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LARISSA MORENO MARTINEZ FARIA

**DIFERENÇA ENTRE AS CAPACIDADES VITAIS LENTA E
FORÇADA E SUA RELAÇÃO COM A HIPERINSUFLAÇÃO
DINÂMICA EM INDIVÍDUOS COM DOENÇA PULMONAR
OBSTRUTIVA CRÔNICA**

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

Orientador: Prof. Dr. Fabio Pitta.

Londrina
2018

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**Dedico este trabalho a minha família, pelo incentivo e por serem a razão
para eu sempre continuar.**

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“Um passo a frente e você não está mais no mesmo lugar.”

(Chico Science)

FARIA, Larissa M. M. **Diferença entre as capacidades vitais lenta e forçada e sua relação com a hiperinsuflação dinâmica em indivíduos com doença pulmonar obstrutiva crônica.** 2018. 67f. Dissertação de mestrado (Programa de Pós-Graduação em Ciências da Reabilitação – Programa Associado entre UEL e UNOPAR) – Universidade Estadual de Londrina, Londrina, 2018.

RESUMO

Introdução: A capacidade vital (CV) é uma soma de volumes pulmonares que pode ser avaliada por meio das manobras lenta (CVL) e forçada (CVF). Em pacientes com doença pulmonar obstrutiva crônica (DPOC) a CVF é menor do que a CVL, sendo que a diferença entre essas duas variáveis (CVL-CVF) está relacionada ao aprisionamento aéreo. A hiperinsuflação pulmonar dinâmica (HD), que ocorre devido ao aprisionamento aéreo, está entre os principais mecanismos limitadores da tolerância ao exercício em pacientes com DPOC. Um dos testes mais comuns para avaliação da tolerância ao exercício em pacientes com DPOC é o teste de caminhada de seis minutos (TC6min). Durante sua execução podem ser utilizados aparelhos que monitoram a ventilação e conseqüentemente, podem ser obtidos valores seriados de capacidade inspiratória (CI), que refletem a HD. No entanto, a relação entre a diferença CVL-CVF e a HD desenvolvida durante o TC6min ainda não foi estudada.

Objetivo: Investigar a relação entre a diferença CVL-CVF com a HD avaliada durante o TC6min em indivíduos com DPOC. **Material e Métodos:** Vinte e quatro indivíduos com diagnóstico de DPOC (12 homens; 67±6 anos; volume expiratório forçado no primeiro segundo [VEF₁] 56±18% predito), realizaram avaliação da função pulmonar por meio de espirometria e pletismografia. A HD ($\Delta CI \geq 150\text{ml}$ ou 10%) foi mensurada com medidas seriadas de CI por meio da manobra de CVL que foi realizada ao repouso, a cada dois minutos durante o TC6min, quinze segundos antes do final do teste, e imediatamente após o seu término. **Resultados:** Foi observada redução significativa da CI durante o TC6min ($\Delta CI: -048 \pm 040\text{L}$; $P < 0.0001$), sendo que dezoito indivíduos (75%) apresentaram HD. Houve diferença significativa da CI mensurada ao repouso com as demais medidas seriadas da CI ($P < 0,0001$). A diferença CVL-CVF (em litros) apresentou apenas fraca correlação com a variação da CI durante o TC6min ($r = -0,38$; $P = 0,06$). **Conclusão:** De acordo com os resultados do estudo que compõe essa dissertação, a diferença CVL-CVF apresenta fraca correlação com o desenvolvimento de HD avaliada por meio da CI durante o TC6 em pacientes com DPOC.

Palavras-chave: Doença pulmonar obstrutiva crônica. Testes de função respiratória. Capacidade vital. Capacidade inspiratória. Exercício.

FARIA, Larissa M. M. **Difference between slow and forced vital capacity and its relationship with dynamic hyperinflation in patients with chronic obstructive pulmonary disease.** 2018. 67p. Masters dissertation (Post-Graduation Program in Rehabilitation Science–Association Program between UEL and UNOPAR) – State University of Londrina, Londrina, 2018.

ABSTRACT

Introduction: Vital capacity (VC) is a sum of pulmonary volumes that can be assessed through slow (SVC) and forced (FVC) maneuvers. In patients with chronic obstructive pulmonary disease (COPD), FVC is generally lower than SVC, and the difference between these two variables (SVC-FVC) is related to air trapping. Dynamic lung hyperinflation (DH), which occurs due to air trapping, is amongst the main limiting mechanisms of exercise tolerance in patients with COPD. One of the most commonly used tests to assess exercise tolerance in patients with COPD is the six-minute walk test (6MWT). Ventilation monitoring devices can be used during the execution of the test, and consequently, serial inspiratory capacity (IC) values can be obtained, therefore reflecting DH. However, the relationship between SVC-FVC and DH developed during the 6MWT has not been studied. **Objective:** To investigate the relationship between SVC-FVC difference with DH during the 6MWT in subjects with COPD. **Methods:** Twenty-four subjects with COPD (12 male; 67 ± 6 years; forced expiratory volume in the first second [FEV₁] 56 ± 18 % predicted), performed lung function assessment by spirometry and plethysmography. DH ($\Delta IC \geq 150$ ml or 10%) was assessed through serial IC measurements using the SVC maneuver at rest, every two minutes during 6MWT, fifteen seconds before the end of the test and immediately upon test completion. **Results:** IC decrease significantly during the 6MWT ($\Delta IC: -0,48 \pm -0,40$ L; $P < 0.0001$), and eighteen individuals (75%) presented DH. There was a significant difference in IC measured at rest with the other serial IC measurements ($P < 0.0001$). The difference SVC-FVC (in liters) presented only weak correlation with changes in IC during the 6MWT ($r = -0.38$; $P = 0.06$). **Conclusion:** According to results of the study which composes this dissertation, the difference SVC-FVC presents weak correlation with the development of DH measured by IC during the 6MWT in patients with COPD.

Keywords: Pulmonary disease chronic obstructive. Respiratory Function tests. Vital capacity. Inspiratory capacity. Total lung capacity. Exercise.

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LISTA DE ABREVIATURAS E SIGLAS

6MWT	Six-minute walk test
ATS	American Thoracic Society
CI	Capacidade inspiratória
CI/CPT	Relação entre a capacidade inspiratória e a capacidade pulmonar total
COPD	Chronic obstructive pulmonary disease
CPT	Capacidade pulmonar total
CRF	Capacidade residual funcional
CV	Capacidade vital
CVE	Capacidade vital expiratória
CVF	Capacidade vital forçada
CVI	Capacidade vital inspiratória
CVL	Capacidade vital lenta
CVL-CVF	Diferença entre a capacidade vital lenta e forçada
DH	Dynamic hyperinflation
DPOC	Doença pulmonar obstrutiva crônica
EELV	End expiratory lung volume
ERV	Expiratory reserve volume
ERS	European Respiratory Society
FEV	Forced expiratory volume in the first second
FVC	Forced vital capacity
GOLD	Global initiative for chronic obstructive disease
HD	Hiperinsuflação dinâmica
HPE	Hiperinsuflação pulmonar estática
IC	Inspiratory capacity
IC/TLC	Relation between inspiratory capacity and total lung capacity
LFIP	Laboratório de Pesquisa em Fisioterapia Pulmonar
LTOT	Long-term oxygen therapy
SVC	Slow vital capacity
SVC-FVC	Difference between slow and forced vital capacity
TC6min	Teste da caminhada de 6 minutos
TLC	Total lung capacity

UEL	Universidade Estadual de Londrina
VC	Vital capacity
VEF ₁	Volume expiratório forçado no primeiro segundo
VEF ₁ /CVF	Relação entre o volume expiratório forçado no primeiro segundo e a capacidade vital forçada

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1. INTRODUÇÃO

A doença pulmonar obstrutiva crônica (DPOC) tem como principal característica a persistente obstrução ao fluxo aéreo¹. Além da obstrução, a DPOC também é caracterizada por inatividade e intolerância ao exercício físico². Esta intolerância ao esforço pode estar associada a diversas características como composição corporal, número de exacerbações prévias, presença de comorbidades, disfunção muscular respiratória e periférica, além do próprio grau de obstrução ao fluxo aéreo, e da hiperinsuflação pulmonar, tanto estática (HPE) quanto dinâmica (HD)^{3,4}.

A HPE pode ocorrer devido à redução do recolhimento elástico pulmonar, limitação ao fluxo expiratório ou ambos, levando ao aprisionamento aéreo. A HPE é observada quando há uma redução da capacidade inspiratória (CI) em repouso⁵. Além disso, a relação entre a CI e a capacidade pulmonar total (CI/CPT) foi identificada como o melhor índice para mensurar a HPE⁶. No entanto, a avaliação da CPT requer o uso de equipamentos complexos e de alto custo, e portanto não largamente disponíveis na prática clínica e muitas vezes nem mesmo para investigação científica⁷.

A HD, que ocorre durante a atividade física em grande parte dos indivíduos com DPOC, é um dos principais fatores que limitam a tolerância ao exercício. Isso ocorre uma vez que a diminuição da CI limita a capacidade de aumentar a ventilação em resposta às crescentes exigências metabólicas durante o exercício⁸, contribuindo assim para a intensa dispneia relatada pelos pacientes com DPOC no momento de realizar atividades físicas⁹.

A estratégia mais efetiva para avaliar a HD é por meio de medidas seriadas da CI durante o exercício progressivo, e não apenas em medidas pré e pós-teste¹⁰. As medidas seriadas da CI refletem com exatidão mudanças no volume pulmonar expiratório final; assume-se que, desde que a capacidade pulmonar total não varie apreciavelmente, a CI e o volume pulmonar expiratório final apresentariam uma relação inversa, resultando em aprisionamento aéreo^{8,9}. A HD pode ser avaliada ao final do teste de caminhada de seis minutos (TC6min) em pacientes com DPOC, sendo esse um teste simples de baixo custo e de fácil aplicabilidade que avalia a capacidade funcional de

exercício¹¹⁻¹⁷. Apesar da aplicabilidade dessa forma de avaliação, é importante ressaltar que a literatura científica ainda não apresenta estudos que tenham avaliado a CI durante o TC6min, apenas medidas antes e imediatamente após o fim do teste¹²⁻¹⁷.

A capacidade vital (CV), mensurada por um espirômetro simples, é uma soma de volumes pulmonares que pode ser avaliada por meio das manobras de capacidade vital lenta (CVL) e forçada (CVF). Em indivíduos normais há uma pequena ou nenhuma diferença entre a CVL e CVF; no entanto alguns estudos mostraram que em pacientes com DPOC a CVF é menor do que CVL, sendo que a diferença entre essas duas variáveis está relacionada à limitação ao fluxo aéreo, e ao aprisionamento aéreo^{18,19,20}.

Sabe-se que a HD, avaliada pela redução da CI durante atividades que aumentam a demanda ventilatória em pacientes com DPOC, também está relacionada à redução do fluxo expiratório, levando esses pacientes a apresentarem maior aprisionamento aéreo²¹. No entanto, ainda não se sabe qual é a relação entre a diferença CVL-CVF avaliada por meio da espirometria simples e a HD avaliada durante o TC6min.

2. OBJETIVO

Investigar a correlação entre a diferença da CVL-CVF avaliada por meio da espirometria simples, com a HD mensurada por meio de medidas seriadas da CI durante o TC6min em indivíduos com DPOC.

3. REVISÃO DE LITERATURA – CONTEXTUALIZAÇÃO

3.1 DOENÇA PULMONAR OBSTRUTIVA CRÔNICA

Segundo a *Global Initiative for Chronic Obstructive Lung Disease* (GOLD), a DPOC é definida como “uma doença prevenível e tratável, caracterizada por obstrução ao fluxo aéreo persistente que é usualmente progressiva e associada a uma resposta inflamatória crônica anormal nas vias aéreas e nos pulmões a partículas nocivas ou gases”¹. Além do comprometimento essencialmente pulmonar, a DPOC apresenta manifestações extrapulmonares importantes como disfunção muscular, distúrbios nutricionais e inatividade física, que juntamente com a presença de exacerbações e comorbidades contribuem para a gravidade geral da DPOC¹.

A DPOC representa um importante desafio às políticas de saúde pública por ser apontada mundialmente como uma das principais causas de morbidade e mortalidade²². Atualmente a DPOC é considerada a quarta principal causa de morte no mundo, e projeções demonstram, que a doença ocupará a terceira posição até a próxima década²³. A doença ocorre tipicamente em indivíduos adultos com 40 anos ou mais, e há maior incidência em homens do que em mulheres²⁴. Infelizmente, estima-se que o número de indivíduos acometidos pela DPOC e das morbidades relacionadas à doença deverá aumentar nas próximas décadas, principalmente devido à contínua exposição aos fatores de risco e ao aumento da expectativa de vida mundial²³.

Dentre os fatores de risco relacionados ao desenvolvimento da DPOC, certamente destaca-se o tabagismo¹. No entanto, a predisposição ao desenvolvimento da doença também está relacionada à interação entre fatores genéticos e ambientais. Dessa forma, indivíduos não fumantes também podem ser acometidos pela DPOC por diferentes causas, tais como asma, exposição ocupacional a poluentes e/ou alérgenos, fumo passivo, infecções respiratórias na infância, ou fatores genéticos como a deficiência da enzima alfa1-antitripsina¹.

A definição da DPOC está também relacionada aos prejuízos respiratórios causados pela doença, e nesse sentido a doença apresenta manifestações locais e sistêmicas¹. Os sintomas respiratórios relatados pelos

pacientes portadores de DPOC são a tosse crônica, expectoração de muco e dispneia, sendo esse último o principal sintoma relacionado à doença^{25,26}. Entretanto, a inflamação e o estresse oxidativo causados pela DPOC não restringem-se apenas às vias aéreas, mas a inflamação sistêmica contribui para as manifestações extrapulmonares, como as anormalidades nutricionais²⁷, disfunção muscular periférica²⁸, e descondiçãoamento físico².

O diagnóstico clínico da DPOC pode ser considerado em pacientes que apresentam história clínica compatível e sintomas característicos. No entanto, além do exame clínico, a espirometria é necessária para confirmação do diagnóstico. Segundo diretrizes internacionais¹, valores ≤ 0.70 da relação entre o volume expiratório forçado no primeiro segundo e a capacidade vital forçada (VEF₁/CVF), após o uso de broncodilatador, confirmam o diagnóstico de DPOC.

A limitação crônica ao fluxo aéreo quantificada pela espirometria é causada pela combinação de obstrução das vias aéreas de pequeno calibre e alterações do parênquima pulmonar¹. A limitação ao fluxo expiratório associada à redução do recolhimento elástico pulmonar diminuem a capacidade das vias aéreas de se manterem abertas durante a expiração, levando ao aprisionamento aéreo e hiperinsuflação pulmonar⁵. A hiperinsuflação é clinicamente relevante para pacientes com DPOC, principalmente por contribuir com a dispneia²⁹ e por ser um preditor de mortalidade^{6,30} e exacerbação da doença³¹.

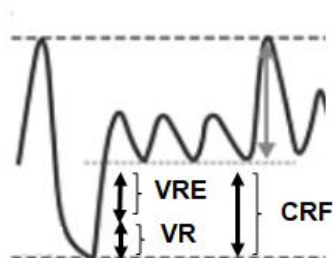
3.2 DPOC E HIPERINSUFLAÇÃO PULMONAR

O principal marcador fisiológico da DPOC é a limitação crônica ao fluxo aéreo causada pela combinação da obstrução das vias aéreas (bronquite crônica) e destruição irreversível do parênquima pulmonar (enfisema)¹. O processo inflamatório crônico presente na DPOC provoca alterações estruturais que culminam em diminuição do diâmetro das vias aéreas³². Já a destruição do parênquima pulmonar leva à diminuição da elasticidade e a danos nas estruturas vasculares adjacentes³³. O desequilíbrio entre as forças de recolhimento e expansão pulmonar diminui a capacidade das vias aéreas de se

manterem abertas, de maneira que o volume ao final de uma expiração torna-se maior, ocasionando aprisionamento aéreo, e conseqüentemente a hiperinsuflação pulmonar²¹.

O aprisionamento de ar nos pulmões em repouso é denominado hiperinsuflação pulmonar estática (HPE)³⁴. A HPE é caracterizada pelo aumento da capacidade residual funcional (CRF) – resultante da soma do volume de reserva expiratório (VRE) e do volume residual (VR)(figura 1). Dessa forma, as medidas da CRF e do VR são consideradas relevantes na avaliação da HPE, uma vez que ambos refletem o volume de ar remanescente nos pulmões, e conseqüentemente o aprisionamento aéreo. Os métodos utilizados para avaliação desses parâmetros são a pletismografia corporal, ou as análises de difusão de gases (lavagem de nitrogênio e diluição de gás hélio), sendo a pletismografia considerada o método padrão ouro⁷. Assim sendo, a avaliação da CRF e do VR requer equipamentos de alto custo e complexo manuseio, dificultando a avaliação da HPE na prática clínica e até mesmo no ambiente científico.

Figura 1 – Curva gráfica dos volumes e capacidades pulmonares que caracterizam a HPE.

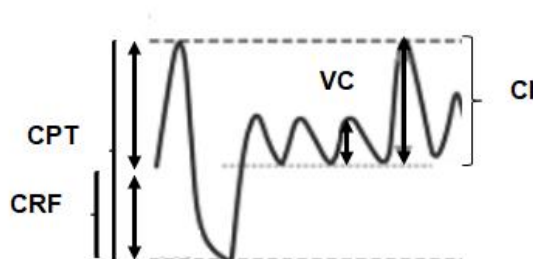


Adaptado de: Thomas M, Decramer M, O'Donnell DE. *Prim Care Respir J* 2013, 22(1):101-111²¹.

Diferentemente, a capacidade inspiratória (CI) pode ser facilmente medida de forma não invasiva por meio da espirometria simples³⁵. A CI é o volume máximo de ar inspirado a partir do nível do volume corrente (VC), equivalente à diferença entre a capacidade pulmonar total (CPT) e o volume expiratório final (*i.e* CRF) (figura 2). A CI é usada frequentemente como uma medida substitutiva na avaliação da hiperinsuflação pulmonar^{7,8}. A HPE, por

meio da espirometria, é observada quando há redução da CI em repouso devido ao aprisionamento aéreo³⁵. Além disso, índices como a relação CI/CPT tem sido identificados como extremamente úteis para a avaliação da HPE⁶.

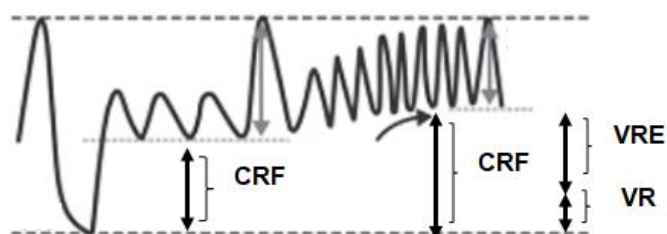
Figura 2 – Curva gráfica dos volumes e capacidades pulmonares que equivalem à CI.



Adaptado de: Thomas M, Decramer M, O'Donnell DE. *Prim Care Respir J* 2013, 22(1):101-111²¹.

A hiperinsuflação pulmonar pode aumentar de forma aguda em situações de estresse do sistema respiratório como em períodos de exacerbação da doença ou na realização de atividades físicas⁵. Por ocorrer aumento da demanda ventilatória durante o esforço físico, a limitação ao fluxo expiratório presente em indivíduos com DPOC em associação à diminuição das propriedades de recolhimento elástico pulmonar culminam em redução do tempo expiratório, que por sua vez aumenta temporariamente o volume expiratório final, caracterizando a hiperinsuflação dinâmica (HD) (Figura 3)³⁶.

Figura 3 – Comportamento da CRF na presença de HD.



Adaptado de: Thomas M, Decramer M, O'Donnell DE. *Prim Care Respir J* 2013, 22(1):101-111²¹.

Dentro de uma perspectiva clínica, a estratégia mais simples, prática e efetiva para avaliação da HD durante o exercício progressivo é por meio de medidas seriadas da CI¹⁰. Assumindo que a CPT mantém-se constante durante o exercício, a redução da CI é capaz de refletir com precisão as mudanças no volume pulmonar expiratório final^{10;37}. A literatura disponível mostra que essa medida é confiável e responsiva ao tratamento em pacientes com DPOC^{38,39}. Ademais, exames funcionais em repouso para avaliação da hiperinsuflação por meio da CI são limitados em justificar as queixas apresentadas pelos pacientes, e nem sempre refletem os mecanismos fisiopatológicos identificados no esforço⁴⁰.

A HPE pode limitar a capacidade de aumentar a ventilação em resposta às crescentes exigências metabólicas durante o exercício⁸. Além dos prejuízos causados pela HPE, a HD durante o exercício está associada à fraqueza muscular respiratória, aumento do trabalho respiratório e pior função cardíaca, o que também pode prejudicar a performance de pacientes com DPOC durante atividades físicas⁴¹⁻⁴³. Além disso, o aumento no volume expiratório final durante o exercício está associado à pior sensação de dispneia, reduzindo o nível de atividade física na vida diária desses pacientes, gerando assim um ciclo vicioso⁴⁴. Também já foi demonstrado que hiperinsuflação pulmonar apresenta relação com a força muscular periférica nessa população⁴⁵. Além disso, a hiperinsuflação pulmonar está associada aos sintomas²⁹ e ao prognóstico da DPOC, sendo considerada um importante preditor de mortalidade^{6,30} e exacerbação da doença³¹. Portanto, a avaliação de índices que refletem o aprisionamento aéreo torna-se indispensável em pacientes com DPOC, aumentando o interesse em estudar os volumes e capacidades pulmonares.

3.3 DPOC E CAPACIDADES VITAIS PULMONARES

Segundo a *American Thoracic Society/European Respiratory Society* (ATS/ERS), a capacidade vital (CV) pode ser definida como a mudança no volume de ar mobilizado entre as posições de inspiração e expiração

completas. A CV, avaliada por um espirômetro simples, pode ser mensurada por duas manobras distintas: a capacidade vital lenta (CVL) e forçada (CVF)³⁵.

Durante a manobra de CVL, a mudança no volume de ar é mensurada sem esforço máximo, podendo ser realizada de duas formas: 1) Capacidade vital inspiratória (CVIL) - partindo da posição de plena expiração até a inspiração máxima; 2) Capacidade vital expiratória (CVEL) - a partir da posição de plena inspiração até a expiração máxima. Já a CVF é medida solicitando-se ao indivíduo que depois de inspirar até a CPT expire tão rápida e intensamente quanto possível⁴⁶.

Portanto, a CV pode ser influenciada pelos fatores determinantes da CPT, e também do VR, já que a CV equivale à diferença entre essas duas variáveis¹⁹. Em pacientes com DPOC, a limitação ao fluxo aéreo, associada à redução do recolhimento elástico, são determinantes do VR, podendo-se inferir por conseguinte que essas mesmas condições influenciam na CV, principalmente na presença de hiperinsuflação pulmonar²⁰.

Durante a realização da manobra forçada para a avaliação da CV pode ocorrer uma maior compressão dinâmica da caixa torácica, resultando no colapso das vias aéreas de pequeno calibre. Isso reduz a capacidade de exalar o ar para fora dos pulmões, levando ao aprisionamento aéreo. Por esse motivo a mudança no volume de ar avaliada por meio da manobra de CVF pode ser inferior à da CVL, já que a manobra realizada de maneira lenta cursa com menor compressão torácica, permitindo com que as vias aéreas permaneçam abertas e mobilizem um maior volume de ar durante a expiração.

Em indivíduos saudáveis há uma pequena ou nenhuma diferença entre a CVL e CVF; no entanto na presença da obstrução de vias aéreas, essa diferença pode acentuar-se. Chhabra e colaboradores¹⁸ verificaram a diferença entre as manobras de CVIL, CVEL, e CVF em pacientes asmáticos, e os resultados mostraram que a medida da CVIL é significativamente maior do que a CVF em indivíduos com asma quando esses foram comparados a indivíduos saudáveis. Além disso, a diferença entre CVIL e CVF mostrou-se maior à medida que a obstrução ao fluxo aéreo aumentou quando os indivíduos foram estratificados em grupos com diferentes graus de gravidade da doença na mesma amostra. A diferença entre a CVL e a CVF também foi estudada em pacientes com DPOC por Yuan e colaboradores⁴⁷, e os autores observaram

que indivíduos com a $CVL > CVF$ apresentam menor VEF_1 do que aqueles com a $CVL \leq CVF$. Adicionalmente, outro estudo mostrou que a diferença entre a CVL e a CVF juntamente com VEF_1 estão associados com hiperinsuflação pulmonar avaliada pela relação VR/CPT ($r^2=0,52$) em indivíduos com DPOC²⁰.

Embora diretrizes nacionais e internacionais recomendem a medida da razão entre VEF_1 e CVF para a confirmação do diagnóstico de DPOC^{35,46}, um estudo prévio mostrou ser relevante a avaliação da relação CVL/VEF_1 na confirmação da presença de obstrução das vias aéreas⁴⁸. Além disso, já foi mostrado por Yuan et al⁴⁷, que a diferença entre a CVL e a CVF está associada ao pior desempenho durante o exercício, sendo que os autores atribuem tal resultado à possível presença de hiperinsuflação pulmonar. Com base nessas informações, poderia ser hipotetizado que a magnitude da diferença entre CVL e CVF está relacionada à magnitude da HD desenvolvida durante o exercício físico em pacientes com DPOC.

3.4 USO DO TC6MIN PARA QUANTIFICAÇÃO DA HIPERINSUFLAÇÃO PULMONAR

Em indivíduos com DPOC, a dispneia que caracteriza a doença ocorre principalmente durante a realização de atividades físicas, tornando esses pacientes menos tolerantes aos esforços¹. Diferentes mecanismos como a fraqueza muscular periférica e a disfunção cardiovascular levam ao conceito de que a redução da capacidade de exercício na DPOC deve ser considerada multifatorial. Dentre as principais causas de intolerância ao exercício, a limitação ventilatória que leva à HD é considerada uma das principais, uma vez que o aprisionamento aéreo dinâmico apresenta relação com o aumento acentuado da dispneia, levando esses pacientes a interromper o esforço^{3,10}.

Na literatura atual, a maioria dos trabalhos que avaliaram a ocorrência de HD e suas repercussões durante o exercício foram realizados em cicloergômetro^{36,49}. A avaliação funcional nessa modalidade apresenta algumas vantagens em comparação ao uso da esteira, como por exemplo a determinação direta da carga de trabalho imposta e menor variabilidade locomotora⁵⁰. Entretanto, um estudo prévio avaliou a HD por meio de manobras seriadas da CI durante a caminhada em esteira em pacientes com DPOC,

modalidade que se aproxima mais das atividades diárias dos pacientes em relação ao cicloergômetro, e demonstrou alta prevalência (63%) de HD em pacientes com DPOC moderada a grave durante esta atividade³⁷. No entanto, esses métodos de avaliação da capacidade de exercício demandam equipamentos caros, e requerem treinamento especializado, o que dificulta a aplicação na prática clínica³⁷.

O teste de caminhada de seis minutos (TC6min) é usado para avaliar a resposta de um indivíduo ao exercício e propicia uma análise global dos sistemas respiratório, cardíaco e metabólico. Trata-se de um teste de baixo custo e de ampla aplicabilidade, já que caminhar é uma atividade de vida diária que quase todos os pacientes com DPOC são capazes de realizar¹¹, além de apresentar boa correlação com as atividades de vida diária (AVDs) e o nível de atividade física na vida diária de pacientes com DPOC².

Marin e colaboradores, avaliaram a HD desenvolvida durante o TC6min¹³. Os autores utilizaram medidas da CI avaliada antes e após o TC6min, e observaram uma redução significativa da CI ao final do teste. Nesse estudo, a variação da CI apresentou correlação com dispneia no repouso avaliada pela escala *Medical Research Council* (MRC) ($r=-0,56$), e com a sensação de dispneia ao esforço mensurada pela escala de Borg ($-0,49$). Além disso, a CI mensurada ao final do TC6min apresentou relação com a capacidade de exercício ($r=0,50$)¹³. Outros estudos também utilizaram o TC6min para avaliar a HD desenvolvida durante o teste^{12,14-17}. Entretanto, é importante ressaltar que nestes estudos não foram realizadas medidas seriadas da CI durante o TC6min, apenas medidas antes e imediatamente ao seu término, que mostraram uma diminuição da CI após o fim do teste. Esses achados prévios sugerem que o TC6min é um teste simples e seguro para detectar a HD em pacientes com DPOC. No entanto, ainda há uma escassez de estudos que avaliem o comportamento da HD durante testes de campo, e quais variáveis ventilatórias podem estar relacionadas com o aprisionamento aéreo durante o exercício. Além disso, a avaliação seriada durante o decorrer do teste permite obter informações mais detalhadas sobre as características e mecanismos envolvidos no desenvolvimento da HD.

Diante do exposto, justifica-se o interesse em estudar a relação entre a diferença CVL-CVF e a HD desenvolvida durante o exercício em pacientes com

DPOC, em especial durante o TC6min. Para isso foi realizado o estudo a seguir, o qual está descrito em forma de artigo científico (*Brief Report*) e formatado de acordo com as normas do periódico para o qual será submetido para publicação.

4. ARTIGO CIENTÍFICO

(Artigo formatado de acordo com as normas do periódico *Lung* no formato de *Brief Report* - Anexo A)

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Difference between slow and forced vital capacity and its relationship with dynamic hyperinflation in patients with chronic obstructive pulmonary disease.

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ABSTRACT

The aim of the study was to investigate the relationship between slow and forced vital capacity difference (SVC-FVC) with dynamic lung hyperinflation (DH) during the six-minute walking test (6MWT) in subjects with chronic obstructive pulmonary disease (COPD). Twenty-four subjects with COPD (12 male; 67 ± 6 years; forced expiratory volume in first second [FEV₁] $56\pm 18\%$ predicted) performed lung function tests by spirometry and plethysmography. DH was assessed by serial measurements of inspiratory capacity (IC) performed during the 6MWT and defined as $\Delta IC \geq 150\text{ml}$ or 10%. IC decrease significantly during the 6MWT ($\Delta IC: -0,48\pm -0,40\text{L}$; $P < 0.0001$), and eighteen individuals (75%) presented DH. There was significant difference when comparing IC measured at rest with the other serial IC measurements ($P < 0.0001$). Correlation between the difference SVC-FVC and DH during the 6MWT was $r = -0.38$; $P = 0.06$. The difference SVC-FVC presented only weak correlation with the development of DH during the 6MWT in patients with COPD.

Keywords: Pulmonary Disease, Chronic Obstructive; Respiratory Function Tests; Vital Capacity; Inspiratory Capacity; Total Lung Capacity; Exercise.

Introduction

Vital capacity (VC) is an important outcome derived from lung function assessment which can be evaluated through slow (SVC) or forced (FVC) maneuvers¹. A few studies described that SVC values are higher than FVC, and the difference between these two variables (SVC-FVC) is related to airflow limitation and air trapping in patients with chronic obstructive pulmonary disease (COPD)^{2,3}.

A considerable proportion of individuals with COPD presents an increase of end-expiratory lung volume (EELV) as a consequence also of airflow limitation combined with reduction in elastic recoil, and this combination may lead to lung hyperinflation⁴. Lung hyperinflation may be increased when the respiratory system is stressed, for example during activities in which there is increase in ventilatory demand coupled with reduction in expiratory time. This phenomenon is called dynamic hyperinflation (DH)⁴.

From a clinical perspective, it is possible to evaluate DH during progressive exercise by performing serial measurements of inspiratory capacity (IC), an accurate measure which reflects changes in EELV⁵. Also from a clinical perspective, an exercise test that can be used to detect DH is the six-minute walk test (6MWT)⁶, a relatively simple test widely used to assess exercise (in)tolerance in COPD⁷.

Both the SVC-FVC and DH evaluated by the reduction of IC during physical exertion in patients with COPD is related to reduction of the expiratory flow and air trapping; however, the relationship between the difference SVC-FVC assessed by simple spirometry and DH assessed during the 6MWT is unknown. Thus, the objective of the present study was to investigate the relationship between the difference SVC-FVC and DH assessed during the 6MWT in subjects with COPD.

Methods

This cross-sectional and quantitative study recruited subjects from the registers of the Laboratory of Respiratory Physiotherapy Research (LFIP), State University of Londrina (UEL), Brazil, as patients previously involved or interested in being involved in a pulmonary rehabilitation program. As inclusion criteria they presented diagnosis of COPD according to international guidelines⁸; clinical stability (at least three months without exacerbation); no indication for long-term oxygen therapy (LTOT); and absence of neuromuscular or skeletal disorders that could impair the performance of the tests.

Subjects were excluded if they were required oxygen supplementation during the tests. The study was approved by the Ethics and Research Committee of the institution (151/2013) (Attachment B), and all patients provided informed consent (Appendix A). Assessments were done in two moments: at the first visit, patients had their anthropometric data collected and underwent pulmonary function evaluation. At the second visit patients performed the 6MWT with concomitant assessment of DH.

Pulmonary Function

The assessment of lung function was performed by spirometry and plethysmography (Vmax, Carefusion, USA), according to the guidelines of the American Thoracic Society and the European Respiratory Society (ATS/ERS)^{1,9}, and post-bronchodilator difference SVC-FVC was calculated in liters. Reference values were those proposed for the Brazilian population by Pereira et al¹⁰ and Neder et al¹¹.

Dynamic Hyperinflation (DH) during the 6MWT

The 6MWT was performed according to the ATS/ERS guidelines⁷, and reference values were those by Britto et al¹². The largest distance of two tests was used for analysis. DH was evaluated with serial IC measurements by the SVC maneuver following international protocols¹ after the use of a short-acting bronchodilator, since this allowed similar conditions for all patients during the test. At rest, reproducibility was defined as a difference of less than 5% between two maneuvers^{1,5}, and the highest reproducible value was considered for analysis. The maneuvers were performed at rest, at the second (2') and fourth (4') minutes, fifteen seconds before the end of the test (5'45''), and immediately at the end of the 6MWT. DH was defined as a decrease in IC at least 150ml or 10% compared to rest^{5,13}. Assessments were done using the Spiropalm portable spirometer (Cosmed, Italy), with a fascial mask coupled to the patient.

Statistical Analysis

Data distribution was analyzed by the Shapiro-Wilk test. According to normality in data distribution, data were described as mean and standard deviation or median and interquartile range. Correlation between difference SVC-FVC and DH was verified

using the Spearman correlation coefficient. For the comparison of resting IC and lowest IC, the paired Student t-test was used. One-way ANOVA with Tukey's post hoc was used to compare serial IC measurements during the 6MWT. Statistical significance was set at $P < 0.05$. The statistical analysis was performed using GraphPad Prism 6.0 (GraphPad Software Inc., La Jolla, California, USA) and Statistical Package for the Social Sciences 22.0 (SPSS Inc., Chicago, USA).

In order to find correlations of at least 0.60 between the difference SVC-FVC and DH, 20 subjects would be necessary to compose the study sample. This calculation was performed by the BioStat 3.0 software considering an $\alpha = 0.05$, $\beta = 0.80$, and 10% dropout rate.

Results

Out of 28 included patients, four did not conclude the assessments due to desaturation during 6MWT⁷ and were therefore excluded. In total, 24 patients were analyzed, and characteristics of the sample are described in table 1. The sample was composed of elderly subjects of both genders, with a BMI characterized as normal to overweight, with the majority of individuals presenting moderate to severe airflow limitation and preserved exercise capacity.

No subject had severe pulmonary hyperinflation verified by the IC/TLC ratio, whereas 9 subjects presented static pulmonary hyperinflation according to TCL values, and 13 subjects presented difference SVC-FVC above 0.20L, likely indicating the presence of air trapping (table 1)¹⁴.

IC decreased significantly during the 6MWT (resting IC: 2.22 ± 0.54 L; lowest IC during the test: 1.74 ± 0.48 L; $P < 0.0001$; Δ CI: -0.48 ± 0.40 L), and 18 subjects (75%) presented DH according to the proposed criteria. There were significant differences between resting IC and measurements at 2' (1.93 ± 0.51 L), 4' (1.90 ± 0.48 L), 5'45'' (1.88 ± 0.51 L), and immediately at the end of the test (1.92 ± 0.53 L) (Figure 1). Six patients had the lowest IC measurement at 2', eight at 4', six at 5'45'' and four immediately at the end of the 6MWT. A weak positive correlation was observed between the difference SVC-FVC and DH measured during the 6MWT ($r = 0.38$; $P = 0.06$) (Figure 2).

Discussion

The main finding of this study is that, in subjects with COPD, difference SVC-FVC (evaluated by simple spirometry) and DH (assessed by serial IC measurements during the 6MWT) are weakly related. A study by Wibmer et al¹⁵ aimed to compare the correlation between 6MWT and lung volumes before and after the 6MWT in patients with COPD. Lung volumes measured immediately after test were more closely related to walking distance than baseline lung volumes in this population. Similarly, only moderate correlation between difference SVC-FVC and maximal oxygen uptake during a cycle-ergometry test ($r=-0.40$) was described in patients with COPD¹⁶. These findings suggest that lung volumes assessed by baseline pulmonary function testing at rest provide insufficient information about the ventilatory constraints during exertion. This can be a possible explanation for the weak correlation between difference SVC-FVC and DH during 6MWT.

The fact that 75% of the individuals developed DH during the 6MWT corroborated with previous findings in the literature^{6,15}. There was no difference between the magnitude of the DH assessed by the measurement of serial IC or at the end of the test. During cycle exercise, IC decreases rapidly in the first 2 minutes, and continues to decrease although less abruptly until symptom limitation¹⁷. The same behavior was observed in IC change during the 6MWT in the present study, and maybe this can be explained by the physiological responses to the 6MWT, in which an increase in cardiac, ventilatory and metabolic variables is observed until the third minute of the test followed by a plateau¹⁸. However, these results are not sufficient to support the premise that serial IC assessment during 6MWT is not necessary. It has already been described by O'Donnell et al¹⁹ that the Δ CI isotime during constant-load symptom-limited cycle exercise correlated better with dyspnea than any other resting or exercise parameter. Thus, future studies that investigate the relationship between DH during the 6MWT with the physiological responses to this test should be encouraged.

Although SVC and FVC are routinely measured in lung function assessment, the difference SVC-FVC has been given little consideration in clinical practice. To our knowledge, there have been no previous studies describing the relationship between SVC-FVC and DH during exercise in patients with COPD. Also, no similar studies involving any other population were found in the literature. Therefore, the present study is the first to investigate this relationship. If these variables were well correlated (which

was not the case), we could assume that patients with increased difference SVC-FVC, would also be those who present DH and possibly more symptoms during exercise.

Limitations of this study include the fact that few individuals in GOLD stages I and IV were included. However, patients with mild airway obstruction are still unusually referred for pulmonary rehabilitation, which was the target population of this study. Furthermore, patients with very severe disease likely present desaturation during exercise tests²⁰. Serial IC measurements during the 6MWT were evaluated with a facial mask, which hindered oxygen supplementation and therefore the inclusion of very severe patients. Perhaps a more heterogeneous sample regarding the degree of disease severity would yield a stronger correlation, since individuals with COPD who have $SVC > FVC$ have worse airflow obstruction than those with $SVC \leq FVC$ ¹⁶. Finally, unfortunately no measure of ventilatory variables was available for use, which could be helpful in explaining and discussing the findings. Future studies with a large number and a wider spectrum of patients are welcome (*i.e.*, including patients with mild and very severe disease).

In conclusion, despite the previously described relationship with airflow limitation and air trapping, the difference SVC-FVC measured by a simple spirometry at rest presented only weak correlation with DH during 6MWT in patients with COPD.

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Table 1. General characteristics of the sample.

Variables	(n=24)
Age, yrs	67±6
Gender (M/F)	12/12
BMI (Kg/m ²)	29±5
FEV ₁ (% predicted)	56±18
FVC (L)	2,8±0,5
FVC (% predicted)	84±17
SVC (L)	3,2±0,6
SVC (% predicted)	92±22
FEV ₁ /FVC (%)	52±10
SVC-FVC (L)	0,21 [0,08-0,40]
TLC (L)	6,3±1,4
TLC (% predicted)	113±16
IC/TLC (%)	43±9
RV (L)	2,7 [2,4-3,8]
RV (%)	135 [116-165]
6MWT (m)	459±46
6MWT (% predicted)	88±11
GOLD (I/II/III/IV)	1/12/10/1

Data presented in absolute frequency, mean ± standard deviation or median [interquartile range]. M: male; F: female; BMI: Body Mass Index; FEV₁: Forced Expiratory Volume in the first second; FVC: Forced Vital Capacity; SVC: Slow Vital Capacity; TLC: Total Lung Capacity; CI: Inspiratory Capacity; RV: Residual Volume; 6MWT: 6 Minute Walk Test; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

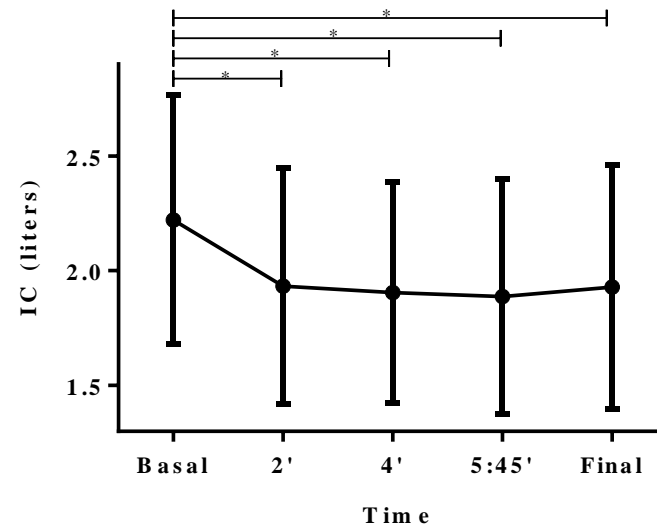


Fig. 1. Comparison between serial IC measurements during 6MWT.
IC = inspiratory capacity; * $P < 0.0001$.

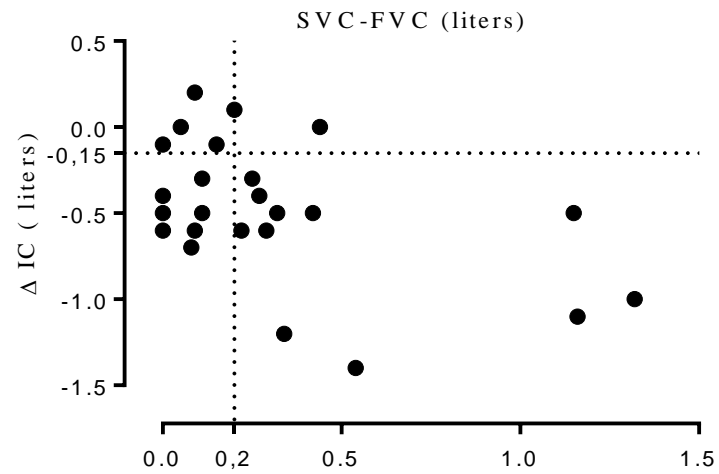


Fig. 2. Correlation between difference SVC-FVC and change in IC during the 6-minute walk test. SVC-FVC = difference between slow and forced vital capacity; IC = inspiratory capacity; Δ IC = difference between resting IC and the lowest IC value during the 6-minute walk test ($r=-0.38$; $P=0.06$). Correlation analyzed by the Spearman Coefficient. Dotted lines indicate cut-off values for DH (Δ IC>150ml) and air trapping (SVC-FVC>0,2L).

5. CONSIDERAÇÕES FINAIS

De acordo com a literatura vigente, não foram encontrados estudos prévios que investigaram a HD avaliada por meio de medidas seriadas da capacidade inspiratória durante o TC6min, tornando este estudo o primeiro. Os resultados encontrados sugeriram não haver diferença entre as medidas seriadas ou imediatamente ao final do teste para identificar a presença de hiperinsuflação dinâmica. No entanto, esses resultados não permitem concluir que avaliação da capacidade inspiratória seriada durante o TC6min não se faça necessária, uma vez que a hiperinsuflação dinâmica durante o exercício é um determinante de desfechos clínicos importantes em pacientes com DPOC.

Ainda de acordo com resultados do estudo que compõe a presente dissertação, pode-se concluir que apesar de sua relação com o aprisionamento aéreo previamente descrita na literatura, a diferença entre as capacidades vitais medidas de maneira lenta ou forçada apresenta correlação apenas fraca com a hiperinsuflação dinâmica desenvolvida durante o TC6min em pacientes com DPOC. Como já demonstrado, a avaliação de volumes e capacidades pulmonares mensuradas no repouso talvez não ofereça informações suficientes sobre os mecanismos ventilatórios que ocorrem durante o exercício.

Pesquisas futuras nessa área são bem vindas, visto que a avaliação do comportamento da hiperinsuflação pulmonar e sua repercussão durante atividades que aumentam a demanda ventilatória em indivíduos com DPOC é um alvo almejado no tratamento medicamentoso e não medicamentoso (*i.e* reabilitação pulmonar) desses pacientes.

6. REFERÊNCIAS

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APÊNDICES

APÊNDICE A

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Prezado(a) Senhor(a):

Gostaríamos de convidá-lo (a) a participar da pesquisa “Estudo cruzado para avaliar a relação entre a magnitude da hiperinsuflação dinâmica desenvolvida durante atividades de vida diária e o teste da caminhada de 6 minutos”, realizada no Laboratório de Pesquisa em Fisioterapia Pulmonar da Universidade Estadual de Londrina (Londrina, Brasil). O objetivo da pesquisa é avaliar e quantificar o aprisionamento de ar que ocorre durante as atividades simples de vida diária e também durante o teste de caminhada de seis minutos de pacientes com doença pulmonar obstrutiva crônica (DPOC). Além disso, objetiva-se estudar os possíveis fatores que possam influenciar no aprisionamento de ar durante atividades de vida diária (hiperinsuflação dinâmica) e determinar quais das atividades cotidianas (como por exemplo: caminhar livremente, caminhar segurando sacolas e organizar prateleiras) resultam em maior hiperinsuflação dinâmica e conseqüentemente sensação de falta de ar em pacientes com DPOC. As avaliações serão realizadas no Laboratório de Pesquisa em Fisioterapia Pulmonar da Universidade Estadual de Londrina (Londrina, Brasil). Gostaríamos de esclarecer que sua participação é totalmente voluntária, podendo você: recusar-se a participar, ou mesmo desistir a qualquer momento, sem que isto acarrete qualquer custo ou prejuízo à sua pessoa. Informamos ainda que o presente estudo não acarreta qualquer risco para a integridade física ou moral dos indivíduos envolvidos, e que mesmo assim, se durante o estudo o(a) senhor(a) se sentir mal, poderemos encaminhar para atendimento no Hospital Universitário de Londrina. As informações serão utilizadas somente para os fins desta pesquisa e serão tratadas com o mais absoluto sigilo e confidencialidade, de modo a preservar a sua identidade.

Os benefícios esperados são principalmente para a prática clínica da Fisioterapia Respiratória, pois ao detectar em qual atividade do cotidiano existe maior aprisionamento de ar e também ao verificar se há relação entre a hiperinsuflação dinâmica durante um protocolo de atividades de vida diária e

durante um simples teste de caminhada de seis minutos, a prescrição de atividade física terapêutica para o tratamento futuro dos pacientes com DPOC será diretamente influenciada, pois será possível mostrar quais atividades devem ser foco de adaptações, para que os indivíduos as realizem de forma mais eficiente do ponto de vista ventilatório. Com isso, também será possível traçar estratégias de tratamento específicas e eficazes baseadas nas atividades que causam menor sensação de falta de ar, já que a hiperinsuflação dinâmica é uma das principais causas deste desconforto.

Informamos que o(a) senhor(a) não pagará por sua participação neste estudo. Garantimos, no entanto, que todas as despesas decorrentes da pesquisa serão ressarcidas quando devidas e decorrentes especificamente de sua participação na pesquisa, como qualquer gasto com alimentação e transporte nos dias de avaliação.

Caso você tenha dúvidas ou necessite de maiores esclarecimentos pode nos contatar nos telefones (43) 3371 2477 ou 3371 2252 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 – fabiopitta@uol.com.br ou no telefone (43) 91144621 (falar com Karina C. Furlanetto), ou ainda, procurar o Comitê de Ética em Pesquisa Envolvendo Seres Humanos da Universidade Estadual de Londrina, na Avenida Robert Kock, nº 60, ou no telefone 33712490. Este termo deverá ser preenchido em duas vias de igual teor, sendo uma delas, devidamente preenchida e assinada entregue a você.

Londrina, ____ de _____ de 2014.

Prof. Fábio de Oliveira Pitta
RG: 3626743-7

Pesquisador Responsável e Coordenador do Projeto

_____ (nome por extenso do sujeito de pesquisa), tendo sido devidamente esclarecido sobre os procedimentos da pesquisa, concordo em participar **voluntariamente** da pesquisa descrita acima.

Assinatura (ou impressão dactiloscópica): _____

Data: _____

Obs: Caso o participante da pesquisa seja menor de idade, deve ser incluído o campo para assinatura do menor e do responsável.

ANEXOS

ANEXO A

Normas de formatação do periódico *Lung*

Word and Figure Counts

Please note that the title page of manuscripts should include:

- Word count for the abstract (should be 250 or less)
- Word count for the body of the manuscript (should be 2600 or less)
- Number of tables and figures
- The limit for the number of figures is 5 or less

Types of papers

The journal accepts the following types of papers: original research, letter to the editor, state of the art reviews, brief report, editorial, and lung images.

Original Research

Original research should not exceed 2600 words. This does not include abstract, tables and figures or references. Please include sub-headings: introduction, methods, results and conclusion in the abstract.

Brief Report

A Brief Report is limited to 1600 words and 20 references. It should have Abstract, Introduction, Methods, Results and Discussion sections. The Abstract should be 150 words and does not need subheadings. There can be a combined total of up to 3 figures and tables (i.e. 2 figures and 1 table, 1 figure and 3 tables, 3 tables, or 3 figures).

Letter to the editor

Text is limited to 750 words, with no abstract. There may be 1 figure, up to 3 references, and no more than 3 authors, with author affiliations only including main institution, place name and (state plus) country (i.e. no departments, etc.).

State of the Art Review

An abstract of not more than 250 words is needed, but does not require sub-headings. There should be 3-6 figures or tables, no more than 80 references, and body text of no more than 3000 words.

Editorial procedure

Additional Info: It would be useful if the authors would submit the names, telephone and fax numbers, and addresses of three to five people who might review the manuscript.

Manuscript Submission

Submission of a manuscript implies: that the work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors, if any, as well as by the responsible authorities – tacitly or explicitly – at the institute where the work has been carried out. The publisher will not be held legally responsible should there be any claims for compensation.

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Please follow the hyperlink “Submit online” on the right and upload all of your manuscript files following the instructions given on the screen.

ORCID ID

This publication requires that the corresponding author provides his/her ORCID ID before proceeding with submission.

For more information about this journal’s ORCID policy, please visit the [ORCID FAQ](#).

Title Page

The title page should include:

- The name(s) of the author(s)
- A concise and informative title
- The affiliation(s) and address(es) of the author(s)
- The e-mail address, and telephone number(s) of the corresponding author
- If available, the 16-digit ORCID of the author(s)

Abstract

Please provide a structured abstract of 150 to 250 words which should be divided into the following sections:

- Purpose (stating the main purposes and research question)
- Methods
- Results

- Conclusions

Keywords

Please provide 4 to 6 keywords which can be used for indexing purposes.

Text

Text Formatting

Manuscripts should be submitted in Word.

- Use a normal, plain font (e.g., 10-point Times Roman) for text.
- Use italics for emphasis.
- Use the automatic page numbering function to number the pages.
- Do not use field functions.
- Use tab stops or other commands for indents, not the space bar.
- Use the table function, not spreadsheets, to make tables.
- Use the equation editor or MathType for equations.
- Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).
- Manuscripts with mathematical content can also be submitted in LaTeX.
- [LaTeX macro package \(zip, 182 kB\)](#)

Headings

Please use no more than three levels of displayed headings.

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Footnotes

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

Scientific style

- Please always use internationally accepted signs and symbols for units (SI units).
- Nomenclature: Insofar as possible, authors should use systematic names similar to those used by Chemical Abstract Service or IUPAC.
- Please use the standard mathematical notation for formulae, symbols etc.:
- Italic for single letters that denote mathematical constants, variables, and unknown quantities
- Roman/upright for numerals, operators, and punctuation, and commonly defined functions or abbreviations, e.g., cos, det, e or exp, lim, log, max, min, sin, tan, d (for derivative)
- Bold for vectors, tensors, and matrices.

Terminology

Generic names of drugs and pesticides are preferred; if trade names are used, the generic name should be given at first mention.

References

Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:

1. Negotiation research spans many disciplines [3].
2. This result was later contradicted by Becker and Seligman [5].
3. This effect has been widely studied [1-3, 7].

Reference list

The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text. Do not use footnotes or endnotes as a substitute for a reference list.

The entries in the list should be numbered consecutively.

- Journal article
- Gamelin FX, Baquet G, Berthoin S, Thevenet D, Nourry C, Nottin S, Bosquet L (2009) Effect of high intensity intermittent training on heart rate variability in prepubescent children. *Eur J Appl Physiol* 105:731-738. doi: 10.1007/s00421-008-0955-8
- Ideally, the names of all authors should be provided, but the usage of “et al” in long author lists will also be accepted:
- Smith J, Jones M Jr, Houghton L et al (1999) Future of health insurance. *N Engl J Med* 965:325–329
- Article by DOI
- Slifka MK, Whitton JL (2000) Clinical implications of dysregulated cytokine production. *J Mol Med*. doi:10.1007/s001090000086
- Book
- South J, Blass B (2001) *The future of modern genomics*. Blackwell, London
- Book chapter
- Brown B, Aaron M (2001) The politics of nature. In: Smith J (ed) *The rise of modern genomics*, 3rd edn. Wiley, New York, pp 230-257
- Online document
- Cartwright J (2007) Big stars have weather too. IOP Publishing PhysicsWeb. <http://physicsweb.org/articles/news/11/6/16/1>. Accessed 26 June 2007
- Dissertation
- Trent JW (1975) *Experimental acute renal failure*. Dissertation, University of California
- Always use the standard abbreviation of a journal’s name according to the ISSN List of Title Word Abbreviations, see
- [ISSN.org LTWA](http://www.issn.org/LTWA)
- If you are unsure, please use the full journal title.
- For authors using EndNote, Springer provides an output style that supports the formatting of in-text citations and reference list.
- [EndNote style \(zip, 2 kB\)](#)
- Authors preparing their manuscript in LaTeX can use the bibtex file `spbasic.bst` which is included in Springer’s LaTeX macro package.

Specific remark about the use of "et al."

In the case where there are more than three authors, please refer to them as ‘et al’.

Tables

- All tables are to be numbered using Arabic numerals.
- Tables should always be cited in text in consecutive numerical order.

- For each table, please supply a table caption (title) explaining the components of the table.
- Identify any previously published material by giving the original source in the form of a reference at the end of the table caption.
- Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

Artwork and Illustrations Guidelines

Electronic Figure Submission

- Supply all figures electronically.
- Indicate what graphics program was used to create the artwork.
- For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MSOffice files are also acceptable.
- Vector graphics containing fonts must have the fonts embedded in the files.
- Name your figure files with "Fig" and the figure number, e.g., Fig1.eps.

Line Art

- Definition: Black and white graphic with no shading.
- Do not use faint lines and/or lettering and check that all lines and lettering within the figures are legible at final size.
- All lines should be at least 0.1 mm (0.3 pt) wide.
- Scanned line drawings and line drawings in bitmap format should have a minimum resolution of 1200 dpi.
- Vector graphics containing fonts must have the fonts embedded in the files.

Halftone Art

- Definition: Photographs, drawings, or paintings with fine shading, etc.
- If any magnification is used in the photographs, indicate this by using scale bars within the figures themselves.
- Halftones should have a minimum resolution of 300 dpi.

Combination Art

- Definition: a combination of halftone and line art, e.g., halftones containing line drawing, extensive lettering, color diagrams, etc.
- Combination artwork should have a minimum resolution of 600 dpi.

Color Art

- Color art is free of charge for online publication.

- If black and white will be shown in the print version, make sure that the main information will still be visible. Many colors are not distinguishable from one another when converted to black and white. A simple way to check this is to make a xerographic copy to see if the necessary distinctions between the different colors are still apparent.
- If the figures will be printed in black and white, do not refer to color in the captions.
- Color illustrations should be submitted as RGB (8 bits per channel).

Figure Lettering

- To add lettering, it is best to use Helvetica or Arial (sans serif fonts).
- Keep lettering consistently sized throughout your final-sized artwork, usually about 2–3 mm (8–12 pt).
- Variance of type size within an illustration should be minimal, e.g., do not use 8-pt type on an axis and 20-pt type for the axis label.
- Avoid effects such as shading, outline letters, etc.
- Do not include titles or captions within your illustrations.

Figure Numbering

- All figures are to be numbered using Arabic numerals.
- Figures should always be cited in text in consecutive numerical order.
- Figure parts should be denoted by lowercase letters (a, b, c, etc.).
- If an appendix appears in your article and it contains one or more figures, continue the consecutive numbering of the main text. Do not number the appendix figures,
- "A1, A2, A3, etc." Figures in online appendices (Electronic Supplementary Material) should, however, be numbered separately.

Figure Captions

- Each figure should have a concise caption describing accurately what the figure depicts. Include the captions in the text file of the manuscript, not in the figure file.
- Figure captions begin with the term Fig. in bold type, followed by the figure number, also in bold type.
- No punctuation is to be included after the number, nor is any punctuation to be placed at the end of the caption.
- Identify all elements found in the figure in the figure caption; and use boxes, circles, etc., as coordinate points in graphs.
- Identify previously published material by giving the original source in the form of a reference citation at the end of the figure caption.

Figure Placement and Size

- Figures should be submitted separately from the text, if possible.
- When preparing your figures, size figures to fit in the column width.
- For most journals the figures should be 39 mm, 84 mm, 129 mm, or 174 mm wide and not higher than 234 mm.
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