UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS PNEUMOLÓGICAS

Tese de Doutorado

Impacto da função pulmonar sobre a qualidade do sono avaliada por polissonografia em pacientes com DPOC

Renata Diniz Marques

Porto Alegre, 2019

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AHI - ***apnea/hypopnea index***

AOS - apneia obstrutiva do sono

BMI – ***body mass index***

CI - capacidade inspiratória

CNS - central nervous system

COPD - ***chronic obstructive pulmonary disease***

CO_2 - dióxido de carbono

CPT - capacidade pulmonar total

CVF- capacidade vital forçada

DL_{CO} – capacidade de difusão pulmonar para o monóxido de carbono (***lung diffusion capacity for carbon monoxide***)

DPOC - doença pulmonar obstrutiva crônica

EMG - ***electromyography***

FEV_1 - ***forced expiratory volume in one-second***

FRC - ***functional residual capacity***

FVC - ***forced vital capacity***

GERD - ***gastroesophageal reflux disease***

IAH - índice de apneia e hipopneia

IC - ***inspiratory capacity***

ICS - ***inhaled corticosteroid***

IMC - índice de massa corpórea

LABA - ***long-acting β_2-agonists***

LAMA= ***long-acting muscarinic antagonist***

OSA - ***obstructive sleep apnea***

$PaCO_2$ - pressão arterial do dióxido de carbono

PaO_2 - pressão arterial de oxigênio

%REM - ***proportion of REM stage over total sleep time***

PSG – polissonografia (***polysomnography***)

PSQI - ***Pittsburgh Sleep Quality Index***

RDI - ***respiratory disturbance index***

REM – ***rapid-eye-movement***

RV - ***residual volume***

SABA - ***short-acting β_2-agonist***

SAMA - ***short-acting muscarinic antagonists***

SD - ***standard deviation***

SNC - Sistema Nervoso Central

SOH - síndrome de obesidade e hipoventilação

SpO_2 - oximetria de pulso (***pulse oximetry***)

TLC – ***Total lung capacity***

T90 - ***percent time of overnight sleep oxygen saturation by pulse oximetry< 90%***

VA - volume alveolar

VAS - via aérea superior

VEF_1 - volume expiratório forçado no primeiro segundo

VRE - volume de reserva expiratório

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INTRODUÇÃO: Os distúrbios do sono são comuns e subdiagnosticados na população em geral, sendo muito frequentes em indivíduos com doenças respiratórias. As alterações fisiopatológicas típicas da doença pulmonar obstrutiva crônica (DPOC) podem exacerbar os efeitos do sono sobre a ventilação.

OBJETIVOS: Investigar a relação entre variáveis de função pulmonar e da polissonografia (PSG) de noite inteira com medidas objetivas de qualidade do sono em indivíduos portadores de DPOC com indicação clínica de realização de PSG.

MÉTODOS: Estudo transversal. Todos os pacientes com mais de 40 anos de idade que realizaram espirometria, mensuração de volumes pulmonares por pletismografia de corpo inteiro, teste de difusão pulmonar para o monóxido de carbono (DL_{CO}) e PSG em um hospital universitário no período de 2008-2016 foram avaliados para inclusão. Os participantes foram considerados como tendo DPOC se VEF_1/CVF após broncodilatador for <0,70. Critérios de exclusão incluíram outras condições clínicas que pudessem comprometer a qualidade do sono ou outras doenças respiratórias, ausência de história tabágica, capacidade pulmonar total <80% do previsto, curto período de sono durante a PSG (eficiência do sono<20%) e/ou ter apresentado episódios de apneia central>5/hora. A amostra mínima calculada foi 134 indivíduos com DPOC para detectar associação significativa em modelos estatísticos de regressão linear múltipla entre variáveis dependentes de qualidade do sono (eficiência do sono e percentagem de sono REM/tempo total de sono (%REM)) e 5 fatores independentes (considerando variáveis funcionais,

polissonográficas, comorbidades e medicações que mostraram associação significativa com qualidade do sono em regressão univariada). Indivíduos sem DPOC foram incluídos para contrastar a qualidade do sono em relação a pacientes com DPOC e a associação de variáveis de função pulmonar com qualidade do sono.Comorbidades e medicações com potencial de afetar o sistema nervoso central foram controladas em modelos de regressão linear multivariados.

RESULTADOS: Participantes com DPOC (n=181) tiveram menor %REM e índices de oxigenação noturna comparado com os controles (n=153) ($p<0.05$). Maior limitação ao fluxo aéreo (↓FEV_1/FVC; β=25.366; p=0.025) e idade (β=-0.530; $p<0.001$) foram associadas com pior eficiência do sono (R=0.379; $p<0.001$) enquanto DL_{CO} foi diretamente relacionada com %REM (β=0.097; R=0.254; p=0.001) em pacientes com DPOC nos modelos multivariados incluindo variáveis de função pulmonar e polissonográficas, mesmo ajustados para comorbidades e medicações. Nenhum parâmetro de função pulmonar permaneceu associado com qualidade do sono nas análises de regressão linear múltiplas em indivíduos controles.

CONCLUSÃO: Pacientes com DPOC têm pior qualidade de sono e oxigenação noturna quando comparados a controles sem DPOC. Um índice tradicional de limitação ao fluxo aéreo (FEV_1/FVC) foi a única variável além da idade independentemente associada com eficiência do sono na DPOC enquanto DL_{CO} persiste como único preditor fisiológico de %REM, mesmo após controlar para comorbidades e uso de medicações crônicas.

Palavras-chave: Doença pulmonar obstrutiva crônica, testes de função respiratória, sono, apnéia obstrutiva do sono, comorbidades.

ABSTRACT

The typical functional impairment of chronic obstructive pulmonary disease (COPD) can potentiate the physiological effects of sleep on breathing. Our objective was to investigate the relationship between resting lung function and polysomnographic variables against objectively measured sleep quality contrasting subjects with and without COPD in a real-life scenario. Cross-sectional study. All consecutive subjects (> 40 years-old) referred for spirometry, whole body plethysmography and overnight (PSG) at a single-center university hospital were reviewed. They were analyzed according to the presence (FEV_1/FVC post-bronchodilator <0.70) or not (controls) of COPD. The potential modulating effects of comorbidities and medication was adjusted.

Participants had worse sleep quality compared to historical controls. Patients with COPD (n=181) showed an even greater reduction in the proportion of REM stage over total sleep time (%REM) and nocturnal oxygenation than controls (n=153) ($p<0.05$). Higher airflow limitation (↓FEV_1/FVC ratio; $\beta=25.366$; $p=0.025$)and age ($\beta=-0.530$; $p<0.001$) were independently associated with lower sleep efficiency ($R=0.379$;$p<0.001$) while lung diffusion capacity for carbon monoxide (DL_{CO}) was directly related to %REM ($\beta=0.097$;$R=0.254$; $p=0.001$) in COPD, even after controlling for comorbidities and medication. No lung functional parameter remained in the multivariate models to predict sleep quality in controls.

In conclusion, the presence of COPD was associated with worse sleep quality and nocturnal deoxygenation compared to controls. Airflow limitation was independently related to sleep efficiency whereas DL_{CO} persisted as the unique predictor of %REM in COPD, even after controlling for confounders.

Keywords: Chronic Obstructive Pulmonary Disease; Respiratory Function Tests; Sleep; Obstructive Sleep Apnea; Comorbidity.

1. INTRODUÇÃO

A doença pulmonar obstrutiva crônica (DPOC) pode potencializar os efeitos fisiológicos do sono na respiração, exacerbando alterações no controle respiratório, resistências das vias aéreas e na contratilidade muscular (1). Dessa forma, pacientes com DPOC frequentemente queixam-se de qualidade do sono ruim (2), que costuma ser classificada como a terceira queixa mais importante após dispneia e fadiga (3). A etiologia para uma significativa sobreposição entre distúrbios do sono e a DPOC não é clara, provavelmente havendo uma interação bidirecional entre qualidade do sono e gravidade da DPOC com desfechos clínicos (4). Considerando a observada associação entre qualidade do sono reduzida com quantidade de sintomas diurnos (5, 6) e desfechos clínicos (7), que são correlacionados com a gravidade da alteração funcional pulmonar (8), acreditamos que a magnitude da disfunção respiratória possa de forma independente impactar a qualidade de sono nesses pacientes.

2. REFERENCIAL TEÓRICO

2.1 Definição da DPOC e relevância clínica

A DPOC é um problema de saúde global caracterizado por limitação persistente ao fluxo aéreo, geralmente progressiva, e associada com uma resposta inflamatória crônica anormal das vias aéreas secundária à inalação de partículas e gases nocivos. A presença de um volume expiratório forçado no primeiro segundo (VEF_1)/capacidade vital forçada (CVF) após broncodilatador menor que 0,70 demonstra a presença de limitação ao fluxo aéreo persistente que no contexto clínico adequado confirma o diagnóstico de DPOC (9).

O tabagismo é o fator de risco mais comumente associado à DPOC. Embora seja o fator de risco mais bem estudado, existem evidências epidemiológicas consistentes de que não tabagistas também desenvolvem limitação crônica ao fluxo aéreo (10, 11).

Exacerbações e comorbidades contribuem para a gravidade da doença (9). As comorbidades, além de serem comuns, também influenciam no prognóstico e qualidade de vida do paciente além de estarem associadas com desfechos clínicos desfavoráveis.

A prevalência da DPOC e sua morbidade variam entre os países. Apesar da complexidade, subdiagnóstico e dificuldade de reconhecimento da doença (12), dados do Projeto de Investigação da Doença Pulmonar Obstrutiva na América Latina (Projeto Platino) encontraram taxas de DPOC variando de 7.8% (95% CI 5.9–9.7) no México a 19·7% (17.2–22.2) em Montevideo. No Brasil, dados obtidos em São Paulo, a prevalência geral de DPOC foi de 15.8% (13.5–18.1) (13).

2.2 Sono na DPOC

Os efeitos do sono na respiração são bem reconhecidos, e geralmente, não apresentam repercussão clínica negativa em indivíduos saudáveis. Estas alterações incluem leve grau de hipoventilação com consequente hipercapnia e redução da responsividade a estímulos respiratórios. Entretanto, estas consequências fisiológicas do sono podem ter repercussão profunda em pacientes com DPOC. De fato, qualidade do sono reduzida tem sido indicada em vários estudos usando polissonografia (PSG): redução do tempo total de

sono, fragmentação do sono com aumento do índice de microdespertares e alterações na arquitetura do sono (14-17). Essas alterações na qualidade do sono, por sua vez, demonstraram estar relacionadas à pior qualidade de vida na DPOC (5, 18).

Alterações no controle ventilatório e na musculatura respiratória durante o sono tornam-se ainda mais importantes nos pacientes com oxigenação basal reduzida e mecânica respiratória mais alterada (19). Estes fatores podem contribuir para o agravamento de hipoventilação durante o sono com consequente hipercapnia e dessaturação da oxihemoglobina noturna (20). Estudo fisiológico que avaliou pacientes com DPOC através de eletromiografia diafragmática evidenciou uma redução na ventilação em torno de 30% durante o sono NREM e 44% durante o sono REM, demonstrando que o *drive* neural ventilatório está reduzido durante o sono (21). Assim, a redução do *drive* neural para a musculatura respiratória, em especial para o diafragma, é mais acentuada durante o sono REM, resultando em níveis mais acentuados de dessaturação e comumente causando hipoxemia durante este estágio do sono em pacientes com saturação limítrofe em vigília. Somado a tudo isso, alterações na mecânica respiratória ↑ capacidade residual funcional (CRF) e desequilíbrio ventilação/perfusão,poderiam agravar o quadro de hipoventilação (22) .

A hipoxemia e hipercapnia induzidas pelo sono nesses pacientes pode resultar em arritmias cardíacas e hipertensão pulmonar (23, 24), bem como morte noturna em momentos de exacerbação da doença (25). Dessaturação noturna, entretanto, não foi associada com prejuízo na qualidade de vida, qualidade do sono ou sintomas diurnos em estudo prévio (26). É coerente

supor que a taxa de despertares noturnos pode estar aumentado na DPOC em reposta à hipoxemia. Entretanto, oxigenoterapia não apresentou efeitos na frequência de despertares associados a quedas transitórias da oximetria de pulso (SpO_2) (15). Isso sugere que os despertares não são devido à hipoxemia *per se* mas associados a outros fenômenos, talvez hipercapnia e acidemia. A maior frequência de despertares parece afetar as características do sono na medida em que estão associadas com menor percentagem de estágios do sono 3 (N3) e *rapid-eye movement* (REM) (27). Por fim, a apneia obstrutiva do sono (AOS) é considerada uma entidade a parte das alterações do sono anteriormente mencionadas (28). A coexistência de SAOS e DPOC é comum, principalmente devido à alta prevalência de cada doença isoladamente. Apesar da prevalência de AOS ser previamente descrita como semelhante em pacientes com e sem obstrução da via aérea (29), a pressão arterial de oxigênio (PaO_2) foi menor e a pressão arterial do dióxido de carbono ($PaCO_2$) maior em grupo com sobreposição (DPOC+AOS) bem como a SpO_2 noturna média foi significantemente menor, embora não tenha sido encontrado diferença no índice de apneia e hipopneia (IAH) (30). Resposta atenuada do centro respiratório, medida pela técnica de respiração repetida do dióxido de carbono (CO_2), poderia explicar alguns destes achados (31). Seria concebível ainda que nesses pacientes com alteração na mecânica e musculatura respiratória, a capacidade ventilatória poderia ficar ainda mais comprometida devido à queda do estímulo ventilatório, particularmente durante a fase REM do sono (32). Estratégias terapêuticas capazes de melhorar a mecânica respiratória, como cirurgia redutora de volume pulmonar (33) e terapia broncodilatadora (especialmente com reforço da dose de medicação de longa

duração noturna) (34), demonstraram melhora na qualidade do sono mensurada objetivamente com PSG noturna. Por sua vez, o uso da ventilação não invasiva mostrou melhora da dispneia, tolerância ao exercício, qualidade de vida e possível aumento na sobrevida de pacientes com DPOC e hipercapnia (35). Entretanto, o efeito da ventilação não invasiva na qualidade do sono desses pacientes ainda necessita ser melhor estudada, tendo sido avaliada em poucos estudos e apenas com mensuração subjetiva(36-38).

2.3 Comorbidades na DPOC com potencial influenciar a qualidade do sono

A maioria dos estudos de diferentes regiões têm sido consistentes em demonstrar que a presença de comorbidades é um problema ubíquo na DPOC, estimando-se que mais de 80% dos pacientes tenham pelo menos uma condição crônica associada e que a quantidade média de comorbidades por indivíduo varia de 1,2 - 4,0 (39). A análise de uma grande coorte de pacientes com DPOC mostrou elevada prevalência de hipertensão arterial sistêmica (60,4%), artrite (54,6%), dislipidemia (47,6%), obesidade (40,3%), depressão (20,6%), diabetes (16,3%), câncer (16,5%), doença coronariana (12,7%) e insuficiência cardíaca (12%) (40). Essas comorbidades contribuem para piorar desfechos centrados no paciente, aumentando custos de utilização de saúde e mortalidade (9). Embora o principal fator de risco da DPOC também seja um reconhecido fator de risco para muitas outras doenças não pulmonares, cada vez mais se acredita que os pacientes com DPOC apresentam uma alta carga de comorbidades que podem ocorrer independentemente do tabagismo (39). É sabido, ainda, que a eficiência do sono reduz 1,6% e o tempo total de sono 6

min, bem como o índice de despertares aumenta 0,8, a cada década de envelhecimento após os 40 anos de idade (41). Duas grandes revisões sistemáticas com metanálise confirmaram esse papel do envelhecimento na qualidade do sono, demonstrando uma pequena redução na eficiência do sono a cada 10 anos, sem alterações significativas nos percentuais do estágio 3 do sono NREM e sono REM com o envelhecimento (42, 43). Dessa forma, distúrbios no sono, particularmente entre os idosos, frequentemente são associados com doenças coexistentes (44). Embora a qualidade do sono diminua com o envelhecimento, essa piora não atinge a má qualidade usualmente encontrada em pacientes com distúrbios do sono (45).

Análises multivariadas em estudos comunitários com milhares de pacientes mostram que as queixas de sono são associadas com número aumentado de sintomas respiratórios, incapacidade física, uso de medicações sem prescrição e sedativos, sintomas depressivos e pobre autopercepção de saúde (44, 46). Diversas dessas condições são frequentemente encontradas na DPOC associadas com diferentes desfechos clínicos desfavoráveis (**Quadro 1**) (39) e que poderiam interferir na investigação de fatores associados com má qualidade do sono (44, 46).

Dentre essas diversas comorbidades, a depressão maior usualmente cursa com sono alterado. Embora a maioria desses pacientes queixe-se de insônia, alguns pacientes podem relatar hipersonia (47, 48). Estudos com PSG têm demostrado distúrbios na arquitetura e continuidade do sono desses pacientes. Disfunção na continuidade do sono refere-se à dificuldade para iniciar ou manter o sono. As alterações na arquitetura do sono compreendem redução no sono de ondas lentas, despertares intermitentes, latência de sono

Quadro 1. Prevalência das principais comorbidades na DPOC e desfechos clínicos associados.

Comorbidade	Prevalência	Associação com desfechos
Doença alérgica	18–42%	Tosse, expectoração, sibilância Utilização de serviços de saúde
Anemia	7–43,9%	Mortalidade Hospitalização, duração da hospitalização e readmissão Dispneia
Cardiovascular	29–70% (geral) 4,7–60% (insuficiência cardíaca) 7,1–31,3% (doença coronariana)	Mortalidade Qualidade de vida Dispneia, capacidade de exercício Hospitalização Custo e utilização de serviços de saúde
Disfunção cognitiva	2–20%	Qualidade de vida Duração de hospitalização
Depressão	16,5–42%	Mortalidade Dispneia, capacidade de exercício Qualidade de vida Risco de hospitalização Risco de exacerbação Atividades da vida diária
Diabetes	10,1–23%	Mortalidade Hospitalização Capacidade de exercício
Refluxo gastroesofágico	37–78%	Qualidade de vida Sintomas de bronquite crônica Custo com serviços de saúde Risco de exacerbação
Câncer de pulmão	3,8–8,0%	Mortalidade Recorrência de malignidade
Síndrome metabólica	21–57%	Outras comorbidades Hospitalização Risco de exacerbação
Obesidade	29,1–43%	Qualidade de vida Dispneia, capacidade de exercício Utilização de serviços de saúde
Osteoporose	21–66%	
Apneia do sono	22,3–51,4%	Mortalidade Risco de exacerbação Custo com serviços de saúde Cardiovasculares

Adaptado da referência (39).

prolongada e latência para o sono REM encurtado (47). Ainda, a qualidade do sono subjetiva avaliada pela *Pittsburgh Sleep Quality Index* (PSQI) mostrou-se reduzida em comparação a indivíduos com outras desordens do sono (49).

2.4 Influência da obesidade sobre a função pulmonar e qualidade do sono

Pacientes com obesidade mórbida (índice de massa corpórea (IMC)> 40 Kg/m^2) apresentam frequência respiratória aumentada e redução variável no volume de ar corrente em comparação a indivíduos eutróficos, resultando, em aumento da ventilação-minuto. Esses indivíduos também apresentam variação na complacência pulmonar em relação indireta com o índice de deposição de gordura cintura-quadril. Disso resulta que a obesidade usualmente acarreta um aumento no trabalho ventilatório *per se* (50). O trabalho respiratório aumenta ainda mais no decúbito em virtude da projeção cefálica do diafragma devido à adiposidade central. A demanda do diafragma se torna ainda maior durante o sono REM com a atonia da musculatura acessória respiratória.

Dentre as medidas de volumes pulmonares, a que melhor se correlaciona negativamente com o IMC é o volume de reserva expiratório (VRE). Os fluxos geralmente são normais ou levemente reduzidos, proporcionalmente à redução dos volumes, de tal forma que a relação VEF_1/CVF é usualmente preservada. A eficiência da troca gasosa, estimada pela mensuração da capacidade de difusão pulmonar do monóxido de carbono (D_LCO), é normal e pode estar elevada quando corrigida em relação ao volume alveolar (D_LCO/VA)(50). Não obstante, a obesidade pode acarretar hipoxemia de três formas: 1) através da síndrome de obesidade e hipoventilação (SOH); 2)

associada à doença cardíaca congestiva, e; 3) através de redução mecânica da capacidade residual funcional levando ao fechamento precoce das pequenas vias aéreas durante a expiração (desequilíbrio ventilação/perfusão).

Além das alterações respiratórias funcionais, a obesidade também potencialmente influencia negativamente a qualidade do sono. A AOS é a consequência mais prevalente da obesidade. Já tem sido demonstrado que existe uma correlação forte entre as duas entidades e quanto maior o IMC maior a gravidade da AOS. Estudos randomizados também têm demonstrado que a perda de peso está associada com redução na severidade da AOS. Os mecanismos implicados no desenvolvimento de AOS em pacientes obesos são múltiplos, incluindo a compressão direta da via aérea superior (VAS) pela gordura parafaríngea, aumento da colapsibilidade da VAS pela redução do volume pulmonar e consequente diminuição da tração traqueal e, por fim, através do depósito intramuscular de gordura em regiões como a língua (51).

2.5 Medicações que atuam no sistema nervoso central

Uma significativa proporção das queixas durante o sono são relacionadas com condições psiquiátrias tais como ansiedade e depressão. Os tratamentos medicamentosos dessas condições podem exercer benefícios diretos e indiretos, de tal modo que o uso de antidepressivos para tratar sintomas de insônia *per se* (sem evidência de doença psiquiátrica concomitante) tem se tornado cada vez mais frequente (52). Por outro lado, essas medicações também podem ter efeitos negativos no sono. Praticamente todas as drogas antidepressivas alteram a arquitetura e a qualidade do sono (52, 53).

Diversos sistemas neurotransmissores têm sido implicados na manutenção da vigília, no início e manutenção do sono e na transição de um estágio para outro do sono (especialmente na transição do sono NREM-REM). Considerando que todos os antidepressivos atualmente usados exercem efeitos em um ou mais desses sistemas neurotransmissores, ou relacionado com seu suposto mecanismo de ação ou efeito adverso indesejado, não é surpreendente que as medicações psiquiátricas tenham demonstrado causar efeitos proeminentes e diversos no sono e na vigília. Considerações sobre os perfis farmacológicos das diferentes classes de drogas fornecem as bases para entender seus respectivos efeitos na fisiologia do sono. Um sumário das evidências a respeito de cada classe de drogas é fornecido no **Quadro 2**.

Falando especificamente a respeito dos inibidores seletivos da recaptação da serotonina, esta classe de medicações sabidamente está associada com insônia (54). Entretanto, doses maiores podem causar sonolência diurna (55). Achados polissonográficos têm demonstrado redução na eficiência do sono e no tempo total de sono, aumento no número de despertares e latência do sono em indivíduos saudáveis e naqueles com depressão quando em uso dos inibidores seletivos da recaptação da serotonina (56).

A fluoxetina, representante mais usado da classe, é um potente supressor do sono REM com efeitos de prolongar a latência do sono REM, reduzir a sua duração e densidade (57) com efeitos prolongados devido ao seu longo tempo de meia-vida (58). Aumento no número de despertares e nas mudanças de estágio do sono também foi descrito em pacientes com depressão (59). Uso de fluoxetina em voluntários saudáveis tem demonstrado

redução na eficiência do sono, aumento da latência do sono e latência do sono REM (60).

Quadro 2. Medicações psiquiátricas e efeitos na fisiologia do sono.

Droga	Mecanismos de ação	Efeitos
Antidepressivos		
Tricíclios sedativos: amitriptilina, doxepina	Antagonista H_1, inibição da recaptação da serotonina, inibição da recaptação da noradrenalina, antagonista α_1, antagonista M_1	↓ latência do sono ↑ tempo total de sono ↑ sono de onda lenta Supressão do sono REM
Tricíclicos ativadores: desipramina, protryptilina	Inibição da recaptação da noradrenalina	↑ latência do sono ↑ despertares ↓ tempo total de sono
Trazodona	Inibição dos receptores da serotonia (5-HT_{1A}, 5-HT_{1C} and 5-HT_2), antagonista H_1, antagonista α_1, inibição fraca da recaptação da serotonina	↑ tempo total de sono ↑ sono de onda lenta Supressão do sono REM
Fluoxetina (inibidores seletivos da recaptação da serotonina)	Inibição da recaptação da serotonina	↑ latência do sono ↓continuidade do sono ↑ despertares e despertares após tempo de início do sono (WASO) ↓ tempo total de sono Supressão do sono REM
Bupropiona	Inibição da recaptação da dopamina e noradrenalina	↑ eficiência do sono ↓ latência do REM ↑ tempo de sono REM
Mirtazapina	Antagonista 5-HT_2 e 5-HT_3, antagonista H_1	↓ latência do sono ↑ tempo total de sono
Antipsicóticos		
Olanzapina	Antagonista 5-HT_2antagonista H_1	↑ continuidade do sono ↑ sono de onda lenta
Quetiapina	Antagonista 5-HT_2antagonista H_1	↑ continuidade do sono ↑ sono de onda lenta ↑ sono estágio 2

Droga	Mecanismos de ação	Efeitos
		↑ qualidade subjetiva do sono
Anticonvulsivantes		
Gabapentina	Modulador do canal de cálcio α2delta	300&600mg: ↓ despertares, ↑ eficiência do sono, ↓ sono estágio 1; 600mg: ↑ sono de ondas lentas, ↓ despertares e ↓ sono REM
Pregabalina	Modulador do canal de cálcio α2delta	↑ sono de onda lenta ↑ sono estágio 4 ↓ latência do sono ↓ duração do sono REM ↓ despertares
Tiagabina	Inibidor transmissores GABA (Ácido gama-aminobutírico)	↑ sono de onda lenta ↓ WASO

Adaptado da referência (52).

Diante de todas as evidências acima expostas, percebe-se que a sobreposição de comorbidades, em especial os distúrbios psiquiátricos e seus tratamentos medicamentosos, bem como a magnitude do IMC podem influenciar tanto a severidade das alterações respiratórias funcionais quanto a qualidade do sono. Nesse contexto, um estudo que objetiva primariamente investigar a relação entre a fisiologia pulmonar e a qualidade do sono na DPOC deve necessariamente ajustar as análises levando em consideração esses potenciais confundidores.

3. JUSTIFICATIVA

Como previamente mencionado, sabe-se de longa data que a qualidade do sono é adversamente afetada na DPOC (61). Estudos recentes com medidas subjetivas (questionários específicos para avaliar a qualidade do sono) (6) e objetivas (PSG de noite inteira) (17) corroboraram a presença de qualidade de sono ruim nesses pacientes.

Embora a qualidade do sono tenha demonstrado direta associação com variáveis de limitação ao fluxo expiratório (16) e hiperinsuflação (62) /aprisionamento aéreo (16) em alguns poucos e pequenos estudos incluindo principalmente pacientes com DPOC grave, outros estudos não demonstraram haver relação entre gravidade da alteração do VEF_1 e pior qualidade de sono (7, 29, 63). Ainda, enquanto alguns estudos demonstraram melhora da qualidade do sono e oxigenação noturna em pacientes com DPOC grave após cirurgia redutora de volume pulmonar (33) e terapia broncodilatadora (27, 34), muitos pacientes com DPOC continuam a relatar pobre qualidade de sono subjetiva e fadiga diurna apesar de estarem recebendo terapia direcionada para melhora funcional (62). Pobre qualidade do sono pode contribuir com a DPOC para piora de desfechos clínicos através de diferentes mecanismos (7).

Um melhor entendimento dos fatores contribuintes para a má qualidade do sono na DPOC nos remete a expandir nosso conhecimento sobre a doença e conceber estratégias terapêuticas cada vez mais efetivas.

4. OBJETIVOS

4.1. Objetivo geral

Investigar a relação entre função pulmonar em repouso e qualidade do sono avaliada por polissonografia de noite inteira em pacientes com DPOC, ajustada pela presença de potenciais fatores confundidores.

4.2. Objetivos específicos

4.2.1. Comparar a qualidade do sono avaliada por PSG de noite inteira entre indivíduos com e sem DPOC;

Em indivíduos com DPOC:

4.2.2. Analisar a relação entre a alteração funcional pulmonar (avaliada por parâmetros de limitação ao fluxo aéreo, hiperinsuflação pulmonar e alteração difusional pulmonar) com parâmetros objetivos de qualidade do sono (eficiência do sono e proporção de sono REM/tempo total de sono), ajustada pela idade, parâmetros polissonográficos (IAH, oxigenação noturna) e IMC;

4.2.3. Ajustar as possíveis associações acima encontradas conforme a presença de comorbidades e uso crônico de medicações com potencial de afetar o sistema nervoso central (SNC).

Em participantes sem DPOC:

4.2.4. Investigar a relação entre parâmetros de função pulmonar e de qualidade do sono, controlada pela idade, variáveis antropométricas e derivadas da PSG.

5. HIPÓTESES

Esta tese trabalha com a hipótese alternativa de que indivíduos com DPOC têm pior qualidade de sono quando comparados a controles sem DPOC, independentemente de fatores extrínsecos (medicações) e intrínsecos (comorbidades) que potencialmente possam interferir nessa relação.

6. IMPLICAÇÕES DO ESTUDO

Uma vez confirmada a hipótese principal, os resultados do estudo poderão indicar qual(is) o(s) parâmetro(s) funcional(ais) em repouso da DPOC esta(ão) independentemente associado(s) com medidas objetivas de qualidade do sono. Além disso, pode servir de base para demonstrar que a magnitude da disfunção pulmonar característica da DPOC representaria associação independente com a qualidade do sono. Pacientes com acentuada alteração desses marcadores poderiam ser ativamente questionados e investigados quanto à presença de distúrbio do sono. Por fim, estratégias que levem a melhora desse(s) parâmetro(s) poderia(m) contribuir para melhora dos desfechos clínicos relacionados à qualidade do sono.

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8. ARTIGO CIENTÍFICO

Avaliação da Relação entre Função Pulmonar e Parâmetros de PolissonografiaNoturna com Baixa Qualidade do Sono em Pacientes com DPOC

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Revisiting the Relationship between Lung Function and Sleep Parameters with Poor Sleep Quality in COPD Patients

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Running Title: Pulmonary Function and Sleep Quality in COPD

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RESUMO

Os distúrbios do sono são comuns e subdiagnosticados na população em geral, sendo muito frequentes em indivíduos com doenças respiratórias.

Nosso objetivo foi investigar a relação entre variáveis de função pulmonar e da polissonografia (PSG) de noite inteira com medidas objetivas de qualidade do sono em indivíduos portadores de DPOC com indicação clínica de realização de PSG.

Estudo transversal. Todos os pacientes com mais de 40 anos de idade que realizaram espirometria, mensuração de volumes pulmonares por pletismografia, teste de difusão pulmonar para o monóxido de carbono (DL_{CO}) e PSG em um hospital universitário no período de 2008-2016 foram avaliados para inclusão. Os participantes foram considerados como tendo DPOC se VEF_1/CVF após broncodilatador for <0,70. Comorbidades e medicações foram controladas em modelos de regressão linear multivariados.

Maior limitação ao fluxo aéreo ($\downarrow FEV_1/FVC$; β=25.366; p=0.025) e idade (β=-0.530; p<0.001) foram associadas com pior eficiência do sono (R=0.379; p<0.001) enquanto DL_{CO} foi diretamente relacionada com %REM (β=0.097; R=0.254; p=0.001) em pacientes com DPOC nos modelos multivariados incluindo variáveis de função pulmonar e polissonográficas, mesmo ajustados para comorbidades e medicações. Nenhum parâmetro de função pulmonar permaneceu associado com qualidade do sono nas análises de regressão linear múltiplas em indivíduos controles.

Pacientes com DPOC têm pior qualidade de sono e oxigenação noturna quando comparados a controles sem DPOC. Um índice tradicional de limitação

ao fluxo aéreo (FEV_1/FVC) foi independentemente associada com eficiência do sono na DPOC enquanto DL_{CO} persiste como único preditor fisiológico de %REM, mesmo após controlar para comorbidades e uso de medicações crônicas.

Palavras-chave: Doença pulmonar obstrutiva crônica, testes de função respiratória, sono, apneia obstrutiva do sono, comorbidades.

Abstract

The typical functional impairment of chronic obstructive pulmonary disease (COPD) can potentiate the physiological effects of sleep on breathing. Our objective was to investigate the relationship between resting lung function and polysomnographic variables versus objectively measured sleep quality contrasting subjects with and without COPD in a real-life scenario.

Cross-sectional study. All consecutive subjects (> 40 years-old) referred for spirometry, whole body plethysmography and overnight polysomnography (PSG) at a single-center university hospital were reviewed. They were analyzed according to the presence (FEV_1/FVC post-bronchodilator <0.70) or not (controls) of COPD. The potential modulating effects of comorbidities and medication was also adjusted.

Participants had worse sleep quality compared to historical controls. Patients with COPD (n=181) showed an even greater reduction in the proportion of REM stage over total sleep time (%REM) and nocturnal oxygenation than controls (n=153) ($p<0.05$). Higher airflow limitation (↓FEV_1/FVC ratio; $\beta=25.366$; $p=0.025$)and age ($\beta=-0.530$; $p<0.001$) were independently associated with lower sleep efficiency ($R=0.379$;$p<0.001$) while lung diffusion capacity for carbon monoxide (DL_{CO}) was directly related to %REM ($\beta=0.097$; $R=0.254$; $p=0.001$) in COPD, even after controlling for comorbidities and medication. No lung functional parameter remained in the multivariate models to predict sleep quality in controls.

In conclusion, the presence of COPD was associated with worse sleep quality and nocturnal deoxygenation compared to controls. Airflow limitation

was independently related to sleep efficiency whereas DL_{CO} persisted as the unique predictor of %REM in COPD, even after controlling for confounders.

Word count= 239

Keywords: Chronic Obstructive Pulmonary Disease; Respiratory Function Tests; Sleep; Obstructive Sleep Apnea; Comorbidity.

Introduction

Chronic obstructive pulmonary disease (COPD) can potentiate the deleterious (physiological) effects of sleep on breathing, by exacerbating changes in central respiratory control, airways resistance, and muscular contractility (1). Accordingly, patients with COPD frequently report impaired sleep (2-5), which was previously ranked as the third more troublesome disturbance after dyspnea and fatigue (4), and the morning was reported as the worst time of the day (6). This reported poor sleep quality has been confirmed by overnight polysomnography showing low sleep efficiency (7, 8) and disturbed sleep architecture (15±14 arousal/hour of sleep) (3). Moreover, COPD patients often report difficulty to initiate and maintain sleep (3, 5, 9, 10), as well as excessive daytime sleepiness (7, 9).

The observed worst sleep quality is correlated to the daytime symptom burden(11), which, in turn, is related to pulmonary function(12). We, therefore, hypothesized that respiratory function would negatively impact sleep quality in these patients. In fact, sleep quality was previously described as associated with measurements of respiratory mechanics and function but not with measurements of daytime or nocturnal oxygenation (8). Interestingly, improved sleep quality and nocturnal oxygenation were observed in patients with severe emphysema after lung volume reduction surgery (13). In addition, increased lung hyperinflation was associated with worse sleep efficiency in patients with overlap syndrome (COPD plus obstructive sleep apnea; OSA) independently of apnea/hypopnea index (AHI) and nocturnal hypoxemia(14), although mean arterial blood saturation was lower and time spent in desaturation was longer in overlap syndrome compared to isolated OSA (15).

Detecting an independent association among respiratory functional parameters and sleep quality may have important clinical implications since there are several available options to improve lung function in COPD (16) with a potentially positive impact on sleep quality, night and early morning symptoms. Owing to the lack of previous studies systematically investigating the relationship of lung function and sleep quality in COPD, adjusted for comorbidities and medication potentially interfering in this relationship (17-19), we intend to address this issue in a large sample of patients with clinical request to perform pulmonary function and sleep quality evaluation. Beyond contrast sleep quality compared to subjects without COPD in this real-life scenario, we mainly aimed to investigate the association of resting functional parameters with sleep quality considering the potential modulating influence of comorbidities and concomitant use of psychotropic medication in patients with COPD. Results from this study may help to identify key physiological markers of COPD related to poor sleep quality and stage the scene for prospective studies evaluating the improvement of such physiological abnormalities on sleep-related outcomes.

Methods

Study Design and Population

Cross-sectional study with retrospective data collection. Using specific pre-specified searchable criteria, all consecutive patients aged 40 years or older referred for spirometry with post-bronchodilator assessment, whole body plethysmography and overnight diagnostic polysomnography (PSG) at Queen's Affiliated Teaching Hospital's Clinical Laboratories **(**Kingston General Hospital and Hotel Dieu Hospital) were reviewed (Figure 1). In the case of sequential

measurements, the last assessment was recorded for analysis.PSG reports were reviewed and the following data recorded for analyses: age, sex, bodymass index (BMI), smoking status (current, ever or never smoker), medications prescribed for COPD and other disorders, and comorbidities.

COPD participants were included based on forced expiratory volume in one second (FEV_1)/ forced vital capacity (FVC) post-bronchodilator (salbutamol 400µ) <0.70 andpositive history of smoking and clinical diagnosis of COPD. Control participants were defined based on FEV_1/FVC post-bronchodilator ≥0.70 and the absence of COPD as reported comorbidity.

Exclusion criteria for both groups included relevant conditions that could affect sleep quality (neuromuscular disease, previous stroke with neurologic sequela, cancer) or other respiratory disease (bronchiectasis, interstitial lung disease, total lung capacity (TLC)<80% of predicted), subjects that did not sleep during PSG (sleep efficiency< 20%) or presented a central apnea score>5/h.

Subjects were unnamed and identified by unique identification numbers. The study protocol (#6020749) was approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (FWA #00004184; IRB #00001173).

Procedures

Spirometry, body plethysmography, and measurements of the diffusing capacity of the lung for carbon monoxide (DL_{CO}) were performed with automated testing equipment (V6200 Autobox; SensorMedics) in the Pulmonary Function Laboratory at Hotel Dieu Hospital according to latest international standards (American Thoracic Society/European Respiratory Society).

Reference values were used according to previously published equations (20-22).

Standard PSG measurements were collected in the Sleep Laboratory at Kingston General Hospital. Continuous recordings using Sandman Elite SD 32+ digital sleep system (Embla; Mallinckrodt/Nellcor Puritan Bennett (Melville) Ltd, Canada) included four electroencephalography channels (C4A1, C3A2, O2A1, O1A2), two electro-oculogram channels (ROCA1, LOCA2), submental electromyography (EMG), bilateral anterior tibialis EMG, electrocardiography, chest and abdominal respiratory belts, nasal pressure via nasal cannula, finger pulse oximetry, and a vibration snore sensor. Sleep was staged and obstructive apneas and hypopneas defined using established criteria (23). Apneas were defined as central if there was a lack of respiratory effort during the period of absent airflow. Daytime sleepiness was assessed using the Epworth Sleepiness Scale (24). A score equal to or higher than 10 points was considered as excessive daytime sleepiness. OSA syndrome was diagnosed if AHI was ≥5/h and accompanied by excessive daytime sleepiness or ≥15 events/h even in the absence of symptoms (25).

Statistical analysis

Values were reported as mean ± standard deviation (SD) unless otherwise specified (IBM® SPPS® Statistics version 24). Non-paired t or a $\chi 2$ test for differences in proportions were used to compare subjects with versus without COPD. Univariate linear regression analyses evaluated the association of age, anthropometric (BMI), resting lung functional and sleep-related variables (AHI and parameters of nocturnal desaturation) with each component of sleep

quality: sleep efficiency (total sleep time/total recording time) and proportion of rapid-eye-movement (REM) stage sleep over total sleep time (%REM) in COPD. Variables with p≤0.10 in univariate models were considered as independent predictors in multivariate analyses (stepwise method). In the case of variables representing the same phenomenon, those with the higher standardized coefficient were used. The significance level for retention a variable in the multivariate model was p≤0.05. Lastly, the models were adjusted for comorbidities (17) and psychotropic drugs (19) that can affect sleep quality. Abnormally reduced values of sleep efficiency and %REM were defined as <85% (26, 27) and <20%(28), respectively.

The minimum required sample size was estimated as 134 COPD subjects to detect association among continuous dependent variables (parameters of sleep quality) and 5 independent predictors considering a p level <0.05, a desired statistical power of 0.8 and an expected small to medium effect size (*f*2) of 0.1 (29).

Results

A total of 181 patients with COPD fulfilled the study criteria and were analysed. The distribution according to the spirometric classification of COPD severity (16) was 40.3% (FEV_1≥80% predicted), 43.1% (50 ≤FEV_1<80% predicted), 13.8% (30 ≤FEV_1<50% predicted), and 2.8% (FEV_1<30% predicted). No difference in gender and anthropometric variables, despite a small but significantly lower age, were observed compared to controls (n=153). As expected, the COPD group presented lower spirometric parameters and DL_{CO}, and higher static lung volumes (Table 1). Both groups showed a reduction in the

indexes of sleep quality compared to historical controls (26-28). Although COPD group presented with worse mean values (Table 1), the proportion of subjects with reduced sleep efficiency (COPD=144 (79.5%) *vs* Control=113 (73.8%); p=0.23) and decreased %REM (COPD=137 (75.7%) *vs* Control=104 (67.9%); p=0.16) were not significantly different between groups. Similarly, based on the predefined diagnosis of OSA, the prevalence was not different between groups (COPD=116 (64.1%) *vs* Control=105 (68.6%); p=0.19). Conversely, parameters of oxygenation at baseline (awake) and during sleep were significantly lower in COPD (Table 1). The prevalence of comorbidities and the use of inhaled and psychotropic medications are described in Table 2 for the COPD group.

Age, AHI, FEV_1/FVC post-bronchodilator (BD), inspiratory capacity (IC) (expressed both as % of predicted and relative to TLC) and residual volume (RV)/TLC were the parameters related to sleep efficiency during univariate linear regression analyses in COPD patients (Figure 2). %REM, in turn, were significantly associated only with age, baseline (awake) oxygen saturation by pulse oximetry (SpO_2), percent time of overnight sleep oxygen saturation by SpO_2 less than 90% (T90) and DL_{CO} (% of predicted) (Figure 3). The results of all univariate linear regression analyzes to predict polysomnographic-derived parameters of sleep quality in the COPD group are presented in Table S1 (supplementary file).

Multivariate linear regression analyses, controlling for potential confounders identified in univariate analyses (those with p≤0.10 in Table S1), only retained age and FEV_1/FVC post-BD to predict sleep efficiency whereasonly DL_{CO}remained significantly associated with %REM in COPD

subjects (Table 3). Conversely, no lung function parameter was independently associated with sleep efficiency in controls. Age and AHI remained in the multivariate linear regression model to predict sleep efficiency in controls (sleep efficiency=106.891 -0.484*Age -0.277*AHI; R=0.481; p<0.001; other variables initially entered in the model (p≤0.1): SpO_2 nadir). %REM, in turn, was only predict in this group by age and BMI (%REM=37.193 -0.250*age -0190*BMI; R=0.389; p<0.001; other variables initially entered in the model (p≤0.1): baseline SpO_2, RV/TLC, IC/TLC, DL_{CO} (% of predicted)).

Finally, when adjusted for the presence of the most frequent comorbidities (prevalence>5%), COPD's medicine and psychotropic drugs (Table 2), the multivariate model to predict sleep efficiency in COPD patients remains unchanged. On the other hand, the concomitant use of anti-psychotics becomes to compose with $DL_{CO}$to predict %REM (%REM= 7.236 +0.090*DL_{CO} (% predicted) -6.768*(1=anti-psychotic); R=0.332; p<0.001; other variables initially entered (yes or no) in the model (p≤0.10): systemic hypertension, depression, diabetes, hypothyroidism, selective serotonin re-uptake inhibitors, benzodiazepines, other hypnotics, opioids).

Discussion

The present study contrasted subjects with versus without COPD that performed comprehensive resting lung function evaluation and overnight PSG by request from their assistant physicians. In this real practice scenario, we mainly investigated the independent relationship between PSG-derived parameters of sleep quality versus lung function and other polysomnographic parameters, adjusted for comorbidities and medication in COPD patients. Three

major findings were observed: 1) in the present environment of expected overall poor sleep quality (request of PSG from the assistant physician), the COPD group presented with worse %REM and nocturnal desaturation than controls; 2) higher airflow obstruction (↓ post-BD FEV_1/FVC ratio)and age was independently related to lower sleep efficiency in COPD, while no lung functional parameter was associated with this parameter of sleep quality in controls; 3) higher DL_{CO} was consistently associated with higher %REM in COPD patients. These relationships remained even after adjusting for comorbidities and medications that interfere on the central nervous system (CNS).

We do not have a full description of daytime symptoms and sleep-related complaints that prompted the polysomnogram in our studied subjects. Based on their “real life” origin, it is reasonable to expect the observed worse sleep quality compared to historical controls (30, 31). Although the clinical relevance of the current worse sleep quality observed in the COPD group compared to controls is questionable, the relationship of sleep quality with resting lung function parameters was independently observed only inCOPD. Increased work of breathing due to airflow limitation (resistive) and/or lung hyperinflation (elastic) plus alteration in gas exchange efficiency, pathophysiological findings of COPD (12), seem to represent a problematic background for the physiological consequences of sleep.

Objective assessment of sleep quality has been previously reported in smaller series including patients with more severe COPD (mean FEV_1 ranging from 28-57% of predicted). In general, nocturnal desaturation (3, 10, 32), indexes of lung hyperinflation (8, 14, 33) and DL_{CO} (33) demonstrated to be

associated with different parameters of sleep quality, although just one study involving 30 patients with overlap syndrome (COPD+OSA) used multivariate linear regression analysis to adjust for potential confounders including BMI, FEV_1, AHI, pulmonary inhaled medications and cardiac diseases (14). Likewise, we found that indexes of airflow obstruction (FEV_1/FVC), static lung hyperinflation (IC/TLC), gas trapping (RV/TLC) and gas exchange efficiency (DL_{CO}) were related to different components of sleep quality (Figures 2 and 3). Interestingly, while predictable variables played the major role in subjects without COPD (age, BMI, AHI), lung functional parameters (FEV_1/FVC for sleep efficiency and DL_{CO} for %REM) appeared as the main variables independently related to sleep quality in COPD (Table 3). This suggests that the physiological consequences of sleep (hypoventilation, hypotonia, increased airway resistance) and comorbidities (AHI, obesity) act on the top of worse airflow limitation and gas exchange efficiency, functioning as determinant contributors of poor sleep quality in COPD.

Sleep physiology is complex and several mechanisms may play a role to impair sleep quality. This seems to constitute the first real-life study including a satisfactory number of subjects with clinical request to investigate sleep performance adequately powered to control for potential confounders. Previous subjective evaluation of sleep quality suggested that part of the sleep complaint in the elderly population is likely secondary to general health burden (34, 35), which was specifically demonstrated in patients with chronic airflow obstruction (5, 36), and respiratory symptoms (37). COPD may contribute to poor sleep quality, therefore, also by respiratory symptoms, such as nocturnal cough and dyspnea, and/or associated comorbidities. In accordance, Chang CH *et*

al(38)demonstrated that the burden of COPD evaluated through the COPD Assessment Test was an independent factor for poor sleep quality,particularly, the presence of phlegm. Unfortunately, we did not have access to the associated symptoms and the frequency of exacerbation in our COPD patients. Additionally, anxiety and depression, highly prevalent (17, 39) and previously found associated with sleep disturbance in COPD(40), can act as major confounders. Poor sleep quality might result in cognitive dysfunction, depression, anxiety, poor survival and poor quality of life (41). Conversely, psychiatric disorders may affect sleep quality (42, 43). Notwithstanding, even after adjusting for this potential confounders, lung function still demonstrates to be related to sleep quality in COPD. The presence of anxiety was not reliably investigated in the present study and may represent an additional factor to influence the sleep quality not studied in our sample.

Interestingly, DL_{CO} remained as an independent index related to %REM even after adjusting for other pulmonary function and polysomnographic variables, comorbidities, and CNS medications. This may reflect the extension of the alveolar-capillary destruction even in the initial stages of COPD (44) with its repercussion on CNS oxygenation and overall burden of the disease. The absence of an independent association between systemic oxygenation indexes with %REM may be explained by the complex cerebrovascular regulation of CNS blood flow in the context of COPD, sleep, and hypercapnia (45). This hypothesis could be further investigated with a concomitant assessment of SpO_2, CNS oxygenation by near-infrared spectroscopy and transcutaneous CO_2 pressure in these patients during sleep.

Surprisingly, despite the high proportion of OSA (~66%), AHI was only associated with poor sleep efficiency in subjects without COPD. In this context, the (functional and symptomatic) burden of more severe COPD may has played a major role leading to disturbed sleep quality in the COPD group regardless the magnitude of OSA and its consequences (hypopneas, apneas, arousals, and desaturation).

The magnitude of the sleep quality impairment observed in the present study (Table 1) resembles those of preceding study also evaluating predominantly mild to moderate COPD compared to controls (sleep efficiency: 75±13 *vs* 82±11%; %REM: 14±7 *vs* 17±7%(7), respectively). Despite the statistical significance, the clinical relevance of these differences in sleep quality is uncertain, especially considering that our COPD patients were slightly older than controls (Table 1). Nevertheless, considering the relationship with important patient-centered outcomes (11, 41, 46, 47), even small impairments in objective parameters of sleep quality during prolonged periods may become clinically relevant. Beyond poor subjective sleep perception (48, 49), sleep deprivation may lead to increased risk for physical (50, 51) and mental disorder (52, 53), reduced cognitive performance (50, 54) and even increased mortality (55). Chronic partial sleep deprivation also alters sleep architecture, with decreased time in non-REM stage 2 sleep and REM sleep, disturbing different aspects of waking cognitive performance (51). After continuous positive airway pressure treatment for OSA, a clinical model of sleep deprivation, patients reported an improved perception of sleep quality associated with increased %REM (56). The clinical relevance of this borderline worse sleep quality

observed in the present (Table 1) and previous study (7) remains to be determined.

The present investigation deserves some methodological considerations. The dwelling origin of our participants with “true” indication to investigate resting lung function and overnight sleep parameters demanded from their assistant physicians approximates our studied population to the scenario expected to be found in the real-life practice, enhancing our external validity. On the other hand, the probable higher-sleep-complaint burden of this population may have influenced the effects of the pathophysiological marks of COPD on sleep performance. In addition, the retrospective nature and obtainment of clinical data from test reports may have introduced bias inherent to this study design. Nevertheless, this seems to represent the highest series investigating the relationship of objectively measured sleep quality with pulmonary function and PSG-derived parameters adjusted for potential clinical confounders in COPD. Finally, the cross-sectional nature of the present work precludes to perform inference causality of the observed relationships.

Concluding, the COPD patients presented worse sleep quality and nocturnal deoxygenation compared to controls without COPD. The magnitude of airflow limitation was the unique independent parameter (beyond age) related to sleep efficiency in COPD. In addition, lung diffusion capacity for gas exchange, an important physiological marker of emphysema extension, was the unique independent predictor of %REM. These relationships persisted even after controlling for comorbidities and medication.

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Table 1. Baseline characteristics of studied subjects.

Variables	Controls (n=153)	COPD (n=181)
Male sex, nº (%)	70 (45.8)	98 (53.8)
Age, years	60.7 ± 10.6	63.5 ± 11.2*
Weight, Kg	91.8 ± 24.8	92.3 ± 24.7
Height, m	1.65 ± 0.09	1.66 ± 0.08
BMI, Kg/m^2	33.5 ± 8.6	33.4 ± 8.5
Resting Lung Function		
FEV_1		
pre SABA, L (% pred)	2.53 ± 0.79 (99.4 ± 15.4)	1.73 ± 0.64* (68.8 ± 20.3)*
Missing data	0	1
post SABA , L (% pred)	2.64 ± 0.83 (103.0 ± 16.1)	1.84 ± 0.65* (73.4 ± 20.2)*
FVC		
pre SABA , L (% pred)	3.36 ± 0.99 (93.9 ± 13.5)	2.99 ± 0.88* (84.2 ± 18.0)*
Missing data	0	1
post SABA , L (% pred)	3.37 ± 1.04 (94.7 ± 14.3)	3.16 ± 0.89 (89.2 ± 17.9)*
FEV_1/ FVC		
pre SABA , %	0.76 ± 0.05	0.57 ± 0.11*
Missing data	0	1
post SABA , %	0.78 ± 0.05	0.58 ± 0.11*
TLC, L (% pred)	5.40 ± 1.25 (100.9 ± 19.4)	5.88 ± 1.27* (109.4 ± 16.3)*
IC, L (% pred)	2.76 ± 0.81 (116.7 ± 22)	2.38 ± 0.74* (99.2 ± 23.7)*
IC/TLC	0.51 ± 0.07	0.40 ± 0.09*
FRC, L (% pred)	2.64 ± 0.68 (102.1 ± 26.3)	3.51 ± 1.07* (132.4± 42.9)*
RV, L (% pred)	1.92 ± 0.52 (98.5 ± 23.2)	2.71 ± 0.97* (132.9 ± 43.3)*
RV/TLC	0.36 ± 0.08	0.46 ± 0.10*
DL_{CO}, ml/min/mmHg (%pred)	20.6 ± 6.9 (86.6 ± 23.5)	17.0 ± 5.9* (74.2 ± 21.7)*
Missing data	0	3
Polysomnography		
Epworth Scale	8.7 ± 4.5	7.7 ± 4.6 p=0.06
Missing data	1	1
Sleep Efficiency, %	71.9 ± 14.7	69.0 ± 17.2 p=0.10
REM, % of total sleep	15.7 ± 8.6	13.5 ± 8.3*
Apnea-Hypopnea Index, nº/h	20.2 ± 16.0	21.9 ± 28.2
Central Apnea, total nº	2.6 ± 6.9	2.9 ± 6.1
SpO_2 baseline,%	94.9 ± 2.1	93.6 ± 2.7*
Missing data	1	0
SpO_2 nadir,%	83.7 ± 7.2	82.2 ± 6.9 p=0.05
Missing data	1	0
SpO_2 below 90%,% total sleep	6.7 ± 15.6	23.3 ± 32.4*
Missing data	2	1
Arousals, nº/h	6.0 ± 4.6	7.0 ± 6.6 p=0.11

Data are mean±SD or number (%).
Definition of abbreviations: BMI= body mass index; FEV_1= forced expiratory volume in one second; SABA= short-acting β_2-agonist (salbutamol); % pred= % of predicted; FVC= forced vital capacity; TLC= total lung capacity; IC= inspiratory capacity; FRC= functional residual capacity; RV= residual volume; DLCO= lung diffusing capacity for carbon monoxide; REM= rapid eye movement sleep stage; RDI= respiratory disturbance index; SpO_2= oxyhemoglobin saturation by pulse oximetry; T90= percent of sleep time with hemoglobin saturation by pulse oximetry<90%.
* P<0.05

Table 2. Prevalence of comorbidities and medication in COPD participants.

Variables	Values
Comorbidities	
Systemic arterial hypertension	85 (46.9)
GERD	52 (28.7)
Depression	47 (25.9)
Coronary artery disease	25 (13.8)
Cancer	22 (12.1)
Diabetes mellitus	19 (10.5)
Chronic pain	19 (10.5)
Osteoarthritis	13 (7.2)
Heart failure	11 (6.1)
Hypothyroidism	10 (5.5)
Atrial fibrillation	8 (4.4)
Chronic kidney disease	7 (3.9)
Inhaled Medication	
SABA	98 (53.9)
ICS	97 (53.4)
LABA	97 (53.4)
LAMA	72 (39.6)
SAMA	24 (13.2)
Psychotropic	
Serotonin reuptake inhibitors	38 (20.9)
Benzodiazepines	23 (12.7)
Antipsychotics (olanzapine, clozapine, quetiapine, risperidone)	13 (7.2)
Other hypnotics (trazodone, zolpidem)	12 (6.6)
Opioids	10 (5.5)
Tricyclic antidepressants	8 (4.4)

Data are number (%).
Definition of abbreviations: GERD= gastroesophageal reflux disease; LABA= long-acting β_2-agonists; ICS= inhaled corticosteroid; SABA= short-acting β_2-agonist; LAMA= long-acting muscarinic antagonist; SAMA= short-acting muscarinic antagonists.

Table 3. Multiple linear regression analyses to predict polysomnographic parameters of sleep quality.

Variables	β (95% confidence interval)	Standard Error	R	p
Sleep Efficiency (N=181)†			0.379	<0.001
Age (years)	-0.530 (-0.720-0.298)	0.107		<0.001
FEV_1/FVC post BD	25.366 (3.250-47.4821)	11.207		0.025
% REM (N=177)‡			0.254	0.001
DL_{CO} (% predicted)	0.097 (0.042-0.152)	0.028		0.001

†Variables initially considered in the model (p<0.10 from univariate linear regression analyses): AHI, RV/TLC; IC/TLC.

‡Variables initially considered in the model (p<0.10 from univariate linear regression analyses): Age, BMI AHI, SpO_2 baseline, SpO_2 nadir, T90, RV/TLC.

Abbreviations: see Table 1.

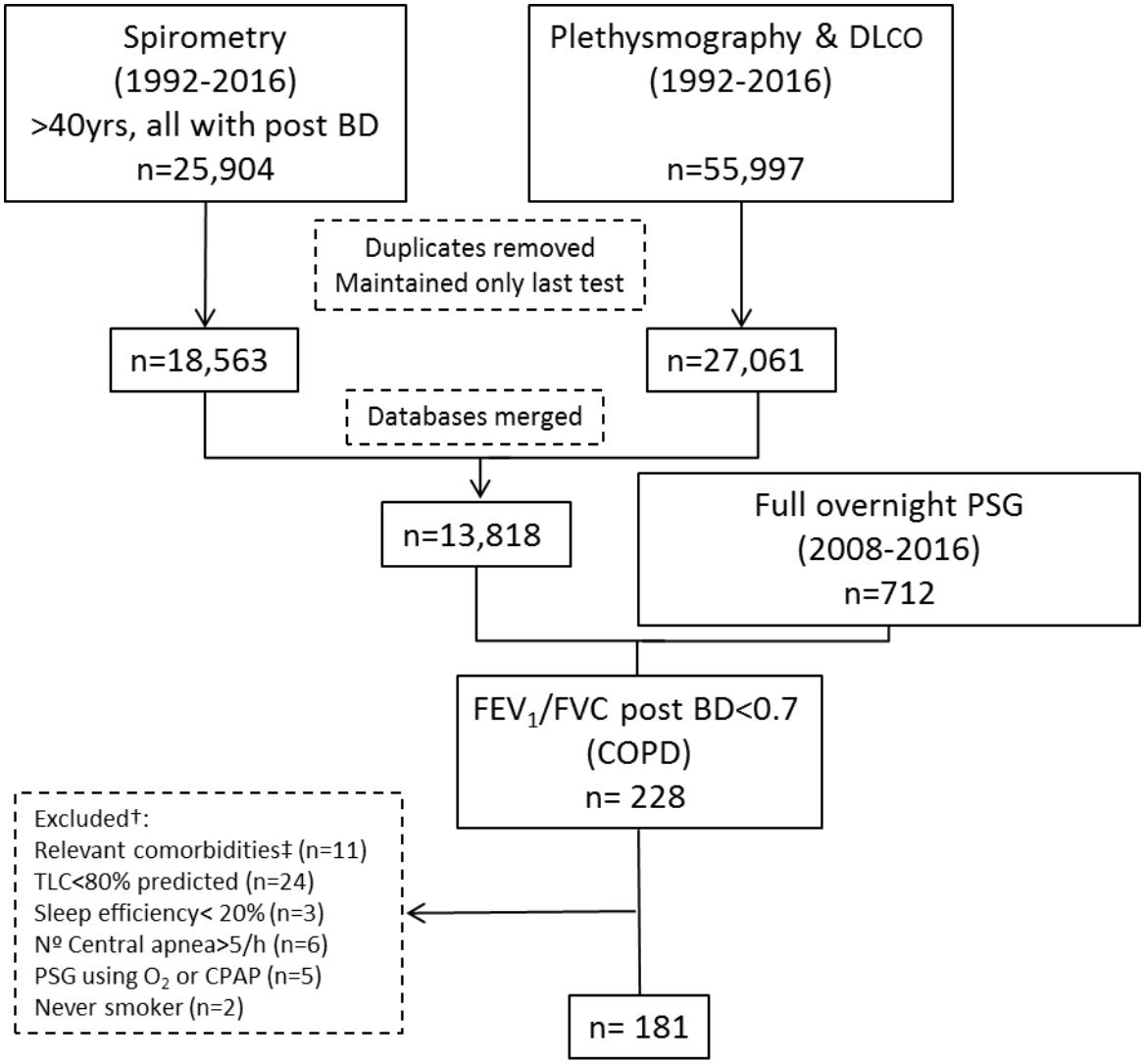

Figure 1. Flowchart of included participants.

Abbreviations: BD= bronchodilator; DL_{CO}= lung diffusing capacity for carbon monoxide; TLC= total lung capacity; PSG= polysomnography; CPAP= continuous positive airway pressure; FEV_1= forced expiratory volume in one second; FVC= forced vital capacity; COPD=chronic obstructive pulmonary disease.

† Each participant may present more than one reason.

‡ Neuromuscular disease, cystic fibrosis, pulmonary fibrosis.

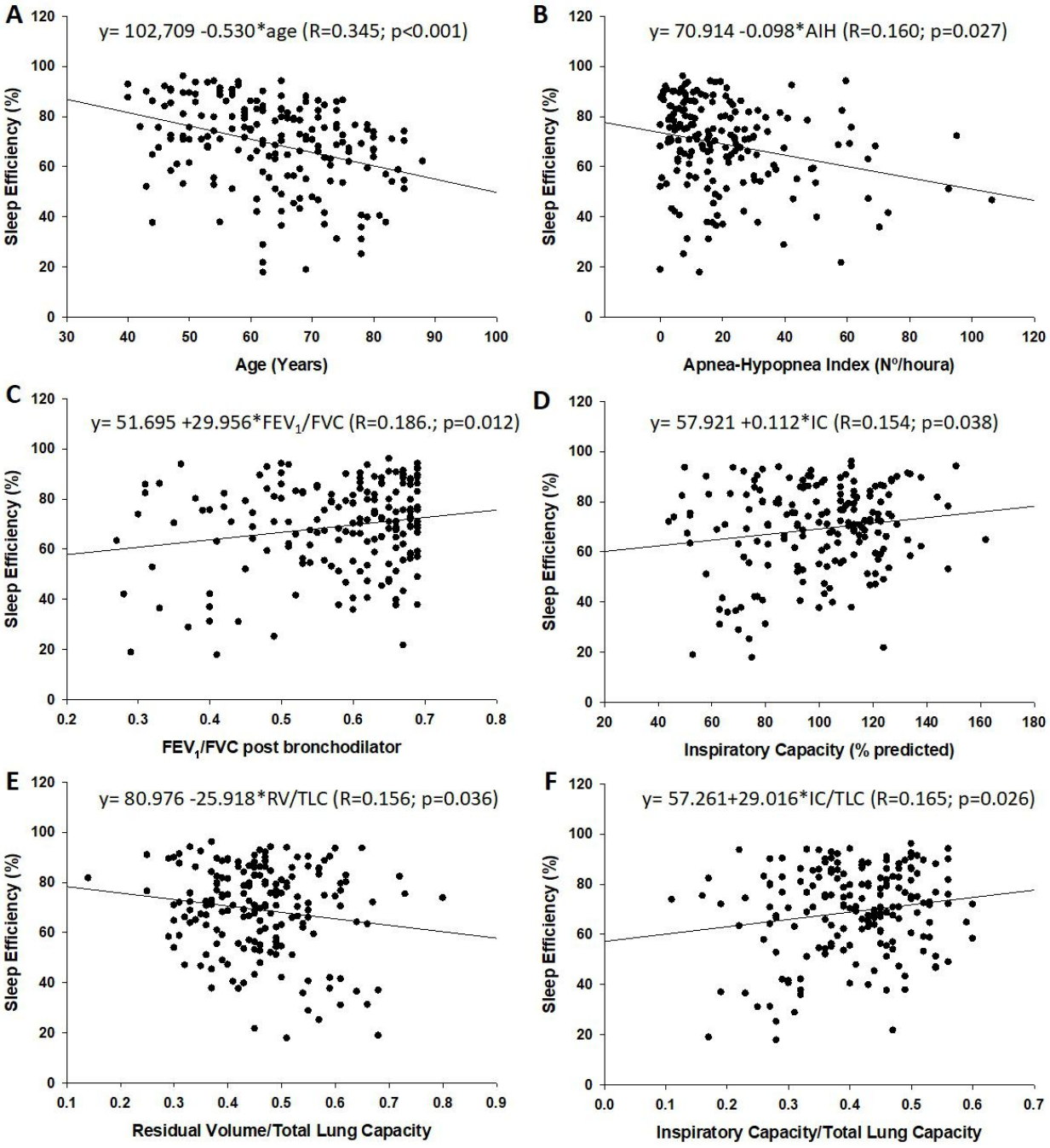

Figure 2. Statistical significant ($p<0.05$) univariate linear regression analyses predicting sleep efficiency in COPD patients.

Abbreviations: AHI= apnea-hypopnea index; FEV_1=forced expired volume in 1s; FVC= forced vital capacity; IC= inspiratory capacity; TLC= total lung capacity; RV= residual volume.

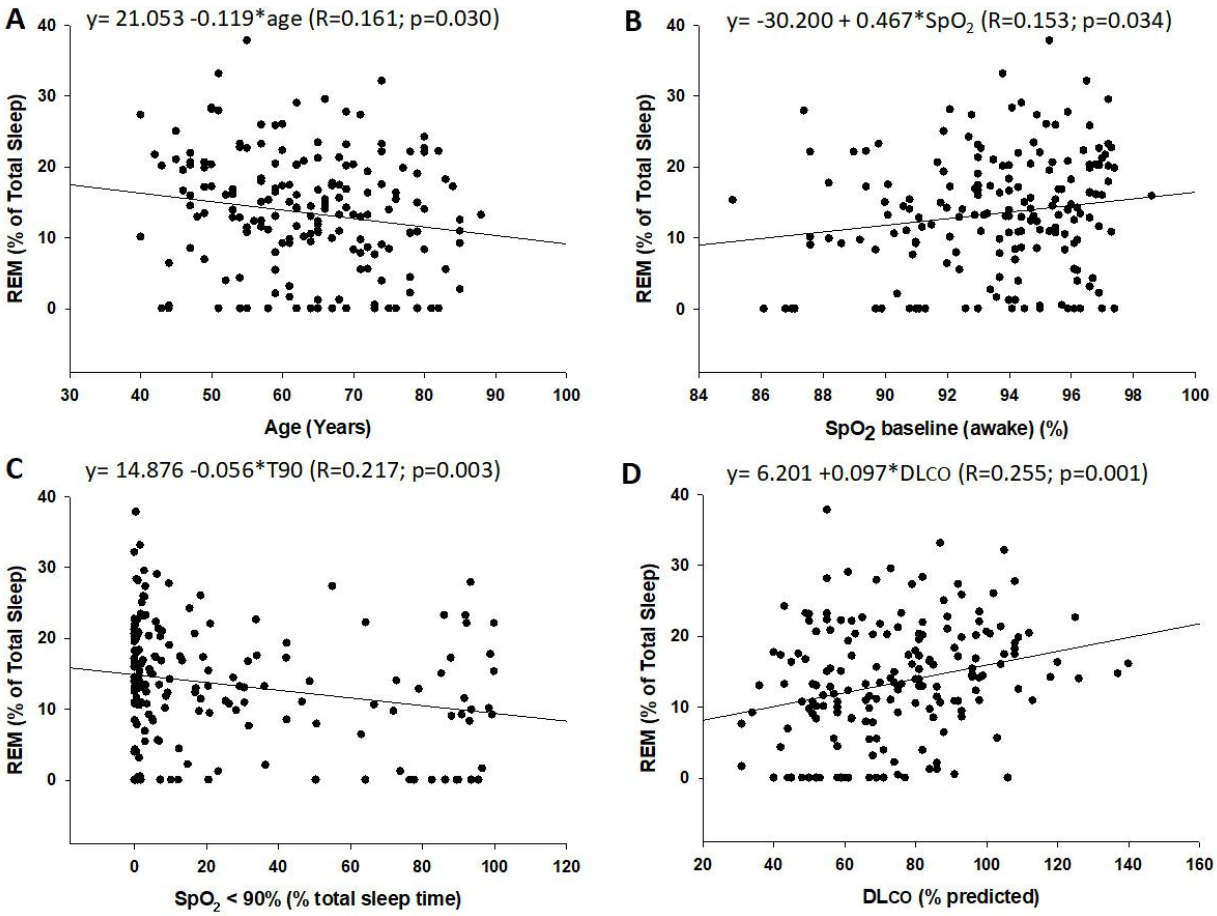

Figure 3. Statistical significant ($p<0.05$) univariate linear regression analyses predicting the proportion of rapid eye movement (REM) sleep stage in relation to total sleep time in COPD patients.

Abbreviations: SpO_2= oxyhemoglobin saturation by pulse oximetry; T90= percent of sleep time with hemoglobin saturation by pulse oximetry<90%; DLCO= lung diffusion capacity for carbon monoxide.

Supplementary file

Table S1. Univariate linear regression analyzes to predict polysomnographic-derived parameters of sleep quality in COPD patients.

Variables	Sleep efficiency (%)		REM (% of total sleep)	
	Unstandardized Coefficient (95% CI)	p	Unstandardized Coefficient (95%CI)	p
Age (Years)	-0.530 (-0.741 to -0.318)	<0.001	-0.119 (-0.227 to -0.012)	0.030
BMI (Kg/m²)	-0.118 (-0.414 to 0.179)	0.434	-0.129 (-0.271 to 0.013)	0.074
Polysomnography				
Apnea-Hypopnea Index (n°/h)	-0.098 (-0.185 to -0.011)	0.027	-0.036 (-0.078 to 0.006)	0.096
SpO_2 baseline (%)	0.042 (-0.854 to 0.938)	0.927	0.467 (0.036 to 0.897)	0.034
SpO_2 nadir (%)	-0.088 (-0.445 to 0.270)	0.629	0.148 (-0.024 to 0.321)	0.091
SpO_2 below 90% (% total sleep)	-0.020 (-0.097 to 0.056)	0.600	-0.056 (-0.092 to -0.020)	0.003
Lung function test				
FEV_1 post SABA (% predicted)	0.082 (-0.043 to 0.208)	0.196	0.040 (-0.020 to 0.101)	0.191
FEV_1/ FVC post SABA	29.956 (6.625 to 53.287)	0.012	6.355 (-5.046 to 17.756)	0.273

TLC (% predicted)	-0.059 (-0.217 to 0.099)	0.464	0.040 (-0.036 to 0.116	0.301
IC (%predicted)	0.112 (0.006 to 0.219)	0.038	0.037 (-0.015 to 0.088)	0.163
FRC (% predicted)	-0.62 (-0.121 to -0.003)	0.040	-0.021 (-0.050 to 0.007)	0.141
RV (% predicted)	-0.013 (-0.073 to 0.047)	0.663	0.002 (-0.027 to 0.031)	0.884
RV/TLC	-25.918 (-50.080 to -1.756)	0.036	-9.845 (-21.540 to 1.849)	0.098
IC/TLC	29.016 (4.443 to 54.590)	0.026	7.897 (-4.539 to 20.333)	0.212
DL_{CO} (% predicted)	0.083 (-0.035 to 0.201)	0.166	0.097 (-0.042 to 0.152)	0.001

Abbreviations: REM= rapid eye movements sleep stage; SpO_2= oxyhemoglobin saturation by pulse oximetry; BMI= body mass index; FEV_1= forced expiratory volume in one second; SABA= short-acting β_2-agonist (salbutamol); FVC= forced vital capacity; TLC= total lung capacity; IC= inspiratory capacity; FRC= functional residual capacity; RV= residual volume; DL_{CO}= lung diffusing capacity for carbon monoxide.
Definition of colors: red ($p<0.05$) and blue ($p<0.10$) variables initially considered to be entered in multivariate linear regression analyses.

9. CONCLUSÕES

9.1Pacientes com DPOC apresentam pior qualidade do sono comparados a indivíduos controles sem DPOC. Especificamente, apresentaram tendência a pior eficiência do sono e significativa menor duração de sono REM em relação ao tempo total de sono, além de pior oxigenaçãobasal e durante o sono.

9.2A relação VEF_1/CVF (um parâmetro de limitação ao fluxo aéreo) foi a única entre as variáveis funcionais pulmonares e derivadas da polissonografia independentemente associada com a eficiência do sono em pacientes com DPOC; mesmo ajustada para a presença de comorbidades e medicações crônicas associadas.

9.3 A capacidade de difusão pulmonar para o monóxido de carbono apresentou associação com duração do sono REM expresso relativo ao tempo total de sono em pacientes com DPOC, independentemente de outras variáveis (funcionais, polissonográficas, comorbidades e medicações) consideradas no modelo estatístico.

9.4 Não há relação independente entre parâmetros de função pulmonar e qualidade do sono (derivadas da PSG) em indivíduos sem DPOC.

10. CONSIDERAÇÕES FINAIS

Uma significativa parcela de pacientes com DPOC refere qualidade do sono prejudicada, a qual está associada com importantes desfechos clínicos centrados no paciente tais como qualidade de vida (1, 2) e sobrevida (3).

Embora os indivíduos com DPOC apresentem diversos mecanismos potenciais, os principais fatores implicados nessa perturbação já descrita há muitos anos (4) ainda permanecem não totalmente esclarecidos. As alterações fisiopatológicas pulmonares típicas da DPOC causam sintomas diurnos e intolerância ao exercício (5), representando potencial mecanismo para também influenciar negativamente o desempenho do sono (6).

Apesar de um crescente número de estudos investigando a qualidade do sono na DPOC, ainda são restritos em número e tamanho amostral (variando de 25-30 pacientes) os estudos que investigaram simultaneamente a qualidade do sono de forma objetiva com PSG de noite inteira e associaram com parâmetros de função pulmonar (7, 8), sendo que um deles somente estudou indivíduos com sobreposição de OSA (7). Esse último estudo ajustou as análises multivariadas considerando diversos outros fatores tais como antropométrico (IMC), fisiopatológicos (IAH, nadir da SpO_2 noturna), medicações inalatórias e comorbidades cardiovasculares, restando somente significativamente associado com a eficiência do sono um índice de hiperinsuflação pulmonar (capacidade inspiratória/capacidade pulmonar total). Esse estudo, entretanto, tem amostra pequena (n=30) para permitir o ajuste confiável do modelo linear multivariado considerando a quantidade de variáveis independentes incluídas. Ainda, os dois estudos não descrevem se havia

queixa de sintomas noturnos nem a origem dos pacientes incluídos, o que diminui sua validade externa.

Como recentemente descrito em um cenário de vida real, é frequente a queixa de sintomas noturnos pelos pacientes com DPOC (78%), havendo boa concordância entre a queixa do paciente e a percepção pelos seus médicos assistentes (9). Pelo que nos consta, o presente estudo parece ser o primeiro investigando a relação das alterações funcionais da DPOC com parâmetros objetivos de qualidade sono em pacientes com real indicação clínica para realização de PSG, ajustando-se para potenciais confundidores, e incluindo uma amostra adequada para avaliar, pelo menos, 5 variáveis independentes. Nesse contexto, alguns dos principais achados já previamente descritos foram novamente reproduzidos: 1) parâmetros de limitação ao fluxo aéreo e hiperinsuflação pulmonar foram os parâmetros funcionais inicialmente associados com eficiência do sono; e 2) parâmetros de oxigenação noturna não tiveram associação com essa variável objetiva de avaliação da qualidade do sono (10, 11).

Em relação àporcentagem de sono REM/tempo do total de sono, destaca-se a associação com parâmetros de oxigenação noturna e eficiência da troca gasosa (DLCO). Quando ajustado por potenciais confundidores, permanecem nos modelos estatísticos multivariados um índice de limitação ao fluxo aéreo (FEV_1/FVC) independentemente associado com eficiência do sono e DLCO com proporção de sono REM. Não obstante, os coeficientes de determinação dos modelos finais calculados foram de pequena magnitude (Tabela 3 na página 40), explicando em torno de 15 a 6% dos respectivos desfechos.

Diante disso, embora a função pulmonar despontou como importante fator associado com a qualidade do sono em pacientes com DPOC, fica evidente que outros fatores não estudados no presente estudo exercem efeito significativo nessas relações. Nesse contexto, a carga de sintomas respiratórios e a possível interferência no sono (12) não foi abordada no presente estudo.

Considerando que reabilitação pulmonar em nada melhora a função pulmonar de pacientes com DPOC, presumimos que o efeito benéfico dessa estratégia sobre a qualidade de sono seja secundário à melhora dos sintomas respiratórios e comorbidades associadas (13, 14).

Outra limitação do estudo é o fato de ser um estudo retrospectivo, possibilitando que existam viéses inerentes a esta metodologia de estudo. Além disso, como foi uma amostra transversal, não é possível inferir relação de causalidade entre as relações observadas.

Num ambiente de multi-comorbidades e polifarmácia, a avaliação integral do paciente almejando maximizar a terapia para alívio da disfunção pulmonar e manejar ativa e efetivamente as comorbidades e a carga de sintomas parece representar a abordagem terapêutica ideal para tratar a prejudicada qualidade do sono em pacientes com DPOC. Futuros estudos clínicos ou observacionais investigando intervenções que melhoram os sintomas, função pulmonar e/ou comorbidades na DPOC podem fornecer informações úteis ao correlacionar esses efeitos com melhora na qualidade do sono.

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12. ANEXOS

12.1 Carta de aprovação do Comitê de Ética

(Queen's University/Kingston/Ontario/Canada)

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD (HSREB)

HSREB Initial Ethics Clearance

April 13, 2017

Dr. Jose Neder Serafini
Department of Medicine
Respiratory Division
Richardson House
102 Stuart Street

ROMEO/TRAQ: #6020749
Department Code: DMED-2027-17
Study Title: Bridging the gap between pulmonary function and sleep assessments in patients with COPD: Does lung hyperinflation predict poor sleep quality?

Review Type: Delegated
Date Ethics Clearance Issued: April 13, 2017
Ethics Clearance Expiry Date: April 13, 2018

Dear Dr. Neder Serafini,

The Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB) has reviewed the application and granted ethics clearance for the documents listed below. Ethics clearance is granted until the expiration date noted above.

- Protocol – 7-April-2017
- Data Collection Sheet – 7-April-2017

Amendments: No deviations from, or changes to the protocol should be initiated without prior written clearance of an appropriate amendment from the HSREB, except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

Renewals: Prior to the expiration of your ethics clearance you will be reminded to submit your renewal report through ROMEO. Any lapses in ethical clearance will be documented on the renewal form.

Completion/Termination: The HSREB must be notified of the completion or termination of this study through the completion of a renewal report in ROMEO.

Reporting of Serious Adverse Events: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information.

Reporting of Complaints: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. Note: All documents supplied to participants must have the contact information for the Research Ethics Board. Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete.

Yours sincerely,

Albert L. Clark.

Chair, Health Sciences Research Ethics Board

The HSREB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations, Canadian General Standards Board, and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP). Federalwide Assurance Number: FWA#:00004184, IRB#:00001173

HSREB members involved in the research project do not participate in the review, discussion or decision.

12.1. Escala de Sonolência de Epworth

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading _____	___
Watching TV _____	___
Sitting, inactive in a public place (e.g. a theatre or a meeting) _____	___
As a passenger in a car for an hour without a break _____	___
Lying down to rest in the afternoon when circumstances permit _____	___
Sitting and talking to someone _____	___
Sitting quietly after a lunch without alcohol _____	___
In a car, while stopped for a few minutes in the traffic _____	

THANK YOU FOR YOUR COOPERATION

13. APÊNDICES

13.1. Trabalho apresentado no Congresso internacional da *European Respiratory Society*

04.01 - Clinical Respiratory Physiology, Exercise and Functional Imaging

5204 Lung hyperinflation is related to poor sleep quality in patients with COPD

Lung function testing, Sleep studies, Apnoea / Hypopnea

R. Diniz Marques[1*], D. Berton[1], N. Domnik[2], H. Driver[2], A. Elbehairy[2], S. Fagondes[3], M. Fitzpatrick[2], D. O'Donnell[2], J. Neder[2]

[1]Universidade Federal do Rio Grande do Sul/Queen's University - Porto Alegre (Brazil), [2]Queen's University - Kingston (Canada), [3]Universidade Federal do Rio Grande do Sul - Porto Alegre (Brazil)

Background: Poor sleep quality as assessed by overnight polysomnography (i.e., low sleep efficiency and/or low % rapid-eye movement (REM) sleep) is frequently reported in COPD. More symptomatic patients tend to present with worst sleep quality (*Scharf et al. Int J Chron Obstruct Pulmon Dis. 2010;6:1–12*). Considering the close association between symptom burden and lung hyperinflation in COPD (*O'Donnell DE et al, Expert Rev Respir Med. 2016;10:823-34*), we hypothesized that hyperinflation would be negatively related to sleep quality in these patients. **Methods**: We retrospectively assessed 182 patients (FEV_1=69±20% predicted, GOLD stages I to IV) who performed spirometry, body plethysmography and overnight polysomnography. **Results**: Sleep efficiency (68±16%) and % REM (14±8%) were reduced compared to historical controls. In a multiple regression analysis, inspiratory capacity/total lung capacity (IC/TLC) ratio, apnea-hypopnea index (AHI) and sleep SpO_2 nadir - but not FEV_1 or body mass index - remained as independent predictors of poor sleep efficiency (p<0.01). IC/TLC (in addition to AHI and % of sleep time with SpO_2<90%) predicted % REM (p<0.01). In fact, subjects with worst sleep quality (i.e., low sleep efficiency (<85%) plus low % REM (<20%)) (n=122) showed lower IC/TLC but similar FEV_1 (% predicted)

than their counterparts with better sleep quality (0.40±0.09 *vs* 0.44±0.09; $p<0.05$). **Conclusion**: Lung hyperinflation is associated with poor sleep quality regardless the severity of airflow obstruction in patients with COPD. Decreasing overnight lung volumes might prove therapeutically useful to improve sleep quality in these patients.

13.2 Projeto de pesquisa aprovado no Comitê de Ética

BRIDGING THE GAP BETWEEN PULMONARY FUNCTION AND SLEEP ASSESSMENTS IN PATIENTS WITH COPD: DOES LUNG HYPERINFLATION PREDICT POOR SLEEP QUALITY?

1. BACKGROUND

Chronic obstructive pulmonary disease (COPD) can potentiate the physiological effects of sleep on breathing, exacerbating changes in central respiratory control, airways resistance, and muscular contractility.[1] In accordance, patients with COPD frequently report impaired sleep,[2,3,4,5] which was previously ranked as the third more troublesome disturbance after dyspnea and fatigue,[3] and morning was reported as the worst time of the day.[6] This reported poor sleep quality has been confirmed by overnight polysomnography showing low sleep efficiency[7,8] and disturbed sleep architecture (15±14 arousal/hour).[4] Moreover, COPD patients often report difficulty to initiate and maintain sleep,[9,10,11,12] as well as excessive daytime sleepiness.[7,9]

The observed worst sleep quality is correlated to daytime symptom burden,[13] which, in turn, is related with pulmonary function.[14]We, therefore, hypothesize that respiratory function would negatively impact sleep quality in these patients. In fact, sleep quality was previously described as associated with measurements of respiratory mechanics and function but not with measurements of daytime or nocturnal oxygenation.[15] In addition, increased lung hyperinflation was associated with worse sleep efficiency in patients with overlap syndrome (COPD plus obstructive sleep apnea; OSA) independently of apnea/hypopnea index (AHI) and nocturnal hypoxemia (**Figure**),[16] although mean arterial blood saturation was lower and time spent in desaturation was longer in overlap syndrome compared to isolated OSA.[17] Interestingly, improved sleep quality and nocturnal oxygenation was observed in patients with severe emphysema after lung volume reduction surgery.[18]

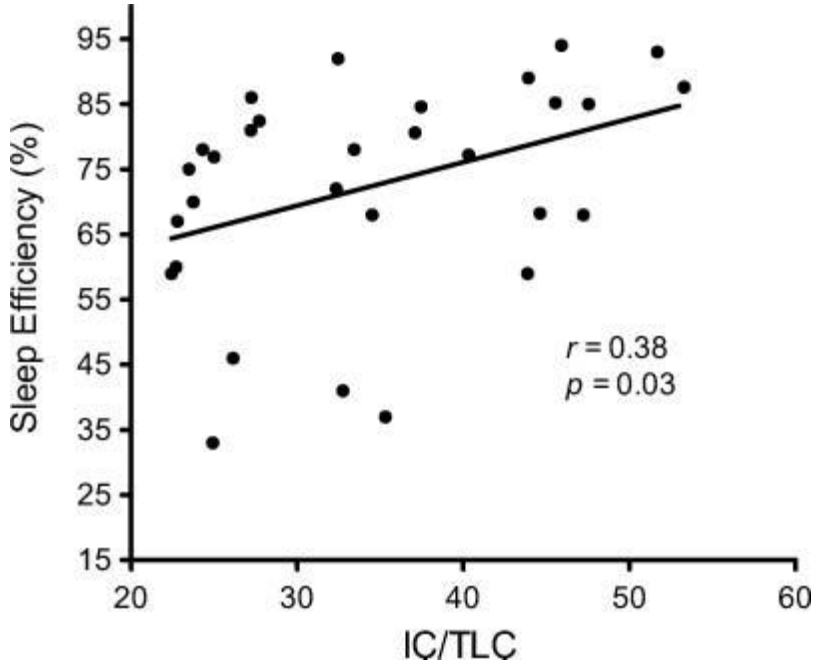

Figure. Correlation between sleep efficiency and an index of hyperinflation (inspiratory capacity/total lung capacity; IC/TLC) in COPD with co-existent obstructive sleep apnea.[16] Higher IC/TLC means less lung hyperinflation.

At last, body mass index (BMI) can reduce pulmonary function[19,20,21] as well as the prevalence and severity of OSA,[22] with negative impact on sleep variables. Detecting an independent association among respiratory functional parameters and sleep quality regardless the influence of other factors has important clinical implications since there are current available options to improve lung function in COPD that may potentially bring associated positive impact on sleep quality as well as night and early morning symptoms. **Owing to the lack of previous investigations systematically investigating the relationship of lung function adjusted to body weight and sleep breathe related disorders with sleep quality in COPD, we intend to address this issue in a population-based study involving a large sample evaluated at the institutional Pulmonary Function Test (PFT) and Sleep Laboratories.**

2. STUDY RELEVANCE

Results from this study may help identifying key physiological marks of COPD related to poor sleep quality, night and early morning related symptoms. This

will stage the scene for prospective studies aimed to improve such physiological abnormalities in order to positively impact on sleep-related outcomes.

3. OBJECTIVE

We aim to investigate the relationship of resting functional parameters with sleep quality in patients with COPD taking into account the potential modulating influence of obesity and obstructive sleep apnea.

4. METHODS

Study design

A cross-sectional study with retrospective data collection. Using specific searchable criteria (**Table 1**), all consecutive subjects with spirometry, whole body plethysmography and overnight polysomnography measurements performed at Queen's Affiliated Teaching Hospital's Clinical Laboratories **(**Kingston General Hospital and Hotel Dieu Hospital) will be reviewed (2008-2016).

Table 1. Main selection criteria

ALL PARTICIPANTS
Age ≥ 40 yrs
Performed Spirometry: YES
Performed Plethysmography: YES
Performed diagnostic overnight polysomnography: YES
List only: last tests (thus, only 1 entry by subject)
COPD
Forced expiratory volume in one-second (FEV_1)/ forced vital capacity (FVC) post bronchodilator (salbutamol 400µ) <0.70: YES
CONTROLS
Forced expiratory volume in one-second (FEV_1)/ forced vital capacity (FVC) post bronchodilator (salbutamol 400µ)<0.70: NO

Subject's name will never be available in the recorded data. After data recovery from the Pulmonary Function Test Laboratory and Sleep

Laboratory remote server by the investigators, the subjects will be consecutively numbered (e.g., first patient ever assessed will be "case 1", second patient will be "case 2" and so on; same procedure for the non-COPD controls). Thus, the data will never be in an identifiable form. Pertinent clinical data (main diagnosis hypothesis, reason for testing, Medical Research Council dyspnea score, co-morbidities, medications) will be obtained from the test requisitions and additional pulmonary lung function and sleep related parameters (**Table 2**) will be obtained from the respective reports. Thus, no contact will ever be established with the participants and/or the recorded information will be merged with other source of data or health records.

Study population

All consecutive subjects aged 40 or older that performed spirometry, lung volume measurements by plethysmography and diagnostic overnight polysomnography from January 2008 to December 2016 at the Kingston General Hospital and Hotel Dieu Hospital Pulmonary Function Test laboratory/Sleep Laboratory. In case of sequential measurements, the last assessment will be recorded for analysis. Subjects will be unnamed and identified by sequential numbers.

Data that will be collected

Pertinent clinical data (main diagnosis hypothesis, reason for testing and Medical Research Council dyspnea score (MRC)[23] and regular used medication) as well as additional anthropometric, physiological and sleep related information will be obtained from the test requisition and respective reports (**Table 2**).

Data and statistical analysis

Values will be reported as mean ± standard deviation (SD) unless otherwise specified (IBM® SPPS® Statistics version 24). Subjects with and without COPD will be contrasted by non-paired t or a $\chi 2$ test for differences in proportions. Univariate and multivariate (backward method) linear regression analyses will evaluate the discriminative value of lung functional variables (FEV_1, IC/TLC) to predict sleep quality (sleep efficiency and % rapid-eye movement (REM) sleep

Table 2. Clinical, functional and sleep-related parameters planned to be collected.

Data collection
Reason for testing/diagnosis
Medications in use
Dyspnea score
Comorbidities
Age
Weight
Height
Gender
Forced expiratory volume in one-second (FEV_1)
Forced vital capacity (FVC)
Vital capacity (VC)
Inspiratory capacity (IC)
Total lung capacity (TLC)
Residual volume (RV)
Functional residual capacity (FRC)
Lung diffusing capacity for carbon monoxide (DLCO)
Alveolar volume (VA)
Epworth sleepiness scale
Sleep efficiency (total sleep time/total recorded time)
% rapid-eye movement (REM) sleep/total sleep time
Apnea-hypopnea index (AIH)
Number of central apnea events
REM related sleep disorders/hour
Arousals/hour
Oxyhemoglobin saturation by pulse oximetry (SpO_2) nadir during sleep
Average baseline SpO_2 in bed before sleep
% of sleep time with SpO_2<90%
Transcutaneos carbon dioxide parcial pressure

/total sleep time) adjusted to BMI, AHI and parameters of nocturnal desaturation in each group (COPD and controls)

A recent preliminary evaluation (January 2017) estimated that more than 200 COPD patients had performed these measurements (Pulmonary Function Test Laboratory and overnight polysomnography) at Queen's Affiliated Teaching Hospital's Clinical Laboratories (directed by the principal investigators of the current proposal) in the above-mentioned period. This number is far more than necessary (estimated minimum required sample size=134) to detect an association among a linear dependent variable (sleep efficiency or % REM sleep/total sleep time) and 5 independent predictor (FEV_1, IC/TLC, AHI, BMI and % of sleep time with SpO_2<90%) considering a probability level of 0.05, a desired statistical power level of 0.8 and an expected small to medium effect size (*f*2) of 0.1.[24]

5. RESEARCH TEAM

The applicants direct the institutional pulmonary function test and sleep laboratories. They will be in charge to search the data as outlined above.

6. EXPECTATIONS

This study will be the first to investigate in a large clinical derived the association between the traditional indexes of functional impairment in COPD (expiratory airflow obstruction and/or lung hyperinflation) with parameters of sleep quality adjusted to potential confounders, namely BMI, AHI and nocturnal desaturation.

We expect to answer the following questions:

1) Is respiratory functional impairment related to sleep quality regardless the presence and severity of OSA and obesity in COPD?

2) If so, what is the best functional parameter to predict sleep quality?

Answering these questions would allow us to stablish an independent connection between respiratory functional impairment with poor sleep quality in COPD. Future perspectives will be opened to investigate whether therapeutic interventions aiming to improve respiratory function in these patients can ameliorate sleep quality and health status.

Results will also be submitted for presentation in international congress and consideration of publication in peer-reviewed journals.

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13.3 Tabela mostrando os resultados das análises univariadas entre parâmetros de qualidade do sono e comorbidades prevalentes (>5%) e medicações em uso pelos pacientes com DPOC.

	Sleep efficiency (%)		REM (% of total sleep)	
	Unstandardized Coefficient	p	Unstandardized Coefficient	p
Comorbididties				
Hypertension	-2,54	0.32	-2.27	0.07
GERD	5.36	0.06	2,09	0.13
Depression	**7.70***	**<0.01**	**-4.24***	**<0.01**
Diabetes mellitus	0.24	0.94	-2.54	0.08
Coronary artery disease	-4.32	0.24	0.02	0.99
Chronic pain	0.76	0.85	-2.23	0.27
Cancer	-6.46	0.09	0.15	0.94
Osteoarthritis	5.61	0.26	-0.82	0.73
Heart failure	-2.34	0.66	-0.35	0.89
Hypothyroidism	6.95	0.22	4.64	0.09
Medication				
Inhaled				
LABA	0.99	0.71	1.50	0.24

ICS	0.34	0.89	0.97	0.43
SABA	-1.70	0.52	-0.89	0.49
LAMA	-4.27	0.11	-1.65	0.19
SAMA	-2.35	0.54	2.51	0.18
Psychotropic				
Serotonin reuptake inhibitors	**7.25***	**0.02**	**-4.19***	**<0.01**
Benzodiazepines	4.10	0.29	**-4.84***	**<0.01**
Antipsychotics	6.50	0.19	**-7.51***	**<0.01**
Other hypnotics (trazodone, zolpidem)	3.68	0.48	**-6.27***	**<0.01**
Opioids	2.62	0.12	**-5.34**	**0.04**
Tricyclic antidepressants	-0.78	0.99	-2.16	0.47

Definition of colors: red ($p<0.05$) and blue ($p<0.10$) variables initially considered to be entered in multivariate linear regression analyses.

13.4 Demais produções bibliográficas relacionadas ao período de doutorado

13.4.1 Characteristics associated with mortality in patients with chronic obstructive pulmonary disease (COPD)-heart failure coexistence.

Plachi F[1], Balzan FM[1], Sanseverino RA[1], PalombiniDV[1], **Marques RD**[1], Clausell NO[1], Knorst MM[1], **Neder JA**[2], Berton DC[1].

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[2] Queen's University & Kingston General Hospital,Kingston, ON, Canada.

Prim Health Care Res Dev. 2018;19 (6): 570-574.

Abstract

Aim: To investigate if cardiac/pulmonary functional tests and variables obtained from clinical practice (body mass index, dyspnea, functional class, clinical judgment of disability to perform an exercise test and previous hospitalization rate) are related to mortality in patients with overlap chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF). BACKGROUND: Although the coexistence of COPD and CHF has been growingly reported, description of survival predictors considering the presence of both conditions is still scarce. METHODS: Using a cohort design, outpatients with the previous diagnosis of COPD and/or CHF that performed both spirometry and echocardiography in the same year were followed-up during a mean of 20.9±8.5 months.FindingsOf the 550 patients initially evaluated, 301 had both spirometry and echocardiography: 160 (53%) with COPD on isolation; 100 (33%) with CHF on isolation; and 41 (14%) with overlap. All groups presented similar mortality: COPD 17/160 (11%); CHF 12/100 (12%); and overlap 7/41 (17%) (P=0.73). In the overlap group (n=41), inability to exercise and hospitalization rate were the unique parameters associated with higher mortality (seven events) in univariate analyses. In conclusion, inability to exercise and hospitalization rate emerged as the unique parameters associated with mortality in our sample.

KEYWORDS: chronic obstructive pulmonary disease; exercise; heart failure; hospitalization; survival

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Primary Health Care Research & Development

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Research

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Characteristics associated with mortality in patients with chronic obstructive pulmonary disease (COPD)–heart failure coexistence

Franciele Plachi[1], Fernanda M. Balzan[1], Renata A. Sanseverino[1], Dora V. Palombini[1], Renata D. Marques[1,2], Nadine O. Clausell[1], Marli M. Knorst[1], J. Alberto Neder[2] and Danilo C. Berton[1,2]

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Abstract

Aim: To investigate if cardiac/pulmonary functional tests and variables obtained from clinical practice (body mass index, dyspnea, functional class, clinical judgment of disability to perform an exercise test and previous hospitalization rate) are related to mortality in patients with overlap chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF). *Background:* Although the coexistence of COPD and CHF has been growingly reported, description of survival predictors considering the presence of both conditions is still scarce. *Methods:* Using a cohort design, outpatients with the previous diagnosis of COPD and/or CHF that performed both spirometry and echocardiography in the same year were followed-up during a mean of 20.9 ± 8.5 months. *Findings:* Of the 550 patients initially evaluated, 301 had both spirometry and echocardiography: 160 (53%) with COPD on isolation; 100 (33%) with CHF on isolation; and 41 (14%) with overlap. All groups presented similar mortality: COPD 17/160 (11%); CHF 12/100 (12%); and overlap 7/41 (17%) ($P = 0.73$). In the overlap group ($n = 41$), inability to exercise and hospitalization rate were the unique parameters associated with higher mortality (seven events) in univariate analyses. In conclusion, inability to exercise and hospitalization rate emerged as the unique parameters associated with mortality in our sample.

Introduction

Chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF) are main causes of dyspnea and exercise intolerance, being highly prevalent in the general elderly population (van Mourik *et al.*, 2014). The coexistence of both diseases is common but often unrecognized. Considering the overlap in signs and symptoms, one condition frequently pass unnoticed once the another disease has been previously diagnosed. This was showed by previous studies describing a high prevalence of unknown CHF in COPD (McCullough *et al.*, 2003; Rutten *et al.*, 2005; Beghé *et al.*, 2013) and vice versa (Macchia *et al.*, 2012; Boschetto *et al.*, 2013). Accordingly, additional investigational tools, such as spirometry and echocardiography, are required for an adequate diagnosis.

Beyond the diagnostic challenge, the overlap of COPD and CHF has been associated with increased morbidity, poor quality of life and greater utilization of healthcare resources. Moreover, overlap frequently compounds with other systemic co-morbidities contributing to poor prognosis (Rutten *et al.*, 2005; Macchia *et al.*, 2012).

Despite the interest in the interactions between both diseases has recently grown (Fabbri *et al.*, 2008; Rutten, 2013), description of survival predictors are still scarce (Alencar *et al.*, 2016). While cardiopulmonary exercise testing (CPET)-derived parameters have demonstrated key prognostic significance in patients with COPD (Oga *et al.*, 2003; Neder *et al.*, 2016), CHF (Mancini *et al.*, 1991; Poggio *et al.*, 2010) and both diseases (Alencar *et al.*, 2016), we must acknowledge that overlap patients are usually extremely frail and frequently never become stable enough to perform an exercise test (Arbex *et al.*, 2016).

In COPD, the severity of the baseline disease is closely related to the severity of exacerbations, that is patients with severe disease are more likely to be hospitalized due to an exacerbation. In the long term, patients who experience severe exacerbations have an increased risk of more severe exacerbations in the future (Garcia-Aymerich *et al.*, 2001; Donaldson *et al.*, 2003). The coexistence with cardiac disease may influence the severity of an exacerbation. In fact, COPD patients with cardiac disease present increased risk of hospitalization due to an exacerbation (Miravitlles *et al.*, 2000) and an increased risk of mortality (Antonelli Incalzi *et al.*, 1997; Macchia *et al.*, 2012).

13.4.2 Effects of acute dual bronchodilator treatment (tiotropium + olodaterol) on cardiopulmonary interactions in hyperinflated patients with COPD

Danilo Cortozi Berton, **Renata Diniz Marques**, Brandon Palmer, Katherine Webb, Denis E O'Donnell, **J Alberto Neder**

European Respiratory Journal 2018 52: OA5340; DOI: 10.1183/13993003.congress-2018.OA5340

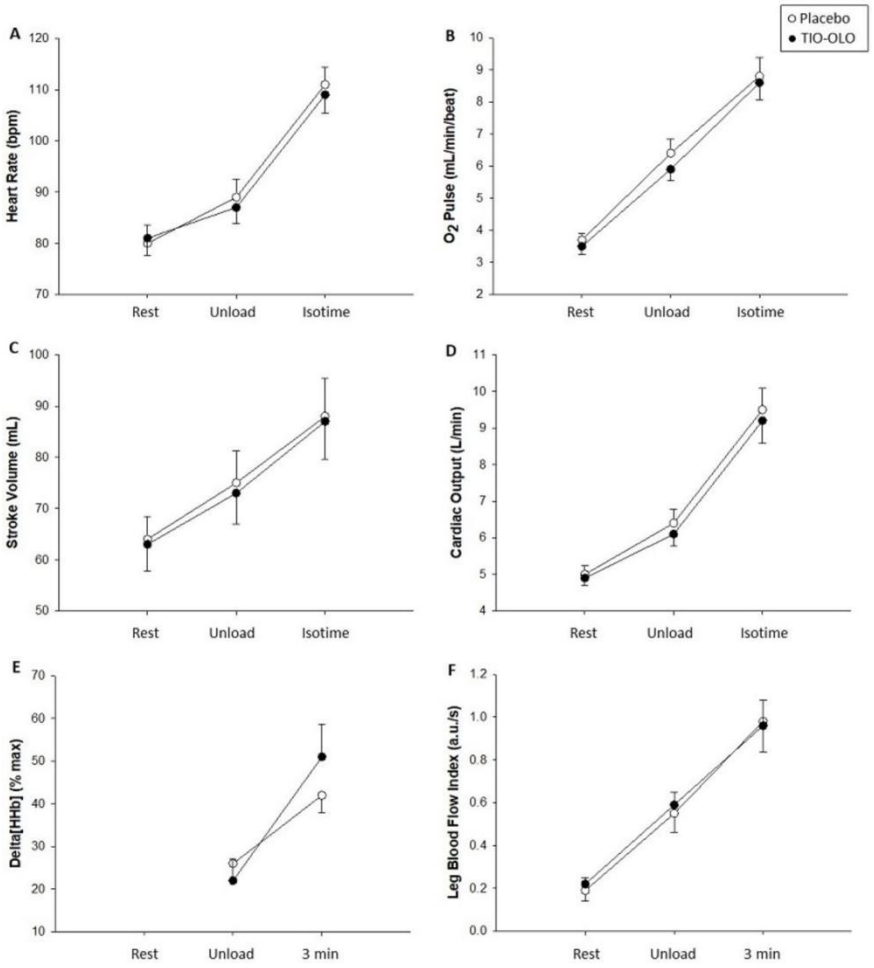
Abstract

We investigated whether lower operating lung volumes after inhaled bronchodilators are associated with beneficial effects on central (stroke volume and cardiac output) and peripheral (skeletal muscle blood flow) hemodynamic responses to exercise in COPD.

In a double-blind, single-dose and placebo-controlled study, 20 patients with moderate-to-severe COPD (12 males, 69.4 ± 13.2yrs, FEV_1= 47 ± 12%, and FRC=154 ± 31% pred) performed, at least 48 hrs apart, high intensity (75% peak work rate) exercise tests after tiotropium+olodaterol Respimat™ (TIO-OLO) or placebo. Impedance cardiography and near-infrared spectroscopy (using the indocyanine green dye) assessed central and peripheral hemodynamics, respectively.

TIO-OLO significantly improved resting lung function, operating lung volumes, and exercise tolerance compared to placebo ($p<0.05$). Contrary to our premises, however, central and peripheral hemodynamics did not improve with TIO-OLO compared to placebo (Figure).Similar results were found in a post-hoc analysis in which patients showing larger lung deflation with TIO-OLO were contrasted with their counterparts ($p>0.05$).

The beneficial effects of TIO-OLO fixed combination on resting and operating lung volumes (i.e., lung deflation) did not translate into enhanced central or peripheral hemodynamics in hyperinflated patients with moderate to severe COPD.


A
Heart Rate (bpm)
120
110
100
90
80
70
Rest
Unload
Isotime
B
Placebo
TIO-OLO
O_2 Pulse (mL/min/beat)
10
9
8
7
6
5
4
3
2
Rest
Unload
Isotime
C
Stroke Volume (mL)
100
90
80
70
60
50
Rest
Unload
Isotime
D
Cardiac Output (L/min)
11
10
9
8
7
6
5
4
Rest
Unload
Isotime
E
Delta[HHb] (% max)
70
60
50
40
30
20
10
Rest
Unload
3 min
F
Leg Blood Flow Index (a.u./s)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Rest
Unload
3 min

13.4.3 Non-invasive assessment of pulmonary microcirculation at rest and exercise in patients with previous pulmonary thromboembolism

Danilo Cortozi Berton, **Renata Diniz Marques**, Brandon Palmer, Christine D'Arsigny, Denis E O'Donnell, **J Alberto Neder**

European Respiratory Journal 2018 52: PA3367; DOI: 10.1183/13993003.congress-2018.PA3367

Abstract

There is renewed interest in non-invasive tests to assess residual lung microcirculatory abnormalities after pulmonary thromboembolism. Lung transfer capacity for carbon monoxide (DL_{CO}) is weighted towards CO uptake by blood microcirculation whereas DL for nitric oxide (NO) is weighted towards the transport of NO through the alveolar-capillary membrane.

We therefore hypothesized that, compared to controls, dyspneic patients with previous large or massive pulmonary thromboembolism would present with larger decrements in DL_{CO} than DL_{NO} and lower pulmonary blood flow (PBF) by inert gas rebreathing.

Fourteen patients (10 females) with previous imaging-proved pulmonary embolism and 10 healthy controls (9 females) performed at rest and 25W measurements of DL_{NO} and DL_{CO} (HypAir, Medisoft™) and PBF by nitrous oxide uptake (Innocor, Innovision™).

At rest, DL_{NO} (93±24 vs 118±25% pred) and DL_{CO} (93±24 vs 118±25% pred) were significantly lower in patients than controls ($p<0.05$). Both variables increased with exercise, resulting in marginally-significant differences ($p= 0.09$). Contrary to our expectations, DL_{NO}/DL_{CO} ratio did not differ either at rest or exercise ($p>0.05$). Albeit not significantly, PBF tended to be lower in patients than controls at similar rates of O_2 uptake (3.9±1.2 L/min vs. 4.3±1.2 L/min).

Our results do not support the use of DL_{NO}/DL_{CO} ratio or inert gas rebreathing to assess microcirculatory abnormalities in patients with previous pulmonary embolism. The role of these tests in patients with chronic thromboembolic pulmonary hypertension, however, remains open to investigation.

13.4.4Effects of lung deflation induced by tiotropium/olodaterolon the cardiocirculatory responses to exertion in COPD

Danilo C Berton, **Renata D Marques**, Brandon Palmer, Denis E O'Donnell, **J Alberto Neder**

Respiratory Medicine, 157 (2019) 59-68

Abstract

BACKGROUND:Hyperinflation has been associated with negative cardiocirculatory consequences in patients with chronic obstructive pulmonary disease (COPD). These abnormalities are likely to worsen when the demands for O2 increase, e.g., under the stress of exercise. Thus, pharmacologically-induced lung deflation may improve cardiopulmonary interactions and exertional cardiac output leading to higher limb muscle blood flow and oxygenation in hyperinflated patients with COPD.METHODS:20 patients (residual volume = 201.6 ± 63.6% predicted) performed endurance cardiopulmonary exercise tests (75% peak) 1 h after placebo or tiotropium/olodaterol 5/5 μg via the Respimat® inhaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany). Cardiac output was assessed by signal-morphology impedance cardiography. Near-infrared spectroscopy determined quadriceps blood flow (indocyanine green dye) and intra-muscular oxygenation.RESULTS:Tiotropium/olodaterol was associated with marked lung deflation ($p < 0.01$): residual volume decreased by at least 0.4 L in 14/20 patients (70%). The downward shift in the resting static lung volumes was associated with less exertional inspiratory constraints and dyspnoea thereby increasing exercise endurance by ~50%. Contrary to our premises, however, neither central and peripheral hemodynamics nor muscle oxygenation improved after active intervention compared to placebo. These results were consistent with those found in a subgroup of patients showing the largest decrements in residual volume ($p < 0.05$).CONCLUSIONS:The beneficial effects of tiotropium/olodaterol on resting and operating lung volumes are not translated into enhanced cardiocirculatory responses to exertion in hyperinflated patients with COPD. Improvement in exercise tolerance after dual bronchodilation is unlikely to be mechanistically linked to higher muscle blood flow and/or O2 delivery.

KEYWORDS: Blood flow; Bronchodilator; COPD; Cardiac output; Dyspnea; Exertion; Lung mechanics

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Effects of lung deflation induced by tiotropium/olodaterol on the cardiocirculatory responses to exertion in COPD

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ABSTRACT

Background: Hyperinflation has been associated with negative cardiocirculatory consequences in patients with chronic obstructive pulmonary disease (COPD). These abnormalities are likely to worsen when the demands for O_2 increase, e.g., under the stress of exercise. Thus, pharmacologically-induced lung deflation may improve cardiopulmonary interactions and exertional cardiac output leading to higher limb muscle blood flow and oxygenation in hyperinflated patients with COPD.

Methods: 20 patients (residual volume = 201.6 ± 63.6% predicted) performed endurance cardiopulmonary exercise tests (75% peak) 1 h after placebo or tiotropium/olodaterol 5/5 μg via the Respimat® inhaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany). Cardiac output was assessed by signal-morphology impedance cardiography. Near-infrared spectroscopy determined quadriceps blood flow (indocyanine green dye) and intra-muscular oxygenation.

Results: Tiotropium/olodaterol was associated with marked lung deflation ($p < 0.01$): residual volume decreased by at least 0.4 L in 14/20 patients (70%). The downward shift in the resting static lung volumes was associated with less exertional inspiratory constraints and dyspnoea thereby increasing exercise endurance by ~50%. Contrary to our premises, however, neither central and peripheral hemodynamics nor muscle oxygenation improved after active intervention compared to placebo. These results were consistent with those found in a subgroup of patients showing the largest decrements in residual volume ($p < 0.05$).

Conclusions: The beneficial effects of tiotropium/olodaterol on resting and operating lung volumes are not translated into enhanced cardiocirculatory responses to exertion in hyperinflated patients with COPD. Improvement in exercise tolerance after dual bronchodilation is unlikely to be mechanistically linked to higher muscle blood flow and/or O_2 delivery.

1. Introduction

Cardiovascular diseases are major co-morbidities of chronic obstructive pulmonary disease (COPD) [1]. In addition to a key common risk factor (cigarette smoking), part of the higher risk of cardiac disease in these patients can be ascribed to negative cardiopulmonary interactions [2]. Lung hyperinflation, in particular, may increase right and left ventricular afterload whilst decreasing their pre-load (as comprehensively reviewed in Ref. [3]). The consequent decrease in stroke volume and cardiac output (if the former is not compensated by a faster heart rate) is likely more relevant when the peripheral demands for oxygen (O_2) increase, e.g., during physical exercise [4]. This scenario is further complicated by the fact that the higher ventilatory requirements of exercise are frequently associated with further (dynamic) hyperinflation [5]. It is therefore conceivable that part of patients' exercise intolerance could be ascribed to the downstream circulatory consequences of a low exertional cardiac output, i.e., poor limb muscle blood flow and oxygenation [6,7]. The latter abnormalities may lead to a perception of leg discomfort [8] and further increase ventilation and dyspnea [9] in a downward spiral which culminates in early exercise termination.

How could we therapeutically address these issues? There is emergent evidence that the greater lung deflation induced by dual long-acting bronchodilation (i.e., an antimuscarinic plus a β_2-adrenoceptor

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