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Perfil Funcional de Pacientes com Insuficiência Cardíaca coexistente à Doença Pulmonar Obstrutiva Crônica

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Orientador: Prof. Dr. Pedro Dal Lago

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Dedico a todos os pacientes que se dispuseram a participar da pesquisa.

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Piés, ¿para qué los quiero si tengo alas para volar?

Frida Kahlo

RESUMO

Introdução: A Insuficiência Cardíaca (IC) e a Doença Pulmonar Obstrutiva Crônica (DPOC) estão entre as principais causas de morbidade e mortalidade no Brasil e no mundo e frequentemente coexistem (IC-DPOC). Isoladamente, ambas são caracterizadas por alterações sistêmicas que culminam em grave intolerância ao exercício e diversas disfunções periféricas. Para avaliar tais repercussões, o Teste de Caminhada de Seis Minutos (TC6) é uma das principais ferramentas e diversos fatores podem influenciar sua performance (mensurada pela distância percorrida- DTC6). Entretanto, quando coexistentes, ainda não está totalmente esclarecido qual o impacto funcional de uma sobre a outra, especialmente em populações brasileiras, e quais fatores podem determinar a DTC6. **Objetivos:** descrever o perfil clínico-funcional de pacientes com IC-DPOC e identificar quais fatores podem ser determinantes da tolerância ao exercício, avaliada pelo TC6. **Materiais e Métodos:** Trata-se de um estudo transversal, com amostra composta por pacientes com diagnóstico de insuficiência cardíaca (IC) e doença pulmonar obstrutiva crônica (DPOC). Foram coletados os dados: idade, sexo, etnia, anos de estudo (<12 anos, 12 anos ou mais), tabagismo (sim ou não / ex) - nos casos de fumantes e ex-fumantes, anos / maço. Fração de ejeção do ventrículo esquerdo (FEVE), classe da New York Heart Association (NYHA), volume expiratório forçado no primeiro segundo (VEF_1), capacidade forçada vital (CVF), classificação da Iniciativa Global para Doença Obstrutiva Pulmonar Crônica (GOLD- A, B, C, D), foram os utilizados como dados clínicos. A avaliação funcional foi composta pelo TC6 (executado conforme recomendações internacionais), fenótipo de fragilidade (CHS index), mensuração das pressões inspiratória (Pimáx) e expiratória (Pemáx) máximas, questionário de qualidade de vida (Minnesota living with heart failure questionnaire- MLHFQ) e função cognitiva (Montreal Cognitive assessment- MOca). **Resultados:** Trinta e dois pacientes foram avaliados em uma amostra de conveniência. A idade média foi de 67,6 ± 8,54 anos, sendo 65,6% do sexo feminino e como diagnóstico inicial de IC em 59,4%. A DTC6 média foi de 281,1 ± 101,9 metros, apresentando correlação significativa com a velocidade da marcha ($r = -0,81$; $p < 0,01$), VEF_1 ($r = 0,63$;

p <0,01), classe NYHA (r = -0,46; p <0,01), VFC (r = 0,61; p <0,01), %VEF_1 (r = 0,58; p <0,01), %VFC (r = 0,56; p <0,01), CHS index (r = 0,53; p <0,01) e escore MLHF-Q (r = -0,47; p <0,01). Na análise de regressão as seguintes variáveis foram incluídas no modelo final para DTC6: velocidade da marcha (p <0,000), VEF_1 (p <0,000) e classe NYHA (p <0,000), onde a equação derivada foi: 494,3 + (-39,5 x velocidade da marcha) + (79 x FEV1) + (-45,7 x classe NYHA). **Conclusão:** Neste estudo os participantes apresentaram importante comprometimento da capacidade funcional, da Pemáx e da função cognitiva. Ainda, os determinantes da DTC6 foram: velocidade da marcha, VEF_1 e classe NYHA.

Palavras-chave: insuficiência cardíaca; doença pulmonar obstrutiva crônica; capacidade funcional; teste de caminhada;

ABSTRACT

Introduction: Heart Failure (HF) and Chronic Obstructive Pulmonary Disease (COPD) are among the leading causes of morbidity and mortality in Brazil and worldwide and often coexist (HF-COPD overlap). Both diseases are characterized by systemic abnormalities that culminate in severe exercise intolerance and many peripheral dysfunctions. To assess these impacts, the Six Minutes' Walk Test (6MWT) is one of the main tools and several factors can influence its performance (measured by the distance covered - 6MWD). However, when coexisting, it is not yet fully clear what the functional impact of one on the other, especially in Brazilian populations, and which factors may determine the 6MWD. **Aims:** To evaluate and describe the clinical and functional profile of patients with HF-COPD and identify which factors may be determinants of exercise tolerance assessed by the 6MWT. **Materials and Methods:** This is a cross-sectional study with a sample of patients diagnosed with HF and COPD. Data were collected: age, sex, ethnicity, years of schooling (<12 years, 12 years or high education), smoking (yes or no / ex) - in the cases of smokers and former smokers, years/pack. Left Ventricular Ejection Fraction (LVEF), New York Heart Association (NYHA) Class, Forced Expiratory Volume on the first second (FEV_1), Vital Forced Capacity (FVC), Global Chronic Obstructive Pulmonary Disease Initiative (GOLD classification- A, B, C, D) were used as clinical data. Functional assessment consisting of 6MWT (following international guidelines), frailty phenotype (CHS index), maximum inspiratory (MIP) and expiratory (MEP) pressure measurements, quality of life questionnaire (Minnesota Living with Heart Failure- MLHF-Q) and cognitive function (Montreal Cognitive Assessment- MoCA). **Results:** Thirty-two patients were evaluated in a convenience sample. The average age was 67.6 ± 8.54 years, 65.6% female, and initial diagnosis of HF in 59.4%. Mean 6MWD was 281.1 ± 101.9 meters, showing a significant correlation with gait speed ($r = -0.81$; $p < 0.01$), FEV_1 ($r = 0.63$; $p < 0.01$), NYHA class ($r = -0.46$; $p < 0.01$), HRV ($r = 0.61$; $p < 0.01$),% FEV_1 ($r = 0.58$; $p < 0.01$), % HRV ($r = 0.56$; $p < 0.01$), CHS index ($r = 0.53$; $p < 0.01$) and MLHF-Q score ($r = -0.47$; $p < 0.01$) . In the regression analysis, the following variables were included in the final model for the 6MWD: gait speed ($p < 0.000$), FEV_1 ($p < 0.000$) and NYHA class ($p < 0.000$), where the derived equation was: 494.3 + (-39.5 x gait speed) + (79 x FEV_1) + (-45.7 x NYHA class). **Conclusion:** In this study,

participants showed significant impairment of functional capacity, measure by 6MWT, MEP and cognitive function. Still, the 6MWT determinants were: gait speed, FEV1 and NYHA class.
Keywords: heart failure; chronic obstructive pulmonary disease; functional capacity; walk test.

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LISTA DE ABREVIATURAS E SIGLAS

AF	Atividades físicas
AVDs	Atividades de vida diária
Ca^{2+}	Cálcio
Clpeak	Área de superfície corporal
DC	Déficit cognitivo
DCL	Déficit cognitivo leve
DCNT	Doenças crônicas não transmissíveis
DCV	Doenças cardiovasculares
DPOC	Doença pulmonar obstrutiva crônica
DTC6	Distância percorrida no teste de caminhada de seis minutos
FEVE	Fração de ejeção do ventrículo esquerdo
FMR	Força muscular respiratória
GOLD	Iniciativa global para doenças pulmonares obstrutivas crônicas
IC	Insuficiência cardíaca
IC-DPOC	Insuficiência cardíaca coexistente à doença pulmonar obstrutiva crônica
ICFEi	Insuficiência cardíaca com fração de ejeção intermediária
ICFEp	Insuficiência cardíaca com fração de ejeção preservada
ICFEr	Insuficiência cardíaca com fração de ejeção reduzida
IL-1	Interleucina um
IL-6	Interleucina seis
IL-8	Interleucina oito
IMC	Índice de massa corporal
MR	Músculos respiratórios
NYHA	New York heart association
O_2	Oxigênio
PCR	Proteína C reativa
PEmáx	Pressão expiratória máxima
PImáx	Pressão inspiratória máxima
Qpeak	Pico do débito cardíaco
TC6	Teste de caminhada de seis minutos
TCP	Teste cardiopulmonar

TNFα	Fator de necrose tumoral alfa
VE	Ventrículo esquerdo
VEF_1	Volume expiratório forçado no primeiro segundo
VO_2	Consumo máximo de oxigênio

SUMÁRIO

1 INTRODUÇÃO

O envelhecimento populacional é um fenômeno demográfico global, que se constitui um fator crucial para a ascensão da prevalência e da mortalidade por doenças crônicas não transmissíveis ([DCNT] NU, 2017; OMS, 2017). Apesar da melhora nos serviços de saúde, doenças como a insuficiência cardíaca (IC) e doença pulmonar obstrutiva crônica (DPOC) ainda estão entre as 5 principais causas de mortalidade no mundo (RICTHE e ROSER, 2019, Figura 1).

Além disso, a IC e a DPOC também estão entre as maiores causas da perda de qualidade de vida, incapacidades, além de impactos econômicos para famílias e a economia dos países (MINISTÉRIO DA SAÚDE, 2011). No Brasil, as DCNT correspondem a 74,7% das causas de anos de vida vividos com incapacidade, sendo 11,2% do total referente às doenças respiratórias crônicas e 2,7% às doenças cardiovasculares ([DVC] SCHRAMM, 2004).

Figura 1: número de óbitos, por causa, em 2016. Adaptado de "Our World in data"

Enquanto síndromes, tanto a IC quanto a DPOC vão além de suas alterações cardíacas e pulmonares, respectivamente. São marcadas por disfunções periféricas, musculares, vasculares, autonômicas, em caráter progressivo, que desempenham papel central na evolução clínica e funcional de ambas (DOURADO,2006; DHAKAL,2015; HAYKOWSKY,2015; MCNAMARA, 2018). E como consequência da somação desses fatores tem-se uma marcada

intolerância ao exercício (O'DONNELL, 2006; UPADHYA, 2015), dispnéia e fadiga precoces (KUPPER, 2016; ANZUETO, 2017) fragilidade (PEDRAZA, 2018; KENNEDY,2019), alterações de humor e declínio cognitivo (ALAGIAKRISHNAN, 2016; CLEUTJENS,2017) além da perda de qualidade de vida (MARK, 2011; LAGOEIRO, 2017).

Na prática clínica a IC e a DPOC frequentemente coexistem (PADELETTI, 2008). Sua prevalência ainda não é consensual, sendo essa discrepância atribuída ao complexo diagnóstico de uma sobre a outra, principalmente pela semelhança em sinais e sintomas como dispnéia e intolerância ao esforço (JEMTEL, 2007; HAWKINS, 2009; TESTA, 2016). Contudo, alguns fatores já foram identificados como bandeiras vermelhas para essa coexistência e devem ser considerados na avaliação (HAWKINS, 2009; FISHER, 2015).

Mesmo os dados ainda discordantes, em pacientes com IC-DPOC os marcadores clínicos e funcionais são piores em comparação àqueles com apenas uma doença (JEMTEL, 2007; MASCARENHAS, 2010). Em relação ao prognóstico, por exemplo, a presença concomitante representa maior risco de hospitalização (RUSINARU, 2008) e maiores taxas de mortalidade quando comparados a pacientes com IC isolada (BOUDESTEIN, 2009; BLOIS, 2010; ZANNAD, 2012).

Tanto na IC quanto na DPOC, isoladas ou coexistentes, a intolerância ao exercício é um dos principais marcadores de evolução da doença e representante de suas alterações multissistêmica (BARNES, 2009; PASSINO, 2018). Assim, resultados abaixo do esperado predizem piores desfechos, sendo o consumo máximo de oxigênio (VO_2), obtido através de testes cardiopulmonares máximos (padrão ouro) ou através de cálculos, um dos principais marcadores (ARENA, 2004; JESSUP, 2009; MALHOTRA, 2016).

Entretanto, alguns dos pacientes com IC e DPOC são fisicamente incapazes de realizar testes máximos, além do elevado custo e necessidade de equipe específica. Assim, avaliações de campo, como o Teste de Caminhada de 6 minutos (TC6), surgem como uma alternativa simples, independente de tecnologias (American Tohracic Society- ATS, 2002; RUBIM, 2006) e sensível para mensurar a capacidade funcional, avaliar o prognóstico e demais desfechos em ambas as populações. O TC6 reflete consistentemente as limitações às atividades de vida diária ([AVDs] ENRIGHT, 2004; RUBIM, 2006,), testa o

comportamento dos sintomas durante o esforço (MORALES, 2011) e apresenta correlação com o VO_2 (COTE, 2007; ROSS, 2010), sendo usado amplamente na prática clínica há décadas.

Ainda, nas populações de IC ou DPOC, diversos fatores podem determinar a distância percorrida no TC6 (DTC6) e sua identificação é primordial para monitorização clínica e funcional. Fatores como idade avançada (PEPERA, 2015), sexo feminino (MORAIS, 2019), humor deprimido (SPRUIT, 2010) já foram descritos como variáveis que alteram a DTC6, resultando em menores distâncias e piores status funcional. Entretanto, em pacientes com IC-DPOC ainda não há descrição destes, especialmente na população brasileira.

Portanto, é imprescindível traçar um perfil clínico-funcional desses indivíduos e identificar quais pontos (função cardíaca, função pulmonar e demais aspectos físico-funcionais) são capazes de explicar a DTC6. Providos desse perfil então será possível propor futuras intervenções que considerem essas particularidades, sejam personalizadas e capazes de modificar seu status funcional e melhorar sua qualidade de vida.

2 REVISÃO DE LITERATURA

2.1 INSUFICIÊNCIA CARDÍACA

A IC atingiu o estado epidêmico, com cerca de 26 milhões de indivíduos vivendo atualmente com essa doença em todo o mundo (PONIKOWSKI et al., 2014; MOZAFFARIAN et al, 2015). Como diagnóstico primário, ela equivale a 4% das internações em países desenvolvidos, sua prevalência aumenta com a idade e tem um prognóstico total adverso, com uma taxa de mortalidade em 5 anos de 45% dos casos (ACHTTIEN et al, 2015; GRAVEN et al., 2017).

Enquanto patologia, a IC é definida por sua incapacidade, enquanto bomba, de manter um suporte adequado à periferia, ou fazê-lo sob altas pressões (AMERICAN HEART ASSOCIATION-AHA, 2017; ROHDE, 2018). Essa alteração de bomba é resultado de anormalidades estruturais e funcionais do coração, que vão desde inabilidade cronotrópica, alterações pressóricas à redução do debito cardíaco e, somadas a suas consequências periféricas, dão origem a síndrome da IC.

Tendo na cardiopatia isquêmica sua principal etiologia (OWEN, 2006; GERBER, 2015; ZIAEIAN, 2016), a disfunção sistólica representada pela fração de ejeção (FE) é o fator peremptório e categoriza os indivíduos em 3 grupos: IC com FE preservada (>50%, ICFEp), intermediária (39-49%ICFEi) e reduzida (ICFEr) (ROHDE, 2018), sendo a ICFEp a mais prevalente, principalmente em faixas etárias mais velhas (STEINBERG, 2012; PONIKOWSKI, 2016). Funcionalmente esses pacientes são classificados de acordo com uma escala proposta pela New York Heart Association (NYHA), onde são estratificados pelo grau de limitação, imposto pelos sintomas, para as AVDs (BENNETT, 2002; BOCCHI, 2012; ROHDE, 2018). Segundo esta, há quatro classificações: Classe I - ausência de sintomas durante atividades cotidianas, com limitação para esforços semelhante à esperada em indivíduos saudáveis; Classe II - sintomas desencadeados por atividades cotidianas; Classe III - sintomas desencadeados em atividades menos intensas que as cotidianas; Classe IV - sintomas em repouso.

Sendo a ICFEp a mais prevalente, apenas a disfunção do ventrículo esquerdo (VE) não seria suficiente para explicar a alta intolerância ao exercício, a dispnéia e os demais sinais e sintomas da IC. Seu desenvolvimento envolve

alterações em diversos sistemas homeostáticos (de forma que a síndrome pode ser vista como uma desordem multiorgânica, de caráter progressivo, que é originada no coração, mas se estende para a periferia, CANDIA, 2007, BOURLANG, 2011), onde provoca disfunções e anormalidades capazes de sobressair às alterações centrais no curso da doença.

A apresentação clínica da IC, no fenótipo com FE preservada, os pacientes geralmente são mais velhos (HOGG, 2004; CLYDE, 2006) mais frequentemente do sexo feminino (LEE, 2009; SHARMA, 2014) e apresentam alta prevalência de comorbidades como obesidade, síndrome metabólica, diabetes mellitus tipo 2, hipertensão, DPOC e disfunção renal (CHAN,2012; DUNLAY, 2017). Os processos fisiopatológicos destas englobam caminhos metabólicos distintos, mas se interligam e interagem entre si, perpetuando e agravando a falência e remodelagem cardíaca, a caquexia esquelética e a disfunções já encontradas na própria IC.

Nesse contexto, a disfunção da resposta imune parece ser o ponto chave e estar diretamente envolvida tanto na patogênese quanto no desenvolvimento e na gravidade da ICFEp. Esse novo paradigma propõe que níveis circulantes elevados de TNFα, Interleucinas 6 e 1 (IL-6 e IL-1) e Pentraxina 3 (Paulus, 2013; LAM, 2016; BORLAUG, 2016; SHAH, 2018), derivados tanto da própria IC quanto das comorbidades, e desacompanhados de uma resposta anti-inflamatória compensatória (YNDESTAD, 2006), levam à anormalidades estruturais e funcionais tanto no músculo cardíaco quanto no leito vascular, musculatura periférica e demais sistemas. Entretanto, a exata origem do processo inflamatório sistêmico ainda não foi totalmente esclarecida.

Para essa questão, alguns estudos propuseram que o próprio cardiomiócito, insuficiente, expressaria níveis elevados dos mediadores inflamatórios (TNFα, citocinas e quimiocinas relacionadas à IL-6 principalmente) elevando os níveis circulantes dos mesmos e causando as alterações periféricas e funcionais características (MABUCHI, 2002; GAERTNER, 2003; TONNESSEN, 2003) ainda, o menor aporte de O_2 aos tecidos extracardíacos provoca lesão celular, via estresse oxidativo (NG, 2012), induzindo a cascata pró-inflamatória na própria periferia e agravando seus efeitos deletérios.

Além da inflamação sistêmica, estresse oxidativo e disfunção endotelial e vascular, somam-se alterações metabólicas (ASHRAFIAN, 2007; ROCHA, 2018), reflexas e autonômicas (TRIPOSKIADIS, 2009; KISHI, 2012), levando ao desequilíbrio entre os sinais anabólicos e catabólicos e diminundo a capacidade de adaptação da periferia, principalmente frente ao esforço. Todas essas anormalidades tornam a IC uma condição complexa e demandam avaliações além da função cardíaca.

2.2 Doença Pulmonar Obstrutiva Crônica

A prevalência global da DPOC ainda é difícil de estimar, principalmente pelas diferentes abordagens utilizadas para diagnosticá-la (i.e, espirometria ou questionamento direto; GOLD, 2017). O Estudo Global da Carga de Doenças (2015) estimou a prevalência global da DPOC em cerca de 174 milhões de casos, sendo atualmente a quarta principal causa de morte no mundo. Projeções trazem que a DPOC alcançará a terceira posição até 2020 (SCHUTTE, 2017). No Brasil os dados são escassos, mas estima-se que 7,5 milhões de indivíduos (5 a 10%) sejam portadores de DPOC, representando um número na ordem de 170 mil admissões hospitalares (DATASUS, 2008; GIACOMELLI, 2014).

Enquanto doença a DPOC é classicamente definida como uma obstrução ao fluxo aéreo, não totalmente reversível, de caráter progressivo, associada à resposta inflamatória pulmonar exacerbada (SBPT, 2004; GOLD, 2018) e induzida por exposição a agentes agressores. Essa ativação, em caráter crônico, induz modificações nos brônquios, destruição do parênquima pulmonar, redução da elasticidade pulmonar, inadequada relação ventilação/perfusão e hiperinsuflação pulmonar, sendo seu grau variável de indivíduo para indivíduo (HOGG, 2009; GOLD, 2018).

Sua principal causa é o tabagismo, com maior prevalência no sexo masculino, e sua classificação mais utilizada é baseada no volume expiratório forçado no primeiro segundo (VEF_1- SBPT, 2004; GOLD 2018), considerada a definição fisiológica da doença. De acordo com a Iniciativa Global para Doenças Pulmonares Crônicas (GOLD), a severidade é graduada em 4 níveis: leve (VEF_1 ≥80% predito), moderada (50% ≤ VEF_1< 80% predito), severa (30%≤ VEF_1 < 50% predito) e muito severa (VEF_1< 30% predito).

Entretanto, existem evidências de que apenas o VEF_1 não é um fator determinante para estabelecer a morbi-mortalidade da doença. Por isto, o impacto dos sintomas, o número de exacerbações, presença de comorbidades e as manifestações sistêmicas da doença estão sendo incluídos na avaliação da gravidade da doença (FRAGOSO, 2015). Assim, em 2018, em sua atualização, a GOLD propôs a estratificação dos pacientes em GOLD A, B, C, D, em ordem crescente de gravidade e incluindo o impacto da dispnéia e o número de exacerbações, além do clássico VEF_1 (GOLD, 2018).

Em relação a seu processo fisiopatológico, o remodelamento da via área de baixo calibre e a perda do recuo elástico, pela alteração no parênquima, resulta em declínio progressivo da função pulmonar (MCNEE, 2016). A exposição crônica ao agente agressor promove desequilíbrio entre a formação de radicais livres de O_2 e a capacidade antioxidante, onde a sobrecarga oxidativa nos pulmões induz lesão celular, hipersecreção mucosa, inativação de anti-proteases, além de aumentar ainda mais a resposta inflamatória (CHUNG, 2008).

Macrófagos, neutrófilos e diversas células do sistema imune estão envolvidos nessa reposta anormal, aumentando o nível de biomarcadores de estresse oxidativo como peróxido de hidrogênio, 8-isoprostano, e marcadores inflamatórios como TNF-α, IL-6 e IL-8 e causando as alterações características (BRUSSELLE, 2011, HOW, 2016). Entretanto, assim como na IC, na maioria dos indivíduos com DPOC o processo inflamatório não se restringe ao sítio central, mas induz um processo sistêmico, marcado por níveis circulantes elevados de proteína C reativa (PCR), TNF-alfa, IL-6, IL-8 (GAN, 2004), e envolvido nas principais disfunções sistêmicas da doença (BARNES, 2009; HUANG, 2019).

A apresentação clínica da DPOC é resultado dessas alterações locais, e, das consequências sistêmicas delas, onde os principais sintomas incluem dispnéia, tosse crônica e hipersecreção brônquica, variando em prevalência, intensidade e progressão nos pacientes (PAUWELS, 2004). Assim, foram propostos fenótipos da doença, ou seja, "características, únicas ou combinadas, que descrevem a diferença entre indivíduos com DPOC e estão relacionadas a resultados clinicamente significativos" (HAN, 2010), para facilitar sua identificação e guiar o tratamento MIRAVITTLES, 2012).

Classicamente os pacientes eram estratificados em 2 fenótipos: o enfisema, no qual o paciente tem dispnéia e acianose, conhecido como *pink puffer,* e o bronquítico crônico, no qual o paciente apresenta congestão e cianose, conhecido como *blue bloater* (DORNHORST, 1955;). Atualmente 3 fenótipos são bem descritos e difundidos: 1) indivíduos com baixo risco de mortalidade, baixa limitação do fluxo aéreo e menos comorbidades; 2) indivíduos mais jovens, com maior limitação do fluxo aéreo, baixo índice de massa corporal e baixa frequência de comorbidades cardiovasculares; 3) indivíduos idosos com menor limitação ao fluxo aéreo, alto índice de massa corporal e altas taxas de comorbidades cardiovasculares e presença diabetes. Dentre eles, os fenótipos 2 e 3 apresentam maior risco de mortalidade (BURGEL, 2012; COSIO, 2016).

Anormalidades nutricionais e perda de peso, disfunção muscular esquelética, maior risco cardiovascular, disfunção cognitva e status de saúde prejudicado estão entre as principais manifestações sistêmicas da DPOC (DOURADO, 2006; PLEGUEZUELOS, 2016; YOHANNES, 2017). Adicionalmente, a presença de comorbidades e outras doenças crônicas concomitantes, ligadas a fatores de risco em comum como tabagismo, envelhecimento e inatividade, apresentam impacto significativo em seu estado de saúde e sobrevida (MILLER, 2013). Nesse contexto, as alterações cardíacas e vasculares, decorrentes das manifestações extrapulmonares e das próprias alterações mecânicas da doença, ganharam notoriedade (WATZ, 2010; FRAZÃO, 2019); não obstante, as disfunções no sistema cardiovascular estão entre as principais causas de mortes, independente da sintomatologia pulmonar, em pacientes com DPOC (MOLINA, 2018).

A relação da DPOC com a função cardíaca e demais manifestações sistêmicas ainda possui lacunas, mas ilustra a necessidade de avaliação multissistêmica, global e além das características pulmonares, para promover impacto real no curso da doença e no status clínico e funcional.

2.3 Insuficiência Cardíaca Coexistente à Doença Pulmonar Obstrutiva Crônica

Tanto a IC quanto a DPOC são doenças crônicas e progressivas, com curso flutuante semelhante, marcadas por exacerbações frequentes que

compartilham fatores de risco comuns, processos fisiopatológicos, sinais e sintomas clínicos (KETEYIAN, 2014) e agem sinergicamente como fatores prognósticos negativos uma da outra. Dada as particularidades, ambas são caracterizadas por alterações centrais que impactam negativamente na periferia, gerando os principais sinais e sintomas das doenças.

Dentre os principais fatores de risco para sua coexistência estão o histórico de tabagismo, a idade avançada (>70 anos) e sexo masculino (UKENA, 2010; DIEZ, 2013). Em estudo multicêntrico sobre a coexistência de IC+DPOC, em comparação com IC isolada, aqueles com ambas eram significativamente mais velhos, mais frequentemente fumantes, eram mais sintomáticos para fadiga e, consequentemente, em uma classe mais alta de NYHA (III / IV- GRIFFO, 2017). Ainda, em sua análise de regressão para o risco de DPOC em pacientes com IC, a idade avançada, o tabagismo e a presença de distúrbio ventilatório moderado-severo foram identificados como fatores preditivos.

O mecanismo fisiopatológico que as conectam ainda não foi totalmente esclarecido, porém as alterações estruturais nos sítios centrais, a inflamação sistêmica e até mesmo o uso de medicamentos (beta-agonistas e beta-bloqueadores) parecem ser os mecanismos de conexão (DIEZ, 2013; HAWKINS, 2013). Já se tem descrito que o caráter inflamatório sistêmico (marcado por alterações nos níveis de PCR, IL-6, TNG-alfa, BNP) da DPOC é um fator de predisposição e aceleração da aterosclerose (ANDRE, 2019), aumentando o risco de IC precoce; ainda, a hiperinsuflação compromete a adequada função do VE (WATZ, 2010; BARR, 2010) gerando, a longo prazo, alterações estruturais e funcionais.

A IC como fator de risco para a DPOC é menos provável e menos elucidada; alterações pressóricas na câmara cardíaca, desbalanço simpato-vagal, alteração da perfusão pulmonar, podem ser fatores desencadeantes da disfunção pulmonar em pacientes com IC, culminando na DPOC, mas ainda não há informações na literatura que afirmem.

Quanto à prevalência da IC-DPOC, ainda é um ponto discutível, complexo e variável. Em pacientes com IC, a prevalência de DPOC varia de 20% a 32%; por outro lado (RUSHTON, 2015; CANEPA, 2017), a presença de IC em pacientes com DPOC chega a 20% (RUSHTON, 2015; PIRINA, 2017). Pode-se atribuir tal discordância a critérios diagnósticos variados, alguns sem

reprodutibilidade, diferentes populações estudadas (comunidade, pacientes ambulatoriais, internados, idosos estáveis ou diferentes fenótipos de DPOC) e gravidade das doenças; a hiperinsuflação na DPOC pode impedir uma avaliação ecocardiográfica acurada e anormalidades de caráter obstrutivo na avaliação da função pulmonar podem estar presentes na IC descompensada, sendo fatores confundidores (HAWKINS, 2013; PELICORI, 2017).

Independente da real prevalência, diversos estudos já ilustraram que, em comparação a grupos com doenças isoladas, os pacientes com IC-DPOC apresentam piores marcadores de função pulmonar e cardíaca (MASCARENHAS, 2010), estado inflamatório mais ativado (contagem elevada de leucócitos, ácido úrico, PCR- CANEPA, 2017), pior tolerância ao exercício (OLIVEIRA, 2016), maiores taxas de exacerbações e mortalidade (MACCHIA, 2007, RUSINARU, 2008; CANEPA, 2017). Por exemplo, a DPOC foi descrita como preditor independente de morte e hospitalizações em pessoas com IC e se sugere que represente maior risco de resultados ruins em relação a outras condições médicas na IC (por exemplo, hipertensão, diabetes) (HAWKINS, 2009).

Entretanto, alguns marcadores funcionais ainda foram pouco descritos, especialmente em populações brasileiras. Em relação a capacidade funcional, avaliada principalmente pelo TC6, alguns autores já descreveram que pacientes com diagnóstico concomitante percorrem distâncias significativamente menores, comparadas a amostras com apenas IC ou DPOC (MENTZ, 2013). Contudo, a maioria dessas análises foi feita de maneira retrospectiva e alguns não utilizaram critérios diagnósticos validados. Outras características como função da musculatura respiratória, função cognitiva, qualidade de vida e presença da síndrome da fragilidade ainda permanecem incertas nessa população.

2.4 Marcadores e Avaliações Funcionais

2.4.1 Intolerância Ao Exercício

Um dos principais marcadores da IC e da DPOC é a grave e progressiva intolerância ao exercício (HAYKOWSKI, 2015; MCNAMARA, 2018). Esta, definida como um comprometimento na capacidade de realizar atividades físicas

(AF) acompanhada por sintomas de dispnéia e / ou fadiga significativas, tem em sua etiologia um desbalanço entre as repostas cardiorrespiratórias, muscular e metabólica (DEL BUONO, 2019).

Na ICFEp é considerada sintoma crônico primário, mesmo em indivíduos compensados. Essa disfunção é um forte determinante do prognóstico e da qualidade de vida reduzidos e é expressa principalmente pela diminuição do pico de VO_2 (MONTERO, 2018); este, alterado principalmente pelo desbalanço entre a oferta e extração de O_2 (princípio de Fick- DHAKAL, 2015) e demarcado por redução no pico de débito cardíaco (Qpeak), sua relação com a área de superfície corporal (índice cardíaco de pico- CIpeak) e diferença arteriovenosa de O_2 (ABUDIAB, 2013).

Os mecanismos fisiopatológicos da intolerância ao exercício na IC são multifatoriais e somam os comprometimentos de reserva cardíaca, disfunção da reserva pulmonar, da perfusão e da função dos músculos esqueléticos e respiratórios (SHIMIAIE, 2015). Do ponto de vista periférico, a menor tolerância ao esforço resulta da diminuição da capacidade oxidativa do músculo esquelético, da menor perfusão muscular, da presença de disfunção endotelial (HOUSTIS, 2018); essas alterações favorecem o aparecimento de acidose ainda nas fases iniciais do exercício, levando a fadiga precoce. A menor oferta de O_2 aos músculos também é resultado da menor biodisponibilidade do vasodilatador endotelial, por estado pro inflamatório e estresse oxidativo, aumento de substâncias vasoconstritoras (endotelina-1, angiotensina-II- BARRET-O'KEEFE, 2014) e aumento da estimulação simpática devido à sensibilização de metaborreflexos (AMANN, 2014), sendo ainda mais exacerbado à medida que a intensidade do exercício aumenta.

Além dessas disfunções decorrentes das próprias alterações da doença, a presença de comorbidades impacta negativamente a capacidade ao exercício. A presença de anemia, diabetes mellitus (DM), DPOC, depressão, obesidade, (MURAD, 2011; SHIBA, 2011; DEL BUONO, 2019) pode acelerar a progressão da intolerância ao exercício na IC, principalmente por adicionar fatores que impactam na adaptação cardiovascular e periférica durante o exercício.

Na DPOC, a intolerância ao exercício também é multifatorial e relacionada a má adaptação dos sistemas frente ao esforço (GUANETTE, 2014). Aqui, um de seus fatores chave é o nível intolerável de dispnéia, resultante da combinação

entre alta demanda ventilatória e mecanismos dinâmicos anormais (alta carga elástica e obstrução ao fluxo aéreo- JAMES, 2019); a diminuição da complacência pulmonar dinâmica e aumento da carga resistiva dos músculos respiratórios resulta em aumento mais acentuado da resposta neural e da sobrecarga muscular, limitando a resposta ao esforço e acentuando a fadiga (MENDONÇA, 2014; O'DONNELL, 2017)

A disfunção da musculatura periférica é considerada determinante chave da limitação ao exercício, principalmente de membros inferiores (BARREIRO, 2015); esta, assim como na IC, é caracterizada por um declínio funcional, de perda de força e *endurance* dos músculos (MALTAIS, 2014; CANNON, 2016) além de anormalidades estruturais, como diminuição da massa muscular e relação capilaridade/mitocôndria, mudanças no tipo e tamanho das fibras musculares, redução das enzimas oxidativase e alteração da bioenergética muscular (GOSKER, 2007; TAIVASSALO, 2016; CECO, 2017), sendo essas atribuídas ao caráter sistêmico da doença.

Em relação a presença de comorbidades, a relação entre DPOC e alterações cardíacas vem ganhando notoriedade na fisiopatologia da intolerância ao exercício. Diversos estudos ilustram que em pacientes com DPOC, a disfunção cardíaca pode, independentemente, contribuir para a intolerância ao exercício na DPOC (FENSTER, 2015). Schoos et al. (2013) encontraram que o volume de regurgitação tricúspide, um marcador da função diastólica do VD, é um preditor independente de tolerância ao exercício, em pacientes com DPOC moderada a severa. Ainda, alterações na resposta cronotrópica (LIU, 2016), atividade nervosa simpática muscular (HAARMAN, 2016) e perfusão muscular (IEPSEN, 2017) já foram descritas como fatores intervenientes na capacidade de exercício em pacientes com DPOC.

2.4.2 Teste de Caminhada de Seis Minutos na Avaliação da Tolerância ao Exercício

Capacidade de exercício e capacidade funcional podem se assemelhar, mas suas definições guardam algumas diferenças, importantes de destacar: a capacidade de exercício pode ser entendida como "máximo de esforço físico que um sujeito pode sustentar" (MARK, 2003), enquanto a capacidade funcional como "a capacidade de realizar atividades da vida diária que exigem um

metabolismo aeróbico submáximo sustentado" (ARENA, 2007); porém, de maneira geral ambas traduzem os esforços integrados dos sistemas pulmonar, cardiovascular e esquelético.

Para sua avaliação o Teste Cardiopulmonar (TCP), com a medida do VO_2 máximo/pico é considerado "padrão ouro" (ATS, 2003). No entanto, este é relativamente caro, consume tempo considerável, exige equipe treinada e não é tolerado pela maioria dos pacientes com IC ou DPOC. Assim, diversos testes clínicos já foram propostos, sendo o TC6 o mais utilizado e descrito na literatura (ATS, 2002). Este, se tornou uma importante ferramenta de estratificação da gravidade da doença, de eficácia e evolução do tratamento, de predição de mortalidade e hospitalizações (KINGA, 2013; ANDRIANOPOULOS, 2015; TUFARO, 2015; CELLI, 2016), principalmente por sua facilidade de execução, simplicidade, além de boa reprodutibilidade. Em pacientes com IC, distâncias (DTC6) < 300m indicam maior risco de mortalidade e desfechos negativos (INGLE, 2007; MANDI, 2018) e na DPOC, DTC6 <350m indicativa de pior prognóstico e mortalidade (CASANOVA, 2008; DAJCZMAN, 2015),

O TC6 é caracterizado como teste submáximo (ATS, 2002), que mesmo limitado em dar informações específicas de cada sistema, representa acuradamente o nível de esforço da maioria das AVDs, logo, a DTC6 pode refletir melhor o nível de exercício funcional em comparação aos testes máximos (POULAIN, 2003). Sua execução segue a normatização proposta pela American Thoracic Society (2002) e equações de predição foram propostas para traçar um comparativo entre o esperado e o executado (dado em % do predito).

A fórmula proposta por Enright e Sherril (1998) é uma das mais utilizadas até hoje, levando em consideração fatores como idade, sexo, peso e altura. Entretanto, trata-se de uma equação que pode falhar ao ser aplicada a população brasileira, por diferenças regionais. Por isso alguns estudos propuseram uma equação brasileira (SOARES, 2001; DOURADO, 2011), dentre eles o de Britto et.al (2013) que propôs a seguinte equação, baseada em um estudo multicêntrico: DTC6: 890.46 - (6.11 x idade) + (0.0345 x idade^2) + (48.87 x sexo) – (4.87 x IMC), onde masculino =1 e feminino =2.

Além do mais, diversos fatores já foram descritos como influenciadores nesse resultado e sua identificação é relevante para monitorização e identificação de maiores riscos. Idade, sexo feminino, humor deprimido, função

cardíaca, função pulmonar, são fatores que podem determinar menores ou maiores DTC6 em pacientes com IC ou DPOC (SCHOOS, 2013; RODRIGUEZ, 2014; LENCER, 2017). Contudo, quando ambas coexistem ainda não se tem descrito qual a mínima distância clinicamente relevante ou quais fatores podem determiná-la.

2.4.3 Função Muscular Respiratória

O caráter sistêmico, somado às alterações mecânicas e adaptativas, da IC e da DPOC comprometem a função da musculatura respiratória, impactando não somente na funcionalidade, mas na sintomatologia e no prognóstico desses indivíduos (MIYAGI, 2017). Entretanto, embora os músculos respiratórios (MR) também sejam "músculos esqueléticos", suas propriedades estruturais, funcionais e metabólicas e a resposta a estressores ou inatividade são notavelmente diferentes dos músculos periféricos (SIECK, 2013).

A força muscular respiratória (FMR) já foi estabelecida como marcador fisiológico da função respiratória, com valor prognóstico e terapêutico, tanto na IC quanto na DPOC (CHIAPPA, 2009; SINGER, 2011). Sua avaliação, dada pelas pressões inspiratória (PImáx) e expiratória (PEmáx) máximas, reflete a função do diafragma e dos músculos abdominais, respectivamente, e já possui forma padronizada de avaliação, através da manovacuometria (ATS, 2002). Para sua determinação diversas equações já foram propostas, principalmente para traçar comparativos e estipular metas (COSTA, 2010; PESSOA, 2014). No Brasil, a fórmula proposta por Souza et.al (2002) é amplamente utilizada e utiliza o sexo e a idade como fatores preditores, sendo para homens de 20 a 80 anos: PImáx (cmH_2O)* = 143 – 0,55 e PEmáx (cmH_2O) = 268 – 1,03; e para mulheres de 20 a 86 anos: PImáx (cmH_2O) = 104 – 0,51 e PEmáx (cmH_2O) = 170 – 0,53.

No geral, tanto na IC (DAL LAGO, 2006) quanto na DPOC (BEAUMONT, 2018), há prejuízo da força e da *endurance* desses músculos, onde o comprometimento do metabolismo energético, do balanço síntese/degradação de proteínas, da disfunção autonômica, aumento de citocinas inflamatórias locais/sistêmicas e do estresse oxidativo (JAENISCH, 2011; MANGNER, 2015) são parte da explicação fisiopatológica.

Na IC, a fraqueza dos MR pode potencializar a sensação de dispnéia e contribuir para a fadiga precoce durante o esforço (DUBÉ, 2016). No diafragma de pacientes com IC há alteração na proporção de fibras tipo I e II, levando a um certo aumento na capacidade oxidativa, porém comprometendo sua capacidade geral de gerar força (KELLEY, 2017). Isso pode ser visto na prática onde, por fatores como a congestão pulmonar, há um aumento da carga de trabalho do diafragma, que se adapta e mantém sua capacidade de resistência a fadiga, porém às custas da perda de força. Adicionalmente, alterações no mecanismo intracelular do cálcio (Ca^{2+}- DOMINGUEZ, 2003), desbalanço simpatovagal e dos barorreflexos (BAEKEY, 2010), contribuem para o comprometimento dessa musculatura.

Na DPOC, os processos fisiopatológicos que aumentam o trabalho respiratório e as demandas ventilatórias provocam um recrutamento exagerado do diafragma, e dos músculos acessórios, mesmo em níveis de volume corrente, resultando em menor capacidade adaptativa ao esforço e em maiores níveis de dispnéia (KLIMATHIANAKI, 2011). Esse comportamento a longo prazo leva a alterações na proporção da fibra muscular, comprimento do sarcômero, massa muscular e seu metabolismo (LEVINE, 2003).

Semelhante ao que ocorre na IC, aqui há aumento na proporção de fibras de contração lenta do tipo I, que são mais resistentes à fadiga, aumentando a resistência diafragmática, mas a degradação de proteínas e uma redução significativa no conteúdo de miosina diminuem sua capacidade de geração de força (OTTENHEIJM, 2008). Além disso, as alterações mecânicas, causadas principalmente pela hiperinsuflação, modificam a forma e a geometria torácica, levando a redução crônica da zona de aposição do diafragma, diminuindo o comprimento das fibras e alterando sua capacidade de gerar força (DOUCET, 2004; LEWIS, 2016). Essas alterações somadas têm impacto negativo na intolerância ao exercício.

Tanto na IC quanto na DPOC, a disfunção diafragmática está associada a maior intolerância ao exercício, pior qualidade de vida, maior tempo de internação hospitalar e pior prognóstico (TAYLOR, 2018; Wolpat, 2017). Em relação a coexistência IC-DPOC, ainda não há dados descritos na literatura.

2.5 FUNÇÃO COGNITIVA

A função cognitiva pode ser entendida como qualquer função cerebral que permita a um indivíduo perceber, registrar, armazenar, recuperar e usar informações (LEZAK, 2012). Tais capacidades permitem adaptação a novas situações e ambientes e são relacionadas a domínios como memória e atenção. O processo de envelhecimento por si traz alterações nesses domínios e culminam no déficit cognitivo leve (DCL), estágio onde ainda não há comprometimento das AVDs ou demais funções básicas e onde as lesões cerebrais, causadas por atrofia cerebral ou degeneração, são seu principal mecanismo (PETERSEN, 2018).

Entretanto, quadros agudos e/ou crônicos podem acelerar esse processo e trazer alterações não esperadas para a faixa etária, além de aumentar o risco de demência, estágio mais grave do déficit cognitivo (DC; LEZAK, 2012). Por exemplo, em comparação a indivíduos saudáveis, pareados em idade, os pacientes com IC tem aumento de 62% nas chances de desenvolver DC (VOGELS, 2007), sendo este um importante fator de comprometimento da independência funcional e da qualidade de vida, tornando imprescindível sua detecção precoce.

Tanto a IC quanto a DPOC relacionam-se ao DCL por mecanismos diretos (alterações vasculares, de perfusão e metabólicas) quanto indiretos (associação com diversas comorbidades; AMPADU, 2015), que comprometem principalmente tarefas executivas, de planejamento, memória e capacidade de resolução de problemas (LETO, 2014). Esses mecanismos ainda não estão integralmente esclarecidos, mas recentes estudos relataram que indivíduos com IC ou DPOC apresentam alterações cerebrovasculares que levam a hipoperfusão cerebral, isquemia ou hipóxia e, portanto, a um processo neurodegenerativo, culminando em prejuízos cognitivos (ALMEIDA, 2012; ABETE, 2014). Na DPOC, a hipercapnia também parece desempenhar um papel na patogênese do DCL através de um mecanismo de toxicidade neuronal (PAREKH, 2005).

Ademais, fatores como tabagismo, inflamação sistêmica/ estresse oxidativo, diabetes mellitus, polifarmácia e inatividade física também parecem estar relacionados ao desenvolvimento do DCL (figura 2), principalmente por induzirem alterações na plasticidade sináptica e neurogênese, bem como nas

cascatas de neurotransmissores envolvidos nos diversos processos cognitivos (MCAFOOSE, 2009; SCIMONELLI, 2013).

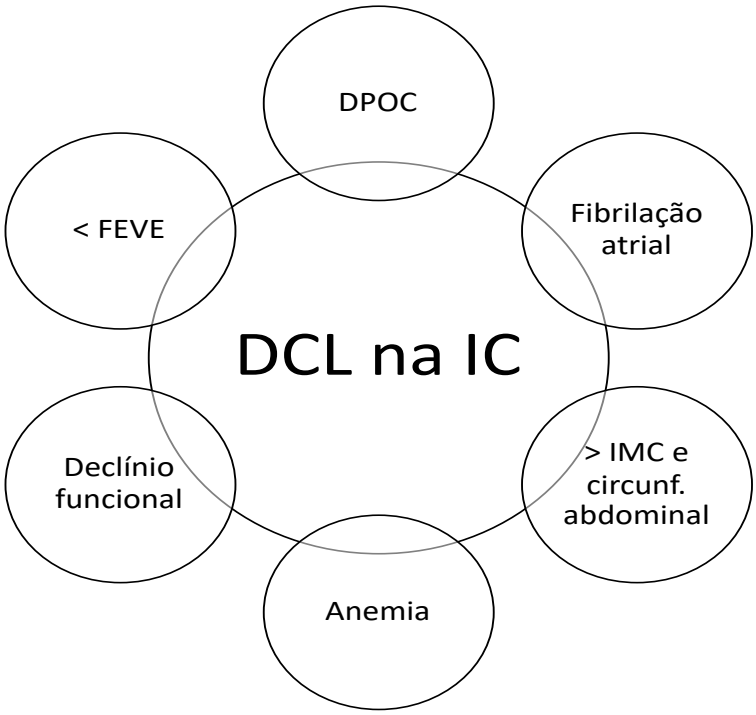

Figura 2: Fatores de risco para o déficit cognitivo leva (DCL) na IC. FEVE: fração de ejeção do ventrículo esquerdo; IMC: índice de massa corporal.

A prevalência do DCL ainda é discutível; Yohannes et al. (2017), em sua meta-análise, encontrou que a prevalência geral de DCL em pessoas com DPOC e IC foi de 32% e 30%, respectivamente. Todavia, os números ainda são discordantes, variando de 13,5-80% na IC (LEVIN, 2014) e de 16-57% na DPOC (SINGH, 2013). Essa discrepância deve-se principalmente as ferramentas utilizadas para avaliação e seus pontos de corte (BEERS, 2018). Dentre as mais utilizadas há o Mini-Exame do Estado Mental (MMSE) e o Montreal Cognitive Assesment (MoCa), onde na comparação de sensibilidade para detecção do DCL, o MoCa se mostrou mais sensível para esse estágio de disfunção (CAMERON, 2012; CIESIELSKA, 2016).

Independente do método de avaliação, deve-se considerar que o DCL é uma importante comorbidade tanto na IC e na DPOC, capaz de comprometer a adesão ao tratamento, a cessação do tabaco, o autocuidado (CLEUTJENS, 2017) e aumentar a prevalência da depressão, outro fator de alto impacto no curso das doenças (ALOSCO, 2014).

Sua relação com a capacidade funcional e a tolerância ao exercício ainda é pouco esclarecida, porém já se sabe que pacientes com menores escores apresentam maior limitação (ALOSCO, 2015) e que o exercício físico regular é capaz de melhorar a atenção visual, memória verbal e as funções visoespaciais (DODD, 2010), ilustrando uma possível correlação.

A coexistência da IC-DPOC já foi ilustrada como um fator de piora da função cognitiva, onde, em uma análise de regressão pacientes com ambas tinham maior comprometimento cognitivo comparados a amostra com apenas IC (ALOSCO, 2015). Uma possível resposta seria que a DPOC pode contribuir com reduções aditivas na oxigenação cerebral, com danos cerebrais resultantes. Porém, quando analisado o impacto dessa disfunção na capacidade funcional, ainda não se tem ilustrado nessa população.

2.6 SÍNDROME DA FRAGILIDADE

A síndrome da fragilidade é considerada uma entidade clínica complexa e multifatorial, refletida por um estado de reserva fisiológica diminuído e maior vulnerabilidade a estressores (FRIED, 2001; GOLDWATER, 2015), baseada majoritariamente no tripé sarcopenia, desregulação neuroendócrina e alterações imunológicas. Foi inicialmente descrita em 1980, por Whoodhouse que definia idosos frágeis aqueles indivíduos com mais de 65 anos de idade, dependentes para suas AVDs e geralmente institucionalizados.

Entretanto, estudos subsequentes trouxeram que essa seria uma definição limitada. Em 2001 o termo voltou a ter notoriedade com a proposta de definição padronizada e operacional de fenótipo de fragilidade, elaborada por Fried e colaboradores, e determinado pela presença de três ou mais de cinco critérios: perda de peso não intencional; exaustão autorrelatada; fraqueza muscular; lentidão da marcha; baixo gasto energético-nível de atividade física; assim classificando-os em robustos, pré-frágeis (1-2 critérios) e frágeis (3 ou mais).

A ausência de um padrão ouro para sua identificação traz discordância entre as taxas de prevalência. Estima-se que de 18%-54% dos pacientes com IC podem ser considerados frágeis (JHA, 2016; DENFELD, 2017), aumentando seu impacto e prevalência com a gravidade e avançada idade (classes III-IV

NYHA, +80 anos); na DPOC, a prevalência de fragilidade pode variar de 5% a 45% (WOO, 2015; LAHOUSSE, 2016). Ainda, se mostrou mais prevalente em mulheres, assim como em populações afro-americanas e latinas (WEISS, 2011).

A fisiopatologia subjacente da fragilidade é complexa e incompletamente entendida. Supõe-se que o desbalanço nos sistemas hematológico, inflamatório-anti-inflamatório e neuroendócrino, característicos tanto da IC quanto da DPOC, sejam a conexão por induzirem redução na homeostasia sistêmica, disfunção muscular e vulnerabilidade imunológica (BARZILAY, 2007; CLEGG, 2013). Fontana et.al (2013) mostram que maior risco de fragilidade foi significativamente associado a marcadores inflamatórios elevados, disfunções endócrinas múltiplas e aumento do estado catabólico, fatores associados diretamente a sarcopenia, logo, a patogênese da fragilidade.

A presença da síndrome da fragilidade em pacientes com IC ou DPOC, se traduz por aumentar os riscos de eventos negativos após quadros agudos ou eventos como quedas (VIDAN, 2016). Acarreta em prejuízos funcionais e clínicos, se tornando fator independente de pior prognostico pós internação hospitalar maiores taxas de readmissão, maiores gastos com serviços de saúde, (PRECIADO, 2017; YAMADA, 2018), incapacidade e mortalidade, em comparação aos pacientes avaliados como robustos (XUE, 2010), devendo ser incluída na avaliação clínica dessas populações.

Em relação a tolerância ao exercício, Boxer et. al (2010) trouxeram que a fragilidade estava associada a baixa tolerância ao esforço, avaliada pelo TC6; posteriormente, encontraram associação entre a fragilidade e menores distâncias no TC6 (r=-0.72) em si.

Contudo, em pacientes com IC coexistente à DPOC, muitos aspectos funcionais ainda não foram descritos, incluindo a síndrome da fragilidade. Portanto se torna imprescindível o delineamento de um perfil dessa população, capaz de ilustrar o impacto da IC-DPOC em parâmetros de fácil avaliação e alta relevância clínica, como a DTC6.

3 OBJETIVOS

3.1 OBJETIVO GERAL

- Descrever o perfil clínico-funcional de pacientes com diagnóstico de insuficiência cardíaca coexistente à doença pulmonar obstrutiva crônica.

3.2 OBJETIVOS ESPECÍFICOS

- Correlacionar os marcadores clínicos e funcionais de pacientes com diagnóstico de insuficiência cardíaca coexistente à doença pulmonar obstrutiva crônica;

- Identificar os fatores determinantes da distância percorrida no teste de caminhada de seis minutos em pacientes com insuficiência cardíaca coexistente a doença pulmonar obstrutiva crônica;

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5 ARTIGO

Determinants of the Distance Covered During a Six Minutes' Walk Test in Patients with Chronic Heart Failure-Chronic Obstructive Pulmonary Disease Overlap

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1. ABSTRACT

Background: HF-COPD frequent coexists in practice and functional capacity, measured by 6 minutes' walk test, play a major role. Several factors can be involved in distance covered during the test. **Materials and Methods:** A cross-sectional study was conducted. Included patients perform 2 6MWT, respiratory muscle strength and CHS index (frailty) evaluation. Also, have quality of life and cognitive function assessed. **Results:** 32 patients were evaluated, mean distance 281.1 ± 101.9 meters. Correlated to the distance covered were VFC ($r = 0.61$; $p < 0.01$), % FEV_1 ($r = 0,58$; $p < 0.01$), %VFC ($r= 0.56$; $p<0.01$), CHS index ($r = 0.53$; $p < 0.01$) and MLHF-Q score ($r = -0.47$; $p < 0.01$). Gait speed ($\beta=-0,54$, $p=0.000$), FEV_1 ($\beta=-0,44$, $p=0.000$) and NYHA class ($\beta=-0,24$, $p=0.000$) were predictors of distance walked in the 6MWT (6MWD). **Conclusions:** Gait speed, FEV_1 and NYHA class may be predictors of shorter 6MWD in HF-COPD patients.

Key words: heart failure; chronic obstructive pulmonary disease; functional capacity; walk test;

2. ABREVIATION LIST

HF- Heart failure

COPD – Chronic obstructive pulmonary disease

CPET- Cardiopulmonary exercise test

6MWT- Six minutes' walk test

6MWD- Distance covered in the six minutes' walk test

LVEF- Left ventricular ejection fraction

NYHA- New York Heart Association

FEV_1- Forced expiratory volume on first second

VFC- Vital forced capacity

L- Liters

m- meters

s- seconds

GOLD- Global Initiative for Chronic Obstructive Lung Disease

BMI- Body mass index

HR – heart rate

SAP- Systolic arterial pressure

DAP- Diastolic arterial pressure

MIP- Maximal inspiratory pressure

MEP- Maximal expiratory pressure

ATS- American Thoracic Society

ERS- European Respiratory Society

cmH_sO- water centimeter

CHS- Cardiovascular Health Study

Kgf- Kilogram force

MOca- Montreal Cognitive Assessment

MLHF-Q- Minnesota living with heart failure questionnaire

MCI- Mild cognitive impairment

QoL- Quality of life

CARS- COPD activity rating scale

mMRC- Modified medical research council

3. INTRODUCTION

Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are major public health diseases, leading cause of death and disability[1,2], and its prevalence tends to increase by population aging. Both diseases have been extensively studied separately and show some similarities in clinical presentation, such as reduced exercise tolerance and muscle weakness[,5,6], frailty[7,8], and low physical activity level[9,10]. Besides, common factors like cigarette smoking, advanced age, and a high level of systemic inflammation[13,14] may be a link to a combined diagnosis.

The coexistence of HF and COPD is common in practice[15,16], but a differential diagnosis may be challenging because shared symptoms like dyspnea and fatigue[17]. So, the real prevalence remains discordant. Previous studies show that COPD is estimated to range from 23 to 33% in patients with HF[18] and HF ranges from 5% to 41% in patients with COPD[19]. Even without a consensus it is well describe that prognosis of patients with HF-COPD overlap is worse than those with only one[21] as well as the quality of life[22] and mortality rates[23].

Either in HF and COPD, the hallmark is exercise intolerance[15,25], and its mechanisms involve not only cardiac and pulmonary abnormalities but also peripheral[26,27], vascular[28], diaphragm[29,30], and autonomic dysfunction[31], and for those with HF-COPD overlap, this effort response is even worse[32]. For its assessment, the gold standard method is cardiopulmonary exercise test (CPET)[33], which many HF and COPD cannot perform for their physical and symptoms limitations. As an alternative, the 6 minutes' walk test (6MWT) has been used as a simple, reproducible, feasible, and sensitive tool[34], well-validated in both disease and with specific guidelines[35].

The primary outcome on 6MWT is the distance walked (6MWD)[35]. Also, 6MWD has been described as an independent predictor of mortality in both HF[37] and COPD[38], and it is essential to identify why some patients perform poorly in terms of this outcome. Many factors may influence 6MWD, including age and gender[39], renal function[40] and body composition[41], and its recognition may help plan interventions.

In HF-COPD overlap, however, is not well describe how they perform 6MWT, what is the overlap impact on functional features, cognitive function or frailty syndrome. Moreover, which features are associated with 6MWTD, especially in the Brazilian population. Therefore, the main aim of this study was to identify the determinants of the 6MWD in patients with HF-COPD overlap.

4. METHODS

This is a cross-sectional study including HF-COPD patients, from two referral hospitals in Porto Alegre, Rio Grande do Sul, Brazil. The sample size was calculated using GPower® software, using a significance level of 5%, a power of 0.80, an effect size of 0.42 (calculated from the determination coefficient – R^2) and the number of predicting variables. A minimum of 31 patients with HF-COPD was required.

Inclusion criteria were: patients of both sexes, aged ≥ 50 years old, with a clinical diagnosis of HF by echocardiography and COPD by spirometry (both at least in last 12 months) and agreed in participated by signing the informed consent form. Patients with stroke, musculoskeletal disorders, understanding impairment, or any limitation that would make it challenging to perform the tests were excluded from the study.

4.1 Ethical Aspects

The ethical research committee of the Santa Casa de Misericordia de Porto Alegre and Fundação Universitaria de Cardiologia do Rio Grande do Sul approved the study (approval number: 3.068.402 and 3.356.737, respectively). This study following the regulatory norms and standards for research involving human subjects (Brazilian National Council, resolution number 466/2012). All participants signed the informed consent form.

4.2 Procedures

Screening of patients was performed by analysis of medical records. Eligible patients were invited to participate in the study on the day of medical consultation or by telephone contact. The same professionals performed all the tests.

The distance covered during the 6MWT was considered the primary outcome whereas sociodemographic, clinical, physical- functional and cognitive data, as well as the quality of life, used as exposure data.

Clinical and Sociodemographic Variables

Questionnaires application and clinical and sociodemographic data were partially complete with data obtained from medical records and complemented by an interview on evaluation day. The mains variables were age (years), sex, ethnicity, years of study (<12 years, 12 years or higher education), smoking (yes or no/ex) - in cases of smokers and ex-smokers, years/pack were registered.

As clinical variables, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class, ischemic etiology of heart failure (yes/no), forced expiratory volume in the first second (FEV_1) and vital forced capacity (VFC), in absolute (liters-L)

and percentage (%) values; Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification (A, B, C, D). Were also collect main comorbidities, use of β-blocker and bronchodilator, number of hospitalizations in the past year and which disease was diagnosed primarily (HF or COPD).

As anthropometric data, height (cm) and weight (kg) were measured with patients standing barefoot, using a Prix® scale (model 2096 Pp), and the values used for body mass index (BMI) calculation (weight in kilograms divided by the square of height in meters).

6 Minutes' Walk Test

The 6MWT was conducted following international guidelines[35]. Two tests were performed with a 30-minute interval. Heart rate (HR), Borg dyspnea scale, peripheral oxygen saturation (SpO_2), systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) were measured before the test, at the end (sixth minute) and during recovery (1 and 2 minutes after the test). Also, measurements of HR, Borg scale, and SpO_2 were got during the test (at the third minute). The distance covered was compared with that expected for the Brazilian population and expressed as total and percentage of predict[42].

Respiratory Muscle Strength

Strength of the respiratory muscles was measured using a pressure transducer (MVD300®, Globalmed). The maximum inspiratory pressure (MIP) and the maximum expiratory pressure (MEP) were registered following the American Thoracic Society (ATS)/ European Respiratory Society (ERS) guidelines [43]. The average mean attempts to obtain a reproducible value were five and results were exposed as absolute (cmH_2O) and percentage (%) of predict, based on previous equation reports[44].

Frailty Evaluation

Frailty phenotype score[45] (also called CHS index) is a multidomain research tool used to identify frailty in clinical practice.

CHS index use five domains: (1) Self-reported unintentional weight loss in past year; (2) Exhaustion: questions 7 and 20 of the Center scale of Epidemiological Scale - Depression (CES-D)[46]; (3) Physical Activity Level: caloric expenditure, by Minnesota Leisure Time Activity questionnaire[47]; (4) Impaired muscle strength: value in kilogram-force (kgf) obtained by the dynamometer Jamar® and adjusted by sex and BMI[45] and (5) Slow gait speed: time, in seconds, spent to cover 4.0 m in a total of 8.0 m and adjusted by sex and height[45]. Criteria for positive in each domain are presented in Table 1.

Fragile individuals were considered to have scored positive in 3, 4 or 5 items, pre-fragile those scored positive on 1 or 2 items and robust those that do not fill any item.

Cognitive Function

To assess the cognitive function, the Montreal Cognitive Assessment (MoCA) was chosen. MoCA considers the cognitive domains of visuospatial skills, executive functions, language, attention, concentration, working memory, memory recall, and orientation.

The total possible score is 30, and the cutoff for MCI describe for the cardiovascular population is 24[48]. Low educational attainment (≤12 years of formal education) was correct by adding 1 point to the participant's final score.

Quality of Life Assessment

The Minnesota Living with Heart Failure Questionnaire (MLHF-Q) was select for quality of life (QoL) estimation. It consists of 21 questions related to how much the disease prevents the patient from living as they would like, taking the last month to answer the questions. The questions involve a physical dimension (from 1 to 7, 12 and 13), an emotional dimension (from 17 to 21) and other issues (questions 8, 9, 10, 11, 14, 15 and 16) which, form the total score (100) as higher the score as worse health status.

There is no specific questionnaire for HF-COPD population, but the MLHF-Q has already been described as a valid and reliable assessment of health status in patients with coexistent COPD and HF[49].

5. STATISTICAL ANALYSIS

Statistical analysis was perform using the Statistical Package of Social Sciences (SPSS), version 24.0. Normality of distribution was verified by the Shapiro-Wilk test. Normally distributed continuous variables were present as absolute numbers and percentages and as mean ± standard deviation. Non-parametric variables were shown as median (minimum-maximum).

For correlation and regression analysis one subject were exclude due to a very shorter distance in 6MWT. Correlations were analyzed using Pearson's test. Multiple linear regression was made to determine the predictive value of the variables on 6MWT, and the stepwise method was used for the selection of the variables. All assumptions made by the multiple linear regression analysis - linear relationship, homoscedasticity, no or little multicollinearity between exposures variables were considered for selection of the model with the highest predictive value.

Besides, T-test was used to compare the mean distance predict by resulting equation and the mean distance covered. The level of significance was 5%.

6. RESULTS

Thirty-two patients were evaluated in a convenience sample. Mean age was 67.6± 8.54 years, 65.6% were female and initial diagnosis was HF in 59,4% (Table 2). Table 3 describes clinical features and table 4 the functional results, as cognitive, quality of life, frailty and 6MWT characteristics.

6MWD mean was 281.1 ± 101.9m and showed significative correlation with gait speed ($r = -0.81$; $p < 0.01$), FEV_1 ($r = 0.63$; $p < 0.01$), NYHA class ($r = -0.46$; $p < 0.01$), VFC ($r = 0.61$; $p < 0.01$), % FEV_1 ($r = 0,58$; $p < 0.01$), %VFC ($r= 0.56$; $p<0.01$), CHS index ($r = 0.53$; $p < 0.01$) and MLHF-Q score ($r = -0.47$; $p < 0.01$). Figure 1 shows the correlation graphic of 6MWD with gait speed (A) and FEV_1 (B).

Following the association tests and exclusion of variables by collinearity, the variables were select in descending order of importance in the stepwise variable selection. Thereby, the following variables were included in the final model for 6MWD: gait speed ($p<0.000$), FEV_1 ($p<0.000$), and NYHA class ($p<0.000$). These variables resulted in a model statistically significant ($p<0.000$, $R^2 = 0.83$) explaining 81% of the variance in the 6MWD in the study population. The derived equation for 6MWT based on this analysis was: 494.3 + (-39.5 x gait speed) + (79 x FEV_1) + (-45.7 x NYHA class).

On validation analysis, no significant difference was found between mean covered distance (281.1± 101.9 m) and mean predicted by the resulting equation (290,6 ± 82,7 m- figure 2).

7. DISCUSSION

The main finding of the present study was that distance covered in the 6MWT could be determined by gait speed (s), FEV_1 (L) and NYHA class. These were potential variables with predictive value for shorter distances which explained 81% of the variance for the distance covered in the 6MWT. Furthermore, FVC (L), $\%FEV_1$, %FVC, QoL score, and CHS index were also correlated with 6MWD.

The determinants of reduced 6MWD are complex and depend on both physical and psychological factors. For COPD patients, a 6MWD lower than 350 m[50,51] and for HF patients a 6MWD lower than 300 m[52,53], has prognostic value in identifying high-risk patients. In the current study, 6MWD mean was 281.1 m, suggesting that HF-COPD overlap represents a higher risk profile for adverse outcomes.

A substantial body of previous research has shown that slow gait speed is the most useful single indicator of frailty, is consistently associated with reduced survival in different cohort studies[54] and predicting major adverse cardiac events in different groups[55,56]. Previous studies in COPD population has report findings similar to presented here, where gait speed was found to have a strong correlation with 6MWD ($r = 0.70$, $p < .001$)[57,58]. Our study extended their findings by demonstrating that gait speed not only corelates to 6MWD but can be a robust predictive variable for shorter distances covered.

Gait speed is a reliable and easy-to-perform measurement in both COPD and HF[59,60], is mainly determined by exercise capacity and reflects the multisystemic effects of disease severity. Inefficient gait mechanics may contribute to exercise limitation in these patients because of their wasteful skeletal muscle[61,62] which is unable to sustain the necessary action to perform a longer stride. As consequence, in HF and COPD

patients a shorter stride could minimize muscular discomfort, slowing down the average speed.

In COPD patients lower FEV_1, in both absolute and % of predict values, were correlated to poor distances ($r= -0.34$, <0.001)[63] and in HF, lower FVC was predictive to determine lower 6MWD[64] ($r = -0.42$, $p < 0.01$), indicating that lung function also is relate to functional capacity in both populations. Despite, a scope of reports also has shown that these variables, isolated, are inadequate predictive tools, and its interpretation must be associated with other clinical-functional parameters to achieve better understandings of its role on exercise and functional capacity.

Airflow limitation leads to some pulmonary abnormalities such as hyperinflation[65], which has come to be considered one of the leading pulmonary causes of exercise limitation in patients with COPD[66] as well in HF[67]. The decrease of exercise tolerance matches well with the decline of pulmonary function, i.e., the more severe is airflow obstruction, the worse is 6MWD. These findings were about isolated diseases, but when HF-COPD coexists, the pulmonary function may play a more significant role in exercise intolerance.

The relation between NYHA class and 6MWD it is poorly described. However, in one of the few studies, Pepera et. al. (2012) found results similar to presented here, where NYHA class was a predicted variable for 6MWD in HF patients ($p = 0.06$). Both 6MWT and NYHA classification are available and practical tools for the functional capacity measure, but the subjectivity of NYHA classification demands prudent interpretation. A review conducted by Yap et. al. (2015) has brought an inverse correlation between NYHA class and 6MWD, especially in more severe classes (III/IV).

In a COPD population study, the degree of perceived symptoms was found to be correlated to 6MWD ($r=0.56$, $p < 0.00002$)[70], illustrating that how patients perceive

their limitations can impact on their functional capacity. Therefore, once NYHA class is related to the influence of symptoms, the relation with 6MWD possible lays on the impact of dyspnea/fatigue in exercise tolerance.

The association between 6MWD and other variables – bivariate analyses

To our knowledge, this is the first study that evaluated the determinants of 6MWD in HF-COPD overlap population. Previous studies have reported several predictive variables of the 6MWD in HF and COPD samples, including age[71], sex[72], weight, and BMI[73]., left ventricular end-systolic volume[74], depression[75], and quadriceps force[76].

Regarding QoL evaluation, by MLHF-Q, our findings are in line with previous studies that had exposed a positive correlation between 6MWD and QOL score in HF patients. Nogueira et al. showed a significant moderate correlation ($r=-0.5$, $p<0.001$) between 6MWD and QoL. Also, the mean score of MLHF-Q in this study (58.4 ± 20.6) was similar to average reported for HF patients[77], illustrating that maybe the presence of COPD does not add an extra impact on health status. However, the relation with 6MWT found in this study expose that patient's motivation plays a pivotal role and can be altered by depressive symptoms and lower health status.

Several studies have reported frailty phenotype as an independently predictive of mortality, with a hazard ratio between 1.58 to 1.69 for each unit of increase[78,79] in either HF and COPD patients. Our findings were in agreement with Boxer et. al. (2010), that brought a negative, robust, correlation between frailty and functional capacity ($r= -.72$, $p<0.001$), measured by 6MWT. Frailty is a measure of increased vulnerability to the adverse outcome, and the 6MWT is a measure of functional ability and aerobic

capacity. These two measures together can theoretically capture the patients most at risk for adverse events and a decline in the physical function.

About HF-COPD overlap sociodemographic features, previous reports have shown some different findings to ours: male sex was described as most frequent [80] and older age[81,,82]. One possible reason is that in our study, most of the participants had HF with preserved ejection fraction (HFpEF -mean 54.7 ± 15.9 %) which is more prevalent in women[83] and younger subjects[84]. Concerning age, our results suggested that HF-COPD overlap represents a critical negative effect on functional capacity, even in younger subjects.

In one of the few studies that explored 6MWT in HF-COPD overlap, the mean distance was 295.0 ± 95.2[85], similar to ours (281.1 ± 101.9). These findings suggest that the pathophysiologic mechanisms most closely associated with aerobic exercise abnormalities in patients with HF may be influenced by COPD comorbidity and vice-versa, leading to a worse functional capacity.

Limitations of the Study

This study has limitations associated with: 1) the absence of other functional tests like mMRC (Modified Medical Research Council) Dyspnea Scale, to measure restrictions and symptoms impact on daily living activities; 2) most of our tests were self-dependent, and the results may not reflect the full functional capacity, exposing a need for studies with cardiopulmonary tests to access their real limitations.

8. CONCLUSION

Determinants of functional capacity are multifactorial, depending on demographics, physiological, and psychosocial factors. In our study three variables, slow gait speed (s), lower FEV_1 (L) and higher NYHA class, were identified as determinants of a shorter 6MWD in patients with HF-COPD overlap, explaining 81.2% of the variance. Other variables, such as QoL and Frailty CHS index were also correlated to 6MWD indicating the multidimensionality of functional capacity in HF-COPD patients.

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Figure 1. Correlation graphics

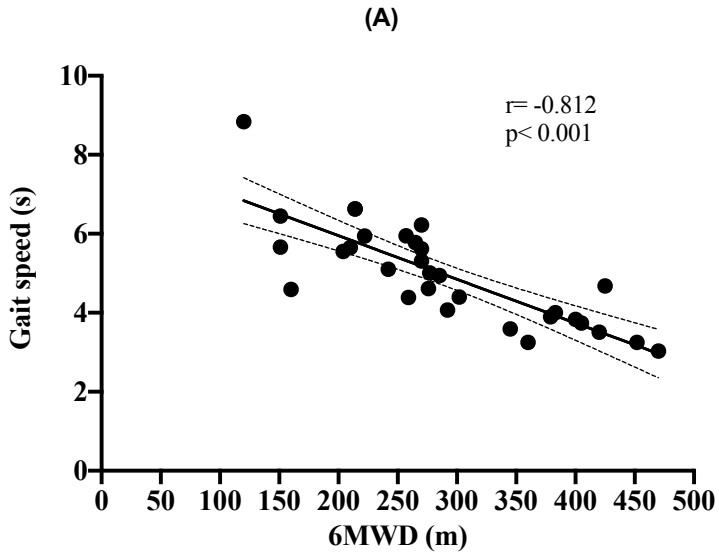

Figure A: correlation of 6MWD (in meters) and Gait Speed (time, in seconds).

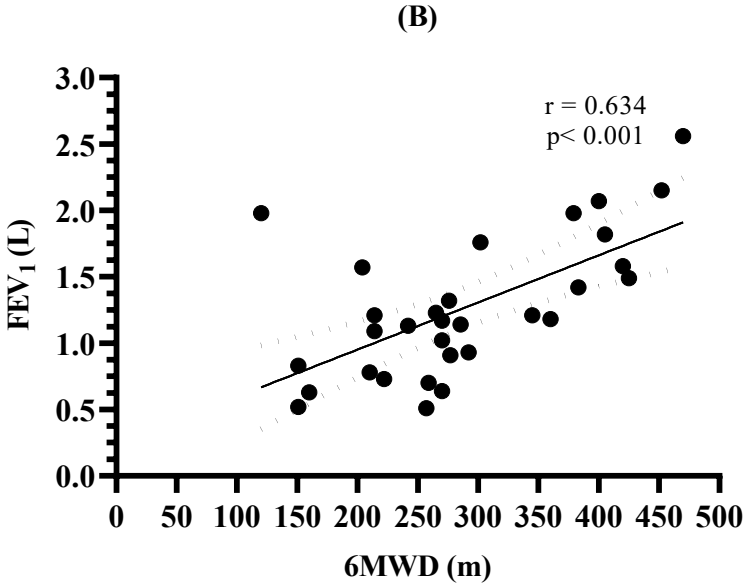

Figure B: correlation of 6MWD and Forced Expiratory Volume on 1 second (absolute value, in liters).

Figure 2. Six Minutes'walk test distances

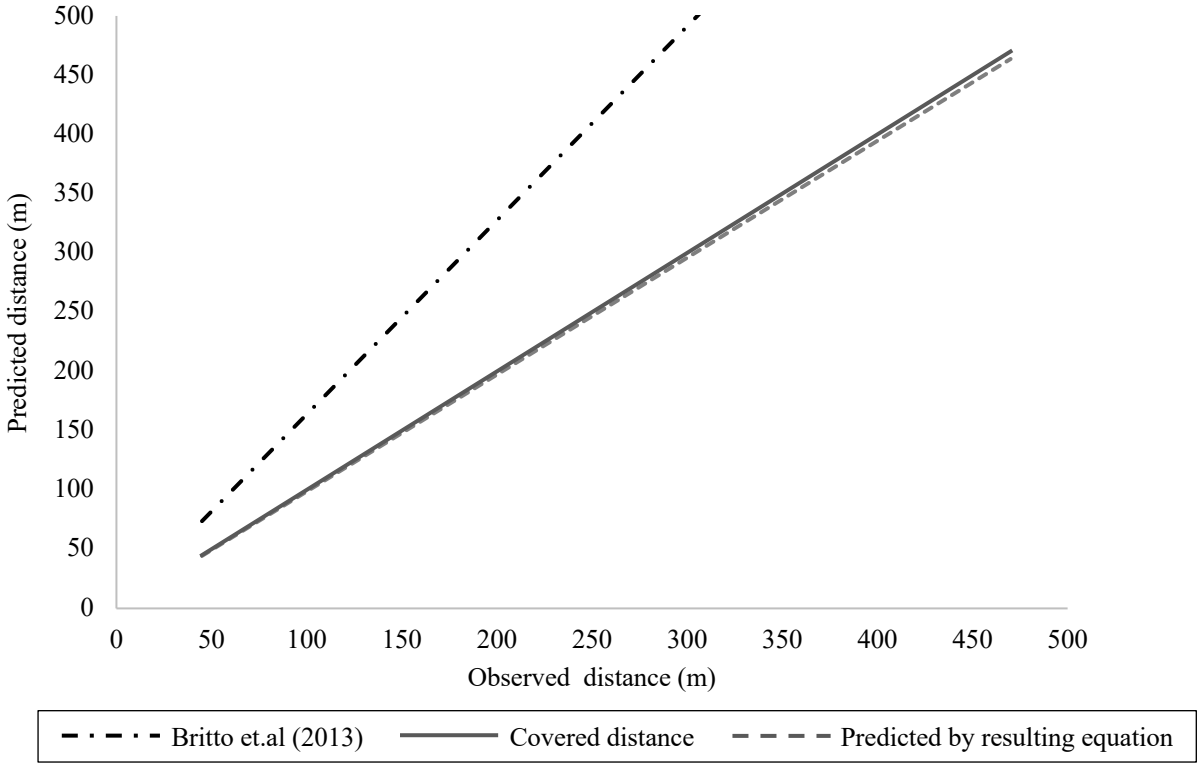

Figure 2. 6MWD (in meters) mean differences between covered, predicted by Britto et. al (2013) and predicted by resulting regression equation.

Table 1. Criteria for pointing positive in each domain of CHS index.

Domain	Criteria for positive
Weight loss	> 4kg (~10 pounds)
Exhaustion	Questions 7 and 20 answered **"most of the time"** and **"always"** to at least one of the questions
Physical Activity Level	**<270kcal** for women and **<383kcal** for men, per week
Handgrip strength	**<17 kgf (BMI <23)**, **<17.3 kgf (BMI 23.1-26), <18 kgf (BMI 26.1-29**) and **<21 kgf (BMI> 29)** for women; **<29 kgf (BMI <24)**, **<30 kgf (BMI 24.1-28)** and **<32 kgf (BMI> 28)** for men
Gait speed	**> 7s (<159cm)** or **6s (> 160cm)** for women **> 7s (<173cm)** or **6s (<173cm)** for men

*kg (kilos); BMI (Body mass index); Kgf (Kilogram-force); S (seconds);

Table 2. Characteristics of patients.

Sociodemographic Characteristics	Values
Age, years	67.7 ± 8.54
Female sex – no./total no. (%)	21/32 (65.6)
Ethnicity	
White- no./total no. (%)	23/32 (71,9)
Black- no./total no. (%)	3/32 (9.4)
Brown- no./total no. (%)	6/32 (18.8)
Education attainment, years	
<12 years- no./total no. (%)	26/32 (84.4)
> 12 years- no./total no. (%)	4/32 (12.5)
Higher education – no./total no. (%)	1/32 (3.1)
Smoking	
Yes- no./total no. (%)	8/32 (25%)
Ex-smokers- no./total no. (%)	24/32 (75%)
Years/pack	45 (9.75 to 250)

Table 3. Clinical characteristics

Characteristics	Values
HF ischemic etiology-no. / total no. (%)	21/32 (65.6)
LVEF %	54.7 ± 15.9
NYHA class	
Class II- no./ total no. (%)	19/32 (59.4)
Class III- no./ total no. (%)	13/32 (40.6)
GOLD classification	
A- no./ total no. (%)	1/32 (3.1)
B- no./ total no. (%)	8/32 (25)
C- no./ total no. (%)	5/32 (15.6)
D- no./ total no. (%)	18/32 (56.3)
FEV_1 (L)	1.3 ± 0.52
% FEV_1	50.8 ± 3.37
VFC (L)	2.0 ± 0.58
% VFC	62.1± 2.54
% FEV_1/ VFC	59.6 ± 7.9
Co-morbidities	
Hypertension- no./ total no. (%)	30/32 (93.8)
Diabetes- no./ total no. (%)	10/32 (31.3)
Pulmonary hypertension	6/ 32 (18.8)
Depression	12/32 (37.5)
Medications	
β-blocker- no./total no. (%)	20/32 (62.5)
Bronchodilator – no./ total no. (%)	22/32 (68.8)

*HF (Heart failure); LVEF (Left Ventricular Ejection Fraction); NYHA (New York Heart Association); GOLD (Global Iniative for Lung Disease); FEV_1 (Forced expiratory volume on first second); VFC (Vital Forced Capacity).

Table 4. Functional features

Characteristics	Values
6MTWD (m)	281.1 ± 101.9
% predict	54.4 ± 3.4
MIP (H_2Ocm)	57.6 ± 15.4
% predict	72.4 ± 3.4
MEP (H_2Ocm)	79.3 ± 22.8
% predict	51.7 ± 2.7
Frailty domains	
Handgrip (kgf)	16.3 (10 to 30.6)
Gait speed (s)	5 ± 1.26
Sedentary-no./total no. (%)	21/32 (65.6)
Frailty classification	
Non-frail- no./ total no. (%)	2/32 (6.3)
Pre-frail no./ total no. (%)	13/32 (40.6)
Frail no./ total no. (%)	17/32 (53.1)
MOca	17.7 ± 3.71
MLFH-Q	58.4 ± 20.6

*6MWD: Six Minutes Walk Distance; MIP (Maximal Inspiratory Pressure); MEP (Maximal Expiratory Pressure); MoCA (Montreal Cognitive Assessment); MLHF-Q (Minnesota Living with Heart Failure Questionaire); m (Distance in meters); kgf (Kilogram force); s (Time in seconds).

6 CONCLUSÃO GERAL

Concluímos que os determinantes da capacidade funcional, avaliada pelo TC6, em pacientes com IC-DPOC, são multifatoriais, e se relacionam fatores clínicos, funcionais e psicossociais. A QV e índice de fragilidade CHS estão correlacionadas ao desempenho no TC6 e velocidade (s) lenta (s) da marcha, menor VEF_1 (L) e maior classe da NYHA além da correlação foram identificadas como determinantes de um TC6 menor em pacientes com IC-DPOC - explicando 81,2% da variância. Esses achados indicam a multidimensionalidade da capacidade funcional em pacientes com IC-DPOC.

ANEXOS

ANEXO A

Carta de aprovação do Comitê de Ética e Pesquisa (CEP)

UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Efeito do treinamento físico na capacidade funcional em pacientes com insuficiência cardíaca coexistente à doença pulmonar obstrutiva crônica

Pesquisador: Pedro Dal Lago

Área Temática: **Versão:** 3

CAAE: 81421817.0.0000.5345

Instituição Proponente: Universidade Federal de Ciências da Saúde de Porto Alegre

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER
Número do Parecer: 2.733.736
Apresentação do Projeto:

O objetivo deste estudo é avaliar o efeito do exercício físico em variáveis funcionais e clínicas em pacientes com DPOC coexistente à IC, bem como descrever a amostra. Trata-se de um estudo clínico controlado,incluindo 56 indivíduos, sendo 28 portadores de IC e 28 de IC concomitante à DPOC, com quadro estável, classes II e III (New York Heart Association-NYHA) e GOLD II e III (baseados na avaliação espirométrica). Estes serão avaliados quanto a sua capacidade funcional, status de fragilidade, qualidade de vida,independência funcional, força muscular respiratória, função cognitiva e perfil clínico e inflamatório. As avaliações serão realizadas através de testes funcionais, como o teste de caminhada de 6 minutos (TC6'), e clínicos (coleta sanguínea). O estudo será conduzido na Irmandade Santa Casa de Misericórdia de Porto Alegre ou no Instituto de Cardiologia do Rio Grande do Sul.

Objetivo da Pesquisa:

Objetivo Geral:

Avaliar o efeito do exercício físico sobre a capacidade funcional em pacientes com insuficiência cardíaca coexistente à doença pulmonar obstrutiva crônica.

Endereço: Rua Sarmento Leite, ,245 **Bairro:** Sarmento **CEP:** 90.050-170
UF: RS **Município:** PORTO ALEGRE
Telefone: (51)3303-8804 **E-mail:** cep@ufcspa.edu.br

Objetivos Específicos:

-Verificar o grau de fragilidade em pacientes com diagnóstico de insuficiência cardíaca coexistente à doença pulmonar obstrutiva crônica;

-Verificar o nível de independência funcional em pacientes com diagnóstico de insuficiência cardíaca coexistente à doença pulmonar obstrutiva crônica;

-Verificar o nível de atividade física diária em pacientes com diagnóstico de insuficiência cardíaca coexistente à doença pulmonar obstrutiva crônica;

-Verificar a força muscular respiratória (Pressão inspiratória máxima e Pressão expiratória máxima) em pacientes com diagnóstico de insuficiência cardíaca coexistente à doença pulmonar obstrutiva crônica; -Verificar a qualidade de vida em pacientes com diagnóstico de insuficiência cardíaca coexistente à doença pulmonar obstrutiva crônica;

-Verificar a função cognitiva em pacientes com diagnóstico de insuficiência cardíaca coexistente à doença pulmonar obstrutiva crônica;

-Avaliar níveis séricos de marcadores inflamatórios: TNF – , interleucina 6 e Proteína C reativa (PCR), em pacientes com diagnóstico de insuficiência cardíaca coexistente à doença pulmonar obstrutiva crônica;

Avaliação dos Riscos e Benefícios:

BENEFÍCIOS:

Os possíveis benefícios deste estudo são a diminuição do cansaço para realizar suas atividades diárias ou algum esforço físico, bem como melhora na sua qualidade de vida.

RISCOS:

As avaliações que serão realizadas apresentam um risco mínimo levando em consideração que todas são funcionais. O exercício aeróbico pode levar a efeitos como taquicardia, sudorese, cansaço, algum desconforto relacionado à utilização do equipamento, desconforto nos membros inferiores e cansaço muscular leve após treinamento em esteira. As coletas sanguíneas apresentam possibilidade de danos como hematomas, sangramento e desconforto. Caso ocorra qualquer episódio supracitado, os pacientes serão encaminhados ao atendimento médico do Pavilhão Pereira Filho, ou do Instituto de Cardiologia, para os devidos cuidados. Não haverá danos de ordem psíquica, moral, intelectual, social, cultural ou espiritual do ser humano, em qualquer fase desta pesquisa, bem como não há

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risco processo e risco produto, visto que, garante-se o total sigilo dos dados obtidos e o repasse a sociedade preservando a fidedignidade desta pesquisa.

Comentários e Considerações sobre a Pesquisa:

Há dois coparticipantes: Instituto de Cardiologia do RS / Fundação Universitária de Cardiologia e Irmandade da Santa Casa de Misericordia de Porto Alegre - ISCMPA.

Os nomes do responsáveis pelos respectivos CEPs foi ajustado no PB.

O TCLE apresenta o endereço do CEP.

Considerações sobre os Termos de apresentação obrigatória:

Folha de rosto devidamente assinada e carimbada.

Declaração de termo de compromisso para utilização de material biológico, devidamente assinado. Não há previsão de retensão de amostras.

Termo de entrega de relatoria parcial (agosto/2018) e final (agosto/2019).

Declaração de uso de dados secundários (prontuário).

Declaração isenção de ônus institucional.

Declaração e confidencialidade.

Termo de anuência do responsável pela instituição ISCMPA e ICFUC assinada e carimbadas.

Recomendações:

Todas as recomendações foram atendidas.

Conclusões ou Pendências e Lista de Inadequações:

Aprovar

Considerações Finais a critério do CEP:

De acordo com o parecer do Relator.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1050088.pdf	22/05/2018 15:24:14		Aceito
Outros	resposta_parecer_versao3.pdf	22/05/2018 15:20:02	Maria Luísa Rocha Dadalt	Aceito
TCLE / Termos de Assentimento / Justificativa de	TCLE_VERSAO3.pdf	22/05/2018 12:10:21	Maria Luísa Rocha Dadalt	Aceito

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Ausência	TCLE_VERSAO3.pdf	22/05/2018 12:10:21	Maria Luísa Rocha Dadalt	Aceito
Projeto Detalhado / Brochura Investigador	projeto_mestrado_versao3.pdf	22/05/2018 12:09:58	Maria Luísa Rocha Dadalt	Aceito
Cronograma	Cronograma_VERSAO3.pdf	22/05/2018 12:09:37	Maria Luísa Rocha Dadalt	Aceito
Orçamento	orcamento_versao_2.pdf	29/03/2018 10:13:25	Maria Luísa Rocha Dadalt	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_versao_2.pdf	29/03/2018 10:10:41	Maria Luísa Rocha Dadalt	Aceito
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Outros	resposta_parecer_revisor_cep.pdf	29/03/2018 09:59:34	Maria Luísa Rocha Dadalt	Aceito
Outros	termo_icfuc.pdf	18/12/2017 09:07:36	Maria Luísa Rocha Dadalt	Aceito
Brochura Pesquisa	resumo_projeto.pdf	14/12/2017 11:10:08	Maria Luísa Rocha Dadalt	Aceito
Outros	declaracao_chefia_responsavel.pdf	14/12/2017 11:07:49	Maria Luísa Rocha Dadalt	Aceito
Outros	termo_anuencia_responsavel.pdf	14/12/2017 11:06:01	Maria Luísa Rocha Dadalt	Aceito
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Declaração de Manuseio Material Biológico / Biorepositório / Biobanco	declaracao_compromisso_utilizacao_material_biologico.pdf	14/12/2017 10:45:56	Maria Luísa Rocha Dadalt	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_MESTRADO.pdf	14/12/2017 10:44:40	Maria Luísa Rocha Dadalt	Aceito

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Folha de Rosto	FOLHA_DE_ROSTO.pdf	14/12/2017 10:36:51	Maria Luísa Rocha Dadalt	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

PORTO ALEGRE, 25 de Junho de 2018

Assinado por:
Luciane Dalcanale Moussalle
(Coordenador)

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ANEXO B

Guia para publicação Heart and Lung

HEART & LUNG

The Journal of Cardiopulmonary and Acute Care

AUTHOR INFORMATION PACK

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ISSN: 0147-9563

DESCRIPTION

Heart & Lung: The Journal of Cardiopulmonary and Acute Care, the official publication of The American Association of Heart Failure Nurses, presents original, peer-reviewed articles on techniques, advances, investigations, and observations related to the care of patients with acute and critical illness and patients with **chronic cardiac** or **pulmonary disorders**.

The Journal's **acute care** articles focus on the care of hospitalized patients, including those in the critical and acute care settings. Because most patients who are hospitalized in acute and **critical care** settings have chronic conditions, we are also interested in the chronically critically ill, the care of patients with **chronic cardiopulmonary disorders**, their rehabilitation, and disease prevention. The Journal's heart failure articles focus on all aspects of the care of patients with this condition. Manuscripts that are relevant to populations across the human lifespan are welcome.

We are interested in publishing articles representing a broad range of science and clinical practice in a variety of settings as it pertains to our target population. Because health care and the health sciences are global, interdisciplinary, multidisciplinary, and transdisciplinary, we encourage authors to submit manuscripts that reflect these perspectives. Many articles also provide nurses with a framework for applying research results in clinical practice.

We publish original research, case reports, reviews, and observations that are on the cutting edge of science and clinical practice. Discussions of costs of care, patient education, and health policy are relevant to our focus. Reports of well-designed clinical trials and systematic reviews are especially welcome.

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GUIDE FOR AUTHORS

Introduction

Heart and Lung: The Journal of Acute and Critical Care, the official publication of The American Association of Heart Failure Nurses, presents original, peer-reviewed articles on techniques, advances, investigations, and observations related to the care of patients with acute and critical illness and patients with **chronic cardiac** or **pulmonary disorders**.

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We are interested in publishing articles representing a broad range of science and clinical practice in a variety of settings as it pertains to our target population. Because health care and the health sciences are global, interdisciplinary, multidisciplinary, and transdisciplinary, we encourage authors to submit manuscripts that reflect these perspectives. Many articles also provide nurses with a framework for applying research results in clinical practice.

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Types of paper

We publish original research, case reports, reviews, and observations that are on the cutting edge of science and clinical practice. Reports of well-designed clinical trials and systematic reviews are especially welcome. Discussions of translational research and implementation and improvement science, as well as costs of care, patient education, and health policy are of high relevance to our focus.

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BEFORE YOU BEGIN

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The manuscript should be arranged as follows: 1) title; 2) structured abstract and key words; 3) abbreviations list; 4) text; 5) references; 6) figure titles and legends; and 7) tables. Page numbering should begin with the first page.

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Manuscript text should be double-spaced, left-aligned (unjustified), and in a 12-point font. The body of text should be structured with the following headings: Introduction, Methods, Results, and Discussion. Sub-headings may be used as appropriate. Each reference, figure and table should be cited in the text in numerical order according to order of first mention.

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State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

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Acknowledgments

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