Ventilation Distribution, Pulmonary Diffusion and Peripheral Muscle Endurance as Determinants of Exercise Intolerance in Elderly Patients with Chronic Obstructive Pulmonary Disease

Short title: Exercise intolerance in elderly with COPD

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Summary

Chronic obstructive pulmonary disease (COPD) is a progressive and disabling disease that has been associated with aging. Several factors may potentially impair performance during exercise in elderly patients with COPD. This study was conducted to evaluate what characteristics related to lung function, peripheral muscle strength and endurance can predict the performance of elderly patients with COPD during cardiopulmonary exercise testing (CPET). Forty elderly patients with COPD underwent resting lung function tests, knee isokinetic dynamometry, and CPET. Three models were developed to explain the variability in peak oxygen uptake (VO_2 peak) after controlling for age as an independent confounder. The pulmonary function model showed the highest explained variance (65.6%); in this model, ventilation distribution (p<0.001) and pulmonary diffusion (0.013) were found to be independent predictors. Finally, the models that included the muscle strength and endurance variables presented explained variances of 51% and 57.4%, respectively. In these models that involved muscular dysfunction, however, only the endurance variables were found to be independent predictors (p<0.05). In conclusion, ventilation distribution and pulmonary diffusion, but not the degree of airway obstruction, independently predict CPET performance in elderly patients with COPD. In addition, peripheral muscle endurance, but not strength, also predicts CPET performance in these subjects.

Key words: Chronic obstructive pulmonary disease - Aged - Functional capacity - Pulmonary function - Muscle function

Introduction

There are many similarities between the lung aging process and chronic obstructive pulmonary disease (COPD), and many of the characteristics of aging are present in COPD, suggesting that accelerated aging may be a pathogenic mechanism in COPD (MacNee 2016). In fact, many of the changes that occur in the lungs with normal aging, such as declining lung function, deterioration of respiratory muscle strength, increased air trapping, loss of lung elastic recoil, and increased distal airspaces, are also present in COPD (MacNee 2016, van Wetering *et al.* 2008). Moreover, in the elderly population, the presence of cardiovascular, osteoarticular, and neurological abnormalities can lead to subclinical COPD symptoms and underdiagnosis of the disease. Therefore, routine evaluation using pulmonary function tests (PFTs) in elderly patients with risk factors for COPD are essential (Incalzi *et al.* 2014).

The loss of muscle strength and/or endurance is an important systemic effect of aging and drops sharply for aging associated with COPD (Evans *et al.* 2015, Maltais *et al.* 2014). These impairments have countless consequences in COPD patients, including low exercise tolerance, decreased quality of life, greater need for healthcare, and increased morbidity and mortality. Dysfunction of the lower limb muscles was even shown to better predict mortality than lung function measurements in COPD patients (Swallow *et al.* 2007). In recent years, isokinetic dynamometry has been used in clinical practice and is currently the standard method for assessing muscle function (Homem *et al.* 2017). However, to our knowledge, the contributions of the isokinetic tests have not been previously evaluated in the elderly populations with COPD.

In COPD, exercise intolerance is multifactorial. Exercise limitations reflect the reduced ventilatory capacity, abnormal gas exchange, and skeletal muscle dysfunction in these patients, especially for the muscles involved in walking. As a result, the exercise capacity and maximum work rate are reduced (Borghi-Silva *et al.* 2009). In this context, ventilatory limitation has been identified as one of the contributors to exercise intolerance, since those with COPD cease exercise because they cannot increase ventilation in response to increasing metabolic demands (O'Donnell, 2001). Several factors determine ventilatory limitation during cardiopulmonary exercise testing (CPET), including abnormal ventilatory mechanics, increased ventilatory demand, and changes in the neuroregulatory

control of breathing (O'Donnell 2001). In addition to ventilatory limitation, peripheral muscle dysfunction syndrome also seems to play a fundamental role in exercise intolerance in patients with COPD (Malaguti *et al.* 2011, Van't Hul *et al.* 2004). Some investigators have suggested that exercise intolerance is partly due to skeletal muscle dysfunction, and in 40-45% of COPD patients, muscle discomfort of the lower limbs is the main symptom that limits physical activity (Borghi-Silva *et al.* 2009). Despite these studies, this issue has not been addressed specifically in the elderly who suffer from COPD.

In elderly persons with COPD, exercise intolerance has a negative impact on the health-related quality of life (HRQL). Several factors may potentially impair performance during exercise in elderly patients with COPD, and understanding the mechanisms involved in functional capacity reduction may help identify new ways of approaching therapy and physical reconditioning for COPD. Thus, the objective of the present study was to evaluate what characteristics related to lung function, peripheral muscle strength and endurance can predict the performance of elderly patients with COPD during cardiopulmonary exercise testing (CPET).

Material and Methods

Participants

Between April 2015 and March 2017, a cross-sectional study was conducted that evaluated 97 consecutive patients with COPD who were recruited at Newton Bethlem Hospital, Rio de Janeiro, Brazil. Only patients aged ≥60 years were included. The diagnosis of COPD was established by spirometry showing a post-bronchodilator forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio of less than 0.7 and a smoking history of more than 10 pack-years (GOLD 2018). Patients with history or radiographic evidence of tuberculosis, bronchiectasis or other pulmonary disorders, those taking oral prednisolone or undergoing supplemental oxygen therapy, those with respiratory exacerbations in the past four weeks, those undergoing pulmonary rehabilitation in the past 12 months, and those with any conditions that prevented CPET were excluded. The cases were classified as stages 1-4 (classification of airflow limitation severity) and A-D (assessment of symptoms and risk of exacerbations) according to the Global Initiative for Chronic

Obstructive Lung Disease (GOLD) (2018). The project was approved by the Research Ethics Committee of the Augusto Motta University Center under number CAAE-52885116.6.0000.5235 and was in compliance with the provisions of the Declaration of Helsinki. All participants signed a consent form.

Resting lung function

Spirometry and the measurement of diffusion capacity of the lung for carbon monoxide (DLco) were carried out using a Collins Plus Pulmonary Function Testing System (Warren E. Collins, Inc., Braintree, MA, USA). DLco was measured using the single breath-hold method measurements with a rapidly responding gas analyzer, and the prediction values of DLco were adjusted according to hemoglobin levels (Graham *et al.* 2017). The FEV_1 value was used to assess the degree of airway obstruction. Both PFTs followed the guidelines of the American Thoracic Society (Miller *et al.* 2005). Reference values for the Brazilian population were considered (Neder *et al.* 1999, Pereira *et al.* 2007).

In addition, all participants performed a nitrogen (N_2) single-breath washout (SBW) test using HDpft 3000 equipment (nSpire Health, Inc., Longmont, CO, USA), following standard recommendations (Robinson *et al*., 2013). Two parameters derived from the SBW test were analyzed, and both were interpreted as percentages of the predicted values (Buist and Ross 1973): the phase III slope of SBW ($SIII_{N2}$), which is defined as the change in the N_2 concentration from 25-75% of the expired volume and considered a marker of ventilation distribution, and the closing volume/vital capacity (CV/VC) ratio, which is defined as the portion of the VC that is exhaled after the initiation of airway closure and is considered a marker of small airway disease (Lopes and Mafort 2014).

Knee isokinetic dynamometry

The quadriceps and hamstring muscles of the dominant lower limb were evaluated using a Biodex System 4 PRO dynamometer (Biodex Medical System, Shirley, NY, USA) at the Admiral Adalberto Nunes Physical Education Center (Brazilian Navy), Rio de Janeiro, Brazil. Briefly, the participants were seated in the equipment, and the trunk, pelvis, and thigh were stabilized using belts.

The rotational axis of the dynamometer was aligned with the lateral epicondyle of the femur, while the range of motion for performing the test was set at 90°. Before the test, the patient underwent familiarization training with three submaximal repetitions (Homem *et al.* 2017, Lopes *et al.* 2016). After this step, strength analysis was performed through an angular velocity of 75°/s with two sets of five repetitions. Subsequently, the participant performed the endurance evaluation through an angular velocity of 240°/s with two sets of 15 repetitions (Justo *et al.* 2017). A rest period of two minutes was given between the tests. The highest value of the different repetitions of each of the following variables was analyzed: peak torque (PT), which is the maximum force produced at a given point of the range of motion (determined in extension) and was evaluated at 75°/s (PT75°/s) and 240°/s (PT240°/s), and agonist/antagonist ratio (AG/ANT), which is the PT of the hamstrings divided by PT of the quadriceps and was evaluated at 75°/s (AG/ANT75°/s) and at 240°/s (AG/ANT240°/s) (Walchan *et al.* 2016).

Cardiopulmonary exercise testing

CPET was performed on a treadmill (Inbramed, ATL, Porto Alegre, Brazil) as subject's respiratory gases were collected using a metabolic analyzer (MedGraphics VO2000, Medical Graphics, Inc., St. Paul, MN, USA) that was operated according to standard procedures (American Thoracic Society and American College of Chest Physicians 2003). A ramp protocol with individualized incline and load was used. The capacity of each individual was adapted so that the duration of exercise intensity was between 8 and 12 minutes, and the subsequent peak oxygen uptake (VO_2 peak) values were calculated. For interpretations of the VO_2 peak, the reference values for the Brazilian population were considered (Neder *et al.* 1999).

Sample size

Considering the association between the VO_2 peak and pulmonary or muscle function variables as the main outcome of this study, a minimal sample size of 36 participants was necessary to observe a minimal correlation of 0.41 (weak or higher) at a 5% significance level and 80% study power.

Statistical analysis

Variables were described as the mean ± SD or number (percentage) as appropriate. Bivariate associations were examined using the two-tailed Pearson's *r* correlation coefficient between VO_2 peak (% predicted values) and clinical (age, sex ['male' = 1 and 'female' = 0], body mass index (BMI), pulmonary (FEV_1, DLco, $SIII_{N2}$, and CV/VC), peripheral muscle strength (PT75°/s and AG/ANT75°/s) and endurance (PT240°/s and AG/ANT240°/s) variables. Independent linear regression models were generated to explore the role of clinical, pulmonary, and peripheral muscle function variables as predictors of VO_2 peak. Due to the proportion of the minimum number of variables per participant for developing prediction models (10:1) (Babyak 2004), our model included up to four independent variables simultaneously. We grouped variables to determine to what extent the independent predictors related to the same domain can predict the dependent variable. The models of muscle strength and endurance that were examined included age, gender, or BMI as covariates, provided they were identified as significantly correlated to VO_2 peak. Because lung function variables were included as percentages of the predicted values (already considering general confounders), this model did include other covariates. The adjusted R^2 and respective *p*-values as calculated from analysis of variance (ANOVA) tables were used to evaluate the fit of each model; regression coefficients and the respective 95% confidence intervals (95% CIs) are also reported alongside the *p*-values. Multicollinearity was assessed using the variance inflation factor (VIF). Differences were considered statistically significant at $p<0.05$ with a 95% confidence interval. Analyses were conducted using SPSS 22 (SPSS, Chicago, IL, USA).

Results

Subject characteristics

Of the 97 participants eligible for evaluation, 40 completed the study (see Figure 1). The mean age was 70.2±7.46 years, and the smoking load was 45.2±19.8 pack-years. The clinical data, lung and muscle function, and CPET results are summarized in Table 1.

Correlation analysis

The VO_2 peak was positively correlated with AG/ANT240°/s (r=0.574, p<0.001), PT240°/s (r=0.552, p<0.001), DLco (r=0.506, p=0.001), PT75°/s (r=0.409, p=0.009), AG/ANT75°/s (r=0.401, p=0.010), and FEV_1 (r=0.396, p=0.012). Conversely, the VO_2 peak was significantly negatively correlated with age (r=-0.673, p<0.001) and $SIII_{N2}$ (r=-0.557, p<0.001). Sex (r=0.289, p=0.070), BMI (r=-0.068, p=0.676), and CV/VC (r=0.007, p=0.968) were not significantly correlated with VO_2 peak.

Explaining the VO_2 peak using clinical, pulmonary function, and peripheral muscle function variables

The average VO_2 peak was significantly predicted by all models (p=0.008 or lower). Tables 2 and 3 show the raw and adjusted models after controlling for possible confounders. Figures 2 and 3 show the regression plot for each tested model accordingly. The clinical model yielded an even higher explained variance (44.2%), with age as the sole independent predictor negatively associated with VO2 peak (p<0.001) identified in this analysis.

The model including peripheral muscle strength variables exhibited the lowest explained variance (19%), whereas neither the PT nor AG/ANT at 75°/s were independent predictors of VO_2 peak (p=0.074 or higher). After controlling for age, both PT and AG/ANT at 75°/s were not independent predictors of VO_2 peak (p=0.125 or higher). Conversely, the model including peripheral muscle endurance variables showed a higher explained variance (42.8%), and both PT and AG/ANT at 240°/s were independent predictors positively associated with VO_2 peak (p=0.006 or lower). After adjustment for age, both PT and AG/ANT at 240°/s remained as independent predictors of VO_2 peak (p=0.041 or lower). Finally, the pulmonary function model showed the highest explained variance (50.9%) in which $SIII_{N2}$, DLco, and FEV_1 (p=0.010 or lower) but not CV/VC (p=0.170) were found to be independent predictors of VO_2 peak. In this last model, $SIII_{N2}$ was negatively associated with VO_2 peak, whereas DLco and FEV_1 were both positively associated. Multicollinearity was not identified in any model, as assessed by low VIF values (VIF=1.499 or lower). After adjustment for age, however, only $SIII_{N2}$ and DLco remained as independent predictors of VO_2 peak (p=0.013 or lower).

Discussion

This study contributes the following new findings to our knowledge of systemic manifestations in elderly patients with COPD. Deterioration of lung function is the main contributor to poor performance during exercise in the elderly population with COPD. Thus, the greater the heterogeneity in the ventilation distribution and the decrease in pulmonary diffusion are, the lower the VO_2 peak. In elderly people with COPD, muscle endurance (i.e., loss of the ability to sustain a specific task over time) but not muscle strength contributes strongly to exercise performance. In addition, older age was the only demographic variable that negatively impacted performance during the CPET.

The CPET provides an overview of the systems involved in transporting oxygen from ambient air to mitochondria and shows the performance of these systems during exercise. Among the four models we constructed before controlling for age as independent confounder (see Table 2), the model including clinical variables presented an explained variance of almost 45% for VO_2 peak, with age being the only independent predictor of VO_2 peak. This finding is in line with those from a study by Betik and Hepple (2008), which demonstrated that VO_2 peak decreases by an average of 10% per decade after the age of 30 due to the decreases in maximal heart rate, stroke volume, blood flow to skeletal muscle and skeletal muscle aerobic potential. Since the main feature of COPD is its progressive course with steadily increasing multisystem involvement (GOLD 2018), an even greater decline in VO_2 peak is expected as aging progresses. In elderly patients with COPD, a reduced ability to perform physical exercise is a complicating factor and increases the mortality associated with COPD (Incalzi *et al.* 2014). Since age was the sole independent predictor negatively associated with peak VO_2 ($p < 0.001$), it is worth noting that the other models were then age-controlled as a confounding factor (see Table 4).

In COPD, increased ventilatory demand during exercise worsens air trapping and causes dynamic hyperinflation (DH) above the already increased resting volumes; DH, in turn, compromises the ability of the inspiratory muscles to generate adequate intrathoracic pressures (O'Donnell 2001).

In the present study, the pulmonary function model for elderly patients with COPD was the one that presented the highest explained variance for VO_2 peak, surpassing 65% after controlling for age as an independent confounder. In this model, the pulmonary function variable that presented the greatest explanatory power was the elevation of $SIII_{N2}$, which denotes heterogeneity in the ventilation distribution due to inefficient ventilation and greater ventilatory demand during exercise. Importantly, the main mechanism that generates alteration in ventilation comes from convection-dependent inhomogeneity in the conducting airway zone (i.e., airways proximal to terminal bronchioles), which contributes to an increased $SIII_{N2}$ in SBW (Crawford *et al.* 1985, Robinson *et al.* 2013). In view of the difficulty of performing CPET in elderly patients with COPD because of the contraindications inherent to the test, we believe that SBW may contribute as a predictor of poor performance during exercise in these individuals (Lopes and Mafort 2014; Robinson *et al.* 2013).

Nevertheless, for our pulmonary function model proposed for elderly patients with COPD, the drop in pulmonary diffusion was also a predictor of reduced VO_2 peak during exercise. Similar to our findings, Franssen *et al*. (2004) demonstrated that DLco, along with age and fat-free mass, explained 56% of the VO_2 peak variance in COPD patients. Another study also found that DLco and quadriceps strength were independently associated with VO_2 peak in these patients (van Wetering *et al.* 2008). In addition to varying with age, sex and height, DLco values also depend upon a number of physiological factors including hemoglobin levels, lung volume, carboxyhemoglobin, oxygen inspired tension, and exercise (Graham *et al.* 2017). Thus, our study provides further evidence that DLco may be a useful marker of exercise intolerance in elderly patients with COPD, especially in those with predominant emphysema and consequently reduced membrane surface area available for gas exchange (Neder *et al.* 2017). Interestingly, we also observed that FEV_1—the marker of the degree of airway obstruction most commonly used in clinical practice— did not enter our pulmonary function model after controlling for age as an independent confounder. Interestingly, the potential relationship between ventilatory inefficiency and exertional dyspnea in patients with symptomatic COPD and preserved FEV_1 was already clearly established in a previous study (Franssen *et al.* 2004). This result

reinforces the importance of a more detailed evaluation of lung function, in addition to FEV_1, in this population of patients.

Muscle dysfunction in COPD shows a regional distribution, with relative preservation of muscle function of the trunk and upper limbs and deterioration of lower limb muscle function (Malaguti *et al.* 2011, Van't Hul *et al.* 2004). Thus, specific muscle groups of interest should be tested, since muscle weakness does not affect all muscles in a similar way, with variations depending on the anatomical region studied (Pleguezuelos *et al.* 2016, Robles *et al.* 2011). Using knee isokinetic dynamometry, we were able to demonstrate the negative impact of lower limb muscle dysfunction on VO_2 peak in elderly patients with COPD. Potential factors contributing to aging-related functional impairment in COPD patients include reduced motor neuron activity and changes in muscle morphology and energy metabolism leading to apoptosis, muscle atrophy, oxidative stress, reduced muscle capillarity, and intramuscular fat accumulation (Franssen *et al.* 2004, Robles *et al.* 2011). In addition, there are several adjuvant factors responsible for peripheral muscle dysfunction in these patients, including deconditioning/disuse, local inflammation, tissue hypoxia, hypercapnia, nutritional depletion, corticosteroid use, and hormonal changes, which promote structural and functional changes in contractile tissue (Evans *et al.* 2015, Janaudis-Ferreira *et al.* 2006, Maltais *et al.* 2014, Pleguezuelos *et al.* 2016, Robles *et al.* 2011). The relationship between lower limb muscle dysfunction and clinical outcomes in COPD suggests that clinical evaluation of muscle dysfunction in these patients may identify those at increased risk of exercise intolerance and premature death (Maltais *et al.* 2014).

Interestingly, the aging process may impact peripheral muscle function differently in individuals with COPD. In fact, our models that included the peripheral muscle function variables reached an explained variance of VO_2 peak of 19% for muscle strength and 42.8% for muscle endurance. However, only the muscular endurance variables presented as independent predictors after controlling for age as a confounding factor (p=0.041 or lower). These differences can be justified at least in part by the significant deviation in the proportion of muscle fibers from type I to type II, the reduction in capillarity, and the altered metabolic enzyme levels (Borghi-Silva *et al.* 2009, van den Borst *et al.* 2013). In line with our findings, Malaguti *et al.* (2011) observed that in patients with COPD, muscle endurance and aerobic capacity are more greatly affected than muscle strength, even

in patients with preserved muscle mass. However, there is no consensus about the main mechanisms involved in the decreasing muscle endurance in these patients. While one study showed that the impairment of quadriceps muscle endurance was associated with physical inactivity and the degree of pulmonary obstruction (Serres *et al.* 1998), another study demonstrated that quadriceps endurance was impaired independently of the level of physical activity (Coronell *et al.* 2004). More recently, Malaguti *et al.* (2011) reported that muscle atrophy seems to be the main determinant in the reduction of muscle strength among patients with COPD, whereas endurance reduction seems to be more related to the imbalance between oxygen supply and consumption due to low capillarity, bioenergetic abnormalities, and intrinsic alterations in the muscle contractility of the lower limbs.

Finally, in our muscle endurance model, both the reduction of the PT240°/s and the decrease in the AG/ANT240°/s ratio contributed to the decrease in VO_2 peak. The AG/ANT ratio is one of the parameters that has aroused great interest in isokinetics since this value describes the muscle balance in the knee joint. A change in the relationship between the PT of the hamstrings and the quadriceps indicates that there are excessive muscle imbalances, which predisposes the knee joint to injury (Walchan *et al.* 2016). Thus, lower limb training in elderly patients with COPD with consequent improvement in the AG/ANT ratio can provide several benefits, including greater exercise tolerance and better HRQL, since upper limb training has not shown the same benefits (Evans *et al.* 2015).

The strength of this study is that it is the first to evaluate the contribution of lung and muscle functions in exercise performance in elderly patients with COPD using the gold standard methods. However, like any study, ours also has limitations. First, we acknowledge that including GOLD stages as an independent variable to the pulmonary function model would be interesting from a clinical point of view. However, as related to lung function, our study focused on what variables predict CPET performance in patients with COPD. In this way, the inclusion of GOLD stages would not further understanding of the pathophysiologic mechanisms that may impair exercise tolerance in these subjects. Second, measurements of static lung volumes and peripheral muscle strength could possibly have contributed to increase the explained variance of the pulmonary function model for VO_2 peak. Third, the inclusion of the six-minute walk test could have allowed the creation of models for distance

traveled, since this test is much more commonly used in clinical practice due to its simplicity. Despite these limitations, our results may be important for establishing rehabilitation strategies for elderly patients with COPD, since the findings suggest that both lung function and lower limb muscle function play a prominent role in the functional capacity of these subjects. These results become even more significant when considering that only 20% of pulmonary rehabilitation programs use a detailed assessment of pulmonary and peripheral muscle function in COPD patients (Spruit *et al.* 2014).

In conclusion, the present study shows that ventilation distribution and pulmonary diffusion, but not the degree of airway obstruction, independently predict CPET performance in elderly patients with COPD. Aging has a differential impact on the lower limb muscle function in elderly patients with COPD, whereas peripheral muscle endurance but not strength also predicts CPET performance in these subjects. In addition, older age is the main demographic variable that reduces functional capacity during exercise in the elderly population with COPD.

Conflict of Interest

There are no conflicts of interest to disclose.

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Table 1. Subject characteristics (*n*=40).

Variable	Values
Demographics	
Age (years)	70.2 ± 7.46
Sex (male)	21 (52.5)
BMI (kg/m^2)	23.7 ± 5.07
GOLD stages	
1–2	20 (50)
3–4	20 (50)
A–B	17 (42.5)
C–D	23 (57.5)
Use of medications	
LAMA	31 (77.5)
LABA	24 (60)
ICS	15 (37.5)
Resting lung function	
FEV_1 (% predicted)	43.5±13.1
DLco (% predicted)	43.1±13.7
$SIII_{N2}$ (% predicted)	302.9±192.7
CV/VC (% predicted)	182.4±89.6
Knee isokinetic dynamometry	
PT75°/s	89.6±27.4
AG/ANT75°/s	54.1±15.9
PT240°/s	53.8±22.2
AG/ANT240°/s	55.4±16.3
Cardiopulmonary exercise testing	
VO_2 peak (% predicted)	53.3±18.5

Data are listed as the mean ± SD or number (percentage).

BMI – body mass index, GOLD – Global Initiative for Obstructive Lung Disease, LABA – long-acting β2-agonist, LAMA – long-acting antimuscarinic agent, ICS – inhaled corticosteroid, FEV_1 – forced expiratory volume in one second, DLco – diffusing capacity of the lung for carbon monoxide, $SIII_{N2}$ – phase III slope of nitrogen single-breath washout, CV/VC – closing volume/vital capacity ratio, PT75°/s – peak torque at 75º/s, AG/ANT75°/s – agonist/antagonist ratio at 75º/s, PT240°/s – peak torque at 240º/s, AG/ANT240°/s – agonist/antagonist ratio at 240º/s, VO_2 peak – peak oxygen uptake.

Table 2. Independent linear models of peak oxygen uptake (% predicted) using muscle function, clinical, and pulmonary function (*n*=40).

Model	**Variables**	**Adjusted R^2**	**SE of estimate**	**ANOVA**	**B [95%CI]**	**VIF**	***p*-value**
Muscle strength		0.190	16.899	$F_{2,37}$=5.567			**0.008**
	Constant				21.279 [0.724; 41.834]		**0.043**
	PT75°/s				0.162 [-0.016; 0.340]	1.211	0.074
	AG/ANT75°/s				0.324 [-0.049; 0.696]	1.211	0.087
Muscle endurance		0.428	14.205	$F_{2,37}$=15.564			**<0.001**
	Constant				14.070 [-0.933; 29.073]		0.065
	PT240°/s				0.323 [0.101; 0.546]	1.179	**0.006**
	AG/ANT240°/s				0.395 [0.146; 0.643]	1.179	**0.003**
Clinical		0.442	14.021	$F_{3,36}$=11.310			**<0.001**
	Constant				166.773 [117.738; 215.808]		**<0.001**
	Age				-1.595 [-2.208; -0.981]	1.035	**<0.001**
	Sex				6.345 [-2.814; 15.505]	1.035	0.169
	Body mass				-0.204 [-1.091; 0.683]	1.001	0.644
Pulmonary function		0.509	13.161	$F_{4,35}$=11.091			**<0.001**

Constant	23.754 [0.190; 47.319]		**0.048**
$SIII_{N2}$	-0.057 [-0.083; -0.030]	1.499	**<0.001**
DLco	0.081 [0.025; 0.137]	1.420	**0.006**
FEV_1	0.490 [0.123; 0.857]	1.275	**0.010**
CV/VC	0.248 [-0.111; 0.606]	1.360	0.170

Bold-formatted values represent statistical significance at level $p<0.05$. R^2 – determination coefficient, SE – standard error, ANOVA – analysis of variance, CI – confidence interval, VIF – variance inflation factor, PT75°/s – extension peak torque at 75°/s, AG/ANT75°/s – agonist/antagonist ratio at 75°/s, PT240°/s – extension peak torque at 240°/s, AG/ANT240°/s – agonist/antagonist ratio at 240°/s, $SIII_{N2}$ – phase III slope of nitrogen single-breath washout, DLco – diffusing capacity of the lung for carbon monoxide, FEV_1 – forced expiratory volume in one second, CV/VC – closing volume/vital capacity ratio.

Table 3. Independent linear models of peak oxygen uptake (% predicted) using muscle function and pulmonary function after controlling for age as independent confounder (*n*=40).

Model	Variables	Adjusted R^2	SE of estimate	ANOVA	B [95%CI]	VIF	*p*-value
Muscle strength		0.510	13.145	$F_{3,36}$=14.518			**<0.001**
	Constant				134.074 [85.734; 182.414]		**<0.001**
	PT75°/s				0.102 [-0.039; 0.243]	1.248	0.151
	AG/ANT75°/s				0.226 [-0.066; 0.519]	1.233	0.125
	Age				-1.455 [-2.043; -0.867]	1.083	**<0.001**
Muscle endurance		0.574	12.248	$F_{.3,36}$=18.547			**<0.001**
	Constant				105.117 [53.698; 156.536]		**<0.001**
	PT240°/s				0.211 [0.009; 0.412]	1.300	**0.041**
	AG/ANT240°/s				0.270 [0.045; 0.495]	1.298	**0.020**
	Age				-1.112 [-1.712; -0.504]	1.333	**0.001**
Pulmonary function		0.656	11.012	$F_{5,34}$=15.872			**<0.001**
	Constant				119.932 [67.223; 172.641]		**<0.001**
	$SIII_{N2}$				-0.051 [-0.073; -0.028]	1.526	**<0.001**

DLco	0.062 [0.014; 0.110]	1.481	**0.013**
FEV_1	0.318 [-0.002; 0.637]	1.378	0.051
CV/VC	0.041 [-0.278; 0.359]	1.527	0.797
Age	-1.112 [-1.678; -0.547]	1.419	**<0.001**

Bold-formatted values represent statistical significance at level $p<0.05$. R^2 – determination coefficient, SE – standard error, ANOVA – analysis of variance, CI – confidence interval, VIF – variance inflation factor, PT75°/s – extension peak torque at 75°/s, AG/ANT75°/s – agonist/antagonist ratio at 75°/s, PT240°/s – extension peak torque at 240°/s, AG/ANT240°/s – agonist/antagonist ratio at 240°/s, $SIII_{N2}$ – phase III slope of nitrogen single-breath washout, DLco – diffusing capacity of the lung for carbon monoxide, FEV_1 – forced expiratory volume in one second, CV/VC – closing volume/vital capacity ratio.

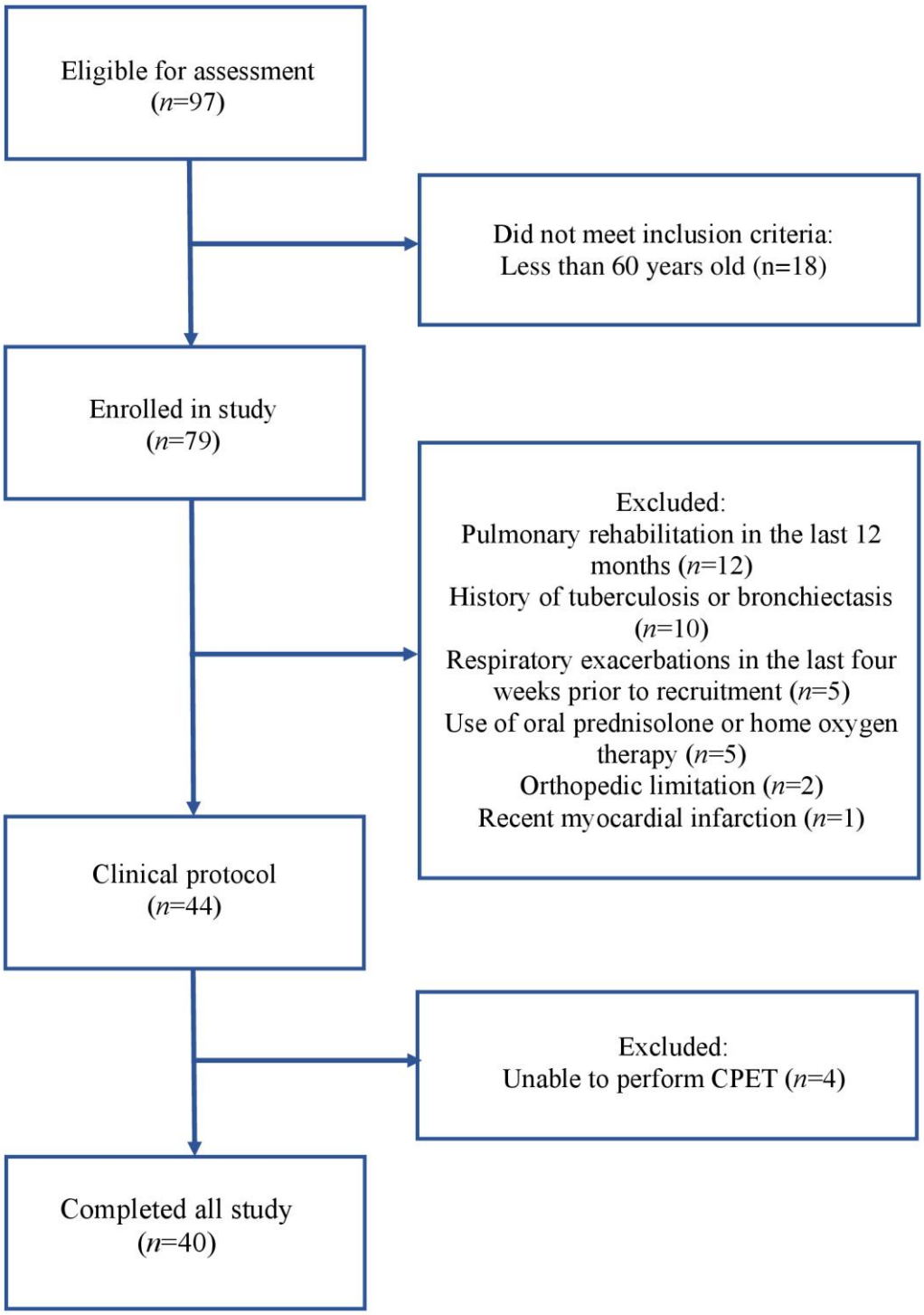

Fig. 1. Chart diagram indicating the flow of patients over the enrollment period.

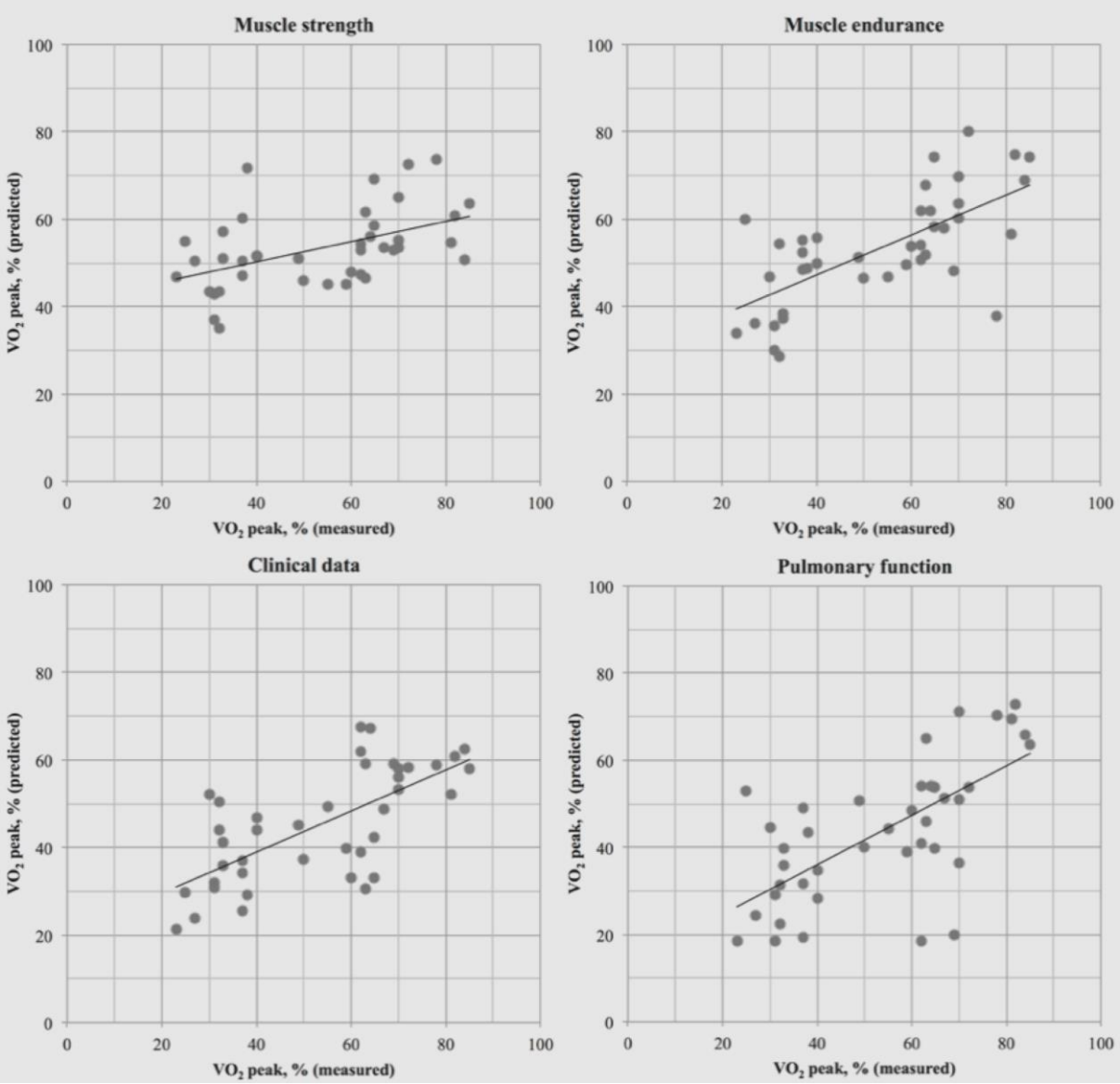

Fig. 2. Regression plots of the peak oxygen uptake (VO_2 peak) models (measured vs. predicted). The adjusted R^2 for the models of VO_2 peak were as follows: muscle strength, R^2=0.190; muscle endurance, R^2=0.428; clinical, R^2=0.442; and pulmonary function, R^2=0.509.

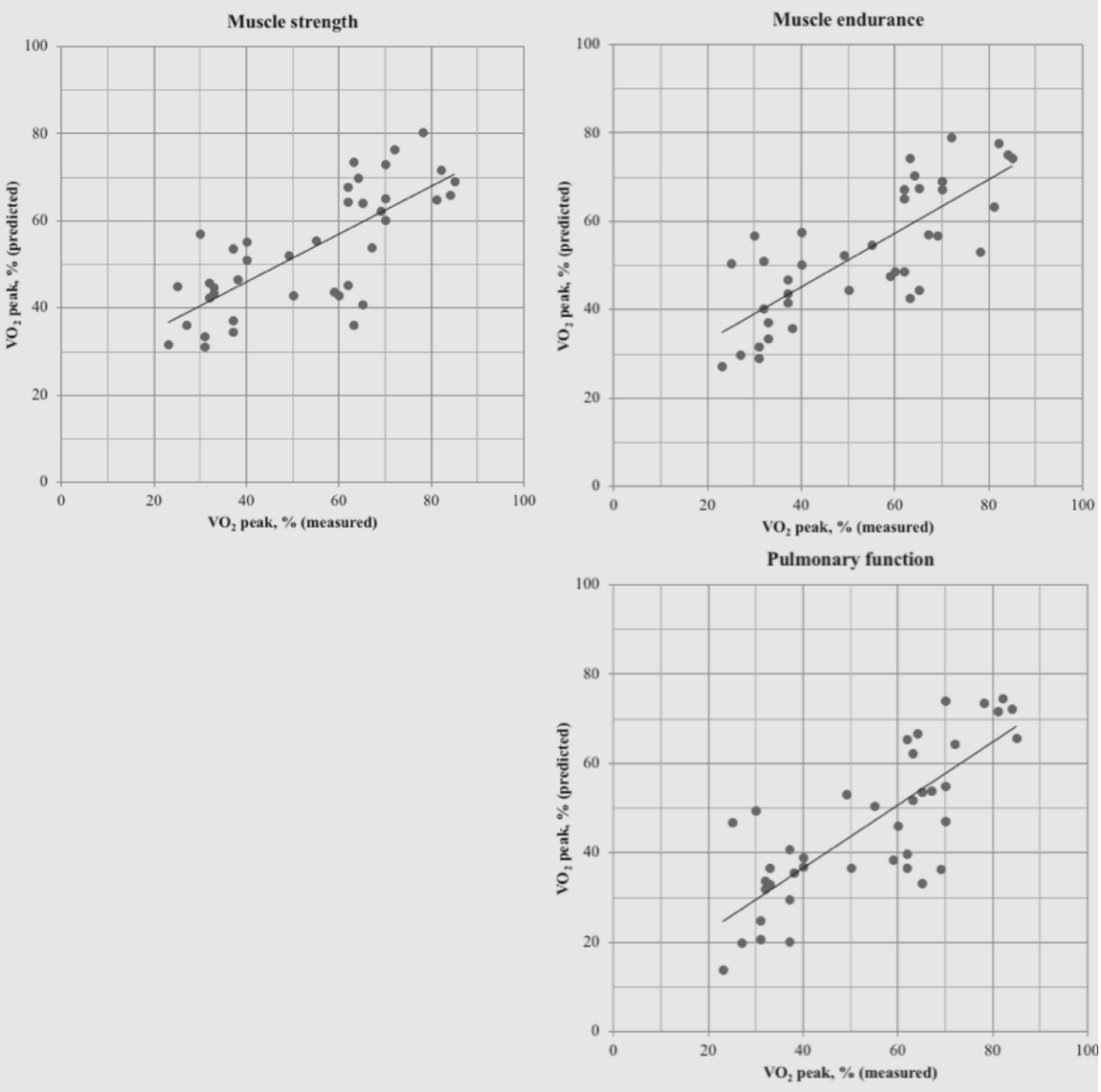

Fig. 3. Regression plots of the peak oxygen uptake (VO_2 peak) models (measured vs. predicted) after controlling for age as an independent confounder. The adjusted R^2 for the models of VO_2 peak were as follows: muscle strength, R^2=0.510; muscle endurance, R^2=0.574; and pulmonary function, R^2=0.656.