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RAFAEL BARRETO DE MESQUITA

FORÇA MUSCULAR RESPIRATÓRIA EM PACIENTES COM DPOC DURANTE E APÓS HOSPITALIZAÇÃO POR EXACERBAÇÃO: ESTUDO PROSPECTIVO

Londrina
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Orientadora: Prof.ª Dr.ª Vanessa Suziane Probst

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Londrina, 07 de fevereiro de 2013.

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"Não considere nenhuma prática
como imutável.
Mude e esteja pronto a mudar novamente.
Não aceite verdade eterna.
Experimente."

Burrhus Frederic Skinner

MESQUITA, Rafael Barreto de. **Força muscular respiratória em pacientes com DPOC durante e após hospitalização por exacerbação: estudo prospectivo**. 2013. 68 fls. Trabalho de Conclusão de Curso do Programa de Pós-Graduação em Ciências da Reabilitação (Programa Associado entre Universidade Estadual de Londrina [UEL] e Universidade Norte do Paraná [UNOPAR]) – Universidade Norte do Paraná, Londrina, 2013.

RESUMO

Introdução: As exacerbações da Doença Pulmonar Obstrutiva Crônica (DPOC) já estão bem descritas na literatura como eventos nocivos, embora comuns, no curso natural da doença. Muitos desfechos já foram investigados durante a exacerbação da DPOC. Uma investigação detalhada a respeito da força dos músculos respiratórios durante esse evento, contudo, ainda não foi realizada. **Objetivo:** Investigar a força dos músculos respiratórios e fatores a ela relacionados em pacientes com DPOC durante e após uma hospitalização por exacerbação da doença. **Métodos:** Dezenove pacientes com DPOC (12 homens, idade média 67 [11] anos, mediana de volume expiratório forçado no primeiro segundo [VEF_1] 26 [19-32]% do previsto) hospitalizados por exacerbação da doença foram estudados. Função pulmonar, por meio de espirometria (Spirobank G, MIR, Itália); força muscular respiratória, por meio da medida das pressões inspiratória e expiratória máximas, PImax e PEmax, respectivamente (MVD 300, GlobalMed, Porto Alegre, Brasil) e; força de quadríceps, por meio de dinamometria (microFET2, HogganHelth, EUA) foram avaliadas na admissão, na alta hospitalar e um mês após a alta hospitalar. **Resultados:** Na admissão, 68% dos pacientes apresentaram disfunção muscular inspiratória (PImax < 70% previsto), enquanto que na alta e um mês após, a prevalência de indivíduos com essa condição foi menor (58% para ambos os dias). A força muscular inspiratória aumentou da admissão para um mês após a alta (56 [45-64] *vs* 65 [51-74] cmH_2O, respectivamente; $p<0,05$) e a força dos músculos expiratórios aumentou da admissão para a alta e para um mês depois da alta (99 [65-117] *vs* 109 [77-136] e 114 [90-139] cmH_2O, respectivamente; $p<0,05$). A capacidade inspiratória aumentou da alta para um mês depois da alta hospitalar (1,59 [0,44] *vs* 1,99 [0,54] litros, respectivamente; $p<0,05$). Nenhuma mudança significante foi observada nas demais variáveis de função pulmonar ou na força de quadriceps ($p>0,05$ para todas). Adicionalmente, a disfunção muscular inspiratória e a redução da capacidade inspiratória (< 80% previsto) se correlacionaram linearmente na admissão ($r\varphi=0,62$, $p=0,03$), enquanto que a força dos músculos expiratórios se correlacionou inversamente com o VEF_1 (rho de Spearman=-0,61, $p=0,005$) e com a capacidade inspiratória (rho de Spearman=-0,54, $p=0,02$), ambos em % do previsto. **Conclusão:** Houve uma alta prevalência de disfunção muscular inspiratória na hospitalização por exacerbação da DPOC. Contudo, tanto a força dos músculos inspiratórios quanto a dos músculos expiratórios melhoraram consideravelmente durante e após a hospitalização. A função pulmonar na admissão hospitalar esteve relacionada a essas variáveis.

Palavras-chave: Doença Pulmonar Obstrutiva Crônica. Exacerbação. Hospitalização. Força dos Músculos Respiratórios.

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ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) exacerbations are already well known in the literature as harmful, although commun, events in the natural course of the disease. Many outcomes have been investigated during COPD exacerbations. A more profound investigation of the respiratory muscle strength during this event, however, still needs to be done. **Objective:** To investigate the strength of the respiratory muscles and its related factors in COPD patients during and after a hospitalization for an exacerbation of the disease. **Methods:** Nineteen COPD patients (12 males, mean age 67 [11] years, median forced expiratory volume in the first second [FEV_1] 26 [19-32]% of predicted) hospitalized due to disease exacerbation were studied. Lung function, by spirometry (Spirobank G, MIR, Italy); respiratory muscle strength, by the measure of maximal inspiratory and expiratory pressures, MIP and MEP, respectively (MVD 300, GlobalMed, Porto Alegre, Brazil); and quadriceps muscle strength, by dynamometry (microFET2, HogganHelth, USA) were assessed on admission, at discharge and one month after discharge. **Results:** At admission, 68% of the patients presented inspiratory muscle dysfunction (MIP < 70% predicted), while at discharge and one month after, the prevalence of individuals presenting this condition was lower (58% for both days). The inspiratory muscle strength increased from admission to one month after discharge (56 [45-64] *vs* 65 [51-74] cmH_2O, respectively; $p<0.05$), as well as the expiratory muscle strength from admission to both discharge and one month after discharge (99 [65-117] *vs* 109 [77-136] and 114 [90-139] cmH_2O, respectively; $p<0.05$). The inspiratory capacity increased from discharge to one month after discharge (1.59 [0.44] *vs* 1.99 [0.54] liters, respectively; $p<0.05$). No significant change was observed in other lung function variables or in quadriceps muscle strength ($p>0.05$ for all). Moreover, at admission the inspiratory muscle dysfunction and the reduction in inspiratory capacity (< 80% predicted) correlated linearly ($r\varphi=0.62$, $p=0.03$), while the expiratory muscle strength correlated inversely to the FEV_1(Spearman's rho=-0.61, $p=0.005$) and the inspiratory capacity (Spearman's rho=-0.54, $p=0.02$), both in % predicted. **Conclusion:** There was a high prevalence of inspiratory muscle dysfunction during hospitalization due to COPD exacerbation. Inspiratory and expiratory muscle strength, however, increased markedly during and after hospitalization. Lung function at hospital admission was found to be related to both these variables.

Key words: Chronic Obstructive Pulmonary Disease. Exacerbation. Hospitalization. Respiratory Muscle Strength.

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LISTA DE ABREVIATURAS E SIGLAS

1mD	*One month after discharge*
ATS/ERS	*American Thoracic Society/European Respiratory Society*
BMI	*Body Mass Index*
CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
CNPq	Conselho Nacional de Desenvolvimento Científico e Tecnológico
COPD	*Chronic Obstructive Pulmonary Disease*
CPCS	Centro de Pesquisa em Ciências da Saúde
DPOC	Doença Pulmonar Obstrutiva Crônica
eDPOC	Exacerbação da Doença Pulmonar Obstrutiva Crônica
FEV_1	*Forced Expiratory Volume in the First Second*
FVC	*Forced Vital Capacity*
GOLD	*Global Initiative for Chronic Obstructive Lung Disease*
IC	*Inspiratory Capacity*
IMD	*Inspiratory Muscle Dysfunction*
LFIP	Laboratório de Pesquisa em Fisioterapia Pulmonar
MCAR	*Missing Completely at Random*
MEP	*Maximal Expiratory Pressure*
MIP	*Maximal Inspiratory Pressure*
MRC	*Medical Research Council*
OMS	Organização Mundial de Saúde
$PaCO_2$	*Arterial partial pressure of carbon dioxide*
PaO_2	*Arterial partial pressure of oxygen*
PROSUP	Programa de Suporte à Pós-graduação de Instituições de Ensino Particulares
QPT	*Quadriceps Peak Torque*
SPSS	*Statistical Package of Social Science*
UEL	Universidade Estadual de Londrina
UNOPAR	Universidade Norte do Paraná

SUMÁRIO

1 INTRODUÇÃO

Exacerbações da Doença Pulmonar Obstrutiva Crônica (DPOC) já estão bem descritas na literatura como eventos nocivos, embora comuns, no curso natural da doença. A Iniciativa Global para Doença Pulmonar Obstrutiva Crônica (do inglês, GOLD) define as exacerbações da DPOC como um evento agudo, caracterizado por piora dos sintomas respiratórios do paciente, que vai além das variações normais do dia a dia e que leva a mudanças no uso das suas medicações[1].

Dentre as principais consequências das exacerbações da DPOC, as seguintes merecem destaque devido ao impacto direto que têm na saúde dos pacientes com essa doença: aumento da mortalidade[2], piora da qualidade de vida relacionada à saúde[3], declínio mais acelerado da função pulmonar[4], redução importante dos níveis de atividade física na vida diária[5] e agravamento da fraqueza muscular periférica[6].

Poucos estudos, contudo, focaram-se em investigar os efeitos das exacerbações sobre os músculos respiratórios, apesar da importância central dessas estruturas para o manejo da DPOC. Dois estudos transversais recentes observaram que a disfunção dos músculos respiratórios está associada a um risco aumentado para hospitalização por exacerbação da DPOC[7;8]. Outros dois estudos com delineamento prospectivo identificaram a sobrecarga dos músculos inspiratórios como um fator de risco para a admissão hospitalar por DPOC exacerbada[9;10]. Surpreendentemente, a função dos músculos respiratórios durante e após uma exacerbação parece ter sido pouco investigada. Somente três estudos que avaliaram a função muscular respiratória durante e após uma exacerbação da DPOC foram identificados[5;11;12], e ainda sim alguns deles apresentam resultados inespecíficos e/ou até divergentes. De forma resumida, González et al.[11] e Martínez-Llorens et al.[12] verificaram um aumento na força dos músculos inspiratórios da admissão para a alta hospitalar após uma internação por exacerbação da DPOC, enquanto que Pitta et al.[5] afirmaram ter encontrado apenas uma tendência de aumento da alta para um mês depois. A força dos músculos expiratórios, por sua vez, diminuiu durante a hospitalização no estudo de Martínez-Llorens et al.[12], mas apresentou um padrão crescente da admissão para depois da alta no estudo de Pitta et al.[5], embora sem diferença estatística. Dessa forma, o comportamento da força

dos músculos respiratórios durante e/ou após uma exacerbação da DPOC necessita ser melhor investigado.

O presente estudo teve o objetivo de investigar em profundidade a força dos músculos respiratórios (inspiratórios e expiratórios), e fatores a ela relacionados, em pacientes com DPOC durante e após o curso de uma hospitalização por exacerbação da doença.

2 REVISÃO DE LITERATURA – CONTEXTUALIZAÇÃO

2.1 DOENÇA PULMONAR OBSTRUTIVA CRÔNICA (DPOC)

A definição de DPOC mais utilizada na literatura é a estabelecida pelo GOLD, que afirma que a DPOC é uma doença comum, que pode ser prevenida e tratada, caracterizada por persistente limitação ao fluxo aéreo, geralmente progressiva e associada a uma resposta inflamatória crônica aumentada das vias aéreas e pulmões a partículas e gases nocivos[1]. Anualmente o GOLD lança um documento com diretrizes para o manejo dos pacientes com DPOC, e na atualização de 2011 houve um acréscimo à definição informando que as exacerbações e as comorbidades contribuem para a gravidade geral da doença[1].

Dados da Organização Mundial de Saúde (OMS) apontam que, em 2002, a DPOC foi classificada como a quinta maior causa de morte no mundo, e estimativas apontam que se medidas urgentes não forem adotadas ela pode passar a ser a terceira maior causa em 2030[13]. No Brasil, dados recentes de um estudo de prevalência em indivíduos adultos (acima de 40 anos) de uma grande cidade do sudeste do país revelam que 4,2% dos indivíduos referem ter DPOC[14]. Não obstante, em outro estudo onde um método objetivo para o diagnóstico da doença (i.e., espirometria) foi utilizado, na mesma cidade e numa população com mesma faixa etária observou-se uma prevalência ainda maior, de quase 16%[15].

O surgimento da DPOC está associado à interação entre susceptibilidade genética e exposição a fatores de risco[16]. Dentre os fatores de risco, certamente o tabagismo representa o principal deles, porém outros fatores também estão descritos na literatura como a presença de asma na infância, a exposição a partículas e/ou gases nocivos, e a presença de tuberculose prévia[1;16].

São muitas as consequências da DPOC, indo desde alterações pulmonares como a obstrução ao fluxo aéreo, que é a principal característica da doença, até manifestações sistêmicas como anormalidades nutricionais e disfunção muscular esquelética respiratória e periférica[17]. A disfunção muscular na DPOC está associada à sarcopenia (i.e., perda de massa muscular) e à disfunção das células musculares restantes[18]. As causas dessas alterações são, principalmente, a inflamação sistêmica, a inatividade, a hipoxemia e carências nutricionais[1]. Os músculos respiratórios, além desses fatores, estão sujeito também à limitação

funcional causada pela hiperinsuflação pulmonar, verificada principalmente durante o esforço[19].

Para o tratamento da DPOC as principais estratégias adotadas focam-se na interrupção e/ou desaceleração da evolução da doença e na melhora e/ou resolução dos sintomas a ela associados. A cessação do tabagismo é um importante passo para evitar a evolução da doença, podendo reduzir a mortalidade em até 18%[20]. Em relação ao tratamento medicamentoso, os broncodilatadores são os medicamentos mais utilizados, enquanto que os corticosteroides são úteis em pacientes específicos, mas ambos têm como principal objetivo a melhora da obstrução ao fluxo aéreo[1]. Para o tratamento dos efeitos sistêmicos da doença, a reabilitação pulmonar provavelmente é o tratamento mais indicado. Tendo como base a utilização de medidas educativas e a prática de exercícios físicos, a reabilitação pulmonar visa principalmente a redução dos sintomas, a otimização do estado funcional e a redução dos gastos com saúde[21]. A fisioterapia respiratória, por meio de recursos e técnicas de higiene brônquica, também pode ser importante no tratamento de pacientes com DPOC, principalmente naqueles com produção de secreção pulmonar aumentada[22].

Conforme incluído na própria definição da DPOC, as exacerbações desempenham importante papel na gravidade geral da doença. Essa questão merece especial atenção, principalmente por ser um dos principais fatores de risco para mortalidade entre indivíduos com DPOC[23].

2.1.1 Exacerbação da DPOC

A exacerbação da DPOC (eDPOC) é definida pelo GOLD como um evento agudo, caracterizado por piora dos sintomas respiratórios do paciente, que vai além das variações normais do dia a dia e que leva a mudanças no uso das suas medicações[1]. Sabe-se que em metade dos pacientes com eDPOC os sintomas retornam aos valores estáveis dentro de aproximadamente 7 dias. Contudo, foi evidenciado que em cerca de 14% dos indivíduos esses sintomas ainda não haviam regredido totalmente após 35 dias do seu surgimento, e que numa minoria de pacientes eles nem regrediram completamente[24].

As exacerbações configuram como a principal causa de morbidade, mortalidade e piora do estado geral de saúde nos indivíduos com DPOC[25]. Estima-

se que nos pacientes hospitalizados que necessitaram de suporte ventilatório mecânico a mortalidade chegue a 40% em até 1 ano após a alta, aumentando para 49% após três anos se consideradas as mortes por qualquer causa[1]. Sabe-se atualmente que, dentre outros fatores, a frequência das eDPOC está assoaciada à gravidade da limitação ao fluxo aéreo. Um recente estudo de revisão de literatura evidenciou que em indivíduos com o grau leve da doença (GOLD I) a frequencia anual de eDPOC é de 0,82 exacerbações por ano, aumentando gradativamente com a gravidade da doença até 2,01 exacerbações por ano naqueles com grau muito grave (GOLD IV) da doença[26].

Para melhor entendimento, as principais causas da eDPOC podem ser divididas em três categorias, de acordo com o agente causador: causas infecciosas, comorbidades e fatores ambientais[16]. As causas infecciosas são as principais, sendo os vírus e as bactérias os principais agentes causadores. As infeções virais costumam ser desencadeadas por infecções do trato respiratório superior, enquanto as bacterianas são causadas por agentes já presentes no próprio trato respiratório dos pacientes durante o estado estável, mas que se proliferam por diferentes motivos durante a exacerbação[27]. Dentre as comorbidades que podem levar à eDPOC podem-se citar as disfunções cardíacas (direita e/ou esquerda), a embolia pulmonar, as infecções não pulmonares e até eventos funcionais/mecânicos como o pneumotórax[28]. Fatores ambientais como a redução da temperatura do ar, partículas poluentes, alérgenos e até a não aderência à terapia medicamentosa também podem contribuir para o surgimento da eDPOC[16].

A literatura tem indicado diversas terapias para o tratamento da eDPOC. De acordo com o GOLD[1], como terapia medicamentosa os broncodilatadores, corticosteroides e antibióticos são os principais utilizados. Muitos dos medicamentos utilizados durante a exacerbação são os mesmos utilizados durante a fase estável da doença, porém com doses ajustadas e em associação a outros medicamentos[1]. A maioria dos pacientes com eDPOC que necessitam de internação hospitalar também necessitam de oxigênioterapia, devido aos baixos níveis de oxigênio na corrente sanguínea, e alguns deles acabam necessitando também de suporte ventilatório, invasivo ou não, devido à presença de insuficiência respiratória[29]. No caso da necessidade de suporte ventilatório invasivo, a internação em Unidade de Terapia Intensiva também se faz necessária na maioria dos casos. Alguns pacientes com DPOC desenvolvem também hipersecreção pulmonar

importante durante a exacerbação[1]. Assim, a fisioterapia respiratória por meio de recursos e técnicas de higiene brônquica pode contribuir para a facilitação da remoção das secreções e para a melhora da função pulmonar[30]. Além disso, nos últimos anos cada vez mais tem se discutido a inclusão de exercícios físicos durante a exacerbação - principalmente nas eDPOC graves (i.e., que requerem hospitalização) -, como alternativa de tratamento. Apesar de pouco estudada, essa abordagem foi investigada por Troosters et al.[31], que observaram que um programa de fortalecimento de quadríceps em pacientes com DPOC hospitalizados por exacerbação não somente evitou a perda na força de quadríceps verificada em outros estudos[5;6], como também permitiu o ganho de 10% nessa variável. Além disso, observou-se também que o treinamento foi seguro e que não houve aumento significativo da inflamação sistêmica. No entanto, a prática de exercícios físicos após a exacerbação está mais estabelecida na literatura. Puhan e colaboradores[32] concluíram recentemente num estudo de revisão sistemática que a prática de exercícios físicos por meio da reabilitação pulmonar é segura e efetiva em reduzir as admissões hospitalares e a mortalidade, e em melhorar a qualidade de vida relacionada a saúde em pacientes com DPOC após exacerbação da doença. Tão importante quanto o tratamento, contudo, é a prevenção da eDPOC. Terapias medicamentosas e não medicamentosas têm sido descritas na literatura, indo desde de vacinas contra o vírus da gripe até a prática de exercícios físicos por meio da reabilitação pulmonar[27].

São muitas as consequências das exacerbações da DPOC sobre o organismo dos indivíduos com essa doença. Já foi descrito na literatura que as exacerbações estão associadas a redução mais acelerada da função pulmonar[4], agravamento da fraqueza muscular periférica[6], piora da capacidade de exercício[33], importante redução do nível de atividade física na vida diária[5], e consequente piora da qualidade de vida[34]. Em relação à força dos músculos respiratórios, os estudos atuais sugerem que ela é afetada pela eDPOC[5;11;12], porém o seu comportamento durante e após uma exacerbação precisa ser melhor investigado.

2.1.2 Força Muscular Respiratória na DPOC

O ato de respirar depende da ação coordenada dos músculos respiratórios para gerar pressões subatmosféricas[19]. O principal músculo da

respiração é o diafragma, porém em situações de aumento da demanda ventilatória (e.g., durante o exercício) outros músculos também podem contribuir para a respiração como os intercostais externos, o esternocleidomastóideo e os escalenos[35]. Durante a respiração tranquila, a expiração é um processo passivo, porém durante o esforço ela pode passar a ser ativa pela ação dos seguintes músculos: intercostais internos, reto abdominal, oblíquo interno, oblíquo externo e transverso do abdome[35]. Em indivíduos com doenças respiratórias crônicas como a DPOC, os músculos respiratórios - tanto inspiratórios quanto expiratórios -, podem ser afetados de diferentes formas, e diversas causas estão associadas à disfunção dos mesmos.

A hiperinsuflação pulmonar, o uso crônico de corticosteroides sistêmicos e déficites nutricionais estão entre as principais causas de disfunção muscular respiratória[19]. A limitação ao fluxo aéreo, principal característica da DPOC, pode levar ao aprisionamento de ar que se traduz na hiperinsuflação pulmonar[1]. Essa, por sua vez, tende a colocar a caixa torácia em constante posição inspiratória, deixando os músculos inspiratórios em desvantagem mecânica, principalmente o diafragma[36]. Assim, a hiperinsuflação pode levar a fraqueza muscular inspiratória devido a disfunção mecânica. Outra causa comum dessa condição em indivíduos com DPOC é o uso crônico de corticosteroides sistêmicos[19]. A miopatia induzida por corticosteroides pode estar presente tanto de forma aguda quanto crônica, e pode afetar tanto os músculos respiratórios (inspiratórios e expiratórios) quanto os periféricos[19;37]. Disfunções nutricionais também são verificadas com frequência nos indivíduos com DPOC, e também já foram descritas como possível causa de disfunção muscular respiratória e periférica, estando associadas principalmente à redução da massa magra[19]. Outras causas de disfunção muscular como hipoxemia, hipercapnia, inflamação e estresse oxidativo também podem ser identificadas na literatura[38].

Durante as exacerbações da DPOC muitas das causas de disfunção muscular respiratória acima descritas estão presentes. Spruit et al.[6] demonstraram em seu estudo que durante uma internação hospitalar por exacerbação os pacientes com DPOC apresentaram redução de 5% do previsto na força de quadriceps, e que esta redução estava associada a níveis mais elevados de interleucina 8, um mediador inflamatório possivelmente envolvido na resposta inflamatória brônquica. Pitta et al.[5] encontraram resultados semelhantes em relação à força de quadríceps,

mas avaliaram também a força dos músculos respiratórios. Nesse estudo, tanto em relação à força dos músculos inspiratórios quanto em relação à força dos músculos expiratórios não foi observada mudança estatística durante ou após a internação hospitalar. Contudo, houve uma tendência de melhora na força dos músculos inspiratórios da alta hospitalar para um mês após, e observou-se um padrão crescente na força dos músculos expiratórios desde o terceiro dia de internação até um mês depois da alta hospitalar. Outros estudos também avaliaram a força dos músculos respiratórios prospectivamente durante e/ou após uma internação por exacerbação. González et al.[11] verificaram um aumento da força muscular inspiratória da admissão para a alta hospitalar, enquanto que Martínez-Llorens et al.[12] encontraram resultados semelhantes para os músculos inspiratórios, mas verificaram redução da força dos músculos expiratórios durante a hospitalização (da admissão para a alta hospitalar). Dessa forma, observa-se que o comportamento da força dos músculos respiratórios durante e/ou após uma exacerbação grave da DPOC ainda não está bem definido na literatura, e que por isso novos estudos são necessários.

3 ARTIGO

RESPIRATORY MUSCLE STRENGTH DURING AND AFTER HOSPITALIZATION FOR COPD EXACERBATION: PROSPECTIVE STUDY.

(Em revisão no periódico *Respiratory Care*)

Running head

RESPIRATORY MUSCLE STRENGTH DURING COPD EXACERBATION.

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The authors report no conflicts of interest.

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Previous presentations

Mr Mesquita presented preliminary results of this paper at the Annual Congress of the European Respiratory Society, held September 24-28, 2011, in Amsterdam, the Netherlands.

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Abstract

BACKGROUND: A more profound investigation of the respiratory muscle strength during exacerbations of Chronic Obstructive Pulmonary Disease (COPD) still needs to be done. We aimed to investigate the strength of the respiratory muscles and its related factors in patients with COPD during and after hospitalization for exacerbation. METHODS: Nineteen patients (12 males, mean age 67[11] years, median forced expiratory volume in the first second [FEV_1] 26[19-32]%predicted) had their lung function, respiratory and quadriceps muscle strength assessed at admission (day 1), discharge and one month after discharge (1mD) for a hospitalization due to disease exacerbation. RESULTS: At admission, 68% of the patients presented inspiratory muscle dysfunction (IMD, maximal inspiratory pressure [MIP]<70%predicted). The inspiratory muscle strength increased from day 1 to 1mD (56[45-64] *vs* 65[51-74] cmH_2O, respectively; $p<0.05$), as well as the expiratory muscle strength from day 1 to both discharge and 1mD (99[65-117] *vs* 109[77-136] and 114[90-139] cmH_2O, respectively; $p<0.05$). The inspiratory capacity (IC) increased from discharge to 1mD (1.59[0.44] *vs* 1.99[0.54] liters, respectively; $p<0.05$). No significant change was observed in other lung function variables or in quadriceps strength ($p>0.05$ for all). Moreover, at admission the IMD and the reduction in IC (<80%predicted) correlated linearly ($r\varphi=0.62$, $p=0.03$), while the expiratory muscle strength correlated inversely to the FEV_1 (Spearman's rho=-0.61, $p=0.005$) and the IC (Spearman's rho=-0.54, $p=0.02$). CONCLUSIONS: There was a high prevalence of inspiratory muscle dysfunction during hospitalization due to COPD exacerbation. Inspiratory and expiratory muscle strength, however, increased markedly during and after hospitalization. Lung function was found to be related to both these variables.

Keywords: Chronic Obstructive Pulmonary Disease; Exacerbation; Hospitalization; Respiratory Muscle Strength.

Introduction

Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) are well known as harmful, although common, events in the natural course of the disease. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD exacerbation as an acute event characterized by a worsening in the respiratory symptoms of the patients, that is beyond normal day-to-day variations and require a change in medication[1].

Among the main consequences of COPD exacerbation presented in the literature, the following ones can be highlighted due to their direct impact on patient's health: increase in mortality[2], impairment in health-related quality of life[3], faster decline in lung function[4], marked reduction in physical activity levels[5], and worsening of peripheral muscle weakness[6].

A few studies only, however, have focused in understanding the effects of a COPD exacerbation on respiratory muscles, despite the key importance of these structures in the disease management. Two recent cross-sectional studies have observed that respiratory muscle dysfunction is associated with an increased risk for hospital admission due to exacerbation[7;8]. Two other studies with prospective designs have identified inspiratory muscle overload as a risk factor for hospitalization due to exacerbation[9;10]. Surprisingly, the function of the respiratory muscles during and after an exacerbation of COPD seems to have been poorly investigated. We identified only three studies that assessed the respiratory muscle strength prospectively during and after hospitalizations for COPD exacerbation[5;11;12]. In brief, González et al.[12] and Martínez-Llorens et al.[11] found an increase in inspiratory muscle strength from admission to discharge, while Pitta et al.[5] stated they found

only a trend of improvement from discharge to one month after. The expiratory muscle strength, in turn, decreased during the hospitalization in the study of Martínez-Llorens et al.[11], but presented an increasing pattern from admission to after discharge in the study of Pitta et al.[5], although without statistical significance. Thus, the time course evolution of the respiratory muscle strength during exacerbations still needs to be better understood.

Therefore, the aim of the present study was to investigate in depth the strength of the respiratory muscles (inspiratory and expiratory), and its related factors, in patients with COPD during and after the course of a hospitalization for exacerbation of the disease.

Methods

Study design

This observational and prospective study was carried out from January 2010 to February 2012 involving patients with COPD hospitalized due to an exacerbation of the disease in an university hospital (State University of Londrina, Brazil). Respiratory and quadriceps muscle strength, and lung function were assessed in the first 24h of hospitalization (day 1) and reassessed at discharge and 1 month after discharge (1mD). In the last assessment (1mD), patients returned to the hospital to be reassessed. Arterial blood gases, limitations in activities of daily living, and the combined COPD assessment were investigated at day 1 only. This study was approved by the ethics committee of the State University of Londrina and all patients gave written informed consent.

Patients

Patients were included in the study if they presented: COPD diagnosis based on GOLD criteria (post-bronchodilator forced expiratory volume in the first second [FEV_1]·forced vital capacity [FVC]$^{-1}$ < 0.70)[1]; hospital admission due to an exacerbation of the disease (i.e., severe exacerbation according to the definition of Rodriguez-Roisin[13]); spontaneous breathing on hospital admission (i.e., not being on mechanical ventilation); absence of pathological conditions (e.g., neuromuscular, cerebrovascular, or severe cardiac diseases) that could impair the performance on the proposed tests; no recent hospitalization due to COPD exacerbation[14]; and no participation in any exercise training in the previous six months. The decision to admit patients to the hospital was made by the attending physician who was not involved in the present study. Patients were excluded in case of death, withdrawing consent, or missing values in more than one day of assessment (i.e., discharge and 1mD).

Assessments

Gender, age, anthropometric variables (weight, height, and body mass index [BMI]), and clinical variables (number of exacerbations in the previous year and previous corticosteroids use) were collected at the moment of inclusion in the study. Data concerning corticosteroid use and physiotherapy treatment during the hospitalization were retrieved retrospectively from the patients' medical file after discharge.

Respiratory muscle strength, the primary outcome, was measured by the assessment of maximal inspiratory and expiratory pressures (MIP and MEP, respectively) using a digital manovacuometer (MVD 300, GlobalMed, Porto Alegre,

Brazil) and a plastic tube mouthpiece with a small leak to prevent glotic closure and reduce the use of buccal muscles[15]. The Black and Hyatt[16] protocol was used, in which patients were assessed in the seated position, wore a noseclip, and had the MIP measured near residual volume and the MEP near total lung capacity. MIP and MEP were maintained for at least two seconds and the peak value was recorded. Although negative, the values of MIP were presented as positive values to avoid misinterpretation of its changes. The best of three acceptable and reproducible consecutive maneuvers was considered for analysis. The criteria for acceptability were adequate effort and duration, no postural compensation, and no cough or perioral air leak during the maneuvers, while the criterion for reproducibility was a difference ≤ 10% of the highest value between the two highest values[17]. Reference values were also used to express the results[18].

Quadriceps muscle strength was measured by the assessment of quadriceps peak torque (QPT) from an isometric contraction of the quadriceps at the dominant side and at 60º of knee flexion[14]. A hand-held electrical dynamometer (microFET2, HogganHelth, USA) anchored in a fixed multigym equipment was used to register the QPT; this adaptation was previously validated[19]. The best of three acceptable and reproducible maneuvers was considered for analysis. QPT was expressed in Newton meters (N·m), Newton per kilogram ($N \cdot kg^{-1}$), and as percentage of the predicted values[20]. Lung function was measured with spirometry (Spirobank G, MIR, Italy) by the assessment of slow and forced vital capacities after bronchodilation, according to international reccomendations[21] and considering national reference values[22;23]. All the tests were performed by a trained physiotherapist.

Arterial blood gases levels (i.e., partial pressure of oxygen and

carbon dioxide) were assessed at admission by the hospital staff. Also at admission, the combined COPD assessment[1] was performed to get a multidimensional estimate of disease severity. This assessment involves airflow limitation, exacerbation frequency, and symptoms - which were assessed by the Medical Research Council (MRC) scale[24] -, and classifies patients in one of the four groups: A (low risk, less symptoms), B (low risk, more symptoms), C (high risk, less symptoms), or D (high risk, more symptoms).

Statistical Analyses

The study by González et al.[12] was used for sample size calculation. Considering the difference in means (pooled standard deviation) of 15 (21) cmH_2O between hospital admission and discharge concerning the maximal inspiratory muscle pressure, an alpha value of 0.05, and a power of 80%, the present study needed a sample size of 17 participants. Adding a drop out rate of 25%, verified in a previous study with similar design[5], the required sample size increased to 21 subjects.

Categorical variables were described as absolute and/or relative frequencies, while continuous variables were tested for normality by the Shapiro-Wilk test and presented as mean (standard deviation), when normally distributed, or median (interquartile range 25%-75%), when non-normally distributed. Multiple imputation method was used to impute the missing values, which were considered missing completely at random (MCAR) according to Little's MCAR test. Only the results with imputed data were presented, since no difference between these and the results from complete-case analysis was verified.

Chi-square test was used for the comparison of categorical data.

Repeated measures ANOVA or Friedman test was used for the comparisons among the three days of assessment, with Tukey's or Dunn's tests as post hoc test, respectively. The changes (delta) in respiratory pressures were compared by the paired t test or Wilcoxon test, and the comparison of these deltas between MIP and MEP was performed by the unpaired t test or Mann-Whitney test. Spearman or Phi coefficient was used to analyze correlations. The level of statistical significance was considered as $p<0.05$ and all the analyses were performed using the Statistical Package of Social Science (SPSS) 17.0 (SPSS Inc., Chicago, IL, USA) or the GraphPad Prism 5 (GraphPad Software Inc., La Jolla, California, USA).

Results

Twenty-one exacerbated patients with COPD were included. During the course of the study, two patients died from respiratory complications of COPD (one during hospitalization and the other nearly before the 1mD assessment) and two did not attend the last assessment. The two patients who died were excluded and the two who did not attend the follow-up were handled with the multiple imputation method. Only one patient was hospitalized again after discharge, but before the 1mD assessment. This patient, however, did not bias the results. Patients who dropped out and the remainder patients had similar age, anthropometric measures and lung function.

Clinical information before and during hospitalization

Table 1 describes the clinical characteristics of the nineteen patients included in the study on the first day of assessment (day 1). It can be noticed that the

majority of patients were classified as GOLD IV and belonged to group D in the combined COPD assessment. During hospitalization, sixteen patients (84%) received systemic corticosteroids (hydrocortisone, prednisone, prednisolone or methyl-prednisolone) and three (16%) did not receive them. Still regarding the hospitalization period, nine patients (47%) received respiratory physiotherapy and ten (53%) did not receive it. The physiotherapy techniques were mainly calisthenics-and-breathing exercises or bronchopulmonary hygiene techniques, with no endurance, strength or respiratory muscle training. The hospitalization lasted a median period of 4 (3-5) days.

Respiratory muscle strength during and after hospitalization

At the first 24h of hospitalization, assessment of the inspiratory pressure revealed that the median MIP was 52 (43-80)% predicted, and that 13 patients (68%) presented inspiratory muscle dysfunction (IMD, MIP<70% predicted[7]). This number decreased to 11 patients (58%) at discharge and remained the same at 1mD, with no statistical difference in the comparison among the three moments ($p=0.5$, Figure 1).

The behavior of MIP during and after hospitalization is presented in Figure 2A. In comparison to day 1 (56 [45-64] cmH_2O), MIP did not change significantly at discharge (62 [45-69] cmH_2O, $p>0.05$), but did increase at 1mD (65 [51-74] cmH_2O, $p<0.05$). MEP showed similar pattern (Figure 2B); however, the post hoc test revealed that, in comparison to day 1 (99 [65-117] cmH_2O), MEP increased already at discharge (109 [77-136] cmH_2O, $p<0.05$) and also at 1mD (114 [90-139] cmH_2O, $p<0.05$).

No statistical difference was found when the delta (i.e., the relative

change normalized to the values obtained at day 1) between day 1 and discharge was compared to the delta between day 1 and 1mD, for both MIP and MEP ($p>0.05$ for all, Figure 3), and it was noticed that the improvement in MIP and MEP from day 1 to discharge accounted for 68% and 61%, respectively, of the improvement from day 1 to 1mD. MEP was higher than MIP in the comparison of both the delta from day 1 to discharge (14 [22] *vs* 13 [20] %, respectively; $p=0.001$, Figure 3) and from day 1 to 1mD (23 [31] *vs* 19 [22] %, respectively; $p=0.003$, Figure 3).

At day 1, MIP correlated significantly with MEP (Spearman's rho=0.49, $p=0.04$) and with QPT (Spearman's rho=0.57, $p=0.01$), while MEP, in addition to the correlation with MIP, correlated inversely to the FEV_1 (Spearman's rho=-0.61, $p=0.005$) and the inspiratory capacity (IC) (Spearman's rho=-0.54, $p=0.02$), both in % predicted. It was also observed that, still at day 1, the proportion of patients with reduced IC (< 80% of predicted[25]) was exactly the same as with IMD (< 70% of predicted[7]), which is 13 patients (68%). Indeed, the IC of patients with IMD was observed to be lower than the IC of patients without IMD (62 [53-72] *vs* 93 [71-139] % predicted, respectively; $p=0.02$) and the classifications of reduced IC and IMD were associated ($r\varphi=0.62$, $p=0.03$). The delta of MIP between day 1 and 1mD linearly correlated with the same delta of MEP (Spearman's rho=0.58, $p=0.01$), both in cmH_2O, while the latter inversely correlated with the MEP assessed at day 1 (Spearman's rho=-0.52, $p=0.02$).

Lung function and peripheral muscle strength during and after hospitalization

The behavior of lung function and peripheral muscle strength during and after hospitalization is shown in Table 2. It can be observed that no statistical difference was found in the comparison of FEV_1 and FVC among the three

assessment points. The IC in liters significantly increased from discharge to 1mD ($p<0.05$).

There was no statistical difference in the comparison of QPT among the three assessment points. During all the assessments, no adverse effects were observed.

Discussion

This study clearly showed that the inspiratory muscle strength is reduced at the onset of a hospitalization for COPD exacerbation, but increases markedly by one month after discharge. The expiratory muscle strength presents similar pattern, but already increases from admission to discharge and also to one month after discharge. Lung function at hospital admission was found to be related to both inspiratory and expiratory muscle strength.

Two out of the three studies that prospectively evaluated the inspiratory muscle strength during and/or after hospitalization found that this variable increased from admission to discharge[11;12], while the other study found a trend of improvement from discharge to one month after[5]. At first glance it may seem that our results do not corroborate any of these studies, as we found significant difference only between day 1 and one month after discharge, however these results actually do agree with the two formers. Although the comparison between MIP from admission to discharge in our study was not statistically different, higher values were observed at discharge (which represent an increase of 11% in MIP in comparison to day 1). This represented 68% of the whole improvement observed in MIP. One possible explanation to the lack of statistical significance may rely on the post hoc

analysis, which might have been underpowered.

At hospital admission, inspiratory muscle dysfunction was observed in 68% of patients, presenting a lower value (58%) at discharge and remaining the same (58%) one month after. These values are higher than those reported by Vilaró et al.[7], who found prevalence values of IMD between 45% to 55%. However, these discrepancies might have occurred since patients from our study presented a more severe disease status in comparison to the ones from Vilaró et al.[7]. Still at hospital admission, the IMD was found to be related to the reduction in inspiratory capacity. Indeed, this supports previous explanations for the reduction in inspiratory muscle strength during exacerbation. Martínez-Llorens et al.[11] and González et al.[12] justify this reduction by the mechanical disadvantage caused by hyperinflation. O'Donnell and Parker[26] explain this phenomenon in more details stating that, during exacerbation, the dynamic hyperinflation may further shortens the inspiratory muscles, leading to a functional muscle weakness. Although in our study we used a static measure of hyperinflation, we may infer that the reduction observed in the IC is probably a consequence of dynamic hyperinflation. Another factor that supports this hypothesis is the rapid improvement observed in the absence of any specific treatment for the inspiratory muscles. Nevertheless, other factors such as malnutrition, inflammatory markers and corticosteroids use should be investigated in details, since they might contribute to respiratory muscle dysfunction. Regarding corticosteroids, only three patients in our study were using this class of medication on a regular basis before hospitalization, and during the hospitalization period it was used by sixteen patients. The negative effects of systemic corticosteroids on muscle function are very well known in the literature[20;27;28]; however, as in our study the main results were based on within-subject comparisons, we do not believe that this factor

could have been a source of bias.

Besides investigating other causal factors of muscle dysfunction, another interesting approach would be the investigation of the possible consequences of IMD. Nevertheless, this would be a difficult task as the main consequences of IMD (i.e., dyspnoea and exercise intolerance) are also common to other functional impairments such as hyperinflation.

From the best of our knowledge only two studies prospectively assessed the strength of the expiratory muscles during the course of a hospitalization for COPD exacerbation, and their results were divergent. Martínez-Llorens et al.[11] verified a significant decrease in the expiratory muscle strength from hospital admission to discharge. On the other hand, Pitta et al.[5] did not find significant differences among three assessment days (two during hospitalization and one after discharge), but did find an increasing pattern from hospital admission to after discharge. We observed the same pattern in our study, and even reached statistical significance. Martínez-Llorens et al.[11] stated that the expiratory muscles are not affected by dynamic hyperinflation. We agree that they may not be directly affected as much as the inspiratory muscles, but based on previous findings[29] and on our own results, it is reasonable to postulate that these variables might be at least related. We observed a negative correlation between expiratory muscle strength and the degree of airflow limitation and hyperinflation. It is well known in the literature that during hyperinflation the activity of the expiratory muscles is increased[29;30]. Hence, we believe that the hyperinflation elicited by the exacerbation may have over-recruited the expiratory muscles, which might explain the observed negative correlations between MEP and IC. In fact, it has been shown that patients with history of multiple hospital admissions due to exacerbations present higher values of expiratory muscle

strength in comparison to more stable patients[7;8].

IC increased from the hospitalization period in comparison to one month after discharge, i.e., a more hyperinflated pattern was observed during hospitalization, corroborating previous results in which reduced values of respiratory muscle strength were observed during hospitalization. Parker et al.[31] found an increase of 300 ml in IC from hospitalization to one month after, while in our study we found an increase of 400 ml for a similar period of time. The reasons for this average difference of approximately 100 ml may be related to differences in sample characteristics or treatments adopted. Regarding QPT, we observed no difference in this variable among the three assessment moments, similarly to Troosters et al.[14]. Two other studies[5;6], however, verified a decrease of 5% predicted in the QPT during the hospitalization period. Therefore, the decrease in quadriceps strength during exacerbations does not seem to be a recurrent finding in patients with COPD. Besides the study of Troosters et al.[14], which found no decrease in this variable, in the study of Spruit et al.[6] 48% of patients presented no change or even an increase in this variable, allowing to hypothesize that maybe there is a phenotype of patients more prone to show peripheral muscle dysfunction during exacerbations. Furthermore, also for QPT, differences in sample characteristics, pharmacological treatment adopted and physiotherapy regimen performed during the hospitalization period may account, at least in part, for these conflicting results.

This study was useful to clarify previous findings in the literature, and its main message is possibly that the hyperinflation observed during the onset of an exacerbation has an impact on the respiratory muscles, further reducing their strength. Thus, the condition of the respiratory muscles should be a factor to be taken into consideration during and after a hospitalization due to COPD exacerbation,

especially if important airflow limitation/hyperinflation is present. However, despite our useful findings, our study has some limitations that should be clearly acknowledged. Probably the main one relies on the fact that we were not aware of the respiratory muscle strength before hospitalization. This information would confirm if in fact there was a decrease in the respiratory strength at the moment of hospital admission. However, the inclusion of this assessment moment would logistically complicate the study, probably demanding much more time and patients than the already needed. Furthermore, the increase observed after discharge indicates that values are possibly returning to the stable condition, which confirms the decrease at the moment of hospital admission. Another point of concern could be the use of a volitional test (maximal static pressures measured at the mouth) for the assessment of respiratory muscle strength. The test used, however, has shown to be valid, simple to perform, and better tolerated by patients than non-volitional tests[15], which, despite being considered by some authors the gold-standard for the measurement of resipiratory muscle strength, might be complex to perform and analyze, and might involve high costs. Finally, the use of peak respiratory pressures instead of one-second plateau pressures or the mean pressure over one second, most frequently used, might be another point of criticism. The American Thoracic Society/European Respiratory Society (ATS/ERS) statement on respiratory muscle testing suggests the use of plateau or mean pressure, stating that the peak pressure is believed to be less reproducible[15]. A very well designed study[18] published after the ATS/ERS statement however, concluded that peak and plateau pressures were comparable in terms of predicted variables, between-subject variability and reproducibility. In addition, our main results were based on prospective comparisons, so we believe that the consistent use of either peak, plateau or mean pressure in all

assessments would likely generate similar findings.

Conclusions

In summary, the present study showed that there is inspiratory muscle dysfunction at hospital admission and that the inspiratory muscle strength increases markedly by one month after discharge. The expiratory muscle strength, in turn, already increases from admission to discharge and also to one month after discharge. Lung function at hospital admission was found to be related to both inspiratory and expiratory muscle strength. The understanding of the possible causes of the changes occurred in respiratory muscle strength during an exacerbation are important to be investigated in future studies, as well as the possible consequences of these changes.

Acknowledgments

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FIGURE LEGENDS

Figure 1. Proportion of patients with (black) and without (white) inspiratory muscle dysfunction during and after hospitalization.

Figure 2. Maximal respiratory pressures (in cmH_2O; A: maximal inspiratory pressure; B: maximal expiratory pressure) during and after hospitalization. p value from Friedman test: A) p=0.03; B) p=0.005.

Figure 3. Changes in maximal respiratory pressures (in percentage of the values obtained at day 1, solid circles: maximal inspiratory pressure; open circles: maximal expiratory pressure) through the days of assessment. The dotted line corresponds to the zero value. Data presented as mean ± standard deviation.

FIGURE 1

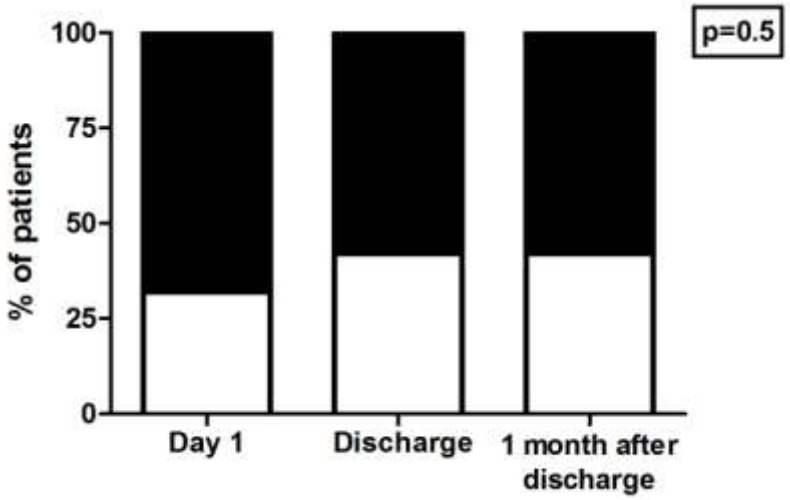
p=0.5
100
75
50
25
0
% of patients
Day 1
Discharge
1 month after discharge

FIGURE 2

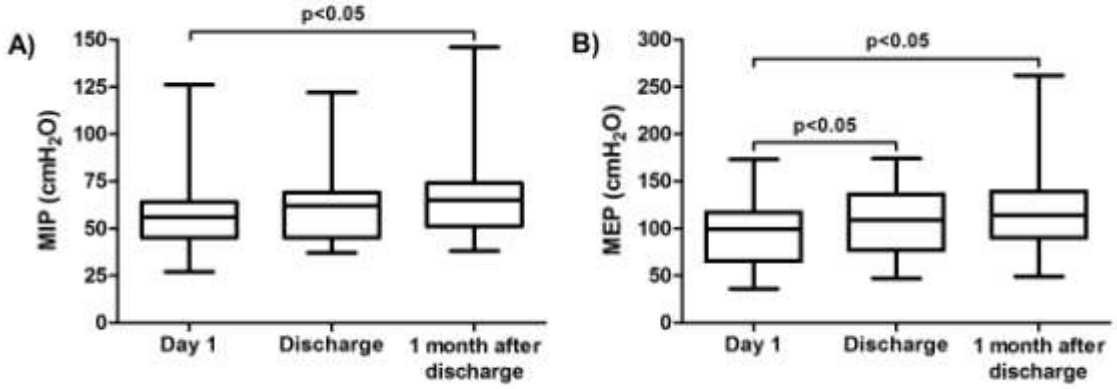
A)
p<0.05
MIP (cmH2O)
150
125
100
75
50
25
0
Day 1
Discharge
1 month after discharge
B)
p<0.05
p<0.05
MEP (cmH2O)
300
250
200
150
100
50
0
Day 1
Discharge
1 month after discharge

FIGURE 3

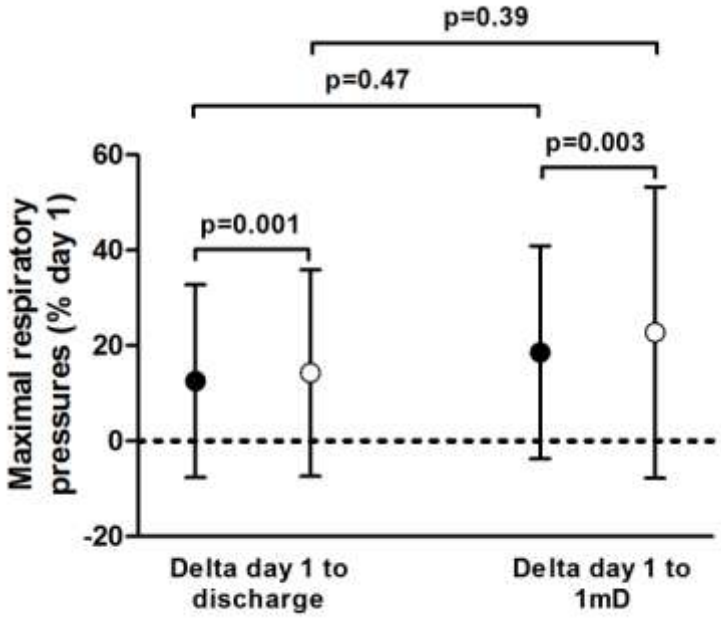
p=0.39
p=0.47
p=0.003
p=0.001
60
40
20
0
-20
Maximal respiratory pressures (% day 1)
Delta day 1 to discharge
Delta day 1 to 1mD

Table 1. Clinical characteristics of the patients in the first 24h of hospitalization.

Characteristics	Values
Gender (n, M / F)	12 / 7
Age (years)	67 (11)
BMI ($kg \cdot m^{-2}$)	23 (19-27)
FEV_1 (% pred)	26 (19-32)
$FEV_1 \cdot FVC^{-1}$ (%)	38 (12)
GOLD grades (n, I / II / III / IV)	0 / 1 / 6 / 12
Previous exacerbations (n / %)	
0-1	15 / 79
≥ 2	4 / 21
Symptoms (MRC scale)*	3 (1)
Combined COPD assessment* (%, A / B / C / D)	0 / 0 / 25 / 75
Previous corticosteroid use (n / %)	
Inhaled corticosteroids†	9 / 47
Oral corticosteroids‡	3 / 16
Pa_{O_2} (mmHg)	61 (14)
Pa_{CO_2} (mmHg)	39 (31-43)

Data expressed as absolute frequency, relative frequency, mean (standard deviation) or median (interquartile range). *Data available for eight patients only, who did not differ from the remainder patients of the sample in terms of age, anthropometric variables, and lung function. †For a mean period of 24 months. ‡20 $mg \cdot day^{-1}$ of prednisone or prednisolone for a mean period of 26 months. BMI: body mass index; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; MRC: Medical Research Council; Pa_{O_2}: arterial partial pressure of oxygen; Pa_{CO_2}: arterial partial pressure of carbon dioxide.

Table 2. Lung function and peripheral muscle strength during and after hospitalization.

	LUNG FUNCTION			
Characteristics	**Day 1**	**Discharge**	**One month after discharge**	**p value**
FEV_1				
L	0.74 (0.61-0.86)	0.75 (0.61-0.86)	0.69 (0.59-0.90)	0.21
% predicted	26 (19-32)	25 (19-32)	26 (21-35)	0.75
FVC				
L	2.07 (0.80)	2.04 (0.68)	2.10 (0.84)	0.91
% predicted	50 (43-68)	51 (41-73)	62 (41-76)	0.78
IC				
L	1.93 (0.60)	1.59 (0.44)	1.99 (0.54)*	0.02
% predicted	71 (58-85)	54 (43-85)	70 (58-91)	0.12
	PERIPHERAL MUSCLE STRENGTH			
Characteristic	**Day 1**	**Discharge**	**One month after discharge**	**p value**
QPT				
N·m	79 (34)	78 (35)	85 (38)	0.10
% predicted	66 (45-77)	65 (51-77)	72 (44-81)	0.37
$N \cdot kg^{-1}$	4.00 (1.49)	3.87 (1.39)	4.20 (1.36)	0.34

Data expressed as mean (standard deviation) or median (interquartile range). *p<0.05 *vs* discharge. FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; IC: inspiratory capacity; QPT: quadriceps peak torque.

CONCLUSÃO GERAL

O presente estudo mostrou que há importante disfunção muscular inspiratória na admissão hospitalar por exacerbação, e que há uma melhora da função muscular inspiratória em até um mês após a alta hospitalar. A força dos músculos expiratórios, por sua vez, já apresenta aumento da admissão para a alta hospitalar e também para um mês após a alta hospitalar. Além disso, a função pulmonar na admissão esteve relacionada tanto com a força dos músculos inspiratórios quanto com a força dos músculos expiratórios. O entendimento das possíveis causas das mudanças ocorridas na força muscular respiratória durante uma exacerbação é um ponto importante a ser investigado em estudos futuros, bem como as possíveis consequências dessas mudanças.

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APÊNDICES

APÊNDICE A

Termo de consentimento livre e esclarecido

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 “Força muscular respiratória em pacientes hospitalizados por exacerbação aguda da Doença Pulmonar Obstrutiva Crônica (DPOC)”, cujo pesquisador responsável é o Prof. Dr. Fabio Pitta, do Departamento de Fisioterapia da Universidade Estadual de Londrina (UEL). O estudo analisará principalmente as possíveis mudanças ocorridas na força dos músculos responsáveis pela respiração durante e após uma internação por exacerbação da DPOC.

Justificativa: O presente estudo contribuirá para o melhor entendimento de como se dá a evolução da força dos músculos respiratórios no paciente com DPOC no período durante e após uma exacerbação aguda da doença, contribuindo para um melhor entendimento de aparentes divergências vigentes na literatura científica. O esclarecimento das diferenças na evolução dos músculos inspiratórios e expiratórios durante uma exacerbação aguda da DPOC permitirá uma discussão mais baseada em evidências sobre as melhores opções terapêuticas no combate à disfunção muscular respiratória durante o difícil processo de recuperação de uma exacerbação grave.

Objetivo: Avaliar a evolução da força dos músculos respiratórios (inspiratórios e expiratórios) e de fatores relacionados, em pacientes durante e após a hospitalização por exacerbação aguda da DPOC.

Procedimentos: Os participantes realizarão uma série de testes que incluirá a avaliação de medidas antropométricas (idade, altura e peso), da força dos músculos respiratórios e periféricos e da função pulmonar. Os testes serão realizados em até 24 horas após a internação hospitalar, no dia da alta hospitalar e no final da 4ª semana após a alta hospitalar, ou seja, nesse último momento os pacientes terão que realizar uma visita ao Hospital Universitário (HU) da UEL - Londrina. As avaliações são de fácil realização, tem duração de 5 a 30 minutos cada teste e serão realizadas no próprio leito de internação do paciente, sem necessitar de qualquer deslocamento do mesmo para outro setor, com exceção da última avaliação (na 4ª semana após a alta hospitalar), que será realizada em laboratório de pesquisa apropriado, localizado no próprio HU-UEL.

Custos: A pesquisa é gratuita e portanto não envolve qualquer custo por parte dos indivíduos. Não haverá qualquer gratificação financeira pela participação. No entanto, em caso de eventuais danos

ocorridos exclusivamente por causa deste estudo, o Sr(a) terá direito a tratamento médico completo oferecido pela instituição.

Riscos: Nenhum dos procedimentos utilizados constitui risco direto para a integridade física ou moral dos participantes. Além disso, os participantes poderão abandonar o estudo a qualquer momento que se achar conveniente, sem qualquer prejuízo em nenhum sentido.

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

Caso o(a) Sr(a) aceite esse convite e concorde voluntariamente em participar do estudo assinando este termo de consentimento, consideramos que o Sr(a) acredita que foi suficientemente informado(a) pelo(a) pesquisador(a) _____ 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:_____
Nome do pesquisador: _____
Assinatura do pesquisador: _____

Colocamo-nos à disposição para qualquer esclarecimento que se fizer necessário nos telefones (43) 3371 2288 ou 3371 2252 ou pessoalmente no Ambulatório de Fisioterapia Respiratória do Hospital Universitário da Universidade Estadual de Londrina (UEL): Av. Robert Koch, 60 – Vila Operária – Londrina – PR (perguntar pelo Professor Fabio Pitta).

Atenciosamente,

Prof. Fabio Pitta
Coordenador do Projeto

ANEXOS

ANEXO A

Normas de formatação do periódico

Respiratory Care

Preparing the Manuscript

• Required Sections of Manuscript

- **Title Page**
- **Abstract**
- **Key Words**
- **Text**
- **References**

• Optional Sections of Manuscript

- **Original Figures**
- **Figure Legends**
- **Borrowed Figures**
- **Permissions**
- **Tables**
- **Acknowledgements**
- **Equations**
- **Statistical Analysis**
- **Units of Measurement**
- **Abbreviations and Symbols**
- **Pulmonary Terms and Symbols**
- **Drugs and Commercial Products**
- **Ventilator Modes**

• Back to Guidelines for Authors

For guidance on preparing a scientific manuscript, the Journal recommends 2 manuals:

• AMA manual of style: a guide for authors and editors, 10th edition. New York: Oxford University Press; 2007.

• Council of Biology Editors. Scientific style and format: the CSE manual for authors, editors, and publishers, 7th edition. Reston VA: Council of Science Editors and Rockefeller University Press; 2006.

For further study, please see the special issue devoted to Research and Publication in Respiratory Care (Respir Care 2004;49(10):1121-1272).

Required Sections of Manuscript

Title Page

Title page should include the following:

Full title

For all authors:

- Full first and last name (including middle initials)
- Highest academic or professional degrees (but not including honorific designations other than FAARC)
- Institutional affiliation and location (division, department, hospital, school, university, city, state)
- The name and location of the institution where the study was performed
- Name, date, location of any meeting or forum in which research data have been previously presented in poster or other sessions, and the name of the author presenting such data
- Sources of financial support (grant funding sources, etc)
- Conflict-of-interest statement for each author: Disclosures of potential conflicts of interest should be for the previous 2-year period. Authors should provide full disclosure of all potential conflicts of interest (whether or not related to the content of the paper). Type of relationship (eg, consultant, speaker, employee, etc) and monetary amount need not be specified. For each author, if no financial or other potential conflicts of interest exist, a statement to this effect should be included.

Abstract

For Original Research articles, provide a structured abstract that includes the following 4 sections: Background (the issue addressed in the study), Methods (how

the study was performed, including the number of patients), Results (brief summary of the data), and Conclusions (the take-home message). Abstracts for Special Articles, Review Articles, Case Reports, and Conference Proceedings should be in the form of a narrative paragraph. Please limit the abstract to less than 300 words (150 words for Case Reports). The abstract must not contain any facts or conclusions that do not also appear in the body text.

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Include with the abstract a list of 6 to 10 key words or phrases that best reflect the content of your manuscript. Key words can be selected from the **Medical Subject Headings** (MeSH terms) used by MEDLINE. [Note: You will also be asked to provide 3 categories in RESPIRATORY CARE Manuscript Central. These are more general terms that are used in the selection of reviewers and do not have to match the terms used in your manuscript.]

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Double-space the text and number the pages. Center and bold the 1st level headings; flush-left and bold any 2nd level headings. Indent and bold any 3rd level headings.

References

References must be listed and numbered in the sequence in which each referenced document is first cited in the text, tables, and figures. Authors are responsible for the accuracy and completeness of the citations. Regarding the use of citation management software in your word processing files, **The EndNote Styles** collection contains the style for RESPIRATORY CARE. Authors can download this style and designate it as the Output Style from within Endnote, which allows formatting of the manuscripts using EndNote. Because EndNote always adds the references to the very end of the document, it may be necessary to cut and paste them to the correct

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The following examples show the Journal's style for the most common types of references.

Manuscript accepted but not yet published:

Hess DR. New therapies for asthma. Respir Care (2008, in press).

(One copy of manuscripts cited as "in press" should be uploaded onto Manuscript Central as supplementary material.)

Article in a journal carrying pagination throughout the volume; for citations with multiple authors, list the first 6 authors, and then "et al": (Exception: in the case of a paper with a total of 7 authors, list all seven.)

Stoller JK, Kester L, Roberts VT, Orens DK, Babic MD, Lemin ME, et al. An analysis of features of respiratory therapy departments that are avid for change. Respir Care 2008;53(7):871-884.

Corporate author journal article:

Pérez-Padilla R, Vázquez-Garcia JC, Márquez MN, Menez AMB on behalf of the PLATINO Group. Spirometry quality-control strategies in a multinational study of the prevalence of chronic obstructive pulmonary disease. Respir Care 2008;53(8):1054-1080.

Article in journal supplement (journals differ in numbering and identifying supplements. Supply information sufficient to allow retrieval):

Shields MD, Bush A, Everard ML, McKenzie S, Primhak R; British Thoracic Society Cough Guideline Group.

BTS guidelines: Recommendations for the assessment and management of cough in children. Thorax 2008;63(Suppl 3):iii1-iii15.

Abstract (citing abstracts is discouraged, but permissible; those more than 3 years old should not be cited):

Brown MK, Willms DC. A comparison of heliox consumption in three ventilators (abstract). Respir Care 2007;52(11):1610.

Editorial in a journal:

Doherty DE. Documentation of airflow obstruction is essential to confirm the diagnosis of COPD: are handheld spirometers in an office setting valid? (editorial). Respir Care 2008;53(4):429-430.

Editorial with no author given:

Allergic rhinitis: common, costly, and neglected (editorial). Lancet 2008;371(9630):2057.

Letter in journal:

Labeau SO, Vandijck DM, Vandewoude KH, Blot SI. Obstacles to implementing evidence-based guidelines (letter). Respir Care 2008;53(4):505-506; author reply 506.

Book (specific pages should be cited whenever reference is made to specific statements or other content):

White GC. Respiratory notes: respiratory therapist's pocket guide. Philadelphia: FA Davis; 2008: 230.

Corporate author book:

Committee on Implementation of Antiviral Medication Strategies for an Influenza Pandemic, Institute of Medicine. Antivirals for pandemic influenza: guidance on developing a distribution and dispensing program. Washington DC: National Academies Press; 2008.

Chapter in book with editor(s):

Clini EM, Trianni L, Ambrosino N. Nutrition in the ICU. In: Goldstein N, Goldstein RS, editors. Ventilatory support for chronic respiratory failure. Lung Biology in Health and Diseases, Vol 225. New York: Informa; 2008:401-413.

Internet Material:

Static Internet material should be listed in the references and used only when a printed citation is not available (such as when citing an online journal; always include the digital object identifier [DOI]; if available). Because the citation is static, there is no need to include the access date.

Ehrenstein BP. Pandemic influenza: are we prepared to face our obligations? Critical Care 2008;12:165. doi:10.1186/cc6938.

Published articles ahead of print should be cited in the same manner, including the DOI, or if that is lacking, add "[epub ahead of print]". Update the pagination data when available upon final publication of the cited paper.

Frequently changing Internet material used only as a background source can be cited in the text, using only the URL and access date, and does not need to be added to the reference list, eg, "….as recommended by the American Lung Association (http://www.lungusa.org/, *Accessed July 16, 2008*) …"

General news sources can be cited as a URL within the text, with the date last accessed.

(Aisen CF. Taking action against hospital acquired infection. Medical News Today: July 2, 2008. Available at http://www.medicalnewstoday.com/articles/113508.php. *Accessed July 16, 2008*.)

Unpublished Work:

If research has not yet been accepted for publication, it should not be cited in the reference list but may be cited in full parenthetically within the text as a personal communication, Example: “Recently, Jones et al found this treatment effective in 45 of 83 patients (Jones HI, personal communication, 2008).” You must obtain written permission from the author to cite his or her unpublished data. Permission to cite unpublished work as a personal communication ensures that this information is not misrepresented, either in error or intentionally, or included without the knowledge and approval of the individuals providing the information. Reference to your own unpublished work that has not been accepted for publication should not be included in the reference list but must be mentioned as follows: “Recently, we found that this type of aerosol is no more effective than placebo (unpublished data).”

Optional Sections of Manuscript

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Use only illustrations that clarify and augment the text. All the figures must be called-out in the text. Number figures consecutively as Figure 1, Figure 2, etc.

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A table should be self-explanatory and should not duplicate information in the text. Tables should be numbered and cited consecutively in the text. All abbreviations and

symbols should be explained in notes at the bottom of the table. For footnotes use the following symbols, superscripted, in the table body, in the following order: *, †, ‡, §, ||, ¶, **, ††.

With “±” values, indicate whether the value is a standard deviation or standard error of the mean. Note: It is rarely correct to report standard error values when describing a study’s findings. Consult a statistician if this is in doubt.

Acknowledgements

The names of persons helping the authors, but not eligible for author status, along with their contribution and institutional affiliation, may be mentioned in the Acknowledgments section. You must obtain written permission from all individuals before they are named in the Acknowledgments section, because inclusion of names can be taken as signifying the individuals’ approval of the paper’s contents. You must notify the editorial office that you have obtained such permission.

Equations

Create equations as normal text. Do not use Microsoft Word’s equation creation function or other mathematics software.

Statistical Analysis

For manuscripts that report complex statistics, the Editor recommends statistical consultation (or at least expertise); a biostatistician may review such manuscripts during the review process.

In the Methods section:

Identify the statistical tests used to analyze the data.

Indicate the prospectively determined *P* value that was taken to indicate a significant difference.

Cite only textbook and published article references to support your choices of tests.

Identify any statistics software used.

In the Results section:

Note that following the *AMA manual of style: a guide for authors and editors*, 10th edition. New York: Oxford University Press; 2007, page 889, the Journal does not use a zero to the left of the decimal point, because “…statistically it is not possible to

prove or disprove the null hypothesis completely when only a sample of the population is tested (*P* cannot equal 0 or 1, except by rounding)."

Report actual *P* values rather than thresholds: not just whether the *P* value was above or below the significant-difference threshold. Example: write "*P* = .18", not "*P* > .05" or "*P* = NS."

P should be expressed to 2 digits for *P* ≥ .01, because expressing *P* to more than 3 digits does not add useful information. If *P* < .001, it should be expressed as *P* < .001, rather than *P* < .0001 or *P* = .00001 for example.

If *P* > .99, *P* = .999 for example, it should be expressed as *P* > .99.

Units of Measurement

Always report the units of measurement according to current scientific usage. Standard units of measurement and scientific terms can be abbreviated without explanation (eg, L/min, mm Hg, pH, O_2). Use the **units and conversion factors**.

Abbreviations and Symbols

Use sparingly; refer to the **standard abbreviations and symbols**. Do not invent new abbreviations for terms that have long had standard abbreviations. Use an abbreviation only if the term occurs 4 or more times in the manuscript. Abbreviate the term parenthetically at first mention in the text; thereafter use only the abbreviation. Example: arterial blood gas (ABG).

Pulmonary terms and symbols

Refer to **a report of the ACCP-STS Joint Committee on Pulmonary Nomenclature** which is adapted from the document *Pulmonary terms and symbols* (originally published in Chest 1975;67[5]:583–93).

Drugs and Commercial Products

Precisely identify all drugs and chemicals, doses, and methods of administration. Use generic names instead of trade (proprietary) names for both drugs and equipment.

At first mention, trade names may be given parenthetically after generic names, including the name and location (city, state, country) of the manufacturer. For

equipment, provide model numbers (if available) and the manufacturer's suggested price if the study has cost implications. Example: "Pleural pressure was measured using 2 balloon-tipped catheter systems connected to 2 differential pressure transducers (143PC03D; Micro Switch, Honeywell, Freeport, IL)."

Ventilator Modes

The Journal endorses adoption of standard terminology to describe ventilator modes. The **preferred nomenclature** and **a glossary of terms** is available.

ANEXO B

Parecer de aprovação do comitê de ética em pesquisa

Universidade Estadual de Londrina
COMITÊ DE ÉTICA EM PESQUISA

COMITÊ DE ÉTICA EM PESQUISA ENVOLVENDO SERES HUMANOS
Universidade Estadual de Londrina/ Hospital Universitário Regional Norte do Paraná
Registro CONEP 268

Parecer PF Nº 206/09 **CAAE Nº 0154.0.268.000-09** **FOLHA DE ROSTO Nº 276559**	Londrina, 23 de outubro de 2009.

PESQUISADOR: **FABIO DE OLIVEIRA PITTA**

Prezado(a) Senhor(a)

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

"FORÇA MUSCULAR RESPIRATÓRIA EM PACIENTES HOSPITALIZADOS POR EXACERBAÇÃO AGUDA DA DOENÇA PULMONAR OBSTRUTIVA CRÔNICA (DPOC)"

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

Situação do Projeto: **APROVADO**

Atenciosamente,

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