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Clinical Review

Systematic Review of the Association Between Laboratory- and Field-Based Exercise Tests and Lung Function in Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Introduction: Typical symptoms of chronic obstructive pulmonary disease (COPD) include breathlessness and reduced exercise capacity. Several laboratory- and field-based exercise tests are used to assess the exercise capacity of patients with COPD. It is unclear whether these exercise tests reflect the spirometric measures recommended for diagnosis of COPD. We therefore aimed to systematically assess the correlation between these exercise tests and common measures of lung function.

Methods: A search of Embase™, MEDLINE® and The Cochrane Library identified primary publications in English that reported data on the correlations (Pearson's *r* or Spearman's rho) between the outcomes of exercise tests and the physiological measures of interest: forced expiratory volume in 1 second (FEV_1), forced vital capacity, inspiratory capacity and arterial oxygen saturation. We included studies reporting on the following exercise tests: 6- and 12-minute walk tests (6MWT and 12MWT), incremental and endurance shuttle walk tests, incremental and endurance cycle ergometer tests, and treadmill tests.

Results: Of 1781 articles screened, 45 were ultimately deemed eligible for inclusion in this review. The most commonly reported lung function variable was FEV_1 (reported by 39 studies); the most commonly reported exercise test was the 6-minute walk test (reported by 24 studies). FEV_1 appears to correlate moderately-to-strongly with 6MWT and 12MWT; and moderately-to-very strongly with incremental cycle ergometer tests (ICET); evidence for other exercise tests was limited.

Conclusion: There is evidence that 6MWT, 12MWT and ICET correlate with FEV_1 to some degree; evidence for associations of other exercise tests with measures of lung function in patients with COPD is limited. Clinicians must consider this when deciding to use these tests. Further comparisons of these tests must be made in order to assess which physiological and hemodynamic characteristics they reflect in patients with COPD.

Abbreviations: chronic obstructive pulmonary disease, **COPD**; forced expiratory volume in 1 second, **FEV_1**; 6-minute walk test, **6MWT**; 12-minute walk test, **12MWT**; incremental cycle ergometer test, **ICET**; Global initiative for chronic Obstructive Lung Disease, **GOLD**; American Thoracic Society, **ATS**; incremental shuttle walk test, **ISWT**; endurance shuttle walk test, **ESWT**; endurance cycle ergometer test, **ECET**; treadmill test, **TT**; forced vital capacity, **FVC**; inspiratory capacity, **IC**; partial pressure of arterial oxygen, **PaO_2**; Preferred Reporting Items for Systematic Reviews and Meta-Analyses, **PRISMA**; body mass index, **BMI**; arterial oxygen saturation (pulse oximetry), **SaO_2**; liters, **L**; functional residual capacity, **FRC**; total lung capacity, **TLC**; residual volume, **RV**; arterial oxygen saturation, **SpO_2**; oxygen consumption, **VO_2**; heart rate, **HR**; health-related quality of life, **HRQoL**; BMI, airflow Obstruction, Dyspnea & Exercise Capacity index, **BODE**; highest volume of oxygen consumption achieved, **peak VO_2**; highest workload achieved, **W_{max}**; National Institute for Health Research, **NIHR**; Collaboration for Leadership in Applied Health Research and Care East Midlands, **CLAHRC EM**; National Health Service, **NHS**; British Thoracic Society, **BTS**; European Respiratory Society, **ERS**; interquartile range, **IQR**; inspiratory slow vital capacity, **IVC**; kilopascal, **kPa**; Medical Research Council, **MRC**; maximal voluntary ventilation, **MVV**; not reported, **NR**; partial pressure of arterial carbon dioxide, **$PaCO_2$**; respiratory exchange ratio, **RE**; standard deviation, **SD**; vital capacity, **VC**; correlation, **Corr**; studies reporting no significant correlation, **NS**; Spearman's rank coefficient, **ρ**; Pearson's regression coefficient, ***r***

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Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide and its global prevalence is projected to increase.[1-3] COPD is characterized by breathlessness, episodes of exacerbations and reduced exercise capacity.[4] COPD can lead to a progressive loss of daily activities and increased sedentary behavior, further exacerbating exercise capacity impairment.[5,6] Even in patients with mild COPD, physical activity[7] and exercise performance[8] are compromised, and exercise tolerance is increasingly attenuated with disease progression.[7] The mechanisms underlying reduced exercise capacity in patients with COPD are varied, but include increased metabolic costs of breathing[9]; deficits in gas exchange and ventilatory mechanics[6]; and peripheral muscle dysfunction.[8,10]

Spirometry is recommended by the Global initiative for chronic Obstructive Lung Disease (GOLD) for the diagnosis of COPD.[4] However, spirometry alone is a poor predictor of disability and quality of life in patients with COPD[11,12] and correlates only weakly with dyspnea and health status.[12,13,14] In contrast, exercise test outcomes have been shown to have good prognostic capabilities in patients with COPD.[15-21] Guidelines published by the National Institute for Clinical Excellence and the American Thoracic Society (ATS)/European Respiratory Society on the diagnosis and treatment of COPD now indicate that prognosis and assessment of disease severity is improved by using functional criteria such as exercise capacity.[22,23] Furthermore, the European Medicines Agency also supports the assertion that exercise testing in the clinical setting is a useful tool in COPD prognosis and monitoring the effectiveness of therapeutic intervention.[24]

Several test modalities are available for the assessment of exercise capacity in patients with limited exercise tolerance; the most common include the 6- and 12-minute walk tests (6MWT and 12MWT), the incremental and endurance shuttle walk tests (ISWT and ESWT), incremental and endurance cycle ergometer tests (ICET and ECET), and incremental treadmill tests (TT) and all are well established for clinical use in areas such as cardiovascular disease.[25] However, it is currently unknown which of these tests best represents the physiological constraints of the disease. The relationship between exercise test performance and the spirometric measurement forced expiratory volume in 1 second (FEV_1)[26,27,28] has been established,[29] however, other key parameters such as forced vital capacity (FVC)[30] and inspiratory capacity (IC),[31,32] as well as downstream manifestations of impaired lung function such as reduced partial pressure of arterial oxygen (PaO_2),[33] have not.

This systematic review was conducted to assess the correlation between the main outcomes of exercise tests and the most commonly reported physiological and systemic measures of impaired lung function (FEV_1, FVC, IC and PaO_2) in patients with COPD.

Methods

Search Strategy

Literature searches were conducted using Ovid® (Ovid Technologies Inc., New York, New York), incorporating Ovid MEDLINE® (U.S. National Library of Medicine, Bethesda, Maryland) for the period from 1948 to January 22, 2013, Ovid Embase™ (Elsevier Inc., Philadelphia, Pennsylvania) from 1974 to January 22,

2013, and The Cochrane Library (John Wiley & Sons Ltd, Hoboken, New Jersey) from 1962 to January 22, 2013. Search strings were constructed to identify studies reporting primary data on the outcomes of the following exercise tests in patients with COPD (including emphysema- and bronchitis-specific studies): 6MWT, 12MWT, ISWT, ESWT, ICET, ECET and TT. The full search strings used have been published previously.[34] An example Embase search string is given in the online supplement Figure S1.

Study Selection

Study selection followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for performing a systematic literature review.[35] One researcher screened each reference for inclusion based on title and abstract, and a second researcher performed a full quality-control check. A third researcher resolved any disputes. All publications that met entry criteria for the review were obtained as full articles and reassessed against the review criteria. Data from the selected studies were subsequently used to populate predefined summary tables. All data were fully checked by a second analyst. The review criteria are shown in Table 1. Publications were initially screened based on titles and abstracts, and full articles were reviewed when their relevance was unclear from the abstract. Publications were excluded if they were review articles, were not in English, studied patients with confounding comorbidities (e.g., cancers or diabetes), were unclear on the precise variables used for regression analysis or examined an inappropriate intervention (e.g., non-bronchodilatory pharmacotherapy or homeopathy). Studies were subsequently included for assessment only if they reported data on the correlations (Pearson's r [r] and/or Spearman's rho [ρ]) between the outcomes of any of the pre-specified exercise tests and the physiological measures of interest: FEV_1, FVC, IC and PaO_2.

Table 1. Summary of Systematic Review Inclusion/Exclusion Criteria

	Inclusion	Exclusion
Patient Population	Adult patients with COPD	• Pediatric populations • Patients with suspected/non-confirmed COPD • Animal/*in vitro* studies • Patients with significant compounding comorbidities (e.g., cancer or diabetes)
Interventions	All forms of approved bronchodilatory pharmacotherapy or no active therapy	Unapproved or experimental therapy (e.g., homeopathy)
Outcomes	Correlation (Pearson's r [r] and/or Spearman's rho [ρ]) between 1 of the following: • 6MWT • 12MWT • ISWT • ESWT • ICET • ECET • TT AND one of the following: • FEV_1 • FVC • IC • PaO_2	• Interventional outcomes • Multivariate analysis results • Other forms of correlation (including partial correlation analyses)
Study Design	Prospective or retrospective clinical trial or observational study	Reviews/editorials
Publication	English language	Non-English language

COPD=chronic obstructive pulmonary disease; ECET=endurance cycle ergometer test; ESWT=endurance shuttle walk test; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; IC=inspiratory capacity; ICET=incremental cycle ergometer test; ISWT=incremental shuttle walk test; 6MWT=6-minute walk test; 12MWT=12 minute walk test; PaO_2=partial pressure of arterial oxygen; TT=treadmill test.

Data Abstraction

Data were primarily abstracted by a single author (M.B.) and reviewed by all co-authors. A randomly generated selection of 30% of all articles was reviewed by a second author (I.F.) for quality control purposes. Extracted study characteristics were: 1)Study objectives (prospective/retrospective); 2)Study inclusion/exclusion criteria; 3)Study population size; 4)Population baseline characteristics (age, gender, body mass index [BMI], disease severity [staging method and score] and pulmonary function); 5)Methodological information (ECM [protocol, period] and univariant analysis); 6)Results: Pre-test physiological measures, PaO_2, arterial oxygen saturation (SaO_2) (%), FEV_1 (%), FVC (%), FEV_1 (L), FVC (L), IC (L), IC (% pred), functional residual capacity [FRC](%pred), total lung capacity (TLC) (L), TLC (% pred), residual volume in liters (RV) (L), RV (% pred), IC/TLC (%), measure of strength, strength, measure of physical activity, physical activity; 7) Results: Peak physiological measures during test, arterial oxygen saturation (SpO_2), oxygen consumption (VO_2), VO_2/kg, heart rate (HR); 8) Results: Patient reported outcomes, exertion (Borg scale), measure of dyspnea, dyspnea, measure of health-related quality of life (HRQoL), HRQoL; 9) Results: demographics, age, sex, height, weight, BMI; 10) Multivariate analyses to explain variance in ECM (parameters, analysis, r^2); 11) Discussion (conclusions, limitation, comment).

The following outcomes of exercise tests were recorded: distance or stages achieved for the 6MWT, 12MWT, ISWT; duration of exercise for the ESWT and ECET; and the highest recorded volume of oxygen consumption (peak VO_2) and maximum workload (W_{max}) for the TT and ICET. Publications involving studies assessing multivariate regressions were not included owing to the multifactorial nature of the statistical approach and the unsuitability of the output for aggregation.

Statistical Analysis

Pearson's and Spearman's correlations between lung function test results and the most commonly reported exercise test outcomes are presented. Pearson's correlations are often used to describe the linear association between 2 variables when comparing continuous variable data. Spearman's correlations are commonly used to describe the linear association between 2 sets of ranked (ordinal) data. Correlations are presented as the range of significant values reported in the study publications reviewed. Only those correlations deemed to have achieved significance by the authors of the original articles were included in our descriptive data analysis (i.e., $p<0.05$). However, all correlation statistics generated, regardless of significance were extracted (when available, many studies did not provide r values for non-significant correlations). The strength of (significant) correlations is classified according to *British Medical Journal* guidelines, which regard significant correlation coefficients of 0.0–0.19 as very weak, 0.20–0.39 as weak, 0.40–0.59 as moderate, 0.60–0.79 as strong and 0.80–1.00 as very strong correlations.

Inclusion/Exclusion Criteria

Owing to a lack of high quality evidence for associations between these tests and our stated measures of lung function, we included observational studies in our final analysis in addition to randomized controlled trials. Within the results of this search, we reviewed articles to identify those presenting Pearson's and Spearman's correlations between FEV_1, FVC, IC and PaO_2, and the most commonly reported exercise test outcomes (described above). Studies reporting lung function variables only as a percentage of age-, sex- and BMI-predicted values were excluded from these results. Publications involving studies assessing multivariate regressions were not included owing to the multifactorial nature of the statistical approach and the unsuitability of the output for aggregation.

Results

Overview of Identified Studies

The PRISMA-compliant search methodology used to identify relevant articles is summarized in Figure 1. Of 1781 articles screened, 45 studies were ultimately deemed eligible for inclusion in this review. Table 2 provides a summary of included studies.

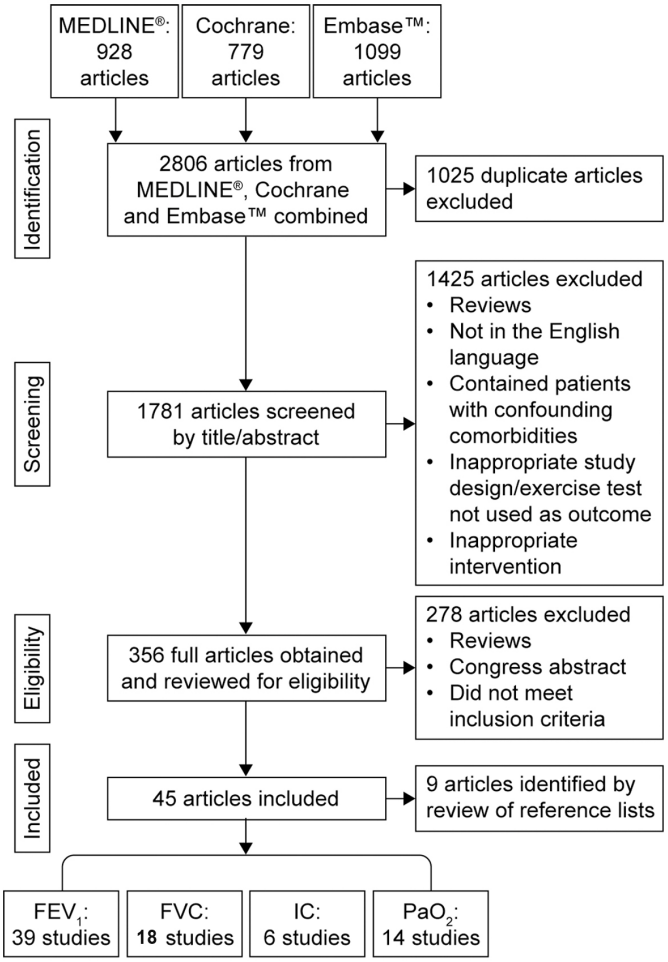
Correlations Between Exercise Test Outcomes and FEV_1

A total of 39 studies[16,36-65,66-71,72,73] reported significant Pearson's correlations between an exercise test outcome and baseline FEV_1 (Table 3). The ranges of correlations reported by studies are presented in Figure 2.

FEV_1 and 6MWT

The most commonly reported test was the 6MWT; of 17 studies[16,36,37,39-41,43,44,46,47,52,54,56,62,65,66,72]

Figure 1. PRISMA-compliant Screening and Identification Process



FEV_1=forced expiratory volume in 1 second;
FVC=forced vital capacity;
IC=inspiratory capacity;
PaO_2=partial pressure of arterial oxygen

assessing Pearson's correlations, 12 studies[16,36,39-41,43,47,52,62,65,66,72] showed significant correlations (weak to strong; r=0.23–0.62) and 5 reported no statistically significant Pearson's correlation between the 6MWT and FEV_1.[37,44,46,54,56] Additionally, 2 studies [42,63] out of 3 studies[42,63,73] assessing Spearman's correlations between FEV_1 and 6MWT reported significant correlations (moderate; ρ=0.41–0.44), with the remaining study[73] reporting no correlation.

FEV_1 and 12MWT

The 12MWT was also reported frequently, with 5 studies[38,48,58,60,68] out of 8 studies[38,48,58-61,64,68] reporting significant Pearson's correlations between distance achieved and baseline FEV_1 (very weak to strong; r=0.15–0.62); the remaining 3 studies reported no significant Pearson's correlations.[59,61,64] One study reported significant correlations between ISWT and FEV_1 (weak to moderate; r=0.22–0.51).[69]

FEV_1 and ICET

The strongest relationship between FEV_1 and exercise tests was in studies reporting ICET correlations; all 7 studies[45,47,49,54,59,62,71] assessing Pearson's correlations between peak VO_2 achieved during ICET reported significant correlations (moderate to very strong; r=0.42–0.83); in 5 studies in which W_{max} was assessed as the ICET outcome, correlations were also significant (weak to very strong; r=0.34–0.81).[41,55,57,71,72] These observations were supported by 1 further study, which reported positive Spearman's correlations for peak VO_2 and W_{max} during the ICET (ρ=0.37 and 0.55, respectively).[63]

FEV_1 and ISWT and TT

Limited evidence was available for other test outcomes and baseline FEV_1; 1 study each reported significant Pearson's correlations between FEV_1 and ISWT (weak to moderate; r=0.22–0.51)[69] and TT (moderate; r=0.47, p<0.05)[70] (Table 3; Figure 2a).

Correlations Between Exercise Test Outcomes and FVC

Baseline FVC and exercise test outcomes were reported by 18 studies (Table 3; Figure 2b).[38,39,41-46,49,50,53,58-62,70]

FVC and 6MWT

Again, the most commonly reported Pearson's correlations were between the 6MWT and FVC; 4 studies[39,41,43,62] out of 6 studies[39,41,43,44,46,62] assessing Pearson's correlations reported significant correlations (weak to moderate; r=0.32–0.59), with the remaining 2 studies[44,46] reporting no significant Pearson's correlation. One further study reported a significant Spearman's correlation (moderate; ρ=0.54).[42]

FVC and 12MWT

The 12MWT was also assessed frequently, with 4 studies[38,58-60] of 6 studies[38,58-61,64] reporting

Table 2. Summary of Included Studies

Author	Country	N	Inclusion & Exclusion Criteria	Age (years), Sex (n), BMI (kg/m^2)	Disease Severity	Pulmonary Function
McGavin 1976[59]	United Kingdom	35	• Inclusion = Patients with chronic bronchitis • Exclusion = Not stated	• Age = 40–70 • Male = 35, Female = 0 • BMI = Not stated	Chronic bronchitis according to MRC criteria	• FEV_1, L = 1.05 ± 0.58 • FVC, L = 2.84 ± 0.93
Mungall 1979[61]	United Kingdom	13	• Inclusion = Patients with chronic bronchitis or radiological emphysema with no evidence of ischemic heart disease or other serious illness or reversible bronchoconstriction • Exclusion = Not stated	• Age = 55.4 (47–64 range) • Male = 13, Female = 0 • BMI = Not stated	Chronic bronchitis according to MRC criteria or radiological emphysema	[*Individually listed in paper*]
O'Reilly 1982[64]	United Kingdom	10	• Inclusion = Males with chronic airways obstruction • Exclusion = Not stated	• Age = 61 (52–70 range) • Male = 10, Female = 0 • BMI = Not stated	• Chronic bronchitis (n = 8) • Radiological features of emphysema (n = 2)	• FEV_1, L = 0.81 ± 0.21 • FVC, L = 2.560 ± 0.593
Morgan 1983[60]	United Kingdom	50	• Inclusion = Patients with chronic bronchitis from several respiratory clinics, not referred on account of disproportionate dyspnea, no history of psychiatric illness, and not taking antidepressant or anxiolytic drugs • Exclusion = Patients with any other disorders that might limit exercise tolerance	• Age = 60.5 ± 6.8 • Male = 38, Female = 12 • BMI = Not stated	Chronic bronchitis according to MRC criteria and with MRC grade 3–5 dyspnea	• FEV_1, L = 0.97 ± 0.6 • FVC, L = 2.59 ± 0.96
Light 1985[58]	United States	45	• Inclusion = Patients with COPD, FEV_1 < 1.25 L, FEV_1/FVC < 50%, 40–70 years old, dyspnea-limited exercise tolerance • Exclusion = Patients who had received tricyclic antidepressants or other major antipsychotic drugs in preceding 2 months, or who had other significant complicating diseases such as uncontrolled malignancy, hepatic insufficiency, insulin-dependent diabetes mellitus, angina pectoris, myocardial infarction within previous year, cardiac arrhythmias, neuromuscular disease limiting ambulation, or blindness	• Age = 62.4 ± 4.3 • Male = 45, Female = 0 • BMI = Not stated	"Moderate or severe COPD"	• FEV_1, L = 0.908 ± 0.262 • FEV_1, % predicted = 29.0 ± 9.0 • FVC, L = 2.500 ± 0.606 • FVC, % predicted = 62.0 ± 15.5
Dekhuyzen 1986[48]	Nether-lands	50	• Inclusion = Patients from outpatient department, age 40–65 years, suffering from emphysema and/or chronic bronchitis with chronic airflow obstruction, steady clinical condition for preceding 2 months, FEV_1 increased by < 20% after inhalation of salbutamol • Exclusion = Patients with hypertension, ischemic heart disease, peripheral vascular disease or muscular disease	• Age = 57.2 ± 7.3 • Male = 37, Female = 13 • BMI = Not stated	As per MRC criteria	• FEV_1, L = 1.463 ± 0.566 • IVC, L = 3.712 ± 1.059

Chonan 1988[78]	Japan	15	• Inclusion = Patients with clinically stable chronic emphysema and chronic bronchitis who had been observed in pulmonary clinic for > 1 year, had undergone repeated pulmonary function tests demonstrating chronic airway obstruction and lung hyperinflation, had no substantial changes in pulmonary function during preceding 6 months • Exclusion = Not stated	• Mean age = 63 ± 6.5 • Male = 15, Female = 0 • BMI = Not stated	Diagnoses consistent with ATS standards	• FEV_1, % predicted = 36.9 ± 13.6 • VC, % predicted = 74.6 ± 21.5
Chetty 1989[45]	United States	37	• Inclusion = Patients with clinically stable COPD with no heart failure on clinical examination or symptomatic coronary artery disease • Exclusion = Not stated	• Age = 60 ± 6 • Male/Female = Not stated • BMI = Not stated	Moderate to severe COPD	• FEV_1, L = 1.49 ± 0.59 • FEV_1/FVC, % = 48 ± 12
Dillard 1989[49]	United States	20	• Inclusion = Patients fulfilling the study definitions of chronic airflow obstruction and ventilatory limitation of exercise, the latter defined by: (1) Peak exercise cardiac frequency < 2 SD below predicted maximum, (2) dyspnea as exercise limiting symptom, (3) exercise ventilation > 80% of 12s MVV • Exclusion = Patients who did not meet the definitions or who had a history of prior acute or chronic ventilatory failure or cardiac disease	• Age = 56 ± 3 • Male = 20, Female = 0 • BMI = Not stated	Chronic airflow obstruction defined by: (1) FEV_1 /FVC < 0.7 (2) TLC > 80% predicted (3) change in FEV_1 < 15% after bronchodilation	• FEV_1, L = 1.72 ± 0.21 • FVC, L = 3.27 ± 0.26
Schols 1989[68]	Nether-lands	83	• Inclusion = Patients with clinically stable severe COPD admitted to PR program • Exclusion = Patients with cardiovascular, neurological, endocrine and locomotor diseases and those with PaO_2 < 7.3 kPa	• Age = 62 ± 8 • Male = 71, Female = 12 • BMI = Not stated	Severe COPD	• FEV_1, L = 0.9 ± 0.3 • IVC, L = 2.7 ± 0.6
Singh 1992[69]	United Kingdom	10	• Inclusion = Patients with COPD recruited from medical clinics • Exclusion = Patients known to be hypoxic with cor pulmonale or ischemic heart disease, participants with neurological or locomotor disorders	Groups A, B, C: • n = 10, 10, 15 • Age = 64 (54–73 range), 63 (52–74 range), 64 (45–71 range) Male = 9, 6, 10 • BMI = Not stated	NR	Groups A, B, C: • FEV_1, L = 0.50 (0.36–1.45 range), 1.10 (0.60–2.10 range), 1.20 (0.50–2.85 range)
Wakayama 1993[70]	Japan	20	• Inclusion = Patients with clinically stable pulmonary emphysema who entered a PR program and free of other diseases, except for mild hypertension • Exclusion = Patients receiving home oxygen therapy	• Age = 66 ± 6 • Male/Female = Not stated • BMI = Not stated	Not stated	• FEV_1, L = 1.67 ± 0.50 • FEV_1, % predicted = 52 ± 22 • FVC, L = 2.62 ± 0.68 • FVC, % predicted = 80 ± 19
Bernstein 1994[38]	United States	9	• Inclusion = COPD patients with FEV_1 < 1.4 L, FEV_1/FVC < 0.50, exercise limited by dyspnea, stable disease state, and of age 40–75 years • Exclusion = Patients with known left ventricular disease or neuromuscular or other medical problems which would preclude them from walking for 12 min or performing cycle ergometry	• Age = 67 ± 4 • Male = 9, Female = 0 • BMI = Not stated	"Average patient had moderate COPD" based on mean FEV_1	• FVC, L = 3.40 ± 0.61 • FEV_1, L = 1.32 ± 0.28

Wijkstra 1994[72]	Nether-lands	40	• Inclusion = Patients with known COPD with post-bronchodilator FEV_1 < 60% predicted and FEV_1/IVC < 50%, and clinically stable • Exclusion = Patients with evidence of ischemic heart disease, intermittent claudication, musculoskeletal disorders, or other disabling diseases that might restrict a pulmonary rehabilitation program	• Age = 62.4 ± 5.0 • Male/Female = Not stated • BMI = Not stated	Severe airways obstruction, based on pulmonary function indices	• FEV_1, L = 1.2 ± 0.3 • FEV_1, % predicted = 44.3 ± 10.6 • IVC, L = 3.6 ± 0.9 • IVC, % predicted = 91.3 ± 17.2
Gosselink 1996[54]	Belgium	41	• Inclusion = Patients with COPD attending the outpatient clinic for dyspnea and poor exercise tolerance with: FEV_1 between 20% and 60% of predicted value, clinically stable condition, < 75 years old, no recent cardiac complaints, and no other pathological conditions • Exclusion = Not stated	• Age = 58 ± 10 • Male = 32, Female = 9 • BMI = 23 ± 5	"Moderate to severe COPD"	• FEV_1, % predicted = 43 ± 19 • FVC, % predicted = 79 ± 21
Baarends 1997[80]	Nether-lands	62	• Inclusion = Patients with COPD admitted to pulmonary rehabilitation center in stable clinical condition, who were not suffering from respiratory tract infection or clinically visible signs of edema at the time of study, who did not require supplemental oxygen, and had no known cardiovascular, neurological, endocrine or locomotive diseases • Exclusion = Patients with an increase in FEV_1 of > 10% baseline after inhalation of beta2-agonists	• Age = 63 ± 9 • Male = 44, Female = 18 • BMI = 23.2 ± 4.8	Moderate to severe COPD, as per ATS definitions	• FEV_1, % predicted = 39 ± 13 • FVC, % predicted = 87 ± 16
Borak 1998[39]	Poland	49	• Inclusion = Patients with COPD diagnosis, based on history, clinical examination, lung function tests and chest radiography, in stable state, with no signs of respiratory infection or heart failure or any concomitant disease that could influence their exercise tolerance or their psychological status. They were treated with inhaled bronchodilators – ipratropium bromide, beta2-agonists and oral theophylline. Six patients were on domiciliary long-term oxygen therapy • Exclusion = patients with asthma, > 10% improvement in FEV_1 and/or FVC after inhalation of beta2-agonists, and blood or sputum eosinophilia	• Age = 58 ± 8 • Male = 38, Female = 11 • BMI = Not stated	"wide spectrum of airway limitation severity and hypoxemia"	• FVC, L = 2.6 ± 0.7 • FVC, % predicted = 60 ± 16 • FEV_1, L = 1.0 ± 0.5 • FEV_1, % predicted = 32 ± 14
Revill 1999[67]	United Kingdom	10	• Inclusion = Patients in Group A were recruited from outpatient respiratory clinics, patients in Groups B & C were recruited from waiting lists for pulmonary rehabilitation, all patients had COPD, FEV_1 < 60% predicted, and self-reported breathlessness due to exercise • Exclusion = Not stated	• Age = 63.7 ± 5.5 • Male = 9, Female = 1 • BMI = Not stated	COPD diagnosed according to BTS guidelines	• FEV_1, L = 1.01 ± 0.36 • FEV_1, % predicted = 35 ± 4 • FVC, L = 2.92 ± 0.55 • FVC, % predicted = 81 ± 20

Yoshikawa 1999[71]	Japan	27	• Inclusion = Male patients with stable COPD, no other pathologic conditions and not receiving oral corticosteroids • Exclusion = Not stated	• Age = 68.4 ± 5.8 • Male = 27, Female = 0 • BMI = 18.4 ± 2.3	COPD as per ATS	• FEV_1, L = 1.18 ± 0.66 • FEV_1, % predicted = 49.8 ± 26.4 • VC, L = 2.75 ± 0.83 • VC, % predicted = 84.0 ± 23.5
Rejeski 2000[66]	United States	209	• Inclusion = Diagnosis of COPD, 55–80 years old, self-reported disability attributed to breathlessness when performing daily activities, prior or current history of smoking, FEV_1/FVC ratio ≤ 70% and FEV_1 > 20% of predicted. • Exclusion = Not stated	• Age = 67.2 ± 6.0 • Male = 117, Female = 92 • BMI = Not stated	n in ATS stage of COPD: • Stage I mild: 134 • Stage II moderate: 55 • Stage III severe: 20	• FEV_1, L = 1.57 ± 0.58 • FEV_1, % predicted = 57.10 ± 17.00
Chuang 2001[46]	United States/ Taiwan	27	• Inclusion = Outpatients with clinically stable COPD, receiving a regular schedule of administered bronchodilators with or without oral prednisolone of < 10 mg/day, who had peak exercise heart rate ≥ 85% of the maximally predicted, RER ≥ 1.09 at peak exercise, arterial plasma bicarbonate at peak exercise decreases from resting baseline level by at least 4 mmol/L, plasma pH value at peak exercise ≤ 7.35 • Exclusion = Patients with significant arrhythmia or having a history of malignancy, cardiovascular or peripheral vascular disease, or locomotion problems	• Age = 65 ± 6 • Male = 27, Female = 0 • BMI = Not stated	Moderate to severe COPD, based on most (~90%) patients having FEV_1/VC < 65%	• FEV_1, L = 1.2 ± 0.4 • FEV_1, % predicted = 49 ± 10 • VC, L = 2.8 ± 0.5
Dowson 2001[50]	United Kingdom	29	• Inclusion = Patients with α1-antitrypsin deficiency and macroscopic emphysema selected consecutively from a treatment center • Exclusion = Patients with asthma, bronchiectasis, liver disease or other medical problems likely to limit exercise or alter health status	• Median age = 52 (IQR: 46–60) • Male = 19, Female = 10 • BMI = Not stated	Moderate to severe airflow obstruction	• Median FEV_1, L = 1.03 (IQR: 0.84–1.41) • Median FEV_1, % predicted = 35 • Median FEV_1/VC, L = 0.31 (IQR: 0.25–0.43) • Median FEV_1/VC, % predicted = 37
Fujita 2002[53]	Japan	20	• Inclusion = Patients with chronic stable emphysema • Exclusion = Not stated	• Age = 66.9 ± 8.6 • Male = 18, Female = 2 • BMI = Not stated	Not stated	• FEV_1, L = 1.31 ± 0.61 • FEV_1, % predicted = 44.4 ± 19.8 • VC, L = 3.1 ± 0.8 • VC, % predicted = 94.7 ± 17.8

Oga 2002[63]	Japan	36	• Inclusion = Consecutive male patients with stable COPD from placebo arm of previously reported clinical trial with age > 45 years, smoking history > 20 pack years, chest radiographs showing hyperinflation, FEV_1 predicted < 80%, post-bronchodilator FEV_1/FVC < 0.7 • Exclusion = Patients with exacerbations in preceding 3 months, history of asthma, other diseases likely to affect exercise, or hypoxemia at rest	• Age = 69 ± 7 • Male = 36 Female = 0 • BMI = 20.3 ± 3.2	COPD as per ATS	• FEV_1, L = 1.07 ± 0.45 • FEV_1, % predicted = 40.3 ± 16.7
Carter 2003[43]	United States	124	• Inclusion = Individuals with moderate to very severe COPD, capable of undergoing exercise testing to peak effort, greater than 8th grade education and able to read, no interfering coexisting medical conditions • Exclusion = cardiac, renal or endocrine disease, claudication limiting exercise capacity, musculoskeletal pain, syncope, significant ST-T depression or cardiac arrhythmia on exercise testing, or a pattern for restrictive lung disease	• Age = 66.8 ± 7.3 • Male = 90, Female = 34 • BMI = 27.1 ± 5.2	Moderate to severe airway obstruction as determined by pulmonary function indices	• FEV_1, L = 1.33 ± 0.43 • FEV_1, % predicted = 45.9 ± 12.5 • FVC, L = 3.25 ± 0.91 • FVC, % predicted = 82.9 ± 15.5
Hodgev 2003[56]	Bulgaria	20	• Inclusion = Patients with clinically stable COPD who had not received systemic steroids at least 2 months prior to study, but did receive therapy with bronchodilators during study • Exclusion = Patients with history of asthma, allergic rhinitis or atrophy; active lung tuberculosis or lung carcinoma; cardiovascular disorders including myocardial infarction, angina pectoris, pericarditis, valvular diseases (excepting relative tricuspid insufficiency), arrhythmia, arterial hypertension requiring drug treatment; disorders of locomotor apparatus; anemias; kidney, liver or metabolic disorders	• Age = 55.9 ± 8.7 • Male = 20, Female = 0 • BMI = 27.8 ± 7.7	COPD diagnosed as per guidelines recommended by the National Consensus Conference	• FEV_1, L = 1.35 ± 0.72 • FEV_1, % predicted = 42 ± 19
Peruzza 2003[65]	Italy	60	• Inclusion = Patients with COPD over the age of 65 years • Exclusion = Patients who were underweight (BMI < 18.5 kg/m^2) or obese (BMI > 30 kg/m^2), had ischemic heart disease, or experienced changes in medication in preceding 30 days or hospital admission in preceding 6 weeks	• Age = 74.5 ± 5.8 • Male = 60, Female = 0 • BMI = 25.1 ± 3.8	As per ERS criteria	• FEV_1, L = 1.1 ± 0.5 • FEV_1, % predicted = 48.1 ± 18.3
Vagaggini 2003[76]	Italy	18	• Inclusion = Patients who were in the recovery phase of an exacerbation of COPD that had required hospitalization, had never performed a 6MWT or ISWT, were taking bronchodilators and/or inhaled corticosteroids at the time of study, and were examined at least 14 days after the beginning of the exacerbation • Exclusion = Not stated	• Age = 67 ± 8.2 • Male = 15, Female = 3 • BMI = Not stated	Moderate to severe COPD	• FEV_1, % predicted = 48 ± 14 • FVC, % predicted = 74.4 ± 16.2

Nakamura 2004[62]	Japan	38	• Inclusion = Male patients with clinically stable COPD and FEV_1 < 70% predicted, age < 80 years, and no other pathological conditions • Exclusion = Not stated	• Age = 69.8 ± 6.7 • Male = 38, Female = 0 • BMI = 21.4 ± 3.1	"Moderate to severe COPD"	• FEV_1, L = 1.33 ± 0.55 • FEV_1, % predicted = 49.5 ± 19.6 • FVC, L = 2.79 ± 0.70
Pinto-Plata 2004[16]	United States	198	• Inclusion = Patients with COPD referred to hospital pulmonary department • Exclusion = Patients who had had an exacerbation in preceding 4 months or another unstable medical problem	• Age = 68 ± 9 • Male = 168, Female = 30 • BMI = 24.86 ± 5.74	COPD as per ATS	• FEV_1, L = 1.04 ± 0.39
Behnke 2005[37]	Germany	88	• Inclusion = Individuals with COPD and FEV_1 ≤ 75% predicted and no other significant airway disease • Exclusion = Not stated	Training group (n = 66): • Age = 61.2 ± 8.6 • Male = 51, Female = 15 • BMI = 24.5 ± 3.0 Control group (n = 22): • Age = 58.4 ± 6.7 • Male = 20, Female = 2 • BMI = 23.8 ± 4.9	Mild to severe COPD diagnosis as per international guidelines (GOLD)	Training group, control group: • FEV_1, L = 1.30 ± 0.49, 1.45 ± 0.51 • FEV_1, % predicted = 41.9 ± 13.9, 46.9 ± 15.1
Rosa 2006[77]	Brazil	24	• Inclusion = Consecutive patients with COPD from pulmonary rehabilitation center with: PaO_2 = 55 mmHg or SpO_2 = 92% (at rest and on room air), at least 6 weeks of clinical stability, and satisfactory ability to walk unaided. • Exclusion = Patients with SpO_2 of 80% during exercise, suffering from other pulmonary diseases, heart diseases, cardiac insufficiency or other comorbidities considered uncontrolled or significant, and those presenting formal contraindications for performing exercise tests	• Age = 67.8 ± 7.5 • Male = 17 Female = 7 • BMI = 24.2 ± 4.2	n in GOLD stage of COPD: • Stage I mild: 2 • Stage II moderate: 7 • Stage III severe: 12 • Stage IV: 3	• FEV_1, % predicted = 48.6 ± 21.0 • FVC, % predicted = 80.9 ± 21.0
Cote 2007[47]	United States	365	• Inclusion = Consecutive patients with COPD recruited to the BODE protocol between 1994 and 2005, with smoking history > 10 pack years, FEV_1/FVC < 0.70, response to bronchodilation of 12% or 200 mL, clinically stable for preceding 6 weeks • Exclusion = Not stated	• Age = 67 ± 8 • Male/Female = "mostly men" • BMI = 26.8 ± 5.4	"Wide range of COPD severity"	• FEV_1, L = 1.2 ± 0.48 • FEV_1, % predicted = 40 ± 14 • FVC, L = 2.8 ± 0.79
Emtner 2007[51]	Sweden	21	• Inclusion = Consecutive patients who had been admitted to hospital with acute exacerbation of COPD; patients split into 2 groups for baseline parameters, but not for analyses • Exclusion = Not stated	No hospitalization group (n = 12): • Age = 65 ± 10 • Male = 2, Female = 10 • BMI = 23 ± 4 Hospitalization group (n = 9): • Age = 65 ± 9 • Male = 5, Female = 4 • BMI = 22 ± 4	Not stated	• FEV_1, % predicted = 40 ± 12, 32 ± 17

Brown 2008[41]	United States	1218	• Inclusion = COPD patients enrolled in National Emphysema Treatment Trial with radiographic evidence of emphysema, FEV_1 ≤ 45% predicted, TLC ≥ 100% predicted, RV ≥ 150% predicted and $PaCO_2$ ≤ 60 mmHg, who had not smoked in prior 4 months and did not have severe co-morbid conditions • Exclusion = Not stated	• Age = 66.6 ± 6.13 • Male = 746, Female = 472 • BMI = 24.7 ± 3.88	COPD patients with severe or very severe emphysema who were participating in a trial of lung volume reduction surgery	• FEV_1, L = 0.77 ± 0.24 • FEV_1, % predicted = 26.9 ± 7.12 • FVC, L = 2.50 ± 0.78 • FVC, % predicted = 66.8 ± 15.2
Hill 2008[55]	Australia/ Canada	50	• Inclusion = Patients with diagnosis of COPD, smoking history > 10 pack years, and 15% < FEV_1 predicted < 70% • Exclusion = History of lung surgery or spontaneous pneumothorax, use of gait aids or long-term oxygen therapy, any comorbid condition thought to adversely affect exercise performance (e.g., musculoskeletal conditions, symptomatic ischemic heart disease, neurologic or cognitive impairment), BMI > 35 kg/m^2, or tapering doses of corticosteroids or methylxanthines	• Age = 68 ± 8 • Male = 36, Female = 14 • BMI = 23.4 ± 3.5	Not stated	• FEV_1, L = 1.0 ± 0.4 • FEV_1, % predicted = 37 ± 11 • FEV_1/FVC, % = 37 ± 9
Pitta 2008[79]	Brazil	40	• Inclusion = Consecutive patients in screening process for PR program between June 2006 and June 2007 with clinically stable COPD, and no osteo-neuro-muscular comorbidities that might interfere with assessments • Exclusion = Patients not able to finalize proposed assessments	• Age = 68 ± 7 • Male = 21, Female = 19 • BMI = 24 ± 6	n in each GOLD stage of COPD: • Stage I mild: 1 • Stage II moderate: 11 • Stage III severe: 19 • Stage IV: 9	• FEV_1, L = 0.90 ± 0.26 • FEV_1, % predicted = 41 ± 14 • FVC, % predicted = 66 ± 19
Brasil Santos 2009[40]	Brazil	91	• Inclusion = Patients with COPD as outpatients from pulmonary unit during 2004 whose records were chosen randomly and then filtered according to following exclusion criteria • Exclusion = Patients enrolled in or who had taken part in a pulmonary rehabilitation program in preceding 6 months, or those with skeletal-muscular dysfunctions that prevented normal walking, orthopedic appliances and/or prostheses, hemodynamic instability with infection or acute episodes in preceding 8 weeks, or with prolonged oxygen therapy	• Age = 64.4 ± 8.5 • Male/Female = Not stated • BMI = Not stated	COPD of all levels of obstruction as per GOLD guidelines	• FEV_1, % predicted = 63.4 ± 25.3 • FEV_1/FVC, % = 50.8 ± 12.4
Camargo 2010[42]	Brazil	50	• Inclusion = Consecutive patients with symptomatic COPD (≥ 40 years old) treated between March 2008 and July 2009, with a documented post-bronchodilator FEV_1 predicted ≤ 65% within last 12 months, and with a smoking history of ≥ 10 pack years • Exclusion = Patients with dyspnea from any other cause than COPD, those using supplemental oxygen, those unable to perform the 6MWT, answer the dyspnea questionnaires or perform pulmonary function tests, those presenting with exacerbation in the last 3 months and those presenting radiological abnormalities indicative of other conditions	• Age = 69 ± 8 • Male = 35, Female = 15 • BMI = 27 ± 5	Not stated	• FEV_1, L = 1.3 ± 0.4 • FEV_1, % predicted = 52 ± 12 • FVC, L = 2.7 ± 0.7 • FVC, % predicted = 85 ± 14

Kozu 2010[57]	Japan	45	• Inclusion = Patients with COPD who were clinically stable and had had no changes in medication for at least 4 weeks prior to the study • Exclusion = Patients with very mild symptoms, or those who had comorbid conditions affecting exercise performance (e.g. muscloskeletal or neurological impairment, cardiac disease, severe cognitive impairment)	• Age = 67.3 ± 5.1 • Male = 38, Female = 7 • BMI = 20.8 ± 2.2	Diagnosis of COPD was made according to established criteria (GOLD)	• FEV_1, L = 1.10 ± 0.50 • FEV_1, % predicted = 45 ± 12 • FVC, % predicted = 81 ± 22
Fujimoto 2011[52]	Japan	130	• Inclusion = Consecutive middle-aged and elderly outpatients with COPD recruited between April 1997 and October 2009 • Exclusion = Patients who had had exacerbation or uncontrolled comorbidities, such as malignancy, cardiovascular disease, cerebrovascular disease, and active musculoskeletal disease, during 6 weeks preceding measurements	• Age = 72.14 ± 7.37 • Male = 121, Female = 9 • BMI = 21.05 ± 3.68	n in GOLD stage of COPD: • Stage I mild: 44 • Stage II moderate: 53 • Stage III severe: 29 • Stage IV: 4	• FEV_1, L = 1.28 ± 0.52 • FEV_1, % predicted = 70.61 ± 28.03
Annegarn 2012[36]	Nether-lands	79	• Inclusion = Patients with COPD recruited from pre-rehabilitation assessment • Exclusion = Patients who had had exacerbation-related hospitalization within 4 weeks prior to assessment, who used a rollator, or who were unable to complete at least one 6MWT without stopping	• Age = 64.3 ± 8.9 • Male = 47, Female = 32 • BMI = 24.7 ± 4.5	n in GOLD stage of COPD: • Stage I mild: 8 • Stage II moderate: 36 • Stage III severe: 28 • Stage IV very severe: 7	• FEV_1, % predicted = 53.5 ± 18.7
Chen L 2012[74]	Taiwan	17	• Inclusion = Patients with clinically stable COPD without baseline oxygen saturation recruited from July 2008 to July 2010 who were 60–80 years old, non-smokers or smoking history of 10 pack years, with no pathology that could interfere with the ability to perform exercises • Exclusion = Not stated	• Age = 73.5 ± 5.7 • Male = 17, Female = 0 • BMI = 22.3 ± 3.5	n in GOLD stage of COPD: • Stage I mild: 1 • Stage II moderate: 6 • Stage III severe: 6 • Stage IV very severe: 4	• FEV_1, L = 0.9 ± 0.1 • FEV_1, % predicted = 43.1 ± 16.2 • FVC, L = 1.7 ± 0.1 • FVC, % predicted = 54.5 ± 13.2
Chen S 2012[44]	Taiwan	37	• Inclusion = COPD patients with chronic hypercapnia, FEV_1 < 50% predicted, daytime awake $PaCO_2$ > 45 mmHg, PaO_2 < 80 mmHg, pH 7.30–7.45 with room air, medical stability in preceding 3 months, good motivation to participate in study, and have not participated in pulmonary rehabilitation programs • Exclusion = Patients who could not perform 6MWT owing to various other diseases (e.g., orthopedic or neuromuscular problems or other systematic diseases) and were uncooperative or poorly motivated to participate	• Age = 64.4 ± 10.9 • Male = 28, Female = 9 • BMI = 21.4 ± 4.8	Not stated	• FVC, L = 1.2 ± 0.5 • FVC, % predicted = 41.4 ± 17.1 • FEV_1, L = 0.6 ± 0.20 • FEV_1, % predicted = 26.1 ± 7.7 • FEV_1/FVC, % = 50.9 ± 12.7
Waatevik 2012[75]	Norway	370	• Inclusion = Patients with COPD included in the previously published Bergen COPD cohort study who were able to complete a 6MWT without stopping and without supplemental oxygen • Exclusion = Not stated	• Age = 63.3 ± 6.8 • Male = 223, Female = 147 • BMI = Not stated	Not stated	• FEV_1, % predicted = 50.4 ± 13.8

ATS=American Thoracic Society; BMI=body mass index; BODE=Body mass index, airflow Obstruction, Dyspnea and Exercise capacity index; BTS=British Thoracic Society; COPD=chronic obstructive pulmonary disease; ERS=European Respiratory Society; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; HR=heart rate; IQR=interquartile range; ISWT=incremental shuttle walk test; IVC=inspiratory slow vital capacity; kPa=kilopascal; L=litres; 6MWT=6-minute walk test; MRC=Medical Research Council; MVV=maximal voluntary ventilation; NR=not reported; $PaCO_2$ =partial pressure of arterial carbon dioxide; PaO_2=partial pressure of arterial oxygen; PR=pulmonary rehabilitation; RER=respiratory exchange ratio; RV=residual volume; SD=standard deviation; SpO_2=arterial oxygen saturation; TLC=total lung capacity; VC=vital capacity.

Values presented are mean ± standard deviation unless otherwise stated.

significant Pearson's correlations (very weak to moderate; r=−0.16–0.41), with 1 study[38] reporting a negative correlation. The remaining 2 studies reported that Pearson's correlations were not significant.[61,64]

FVC and ICET, TT and VO_2

Of 4 studies[45,49,59,62] assessing associations between FVC and peak VO_2 obtained during ICET, 3 studies[45,49,59] presented significant Pearson's correlations (strong; r=0.54–0.67); the remaining study reported that Pearson's correlations were not significant.[62] One further study reported a significant Pearson's correlation between FVC and W_{max} achieved during ICET (moderate; r=0.58).[41] One other study reported a significant Pearson's correlation between FVC and peak VO_2 during TT (strong; r=0.63).[70]

Correlations Between Exercise Test Outcomes and IC

Baseline IC was reported in 6 studies (Table 3; Figure 2c).[41,42,50,52,73,74]

IC and 6MWT

Of these, all 3 studies[41,52,74] assessing Pearson's correlations for IC and the 6MWT found significant relationships (weak to moderate; r=0.38–0.62); a further 2 studies also reported significant Spearman's values for this relationship (moderate; ρ=0.51 and 0.57).[42,73]

IC and ISWT, ICET and TT

Significant moderate correlations were also reported between IC and ISWT (ρ=0.50), and W_{max} during ICET (r=0.59) and TT (ρ=0.48).[50]

Correlations Between Exercise Test Outcomes and Exercise-induced Changes in PaO_2

A total of 14 studies assessed correlations between change in PaO_2 and exercise test outcomes (Table 3; Figure 2d).

PaO_2 and 6MWT

Three[44,47,75] of 5 studies[39,40,44,47,75] studies assessing Pearson's correlations between 6MWT and PaO_2 reported significant correlations (very weak to weak; r=0.15–0.35), with the 2 remaining studies[39,40] reporting no significant correlation. Of 3 studies[63, 76,77] reporting Spearman's correlations between 6MWT and PaO_2, 2 studies[63,76] found no significant association and 1 study[77] found a significant correlation (moderate; ρ=0.42).

PaO_2 and 12MWT

Pearson's correlations for 12MWT were assessed in 4 studies[48,58,68,78]: 2 studies[48,68] reported moderate correlations (r=0.42–0.44) with the remaining 2 studies[58,78] reporting no correlation.

PaO_2 and ISWT

Of 3 studies reporting Spearman's correlations for the ISWT,[50,76,77] 2 studies[50,77] found moderate correlations (ρ=0.42–0.53) with 1 study[76] reporting no correlation. In the 3 studies assessing ICET (peak VO_2),[47,63,80] 2 studies[47,80] reported only weak Pearson's correlations (r=0.21–0.28) with 1 study[63] reporting no Spearman's correlation.

Correlations Between Exercise Test Outcomes and TLC

Additionally, it was anticipated that associations between exercise and TLC would be included in the review. However, too few studies were found and therefore not included in the final results.

Discussion

This study has shown that there are limited data supporting strong correlations between exercise test outcomes and commonly used assessments of lung function. FEV_1 appears to correlate well with the outcomes of the ICET (both VO_2 and W_{max}). The association between the most commonly used field-

Table 3. Correlations Between Exercise Test Outcomes and Selected Physiological Variables

	6MWT		12MWT		ISWT		ESWT		ICET (VO_2)		ICET (W_{max})		ECET		TT	
	Corr	N	Corr	N	Corr	N	Corr	N	Corr	N	Corr	N	Corr	N	Corr	N
FEV_1																
r	0.23*[47]	365	0.15*[38]	9	[0.51, 0.22, 0.25]*[69]	10			0.42*[62]	38	0.34*[57]	45			0.47*[70]	20
	0.33***[52]	130	0.26*[60]	50					0.46*[47]	365	0.51***[55]	50				
	0.37*[65]	60	0.29**[68]	83					0.53**[45]	37	0.58**[72]	40				
	0.37*[66]	209	0.31*[58]	45					0.64**[54]	41	0.65***[41]	1218				
	0.38***[43]	124	0.62**[48]	50					0.65**[59]	35	0.81**[71]	27				
	0.38***[41]	1218							0.76*[49]	20						
	0.40**[40]	91							0.83**[71]	27						
	[0.44**, 0.56**][16]	198														
	0.45**[36]	79														
	0.55**[72]	40														
	0.58*[62]	38														
	0.62***[39]	49														
	NS[64]	41	*NS*[59]	35	0.40[51]	21	*NS*[67]	10								
	0.31[46]	27	*NS*[61]	13	0.30[56]	20										
	0.36[56]	20	0.28[64]	10												
	NS[37]	88														
	0.18[44]	37														
ρ	0.44**[42]	50			0.65**[50]	25			0.37*[63a]	36	0.55[63a]	36	0.58[63a]	36	0.64*[50]	29
	0.41*[63a]	36													0.65**[53]	20
	0.29[73]	40														
FVC																
r	0.32*[41a]	1218	−0.16[38]	9					0.54**[45]	37	0.58*[41a]	1218			0.63**[70]	20
	0.38***[43]	124	0.29*[60]	50					0.66*[49]	20						
	0.58***[39]	49	0.35*[58]	45					0.67**[59]	35						
	0.59*[62]	38	0.41*[59]	35												
	0.34[46]	27	*NS*[61]	13					0.32[62]	38						
	0.16[44]	37	0.00[64]	10												
ρ	0.54**[42]	50			0.52*[50]	25									0.46*[50]	29
															0.77***[53]	20
IC																
r	0.38***[41]	1218									0.59*[41]	1218				
	0.43***[52]	130														
	0.62**[74]	17														
ρ	0.51**[73]	40			0.50*[50]	25									0.48*[50]	29
	0.57**[42]	50														
PaO_2																
r	0.15*[47]	365	0.42[68]	83					0.21*[47]	365					0.56*[78]	15
	0.23***[75]	370	0.44**[48]	50					0.28*[80]	62						
	0.35*[44]	37														
	0.27[39]	49	0.50[78]	15												
	NS[40]	91	−0.29[58]	45												
ρ	0.42*[77]	24			0.42*[77]	24									0.67**[50]	29
					0.53**[50]	25										
	NS[76]	18			*NS*[76]	18			*NS*[63]	36	*NS*[63]	36	*NS*[63]	36		
	NS[63]	36														

Corr=correlation; ECET=endurance cycle ergometer test; ESWT=endurance shuttle walk test; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; IC=inspiratory capacity; ICET=incremental cycle ergometer test; ISWT=incremental shuttle walk test; 6MWT=6-minute walk test; 12MWT=12-minute walk test; NS=studies reporting no significant correlation; ρ=Spearman's rank coefficient; PaO_2=partial pressure of arterial oxygen; r=Pearson's regression coefficient; TT=treadmill test; VO_2=oxygen consumption; W_{max}=highest workload achieved.

Square parentheses enclose the results of different subgroups within the same study.

*p <0.05,**p <0.01, ***p <0.001, No (*), not significant r value, NS not significant (r value not provided in original article)
[a] significance assumed as p<0.05 from table inclusion criteria, actual value not given in text. However, only those p values deviating from table inclusion criteria are shown.

based tests of exercise capacity, the 6MWT and 12MWT, and FEV_1 is unclear.

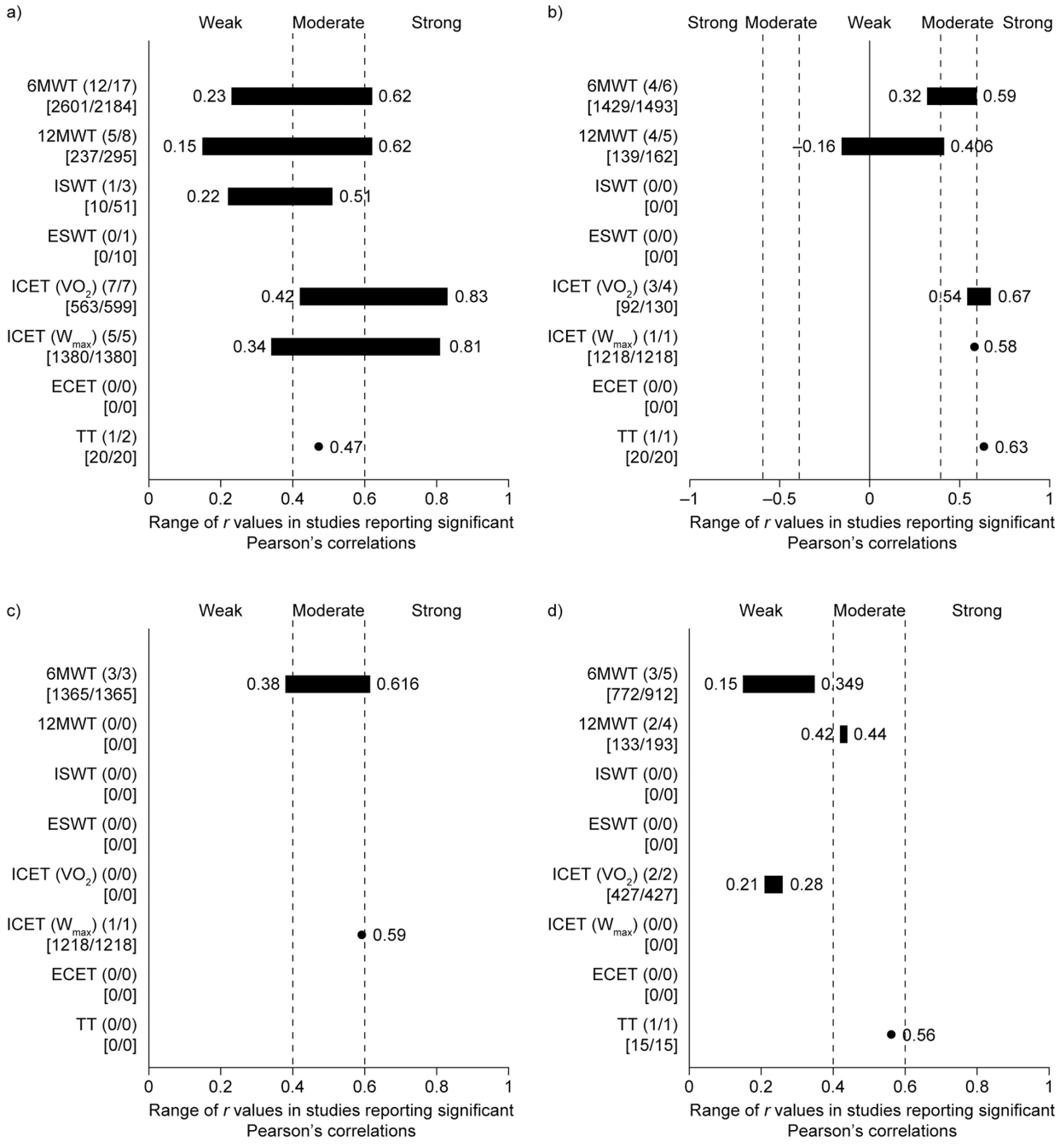
FEV_1 is used as the main diagnostic criterion for COPD,[4, 22, 23] and the European Medicines Agency also suggests that pre- and post-bronchodilator FEV_1, both at baseline and repeatedly during follow-up, is used to demonstrate the efficacy of therapeutic interventions in clinical trials.[24] FEV_1 correlates better with laboratory-based tests such as the ICET (primarily moderate to very strong correlations) than with field-based tests, such as 6MWT and the 12MWT (although these do consistently demonstrate weak/moderate correlations). The ICET also appeared to have the closest relationship to FVC and IC, albeit with very limited evidence. Conversely, ICET correlated only weakly with PaO_2 in studies reporting this relationship.

Some caution is warranted in placing too much emphasis on lung function alone as a gold standard assessment in COPD relative to exercise tests. While individual lung function measurements, such as FEV_1, are used in diagnosing the severity of COPD and predicting mortality,[27] it should be remembered that COPD patients have systemic disease manifestations that are not necessarily reflected by a single lung function result. Patients with similar FEV_1 may nevertheless have significantly different function defects not captured by this test. Exercise tests, in measuring whole lung functionality, may be expected to correlate imprecisely with individual lung function parameters. Furthermore, their design may capture the systemic aspects of COPD lung dysfunction more effectively and thus provide additional prognostic information. In fact, several prospective studies have shown that 6MWT is a better predictor of mortality than FEV_1 in patients with severe COPD[16,81] and coupling 6MWT output to individual lung function parameters like FEV_1 and PaO_2 has proven utility[82,83] and underpins the rationale for the multidimensional grading system for COPD, the BMI, airflow, Obstruction, Dyspnea and Excercise capacity (BODE) index.[84]

The observation that the 6MWT and the 12MWT are the most often reported in conjunction with measures of lung function is unsurprising as they are well established, require little equipment, training or preparation, and (for the 6MWT at least) minimal, clinically important, difference reference values are available. Of the laboratory-based tests, the ICET is by far the most widely used. However, this serves to highlight the paucity of data reporting the relationship between other exercise tests and measures of lung function. When reported, for example, the ISWT and TT exhibited mostly moderate to good correlations with the 4 physiological parameters assessed in this review. However, it is difficult to draw definitive conclusions about the applicability of these tests when the data are so rarely reported. Correlations between the FEV_1, FVC, IC and PaO_2 and the ESWT and ECET have so seldom been reported that no meaningful interpretation of these relationships can be made.

Exercise tests, such as those reviewed here, are used to assess the exercise capacity of patients with COPD. These tests are important because the systemic consequences of COPD include reduced exercise capacity and ensuing decreases in physical activity. However, the findings of this systematic review suggest that the relationships between exercise and FEV_1, FVC, IC and PaO_2 are under-reported for most tests, and even for the most commonly reported tests, these associations are often equivocal. This suggests that although the information obtained from these tests may be of use in assessing exercise tolerance, caution should be used before applying the results of these tests to make assessments of physiological effects of COPD. Exercise capacity appears to be such a multi-factorial outcome that it is difficult to conclusively link test performance to any of the physiological variables reviewed. This supports a recent systematic review that qualitatively compared patients' performance in these

Figure 2. Ranges of Reported Pearson's Correlations



Ranges of reported Pearson's correlations in studies reporting significant associations between exercise tests and: a) FEV_1; b) FVC; c) IC and d) PaO_2. Brackets indicate the number of studies reporting significant correlations/total number of studies reporting Pearson's correlations. Square brackets indicate number of patients in studies reporting significant Pearson's correlations/total number of patients in studies assessing Pearson's correlations.

ECET=endurance cycle ergometer test; ESWT=endurance shuttle walk test; ICET=incremental cycle ergometer test; ISWT=incremental shuttle walk test; 6MWT=6-minute walk test; 12MWT=12-minute walk test; *r*=Pearson's regression coefficient; TT=treadmill test; VO_2=oxygen consumption; W_{max}=highest workload achieved.

exercise tests and found no discernible advantage of any particular test.[34]

Limitations of this review include the wide range of study designs and patient cohorts involved. Furthermore, the association between lung function and exercise performance are most probably not adjusted for important confounders such as age, gender, height, comorbidities and weight. It is also possible that study results are confounded by limited patient numbers. Using the most commonly reported association as an example, the 12 studies reporting a significant Pearson's correlation between 6MWT and FEV_1 had a median *n* of 108 (range: 38–1218); the 5 studies that reported no significant association between these parameters had a median *n* of 39 (range: 20–88). It is therefore possible that significant associations could be underreported owing to a type II statistical reporting error. On the other hand, it can be seen where r/ρ are reported for correlations between the same 2 parameters, that there is a tendency for larger populations to have a lower value and associated lower significance, suggesting that smaller populations can over-emphasize a genuine relationship. Both of these factors must be considered when designing studies assessing these exercise tests as well as the ability of pharmacological interventions to affect their output. Other confounding variables that are difficult to control for in such a review include whether or not the guidelines from the ATS were strictly adhered to in all the tests. This is particularly important regarding the technical aspects of tests such as 6MWT where even small deviations in methodology can influence output.[85] Finally, the inclusion criteria and COPD severity are often not clearly stated by the studies included in this review. Therefore, there is a risk that the patients in the included studies are not broadly homogenous. However, in this case the weakness lies in the reporting of studies, and we recommend that future studies clearly state inclusion criteria and clinical rationale for diagnosis whenever possible.

Recent guidelines on the diagnosis and treatment of COPD indicate that assessment of disease severity is improved by using functional criteria such as exercise capacity.[4,22,23] However, no distinction is made in these guidelines between the different exercise tests. For example, ICET and 6MWT output are thought to measure different physio-biochemical variables,[86] and it has been argued that the latter is a better reflection of a patient's ability to carry out daily activities.[87] The current findings suggest that clinicians or investigators wishing to assess exercise capacity in patients with COPD must carefully consider the physiological consequences of COPD when interpreting the results of these tests. In particular, based on our review of the available data, it is important not to choose an exercise test based solely on patient lung function. Rather, tests should be chosen based on the ability of a pharmaceutical agent to influence the test based on the effect that agent is anticipated to have. For example, an agent that primarily affects lungs and subsequently improves tests measuring lung function, volume and breathlessness may well differ from an agent anticipated to have more systemic consequences.

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Declaration of Interest:
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