

# Determinants of the Six-Minute Walk Distance in Subjects with Heart Failure-Chronic Obstructive Pulmonary Disease Overlap

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## Abstract

**Background:** Heart failure (HF) and chronic obstructive pulmonary disease (COPD) frequently coexist in clinical practice, with both conditions negatively affecting individuals' functional capacity, often measured using the 6-minute walk test (6MWT). Cardiovascular, pulmonary, and metabolic impairments may influence the 6-minute walk distance (6MWD).

**Objective:** This study aims to identify and analyze the critical determinants of the 6MWD among subjects with HF-COPD overlap.

**Methods:** A cross-sectional study was conducted. Individuals underwent the 6MWT. Respiratory muscle strength was assessed by measuring maximum inspiratory pressure and maximum expiratory pressure. Pulmonary function was evaluated using forced expiratory volume in the first second (FEV<sub>1</sub>) and forced vital capacity (FVC). Physical frailty was assessed using the Cardiovascular Health Study frailty index. Quality of life was assessed with the Minnesota Living with Heart Failure Questionnaire, and cognitive function was assessed using the Montreal Cognitive Assessment.

**Results:** Thirty-two individuals were evaluated, with a mean age of  $67.6 \pm 8.5$  years; 65.6% were women. The mean left ventricular ejection fraction was  $54.7 \pm 15.9\%$ , and the mean 6MWD was  $281 \pm 102$  meters. The 6MWD was significantly correlated with FVC ( $r = 0.61$ ,  $p < 0.01$ ); percentage of predicted FEV<sub>1</sub> ( $r = 0.58$ ,  $p < 0.01$ ); percentage of predicted FVC ( $r = 0.56$ ,  $p < 0.01$ ); Cardiovascular Health Study frailty index ( $r = 0.53$ ,  $p < 0.01$ ); and Minnesota Living with Heart Failure Questionnaire score ( $r = -0.47$ ,  $p < 0.01$ ). Gait speed ( $\beta = -0.54$ ,  $p < 0.001$ ); FEV<sub>1</sub> ( $\beta = -0.44$ ,  $p < 0.001$ ); and New York Heart Association functional class ( $\beta = -0.24$ ,  $p < 0.001$ ) were identified as significant predictors of 6MWD.

**Conclusions:** These findings suggest that an integral approach, incorporating both physical and psychosocial assessments, may be essential for effectively managing functional limitations in patients with HF-COPD. Identifying these predictors can aid clinicians in tailoring treatment strategies, optimizing rehabilitation programs, and improving this population's overall quality of care.

**Keywords:** Chronic Obstructive Pulmonary Disease; Heart Failure; Functional Status; Walk Test.

## Introduction

Heart failure (HF) and chronic obstructive pulmonary disease (COPD) rank highly as causes of death and disability, with their prevalence increasing alongside an aging population.<sup>1</sup> Studied in isolation, both HF and COPD exhibit clinical similarities such as reduced exercise tolerance, muscle weakness, and frailty.<sup>2–5</sup> Common risk factors such as smoking, age, and systemic inflammation often lead to their

co-diagnosis. The co-occurrence of HF and COPD is common, affecting up to 30% of patients, yet it remains underdiagnosed. This overlap significantly compounds organ dysfunction, symptom severity, and risk of mortality, particularly in older individuals.<sup>6</sup> While primary organ failure is often cardiac or pulmonary, the decline in functional capacity is also linked to musculoskeletal and systemic changes (muscle strength and muscle mass).<sup>7</sup> A differential diagnosis may be challenging due to shared symptoms like dyspnea and fatigue.<sup>8</sup> These symptoms are associated with worse prognosis, quality of life, and survival in patients with HF-COPD overlap compared to those with only one condition.<sup>7–9</sup>

Exercise intolerance is a defining feature of HF and COPD, arising from cardiac and pulmonary deficits and changes in peripheral, vascular, diaphragmatic, and autonomic functions.<sup>10,11</sup> This multifactorial decline is exacerbated in patients with HF-COPD overlap.<sup>7,9,12</sup> The cardiopulmonary exercise test is the gold standard for evaluating exercise

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**Central Illustration:** Determinants of the Six-Minute Walk Distance in Subjects with Heart Failure-Chronic Obstructive Pulmonary Disease Overlap



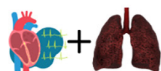
ABC Heart Failure & Cardiomyopathy

## Six-Minute Walk Distance in HF-COPD Overlap

### SUBJECTS

Cross-Sectional Study  
21 Women, 11 men

### HF + COPD



**AIM:** to identify the critical determinants of the 6MWD

### MEASUREMENTS

FVC, FEV<sub>1</sub>, MIP and MEP

6MWT

NYHA Class HF

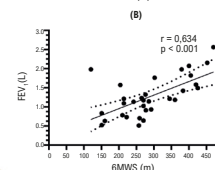
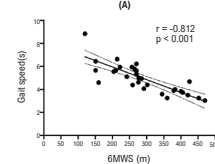
GOLD Class COPD

MoCA

MLHF-Q

Frailty

### FINDINGS



### CONCLUSION:

Gait speed, FEV<sub>1</sub>, and NYHA class were significant predictors of 6MWD in individuals with HF-COPD overlap.

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*COPD: chronic obstructive pulmonary disease; FEV<sub>1</sub>: forced expiratory volume in the first second; GOLD: Global Initiative for Obstructive Lung Disease; HF: heart failure; MLHF-Q: Minnesota Living with Heart Failure Questionnaire; MEP: maximum expiratory pressure; MIP: maximum inspiratory pressure; MoCA: Montreal Cognitive Assessment; NYHA: New York Heart Association; 6MWD: 6-minute walk distance; 6MWT: 6-minute walk test.*

capacity. Nonetheless, the 6-minute walk test (6MWT) has been used as a practical alternative due to its simplicity, reproducibility, and validation for both conditions.<sup>13</sup>

The primary measure of the 6MWT, the 6-minute walk distance (6MWD), effectively reflects an individual's functional exercise capacity for daily activities. Notably, 6MWD is an independent mortality predictor in both diseases,<sup>14,15</sup> making it crucial to understand the underlying causes of poor performance. Various elements, including demographic, renal, and body composition factors, can impact 6MWD, and identifying these can guide targeted interventions.<sup>16</sup> However, the literature seldom details how patients with HF-COPD overlap perform on the 6MWT, and the factors associated with the performance are still unknown. Therefore, this study seeks to unravel the main determinants of 6MWD among patients with HF-COPD overlap. Given the complexity of predicting exercise capacity in this unique population, developing a reliable prediction equation based on these determinants is essential for personalizing interventions and improving outcomes.

## Methods

### Study design and patients

This cross-sectional study enrolled patients diagnosed with HF and COPD from two referral hospitals in Porto Alegre, Rio Grande do Sul, Brazil, between October

2018 and March 2019. The sample size was calculated to ensure a 5% significance level and an 80% statistical power, anticipating an effect size of 0.42 based on the determination coefficient ( $R^2$ ) and the number of predictive variables. Using GPower® software, this calculation indicated a minimum of 31 patients for the study.

Eligible participants were men and women aged 50 years or older, as this age group represents the highest prevalence of the diseases under study. The attending physician confirmed HF diagnosis before the study based on clinical findings and echocardiography, regardless of etiology or severity, as defined by ejection fraction. In contrast, COPD was confirmed by spirometry performed within the last 12 months before inclusion in the study. Exclusion criteria included a history of stroke, cognitive impairment, or any other limitation that would impede the ability to perform the tests required by the study.

### Ethical aspects

The study was approved by the ethical research committees of Instituto de Cardiologia - Fundação Universitária de Cardiologia (IC-FUC) and Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA), under approval numbers 3.068.402 and 3.356.737, respectively. The study followed the regulatory norms and standards for research involving human subjects stipulated by the Brazilian National Council (Resolution Number 466/2012).

Informed consent was obtained from all participants via signed consent forms.

## Procedures

### Patient screening and data collection

Researchers identified patients through medical record reviews. Those meeting the eligibility criteria were invited to participate during their medical visits or through telephone contact. All assessments were conducted by researchers who received standardized training to ensure consistency in data collection procedures.

### Clinical and sociodemographic data

We gathered clinical and sociodemographic information using questionnaires supplemented by medical record reviews and interviews on the evaluation day. Key sociodemographic variables included age, sex, ethnicity, educational level, and smoking status. For smokers and former smokers, the pack-years of smoking were also recorded.

The clinical data encompassed anthropometric measurements (height, weight, and body mass index [BMI]), left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) functional class, and etiology of HF. Pulmonary function was assessed by forced expiratory volume in the first second (FEV<sub>1</sub>) and forced vital capacity (FVC), both reported in liters and as a percentage of the predicted value.<sup>17</sup> We also collected information on primary comorbidities, use of betablockers and bronchodilators, number of hospitalizations in the preceding year, and primary diagnosis (HF or COPD).

### Six-minute walk test

The 6MWT was conducted following international guidelines.<sup>13</sup> Participants performed two tests, separated by a 30-minute rest period. Considering the learning effect of the 6MWT, as reported in a previous study,<sup>18</sup> two tests were conducted to account for this effect. This study analyzed only the parameters from the second test. We measured heart rate, Borg dyspnea scale ratings, pulse oxygen saturation, and

systolic and diastolic blood pressure immediately before the 6MWT, at the conclusion (sixth minute) and during recovery (at the first and second minute after the test). Heart rate, Borg scale, and pulse oxygen saturation were also recorded at the midway point (third minute). The 6MWD was recorded and compared to expected values for the Brazilian population, with results presented in meters and as a percentage of the predicted distance.<sup>19</sup>

### Respiratory muscle strength

Respiratory muscle strength was assessed using a pressure transducer (MVD300®, Globalmed, Porto Alegre, Brazil). Maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) measurements followed international guidelines.<sup>20</sup> For each measurement, the best of five attempts was recorded to ensure reproducibility. Results were expressed in absolute terms (cmH<sub>2</sub>O) and as a percentage of predicted values.<sup>21</sup>

### Frailty evaluation

The Frailty Phenotype Score,<sup>22</sup> also known as the Cardiovascular Health Study (CHS) frailty index, is a tool for identifying physical frailty in clinical settings. The CHS frailty index evaluates the following 5 domains:<sup>22</sup> (1) unintentional weight loss: self-reported in the past year; (2) exhaustion: determined by questions 7 and 20 from the Center of Epidemiological Studies Depression Scale (CES-D); (3) physical activity level: measured through caloric expenditure as reported in the Minnesota Leisure Time Activity Questionnaire; (4) muscle strength: measured in kilogram-force (kgf) using a Jamar® dynamometer (Hydraulic Hand Dynamometer, Warrentville, IL, United States), with values adjusted for sex and BMI; and (5) gait speed: measured as the time taken to walk of 4 meters within an 8-meter path, adjusted for sex and height.<sup>22</sup> The criteria for scoring positively in each domain of the CHS index are presented in Table 1. Individuals are categorized as frail if they score positively in 3 to 5 domains, as pre-frail if they score positively in 1 or 2 domains, and robust if they do not score positively in any domain.

**Table 1 – Criteria for pointing positive in each domain of the Cardiovascular Health Study index<sup>22</sup>**

Domain	Criteria for positive score
Weight loss	Unintentional weight loss of ≥ 10 pounds (4.5 kg) in prior year
Exhaustion	Questions 7 and 20 answered “most of the time” and “always” to at least one of the questions
Physical activity level	Women: < 270 kcal per week Men: < 383 kcal per week
Handgrip strength	Women: < 17 kgf (BMI < 23), < 17.3 kgf (BMI 23.1 to 26), < 18 kgf (BMI 26.1 to 29), and < 21 kgf (BMI > 29) Men: < 29 kgf (BMI < 24), < 30 kgf (BMI 24.1 to 28), and < 32 kgf (BMI > 28)
Gait speed	Women: > 7 s (< 159 cm) or 6 s (> 160 cm) Men: > 7 s (< 173 cm) or 6 s (< 173 cm)

BMI: body mass index.

### Cognitive function

The Montreal Cognitive Assessment (MoCA) was utilized to evaluate cognitive function. This tool measures the following cognitive domains: visuospatial abilities, executive functions, language, attention, concentration, working memory, memory recall, and orientation. MoCA scores range up to 30, with scores below 24 indicating mild cognitive impairment in cardiovascular patients. For participants with 12 years of education or less, 1 additional point was added to their total MoCA score to account for lower educational levels.<sup>23</sup>

### Quality of life assessment

The Minnesota Living with Heart Failure Questionnaire (MLHF-Q) was used to assess patients' quality of life. This 21-item questionnaire evaluates how HF has affected the patient's lifestyle over the past month, with questions addressing physical aspects (questions 1-7, 12, 13); emotional aspects (questions 17-21); and additional considerations (questions 8-11, 14-16). The total score ranges from 0 to 100, with higher scores indicating a lower health-related quality of life. Although there is no questionnaire specifically tailored for the HF-COPD population, the MLHF-Q is a validated tool for assessing health status in patients with both COPD and HF.<sup>24</sup>

### Statistical analysis

The normality of distribution was assessed using the Shapiro-Wilk test. Continuous variables were reported as means  $\pm$  standard deviation when normally distributed and as medians with minimum and maximum values when non-normally distributed. Categorical variables were expressed in absolute numbers and percentages. One subject was excluded from the correlation and regression analyses due to excessive 6MWD variance between tests. Pearson's correlation test was used to examine relationships between variables. Multiple linear regression analysis with stepwise selection was conducted to identify predictors of 6MWT performance. Before model selection, the assumptions of linearity, homoscedasticity, and minimal multicollinearity were verified. A significance level of 5% was applied for all tests. Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS), version 24.0.

## Results

### Baseline characteristics

A sample of 32 patients was evaluated, with a mean age of  $67.6 \pm 8.5$  years; 65.6% of the participants were women; and 59.4% of the participants were first diagnosed with HF, followed by COPD. The remainder were first diagnosed with COPD or concomitant HF-COPD. Tables 2, 3, and 4 present detailed clinical characteristics and functional outcomes.

### Six-minute walk test and correlations

The average 6MWD was  $281.1 \pm 101.9$  meters. It showed significant correlations with gait speed ( $r = -0.81$ ,  $p < 0.01$ );  $FEV_1$  ( $r = 0.63$ ,  $p < 0.01$ ); NYHA class ( $r = -0.46$ ,  $p < 0.01$ ); FVC ( $r = 0.61$ ,  $p < 0.01$ ); percentage of predicted  $FEV_1$

**Table 2 – Sociodemographic characteristics of patients**

Characteristics	Values
Age, years	67.7 $\pm$ 8.5
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	
Smokers, no./total no. (%)	8/32 (25%)
Ex-smokers, no./total no. (%)	24/32 (75%)
Pack-years	45 (9.75 to 250)

( $r = 0.58$ ,  $p < 0.01$ ); percentage of predicted FVC ( $r = 0.56$ ,  $p < 0.01$ ); CHS frailty index ( $r = 0.53$ ,  $p < 0.01$ ); and MLHF-Q score ( $r = -0.47$ ,  $p < 0.01$ ). Figure 1 illustrates the correlations between 6MWD and gait speed (Panel A) and  $FEV_1$  (Panel B).

### Six-minute walk test and regression equation

After eliminating variables due to collinearity, a stepwise selection process identified the most impactful predictors of 6MWD. The final model included gait speed,  $FEV_1$ , and NYHA class, all with  $p$  values  $< 0.001$ . This model was statistically significant ( $p < 0.001$ ), explaining 83% of the variance in 6MWD among our study participants ( $r = 0.83$ ). The regression equation formulated from this model for predicting 6MWD is:

$$6MWD (m) = 494.3 + (-39.5 \times \text{gait speed}) + (79 \times FEV_1) + (-45.7 \times \text{NYHA class})$$

## Discussion

This study identified 3 key predictors, gait speed,  $FEV_1$ , and NYHA functional class, which collectively explain 83% of the variance in the 6MWD among patients with concomitant HF and COPD. These variables play a critical role in assessing physical capacity in this patient population. Additionally, significant correlations between 6MWD and other measures, such as FVC, percentage of predicted  $FEV_1$ , percentage of predicted FVC, quality of life scores, and the CHS frailty index, reveal a complex interplay between pulmonary function, HF severity, and overall health status in determining exercise tolerance. These findings enhance our understanding of exercise tolerance in this population and offer valuable insights for clinicians in tailoring interventions and monitoring progress in patients with HF-COPD overlap.



# Original Article

**Table 3 – Clinical characteristics**

Characteristics	Valores
<b>HF ischemic etiology, no./total no. (%)</b>	21/32 (65.6)
<b>LVEF, %</b>	54.7 ± 15.9
HFpEF, no. (%)	23 (71.9)
HFmrEF, no. (%)	3 (9.4)
HFrEF, no. (%)	6 (18.7)
<b>NYHA class</b>	
Class II, no./total no. (%)	19/32 (59.4)
Class III, no./total no. (%)	13/32 (40.6)
<b>GOLD classification</b>	
A, no./total no. (%)	1/32 (3.1)
B, no./total no. (%)	8/32 (25)
E, no./total no. (%)	23/32 (71.9)
<b>FEV<sub>1</sub> (L)</b>	1.3 ± 0.52
Percentage of predicted FEV <sub>1</sub>	50.8 ± 3.37
<b>FVC (L)</b>	2.0 ± 0.58
Percentage of predicted FVC	62.1 ± 2.54
<b>Percentage of predicted FEV<sub>1</sub>/FVC</b>	60.6 ± 9.9
<b>Comorbidities</b>	
Hypertension, no./total no. (%)	30/32 (93.8)
Diabetes, no./total no. (%)	10/32 (31.3)
Pulmonary hypertension, no./total no. (%)	6/32 (18.8)
Depression, no./total no. (%)	12/32 (37.5)
<b>Medications</b>	
Betablocker, no./total no. (%)	20/32 (62.5)
Bronchodilator, no./total no. (%)	22/32 (68.8)

FEV<sub>1</sub>: forced expiratory volume in the first second; FVC: forced vital capacity; GOLD: Global Initiative for Lung Disease; HF: heart failure; HFmrEF: heart failure with moderate or mildly reduced ejection fraction (LVEF 41% to 49%); HFpEF: heart failure with preserved ejection fraction (LVEF ≥ 50%); HFrEF: heart failure with reduced ejection fraction (LVEF ≤ 40%); LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

The determinants of 6MWD are multifaceted, encompassing a range of physical and psychological factors. Walking distance less than 350 meters in patients with COPD<sup>25</sup> and less than 300 meters in patients with HF<sup>26</sup> is considered prognostically significant, indicating high-risk individuals. In our cohort, the average 6MWD was 281 meters, reflecting a marked decline in functional capacity and suggesting that patients with coexisting HF and COPD may face an elevated risk for poor health outcomes. Notably, 23 patients (71.8%) in our study group could not walk 350 meters, and 21 patients (65.6%) did not reach the 300-meter threshold, further underscoring the severity of their impaired physical capacity.

**Table 4 – Functional characteristics**

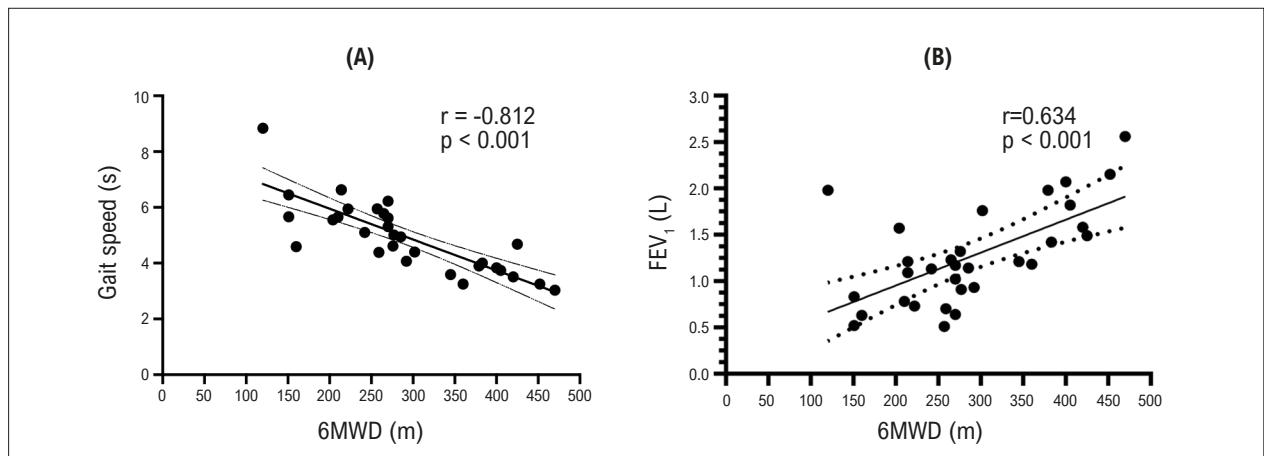
Characteristics	Values
<b>6MWD (m)</b>	281 ± 102
Percentage of predicted	54.4 ± 3.4
<b>MIP (cmH<sub>2</sub>O)</b>	57.6 ± 15.4
Percentage of predicted	72.4 ± 3.4
<b>MEP (cmH<sub>2</sub>O)</b>	79.3 ± 22.8
Percentage of predicted	51.7 ± 2.7
<b>Frailty domains</b>	
Handgrip, kgf	16.3 (10 to 30.6)
Gait speed, s	5 ± 1.26
Sedentary, no./total no. (%)	21/32 (65.6)
<b>Frailty classification</b>	
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)
<b>MoCA</b>	17.7 ± 3.71
<b>MLFH-Q</b>	58.4 ± 20.6

MEP: maximum expiratory pressure; MIP: maximum inspiratory pressure; MLHF-Q Minnesota Living with Heart Failure Questionnaire; MoCA: Montreal Cognitive Assessment; 6MWD: 6-minute walk distance.

Frailty is frequently observed in individuals with HF and COPD. Gait speed, as a composite indicator of overall health, mainly reflects frailty because it encompasses various functional domains, including sensory perception, motor skills, coordination, nutritional and cognitive status, and cardiorespiratory health. Extensive research has shown that reduced gait speed is a reliable predictor of frailty and is closely associated with decreased survival across multiple cohorts.<sup>27</sup> Furthermore, gait speed measured during the 6MWT has been shown to predict major adverse cardiac events in various populations. Specifically, slower gait speeds during the 6MWT in patients who have survived acute hypercapnic respiratory failure are associated with an increased risk of death or hospital readmission.<sup>28</sup>

Additionally, gait speed has been shown to predict mortality among older adults, with each increase of 0.1 m/s significantly associated with improved survival rates.<sup>29</sup> Consistent with our findings, previous research in COPD populations has identified a strong correlation between gait speed and 6MWD, with correlation coefficients as high as  $r = 0.70$ .<sup>30</sup> Building on this research, our study demonstrates that gait speed not only correlates with 6MWD, but also serves as a strong predictor of shorter walked distances.

Gait speed is a straightforward and reliable metric for assessing exercise capacity in COPD and HF, reflecting the multisystem impact of disease severity. In these patients, exercise limitation may be exacerbated by inefficient gait mechanics caused by



**Figure 1** – Correlation graphics. Panel A: Correlation of 6MWD (in meters) and gait speed (time, in seconds). Panel B: Correlation of 6MWD and FEV<sub>1</sub> (absolute value, in liters). FEV<sub>1</sub>: forced expiratory volume in the first second; 6MWD: 6-minute walk distance.

compromised skeletal muscle function,<sup>8,9</sup> which impairs their ability to maintain longer strides. As a result, individuals with HF and COPD may adopt shorter strides to reduce muscular discomfort, leading to a decrease in their average walking speed.

In patients with COPD, lower FEV<sub>1</sub> values, both absolute and as a percentage of predicted, have been linked to shorter walking distances.<sup>16</sup> Similarly, in HF patients, reduced FVC is inversely correlated with 6MWD,<sup>31</sup> highlighting the relationship between lung function and functional capacity in both groups. However, these variables alone are insufficient for accurate prognostication. A more nuanced understanding requires integrating them with other clinical-functional parameters to assess better their impact on exercise tolerance and overall functional capacity. Airflow limitation, leading to pulmonary abnormalities such as hyperinflation, is increasingly recognized as a critical contributor to exercise limitation, not only in patients with COPD but also in those with HF.<sup>6,7,12</sup> A direct correlation exists between the severity of airflow obstruction and decreased exercise tolerance, as reflected by reduced 6MWD. While these associations have been well documented in studies of each condition independently, in coexisting HF and COPD, pulmonary function may exert an even more significant influence on exercise capacity.

The correlation between NYHA class and 6MWD has not been extensively explored. However, one study<sup>32</sup> closely aligns with our findings, identifying NYHA class as a predictor of 6MWD in individuals with HF, although its *p* value was marginally above the conventional threshold for significance (*p* = 0.06). While the 6MWT and NYHA classifications are accessible and pragmatic tools for assessing functional capacity, the subjectivity inherent in the NYHA classification necessitates careful interpretation. A review has highlighted an inverse relationship between NYHA class and 6MWD, particularly in the more advanced classes (III/IV).<sup>33</sup>

In a COPD cohort study, perceived symptom severity was correlated with 6MWD, with a correlation coefficient of  $r = 0.56$ .<sup>34</sup> This suggests that individuals' subjective experience of symptoms, such as dyspnea and fatigue, can directly impact functional capacity. Since the NYHA class is based on symptom

assessment, its association with 6MWD likely reflects the influence of these symptoms on exercise tolerance.

#### The association between 6MWD and other variables

To our knowledge, this study is one of the first to comprehensively identify the determinants of 6MWD in patients with concurrent HF and COPD. Previous research has identified numerous predictors of 6MWD in individuals with either HF or COPD, including demographic factors such as age and sex, physiological measurements such as weight and BMI, cardiac parameters such as left ventricular end-systolic volume, psychological factors such as depression, and muscle-specific measures including quadriceps strength.<sup>35,36</sup>

In our assessment of quality of life using the MLHF-Q, our results align with earlier studies that found a significant positive correlation between 6MWD and quality of life in patients with HF. For example, one prior study<sup>37</sup> reported a moderate correlation between 6MWD and quality of life scores.

Frailty has consistently been identified as a predictor of mortality, independent of other factors, with reported hazard ratios ranging from 1.58 to 1.69 for each incremental increase in frailty score among both HF and COPD populations.<sup>38,39</sup> In line with previous research,<sup>37,38</sup> our study found a significant negative correlation between frailty and functional capacity ( $r = -0.72$ ), as measured by the 6MWT. Frailty reflects a patient's vulnerability to adverse outcomes, while the 6MWT measures exercise tolerance. Together, these metrics may help identify patients at greater risk of adverse events and further decline in physical function.

Regarding the sociodemographic characteristics of the HF-COPD overlap, previous studies have often reported a higher prevalence of male patients and older age.<sup>6,7,10</sup> In contrast, our cohort was predominantly female and had a younger average age. This discrepancy may be attributed to our sample mainly consisting of individuals with HF with preserved ejection fraction (mean LVEF  $54.7\% \pm 15.9\%$ ), a condition more frequently diagnosed in women<sup>40</sup> and a relatively younger demographic.<sup>41</sup>

### Study limitations

The findings of this study must be considered in light of certain limitations. The lack of comprehensive functional evaluations, such as the Modified Medical Research Council (mMRC) Dyspnea Scale, limits the depth of insight into how symptoms affect daily living and patient quality of life. Additionally, the reliance on self-reported outcomes may not fully capture the range of functional limitations, potentially underestimating the severity of patients' conditions. In our study subjects, the reduced use of betablockers reflects the predominance of cases of HF with preserved ejection fraction, where betablocker therapy has less established benefits. This could limit the generalizability of our findings to populations with more diverse HF subtypes or higher betablocker usage. The low percentage of betablocker use may also have influenced 6MWT performance, as betablockers can affect exercise capacity by modulating heart rate response. Future studies are warranted to explore the impact of pharmacological management, including betablocker use, on functional capacity in patients with overlapping HF and COPD. Finally, we should note that, due to the sample size, participants were not analyzed in a stratified manner by ejection fraction. This reliance highlights the need for future studies to incorporate objective measures, such as cardiopulmonary exercise testing, to assess the functional constraints of individuals with HF-COPD overlap accurately.

### Conclusion

Functional capacity determinants in patients with HF-COPD overlap are multifaceted, encompassing demographic, physiological, and psychosocial components. This study identified 3 critical variables, gait speed, FEV<sub>1</sub>, and NYHA class, that account for 83% of the variation in 6MWD, underscoring their substantial influence on exercise capacity in this population. Additionally, quality of life assessments and the CHS frailty index were significantly correlated with 6MWD, highlighting the complex interplay of factors contributing to functional capacity (Central Illustration). These findings suggest that an integral approach incorporating

both physical and psychosocial assessments may be essential for effectively managing functional limitations in patients with HF-COPD. Future research should include objective functional measures to elucidate these relationships further and improve patient outcomes.

### Author Contributions

Conception and design of the research: Dadalt ML, Dal Lago, P; Acquisition of data: Dadalt ML, Correa IF, Loro FL; Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Dadalt ML, Correa IF, Loro FL, Karsten M, Monteiro MB, Dal Lago, P; Obtaining financing: Dal Lago, P; Critical revision of the manuscript for content: Karsten M, Monteiro MB, Dal Lago, P.

### Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

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### Study association

This article is part of the thesis of master submitted by Maria Luisa Rocha Dadalt, from Universidade Federal de Ciências da Saúde de Porto Alegre.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Irmandade Santa Casa de Misericórdia de Porto Alegre e Fundação Universitária de Cardiologia do Rio Grande do Sul under the protocol number ISCMPA: 3.068.402 e IC-FUC: 3.356.737. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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