Universidade Estadual de Londrina

ANA CAROLINA DOS REIS ANDRELLO

VENTILAÇÃO VOLUNTÁRIA MÁXIMA E SUA RELAÇÃO COM DESFECHOS CLÍNICOS EM PACIENTES COM DPOC

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

Orientador: Prof. Dr. Fabio de Oliveira Pitta

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Londrina, 28 de fevereiro de 2019.

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Muito obrigada!

“Conheça todas as teorias, domine todas as técnicas, mas ao tocar uma alma humana, seja apenas outra alma humana.”

(Carl Jung)

ANDRELLO, Ana Carolina dos Reis. **Ventilação voluntária máxima e sua relação com desfechos clínicos em pacientes com DPOC.** 2019. 62 f. Dissertação (Mestrado em Ciências da Reabilitação) – Programa Associado UEL –UNOPAR – Universidade Estadual de Londrina, Londrina, 2019.

RESUMO

OBJETIVOS: Investigar a relação entre a Ventilação Voluntária Máxima (VVM) e desfechos clínicos na doença pulmonar obstrutiva crônica (DPOC) e adicionalmente, verificar se a VVM é melhor preditora destes desfechos do que o volume expiratório forçado no primeiro segundo (VEF_1). **MÉTODOS:** Estudo transversal com dados de indivíduos diagnosticados com DPOC e avaliados antes da entrada em um programa de reabilitação pulmonar. Eles foram submetidos às avaliações da função pulmonar completa pela espirometria, pressões respiratórias máximas (PRM), capacidade funcional de exercício pelo teste de caminhada de seis minutos (TC6min), dispneia pela versão modificada da escala *Medical Research Council* (mMRC), estado funcional pelo *Pulmonary Functional Status and Dyspnea Questionnaire – modified version* (PFSDQ-m) e qualidade de vida (QV) pelo *COPD Assessment Test* (CAT). As correlações foram avaliadas pelo coeficiente de Spearman e foram usados modelos de regressão linear múltipla por etapas para verificar os preditores dos desfechos clínicos levando em consideração a VVM, VEF_1 e variáveis antropométricas. **RESULTADOS:** Foram incluídos 157 indivíduos (82 homens) com mediana (intervalo interquartílico) de idade de 66 (61-73) anos e que apresentavam IMC de 27 (22-31), VEF_1 de 46 (33-57) % do predito, TC6min de 86 (76-96)% do predito, bom estado funcional com um escore total do PFSDQ-m de 34 (14-57) e impacto moderado na QV com um escore total no CAT de 13 (7-19). Foram encontradas correlações moderadas e estatisticamente significantes da VVM com a pressão inspiratória máxima (PImax) (r=0,40), TC6min (r=0,50) e mMRC (r=-0,56) (P<0,001 para todas), assim como com as pontuações totais do PFSDQ-m (r=-0,40) e do CAT (r=-0,54). As correlações destes desfechos clínicos foram de forma geral mais fortes com a VVM do que com o VEF_1. Nos modelos de regressão, ao contrário do VEF_1, a VVM aparece como preditora de quase todos os desfechos clínicos, com exceção de alguns domínios do CAT. **CONCLUSÃO:** Conclui-se que a VVM se correlaciona moderadamente com vários desfechos clínicos utilizados na avaliação dos indivíduos com DPOC. A VVM mostrou-se também como melhor preditora da força muscular respiratória, capacidade de exercício, dispneia, estado funcional e QV na DPOC do que o VEF_1. Assim, recomenda-se que esse teste não deixe de integrar as avaliações na prática clínica e na pesquisa.

Palavras-chave: Doença pulmonar obstrutiva crônica. Ventilação voluntária máxima. Qualidade de vida. Exercício.

ANDRELLO, Ana Carolina dos Reis**. Maximum voluntary ventilation and its relationship with clinical outcomes in patients with COPD.** 2019**.** 62 p. Dissertação (Mestrado em Ciências da Reabilitação) – Programa Associado UEL – UNOPAR – Universidade Estadual de Londrina, Londrina, 2019.

ABSTRACT

AIMS: To investigate the relationship between Maximum Voluntary Ventilation (MVV) and clinical outcomes in patients with chronic obstructive pulmonary disease (COPD), and to verify if MVV is a better predictor of these outcomes than the forced expiratory volume in the first second (FEV_1). **METHODS**: This was a cross-sectional study with data from individuals diagnosed with COPD assessed pryor to enrollment in a pulmonary rehabilitation program. They underwent assessments regarding lung function by spirometry, maximal respiratory pressures (MRP), functional exercise capacity by the six-minute walk test (6MWT), dyspnea by the modified version of the Medical Research Council scale (mMRC), functional status by the Pulmonary Functional Status and Dyspnea Questionnaire-modified version (PFSDQ-m) and quality of life (QoL) by the COPD Assessment Test (CAT). Correlations were verified by the Spearman's coefficient and stepwise multiple linear regression models were used to verify the independent associations of MVV and FEV_1 with clinical outcomes. **RESULTS:** Data from 157 individuals (82 males) were analyzed , with a median age of 66 (61-73) years,a BMI of 27 (22-31), FEV_1 of 46 (33-57)% predicted, and a 6MWT with a median of 86 (76-96)% predicted, good functional status with a PFSDQ-m total score of 34 (14-57) and moderate impact on QoL, with a CAT total score of 13 (7-19). Moderate and statistically significant correlations of MVV were found with MIP (r=0.40), 6MWT (r=0.50) and mMRC (r=-0.56) (P<0.001 for all), as well as with total score of PFSDQ-m (r=-0.40) and CAT (r=-0.54). Most of the clinical outcomes presented a correlation with MVV higher than with FEV_1. As for the regression models, differently than the FEV_1, MVV appears as a predictor of almost all clinical outcomes, except for some CAT domains. **CONCLUSION:** It is concluded that MVV correlates moderately with most of the clinical outcomes used in the evaluation of individuals with COPD. MVV also proved to be a better predictor of respiratory muscle strength, exercise capacity, dyspnea, functional status and QoL in COPD than FEV_1. Therefore, this test is highly recommended as part of the comprehensive assessment of COPD in clinical practice and research.

Key words: Chronic obstructive pulmonary disease. Maximal voluntary ventilation. Quality of life. Exercise.

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AFVD	Atividade Física de Vida Diária
AVD	Atividade de Vida Diária
CAT	COPD Assessment Test
CI	Capacidade Inspiratória
CPT	Capacidade Pulmonar Total
CVF	Capacidade Vital Forçada
CVL	Capacidade Vital Lenta
DPOC	Doença Pulmonar Obstrutiva Crônica
FMR	Força Muscular Respiratória
GOLD	Global Initiative for Chronic Obstructive Lung Disease
IMC	Índice de Massa Corporal
mMRC	Modified Medical Research Council
OMS	Organização Mundial da Saúde
PEmáx	Pressão Expiratória Máxima
PFSDQ	Pulmonary Functional Status and Dyspnea Questionnaire
PImáx	Pressão Inspiratória Máxima
PR	Pulmonary Rehabilitation
PRM	Pressões Respiratórias Máximas
QoL	Quality of Life
QV	Qualidade de Vida
RP	Reabilitação Pulmonar
TC6min	Teste de Caminhada de Seis Minutos
V_A/Q	Relação Ventilação/Perfusão
VEF_1	Volume Expiratório Forçado no primeiro segundo
VR	Volume Residual
VVM	Ventilação Voluntária Máxima
WHO	World Health Organization

SUMÁRIO

1 INTRODUÇÃO

A doença pulmonar obstrutiva crônica (DPOC) é atualmente um dos principais problemas de saúde pública e ocupa a quarta posição dentre as causas de morte no mundo[1]. É definida como uma doença prevenível e tratável, caracterizada pela limitação persistente ao fluxo aéreo e está associada a uma resposta inflamatória que pode causar remodelamento brônquico e alterações no parênquima pulmonar. Assim, a doença cursa com os sintomas de dispneia, fadiga, tosse crônica e aumento da secretividade, que causam grande impacto na capacidade funcional e qualidade de vida dos pacientes[2,3].

O diagnóstico da doença se dá pela história clínica, sintomas e exames, sendo a espirometria o principal teste utilizado para confirmação diagnóstica. A classificação do grau de obstrução da DPOC é dada pelo valor percentual do predito do volume expiratório forçado no primeiro segundo (VEF_1) após o uso de broncodilatador[2,3]. Essa variável é obtida na espirometria e tem sido amplamente utilizada na prática clínica e na literatura científica nas últimas décadas.

Contudo, a correlação limitada que o VEF_1 apresenta com diversos outros desfechos da doença, como qualidade de vida (QV), capacidade de exercício e atividade física na vida diária (AFVD)[4,5], acentuou o interesse na avaliação de outras variáveis espirométricas e volumes pulmonares que se correlacionassem melhor com esses desfechos, que se encontram afetados pelo comprometimento pulmonar e sistêmico nos pacientes com DPOC[6,7].

Nesse contexto, parece haver espaço para novas evidências sobre a ventilação voluntária máxima (VVM), que é um teste de função pulmonar realizado com um espirômetro e mede o maior volume de ar que uma pessoa consegue inspirar e expirar rápido e voluntariamente em um determinado intervalo de tempo. Alguns estudos anteriores[4,5] já mostraram haver boa correlação da VVM com o gasto energético, AFVD e QV na DPOC. Essa medida da função pulmonar, apesar de simples e pouco estudada, pode fornecer dados úteis para a prática clínica e para pesquisas, pois reflete a mecânica e o *endurance* muscular respiratórios, que são determinantes na limitação ao exercício físico nesses indivíduos[8-11].

Assim, considerando a busca atual por desfechos que possam predizer melhor do que o VEF_1 a globalidade do acometimento de pacientes com DPOC, esse estudo objetiva investigar a relação da VVM com desfechos clínicos nessa população.

2 REVISÃO DE LITERATURA – CONTEXTUALIZAÇÃO

2.1 Doença Pulmonar Obstrutiva Crônica (DPOC)

De acordo com pesquisas da Organização Mundial da Saúde (OMS), a DPOC é um dos principais problemas de saúde pública que ocupa atualmente a quarta posição dentre as causas de morte no mundo, e estima-se que até 2020 ela ocupará a terceira posição[1].

A maior prevalência da DPOC se dá em indivíduos com mais de 40 anos, tabagistas ou ex-tabagistas. No Brasil, estudos recentes mostram que a prevalência da doença varia entre 6% e 15% na população acima de 40 anos. Segundo o boletim epidemiológico do Ministério da Saúde de 2016, a DPOC tem destaque nas taxas de mortalidade na população acima de 50 anos, sendo que o risco aumenta com a progressão da idade[12,13,14].

Causada principalmente pelo tabagismo de longa data, a DPOC é definida pela literatura atual como uma doença prevenível e tratável, caracterizada pela limitação persistente ao fluxo aéreo, decorrente de anormalidades das vias aéreas causadas pela exposição prolongada a agentes nocivos e alérgenos. Essas mudanças pulmonares consistem na obstrução brônquica (bronquite) e na destruição do parênquima pulmonar (enfisema) e resultam principalmente do processo inflamatório crônico característico da doença[2,3].

Além do tabagismo, outros fatores de risco incluem a exposição ambiental e ocupacional a alérgenos, resíduos e poluição, infecções respiratórias recorrentes, bem como prematuridade e fatores genéticos. Comorbidades associadas como cardiopatias e doenças musculoesqueléticas decorrentes do tabagismo e do envelhecimento também têm impacto importante no estado de saúde do paciente com DPOC[3].

Os sintomas respiratórios da doença podem preceder a obstrução aérea crônica e a ocorrência de eventos respiratórios agudos, denominados exacerbações. A dispneia é o sintoma respiratório mais comum e frequente da doença, seguida pela tosse crônica e aumento de secretividade. Qualquer pessoa com mais de 40 anos que apresente esses sintomas e tenha história de exposição prolongada aos fatores de risco deve investigar a possibilidade de ter DPOC[3,15].

Considerando a complexidade do conjunto de alterações causadas pela DPOC, a reabilitação pulmonar (RP) é o tratamento não medicamentoso mais indicado para esses indivíduos. A RP pode ser definida como uma intervenção baseada em uma avaliação detalhada de cada paciente, seguida de terapias individualizadas que incluam treinamento físico, educação e mudança comportamental, com potencial de melhorar a condição física e psicológica dos pacientes a curto e longo prazo[16]. Essa avaliação completa e abrangente inclui testes e instrumentos de avaliação, validados para a população com DPOC, que visam determinar a capacidade física, o estado funcional e psicológico do paciente, possibilitando estabeler prognóstico e possibilitar uma prescrição adequada e individualizada da reabilitação.

2.2 Avaliação da Função Pulmonar

2.2.1 O sistema respiratório na DPOC

Considerando a idade avançada da maioria dos pacientes com DPOC, é importante lembrar que as alterações anatômicas e fisiológicas do sistema respiratório e cardiovascular desses indivíduos consistem em uma somatória dos efeitos do envelhecimento com as manifestações pulmonares e sistêmicas da doença. A literatura atual também ressalta a heterogeneidade do acometimento e manifestações da DPOC, mesmo em pacientes que apresentam o mesmo grau de obstrução[3,17].

A disfunção das vias aéreas de pequeno calibre se deve principalmente ao processo inflamatório característico da doença, causado pela exposição prolongada ao tabaco e outros agentes nocivos, que resulta em broncoconstrição e, a longo prazo, remodelamento brônquico. Além disso, a hipersecretividade consequente desse processo contribui para o estreitamento das vias aéreas periféricas. Essas disfunções levam a limitação progressiva ao fluxo aéreo e são demonstradas pela redução do VEF_1 e da relação VEF_1/CVF, e pelo aumento do volume residual (VR) e da relação VR/CPT que indicam que há aprisionamento aéreo. Adicionalmente, a destruição do parênquima pulmonar (enfisema) juntamente com a inflamação e disfunção vascular, ambos causados pela exposição ao tabaco e outras partículas nocivas, resultam em uma relação ventilação/perfusão (V_A/Q) inadequada, diminuindo a troca gasosa e a oferta de oxigênio[3,17].

Todas essas alterações se tornam ainda mais evidentes durante atividades moderadas e vigorosas que aumentam a demanda ventilatória, gerando maior dispneia frente à resposta fisiológica inadequada a esse incremento, resultando em limitação ao exercício[17].

2.2.2 Espirometria

A investigação da DPOC deve ser feita em qualquer indivíduo com história de exposição aos fatores de risco e que apresente dispneia, tosse crônica e/ou hipersecretividade. A confirmação diagnóstica nesse contexto clínico é feita pelo exame de espirometria[3].

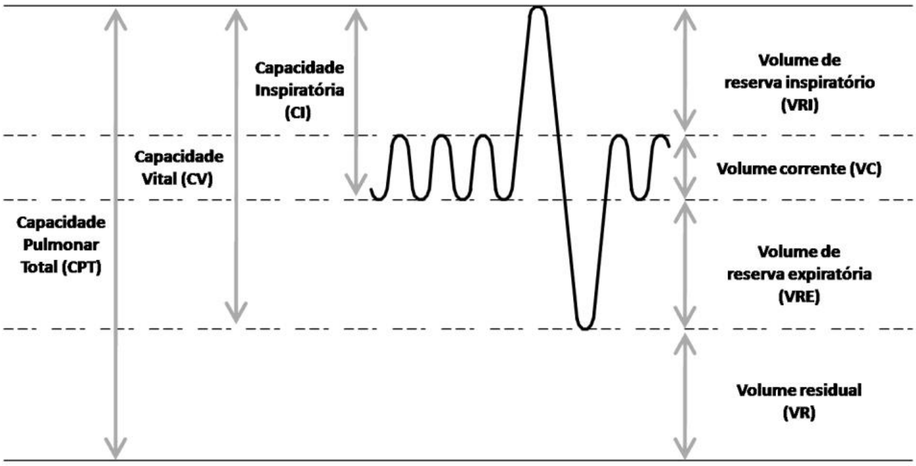
A espirometria é o teste mais aplicado na prática clínica e pesquisa para avaliação da função pulmonar e classificação da gravidade da DPOC. Além disso, esse teste fornece valores considerados preditores da progressão da doença e parâmetros para a resposta terapêutica, principalmente medicamentosa. Esta é considerada uma prova de função pulmonar acessível e não invasiva para avaliar de forma objetiva e reprodutível a limitação ao fluxo aéreo[3,8,10].

2.2.2.1 Capacidade Vital Forçada (CVF) e Volume Expiratório Forçado no primeiro segundo (VEF_1)

A manobra utilizada para obter os valores necessários para a confirmação diagnóstica é a CVF, uma manobra de esforço máximo no qual o paciente é instruído a realizar uma inspiração máxima e em seguida uma expiração máxima de forma rápida e forçada, durante no mínimo 6 segundos. Considerando os volumes e capacidades pulmonares (Figura 1), a CVF deve partir da capacidade pulmonar total (CPT) e progredir até o volume residual (VR)[8,18].

Durante essa manobra se obtém o valor do volume expiratório forçado no primeiro segundo (VEF_1) que é a variável mais usada clinicamente para avaliar os distúrbios obstrutivos (Figura 2). O VEF_1 é também uma variável que conta com grande número de evidências na pesquisa científica, uma vez que é utilizado para classificação da gravidade dos distúrbios e tem valor prognóstico[13-18]. Tratando-se de um teste de esforço máximo, um bom indicativo da colaboração do paciente e execução correta dessa manobra é o valor do pico de fluxo expiratório (PFE), que também se encontra reduzido na DPOC[8,18].

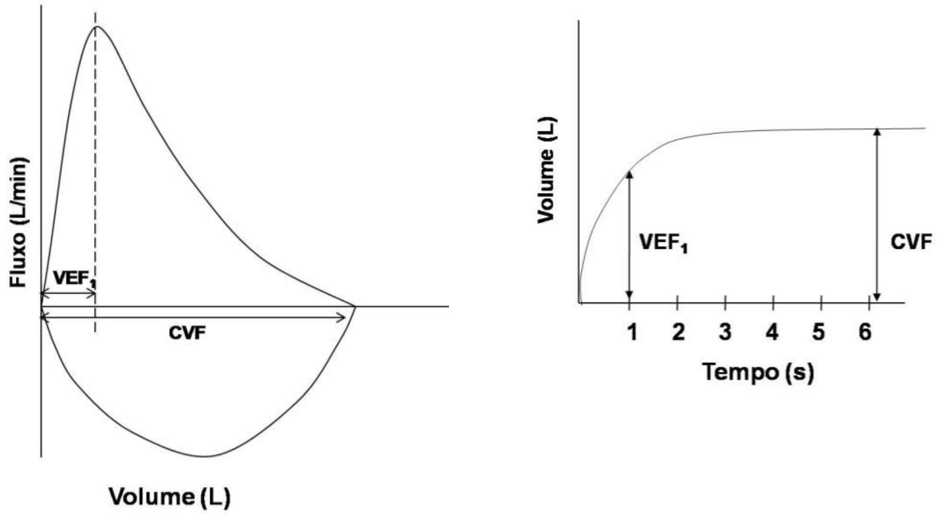
Figura 1: Volumes e capacidades pulmonares



Fonte: o próprio autor

Importantes documentos[8,10,18] foram desenvolvidos ao longo dos anos com o objetivo de padronizar a execução das provas de função pulmonar e tornar as medidas mais confiáveis e reprodutíveis. Assim, as curvas obtidas no exame devem seguir critérios de aceitação e reprodutibilidade e a sua interpretação deve ser feita de acordo com valores de referência adequados para a população[19].

Figura 2: Curvas Fluxo x Volume e Volume x Tempo da manobra espirométrica da CVF.



Fonte: o próprio autor

De acordo com o GOLD Report 2018, o critério para a classificação do distúrbio obstrutivo para diagnóstico da DPOC é a relação fixa, pós-broncodilatador, do $VEF_1/CVF<0,70$. E baseado nesse critério simples e independente dos valores de referência, vários ensaios clínicos contribuem com evidências para a elaboração de recomendações e tratamentos. Já o grau de obstrução e a gravidade da doença se dão pelo valor de porcentagem do predito do VEF_1, como descrito no quadro abaixo[3,19,20].

Quadro 1. Classificação da gravidade da obstrução pulmonar pelo VEF_1, na presença de $VEF_1/CVF<0,70$.

Classificação	VEF_1%predito	Obstrução
GOLD I	$VEF_1 \geq 80\%$	Leve
GOLD II	$50\% \leq VEF_1 < 80\%$	Moderada
GOLD III	$30\% \leq VEF_1 < 50\%$	Grave
GOLD IV	$VEF_1 < 30\%$	Muito grave

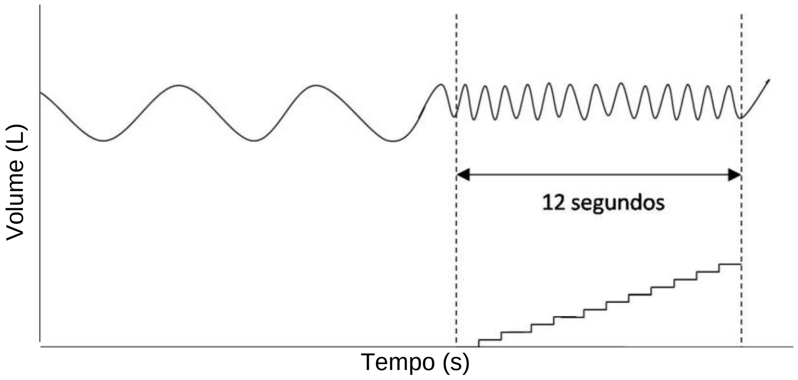
Fonte: o próprio autor

2.2.3 Ventilação Voluntária Máxima (VVM)

A VVM é uma manobra também realizada em um espirômetro e que exige colaboração e esforço máximo do paciente. Essa medida é definida como volume máximo de ar mobilizado durante um determinado período de tempo, realizando uma respiração profunda, rápida e forçada. O tempo de execução da manobra estabelecido pelas diretrizes é de 12 segundos, com o objetivo de manter uma frequência respiratória entre 90 e 110 respirações por minuto[8,9] (Figura 3).

O teste conta com incentivo verbal ao paciente para que este realize esforço máximo; contudo, indivíduos com doença respiratória nem sempre alcançam essa taxa[21]. Assim, para a seleção dos resultados, as diretrizes recomendam a comparação com o VEF_1. A relação $VVM/(VEF_1x40)<0,80$ indica distúrbio ou esforço insuficiente do indivíduo, necessitando melhor investigação[8].

Figura 3: Curva representativa da manobra da VVM



Fonte: o próprio autor

Apesar de simples e pouco estudada, o valor da VVM fornece dados úteis sobre a mecânica e o *endurance* muscular respiratório que, como já dito anteriormente, participam do mecanismo multifatorial causador da dispneia e da limitação ao exercício físico em pacientes com DPOC[22,23].

A VVM pode ser estimada pelo valor do VEF_1. Inicialmente o VEF_1 era usado isoladamente para estimar a VVM quando multiplicado por 40, contudo essa estimativa não levava em consideração que o VEF_1 é, teoricamente, uma medida independente da força muscular respiratória (FMR) e da mobilidade diafragmática e da caixa torácica, enquanto que a VVM além de associada à FMR também é influenciada pela complacência e elastância do sistema respiratório[24].

Neder e colaboradores[24] realizaram um estudo com uma amostra de 100 indivíduos brasileiros entre 20 e 80 anos e analisaram valores de força muscular respiratória e da VVM estratificados por idade, concluindo com sua análise que para estimativa da VVM nessa população a equação mais adequada é $VVM=(VEF_1 x37,5)+15,8$. Porém, vários autores[8,10,24] ressaltam que a VVM deve ser determinada diretamente, pois sua estimativa inclui apenas um parâmetro derivado diretamente do outro e, mesmo considerando a alta correlação entre a VVM e o VEF_1, em muitos casos de distúrbios ventilatórios pode haver diferença significativa entre os valores medidos e estimados[19].

2.2.4 Pletismografia Corporal

Outras medidas de volumes pulmonares absolutos, bem como novas técnicas que fornecem valores que indicam direta ou indiretamente o grau de aprisionamento aéreo e hiperinsuflação, têm ganhado espaço nas pesquisas e são obtidas por testes e equipamentos mais complexos e dispendiosos do que a espirometria simples. Uma dessas técnicas é a pletismografia corporal. Esse método tem a vantagem de ser preciso e de permitir a mensuração de todo o volume pulmonar e adicionalmente avaliar a resistência e condutância das vias aéreas[25,26].

O pletismógrafo é um equipamento de alto custo de aquisição e manutenção e necessita de ambiente controlado para o melhor desempenho do sistema. Basicamente as medidas de pletismografia são realizadas com o paciente dentro de uma cabine hermética, respirando em um bucal, contra um sistema que oclui ou libera o fluxo de ar pela boca. Quando o fluxo está ocluído, as diferenças de pressões na cabine geradas pelo movimento respiratório medem de forma indireta a magnitude da mudança do volume pulmonar. Uma vez que o fluxo de ar é liberado o sistema é capaz de mensurar as variações de pressões proporcionais às pressões alveolares o que permite a avaliação da resistência das vias aéreas[25,26].

A manobra completa de pletismografia consiste em posicionar o paciente na posição sentada dentro da cabine fechada e estabilizada, respirando por um bucal, com clipe nasal e apoio manual bilateral nas bochechas. Inicialmente o paciente realiza de 3 a 8 respirações calmas em volume corrente e em seguida é instruído a realizar movimentos respiratórios rápidos e superficiais mantendo um ritmo entre 60 e 180 respirações por minuto. Nessa fase de respiração rápida é que ocorre a oclusão e liberação do fluxo como descrito anteriormente. Após essa respiração rápida inicial, ainda na mesma manobra, sem remover o paciente do bucal, é realizada uma manobra espirométrica de capacidade vital lenta (CVL) para avaliação da capacidade inspiratória (CI) e cálculo da CPT e do volume residual (VR) [25,26,27]. Desses valores são derivados índices que refletem o aprisionamento aéreo quando a relação VR/CPT se encontra aumentada e a hiperinsuflação quando a relação CI/CPT se encontra diminuída.

2.2.5 Pressões respiratórias máximas

A força muscular respiratória (FMR) pode ser diretamente medida através das pressões respiratórias máximas (PRM) obtidas de forma simples com um manuvacuômetro portátil, que pode ser analógico ou digital. Trata-se de um teste que exige colaboração do indivíduo e esforço máximo sendo, portanto, um teste geralmente cansativo para pacientes com doença pulmonar[28,29].

A técnica utilizada foi descrita anteriormente por Black and Hyatt[30] e deve ser executada com o paciente na posição sentada, utilizando um clipe nasal e um bucal rígido de 25mm de diâmetro interno com um orifício distal de 2mm que tem por objetivo prevenir que os músculos faciais exerçam pressão significativa.

A pressão inspiratória máxima (PImáx) é medida a partir do VR após expiração máxima e a pressão expiratória máxima (PEmáx) a partir da CPT após inspiração máxima. Em ambas as manobras a pressão máxima deve ser sustentada por no mínimo 1 segundo e, assim como na espirometria, deve obedecer critérios de aceitabilidade e reprodutibilidade. A indicação de fraqueza depende da comparação dos valores obtidos com valores de referência para a população[24].

Em pacientes com DPOC menores valores de PImáx podem estar associados a volumes pulmonares aumentados devido à hiperinsulflação e ao aprisionamento aéreo. Essas disfunções colocam o principal músculo da inspiração, o diafragma, em desvantagem mecânica, com suas fibras encurtadas e aplainamento de suas cúpulas, o que diminui sua excursão e consequentemente a pressão gerada[28].

Por ser um teste acessível e de fácil aplicação inclusive a beira leito, os valores das PRM são muito usados na prática clínica para confirmar e acompanhar a progressão de disfunções musculares em diversas condições, doenças neurodegenerativas, miopatias, avaliações pré e pós operatórias de doenças pulmonares, desmame de ventilação mecânica invasiva, entre outros[29].

2.3 Avaliação da dispneia, capacidade funcional de exercício, estado funcional e qualidade de vida na DPOC

Considerando a necessidade de uma avaliação abrangente para o paciente com DPOC, é importante lembrar que a doença cursa com comprometimento pulmonar, mas também com manifestações sistêmicas, que decorrem do estresse oxidativo, inflamação sistêmica e consequente disfunção da musculatura esquelética. Essas alterações podem levar à piora dos sintomas respiratórios bem como perda de peso, disfunções dos músculos periféricos e respiratórios, diminuição da capacidade de exercício, prejuízo na qualidade de vida e um estilo de vida sedentário, o que resulta em pior prognóstico e sobrevida[7,22,31].

2.3.1 Dispneia

A dispneia é o sintoma mais característico da doença e uma das principais causas da diminuição da atividade física na vida diária (AFDV). Os pacientes frequentemente relatam esse sintoma como falta de ar, fome de ar, cansaço para respirar ou peso no peito[3,6].

O mecanismo gerador da dispneia é multifatorial, complexo e não totalmente esclarecido pela literatura. Alguns estudos indicam que os principais fatores desencadeantes da dispneia são a demanda ventilatória aumentada, juntamente com o comprometimento da mecânica respiratória[23,32]. Fatores psicológicos como a ansiedade e a depressão, cuja alta incidência nos indivíduos com DPOC tem sido ressaltada, também podem influenciar esse sintoma, além de causar maior impacto na qualidade de vida e na adesão aos tratamentos[33-35].

Um dos instrumentos mais utilizados para a avaliação da dispneia é a versão modificada da escala *Medical Research Council* (mMRC). Composta por apenas 5 itens que descrevem a sensação de falta de ar em atividades cotidianas, a mMRC fornece uma classificação do sintoma que vai de 0 a 4, sendo 0 a dispneia desencadeada apenas em atividades extenuantes e 4 a dispneia limitante aos mínimos esforços ou em repouso[36]. Essa escala é um instrumento de fácil acesso e aplicação, é validada para a população com DPOC e tem boa associação com medidas de estado de saúde e mortalidade[3,37].

2.3.2 CAPACIDADE FUNCIONAL DE EXERCÍCIO

Um desfecho reconhecidamente preditor de mortalidade na DPOC e que se correlaciona mais fortemente com a AFVD de pacientes com DPOC[25] é a capacidade funcional de exercício. O teste mais amplamente utilizado na prática clínica e nas pesquisas para avaliar esse desfecho é o teste de caminhada de seis minutos (TC6min), que tem se mostrado um bom marcador de piora na capacidade funcional do exercício e um bom parâmetro para avaliar respostas terapêuticas[38,39].

De acordo com o estabelecido pelas diretrizes internacionais[40] para a realização do TC6min, o paciente é orientado a caminhar durante seis minutos a maior distância possível, sem correr, em uma pista plana de 30 metros e recebe incentivos verbais padronizados para persistir na caminhada. É permitido ao paciente automodular a velocidade da caminhada, bem como parar para descansar durante o percurso, porém o cronômetro não é parado. A maior distância percorrida em metros é o desfecho principal do teste. Devido ao efeito aprendizado é recomendado a realização de dois testes, com um intervalo mínimo 30 minutos entre eles, ou até que os sinais vitais retornem aos valores basais estáveis, considerando-se para anállise o teste de maior valor.

Estudos realizados com amostras da população brasileira mostraram que a média da maior distância percorrida no TC6 para essa população é cerca de 500m, acima da média de populações européias e norte americanas[39,41]. Assim, não é aplicável para pacientes brasileiros o ponto de corte de 350m estabelecido na literatura como baixa capacidade funcional de exercício, sendo mais adequada a aplicação do corte de >80% do predito para classificar a capacidade funcional do exercício como preservada, sendo que pacientes que apresentam TC6<80% do predito tem maior risco de exacerbações[41].

2.3.3 ESTADO FUNCIONAL

A estreita relação entre estado funcional, morbidade e mortalidade em pacientes com DPOC ressalta a importância da avaliação adequada das limitações funcionais causadas pela doença e seus sintomas. Para isso existem instrumentos traduzidos e validados para a população brasileira com DPOC, como o *Pulmonary Functional Status and Dyspnea Questionnaire* (PFSDQ). Esse questionário avalia três domínios: influência da dispneia na atividade de vida diária (AVD), influência da fadiga na AVD e a mudança na AVD em comparação ao período anterior à doença. A avaliação é auto-relatada e uma pontuação parcial é calculada para cada domínio, variando de 0 a 100, além de uma pontuação total que varia, portanto, entre 0 e 300. Valores mais altos indicam maior limitação e pior estado funcional[36].

2.3.4 QUALIDADE DE VIDA

Outro desfecho importante na avaliação da DPOC é a qualidade de vida (QV) que se encontra altamente afetada pelas limitações e ansiedade impostas aos indivíduos principalmente devido ao sintoma de dispneia. Com o propósito de avaliar objetivamente a QV foi desenvolvido o *COPD Assessment Test* (CAT). Trata-se de um instrumento de aplicação rápida e prática, composto por 8 itens pontuados de 0 a 5 a respeito dos sintomas (tosse, secreção, pressão no peito, dispneia, limitação na AVD, confiança, sono e energia) e o impacto destes na vida do paciente. O questionário oferece uma classificação numérica do impacto da doença na qualidade de vida sendo que 0-10 representa nenhum impacto, 11-20 leve, 21-30 moderado e 31-40 alto impacto na QV. O total, portanto, pode variar de 0 a 40 com maiores valores indicando pior qualidade de vida[3,42-44].

Em suma, algumas pesquisas apontam que o VEF_1 tem associação limitada com vários desfechos clínicos na DPOC[4,6,7], enquanto estudos anteriores indicaram que a VVM, diferentemente, pode estar melhor associada com essas variáveis[4,5]. A VVM conta com pouca investigação científica sobre sua utilização na prática e na pesquisa, porém pode fornecer informações relevantes sobre a disfunção ventilatória de pacientes com DPOC, justificando, assim, a busca por novas evidências sobre essa medida.

3 ARTIGO ORIGINAL

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MAXIMUM VOLUNTARY VENTILATION AND ITS RELATIONSHIP WITH CLINICAL OUTCOMES IN PATIENTS WITH COPD.

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ABSTRACT

INTRODUCTION: The forced expiratory volume in the first second (FEV_1) is a spirometric variable frequently used to classify the degree of airway obstruction and also as a marker of prognosis and predictor of other disease outcomes. However, the FEV_1 is not strongly correlated with some clinical outcomes such as dyspnea, functional exercise capacity and quality of life. Previous studies have shown that Maximal Voluntary Ventilation (MVV) may be better associated than the FEV_1 with commonly used outcomes in the evaluation of COPD and may provide useful information on respiratory mechanics and endurance. **AIMS:** To investigate the relationship between MVV and clinical outcomes in COPD and additionally to verify whether MVV predicts these outcomes better than the $FEV_{1.}$ **METHODS:** This was a cross-sectional study involving individuals diagnosed with COPD assessed before entering a pulmonary rehabilitation program. They were submitted to assessment of lung function by spirometry, maximal inspiratory and expiratory pressures (MIP and MEP, respectively) by manuvacuometry, functional exercise capacity by the six-minute walk test (6MWT), dyspnea by the modified Medical Research Council (mMRC) scale, functional status by the modified Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ-m) and health status by the COPD Assessment Test (CAT). Correlations were verified by Spearman's coefficient and stepwise multiple linear regression models involving the correlated variables were used to check the predictors of clinical outcomes considering MVV, FEV_1 and anthropometric variables. **RESULTS:** The study included 157 subjects (82 males; median [interquartile range] of age 66 [61-73] years, BMI 27 [22-31] kg/m^2,, FEV_1 46 [33-57] %predicted, 6MWT 86 [76-96] %predicted, PFSDQ-m total score 34 [14-57] and CAT total score 13 [7-19] . Moderate and statistically significant correlations were found between MVV and MIP (r=0.40), 6MWT (r=0.50), mMRC (r=-0.56) and total scores of PFSDQ-m (r=-0.40) and CAT (r=-0.54) *(P*<0.001 for all). These correlations were generally stronger with MVV than with FEV_1. In the regression models, unlike $FEV_{1,}$ MVV appeared as a predictor of almost all clinical outcomes, except for a few CAT domains. **CONCLUSION:** MVV correlates moderately with several clinical outcomes used in the evaluation of individuals with COPD. MVV was also shown as a better predictor than the FEV_1 concerning respiratory muscle strength, functional exercise capacity, dyspnea, functional and health status. Therefore, there is rationale to integrate the assessment of MVV into clinical practice and research.

Key words: Chronic Obstructive Pulmonary Disease, Maximum Voluntary Ventilation, Health Status, Exercise.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major problem of global public health, which assumes nowadays the fourth position among causes of death, leading to great socioeconomic impact and affecting the quality of life of many patients. Recent studies have shown that, in Brazil, the prevalence of the disease varies between 6% and 15% in adults over 40[1-5].COPD is mainly caused by prolonged exposure to tobacco and other harmful particles[2,3]. The main pulmonary symptoms of the disease are dyspnea, chronic cough and increased sputum production, along with extrapulmonary manifestations such as fatigue, muscle dysfunction, reduction in functional exercise capacity and sedentary lifestyle[2,3,6,7].

The diagnostic confirmation of COPD is given by the clinical history along with spirometry, which provides quantification of forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1). FEV_1 is the variable most widely used in research and clinical practice to classify the degree of airflow obstruction in COPD, in addition to its use as prognostic factor and in therapeutic drug response[3,4,5]. However, there is limited correlation of FEV_1 with important outcomes in COPD such as dyspnea, functional exercise capacity and quality of life[8-10]. For this reason, a few studies[11-14] have called attention to other disease markers which correlate best with these variables.

Maximum voluntary ventilation (MVV) is a simple spirometric parameter not commonly explored in the scientific literature, and which has been recently even less explored with the emerging of new methods of lung function assessment. It is a test that evaluates the maximum amount of air a person can inhale and exhale voluntarily in a given period of time. This measure provides information on respiratory muscle mechanics and endurance, which are involved in the mechanism of dyspnea and exercise limitation in these patients[15-18].

The hypothesis tested in this study is that MVV can predict better than the FEV_1 the overall impairment of patients with COPD since it reflects the overall function of the respiratory system and not only the airflow obstruction. In this context, the objective of the present study was to investigate the relationship of MVV with clinical outcomes in this population and, additionally, to verify if MVV is a better predictor of these outcomes than FEV_1.

MATERIALS AND METHODS

This was a cross-sectional study using data from the baseline assessment of individuals with COPD recruited to participate in a pulmonary rehabilitation (PR) program at the University Hospital of State University of Londrina (UEL), Paraná, Brazil. For inclusion, individuals must have a diagnosis of COPD according to the GOLD criteria[3] and clinical stability in the last three months before inclusion, as well as not having participated in any rehabilitation or exercise program in the last year and not presenting any severe cardiovascular disease or musculoskeletal impairment that could potentially limit the tests. Exclusion criteria were the inability to perform the proposed tests or exacerbation occurred during the evaluation protocol. The study was approved by UEL's Ethics Committee and all participants signed an informed consent form.

ASSESSMENTS

Anthropometrics, lung function and respiratory muscle strength

At the first meeting, personal demographic and anthropometric data were collected, as well as information on comorbidities and history of exacerbations. Additionally, patients were also assessed regarding pulmonary function pre and post-bronchodilator (post-BD) using a portable spirometer (SpirobankG®, MIR, Italy). The protocol followed the guidelines of the American Thoracic Society (ATS)/European Respiratory Society (ERS)[15,19]. Reference values were those from Pereira et al[20] for the Brazilian population. Post-BD measurements were used for the analysis .

Plethysmography was performed in part of the sample using the equipment Vmax® (Carefusion, Germany), also according to the ATS/ERS guidelines[24.] It was not possible to perform plethysmography in the complete sample due to the unavailability of the equipment for a period of time.

Respiratory muscle strength was also assessed at the first visit by the maximum inspiratory and expiratory pressures (MIP and MEP, respectively), using a digital manometer (MVD300®, Globalmed, Brazil). Assessment was performed according to the technique described by Black & Hyatt[21] and Brazilian guidelines[22]. Brazilian reference values of Neder et al[23] were used.

All tests were performed with the patient in the seated position, using a nose clip and oriented to keep the lips well coupled avoiding leakage. Patients should also keep feet supported, hands resting on the thigh and upright posture without compensations during the execution of the maneuvers. For all tests individuals received detailed instruction with practical demonstration and standardized verbal encouragement.

Functional exercise capacity

In the second visit, functional exercise capacity was assessed using the six-minute walk test (6MWT), according to international guidelines[25] and reference values of Britto et al.[26] for the Brazilian population. Patients were instructed to walk the farthest possible distance (without running) on a flat corridor of 30 meters for 6 minutes and received standardized verbal encouragement every minute. The subject was allowed to stop during the course, but the stopwatch was not interrupted. Due to the learning effect, two tests were performed, with a minimum interval of 30 minutes between them, or until the vital signs returned to baseline[25]. The largest distance from the two tests was used for analysis.

Dyspnea in daily life

The modified Medical Research Council scale (mMRC)[27,28] was used to assess dyspnea in daily life. The scale consists of 5 items that describe the sensation of dyspnea in daily activities, and provides the rating from 0 to 4, where 0=dyspnea triggered only in stenuous activities and 4=limiting dyspnea on minimal exertion or at rest.

Functional status

For the evaluation of functional status the modified version of the Pulmonary questionnaire Functional Status and Dyspnea Questionnaire (PFSDQ-m) was applied. It assesses three self-reported domains: influence of dyspnea on activities of daily living (ADL), influence of fatigue on ADL and change in ADL in comparision to the period prior to the disease. A partial score is calculated for each domain, ranging from 0 to 1 00, and a total score sums up the three domains, going up to 300, with higher values indicating worse functional status[27,29,30].

Health status

The COPD Assessment Test (CAT), composed by 8 itens scored from 0 to 5, reflected the impact of the disease on health status, with 0-10 representing no impact, 11-20 mild, 21-30 moderate, and 31-40 high impact. The total score varies from 0 to 40, with higher values indicating worse health status[30,31,32].

STATISTICAL ANALYSIS

Normality in data distribution was verified by the Shapiro-Wilk test and the results described in mean ± standard deviation (SD) or median and interquartile range [25%-75%], depending on normal distribution. All variables were correlated with MVV by using the Spearman's correlation coefficient and, for the variables that presented significant correlations, multivariate linear regression models were used to verify the predictors of each clinical outcome taking into consideration the MVV, FEV_1 and the anthropometric variables age, gender, weight and height (as a way to exclude possible confounding factors) . The software used for the analysis were SPSS 22.0 (SPSS Inc. USA) and GraphPad Prism 6.0 (GraphPad Software, California). Statistical significance was set as $P<0.05$.

RESULTS

The analysis included data from 157 subjects who, in general, had normal weight to overweight, moderate to severe airflow obstruction, decreased inspiratory muscle strength, relatively preserved functional exercise capacity, good functional status and moderate clinical impact on health status, as shown in Table 1. A sub-analysis was performed with data available from 37 individuals regarding static lung volumes evaluated by body plethysmography. The characterization of this sample is also found in Table 1.

Table 2 shows the correlations of MVV and FEV_1 with weight, height, comorbidities, BODE index, MIP, MEP,, 6MWT, lung volumes, dyspnea, functional status and health status. There were weak to moderate and statistically significant correlations of both MVV and FEV1 with most of the outcomes analyzed except TLC and RV volumes, and the CAT domains chest pressure and sleep.

Table 1. Characterization of the sample.

VARIABLES			
Gender M/F (%)	82/75 (52/48)	**IC/TLC (n=37)**	38 [32-44]
Age (years)	66 [61-73]	**RV/TLC (n=37)**	52 [46-60]
Weight (Kg)	69 [55-79]	**MVVindex/(FEV_1x40)**	0.9 [0.8-1.1]
Height (m)	1.5 [1.53-1.67]	**MIP (cmH_2O)**	65 [50-80]
BMI (kg/m^2)	27 [22-31]	**MIP (%Predicted)**	75 [56-90]
nComorbidities (n=144)	1 [0-2]	**MEP (cmH_2O)**	95 [75-123]
Comorbidities S/N (%)	90/54 (62/38)	**MEP (%Predicted)**	103 [85-126]
GOLD I/II/III/IV	1/68/57/31	**6MWT (m)**	465 [410-513]
BODE Index	4 [2-5]	**6MWT (%Predicted)**	86 [76-96]
FVC (L)	2.2 [1.7- 2.9]	**mMRC**	3 [1-3]
FVC (%Predicted)	72 [55-84]	**PFSDQ-m Dyspnea**	11 [5-20]
FEV_1 (L)	1.10 [0.81-1.55]	**PFSDQ-m Fatigue**	10 [3-8]
FEV_1 (%Predicted)	46 [33-57]	**PFSDQ-m Activities**	10 [3-23]
FEV_1/FVC (%)	52 [42-62]	**PFSDQ-m Total (n=65)**	34 [14-57]
MVV (L/min)	42 [27-59]	**CAT Cough**	2 [1-3]
MVV (% Predicted)	42 [27-55]	**CAT Secretion**	2 [1-4]
Estimated MVV (L/min)*	57 [46-74]	**CAT Chest pressure**	0 [0-2]
TLC (L) (n=37)	6.85 [5.90-7.50]	**CAT Shortness of breath**	3 [2-5]
TLC (%Predicted)	121 [110-135]	**CAT ADL Limitation**	2 [0-4]
IC (L) (n=37)	2.62 [2.03-3.23]	**CAT Trust**	0 [0-3]
IC (%Predicted)	117 [94-129]	**CAT Sleep**	0 [0-2]
RV (L) (n=37)	3.57 [2.62-4.59]	**CAT Energy**	2 [0-3]
RV (%Predicted)	156 [129-220]	**CAT Total (n=76)**	13 [7-19]

N=157 unless otherwise noted. BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; MVV: maximum voluntary ventilation; TLC: total lung capacity; IC: inspiratory capacity; RV: residual volume; MIP: maximal inspiratory pressure; MEP: maximum expiratory pressure; 6MWT: six-minute walk test; mMRC: Modified version of the Medical Research Council scale; PFSDQ-m: Pulmonary Functional Status and Dyspnea Questionnaire modified version, CAT: COPD Assessment Test; ADL: daily life activity. *Estimated MVV=(FEV_1x37.5)+15

Table 2. Correlations of clinical outcomes with MVV and FEV_1.

	MVV (L/min)	FEV_1 (L)		MVV (L/min)	FEV_1 (L)
Weight (Kg)	0.38**	0.38**	**PFSDQ-m Dyspnea**	-0.44**	-0.43**
Height (m)	0.31**	0.31**	**PFSDQ-m Fatigue**	-0.35**	-0.30*
BODE Index	-0.73**	-0.75**	**PFSDQ-m Activities**	-0.30*	-0.25*
nComorbidities	-0.25**	-0.19*	**PFSDQ-m Total**	-0.40*	-0.36*
MIP (cmH_2O)	0.40**	0.31**	**CAT Cough**	-0.30*	-0.31**
MEP (cmH_2O)	0.34 **	0.28**	**CAT Secretion**	-0.33**	-0.34**
6MWT (m)	0.50**	0.46**	**CAT Chest pressure**	-0.14	-0.12
TLC (L)	0.24	0.28	**CAT Shortness of breath**	-0.46**	-0.41**
IC (L)	0.67**	0.65**	**CAT ADL Limitation**	-0.50**	-0.44**
RV (L)	-0.09	-0.03	**CAT Trust**	-0.47**	-0.36**
IC/TLC	0.48**	0.45**	**CAT Sleep**	-0.07	-0.09
RV/TLC	-0.56**	-0.53**	**CAT Energy**	-0.29**	-0.28*
mMRC	-0.56**	-0.50**	**CAT Total**	-0.54**	-0.49**

FEV_1: forced expiratory volume in the first second; MVV: maximum voluntary ventilation; TLC: total lung capacity; IC: inspiratory capacity; RV: residual volume; MIP: maximal inspiratory pressure; MEP: maximum expiratory pressure; 6MWT: six-minute walk test; mMRC: modified version of the Medical Research Council scale; PFSDQ-m: Pulmonary Functional Status and Dyspnea Questionnaire modified version, CAT: COPD Assessment Test; ADL: activity of daily life. *P <0.05; **P <0.001.

Considering only the magnitude of the correlations, it was observed that for most of the outcomes MVV was shown to be better associated than the FEV_1 (even if slightly), except for the BODE index and CAT domains Cough and Secretion that presented slightly higher correlation values with FEV_1 .

Table 3 shows the results of the linear regression for 6MWT, MIP and MEP. In Table 4 the results of the regression models for mMRC, PFSDQ-m and CAT are presented.

Table 3. Multiple linear regression for respiratory muscle strength and functional exercise capacity.

		Non standardized coefficient (β)	**95% confidence interval for β**	***P***	**r^2 partial (%)**	**r^2 adjusted (%)**
6MWT	Constant	662.35	550 - 774	<0.001		
	MVV (L/min)	2.06	1.54 - 2.57	<0.001	23	23
	Age (years)	-3.16	-4.57 - -1.76	<0.001	30	29
	BMI (kg/m^2)	-3.41	-5.35 - 1.45	0.001	35	34
MIP	Constant	90.26	61.35 -119.18	<0.001		
	MVV (L/min)	0.40	0.25 - 0.56	<0.001	15	14
	Age (years)	-0.64	-1.06 - -0.21	0.003	20	19
MEP	Constant	122.67	78 - 167	<0.001		
	MVV (L/min)	0.84	0.41 - 1.27	<0.001	17	17
	Gender	27.12	17.31-36.43	<0.001	26	25
	Age (years)	-1.20	-1.76 - -0.63	<0.001	33	32
	BMI (kg/m^2)	1.18	0.41 - 1.95	0.003	37	35
	FEV_1 (L)	-22.47	-41.83 - 3.11	0.023	39	37

6MWT: six-minute walk test; MIP: maximal inspiratory pressure; MEP: maximum expiratory pressure; MVV: maximum voluntary ventilation; FEV_1: forced expiratory volume in the first second; BMI: body mass index.

It can be observed in Tables 3 and 4 that, unlike FEV_1, the MVV appears as a predictor of almost all the analyzed outcomes.

Table 4. Multiple linear regression for dyspnea, functional status and health status.

		Non standardized coefficient (β)	95% confidence interval for β	*P*	r^2 partial (%)	r^2 adjusted (%)
mMRC	Constant	3.54	3.18 - 3.90	<0.001		
	MVV (L/min)	-0.03	-0.03 - -0.02	<0.001	28	28
PFSDQ-m dyspnea	Constant	59.43	37.05 - 81.82	<0.001		
	Age (years)	-0.55	-0.88 - -0.23	0.001	14	12
	MVV (L/min)	-0.19	-0.31 - -0.07	0.002	27	24
PFSDQ-m fatigue	Constant	44.43	19.86 - 69	0.001		
	MVV (L/min)	-0.15	-0.28 - -0.03	0.019	8	7
	Age (years)	-0.37	-0.73 - -0.02	0.039	14	11
PFSDQ-m activities	Constant	64.13	32.02 - 96.25	<0.001		
	Age (years)	-0.62	-1.08 - -0.15	0.010	9	8
	MVV (L/min)	-0.17	-0.34 - -0.01	0.041	15	13
PFSDQ-m Total	Constant	168	94.77 - 241.24	<0.001		
	Age (years)	-1.55	-2.62 - -0.48	0.005	12	10
	MVV (L/min)	-0.52	-0.91 - -0.14	0.008	19	17
CAT Cough	Constant	3.17	2.40 - 3.93	<0.001		
	MVV (L/min)	-0.22	-0.038 - -0.007	0.004	10	10
CAT Secretion	Constant	3,80	2.77 - 4.85	<0.001		
	MVV (L/min)	-1,28	-2.08 - -0.47	0.002	12	11
CAT Shortness of breath	Constant	9.39	6.52 - 12.27	<0.001		
	MVV (L/min)	-0.32	-0.47 - -0.02	<0.001	17	16
	Age (years)	-0.07	-0.11 - -0.03	0.001	2 8	26
CAT ADL Limitation	Constant	8.58	5.28 - 11.89	<0.001		
	MVV (L/min)	-0.04	-0.06 - -0.02	<0.001	22	21
	Age (years)	-0.07	-0.11 - -0.02	0.005	30	28
CAT Trust	Constant	7.08	3.94 - 10.21	<0.001		
	MVV (L/min)	-0.04	-0.05 - -0.02	<0.001	19	18
	Age (years)	-0.06	-0.11 - -0.02	0.006	27	25
CAT Energy	Constant	2.78	1.91 - 3.65	<0.001		
	MVV (L/min)	-0.02	-0.04 - -0.01	0.010	8	7
CAT Total	Constant	42.76	28.15 - 57.37	<0.001		
	MVV (L/min)	-0.20	-0.28 - -0.13	<0.001	26	25
	Age (years)	-0.28	-0.49 - -0.07	0.010	33	31

FEV_1: forced expiratory volume in the first second ; MVV: maximum voluntary ventilation; mMRC: modified version of the Medical Research Council scale; PFSDQ-m: Pulmonary Functional Status and Dyspnea Questionnaire modified version, CAT: COPD Assessment Test; ADL: activities of daily living .

DISCUSSION

Both traditionally and currently, the FEV_1 is the most commonly used pulmonary function variable for classification of disease severity and as a predictor of prognosis in patients with COPD. The results presented here show that MVV correlates equally or even better than FEV_1 with outcomes of dyspnea, exercise capacity, functional status and health status in patients with COPD, showing itself as a predictor of variation in these outcomes also in regression models indicating that the MVV is a better predictor of these clinical outcomes than the FEV_1. The explanation for these results may be contained in the fact that, while the FEV_1 basically reflects the airflow limitation, the MVV additionally reflects the available ventilatory reserve to respond to the increase in the physiological demand during exertion[7,8,9].

A study by Rocha et al.[12] assessed the diaphragmatic mobility (DM) of 25 individuals with COPD comparing with 25 matched controls and found reduced DM in individuals with COPD, as well as strong correlations of DM with IC (r=0.81) and with MVV (r=0.76), suggesting that the change in DM in COPD is more associated with hyperinflation and with ventilatory capacity than with the obstruction itself, and consequently also more related to the sensation of dyspnea.

These results can also be pointed out in the present study where moderate positive correlations of MVV were found with IC (r=0.67) and IC/TLC (r=0.48), in addition to moderate and negative correlations with the mMRC scale (r=-0.56) and the PFSDQ-m dyspnea domain (r=-0.44). These values reflect the association of better respiratory mechanics and endurance with lower hyperinflation and less dyspnea sensation.

A study by Yamaguti et al.[14] found a stronger correlation of decrease in DM with indicators of air trapping and ventilatory capacity than with hyperinflation. The present study, in addition to showing a stronger association between hyperinflation and ventilatory capacity, also found a moderate negative correlation of MVV and the RV/TLC ratio, which reflects air trapping.

A study by Pitta et al.[10] demonstrated that MVV correlates better than FEV_1 with the energy expenditure evaluated in daily life with physical activity monitors. In addition, a study by Cavalheri et al.[11] assessed the energy expenditure of individuals with COPD during ADL simulations and also found a better correlation of this outcome with MVV in comparison to FEV_1, FVC and RMS. These results indicate that MVV may reflect the capacity of response to increased respiratory demand and, therefore, also its influence on the physical activity levels of these patients. The present study corroborate and complements these findings, presenting moderate and significant correlations of MVV with the 6MWT, which is already established as an independent predictor of mortality in COPD and is also well associated with PADL levels in this population[33,34]. Furthermore, the correlations with RMS reinforce MVV as a broader measure of the respiratory system than just the degree of airflow obstruction by the $FEV_{1.}$ In this way, the associations demonstrated in this study support the value of MVV as a possible marker of the disease involvement. Thus, the present results reinforce the importance of this test in the comprehensive lung function evaluation in order to assist the assessment of the impact of physical and functional limitation, as well as symptoms' impact on patient's activities, caused by respiratory and systemic dysfunctions that are part of the complex process which triggers exertional dyspnea.

Dugan et al.[32] demonstrated improvement in MVV after a PR program composed by aerobic exercise and upper limb strength exercises, whereas FEV_1 did not improve significantly. The study also showed that, after PR, there was no improvement in quality of life of patients with COPD compared to a control group that received usual care, and suggests the hypothesis that PR promotes the improvement of respiratory muscular strength and endurance, leading to a greater sense of comfort for the individuals in the execution of their daily activities with consequent better perception of quality of life. This study supports this hypothesis by showing best correlation between mMRC, PFSDQ-m and CAT scores with the MVV than with $FEV_{1.}$ This reinforces that MVV is more associated then the degree of obstruction with the sensation of dyspnea, functional limitation and quality of life.

The improvement of MVV (and not necessarily FEV_1) in Dugan's study[32] may reflect a patient's improvement in their daily life after PR, allowing less limitation due to dyspnea, greater functional reserve, improved performance on ADL and a better self-reported quality of life. These findings can contribute to the understanding of the disease complexity and promote improvement in the impact of dyspnea in COPD patients. However, these assumptions are hypothesis, and must be proven in longitudinal studies.

The present study presents as limitation the use of two different devices to perform spirometry. However, it is believed that this does not influence the results, since the technique used was the same, following strictly the standardization of the test proposed by international guidelines[15,19,22,24]. Another limitation is the fact that the sample had only one GOLD I patient and, in general, participants presented preserved functional exercise capacity and good functional status, which hinders the generalization of these results for all COPD severity levels.

In conclusion, MVV correlates with clinical outcomes in COPD, reflecting more widely the ventilatory dysfunction beyond chronic obstruction. In addition, MVV proved to be a better predictor than FEV_1 for functional exercise capacity, inspiratory muscle strength, dyspnea, functional status and quality of life in this population. Therefore, it is recommended that this test must be integrated into clinical practice and research assessments, and that the search for more evidence and standardization should be encouraged.

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4 CONCLUSÃO GERAL

O presente trabalho traz novos achados científicos que contribuem para a literatura científica a respeito da avaliação da função pulmonar em pacientes com DPOC, bem como para o estabelecimento de gravidade e prognóstico da doença. Demonstrou-se com esse estudo que a VVM é melhor preditora da dispneia, capacidade funcional de exercício, força muscular respiratória, estado funcional e qualidade de vida do que o VEF_1 em pacientes com DPOC. Recomenda-se que essa manobra esteja inserida nas triagens e avaliações periódicas dos pacientes, visto que sua realização pode contribuir para um melhor entendimento do quadro clínico apresentado pelos indivíduos com a doença.

Pode-se inferir, com os resultados apresentados sobre a VVM, que a sintomatologia da DPOC, a intolerância ao exercício e as limitações funcionais, bem como a qualidade de vida são influenciadas pelo desempenho da mecânica ventilatória e não somente pela obstrução crônica ao fluxo aéreo. Fica evidente, portanto, a complexidade do conjunto de sintomas e alterações que limitam o indivíduo com DPOC e a importância em dispor de testes práticos que permitam melhor caracterização e acompanhamento dos pacientes.

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APÊNDICES

APÊNDICE A

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Prezado(a) Senhor(a):

O(A) Sr(a) está sendo convidado para participar de um projeto de pesquisa chamado "*A adição do treinamento aeróbico de membros superiores ao treinamento aeróbico de membrosinferiores e exercícios globais de força muscular se traduz em melhor desempenho nas atividadesde vida diária e no nível de atividade física da vida diária em DPOC*?", cujos pesquisadores responsáveis são Prof. Dr. Fábio de Oliveira Pitta e Nidia A. Hernandes, do Departamento de Fisioterapia da Universidade Estadual de Londrina (UEL). O estudo analisará principalmente as melhoras obtidas após 3 meses de treinamento utilizando-se dois tipos diferentes de exercício físico.

Justificativa: O presente estudo contribuirá para solucionar uma questão não resolvida na literatura científica da área, e que tem sido alvo de grande debate entre pesquisadores. Embora a adição do treinamento de membros superiores ao programa de reabilitação pulmonar para pacientes com DPOC já esteja estabelecido na literatura científica e estudos que comprovem a eficiência e a necessidade do treinamento dessa musculatura já tenham sido publicados, ainda não se sabe se um programa de treinamento físico de alta intensidade que inclui exercício aeróbico envolvendo MMSS adicionalmente ao treinamento de MMII, além de exercícios globais de força muscular, resulta em melhora mais acentuada do desempenho nas AVD e do nível de AFVD. Além disso, o presente estudo poderá verificar se esses benefícios serão evidenciados já após os primeiros 3 meses de intervenção. Caso isso ocorra, poderemos sugerir um modelo de protocolo de treinamento físico de curta duração que comprovadamente resulta em melhora de AFVD e desempenho nas AVD.

Objetivo: Comparar os efeitos de dois programas de treinamento físico de alta intensidade que envolvem, por exemplo, exercícios aeróbicos como caminhar em esteira e pedalar com os membros superiores (braços) e membros inferiores (pernas) sobre a função do pulmão, a capacidade realizar exercício, e a capacidade de realizar as atividades cotidianas (atividades físicas de vida diária- AVD) de pacientes com doença pulmonar obstrutiva crônica: um protocolo baseado em treinamento de alta intensidade com exercícios aeróbicos de membros inferiores (caminhada em esteira e pedalar em bicicleta estacionária) e exercícios globais de força muscular; e outro protocolo similar porém adicionando-se o treinamento aeróbico de membros superiores (pedalar com os braços).

Procedimentos: Os pacientes incluídos realizarão uma série de testes que incluirá avaliação da função do pulmão, da capacidade de realizar exercícios, da capacidade de realizar as atividades do dia-a-dia (capacidade funcional), da força muscular dos braços e pernas e da força dos músculos que são usados para respirar (força muscular respiratória), da quantidade de atividade física que é realizada no dia-a-dia (atividade física na vida diária), da composição corporal, da qualidade de vida, do impacto que a doença tem sobre o paciente (estado funcional) e da sensação de falta de ar (dispneia). A realização dos testes requer uma visita de aproximadamente 2 horas ao Hospital Universitário Regional Norte do Paraná, em Londrina, além do uso do pequeno aparelho na cintura durante dois dias (12 horas por dia, apenas durante o dia e não de noite). Após a avaliação inicial, os pacientes serão divididos em dois grupos: um grupo no qual os participantes realizarão um programa de treinamento físico de alta intensidade que incluirá exercícios aeróbicos de membros inferiores (caminhada em esteira e pedalar em bicicleta estacionária) e de força de membros superiores e inferiores; ou no grupo que realizará o mesmo protocolo, porém, com a adição do treinamento aeróbico de MMSS realizado em cicloergômetro próprio para MMSS (pedalar com os braços). Ao final do programa de treinamento, os participantes serão reavaliados seguindo os mesmos testes realizados na avaliação inicial.

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

Riscos: O presente projeto não envolve o uso de qualquer medicação. Os procedimentos envolvidos na pesquisa envolvem riscos mínimos relacionados à realização de exercício físico em intensidade tolerável (exemplo: aumento da sensação de falta de ar durante o exercício; leves dores musculares; leve aumento da pressão arterial e da frequência cardiaca durante o exercício; e risco de queda em caso de tropeços durante a caminhada). Pacientes com contraindicações à realização de exercícios (como por exemplo pacientes com doença cardíaca grave prévia) não serão incluídos neste projeto. Ainda assim, visto que alterações fisiológicas como aumento discreto na pressão arterial e frequência cardíaca, por exemplo, são normais durante a execução de qualquer atividade física, procederemos o monitoramento dos sinais vitais durante as sessões. Em casos que estas respostas não estejam dentro da normalidade esperada o exercício será interrompido. Além disso, quando necessário (i.e., na eventualidade de respostas adversas durante as sessões) os pacientes serão imediatamente encaminhados para atendimento médico no Hospital Universitário de Londrina (HU/UEL), já que o projeto será realizado nas dependências deste hospital.

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

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

Local e data:____

Nome do participante: ____

Assinatura do participante ou responsável:_________________________________

Assinatura do pesquisador: ____

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

Atenciosamente,

Prof. Fábio de Oliveira Pitta
Coordenador do Projeto

Comite de Ética em Pesquisa da UEL (CEP/UEL)

Comitê de Ética em Pesquisa Envolvendo Seres Humanos - CEP/UEL
Rodovia Celso Garcia Cid, Km 380 (PR 445)
Campus Universitário - ao lado do Banco Itaú
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ANEXOS

ANEXO A

Parecer do Comitê de Ética em Pesquisa

Universidade Estadual de Londrina

PARANÁ
GOVERNO DO ESTADO

COMITÊ DE ÉTICA EM PESQUISA ENVOLVENDO SERES HUMANOS
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Registro CONEP 5231

Parecer CEP/UEL:	173/2012
CAAE:	08307812.0.0000.5231
Processo:	26336/2012
Pesquisador(a):	Fábio de Oliveira Pitta
Unidade/Órgão:	CCS – Departamento de Fisioterapia

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:

"SEGUIMENTO A LONGO PRAZO DE UM PROGRAMA DE TREINAMENTO FÍSICO DE LONGA DURAÇÃO SOBRE ASPECTOS PULMONARES E SISTÊMICOS DE PACIENTES PORTADORES DE DOENÇA PULMONAR OBSTRUTIVA CRÔNICA (DPOC)"

Situação do Projeto: **Aprovado**

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

Londrina, 08 de outubro 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 -

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Form. Código 11.764 - Formato A4 (210x297)

ANEXO B

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[2] Van der Geer, J., Hanraads, J.A.J., Lupton, R.A., 2018. The art of writing a scientific article. Heliyon. 19, e00205.https://doi.org/10.1016/j.heliyon.2018.e00205.

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[3] W. Strunk Jr., E.B. White, The Elements of Style, fourth ed., Longman, New York, 2000.

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[4] G.R. Mettam, L.B. Adams, How to prepare an electronic version of your article, in: B.S. Jones, R.Z. Smith (Eds.), Introduction to the Electronic Age, E-Publishing Inc., New York, 2009, pp. 281–304.

Reference to a website:
[5] Cancer Research UK, Cancer statistics reports for the UK. http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/, 2003 (accessed 13 March 2003).

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[dataset] [6] M. Oguro, S. Imahiro, S. Saito, T. Nakashizuka, Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1, 2015. https://doi.org/10.17632/xwj98nb39r.1.

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