of individuals at the very severe end of the disease severity spectrum. It is naturally more difficult to recruit patients with very severe CRD compared to patients with moderate or severe disease; therefore, patients with moderate and severe disease are the predominant population in most studies with CRD. Unfortunately, this recruitment characteristic leads to a relative lack of information regarding PADL in very severe patients who eventually present indication for long-term oxygen therapy (LTOT) or ventilatory support, and are prone to very low levels of PADL[14, 15].

LTOT guarantees blood oxygenation while ventilatory support aims to address reduced ventilatory capacity, improve arterial blood gases, reduce work of breathing and compensate the increased ventilatory demand. Both strategies also aim to enhance quality of life among patients with CRD. The need for modern and practical ways for the use of LTOT and ventilatory support by patients with very severe CRD has stimulated the development of portable devices, which has led to new technologies. Therefore, devices for portable oxygen therapy as well as portable ventilators are and will be present in the routine day of these patients.

A study involving patients with end-stage chronic obstructive pulmonary disease (COPD) suggested that care in this stage of the disease should focus on improving daily life instead of solely aiming to improve the functioning of the lungs[16]. However, current scientific literature does not take this issue into account with the required importance up to this moment. Furthermore, professionals in health care should actively explore what kind of practical help might be welcome and needed by patients on LTOT or receiving ventilatory support in order to keep up with their daily activities[16] and perhaps even improve their PADL level.

Finally, the choice of equipment for oxygen supply or ventilatory support may influence the level of PADL since weight, size and portability might hypothetically reflect on health aspects and functionality of these patients. However, to the best knowledge of the present authors, the current literature does not present yet a review article regarding oxygen therapy devices and portable ventilators for improved physical activity in patients with CRD. Taking this into account, the objective of this review was to analyse the effects of LTOT devices or portable ventilators on PADL improvement in patients with CRD.

OXYGEN THERAPY

Oxygen therapy advantages

The beneficial effects of ambulatory home oxygen have been demonstrated since the 1950s, when Cotes and Gibson gave oxygen to ambulatory COPD patients from small portable high-pressure cylinders in the United Kingdom[17]. Over the ensuing 7 decades, oxygen has been prescribed to numerous patients with COPD in the home setting[17, 18]. Patients with diseases leading to chronic hypoxemia require supplemental oxygen continuously to prevent its consequences and comorbidities[19, 20]. The current recommendations for prescribing LTOT in COPD are presented in Table 1.

Moreover, it is common clinical practice to prescribe supplemental oxygen when chronic hypoxemic respiratory failure not due to COPD (e.g, interstitial lung disease, pulmonary hypertension, kyphoscoliosis, and cystic fibrosis) is detected or in patients with hypoxemia at hospital discharge following flares of their underlying chronic respiratory disorder, without any substantial evidence[17].

In response to innovations in technology, economic pressure from third-party payers, and patient demands, options for home oxygen therapy equipment have increased over the past several decades[19]. Oxygen is a drug which requires prescription, effective delivery system, therapeutic dosing and monitoring for effective therapy. Although oxygen therapy improves exercise tolerance in hypoxemic patients, whether PADL levels are also enhanced is underexplored[2].

Physical activity in daily life in patients on LTOT

Patients with CRD with indication for LTOT have to get used to some oxygen therapy device. The use of this equipment, together with clinical impairments of the disease, may impact on the pattern of PADL. An interesting study published in 2006 explored differences between the profile of daily activity in patients with COPD who are on LTOT or not[21]. It was the first study to use an activity monitor to record spontaneous habitual domestic activity in order to compare PADL of patients with or without LTOT. The authors compared four groups of subjects: group 1 with hypoxic patients with severe COPD receiving LTOT; group 2 with severe COPD who had full knowledge of the activity monitor and the purpose of the study; group 3 had severe COPD but were unaware of the precise nature of the study; and group 4 was a healthy age-matched control group. The healthy group presented better global quality of life and PADL level when compared with all groups of patients with COPD. Moreover, patients on LTOT had a further 50% reduction of physical activity compared with those without LTOT (despite similar impairment of lung function)(Figure 1), and also presented lower score in quality of life questionnaire. The authors suggested that while patients are advised to use LTOT overnight to accumulate their 16 hours of use, they may become dependent on oxygen therapy and consequently housebound for a significant proportion of the day, which reflects the compromised activity profile of patients receiving LTOT compared with non-LTOT. In fact, patients with CRD already present physical limitations and LTOT should allow then to maintain their mobility, and not complicate them even more. Hartman and colleagues have shown that decreased physical activity was more marked in most severe stages of COPD, in which patients were mainly limited by physical disease-specific factors such as oxygen use[15]. Objective assessment of physical activity was used and conclusions also showed that reduced physical activity was found among patients on LTOT. It is possible that the lack of freedom due to the need of carrying an oxygen equipment influence these results; however, up to this moment there is no specific study with a large sample investigating (and therefore confirming) the exact cause of this marked reduction.

A qualitative study investigated why patients did not use their portable oxygen system as prescribed. Patients on LTOT reported that they feel embarrassed for being seen in public with the system and that sometimes they were unable to carry the oxygen system because of the cylinder weight[22].

Indeed, we can hypothesize that previously reported problems with system weight and patient embarrassment may directly affect both adherence to ambulatory oxygen prescription and also physical activity level. Avoiding leaving home and performing fewer tasks in the day-by-day may further reduce PADL and result in deleterious effects. This is in accordance with a Japanese study which assessed PADL with a pedometer in patients under home oxygen therapy and demonstrated that physical activity was related to depressive state[23].

Furthermore, patients with CRD present systemic manifestations of the disease such as skeletal muscle dysfunction, which leads to restrictions on exercise capacity, resulting in reduced level of PADL and consequently enhancing dyspnoea symptoms[24]. Joint effects of both oxygen system device and the vicious cycle of the disease (dyspnea, deconditioning and inactivity) are observed in patients on LTOT.

Therefore, health professionals should address solutions to enhance the physical and social benefits of maintaining mobility in this population, offering environmental conditions to motivate higher levels of PADL and improving adherence to ambulatory oxygen prescription.

Oxygen therapy equipment

Despite the importance of LTOT in clinical home management, there are gaps in our current knowledge regarding its mechanisms of action, indications for prescription, and its effects on important patient outcomes[17]. In an interesting review paper, McCoy investigated the options for home oxygen therapy equipment[19]. Patients requiring LTOT must have access to clinically effective home oxygen equipment while providing a more normal lifestyle and ensuring that the patient preserves adequate oxygenation at all activity levels[19]. The knowledge about different portable devices is of relevance in order to understand its associations with impairments in PADL due to the equipment–related restriction in mobility, adding up to the isolated aspects of disease limitation. Stationary home devices have been technologically improved and new oxygen equipment has been developed to meet the needs of the patient who is more mobile or intends to be less limited in daily life activities.

There are many equipment options available for home oxygen therapy to meet the needs of the patient on LTOT. Among these equipments there are more common options such as compressed oxygen cylinders (Figure 2), liquid oxygen systems (Figure 3), stationary oxygen concentrators (Figure 4) and portable oxygen concentrators (Figure 5). However, physicians usually prescribe a flow rate and frequency for home oxygen therapy regardless of the delivery equipment provided to the patient. This lack of connection has relinquished control of the oxygen therapy delivery equipment to the home medical equipment supplier, who will balance the decision based on its available inventory, distribution economics, market competition and patient demands. This has been discussed in the literature[19] and might be considered as a target issue.

There is no available evidence on improvement of PADL regarding different equipments of oxygen therapy tested by the same patients. Up to this moment, a randomized clinical trial provided lightweight ambulatory oxygen for patients with severe COPD[25]. However, the act of providing lightweight oxygen may not change patients' behaviors since they did not increase either oxygen use or activity[25]. Therefore, empirical choices are usually made based on specialist experience and opinion. Going beyond, in accordance with others[19], we suggest that the equipment choice should focus not only on the known key factors, as previously described, but also on patient mobility due to the largely known benefits derived from physical activity.

Despite the lack of evidence, it is natural to hypothesize that equipment size, weight and facilities for mobility at home have important associations with physical activity improvement in patients on LTOT. Furthermore, although the need for oxygen during activities has stimulated the development of new technologies for home oxygen therapy, mobility and PADL have been poorly evaluated in patients on LTOT. Therefore, evidence-based equipment choices considering daily functioning are still impaired up to this moment, despite the relevant benefits of improved physical activity in patients with CRD.

Oxygen therapy devices for improved PADL

Physically active patients with COPD have lower mortality risk[13]; moreover, ambulation is the most common activity in daily life. A portable oxygen system must be effective and efficient in order to gain patient adherence, yet must also provide therapeutic oxygen at all activity levels[19]. In addition, in the short term, ambulatory oxygen is believed to be effective in increasing exercise tolerance and reducing dyspnea[26]. However, it may be influenced by the oxygen device weight[27] and more longer-term randomized controlled studies examining the domiciliary use of ambulatory oxygen are required, since the results of the available studies still do not provide a solid basis for the use of ambulatory oxygen to improve exercise performance or health status on the long term[20, 28, 29].

In this context, a randomized, double-blind, placebo-controlled trial of cylinder oxygen vs cylinder air study purposed to examine how ambulatory oxygen affects domestic activity in patients with COPD and whether it is able to change the pattern of outdoor activity[30]. Patients were either hypoxic at rest or had desaturation during exercise. Surprisingly, there were no statistical differences in health related quality of life or in domestic activity for either group after 8 weeks of intervention. Although there appeared to be a trend for increase in domestic activity with the oxygen cylinder during the intervention and for decrease with the air cylinder, there were no between-group differences in cylinder use or time spent outside the home. Therefore, ambulatory oxygen therapy was not associated with improvements in physical activity, HRQL or time spent away from home[30]. This may reflect that patients need time to learn how to use oxygen, and ambulatory oxygen appears to enhance activities rather than increasing them. In other words, oxygen reduces dyspnea sensation and allows a better performance of a given activity; however, the amount of activities performed is not significantly increased.

Another randomised trial involving only 22 subjects investigated the influence of lightweight ambulatory oxygen on activity patterns in patients with COPD receiving LTOT[25]. The recruited patients were in current use of E-cylinders as ambulatory supply and were randomly assigned to continue using E-cylinders or to receive a lightweight oxygen supply. The later was an aluminium cylinder with carbon fiber and epoxy overwrap (M06D, Luxfer, Riverside,CA). When filled to 2400 psi, the system (tank, valve and regulator) weighed 3.6 lb. A carrying bag (OxyComfort, Kalispell, MT) was provided allowing the unit to be worn in a shoulder sling. Subjects were monitored for 6 months and PADL was objectively assessed with a tri-axial accelerometer (RT3, Stayhealthy, Monrovia,CA). Compared with using E-cylinders, it was expected that lightweight oxygen devices would increase daily oxygen use and activity level. Activity profiles and wearing times were similar in the 2 groups and, surprisingly, remained essentially unchanged throughout the intervention period. Calculation of average mid-day activity (defined as 10AM–4PM) demonstrated that neither intervention engendered any significant change in physical activity level, which means that the replacement of heavier oxygen tanks by lightweight ambulatory oxygen therapy failed to generate improvements in activity monitor assessments of PADL over a 6-month period[25]. Perhaps only providing lightweight oxygen may not change behaviour, and strategies to encourage oxygen use coupled with a behaviour modification intervention, such as pulmonary rehabilitation, would be more successful on physical activity improvement[2]. However, the reduced sample size was the main limitation of that study and the inability to find differences between the two treatment groups may result from a type 2 error. On the other hand, patients randomized to lightweight oxygen decreased ambulatory oxygen use by 47% compared to when they used E-cylinders.

The comparison of 6 months of stationary oxygen concentrator (OC) and 6 months of portable liquid oxygen (LO) in 30 patients qualified to LTOT demonstrated that both treatments increased exercise tolerance, quality of life and degree of dyspnoea intensity; however, treatment with LO resulted in more marked improvements[31]. Important methodologic limitations were present in this study, and PADL was not assessed. This reflects the scarce literature about PADL and its relations with different equipment suppliers of LTOT. Larger studies should be developed to investigate in depth the advantages of oxygen therapy in terms of PADL.

Although there is limited scientific evidence of portable oxygen therapy devices improving physical activity level, patients almost always prefer the lowest weight and longest lasting portable oxygen concentrators available. Accordingly, home oxygen patients might maintain high mobility to have a normal lifestyle. Moreover, increasing overall healthcare costs of patients by returning to the hospital due to complications associated with under-oxygenation and a sedentary lifestyle can be observed in those who prefer not to receive therapeutic oxygen to enable functional independence from the device and maintain mobility[32]. Despite presenting more dyspnea without oxygen supplement, hypoxemic patients did not always use their portable system as prescribed[22], and low adherence of LTOT may also lead to deleterious effects on the patients' health.

Home oxygen prescription requires detailed instructions on the dose of oxygen the patient will need at all activity levels and the oxygen equipment required to accomplish normal activities within and outside their home[19]. The health care team must take care of many aspects related to the patients receiving LTOT. Physical activity improvement among patients with LTOT should be a goal both for the patient and the caregiver. Although there is no solid evidence up to this moment on how oxygen therapy devices affect PADL, once again it is highlighted that oxygen therapy enhances activities rather than increases them. Moreover, physical activity level among patients with LTOT oxygen appears to be reduced when compared with patients without LTOT.

PORTABLE VENTILATORS

Dealing with ventilator-user patients

In the past, patients requiring mechanical ventilation due to CRD presented a poorer prognosis compared with nowadays. The clinical options and possibilities offered for patients due to the advance of medicine has changed and gained attention. The concern to provide portable ventilators for these patients is relatively recent. Overall, bed rest was frequently prescribed for critically ill patients, and this was assumed for conserving scarce metabolic resources[33]. Furthermore, higher levels of physical activity in patients receiving mechanical ventilation have been assumed to be impractical or not feasible in the past.

Randomized controlled clinical trials failed to demonstrate beneficial effects of bed rest in many conditions such as flares of rheumatoid arthritis, cavitary tuberculosis, acute myocardial infarction, and acute low back pain[33]. Moreover, deleterious effects for patients' health have been shown to be linked to prolonged periods of bed rest. Bed rest can cause several complications including disuse muscle atrophy, joint contractures, thromboembolic disease, and insulin resistance, which may delay or prevent recovery from critical illnesses. Furthermore, recent studies demonstrated the feasibility and safety of physical medicine programs in critically ill patients including those with acute respiratory failure requiring mechanical ventilation[33].

Although many patients with chronic critical illness require ventilatory support, most patients receiving prolonged mechanical ventilation do not have chronic critical illness. In patients with chronic respiratory failure (CRF) surviving prolonged ventilation on intensive care unit (ICU), the presence of CRF itself is the major determinant of health-related quality of life[34]. Therefore, the management of patients who are receiving ventilatory support has changed. Although mechanical ventilation is associated with less mobility[35], nowadays, there is growing interest to offer functional independence for these individuals aiming at improving quality of life and functional outcomes.

Ventilatory support is basically classified in two forms: non-invasive ventilation (NIV) or invasive support. The terminology “mechanical ventilation” is largely used in both cases, since there is a need for an equipment for assisting ventilation administration. NIV is the use of assisted ventilation without an artificial airway (eg, tracheostomy tube or endotracheal tube)[36]. A major driving force behind the increasing use of NIV has been the desire to avoid the complications of invasive ventilation[37]. For home mechanical ventilation, NIV has a number of advantages over invasive mechanical ventilation, including greater ease of administration, reduced need for skilled caregivers, elimination of tracheostomy-related complications, enhanced patient comfort and lower cost[37, 38].

Moreover, many patients use the ventilator for only part of the day, most often at night (i.e. nocturnal NIV), and it would not seem prudent to perform tracheostomy for part-time ventilation. In addition, issues related to the tracheostomy care complicate the management for both patients and caregivers[39]. On the other hand, many patients require continuous ventilatory support (i.e. ventilator-dependent patients). Some investigators have recommended consideration of tracheostomy ventilation when the need for ventilatory assistance exceeds 16 hours daily[40]; however, many still prefer NIV even for ventilator-dependent patients[41, 42]. NIV has become the standard of care for patients with neuromuscular disease and hypoventilation[42]. Moreover, it has been recently shown that NIV prolongs survival and improves or maintains quality of life in people with amyotrophic lateral sclerosis in comparison with tracheostomy[43].

Ventilatory support at the hospital and physical activity

The reduction of regular physical activity is associated with a higher risk of admissions and mortality in patients with COPD[44]. Moreover, physical activity is significantly reduced during hospitalisation due to an exacerbation of COPD even in those patients who do not require mechanical ventilation during hospitalization[2, 45-47]. On the other hand, it is estimated that 13 to 20 million people annually require ventilatory support in intensive care units (ICUs) worldwide[48]. Moreover, in general, inactivity is related to the use of mechanical ventilation and higher mortality[35]. A recent study showed that patients at the ICU who were mechanically ventilated were less likely to be out of bed compared with those who were not (98% reduction in odds) and also had 5 times higher odds of participating in no activity[49]. In a prospective, observational study involving 210 patients admitted to an acute respiratory care unit, the authors examined the longitudinal outcomes of mechanically ventilated patients[50]. Patients who did not come off mechanical ventilation in the respiratory unit were seven times more likely to die within a year than those who did. Additionally, patient ADL scores (0-100 scale) increased progressively from hospital discharge (24±6) through 3 months (54±21) and 6 months (64±22). Therefore, patients who were weaned from mechanical ventilation improved their ADL during the first 6 months after discharge; however, a substantial fraction of patients who were not weaned from mechanical ventilation died from consensual withdrawal of life support after a prolonged and costly hospital stay[50]. This clearly reflects physical activity impairment in mechanically ventilated patients, especially during hospital stay. The reduction of PADL observed during the period in which patients are receiving ventilatory support is easily understandable. If the patient is connected to an equipment which does not allow physical mobility, functionality will be compromised. The accurate monitoring of physical activity in critical ill patients who sometimes receive ventilatory support is essential for proper prescription and has gained attention[51, 52]. Therefore, performing physical activity in mechanically ventilated patients has been investigated[53] and early rehabilitation has been used as an efficient strategy to reduce days to first out of bed, duration of mechanical ventilation and length of ICU stay[54, 55]. Unfortunately, some patients will not be weaned from mechanical ventilation despite all efforts of the healthcare team. This specific population who need ventilatory support has stimulated the development of new technologies to compensate CRF and avoid the deleterious effects of being restricted to bed.

Portable ventilators

A large number of patients with respiratory diseases requiring mechanical ventilation are treated at home, and portable ventilators are typically used. Although less appropriate for the acute care setting where high flow rates may be needed, simple, small, inexpensive portable units are usually adequate for home applications[37]. Moreover, portable ventilators continue to decrease in size though the years while increasing in performance[56].

Bi-level pressure ventilators are commonly used, whereas a new generation of intermediate ventilators which have a long battery life and can be used for NIV and invasive applications are available[39] (Figure 6). Furthermore, type, mode, trigger, rise time, cycle ramp, humidification and safely should be also considered in the selection process of the ventilator[57].

Approximately 87% of patients using home mechanical ventilation are ventilated with NIV[58] and for many patients with CRF requiring ventilatory support, NIV is preferable to invasive support by tracheostomy[39]. This occurs due to the necessity to improve quality of life among patients requiring mechanical ventilation. NIV greatly simplifies care for patients with CRF at home and it has been increasingly used due to the greater comfort, safety, convenience due to portability and lower cost than invasive ventilation[37].

Scientific evidence with portable NIV devices are available in the current literature and the weight of the device must be taken into account[27, 59]. Dreher at al. found that NIV plus supplemental oxygen preserves oxygenation during walking in patients with severe COPD; however, dyspnea and walking distance were not improved due to the burden of carrying the heavy ventilator equipment in a backpack[59]. On the other hand, Porszasz et al. evaluated improvements in exercise tolerance of patients with severe hypoxemic COPD, facilitated by a novel portable lightweight (i.e. 1-lb), noninvasive open ventilation system (NIOV) featuring a nasal pillow interface, which is specifically intended to facilitate ambulation and ADL[60]. The device was tolerated well by the subjects and NIOV plus supplemental oxygen remarkably prolonged exercise tolerance accompanied by respiratory muscle unloading and dyspnea reductions[60]. Therefore, it seems reasonable to conclude that weight of portable ventilator impairs exercise performance and dyspnea of patients with CRD. Additionally, other aspects in the selection of a ventilator for NIV, such as battery life, alarms, costs, among others, should be taken into account[57]. Feasible application of home therapy with mechanical ventilation, especially using NIV, has shown clinical benefits as described below.

Benefits of non-invasive ventilation

In 1999, a consensus document was published with recommendations for the use of NIV in patients with stable COPD[61]. Since 1999, a few large randomized clinical trials (RCT) have been performed to examine the effects of nocturnal NIV on patients with stable COPD[62-64]. Based on the inclusion criteria of these studies, on the abovementioned 1999 consensus[61] and on the 2015 document from the Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (GOLD)[65], Table 2 describes indications for NIV in stable patients with COPD.

Despite some controversies, NIV may be beneficial in different situations for patients with CRD. NIV assists breathing and its primary aim is to augment alveolar ventilation, reduce work of breathing and to improve arterial blood gases (PaO2 and PaCO2). However, some individuals with lung disease will still need supplemental oxygen despite the use of NIV[65]. Its role in the hospital is well established and its benefits in patients treated in the community are of interest[39, 65, 66]. Regarding the effects of home NIV in CRD, a body of evidences is available in the scientific literature. Several outcomes in different clinical conditions have been investigated and the majority of studies included nocturnal NIV as the intervention. Associations between the use of NIV were described with blood gas exchange[62, 67, 68], health-related quality of life[62, 63, 68-70], exercise capacity[62, 63, 67, 68, 70-74] and sleep efficiency[62], among other outcomes

A Cochrane review study concluded that nocturnal NIV for at least three months in hypercapnic patients with stable COPD had no consistent clinically or statistically significant effects on gas exchange, exercise tolerance, health-related quality of life, lung function, respiratory muscle strength or sleep efficiency due to the small sample sizes and limitations of the studies[62]. Recently, Kohnlein et al. published the largest RCT to assess effects on mortality of nocturnal NIV compared with standard medical care in patients with stable COPD and hypercapnic respiratory failure[63]. It was a multicentre, prospective, randomized, controlled clinical trial with recruitment from 36 respiratory units with a follow-up of 12 months, in which a significant improvement of survival, quality of life and exercise capacity with nocturnal NIV compared with standard treatment was found[63]. However, despite the increasingly use of NIV in patients with stable very severe COPD, portable NIV presents some practical disadvantages such as cosmetic, assembly and carrying issues. Moreover, RCTs still provide contradictory results regarding the clinical benefits of long term-NIV in patients with COPD and chronic hypercapnia, especially in terms of health status and survival[62, 63, 65, 69]. Therefore, the use of portable NIV in stable COPD are not yet recommended in the latest 2015 GOLD guidelines due to insufficient evidence[65]. NIV has also been used during exercise since it is believed that its effects may acutely prevent hypoxia-induced complications, reduce exertional dyspnea and improve exercise endurance, in patients with COPD[74]. However, a recent systematic review about NIV during exercise training for people with COPD concluded that its effect on exercise capacity is unclear[75]. Some evidence suggests that NIV during exercise training improves the percentage change in peak and endurance exercise capacity, although these findings are not consistent[75]. NIV during unsupported arm exercise increased endurance time and reduced dyspnoea[76]. Moreover, positive acute effects of adding NIV with high-level pressure support in patients with severe COPD include the increase of almost 50 meters in the 6-minute walk test (6MWT)[77]. In contrast, dyspnoea and walking distance were not improved in ground walking in two other RCTs, perhaps due to the burden of carrying the heavy ventilator equipment in a backpack[59] or the inadequate pressure support provided during walking[76]. Therefore, evidence from the literature is still insufficient[69] and conclusions should be interpreted with caution at this moment.

Portable ventilators and physical activity

Despite the many benefits that ventilatory support can offer to patients with CRD, there is still lack of studies investigating the effects of portable ventilators on PADL. Although “portability” is notorious as a selection item for a ventilator to enable mobility and functional independence among patients using NIV, the minority of studies investigating effects of domiciliary NIV have focused on the PADL assessment. Moreover, a recent Cochrane review concluded that PADL was not assessed in any study about NIV during exercise training [75]. Additionally, as previously discussed, PADL presents a concept that differs from exercise, mobility or functional independence and even from activities of daily living, and the confusion regarding these definitions may also impair solid evidences to conclude whether there is PADL reduction among hypercapnic patients requiring nocturnal NIV in comparison to patients with stable lung disease or healthy elderly individuals. Moreover, the issue of whether or not there is an improvement in PADL when a portable ventilator is used remains a challenge, which will be discussed in the next subsection.

However, the first description of objectively assessed PADL in hypercapnic patients using nocturnal NIV and pedometers was published by Schonhofer et al. in 1997[78]. Patients with COPD who were not hypercapnic and a group of healthy elderly were also assessed in that study, which provides us an interesting comparison of PADL profile. Physical inactivity was markedly reduced in patients requiring nocturnal NIV in comparison to healthy elderly (Figure 7). Moreover, the level of PADL was markedly reduced in patients with hypercapnic ventilatory failure but increased following nocturnal NIV to the level observed in non-hypercapnic COPD patients[78].

Since 1997, just a few studies assessed PADL of patients with CRD requiring nocturnal NIV and no other study had the primary objective of identifying the profile of PADL among these patients[69, 78-82]. Based on five available studies which assessed PADL before and after the use of nocturnal

NIV, Table 3 exemplify objective values (i.e. mean steps/day or counts/day) described as the main results of those studies[69, 78-81]. Additionally, a randomised cross-over study comparing pressure and volume targeted nocturnal NIV in patients with CRF due to chest wall deformity assessed PADL using a pedometer in the final week of each 4-month treatment period[82]. These patients were used to NIV. Their mean daily counts (SE) were 1216 (277) steps/day and 1734 (761) steps/day for pressure and volume target nocturnal NIV, respectively. As a comparison, two previous studies involving stable patients with COPD who did not use nocturnal NIV yielded 5680±3104 [83] and 5584±3360[14] as mean±SD of steps/day. These findings reinforce the hypothesis that patients on NIV have a reduced PADL level when compared with healthy elderly individuals or stable patients with COPD who do not require NIV. Studies using "counts" as outcome still do not allow comparison of results due to different devices and outputs available.

It is noteworthy that pedometers might not be the best device to accurately count the number of steps in patients with CRD. High accuracy of daily step count detected by pedometers in patients with COPD is observed only during high walking speeds[84], since they walk on average 25% less briskly compared with healthy elderly[24]. These facts raise important questions about the use of pedometers to count steps in daily life in patients with CRD requiring NIV, and likewise in healthy elderly who walk slowly. Technologically advanced activity monitors (e.g. triaxial accelerometers) are more indicated for PADL assessments. However, the sensitivity of each activity monitor is determined not only by its type (pedometer, accelerometer) but also by each device's technical specifications, which implies that not necessarily all types of pedometers are less sensitive than all types of accelerometers. Future research on this field is encouraged to use activity monitors to accurately assess PADL[11] and better characterize physical activity profile of patients using nocturnal NIV.

There is no available study objectively comparing PADL of patients using heavy devices or new light and portable NIV devices at home. Moreover, the objectively assessed PADL profile was not compared between patients requiring nocturnal NIV and/or LTOT, as well as with patients with CRD who still need supplemental oxygen therapy despite NIV. All these patients deal with portable devices at home and one could hypothesize that patients using NIV present similar reduction of PADL in comparison to LTOT patients. These issues are also relevant for future research.

Portable ventilators for improved physical activity

There is increasing evidence that NIV enhances exercise capacity in patients with COPD, with a reduction of exercise-induced dyspnea when applied during exertion[74]. Furthermore, a 13% increase in training intensity was observed when NIV was applied during exercise training in these patients. On the other hand, NIV supplied with pre-established pressure may not be enough to prevent dynamic hyperinflation and dyspnea during activities of daily life with upper limbs in patients with COPD[85]. Moreover, an increased exercise capacity does not necessarily translate into an increased PADL level.

Up to this moment, there is no study evaluating the effects of NIV during exercise training on PADL improvement[75]. The available studies which have assessed PADL of patients with CRF using NIV were those in which nocturnal

NIV was applied[78-82]. Out of these, only one study assessed PADL with an objective and accurate device for this population[81]. In this study, patients with super obesity and associated CRF improved their daytime PADL after 3 months of using either volume targeted or bi-level pressure support during nocturnal NIV. More randomized studies with representative samples are strongly encouraged.

In a RCT, Duiverman et al. compared rehabilitation plus nocturnal NIV with rehabilitation alone in patients with COPD. They found that steps/day increased significantly more with nocturnal NIV plus rehabilitation in comparison to rehabilitation alone (P=0.01)[80]. It is known that exercise training may confer a significant but small increase in physical activity[86]. Moreover, the current literature presents mixed results concerning the translation of gains with pulmonary rehabilitation and exercise training alone into gains of PADL[87].

Four studies showed that patients with CRF increased PADL after 3 months of nocturnal NIV use[78-81]. Moreover, increase in daily step count correlated with reduction in PaCO2[78, 80] and was largest in those patients with more severe hypercapnia, suggesting that the improvement was real and not a finding by chance[78]. Only one study did not find significant improvement in PADL after nocturnal NIV[69]. It was the study with the largest sample; however, PADL was a secondary outcome which was not objectively assessed, and therefore this may have influenced negatively the conclusions. A summary of the studies investigating improvement of PADL with nocturnal NIV is presented in Table 3. Future studies investigating the influence of NIV on PADL with robust statistical analysis will corroborate with the understanding of these findings.

In a study by Kortianou and colleagues[88], limitation in tidal volume expansion determined the intensity of physical activity in patients with COPD assessed with an accelerometer during 7 days. The best contributors of the explained variance in daily movement intensity were inspiratory reserve chest wall volume (R^2 = 0.420), expiratory flow (R^2 = 0.174), and Borg dyspnea score (R^2 = 0.123), accounting for 71.7% of its variance. Patients with COPD exhibiting greater ability to expand tidal volume and to maintain adequate inspiratory reserve volume tended to be more physically active[88]. Thus, interventions aiming at mitigating restrictions on operational chest wall volumes and improving ventilation, such as the use of NIV, may enhance PADL in COPD. Above all, studies which use accurate devices to quantify improvement in PADL due to the use of portable ventilators are promising.

EXPERT COMMENTARY

Many studies have focused on quantifying physical activity in daily life (PADL) in different conditions and diseases in the last decade. Studies ranging from acute to stable diseases, from children to elderly patients, from underweight to obese subjects, among others, are found in the current literature.

Despite the growing interest in this issue, there are some aspects regarding PADL, especially in respiratory diseases, which are not yet investigated in depth. We believe that a relevant point is to understand how can we actually change behaviour of our patients and enable them to achieve a clinically relevant improvement of PADL, and then maintain this gain throughout the years.

Regarding physical impairments due to dyspnoea observed in hypoxemic and/or CRF patients, we considered that patients with CRD deserve more attention since increase in improvement in PADL needs to be strongly encouraged. Moreover, the need for a device to supply these patients either with oxygen or positive pressure can aggravate the reduced mobility and consequently PADL. The dependence of a device in day-by-day life will impair patients' PADL; however, the magnitude of their equipment-related physical inactivity is underexplored up to this moment.

Technological advances led to the development of different devices to enable mobility for patients with CRD. Therefore, one can expect that the association of modern portable devices with the known strategies to improve PADL, such as pulmonary rehabilitation, pharmacological therapy, behaviour change, feedback and counselling[2] may present good results on physical activity improvement.

FIVE YEARS VIEW

Technological advances led to the development of new models of portable ventilators and oxygen therapy devices. Nowadays, new equipments are available with modern design, light, small, noiseless, completely safe and which facilitate patients' mobility. However, one can speculate that in the future these devices will be even better qualified to support ventilatory demand allowing functional independence.

Considering the increased interest of researchers on investigating in depth many aspects related to PADL in patients with CRD, we believe and hope that in the following 5 years the detailed objective quantification of PADL among patients receiving LTOT or maintaining ventilatory support at home or during exercise will be performed with technologically advanced activity monitoring devices which are more sensitive to characterize the physical activity profile of these patients. Therefore, it will be possible to better understand the role of LTOT or NIV on PADL expected improvement, and perhaps it will be possible to identify some key characteristics of these patients which are determinants of PADL. This will stimulate manufactures to adapt and improve the devices even more.

Finally, the recent literature introduced an innovative respiratory assist device for patients with respiratory failure[89]. It is a novel portable artificial pump-lung device to provide long-term ambulatory cardiopulmonary and respiratory support for adult patients[90]. There are just few studies available about this new method which is implanted through thoracotomy[89-92]. It is important to highlight that these are animal studies or computer modelling and that no human trials have been conducted up to this moment. Probably five years is not time enough to expect positive results in humans. However, researchers suggest that this novel device can provide efficient respiratory support with good biocompatibility and it is ready for long-term evaluation[91]. Perhaps in the future, it will allow improvement in PADL due to allowing more independence and functionality to the patients. This promising device may be more explored in the coming years.

KEY ISSUES

- Equipment size and weight may impair exercise capacity and perhaps arrangements for mobility at home have important associations with physical activity improvement.
- Patients receiving long-term oxygen therapy (LTOT) present an impaired physical activity profile compared with non-LTOT patients.
- Up to this moment, there is no solid evidence on improvement of physical activity in daily life (PADL) regarding different equipments of oxygen therapy and perhaps providing lightweight oxygen may not in itself change behaviour.
- Ambulatory oxygen appears to enhance activities rather than increase them, and perhaps patients need time to learn how to use oxygen therapy.
- More long-term randomized controlled studies examining the effect of domiciliary use of ambulatory oxygen on PADL are required, as well as the use of non-invasive ventilation (NIV) during exercise.
- PADL is markedly reduced in patients requiring nocturnal NIV in comparison to healthy elderly.
- Four different studies showed improvement of PADL after three months of nocturnal NIV implementation with portable ventilators in hypercapnic patients.
- The clinical message of increased mobility and independence provided by portable ventilators may be considered by health professionals.

- Accurate activity monitors to assess PADL were not explored in depth in hypercapnic patients who require nocturnal NIV, as well as no study investigated the effects on PADL of NIV during exercise training.
- Studies which quantify improvement in PADL due to the use of a portable ventilator are lacking and will be welcome.

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Table 1: Indications for LTOT in patients with stable COPD.

1	Resting PaO_2 ≤ 55mmHg (or 7.3 kPa)	Based on strong evidence[18, 20]; consistent with GOLD guideline reccomendation[65]
2	Resting PaO_2 ≤8 kPa (or 56-59 mmHg) with evidence of peripheral edema, polycythaemia (haematocrit ≥55%) or pulmonary hypertension	Based on strong evidence[18, 20]; consistent with GOLD guideline reccomendation[65]
3	Resting hypercapnia if they fulfil all other criteria for LTOT	Based on strong evidence[20]; not consistent with GOLD guideline reccomendation[65].
4	Desaturation ≤ 88% with activities or at night	Based on less evidence[18]; not consistent with GOLD guideline reccomendation[65]

(Adapted from Stoller et al., 2010[18];Hardinge et al., 2015[20] and GOLD 2015[65]). LTOT: long-term oxygen therapy; COPD: Chronic Obstructive Pulmonary Disease; PaO_2: partial arterial blood pressure of oxygen; GOLD: Global Initiative for Lung Disease.

Table 2: Indications for non-invasive ventilation (NIV) in patients with stable COPD.

1.	GOLD stage III[64] or IV[62-65]
2.	Respiratory acidosis (pH ≤ 7.35)[63] with hypercapnia[39, 61, 63-65] (the more hypercapnic patient might benefit more from NIV[62]); one of the following criteria of hypercapnia: **a.** $PaCO_2$ ≥ 51.9 mmHg (or 7kPa) measured after at least 1h rest in a sitting position[63] **b.** $PaCO_2$ ≥ 46 mmHg at least twice in the previous 6 months during periods of clinical stability[64] **c.** $PaCO_2$ ≥55 mmHg[61] **d.** $PaCO_2$ of 50–54 mmHg and nocturnal desaturation ≤ 88% for 5 continuous minutes while receiving oxygen therapy ≥ 2 L/min[61] **e.** $PaCO_2$ of 50–54 mmHg and hospitalization related to recurrent episodes of hypercapnic respiratory failure (≥ 2 in a 12 month period)[61]

(Adapted from Kohnlein et al., 2014[63]; McEvoy et al., 2009[64]; Hess et al., 2012[39]; Struik et al., 2013[62]; GOLD 2015[65] and Consensus conference, 1999[61]). GOLD: Global Initiative for Lung Disease; $PaCO_2$: partial arterial blood pressure of carbon dioxide.

Table 3: Physical activity changes after nocturnal non-invasive ventilation

	Study population	Study design	Intervention	PADL outcomes and assessments	Main Result
Schonhofer et al., 1997[78]	(n=75) - Group 1: patients with CRF[a]; - Group 2: patients with stable non-hypercapnic COPD; - Group 3: normal healthy subjects studied once.	Non-randomised controlled	- Group 1 (n=25): Three months of nocturnal NIV; - Observational study from groups 2 (n=25) and 3 (n=25).	- Number of steps/day; - Pedometer Digiwalker SW-200; - Group 1: assessed before and three months after nasal nocturnal NIV; - Group 2: assessed twice, one month apart; - Group 3: assessed once.	- Steps/day increased significantly in group 1 after NIV (*P*<0.0001); - Before NIV: median 1,413(IQR=1,870) steps/day; - Last week NIV: median 3,553 (IQR=2,676) steps/day; - Group 3 presented greater daily count movement than Group 1 and Group 2.
Schonhofer et al., 1997[79]	(n=30) Patients with CRF[b]	One-group pre-test – post-test	Three months of nocturnal NIV	- Number of steps/day; - Pedometer Digiwalker SW-200; - Pre and post assessment.	- Steps/day increased significantly after NIV (by 120%; *P*<0.0001); - Before NIV: mean±SD of 1607±1341 steps/day; - Last week NIV: mean±SD of 3535±1814 steps/day.
Duiverman et al., 2008[80]	(n=72) Patients with chronic respiratory failure due to COPD	Parallel group randomised controlled	Three months of pulmonary rehabilitation (PR) in addition to nocturnal NIV (n=37) or rehabilitation alone (n=35)	- Number of steps/day - Pedometer Digiwalker SW-200; - Pre and post assessment.	- Steps/day increased significantly more with nocturnal NIV than with PR alone (median [IQR25-75%] difference of 1269[242-2296] steps/day;*P*=0.01); - Before NIV: median [IQR25-75%] of 1893 [591-3773] steps/day; - Last week NIV: median [IQR25-75%] of2799 [891-6135] steps/day.

Continue with table 3

	Study population	Study design	Intervention	PADL outcomes and assessments	Main Result
Murphy et al., 2012 [81]	(n=46) Patients with CRF due to super obesity	Randomised controlled	Three months of nocturnal NIV (randomised: AVAPS [n=23] versus fixed-levelPS [n=23]) using a strict protocolised setup	- Number of counts/day; - Actiwatch-64 - Assessment during the first week of NIV and after NIV.	- Counts/day significantly increased (*P*=0.016); - 28 patients wore the Actiwatch-64; - First week NIV: mean±SD of 232±100 counts/day; - Last week NIV: mean±SD of 263±94 counts/day; (*P*=0.016); - There was no between-group difference.
Struik et al., 2014 [69]	(n=201) Patients with COPD and prolonged hypercapnia after ventilatory support for acute respiratory failure	Randomised controlled	Twelve months of randomised nocturnal NIV versus standard treatment;optimal medical treatment, with LTOT in case of clinically stable patient with a PaO2<8.0 kPa);	Daily activities score (Groningen Activity and Restriction Scale); - Pre and post assessment.	- Total score of daily activity did not improve; - 50 patients used NIV and completed the daily activity scale; - Before NIV: 36.3 ± 8.3 - Last week NIV: 34.6 ± 9.4; - There was no between-group difference.

CRF: Chronic Respiratory Failure; COPD: chronic obstructive pulmonary disease; NIV: non-invasive ventilation; AVAPS: average volume-assured pressure support; PS: pressure support; LTOT: long-term oxygen therapy;
[a]kyphoscoliosis (n=7); COPD (n=6); post-polio scoliosis (n=5); post-tuberculosis (n=3); thoracoplasty (n=2); and muscular dystrophies (n=2);
[b]Kyphoscoliosis (n = 11), COLD (n = 7), neuromuscular diseases (n = 6), post-tbc sequelae (n = 6).

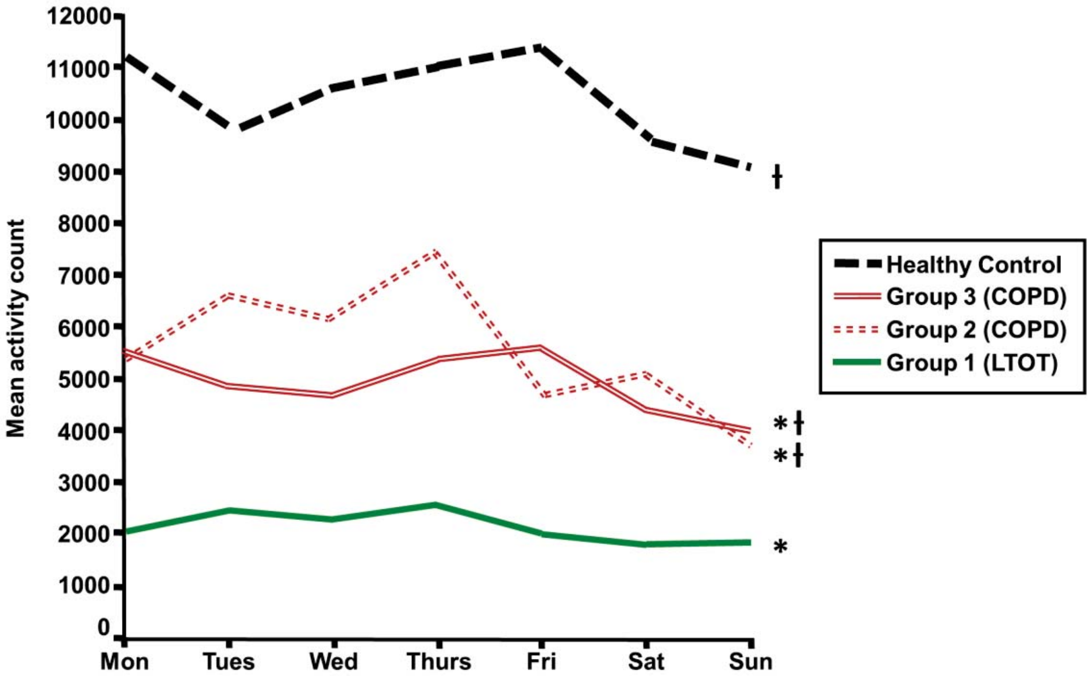

Figure 1: Mean activity count for 7 consecutive days in the four groups of subjects: group 1 with hypoxic patients with severe COPD receiving LTOT; group 2 with severe COPD who had full knowledge of the activity monitor and the purpose of the study; group 3 had severe COPD but were unaware of the precise nature of the study; and group 4 was a healthy age-matched control group.* : $p<0.05$ vs Group 4 (Healthy control); ɫ : $p<0.05$ vs Group 1 (LTOT).

(Adapted from Sandland et al., 2005[21], with permission).

Figure 2: Compressed oxygen cylinders (images from the internet).

Figure 3: Liquid oxygen systems (image from the internet).

Figure 4: Stationary oxygen concentrators (image adapted from the internet).

Figure 5: Portable oxygen concentrators (images from the internet).

Figure 6: Non-invasive ventilation during sleep (image from the internet).

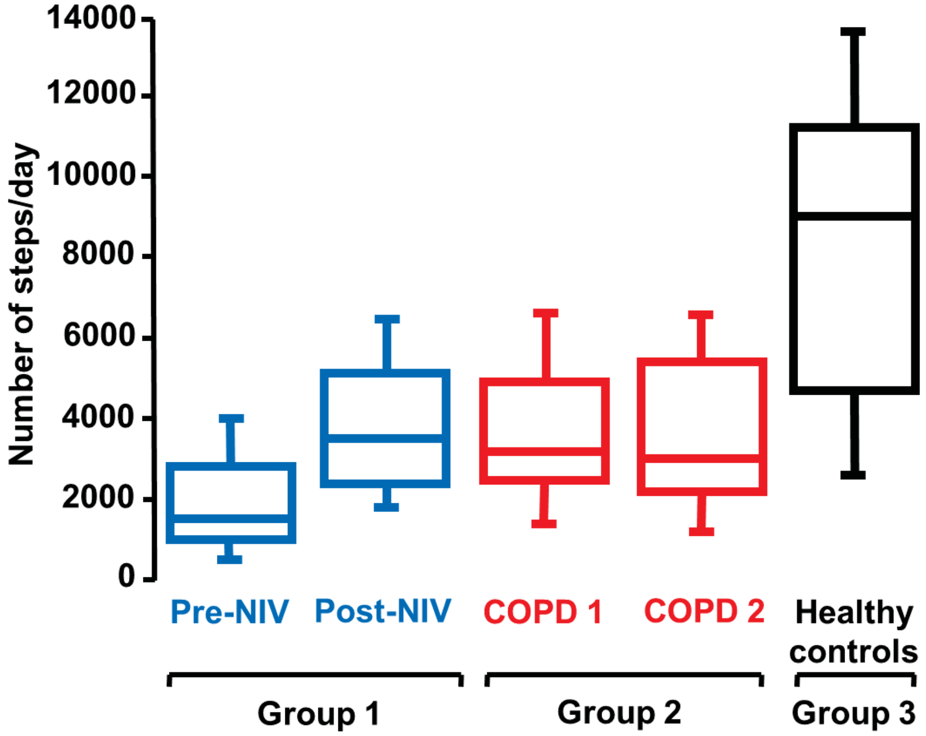

Figure 7: Box plots for the average daily movement count over 1 week (number of steps). The results from the three groups of subjects are shown. Group 1: patients with chronic respiratory failure before and three months after starting nocturnal mechanical ventilation (NIV). The increase in steps was significant at $p<0.0001$. Group 2: patients with chronic obstructive pulmonary disease (COPD) studied on two occasions 4 weeks apart (COPD 1 and COPD 2, respectively). There was no difference in mean number of steps/day ($p=0.1$). Group 3: healthy controls, the mean number of steps/day was significantly greater than any of the measurements obtained in the COPD and NIV patients ($p<0.0001$). The article also states that the number of steps/day in patients in pre-NIV was markedly reduced but increased following nocturnal NIV (post-NIV, group 1) to the level observed in non-hypercapnic COPD patients (group 2). Values are presented as 10th, 25th, 50th (median), 75th and 90th percentile. (Adapted from Schonhofer et al., 1997[78], with permission).

7 CONCLUSÃO GERAL DA TESE E PERSPECTIVAS FUTURAS

A presente tese acrescenta à literatura alguns achados científicos relacionados à atividade física na vida diária em pacientes com DPOC.

O primeiro estudo concluiu que 8:30 horas/dia em atividades que requerem <1.5 equivalente metabólico (MET) é um ponto de corte capaz de identificar pacientes com DPOC sedentários e que apresentam maior risco de mortalidade.

O segundo estudo identificou que pacientes com DPOC fisicamente ativos são caracterizados por melhor capacidade de exercício, função pulmonar, composição corporal e estado funcional quando comparados aos pacientes fisicamente inativos, independente do método de classificação utilizado.

O terceiro estudo concluiu que pacientes brasileiros são mais ativos que pacientes belgas independente das variáveis climáticas, e além disso, sugeriu que a atividade física na vida diária dos pacientes com DPOC está reduzida no período do inverno em ambas as regiões.

Por fim, o quarto estudo identificou, por meio de uma revisão de literatura, que pacientes com doença respiratória que utilizam oxigenoterapia ou VNI domiciliar apresentam a AFVD comprometida e que intervenções com implementação de VNI noturna parecem aumentar a AFVD de pacientes com hipercapnia.

Os quatro artigos científicos desenvolvidos apresentam conclusões clinicamente relevantes e mostram que os fatores pesquisados nesta tese impactam na AFVD de pacientes com DPOC. A associação entre um ponto de corte para sedentarismo e mortalidade abre a hipótese de que estratégias para reduzir o tempo sedentário podem aumentar a sobrevida desses pacientes. Além disso, estratégias para tornar o paciente com DPOC fisicamente mais ativo são fortalecidas com as evidências encontradas por meio da comparação entre os pacientes insuficientemente ou suficientemente ativos. Por fim, a variação climática e o uso de equipamentos portáteis como a oxigenoterapia domiciliar e a ventilação não invasiva noturna devem ser considerados nas avaliações dos pacientes com DPOC pois são fatores que impactam na AFVD desses pacientes. Novas pesquisas em pacientes com DPOC são incentivadas, a ponto de esperar-se que no futuro seja possível determinar quais formas de intervenção que têm como objetivo o aumento da atividade física e a redução do sedentarismo podem resultar em benefícios reais para a saúde desses pacientes.

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APÊNDICE A

Manual de uso dos monitores de atividade física

UNIVERSIDADE ESTADUAL DE LONDRINA

Departamento de Fisioterapia
Laboratório de Pesquisa em Fisioterapia Pulmonar

MANUAL DE INFORMAÇÕES SOBRE O USO DOS MONITORES DE ATIVIDADE FÍSICA NA VIDA DIÁRIA (DYNAPORT E ARMBAND)

INFORMAÇÕES GERAIS

Prezado participante,

Muito obrigado por sua participação nesse estudo. Para que o estudo tenha sucesso, por favor leia com atenção os pontos abaixo:

IMPORTANTE:

- Coloque os aparelhos no mesmo dia em que os recebeu, **antes de dormir.**
- É fundamental que você use os aparelhos durante **o dia todo e a noite toda.**
- Os aparelhos devem ser usados durante **8 dias seguidos.**
- **Não mude sua rotina.** Mantenha suas atividades o mais próximo do normal.
- Retire os aparelhos somente quando for tomar banho. **Os aparelhos não podem ser molhados!** Após o banho, coloque-os novamente.

NÃO ESQUEÇA DE ESCREVER (NO FINAL DESSE MANUAL) QUANDO VOCÊ COLOCOU E RETIROU OS APARELHOS.

CONTATO:

Em caso de dúvida ou problema, por favor entre em contato com:

José Roberto: 9985-4471 (TIM)

Luana: (44) 9829-5666 (TIM)

Patrícia: 9632-0453 (TIM)

Loana: (43) 9650-8424 (TIM)

Bárbara: 9179-8805 (VIVO)

Karina: 9114-4621 (VIVO)

Mariana: 99662-6294 (VIVO)

COMO USAR OS APARELHOS

COMO COLOCAR O APARELHO QUE FICA ABAIXO DA CINTURA

- Você deverá usar o aparelho **por baixo da roupa.**
- Coloque o cinto um pouco **abaixo do umbigo** e feche o velcro, de maneira que fique bem fixo, mas confortável.
- O aparelho deve ficar na parte **de trás do corpo,** sobre a linha da coluna, **com a seta apontando para cima.**

ISSO É MUITO IMPORTANTE! PARA TER CERTEZA DO POSICIONAMENTO CORRETO DO APARELHO, COMPARE COM A FOTO:

O APARELHO POR CIMA DA ROUPA É APENAS ILUSTRATIVO. É NECESSÁRIO USÁ-LO POR BAIXO DA ROUPA.

COMO COLOCAR O APARELHO DO BRAÇO

- O aparelho deve ser colocado no **braço esquerdo**, **por baixo da roupa.**
- Coloque o aparelho no alto do braço, virado para trás.
- Deixe o aparelho **bem fixo** no braço (fechando com o velcro), de maneira confortável.
- O aparelho deve estar posicionado com a com a **seta apontando para cima**.
- Logo depois de ser colocado, o aparelho irá tremer e emitir um som rapidamente. Este é o sinal de que ele está ligando. Quando você retirar o aparelho, ele fará o mesmo sinal, quando estiver desligando.
- Você **não** deve apertar nenhum botão.

ISSO É MUITO IMPORTANTE! PARA TER CERTEZA DO POSICIONAMENTO CORRETO DO APARELHO, COMPARE COM A FOTO:

APÊNCDICE B

Controle de uso dos monitores de atividade física

DIÁRIO DE USO

<u>NÃO DEIXE DE PREENCHER!!!</u>

DIA 1 (__ / __ ________________):
HORÁRIO DE COLOCAÇÃO DOS APARELHOS (Antes de dormir): __________

Outras anotações:

DIA 2 (__ / __ ________________):
Horário que retirou para o banho: __________
Horário que colocou novamente após o banho: __________

Outras anotações:

DIA 3 (__ / __ ________________):
Horário que retirou para o banho: __________
Horário que colocou novamente após o banho: __________

Outras anotações:

DIA 4 (__ / __ ________________):
Horário que retirou para o banho: __________
Horário que colocou novamente após o banho: __________

Outras anotações:

DIA 5 (__ / __ ________________):
Horário que retirou para o banho: __________
Horário que colocou novamente após o banho: __________

Outras anotações:

DIA 6 (__ / __ ________________):
Horário que retirou para o banho: __________
Horário que colocou novamente após o banho: __________

Outras anotações:

DIA 7 (__ / __ ________________):
Horário que retirou para o banho: __________
Horário que colocou novamente após o banho: __________

Outras anotações:

DIA 8 (__ / __ ________________):
Horário que retirou para o banho: __________
Horário que colocou novamente após o banho: __________

Outras anotações:

VOCÊ DEVERÁ **RETIRAR DEFINITIVAMENTE** OS APARELHOS NO DIA: __ / __ / __ (________________), ASSIM QUE LEVANTAR-SE DA CAMA PELA MANHÃ.

HORÁRIO EM QUE RETIROU OS APARELHOS DEFINITIVAMENTE: ____h:____min

ANEXO A

Parecer do Comitê de Ética em Pesquisa

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ESTUDO SOBRE (IN)ATIVIDADE FÍSICA DA VIDA DIÁRIA E MORTALIDADE EM PACIENTES COM DPOC

Pesquisador: KARINA COUTO FURLANETTO

Área Temática:

Versão: 2

CAAE: 41437014.0.0000.5231

Instituição Proponente: CCS - Departamento de Fisioterapia

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 996.413

Data da Relatoria: 20/03/2015

Apresentação do Projeto:

Trata-se de um projeto de pesquisa sob coordenação da Prof. Karina Couto Furlanetto, do Departamento de Fisioterapia da Universidade Estadual de Londrina (UEL). É um "estudo de coorte com análise retrospectiva de prontuários de pacientes com DPOC [doença pulmonar obstrutiva crônica], incluídos em um programa de reabilitação pulmonar nos anos de 2006 a 2014. Na avaliação inicial, os pacientes foram submetidos à avaliação do nível de atividade física na vida diária (AFVD) por meio de acelerômetros, além de avaliações da função pulmonar, força muscular respiratória, capacidade de exercício, força muscular periférica, qualidade de vida, estado funcional e sensação de dispneia. Os dados atuais referentes ao estado vital serão coletados por meio do acesso ao banco de dados do Núcleo de Informação de Mortalidade (NIM) da Autarquia Municipal de Saúde do Estado do Paraná. Caso o paciente tenha ido a óbito, serão coletadas informações sobre a data de morte e a etiologia no referido banco de dados. Após coletadas essas informações, os dados serão analisados levando-se em consideração dois grupos: grupo sobrevivente e grupo não sobrevivente". O estudo parte da seguinte hipótese: "[...] o tempo gasto em sedentarismo ou em atividade física seja um importante fator de predição de mortalidade em pacientes com DPOC".

Objetivo da Pesquisa:

Objetivo Primário:

Definir um ponto de corte para tempo gasto em sedentarismo em pacientes com DPOC, e investigar sua associação com a mortalidade, comparando este ponto de corte a outros fatores preditores de mortalidade já estabelecidos na literatura.

Objetivo Secundário:

• Identificar um ponto de corte para tempo gasto em sedentarismo em pacientes com DPOC a partir da recomendação de 30 minutos de atividade física de intensidade moderada a vigorosa (AFMV).

• Investigar a associação desse novo ponto de corte com a mortalidade nesses pacientes.

• Avaliar o poder de predição de mortalidade de diferentes desfechos de (in)atividade física de vida diária medida objetivamente em pacientes com DPOC e compará-los com o poder de predição de desfechos previamente conhecidos como preditores de mortalidade da doença.

• Determinar a variável de (in)atividade física de vida diária com maior poder de predição de mortalidade em pacientes com DPOC.

Avaliação dos Riscos e Benefícios:

Como não há a previsão de participantes no projeto, apenas a consulta de prontuários, não há riscos para participantes. Com relação aos benefícios, são para a área de estudos.

Comentários e Considerações sobre a Pesquisa:

A pesquisadora sanou todas as pendências, como indicado a seguir, in verbis:

1) TCLE para os participantes da pesquisa prospectiva finalizada, que figurarão como participantes na nova pesquisa;

R: A nova pesquisa é um estudo retrospectivo que dispensa o TCLE, devido à metodologia proposta. Os dados sobre mortalidade dos participantes da nova pesquisa NÃO serão coletados por meio de contato telefônico ou visita domiciliar, e sim em prontuários, por meio do acesso ao banco de dados do Núcleo de Informação de Mortalidade (NIM) da Autarquia Municipal de Saúde do Estado do Paraná (adequações no sistema da Plataforma Brasil foram realizadas).

2) TCLE para os responsáveis por informações sobre a morte dos participantes da pesquisa prospectiva finalizada, que figurarão como participantes na nova pesquisa;

R: A nova pesquisa não realizará ligações telefônicas ou visitas domiciliares. Os dados atuais referentes ao estado vital serão coletados por meio do acesso ao Núcleo de Informação em Mortalidade (NIM) da Autarquia Municipal de Saúde.

3) Folha de rosto assinada pela coordenação do Programa de Doutorado em Ciências da Reabilitação UEL/UNOPAR;
R: Acredito que houve um mal entendido quanto à instituição proponente do projeto de pesquisa devido ao anexo da autorização emitido pela Autarquia. Este projeto não foi cadastrado na UEL como projeto de pós-graduação e sim no meu nome, como docente do departamento de Fisioterapia. Eu também sou aluna de doutorado do programa de Ciências da Reabilitação orientada pelo professor Fabio Pitta, que é colaborador desse projeto, e quando a solicitei a autorização na Autarquia Municipal de Saúde do Estado do Paraná, também forneci essa informação. Os dados coletados neste projeto de pesquisa provavelmente renderão um segundo artigo durante o período do meu doutorado e talvez um segundo artigo da aluna Leila Donária (citado na autorização da Autarquia), por isso achei pertinente informá-los, mas o ESTUDO SOBRE (IN)ATIVIDADE FÍSICA DA VIDA DIÁRIA E MORTALIDADE EM PACIENTES COM DPOC, não é projeto de doutorado ou mestrado e sim do departamento de Fisioterapia. Gostaria gentilmente de solicitar que fosse mantida a folha de rosto previamente enviada para que fosse levado adiante como está, pois este projeto contabiliza carga horária docente na UEL e já está até na pauta da próxima reunião de departamento.

4) Apresentação do "Termo de Sigilo e Confidencialidade";
R: Inclui o "Termo de Sigilo e Confidencialidade" (em anexo no sistema).

5) Indicação de um membro da equipe que propiciará acolhimento ou indicação do tipo de encaminhamento a ser dado no caso dos participantes se sentirem emocionalmente abalados por conta da abordagem da questão da morte.
6) Roteiro das perguntas que serão feitas aos participantes, especialmente aquelas que tratarão sobre óbitos.
R (questões 5 e 6): Visto que os dados serão coletados em prontuários, as questões 5 e 6 também não se aplicam ao presente estudo.

Considerações sobre os Termos de apresentação obrigatória:
Foram contemplados todos os termos de apresentação obrigatória.

Recomendações:
Não há.

Conclusões ou Pendências e Lista de Inadequações:

Não há.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

Prezado (a) Pesquisador (a),

Este é seu parecer final de aprovação, vinculado ao Comitê de Ética em Pesquisas Envolvendo Seres Humanos da Universidade Estadual de Londrina. É sua responsabilidade imprimi-lo para apresentação aos órgãos e/ou instituições pertinentes.

Coordenação CEP/UEL.

LONDRINA, 24 de Março de 2015

Assinado por:
Alexandrina Aparecida Maciel Cardelli
(Coordenador)

ANEXO B

Normas de formatação do periódico *Journal of Cardiopulmonary Rehabilitation and Prevention*

Instructions for Authors

Ethical/Legal Considerations
A submitted manuscript must be an original contribution not previously published (except as an abstract or a preliminary report), must not be under consideration for publication elsewhere, and, if accepted, must not be published elsewhere in similar form, in any language, without the consent of Lippincott Williams & Wilkins. Each person listed as an author is expected to have participated in the study to a significant extent. Although the editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with the Journal, its editors, or the publisher.

All manuscripts must be submitted online through the journal's Web site at http://jcrp.edmgr.com/. See submission instructions, under "manuscript submission."

Permissions
Authors must submit written permission from the copyright owner (usually the publisher) to use direct quotations, tables, or illustrations that have appeared in copyrighted form elsewhere, along with complete details about the source. Any permissions fees that might be required by the copyright owner are the responsibility of the authors requesting use of the borrowed material, not the responsibility of Lippincott Williams & Wilkins.

For permission and/or rights to use content for which the copyright holder is LWW, please go to the journal website and after clicking on the relevant article, click on the "Request Permissions" link under the "Article Tools" box that appears on the right side of the page. Alternatively, send an e-mail to customercare@copyright.com.

Further information available in the LWW Author's Permissions guide: https://www.lww.com/opencms/opencms/web/PEMR/PDFs/docs/authorsPermissionDoc.pdf

For Translation Rights & Licensing queries, contact Silvia Serra, Translations Rights, Licensing & Permissions Manager, Wolters Kluwer Health (Medical Research) Ltd, 250 Waterloo Road, London SE1 8RD, UK. Phone: +44 (0) 207 981 0600. E-mail: silvia.serra@wolterskluwer.com

For Special Projects **and Reprints** (U.S./Canada), contact Alan Moore, Director of Sales, Lippincott Williams & Wilkins, Two Commerce Square, 2001 Market Street, Philadelphia, PA 19103. Phone: 215-521-8638. E-mail: alan.moore@wolterskluwer.com

For Special Projects **and Reprints** (non-U.S./Canada), contact Silvia Serra, Translations Rights, Licensing & Permissions Manager, Wolters Kluwer Health (Medical Research) Ltd, 250 Waterloo Road, London SE1 8RD, UK. Phone: +44 (0) 207 981 0600. E-mail: silvia.serra@wolterskluwer.com

Preparation of Manuscript
Manuscripts that do not adhere to the following instructions will be returned to the corresponding author for technical revision before undergoing peer review.

Manuscript Submission

Authors are invited to submit original investigations, scientific reviews, brief reports, and case reports in all areas relating to the prevention and management of cardiopulmonary disease. These areas include but are not limited to cardiac and/or pulmonary rehabilitation, primary and secondary prevention, epidemiology, and exercise testing and training.

All manuscripts must be submitted on-line through the Journal Web site at http://jcrp.edmgr.com/. **First-time users:** Please click the Register button from the menu above and enter the requested information. On successful registration, you will be sent an E - mail indicating your user name and password. Print a copy of this information for future reference. Note: If you have received an E - mail from us with an assigned user ID and password, or if you are a repeat user, do not register again. Just log in. Once you have an assigned ID and password, you do not have to re-register, even if your status changes (that is, author, reviewer, or editor). **Authors:** Please click the log-in button from the menu at the top of the page and log in to the system as an Author. Submit your manuscript according to the author instructions. You will be able to track the progress of your manuscript through the system. If you experience any problems, please contact **Abigail Lynn, Editorial Coordinator at jcrp@smithbucklin.com**. Requests for help and other questions will be addressed in the order received.

As of January 1, 2013, JCRP no longer requires that manuscripts be submitted in a blinded format. Author names, institutions, funding information, etc, are permissible within manuscript text.

If possible, all tables and figures should be included at the end of the text. The word count for the **text-only** portion for original investigations should be limited to 3000 words. A shortened form of the title should be included at the top of each manuscript page after the title page. A structured abstract and condensed abstract should be included for all manuscripts. Manuscripts are received with the understanding that they have not been previously published and are not currently under consideration for publication in any other journal. Manuscripts will be acknowledged upon receipt; those accepted for publication are subject to copy editing. The name, address, home and work telephone numbers, fax number, and e-mail address of the author responsible for correspondence regarding the manuscript should be included in an accompanying cover letter.

Acknowledgments must be given when material from other publications is included. Copies of the authors' and publishers' permission letters should be included with the manuscript. Provide names of author(s), title of article, title of journal or book, volume number, page(s), month, and year.

Figures:

A) Creating Digital Artwork

Learn about the publication requirements for Digital Artwork: http://links.lww.com/ES/A42

1. Create, Scan and Save your artwork and compare your final figure to the Digital Artwork Guideline Checklist (below).
2. Upload each figure to Editorial Manager in conjunction with your manuscript text and tables.

B) Digital Artwork Guideline Checklist

Here are the basics to have in place before submitting your digital artwork:

- Artwork should be saved as TIFF, EPS, or MS Office (DOC, PPT, XLS) files. High resolution PDF files are also acceptable.

- Crop out any white or black space surrounding the image.
- Diagrams, drawings, graphs, and other line art must be vector or saved at a resolution of at least 1200 dpi. If created in an MS Office program, send the native (DOC, PPT, XLS) file.
- Photographs, radiographs and other halftone images must be saved at a resolution of at least 300 dpi.
- Photographs and radiographs with text must be saved as postscript or at a resolution of at least 600 dpi.
- Each figure must be saved and submitted as a separate file. Figures should not be embedded in the manuscript text file.

Remember:

- Cite figures consecutively in your manuscript.
- Number figures in the figure legend in the order in which they are discussed.
- Upload figures consecutively to the Editorial Manager web site and enter figure numbers consecutively in the Description field when uploading the files.

Color Figures

The journal accepts for publication color figures that will enhance an article. Authors who submit color figures will receive an estimate of the cost for color reproduction. If they decide not to pay for color reproduction, they can request that the figures be converted to black and white at no charge.

Tables: Create tables using the table creating and editing feature of the word processing software (ie, Microsoft Word). Do not use Excel or comparable spreadsheet programs. Group all tables at the end of the manuscript, or supply them together in a separate file. Cite tables consecutively in the text, and number them in that order. Key each on a separate sheet, and include the table title, appropriate column heads, and explanatory legends (including definitions of any abbreviations used). Do not embed tables within the body of the manuscript. They should be self-explanatory and should supplement, rather than duplicate, the material in the text.

ABBREVIATIONS

Abbreviations should be limited to five commonly used terms or phrases per manuscript. Abbreviations should be spelled out at the first mention in the abstract and then again in the body of the text. The abbreviation should follow in parentheses. A term or phrase should be used more than five times to merit abbreviation.

TITLE PAGE

Information on the title page should include the full name, academic degree, hospital or university affiliation of each author and a word count for text only (excluding references). If an author's present affiliation is different from that under which the work was done, both should be given. The name, address, phone, fax, and e-mail of the corresponding author should be provided.

The title page must also include disclosure of funding received for this work from any of the following organizations: National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI); and other(s).

FORMAT AND ABSTRACTS

Original investigations should follow this outline: 1) title page; 2) structured abstract and condensed abstract; 3) introduction and statement of purpose; 4) patients (or subjects) and methods; 5) results; 6) discussion; 7) references; 8) tables; and 9) figure legends.

All submissions should be accompanied by two abstracts: a structured abstract of 250 words or less and a condensed abstract of no more than 50 words for use in the Table of Contents. The structured abstract should consist of four paragraphs, labeled Purpose, Methods, Results, and Conclusions. They should briefly describe, respectively, the rationale for the study, how the study was conducted, the salient results, and what the authors conclude from the findings.

REFERENCES

References should be listed in the order in which they appear in the article and should be typed double-spaced. Authors are responsible for the completeness and accuracy of all references. Journal references should include authors' surnames followed by initials (without punctuation), title of article, name of journal as abbreviated in *Index Medicus*(if not included in *Index Medicus*, the journal name should be spelled out), year of publication, volume number, and inclusive page numbers. If there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first three authors and et al is adequate. Personal communications and unpublished data should be included within the text of the manuscript or as footnotes, not as references. References should be formatted as shown in the American Medical Association Manual of Style 10th edition.

SUBMISSION REQUIREMENTS FOR ALL CATEGORIES

- Manuscripts must conform to "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (*N Engl J Med*. 1997;336:309-315).
- Manuscripts may not contain previously published material or be under consideration for publication elsewhere.
- If an author has work that is in preparation, has been previously submitted or published, or is in press and potentially overlaps the submitted manuscript, the work must be submitted as an attachment with the current submission.
- All sources of support must be cited on the title page. Sources of support and potential conflicts of interest must be stated in the submission letter.
- A statement of submission must accompany the manuscript. It should state the following: "All authors have read and approved submission of the manuscript and the manuscript has not been published and is not being considered for publication elsewhere in whole or part in any language except as an abstract."
- Word count for the text-only portion of the manuscript should be stated in the title page.

AFTER ACCEPTANCE

Page Proofs and Corrections

Corresponding authors will receive electronic page proofs to check the copyedited and typeset article before publication. Portable document format (PDF) files of the typeset pages and support documents (e.g., reprint order form) will be sent to the corresponding author by E - mail. Complete instructions will be provided with the E - mail for downloading and printing the files and for faxing the corrected page proofs to the publisher. It is the author's responsibility to ensure that there are no errors in the proofs. Changes that have been made to conform to journal style will stand if they do not alter the authors' meaning. Only the most critical changes to the accuracy of the content will be made. Changes that are stylistic or are a reworking of previously accepted material will be disallowed. The publisher reserves the right to deny any changes that do not affect the accuracy of the content. Authors may be charged for alterations to the proofs beyond those required to correct errors or to answer queries. Proofs must be checked carefully and corrections faxed within 24 to 48 hours of receipt, as requested in the cover letter accompanying the page proofs.

COMPLIANCE WITH NIH AND OTHER RESEARCH FUNDING AGENCY ACCESSIBILITY REQUIREMENTS

A number of research funding agencies now require or request authors to submit the post-print (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. As a service to our authors, LWW will identify to the National Library of Medicine (NLM) articles that require deposit and will transmit the post-print of an article based on research funded in whole or in part by the National Institutes of Health, Wellcome Trust, Howard Hughes Medical Institute, or other funding agencies to PubMed Central. The revised Copyright Transfer Agreement provides the mechanism.

OPEN ACCESS

LWW's hybrid open access option is offered to authors whose articles have been accepted for publication. With this choice, articles are made freely available online immediately upon publication. Authors may take advantage of the open access option at the point of acceptance to ensure that this choice has no influence on the peer review and acceptance process. These articles are subject to the journal's standard peer-review process and will be accepted or rejected based on their own merit.

Authors of accepted peer-reviewed articles have the choice to pay a fee to allow perpetual unrestricted online access to their published article to readers globally, immediately upon publication. The article processing charge for *Journal of Cardiopulmonary Rehabilitation and Prevention* is $2,600. The article processing charge for authors funded by the Research Councils UK (RCUK) is $3,275. The publication fee is charged on acceptance of the article and should be paid within 30 days by credit card by the author, funding agency or institution. Payment must be received in full for the article to be published open access.

CONFLICTS OF INTEREST

Authors must state all possible conflicts of interest in the manuscript, including financial, consultant, institutional, and other relationships that might lead to bias or a conflict of interest. If there is no conflict of interest, this should also be explicitly stated as none declared. All sources of funding should be acknowledged in the manuscript. All relevant conflicts of interest and sources of funding should be included on the title page of the manuscript with the heading “Conflicts of Interest and Source of Funding.” For example:

Conflicts of Interest and Source of Funding: A has received honoraria from Company Z. B is currently receiving a grant (#12345) from Organization Y, and is on the speaker’s bureau for Organization X—the CME organizers for Company A. For the remaining authors none were declared.

In addition, each author must complete and submit the journal's copyright transfer agreement, which includes a section on the disclosure of potential conflicts of interest based on the recommendations of the International Committee of Medical Journal Editors, "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (www.icmje.org/update.html).

A copy of the form is made available to the submitting author within the Editorial Manager submission process. Co-authors will automatically receive an Email with instructions on completing the form upon submission.

ANEXO C

Parecer do Comitê de Ética em Pesquisa

Universidade Estadual de Londrina

GOVERNO DO PARANÁ

COMITÊ DE ÉTICA EM PESQUISA ENVOLVENDO SERES HUMANOS

Parecer Nº 061/06	**Londrina, 06 de abril de 2006.**

PESQUISADOR(A): FABIO DE OLIVEIRA PITTA

Ilmo(a) Sr(a),

O Comitê de Ética em Pesquisa envolvendo Seres Humanos da Universidade Estadual de Londrina – CEP – UEL – de acordo com as orientações da Resolução 196/96 do Conselho Nacional de Saúde/MS , **APROVA** a realização do projeto: **"PERFIL DE ATIVIDADE FÍSICA NA VIDA DIÁRIA DO PACIENTE PORTADOR DE DPOC NO BRASIL: ESTUDO CONTROLADO".**

Informamos que deverá ser comunicado, por escrito, qualquer modificação que ocorrer no desenvolvimento da pesquisa.

Desejamos sucesso na realização da pesquisa.

Situação do Projeto: **APROVADO**

Atenciosamente,

Profª. Dra. Nilza Maria Diniz
Comitê de Ética em Pesquisa
Coordenadora

Campus Universitário: Rodovia Celso Garcia Cid (PR 445), Km 380 - Fone (43) 3371-4000 - PABX - Fax 3328-4440 - Caixa Postal 6001 - CEP 86051-990 - Internet http://www.uel.br

LONDRINA - PARANÁ - BRASIL

Form. Código 11.764 - Formato A4 (210x297)

ANEXO D

Normas de formatação do periódico *Brazilian Journal of Physical Therapy*

Scope and policies

The Brazilian Journal of Physical Therapy (BJPT) publishes original research articles, reviews, and brief communications on topics related to the professional activity of physical therapy and rehabilitation, including clinical, basic or applied studies on the assessment, prevention, and treatment of movement disorders. Our Editorial Board is committed to disseminating quality scientific investigations from many areas of expertise.

The BJPT follows the principles of publication ethics included in the code of conduct of the Committee on Publication Ethics (COPE).

The BJPT accepts the following types of study, which must be directly related to the journal's scope and expertise areas:

a) Experimental studies: studies that investigate the effect(s) of one or more interventions on outcomes directly related to the BJPT's scope and expertise areas.

The World Health Organization defines a clinical trial as "any research study that prospectively allocates human participants or groups of humans to one or more health-related interventions to evaluate the effect(s) on health outcome(s)". Clinical trials include single-case experimental studies, case series, nonrandomized clinical trials, and randomized clinical trials. Randomized controlled trials (RCTs) must follow the CONSORT (Consolidated Standards of Reporting Trials) recommendations, which are available at: http://www.consort-statement.org/consort-statement/overview0/.

The CONSORT checklist and Statement Flow Diagram, available at http://www.consortstatement.org/downloads/translations, must be completed and submitted with the manuscript.

Clinical trials must provide registration that satisfies the requirements of the International Committee of Medical Journal Editors (ICMJE), e.g. ttp://clinicaltrials.gov/ and/or http://www.anzctr.org.au. The complete list of all clinical trial registries can be found at: http://www.who.int/ictrp/network/primary/en/index.html

b) **Observational studies:** studies that investigate the relationship(s) between variables of interest related to the BJPT's scope and expertise areas without direct manipulation (e.g. intervention). Observational studies include cross-sectional studies, cohort studies, and case-control studies.

c) **Qualitative studies:** studies that focus on understanding needs, motivations, and human behavior. The object of a qualitative study is guided by in-depth analysis of a topic, including opinions, attitudes, motivations, and behavioral patterns without quantification. Qualitative studies include documentary and ethnographic analysis.

d) **Systematic reviews:** studies that analyze and/or synthesize the literature on a topic related to the scope and expertise areas of the BJPT. Systematic reviews that include meta-analysis will have priority over other systematic reviews. Those that have an insufficient number of articles or articles with low quality in the Methods section and do not include an assertive and valid conclusion about the topic will not be considered for peer-review analysis. The authors must follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist to format their systematic reviews. The checklist is available at http://prisma-statement.org/statement.htm and must be filled in and submitted with the manuscript. Potential authors are encouraged to read the paper Mancini MC, Cardoso JR, Sampaio RF, Costa LCM, Cabral CMN, Costa LOP. Tutorial for writing systematic reviews for the Brazilian Journal of Physical Therapy (BJPT). Braz J Phys Ther. 2014 Nov-Dec; 18(6):471-480.http://dx.doi.org/10.1590/bjpt-rbf.2014.0077.

e) **Studies on the translation and cross-cultural adaptation of questionnaires or assessment tools:** studies that aim to translate into and/or cross-culturally adapt foreign questionnaires to a language other than that of the original version of existing assessment instruments. The authors must use the checklist (Appendix) to format this type of paper and adhere to the other recommendations of the BJPT. The answers to the checklist must be submitted with the manuscript. At the time of submission, the authors must also include written permission from the authors of the original instrument that was translated and/or cross-culturally adapted.

f) Methodological studies: studies centered on the development and/or evaluation of clinimetric properties and characteristics of assessment instruments. The authors are encouraged to use the Guidelines for Reporting Reliability and Agreement Studies (GRRAS) to format methodological papers, in addition to following BJPT instructions.

Important: Studies that report electromyographic results must follow the Standards for Reporting EMG Data recommended by ISEK (International Society of Electrophysiology and Kinesiology), available at http://www.isek-online.org/standards_emg.html.

Ethical and legal aspects

Submitting a manuscript to the BJPT implies that the paper has not been submitted simultaneously to another journal. The papers published in the BJPT are free access and distributed under the terms of Creative Commons Attribution, Non-Commercial License (http://creativecommons.org/licenses/by/3.0/deed.pt_BR), which allows free non-commercial use, distribution, and reproduction into any means, as long as the original format is maintained. The reproduction of part of a manuscript, even partially, including translation to another language, requires prior authorization from the editor.

The authors must cite the corresponding credits. Ideas, data or phrases from other authors without the appropriate citations and with hints of plagiarism will be subject to penalties according to the COPE code of conduct.

If part of the material has been presented in a preliminary format (at a symposium, conference, etc.), the reference of the presentation must be cited as a footnote in the title page.

The use of patient initials, names or hospital registration numbers must be avoided. Patients must not be identified in photographs, except with their express written consent attached to the original article at the time of submission.

Studies in humans must be in agreement with COPE ethical standards and must be approved by the institution's ethics committee.

Animal experiments must comply with international guidelines (such as those of the Committee for Research and Ethical Issues of the International Association for the Study of Pain, published in Pain, 16:109110, 1983).

The BJPT reserves the right not to publish manuscripts that do not adhere to the legal and ethical rules for human and animal research.

Authorship criteria

The BJPT accepts submissions of manuscripts with up to six (6) authors. The BJPT's authorship policy follows ICMJE requirements for Manuscripts Submitted to Biomedical Journals (www.icmje.org), which state that "authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published." Conditions 1, 2, and 3 should all be met simultaneously. Grant acquisition, data collection, and/or general supervision of a research group do not justify authorship and must be recognized in the acknowledgements.

In exceptional cases, the editors may consider a request for submission of a manuscript with more than six (6) authors. The criteria for analysis include the type of study, potential for citation, quality, and methodological complexity, among other things. In these exceptional cases, each author's contribution must be described at the end of the text, after the Acknowledgements and right before the References as recommended by the ICMJE and the Guidelines for Integrity of Scientific Activity widely publicized by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (http://www.cnpq.br/web/guest/diretrizes).

All authors are solely responsible for the content of the submitted manuscripts. All published material becomes property of the BJPT, which will retain the copyrights. Therefore, no material published in the BJPT may be reproduced without written permission from the editors. All authors of the submitted manuscript must sign a copyright transfer agreement form valid from the date of the acceptance of the manuscript.

Manuscript form and presentation

Original manuscripts

The BJPT accepts the submission of manuscripts with up to 3,500 words (excluding title page, abstract, references, tables, figures, and legends). The information contained in appendices will be included in the total number of words allowed.

The manuscript must be written preferably in English. Whenever the quality of the English writing hinders the analysis and assessment of the content, the authors will be informed.

It is recommended that manuscripts submitted in/translated into English be accompanied by certification of revision by a professional editing and proofreading service. This certification must be included in the submission. We recommend the following services, not excluding others:

- American Journal Experts (www.journalexperts.com);
- Scribendi (www.scribendi.com);
- Nature Publishing Groups Language Editing (https://languageediting.nature.com/login).

The manuscript must include a title and identification page, abstract, and keywords before the body of the manuscript. References, tables, figures, and appendices should be inserted at the end of the manuscript.

Title and identification page

The title of the manuscript must not exceed 25 words and must include as much information about the study as possible. Ideally, the terms used in the title should not appear in the list of keywords. The identification page must also contain the following details:

Full title and short title of up to 45 characters to be used as a legend on the printed pages;

Author: author's first and last name in capital letters without title followed by a superscript number (exponent) identifying the institutional affiliation (department, institution, city, state, country). For more than one author, separate using commas;

Corresponding author: name, full address, email, and telephone number of the corresponding author who is authorized to approve editorial revisions and provide additional information if needed.

Keywords: up to six indexing terms or keywords in Portuguese and English.

Abstract

The abstract must be concise, not exceeding 250 words in a single paragraph in English, and must be inserted immediately after the title page. Do not include references, footnotes or undefined abbreviations in the abstract. It must be written in a structured format.

Bullet points

On a separate page, the manuscript must identify three to five phrases that capture the essence of the topic under investigation and the main conclusions of the paper. Each bullet point must be written in a summarized fashion and provide the main contributions of the study to the current literature, as well as the clinical implications (i.e., how the results can influence clinical practice or scientific research in the area of physical therapy and rehabilitation). These points must be presented in a text box in the beginning of the article, after the abstract. Each bullet point must have no more than 80 characters (with spaces).

Introduction

This part of the manuscript should describe and define the topic under investigation, explain the relationships with to other studies in the same field, justify the need for the study, and specify the objective(s) of the study and hypotheses, if applicable.

Methods

This section consists in describing the methodological design of the study and presenting a clear and detailed report of the study participants and data collection procedures, transformation/reduction, and analysis in order to allow reproducibility of the study. For clinical trials, the participant selection and allocation process must be organized in a flowchart containing the number of participants in each phase as well as their main characteristics (see model of CONSORT flow diagram).

Whenever relevant to the type of study, the author should include the calculation that adequately justifies the sample size for investigation of the intervention effects. All of the information needed to estimate and justify the sample size used in the study must be clearly stated.

The authors must describe the dependent and independent variables; whether the parametric assumptions were met; specify the software used in the data analysis and the level of significance; and specify the statistical tests and their purpose.

Results

The results should be presented briefly and concisely. Pertinent results must be reported with the use of text and/or tables and/or figures. Data included in tables and figures must not be duplicated in the text.

The results must be summarized into self-explanatory graphs or tables using measures of central tendency and variability (e.g. mean (SD) instead of mean±SD); must include measures of magnitude of effect (e.g. effect size) and/or indicators of the precision of the estimates (e.g. confidence intervals); must report the power of the non-significant statistical tests.

Discussion

The purpose of the discussion is to interpret the results and to relate them to existing and available knowledge, especially the knowledge already presented in the Introduction. Be cautious when emphasizing recent findings. The data presented in the Methods and/or in the Results sections should not be repeated. Study limitations, implications, and clinical application to the areas of physical therapy and rehabilitation sciences must be described.

References

The recommended number of references is 30, except for systematic reviews of the literature. Avoid references that are not available internationally, such as theses and dissertations, unpublished results and articles, and personal communication. References should be organized in numerical order of first appearance in the text, following the Uniform Requirements for Manuscripts Submitted to Biomedical Journals prepared by the ICMJE.

Journal titles should be written in abbreviated form, according to the List of Journals of Index Medicus. Citations should be included in the text as superscript (exponent) numbers without dates. The accuracy of the references appearing in the manuscript and their correct citation in the text are the responsibility of the author(s).

Examples: http://www.nlm.nih.gov/bsd/uniform_requirements.html.

Tables, Figures, and Appendices

An overall total of five (5) tables and figures is allowed. Appendices must be included in the number of words allowed in the manuscript. In the case of previously published tables, figures, and appendices, the authors must provide a signed permission from the author or editor at the time of submission.

For articles submitted in Portuguese, the English version of the tables, figures, and appendices and their respective legends must be attached in the system as a supplementary document.

-Tables: these must include only indispensable data and must not be excessively long (maximum allowed: one A4 page with double spacing). They should be numbered consecutively using Arabic numerals and should be inserted at the end of the text. Small tables that can be described in the text are not recommended. Simple results are best presented in a phrase rather than a table.

- Figures: these must be cited and numbered consecutively using Arabic numerals in the order in which they appear in the text. The information in the figures must not repeat data described in tables or in the text. The title and legend(s) should explain the tables and figures without the need to refer to the text. All legends must be double-spaced, and all symbols and abbreviations must be defined. Use uppercase letters (A, B, C, etc.) to identify the individual parts of multiple figures.

Whenever possible, all symbols should be placed in the legends. However, symbols identifying curves in a graph can be included in the body of the figure, provided this does not hinder the analysis of the data. Figures in color will only be published in the online version. With regard to the final artwork, all figures must be in high resolution or in its original version. Low-quality figures will not be accepted and may result in delays in the process of review and publication.

- Acknowledgements: these must include statements of important contributions specifying their nature. The authors are responsible for obtaining the authorization of individuals/institutions named in the acknowledgements.

Short communications

The BJPT will publish one short communication per issue (up to six a year) in a format similar to that of the original articles, containing 1200 words and up to two figures, one table, and ten references.

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Manuscripts must be submitted, preferably in English, via the website http://www.scielo.br/rbfis. Articles submitted in Portuguese will be reviewed and, if selected for publication, the translation into English of the reviewed version of the manuscript will be the sole responsibility of the authors.

The translated manuscript must be sent within ten days with certification and will be submitted to the BJPT International Editor and proofreader. From volume 19.1 (2015), only English papers will be published.

It is the authors' responsibility to remove all information (except on the title and identification page) that may identify the article's source or authorship.

When submitting a manuscript for publication, the authors must include, in addition to the files described above, the following supplementary documents: Cover letter; 2) Conflict of interest statement; and 3) Copyright transfer statement signed by all authors.

The review process

The submissions that meet the journal's standards and are in accordance with the BJPT editorial policies will be forwarded to the area editors, who will perform an initial assessment and recommend them or not to the chief editor for peer-review. The criteria used for the initial analysis of the area editor include: originality, pertinence, clinical relevance, and methodology. The manuscripts that do not have merit or do not conform to the editorial policies will be rejected in the pre-analysis phase, regardless of the adequacy of the text and methodological quality. Therefore, the manuscript may be rejected based solely on the recommendation of the area editor without the need for further review, in which case, the decision is not subject to appeal. The manuscripts selected for pre-analysis will be submitted to review by specialists, who will work independently. The reviewers will remain anonymous to the authors, and the authors will not be identified to the reviewers. The editors will coordinate the exchange between authors and reviewers and will make the final decision on which articles will be published based on the recommendations of the reviewers and area editors. If accepted for publication, the articles may be subject to minor changes that will not affect the author's style. If an article is rejected, the authors will receive a justification letter from the editor. After publication or at the end of the review process, all documentation regarding the review process will be destroyed.

ANEXO E

Parecer do Comitê de Ética em Pesquisa de Londrina (Brasil)

Universidade Estadual de Londrina

PARANÁ
GOVERNO DO ESTADO

COMITÊ DE ÉTICA EM PESQUISA ENVOLVENDO SERES HUMANOS
Universidade Estadual de Londrina
Registro CONEP 5231

Parecer CEP/UEL:	069/2012
CAAE:	03437712.3.0000.5231
Processo:	15410/2012
Pesquisador(a):	Fábio de Oliveira Pitta
Unidade/Órgão:	CCS – Programa de Pós-graduação em Ciências da Reabilitação – UEL/UNOPAR

Prezado(a) Senhor(a):

O "**Comitê de Ética em Pesquisa Envolvendo Seres Humanos da Universidade Estadual de Londrina**" (Registro CONEP 5231) – de acordo com as orientações da Resolução 196/96 do Conselho Nacional de Saúde/MS e Resoluções Complementares, avaliou o projeto:

"Entendendo em profundidade a inatividade física na vida diária em pacientes com DPOC: comparação da variação do nível de atividade física diária entre verão e inverno em pacientes brasileiros e belgas."

Situação do Projeto: **Aprovado**

Informamos que deverá ser comunicada, por escrito, qualquer modificação que ocorra no desenvolvimento da pesquisa, bem como deverá ser encaminhado ao CEP/UEL relatório final da pesquisa, conforme prevê a Resolução 196/96 do Conselho Nacional de Saúde/MS e Resoluções Complementares.

Londrina, 12 de dezembro de 2012.

Profa. Dra. Alexandrina Aparecida Maciel Cardelli
Coordenadora do Comitê de Ética em Pesquisa Envolvendo Seres Humanos
Universidade Estadual de Londrina

Comitê de Ética em Pesquisa Envolvendo Seres Humanos - UEL

Campus Universitário: Rodovia Celso Garcia Cid (PR 445), Km 380 - Fone (43) 3371-4000 - PABX - Fax 3328-4440 - Caixa Postal 6001 - CEP 86051-990 - Internet http://www.uel.br
LONDRINA - PARANÁ - BRASIL

Form. Código 11.764 - Formato A4 (210x297)

ANEXO F

Parecer do Comitê de Ética em Pesquisa de Leuven (Bélgica)

COMMISSIE MEDISCHE ETHIEK VAN DE UNIVERSITAIRE ZIEKENHUIZEN KULEUVEN
U.Z. GASTHUISBERG
HERESTRAAT 49
B-3000 LEUVEN (BELGIUM)

KATHOLIEKE UNIVERSITEIT LEUVEN

Aan Prof. dr. T. Troosters
Fysische geneeskunde

ONS KENMERK ML8958
LEUVEN, 7 februari 2013

Understanding in depth the physical inactivity of patients with COPD: comparison of the Summer-Winter variability in the level of physical activity in daily life in Brazilian and Belgian patients.

EudraCT OF Belgisch Nummer

S nummer: S55040

DEFINITIEF GUNSTIG ADVIES

Geachte Collega,

De Commissie Medische Ethiek van de Universitaire Ziekenhuizen K.U.Leuven heeft vermeld protocol onderzocht en besproken op haar vergadering van 11 januari 2013.

Na inzage van de bijkomende informatie en/of aangepaste documenten met betrekking tot vermeld dossier is de Commissie van oordeel dat de voorgestelde studie, zoals beschreven in het protocol, wetenschappelijk relevant en ethisch verantwoord is. Ze verleent dan ook een gunstig advies over deze studie.

Bij het beoordelen van dit dossier werd rekening gehouden met de documenten en informatie gerelateerd aan deze studie, ingediend op 18/12/2012 en 29/01/2013

Dit gunstig advies betreft:

- *Protocol : aangepaste versie: versie 3, 23 januari 2013*
- *Protocol gerelateerde documenten : Versie 1 18/12/2012*
- *Patiëntendocumenten: aangepaste versie: versie 2, 23 januari 2013*

De Commissie bevestigt dat ze werkt in overeenstemming met de ICH-GCP principes (International Conference on Harmonization Guidelines on Good Clinical Practice) en met de van toepassing zijnde wetten en regelgeving.

De Commissie bevestigt dat in geval van belangenconflict, de betrokken leden niet deelnemen aan de besluitvorming omtrent de studie.

Een ledenlijst wordt bijgevoegd.

De opdrachtgever is verantwoordelijk voor de conformiteit van de anderstalige documenten met de Nederlandstalige documenten.

SECRETARIAAT: M. LEYS D. VAN MOLL M. VERBEECK H. HUYGHE
Tel +32 16 34 86 00 Fax +32 16 34 86 01 ec@uzleuven.be ec-submission@uzleuven.be www.uzleuven.be/ec

BLAD NR . 2

ONS KENMERK ML8958
UW KENMERK
LEUVEN , 7 februari 2013

<u>Aandachtspunten</u>: (indien van toepassing)

Indien er een Clinical Trial Agreement is, kan de studie in ons centrum pas aangevat worden wanneer dit Clinical Trial Agreement goedgekeurd en ondertekend is door de gedelegeerd bestuurder van UZ Leuven.

Studies met geneesmiddelen en sommige studies met "medische hulpmiddelen" dienen door de opdrachtgever aangemeld te worden bij het FAGG.
Studies met geneesmiddelen mogen slechts aanvangen op voorwaarde dat de minister (FAGG) geen bezwaren heeft kenbaar gemaakt binnen de wettelijke termijnen zoals beschreven in art.13 van de Belgische wet van 7/5/2004 inzake experimenten op de menselijke persoon.
Voor bepaalde studies met medische hulpmiddelen gelden eveneens wettelijke termijnen (zie KB van 17/3/2009).
Voor meer informatie hieromtrent verwijzen we naar de website van het FAGG www.fagg-afmps.be

Gelieve ook rekening te houden met de regelgeving van het ziekenhuis betreffende weefselbeheer.

Dit gunstig advies van de Commissie houdt niet in dat zij de verantwoordelijkheid voor de geplande studie op zich neemt. U blijft hiervoor dus zelf verantwoordelijk. Bovendien dient U er over te waken dat uw mening als betrokken onderzoeker wordt weergegeven in publicaties, rapporten voor de overheid enz., die het resultaat zijn van dit onderzoek.

U wordt eraan herinnerd dat bij klinische studies iedere door U waargenomen ernstige verwikkeling onmiddellijk zowel aan de opdrachtgever (desgevallend de producent) als aan de commissie medische ethiek moet worden gemeld, ook al is het oorzakelijke verband met de studie onduidelijk.

Indien de studie niet binnen het jaar beëindigd is, vereist de ICH-GCP dat een jaarlijks vorderingsrapport aan de commissie wordt bezorgd.

Tenslotte verzoeken wij U ons mee te delen indien een studie niet wordt aangevat, of wanneer ze wordt afgesloten of vroegtijdig onderbroken (met opgave van eventuele reden). Gelieve het (al dan niet vroegtijdig) stopzetten van een studie binnen de door de wet vastgelegde termijnen mee te delen en een Clinical Study Report aan de Commissie te bezorgen.

Met de meeste hoogachting,

Prof. Dr. Walter VAN DEN BOGAERT
Voorzitter Commissie Medische Ethiek
UZ K.U.LEUVEN

Prof. Dr. W. Van den Bogaert
Voorzitter
Commissie Medische Ethiek van de UZ K.U.Leuven

Cc : **FAGG** (Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten)
Departement R&D
Eurostation, blok 2
Victor Hortaplein 40, bus 40
B-1060 Brussel

Clinical Trial Center (CTC), UZ Leuven, Campus Gasthuisberg

SECRETARIAAT: M. LEYS D. VAN MOLL M. VERBEECK H. HUYGHE
Tel +32 16 34 86 00 Fax +32 16 34 86 01 ec@uzleuven.be ec-submission@uzleuven.be www.uzleuven.be/ec

COMMISSIE MEDISCHE ETHIEK VAN DE UNIVERSITAIRE ZIEKENHUIZEN K.U.LEUVEN
TOETSINGSCOMMISSIE
UZ GASTHUISBERG E330
HERESTRAAT 49
3000 LEUVEN BELGIUM

KATHOLIEKE
UNIVERSITEIT
LEUVEN

Ledenlijst Commissie Medische Ethiek/Toetsingscommissie (OG032)
vanaf 21 juni 2012 tot op heden
List of Members Ethics Committee/IRB (OG032)
from June 21st, 2012 until present

Prof. Walter Van den Bogaert, M.D.	Chairman (M)	Radiotherapy-Oncology
Dr. Johan Wildiers, M.D.	Vice-Chairman (M)	Medical Oncology
Dr. Sabine Graux, M.D.	Secretary (F)	Physician
Dr. Sonja Haesendonck, M.D.	Secretary (F)	Physician
Prof. Xavier Bossuyt, M.D.	Member (M)	Immunology
Prof. D. Bullens, M.D.	Member (F)	Paediatrics
Prof. Willem Daenen, M.D.	Member (M)	Cardiac Surgery
Dr. Lut De Groote, M.D.	External Member (F)	General Practitioner
Prof. Jan de Hoon, M.D.	Member (M)	Clinical Pharmacology
Prof. Ivo De Wever, M.D.	Member (M)	Surgical Oncology
De heer Filip Gybels	Member (M)	Head Nurse
Dr. José Thomas, M.D.	Member (M)	Medical Oncology
Dr. Ben Van Calster	Member (M)	Statistics
Prof. Jan Van Hemelrijck, M.D.	Member (M)	Anesthesiology
Prof. Raymond Verhaeghe, M.D.	Member (M)	Cardiology
Prof. Guido Verhoeven, M.D.	Member (M)	Experimental Medicine
Mrs. Christine Mathieu, Law	Member (F)	Medical Legislation

(M) = Male (F) = Female

De Commissie voor Medische Ethiek volgt de voorschriften van ICH Good Clinical Practice en de lokale wettelijke bepalingen terzake (wet van 7 mei 2004 inzake experimenten op de menselijke persoon en bijbehorende KB's en programmawet)

The Ethics Committee operates according to ICH Good Clinical Practice and local applicable regulations.

ANEXO G

Normas de formatação do periódico *Respiratory Medicine*

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We now differentiate between the requirements for new and revised submissions. You may choose to submit your manuscript as a single Word or PDF file to be used in the refereeing process. Only when your paper is at the revision stage, will you be requested to put your paper in to a 'correct format' for acceptance and provide the items required for the publication of your article.
To find out more, please visit the Preparation section below.

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All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Changes to authorship
Authors are expected to consider carefully the list and order of authors **before** submitting their manuscript and provide the definitive list of authors at the time of the original submission. Any addition, deletion or rearrangement of author names in the authorship list should be made only **before** the manuscript has been accepted and only if approved by the journal Editor. To request such a change, the Editor must receive the following from the **corresponding author**: (a) the reason for the change in author list and (b) written confirmation (e-mail, letter) from all authors that they agree with the addition, removal or rearrangement. In the case of addition or removal of authors, this includes confirmation from the author being added or removed.
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Reporting clinical trials
Randomized controlled trials should be presented according to the CONSORT guidelines. At manuscript submission, authors must provide the CONSORT checklist accompanied by a flow diagram that illustrates the progress of patients through the trial, including recruitment, enrollment, randomization, withdrawal and completion, and a detailed description of the randomization procedure. The CONSORT checklist and template flow diagram can be found on http://www.consort-statement.org.

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The journal welcomes submission of state-of-the-art reviews on important topics with a clinical relevance. Potential review authors are encouraged to contact the Deputy Editor Dr N. Hanania hanania@bcm.tmc.edu in advance with their review proposals.

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<Brief Communications
These should be submitted as detailed above but should not exceed 1000 words, and may normally contain only one illustration or table. Brief communications containing new information may be selected for rapid peer review and publication at the discretion of the editor and editorial board.

Preparation

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References
There are no strict requirements on reference formatting at submission. References can be in any style or format as long as the style is consistent. Where applicable, author(s) name(s), journal title/book title, chapter title/article title, year of publication, volume number/book chapter and the pagination must be present. Use of DOI is highly encouraged. The reference style used by the journal will be applied to the accepted article by Elsevier at the proof stage. Note that missing data will be highlighted at proof stage for the author to correct.

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Divide the article into clearly defined sections.

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Please ensure the figures and the tables included in the single file are placed next to the relevant text in the manuscript, rather than at the bottom or the top of the file.

ANEXO H

Autorização de reprodução da figura 1

RE/: RE: Authorization

Bhatia, Payal (payal.bhatia@sagepub.in)

20/11/2015

Para: Fabio Pitta Cc: Morgan, Mike, Singh, Sally, Letts, Shirley, ka_furlanetto@hotmail.com

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Best regards,
Payal

Payal Bhatia
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From: Fabio Pitta [mailto:fabiopitta@uol.com.br]
Sent: Wednesday, November 18, 2015 6:31 PM
To: Bhatia, Payal
Cc: Morgan, Mike; Singh, Sally; Letts, Shirley; ka_furlanetto@hotmail.com
Subject: RE: RE: Authorization

Dear Mrs. Payal Bhatia,

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ANEXO I

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12/01/2016

Para: ka_furlanetto@hotmail.com

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European Respiratory Journal Dec 1997, 10 (12) 2814-2819

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Publication: Expert Review of Medical Devices
Article: Oxygen therapy devices and portable ventilators for improved physical activity in daily life in patients with chronic respiratory disease
Authors: Karina Couto Furlanetto and Fabio Pitta
Editor: Tasnim Zahri
Publication Format: Print and Electronic
Publisher: Taylor and Francis Online
Publication Date: February 2016

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ANEXO J

Normas de formatação do periódico *Expert Review of Medical Devices*

Expert Reviews: Author Guidelines
http://informahealthcare.com/page/ExpertReviews

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The audience for the Expert Review series consists of clinicians, R&D scientists, regulatory and marketing professionals in the pharmaceutical industry and decision-makers in healthcare provision. Authors should bear in mind the multidisciplinary status of the readership when writing the article.
Expert Review articles have been engineered specifically for the online environment. The structure is designed to draw the reader's attention directly to the information they require.

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Please ensure your paper concurs with the following article format:
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Abstract/Summary: approximately 120 words. No references should be cited in the abstract.
Keywords: approximately 5–10 keywords for the review.
Body of the article: article content under relevant headings and subheadings.
Expert commentary: the author's expert view on the current status of the field under discussion.
Five-year view: a speculative viewpoint on how the field will evolve in 5 years time.
Key issues: 8–10 bullet points summarizing the review.
References
Reference annotations: please highlight 6–8 references that are of particular significance to the subject under review as "* of interest" or "** of considerable interest" and provide a brief (1–2 line) synopsis.
Figures/Tables/Boxes: Summary figures/tables/boxes are very useful, and we encourage their use in reviews/perspectives/special reports. The author should include illustrations and tables to condense and illustrate the information they wish to convey. Commentary that augments an article and could be viewed as 'stand-alone' should be included in a separate box. An example would be a summary of a particular trial or trial series, a case study summary or a series of terms explained.
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Reviews
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Each article should concentrate on the most recent developments in the field and should aim for concise presentation of relevant information.
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• Keywords
• Expert commentary
• Five-year view
• Key issues
• References: target of 80 references
• Reference annotations
• Financial disclosure/Acknowledgements
4. Manuscript preparation
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Please use double line spacing throughout the manuscript. No more than four levels of subheading should be used to divide the text and should be clearly designated.
Abbreviations
Abbreviations should be defined on their first appearance, and in any table and figure footnotes. It is helpful if a separate list is provided of any abbreviations.
Spelling
US-preferred spelling will be used in the finished publication. 7

5. Article sections

Summary

Not more than 150 words, this should not be an abstract but merely a scene-setting summary outlining the article scope and briefly putting it in context. The role of the summary is to draw in the interested casual browser.

Keywords

Up to 10 keywords (including therapeutic area, mechanism(s) of action etc.) plus names of drugs and compounds mentioned in the text.

Expert commentary

The authors' recommendations regarding existing and new clinical strategies and drug products, introducing new therapeutic/diagnostic paradigms and discussing their likely impact on current management of disease.

Five-year view

Authors are challenged to include a speculative viewpoint on how the field will have evolved 5 years from the point at which the review was written.

Key issues

An executive summary of the authors' main points (bulleted) is very useful for time-constrained readers requiring a rapidly accessible overview.

Example:

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Authors should focus on recent papers and papers older than 5 years should not be included except for an over-riding purpose.

References should be denoted numerically and in sequence in the text, using Arabic numerals placed in square brackets, i.e., [12].

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References use plain, unformatted text, as in the following examples:

Journals:

1. Weissman P, Goldstein BJ, Rosenstock J, et al. Effects of rosiglitazone added to submaximal doses of metformin compared with dose escalation of metformin in type 2 diabetes: the EMPIRE Study. Curr Med Res Opin 2004;21:2029-35

Books:

2. Gottman J. Time Series Analysis. Cambridge: CUP, 1981

Working party reports and similar:

3. Clinical Disputes Forum Working Party. Pre-action protocol for the resolution of clinical disputes. London: Clinical Disputes Forum, 1998

Pre-publication articles assigned DOI numbers:

4. de Lau LM, Koudstaal PJ, Hofman A, Breteler MM. Subjective complaints precede Parkinson disease: the Rotterdam study. Arch Neurol 2006: published online 9 January 2006, doi:10.1001/archneur.63.3.noc50312

Internet articles and website information:

5. Suicidality in adults being treated with antidepressant medications. FDA Public Health Advisory. Washington, DC: FDA/Center for Drug Evaluation and Research, 2005. Available at: www.fda.gov/cder/drug/advisory/SSRI200507.htm [Last accessed 3 January 2006]

Patents:

6. Basf AG. Means and methods for preventing and treating caries. WO2006027265 (2006)

Use the following formats for patent numbers issued by the World, US and European patent offices, respectively: WO0113324; US6803189; EP1549318

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Figures should be numbered consecutively according to the order in which they have been first cited in the text. Define in the legend all abbreviations that are used in the figure.
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