Comprehensive Lung Function Assessment Does not Allow to Infer Response to Pulmonary Rehabilitation in Patients with COPD

Ingrid M. L. Augustin 1,2,*, Emiel F. M. Wouters 1,3, Sarah Houben-Wilke 1, Swetlana Gaffron 4,*, Daisy J. A. Janssen 1, Frits M. E. Franssen 1,3 and Martijn A. Spruit 1,2,3

1 CIRO+, Center of Expertise for Chronic Organ Failure, 6085 NM Horn, The Netherlands; ewouters@ciro-horn.nl (E.F.M.W.); sarahwilke@ciro-horn.nl (S.H.-W.); daisyjanssen@ciro-horn.nl (D.J.A.J.); fritsfranssen@ciro-horn.nl (F.M.E.F.); martijnspruit@ciro-horn.nl (M.A.S.)

2 NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre+, 6229 ER Maastricht, The Netherlands

3 Department of Respiratory Medicine, Maastricht University Medical Centre+, 6229 HX Maastricht, The Netherlands

4 Viscovery Software GmbH, 1130 Vienna, Austria; s.gaffron@viscovery.net

* Correspondence: ingridaugustin@ciro-horn.nl; Tel.: +31-(0)475-587-601

Received: 19 November 2018; Accepted: 22 December 2018; Published: 27 December 2018

Abstract: The degree of lung function is frequently used as referral criterion for pulmonary rehabilitation. The efficacy of pulmonary rehabilitation was assessed in 518 chronic obstructive pulmonary disease (COPD) patients, after clustering based on a comprehensive pre-rehabilitation lung function assessment. Mean improvements in dyspnea, exercise performance, health status, mood status and problematic activities of daily life after pulmonary rehabilitation were mostly comparable between the seven clusters, despite significant differences in the degree of lung function. The current study demonstrates no significant relationship between the seven lung-function-based clusters and response to pulmonary rehabilitation. Therefore, baseline lung function cannot be used to identify those who will respond well to pulmonary rehabilitation, and moreover, cannot be used as a criterion for referral to pulmonary rehabilitation in patients with COPD.

Keywords: pulmonary rehabilitation; COPD; response

1. Introduction

Pulmonary rehabilitation, defined as a comprehensive non-pharmacological intervention, is generally very effective in patients with chronic obstructive pulmonary disease (COPD) [1]. Indeed, statistically significant and clinically relevant improvements can be obtained for dyspnea, exercise capacity and health status compared to standard care [2–4].

In daily practice and in clinical trials, the degree of airflow limitation is frequently used as an indicator for referral for pulmonary rehabilitation [2]. However, not all patients with COPD with severe to very severe airflow limitation are symptomatic or limited in their daily functioning [5]. Conversely, a proportion of COPD patients with mild to moderate airflow limitation may suffer from severe dyspnea and experience everyday limitations [3]. The degree of airflow limitation, therefore, is a poor determinant of the physical and psychological status of a patient with COPD [6,7]. It has been shown that, mean improvements following exercise-based pulmonary rehabilitation are comparable after stratification for baseline airflow limitation [8,9]. Moreover, there is no difference in baseline forced expiratory volume in 1 s (FEV1) between very good and poor responders to pulmonary
rehabilitation [3]. Thus, the degree of airflow limitation is a poor selection criterion for pulmonary rehabilitation. The same is true for the degree of static lung hyperinflation [10].

Recently, the heterogeneity of respiratory impairment in patients with COPD has been illustrated by the respiratory physiome, in which patients are clustered on multiple lung function attributes [11]. Whether and to what extent the respiratory physiome can be used as an indicator for referral for pulmonary rehabilitation remains currently unknown. A priori, we hypothesize that the respiratory physiome clusters are unable to infer response to pulmonary rehabilitation in patients with COPD.

2. Experimental Section

2.1. Study Design

This is an observational, prospective, single-center study about COPD, health status and cardiovascular comorbidities in relation to the outcomes of pulmonary rehabilitation (the CHANCE study) [12]. This study was approved by the Medical Ethical Committee of the Maastricht University Medical Centre+ (METC 11-3-070) and is registered as “Clinical, physiological and psychosocial determinants of the COPD Assessment Test (CAT)”, NTR 3416 [13].

2.2. Study Sample

Patients with COPD referred by chest physicians for a comprehensive pulmonary rehabilitation program at CIRO (Horn, the Netherlands) were included. CIRO is a third line rehabilitation center in Southern Netherlands. It specializes in offering individualized and multidimensional rehabilitation programs to patients with complex respiratory diseases. Only patients with COPD were included, and all patients gave written informed consent.

2.3. Measurements

In total, 518 COPD patients (44% women; mean FEV1 48.6 (20% predicted); 72% stratified into group D of the Global initiative for Chronic Obstructive Lung Disease (GOLD D); mean body mass index (BMI) 26.2 (5.8 kg/m²)) were included. Before and after a 40-session comprehensive multidimensional pulmonary rehabilitation program, patients underwent an assessment of lung function and health status characteristics [11,12] (Figure 1). Analysis of the respiratory physiome was based on the pre-rehabilitation comprehensive lung function testing. It included post-bronchodilator spirometry to assess forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC); body-plethysmography to determine total lung capacity (TLC), residual volume (RV) and intra thoracic gas volume (ITGV); single-breath determination of carbon monoxide (TLCO); maximal static inspiratory (MIP) and expiratory mouth pressures (MEP); resting arterial partial pressure of oxygen (PaO₂), carbon dioxide (PaCO₂) and oxygen saturation (SO₂). Seven different clusters of lung function impairment could be identified as described in a previous paper [11] (Figure 2). In brief, Cluster 1 had a significantly lower degree of airflow limitation, absence of static hyperinflation, and a higher diffusing capacity compared to the other clusters. Clusters 2 to 4 had similar degree of airflow limitation, but showed significant differences in static lung volumes (Cluster 3 > Cluster 4 > Cluster 2, all \( p < 0.01 \)). Cluster 5 had a significantly lower degree of airflow limitation compared to Clusters 6 and 7 (\( p < 0.01 \)). Static lung volumes were significantly different between Clusters 5 to 7 (Cluster 7 > Cluster 6 > Cluster 5, all \( p < 0.01 \)). Diffusing capacity of the Lung for Carbon Monoxide (DLCO) was higher in Clusters 1, 4 and 5; lower in Clusters 3, 6, and 7, \( p < 0.01 \) and mouth pressures were higher in Clusters 1, 3, 4, and 6; lower in Clusters 2, 5, and 7, \( p < 0.01 \). Arterial blood gas values were within normal range in Clusters 1–6 [11].
The efficacy of pulmonary rehabilitation [3] was measured by the degree of dyspnea. Dyspnea was measured using the modified Medical Research Council (mMRC) scale, ranging from grade 0 (no troubles with breathlessness) to grade 4 (too breathless to leave the house). The COPD-specific version of the St George’s Respiratory Questionnaire (SGRQ-C) was also used, ranging from 0 (optimal) to 100 points (worst). A 6-min walk test (6MWT) was used to assess exercise performance. In addition, a submaximal exercise test (CWRT) was performed at 75% of the pre-determined peak work rate using an electrically braked cycle ergometer (Carefusion, Houten, the Netherlands). The Canadian Occupational Performance Measure (COPM) was used to identify specific problematic activities of daily life. Patients scored how well they were performing the problematic activities of daily life (performance score; COPM-P) and how satisfied they were with this level of performance (satisfaction score; COPM-S). Scores range between 1 (“not able to do it” or “not at all satisfied”, respectively) to 10 points (“able to do it extremely well” or “extremely satisfied”). Symptoms of anxiety and depression were measured by the Hospital Anxiety and Depression Scale (HADS) with a total score ranging from 0 (optimal) to 21 (worst) points. A score of 11 or higher indicates a severe mood disturbance.
2.4. Regular Intervention

The pulmonary rehabilitation program was provided in accordance with the 2013 American Thoracic Society/European Respiratory Society Statement on pulmonary rehabilitation [1], meeting the individual needs of patients with COPD [14]. The program consists of 40 sessions and can be inpatient (8 weeks, 5 days-week⁻¹) or outpatient (8 weeks, 3 half days-week⁻¹, followed by 8 weeks 2 half days-week⁻¹). The program starts with a careful characterization of pulmonary and extra-pulmonary treatable traits in patients with COPD. From this, a patient-tailored program consisting of different treatment modules is composed. Each module consists of different interventions; physical exercise training, occupational therapy, nutritional counselling, psychosocial counselling, education and exacerbation management. Each module has a specific goal, which once achieved, contributes to the patients’ overall goal(s) of the treatment [14].

2.5. Statistics

All statistical analyses were performed using Viscovery Profiler 7.1 by Viscovery Software GmbH, Vienna, Austria. Information available online [15]. Self-organizing maps (SOMs, also referred to as Kohonen maps) were used to create an ordered representation of the selected attributes. The SOM method can be viewed as a nonparametric regression technique that converts multidimensional data spaces into lower dimensional abstractions. A SOM generates a nonlinear representation of the data distribution and allows the user to identify homogeneous data groups visually. Patients have been ordered by their overall similarity concerning the lung function variables measured.
during pre-rehabilitation assessment [11]. Using the SOM-Ward Cluster algorithm of Viscovery, a hybrid algorithm that applies the classical hierarchical method of Ward on top of the SOM topology, the seven lung function clusters have been generated [11]. Viscovery automatically identified patient characteristics that differ significantly from the average of the whole study sample using the integrated two-sided t test, with a confidence of 95% [11]. Simultaneously, the efficacy of the pulmonary rehabilitation program was evaluated for each cluster based on the minimal clinically important difference (MCID). The following MCIDs were used: −1 grade on MRC dyspnoea scale [16]; +30 m on 6-minute walk distance (6MWD) [17,18]; +100 s on cycle endurance time (CWRT [19]; +2 points on COPM-P [20]; +2 points on COPM-S [20]; −1.5 points on Hospital Anxiety and Depression Scale, Anxiety (HADS-A) [21]; −1.5 points on Hospital Anxiety and Depression Scale, Depression (HADS-D) [21]; and −4 points on St George’s Respiratory Questionnaire-Total score.

For comparing outcomes of the clusters, a p-value of ≤0.01 was set as the level of significance.

3. Results

A total of 419 of the 518 patients (80.9%) completed the rehabilitation program. Patients in Cluster 2 showed a significantly higher dropout rate compared to the whole sample (Figure 3). In all clusters, clinically relevant outcomes exceeding a MCID at least once were achieved. The mean improvements in the degree of breathlessness, 6-min walk distance, performance of Activities of Daily Life (ADLs), symptoms of anxiety and depression, and mean improvement in disease specific quality of life were comparable between clusters. Significant differences were only found in Cluster 2, with lower mean improvement in satisfaction with the performance of activities of daily life, and in Cluster 7, with a lower mean improvement in cycle endurance time (Table 1). Figure 3 illustrates the changes of these different outcomes per lung function cluster. Changes following pulmonary rehabilitation could not be clustered to specific physiomics profiles. Compared to the whole sample, Cluster 7 demonstrated a lower proportion of outcomes exceeding a MCID at least once.
Table 1. Changes following a pulmonary rehabilitation program for the seven lung function clusters.

| Outcomes                                      | Whole Sample | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 | Cluster 7 |
|-----------------------------------------------|--------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| All patients                                  | N = 518      | N = 75    | N = 61    | N = 89    | N = 79    | N = 66    | N = 61    | N = 87    |
| Drop out, % patients                          | 19           | 16        | 33 *      | 17        | 11        | 27        | 15        | 18        |
| Number of patients completing pulmonary rehab. | N = 419      | N = 63    | N = 41    | N = 74    | N = 70    | N = 48    | N = 52    | N = 71    |
| Baseline mMRC dyspnea, grade                  | 2.4 (1.0)    | 2.0 (1.0) ** | 2.6 (1.1) | 2.1 (1.0) ** | 2.0 (1.0) ** | 2.7 (0.9) | 2.8 (0.9) * | 2.9 (1.0) * |
| △mMRC dyspnea, grade                         | −0.3 (1.1)   | −0.2 (1.3) | −0.4 (1.1) | −0.2 (1.1) | −0.2 (0.9) | −0.4 (1.0) | −0.5 (1.2) | −0.4 (1.0) |
| • −1 grade, % patients                        | 39           | 3         | 54        | 30        | 33        | 41        | 47        | 47        |
| • −2 grades, % patients                       | 16           | 16        | 15        | 16        | 9         | 21        | 15        | 11        |
| Baseline 6MWD                                 | 424 (124)    | 466 (118) * | 430 (131) | 445 (115) | 495 (94) * | 413 (100) | 400 (112) | 340 (131) ** |
| △6MWD, m                                      | 23 (67)      | 28 (73)   | 28 (71)   | 18 (54)   | 26 (60)   | 32 (55)   | 11 (52)   | 19 (94)   |
| • ≥30 m, % patients                           | 44           | 51        | 54        | 40        | 43        | 54        | 37        | 33        |
| • ≥60 m, % patients                           | 22           | 21        | 28        | 21        | 21        | 23        | 18        | 22        |
| Baseline CWRT, s                              | 296 (219)    | 356 (225) * | 307 (297) | 266 (173) | 353 (221) * | 293 (216) | 247 (136) | 242 (222) |
| △CWRT, s                                      | 206 (306)    | 288 (308) | 189 (290) | 218 (327) | 254 (316) | 280 (305) | 141 (245) | 57 (265) ** |
| • ≥100 s, % patients                          | 52           | 67        | 50        | 47        | 61        | 69 *       | 49        | 23 **     |
| • ≥200 s, % patients                          | 36           | 49        | 32        | 32        | 49        | 42        | 36        | 13 **     |
| Baseline COPM-P, points                       | 3.9 (1.4)    | 3.8 (1.4) | 4.1 (1.4) | 4.0 (1.5) | 4.3 (1.3) * | 3.8 (1.0) | 3.7 (1.4) | 3.4 (1.4) ** |
| △COPM-P, points                              | 2.8 (1.8)    | 3.1 (2.0) | 2.5 (2.0) | 2.6 (2.1) | 2.4 (1.8) | 3.0 (1.5) | 3.0 (1.7) | 2.9 (1.6) |
| • ≥2 points, % patients                       | 68           | 77        | 55        | 62        | 62        | 77        | 72        | 72        |
| • ≥4 points, % patients                       | 26           | 35        | 26        | 25        | 21        | 30        | 26        | 23        |
| Baseline COPM-S, points                       | 3.3 (1.7)    | 3.3 (1.7) | 4.0 (1.7) * | 3.4 (1.6) | 3.7 (1.8) | 3.2 (1.3) | 2.9 (1.6) | 2.9 (1.6) ** |
| △COPM-S, points                              | 3.5 (2.2)    | 3.7 (2.3) | 2.7 (1.9) ** | 3.3 (2.3) | 3.3 (2.3) | 3.8 (1.9) | 4.0 (1.8) | 3.6 (2.2) |
| • ≥2 points, % patients                       | 77           | 77        | 66        | 75        | 70        | 86        | 88        | 75        |
| • ≥4 points, % patients                       | 43           | 46        | 29        | 38        | 44        | 46        | 49        | 49        |
| Baseline HADS-A, points                       | 7.8 (4.5)    | 7.8 (4.2) | 7.1 (4.6) | 7.7 (4.7) | 7.3 (3.5) | 7.6 (4.3) | 8.5 (5.0) | 8.6 (5.0) |
| △HADS-A, points                               | −1.7 (3.7)   | −2.0 (3.8) | −0.9 (2.6) | −1.5 (3.4) | −1.1 (3.9) | −1.4 (3.3) | −2.8 (3.7) | −2.2 (4.3) |
| • ≥−1.5 points, % patients                    | 51           | 48        | 46        | 46        | 48        | 50        | 60        | 56        |
| • ≥−3.0 points or more, % pts                 | 39           | 41        | 29        | 31        | 34        | 41        | 51        | 48        |
| Outcomes                                      | Whole Sample | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 | Cluster 7 |
|-----------------------------------------------|--------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Baseline HADS-D, points                       | 7.5 (4.3)    | 7.2 (4.3) | 7.6 (4.6) | 7.0 (4.4) | 6.9 (4.0) | 7.9 (3.9) | 7.9 (4.2) | 8.3 (4.8) |
| \(\Delta\) HADS-D, points                    | -2.1 (3.7)   | -1.4 (3.7)| -2.2 (3.3)| -2.2 (3.6)| -2.0 (4.0)| -2.6 (3.0)| -2.6 (3.2)| -2.2 (4.5)|
| • \(\geq -1.5\) points, % patients           | 53           | 41        | 51        | 52        | 52        | 69        | 55        | 54        |
| • \(\geq -3.0\) points, % patients           | 39           | 32        | 37        | 36        | 41        | 43        | 47        | 38        |
| Baseline SGRQ total score, points             | 61 (17)      | 57 (21)   | 61 (18)   | 58 (17)   | 53 (15)** | 67 (15)*  | 67 (15)*  | 67 (16)*  |
| \(\Delta\) SGRQ total score, points          | -9 (14)      | -12.3 (14.6)| -9.5 (14.7)| -6.1 (13.1)| -6.6 (15.6)| -10.9 (10.7)| -11.7 (11.9)| -8.8 (15.1)|
| • \(\geq -4\) points, % patients             | 62           | 75        | 54        | 52        | 57        | 71        | 71        | 56        |
| • \(\geq -8\) points or more, % pts          | 51           | 61        | 49        | 42        | 49        | 57        | 57        | 46        |
| Outcomes exceeding \(\geq 1\) MCID, %        | 56           | 59        | 53        | 48        | 52        | 62        | 55        | 45**      |
| Outcomes exceeding \(\geq 2\) MCID, %        | 34           | 37        | 31        | 29        | 35        | 36        | 37        | 29        |

Legend of Table 1: The efficacy of pulmonary rehabilitation based on minimal clinically important difference (MCID). Data is presented as mean (SD), unless otherwise stated. \(\Delta\): change; mMRC: modified Medical Research Council; 6 MWD: 6-min walk distance; CWRT: constant work-rate test; COPM-P: Canadian Occupational Performance Measure, performance score; COPM-S: Canadian Occupational Performance Measure, satisfaction score; HADS-A: Hospital Anxiety and Depression Scale, anxiety scores; HADS-D: Hospital Anxiety and Depression Scale, depression scores and SGRQ-T: St. George’s Respiratory Questionnaire, total score. * = a significantly higher difference compared to the whole sample (\(p < 0.01\)). ** = a significantly lower difference compared to the whole sample (\(p < 0.01\)).
Figure 3. Changes following pulmonary rehabilitation. Different panels illustrating the absolute change in Medical Research Council (MRC) dyspnoea grade, 6-min walk distance (6MWD), cycle endurance time (constant work-rate test; CWRT), Canadian Occupational Performance Measure, Performance (COPM-P), Canadian Occupational Performance Measure, Satisfaction (COPM-S), Hospital Anxiety and Depression Scale, Anxiety (HADS-A), Hospital Anxiety and Depression Scale, Depression (HADS-D), and St. George’s Respiratory Questionnaire total score (SGRQ-T) for the seven lung function clusters. The other three panels demonstrate the proportion of patients not completing the pulmonary rehabilitation program, the proportion of clinically relevant outcomes (exceeding at least one minimal clinically important difference (MCID) and the proportion of clinically relevant outcomes (exceeding at least two MCID) for each lung function cluster.

4. Discussion

This is the first report on the efficacy of pulmonary rehabilitation in patients with COPD after clustering for a comprehensive lung function assessment. The results demonstrate that the
degree of baseline lung function poorly predicts individual improvements in breathlessness, exercise performance, problematic activities of daily living, mood status and disease-specific health status following pulmonary rehabilitation. Even in those with the most severe respiratory impairment (i.e., Clusters 6 and 7), clinically relevant improvements were achieved. Nevertheless, one-third of the patients in Cluster 2 did not complete the program. Why patients within this cluster seem more at risk for drop-out is currently unknown and needs further evaluation.

Based on 65 randomized clinical trials involving 3822 patients for inclusion in the meta-analysis, McCarthy and colleagues concluded that pulmonary rehabilitation relieves dyspnea and fatigue, improves emotional function and enhances the sense of control that individuals have over their condition. Moreover, pulmonary rehabilitation is beneficial in improving health status and exercise capacity [2]. Our study confirms that improvements following pulmonary rehabilitation are clinically relevant and statistically significant [2,3]. According to McCarthy and colleagues, additional RCTs comparing pulmonary rehabilitation with standard COPD care are no longer warranted [2]. In order to improve outcomes, identification of markers predicting outcomes in individual patients could be very interesting. At the very least, our study illustrates that even a comprehensive lung function assessment is unhelpful in achieving this goal. Alternatively, cluster analysis could be helpful to implement specific interventions such as inspiratory muscle training in those COPD patients with respiratory muscle dysfunction but without static hyperinflation [11].

Since quality of life is determined by the degree of dyspnea, depression, anxiety and exercise performance [23], these factors should be taken into consideration in personalizing the intervention. Furthermore, as pulmonary rehabilitation programs change their emphasis towards the ability to adapt and self-manage in the face of social, physical and emotional challenges, traditional disease-related characteristics of disease severity are no longer dominant [24]. The importance of understanding the unique circumstances of the individual is now widely accepted but still neglected in pulmonary rehabilitation. The patient’s health beliefs, the way illness is approached, as well as the interactions of the patient with the medical system are affected by social, psychological, cultural, behavioral and economic factors. These unique circumstances or personomics should be considered in order to understand the patient’s preferences, values and goals [25].

Our study confirms that a comprehensive pulmonary rehabilitation program results in a heterogeneous and differential pattern of patient-related outcomes. This confirms our previous study, that a multidimensional response needs to be considered to evaluate the efficacy of pulmonary rehabilitation services [3]. Furthermore, the differential response pattern, the non-linear responses as well as the absent or poor response illustrate that a “one size fits all” approach is no longer applicable in pulmonary rehabilitation. In addition, non-linear responses as well as unpredictability in response must be considered as a reflection of the intrinsic complexity of the patient themselves [26].

Pulmonary rehabilitation requires multidimensional profiling of patients, not restricted to pathophysiological respiratory system involvement. Future identification of essential components of pulmonary rehabilitation should be based on a personomic perspective [25]. Comprehensive intervention can no longer be based on restoration of impairments, it needs to become person-centered.

5. Conclusions

The current study demonstrates no relationship between the seven lung-function-based clusters and response to pulmonary rehabilitation in patients with COPD. Therefore, baseline lung function cannot be used to identify good responders to pulmonary rehabilitation, and therefore, cannot be used as a criterion for referral to pulmonary rehabilitation in patients with COPD.

Author Contributions: Conceptualization, M.A.S.; Methodology, M.A.S. and S.G.; Software, S.G.; Formal analysis, S.G.; Investigation: S.H.-W.; Data curation: S.H.-W.; Writing—Original Draft Preparation: I.M.L.A.; Writing—Review & Editing: E.F.M.W., S.H.-W., S.G., D.J.A.J., F.M.E.F. and M.A.S.

Funding: The CHANCE study was supported by the Lung Foundation Netherlands (3.4.10.015) and GlaxoSmithKline (SCO115406).
Conflicts of Interest: The authors declare no conflict of interest.

References
1. Spruit, M.A.; Singh, S.J.; Garvey, C.; ZuWallack, R.; Nici, L.; Rochester, C.; Hill, K.; Holland, A.E.; Lareau, S.C.; Man, W.D.; et al. An official American Thoracic Society/European Respiratory Society statement: Key concepts and advances in pulmonary rehabilitation. *Am. J. Respir. Crit. Care. Med.* 2013, 188, e13–e64. [CrossRef] [PubMed]
2. McCarthy, B.; Casey, D.; Devane, D.; Murphy, K.; Murphy, E.; Lacasse, Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* 2015, 2, CD003793. [CrossRef] [PubMed]
3. Spruit, M.A.; Augustin, I.M.; Vanfleteren, L.E.; Janssen, D.J.; Gaffron, S.; Pennings, H.J.; Smeenk, F.; Pieters, W.; van den Bergh, J.J.; Michels, A.J.; et al. Differential response to pulmonary rehabilitation in COPD: Multidimensional profiling. *Eur. Respir. J.* 2015, 46, 1625–1635. [CrossRef] [PubMed]
4. Vaes, A.W.; Delbressine, J.M.L.; Mesquita, R.; Goertz, Y.M.J.; Janssen, D.J.A.; Nakken, N.; Franssen, F.M.E.; Vanfleteren, L.; Wouters, E.F.M.; Spruit, M.A. The impact of pulmonary rehabilitation on activities of daily living in patients with COPD. *J. Appl. Physiol.* 2018. [CrossRef] [PubMed]
5. Annegarn, J.; Meijer, K.; Passos, V.L.; Stute, K.; Wiechert, J.; Savelberg, H.H.; Schols, A.M.; Wouters, E.F.; Spruit, M.A. Problematic activities of daily life are weakly associated with clinical characteristics in COPD. *J. Am. Med. Dir. Assoc.* 2012, 13, 284–290. [CrossRef]
6. Agusti, A.; Calverley, P.M.; Celli, B.; Coxson, H.O.; Edwards, L.D.; Lomas, D.A.; MacNee, W.; Miller, B.E.; Rennard, S.; Silverman, E.K.; et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir. Res.* 2010, 11, 122. [CrossRef] [PubMed]
7. Spruit, M.A.; Watkins, M.L.; Edwards, L.D.; Vestbo, J.; Calverley, P.M.; Pinto-Plata, V.; Celli, B.R.; Tal-Singer, R.; Wouters, E.F. Determinants of poor 6-min walking distance in patients with COPD: The ECLIPSE cohort. *Respir. Med.* 2010, 104, 849–857. [CrossRef]
8. Vogiatzis, I.; Williamson, A.F.; Miles, J.; Taylor, I.K. Physiological response to moderate exercise workloads in a pulmonary rehabilitation program in patients with varying degrees of airflow obstruction. *Chest* 1999, 116, 1200–1207. [CrossRef]
9. Vogiatzis, I.; Terzis, G.; Stratakos, G.; Cherouveim, E.; Athanasopoulos, D.; Spetsioti, S.; Nasis, I.; Manta, P.; Roussos, C.; Zakynthinos, S. Effect of pulmonary rehabilitation on peripheral muscle fiber remodeling in patients with COPD in GOLD stages II to IV. *Chest* 2011, 140, 744–752. [CrossRef]
10. Vanfleteren, M.J.; Koopman, M.; Spruit, M.A.; Pennings, H.J.; Smeenk, F.; Pieters, W.; van den Bergh, J.J.; Michels, A.J.; Wouters, E.F.; Groenen, M.T.; et al. Effectiveness of Pulmonary Rehabilitation in Patients with Chronic Obstructive Pulmonary Disease With Different Degrees of Static Lung Hyperinflation. *Arch. Phys. Med. Rehabil.* 2018, 99, 2279–2286 e3. [CrossRef]
11. Augustin, I.M.L.; Spruit, M.A.; Houben-Wilke, S.; Franssen, F.M.E.; Vanfleteren, L.; Gaffron, S.; Janssen, D.J.A.; Wouters, E.F.M. The respiratory physiome: Clustering based on a comprehensive lung function assessment in patients with COPD. *PLoS ONE* 2018, 13, e0201593. [CrossRef] [PubMed]
12. Smid, D.E.; Wilke, S.; Jones, P.W.; Muris, J.W.; Wouters, E.F.; Franssen, F.M.; Spruit, M.A. Impact of cardiovascular comorbidities on COPD Assessment Test. (CAT) and its responsiveness to pulmonary rehabilitation in patients with moderate to very severe COPD: Protocol of the Chance study. *BMJ Open* 2015, 5, e007536. [CrossRef] [PubMed]
13. Clinical, Physiological and Psychosocial Determinants of the COPD Assessment Test (CAT). Available online: http://www.trialregister.nl (accessed on 26 December 2018).
14. Augustin, I.M.L.; Spruit, M.A.; Franssen, F.M.E.; Wouters, E.F.M. Understanding Complexity of Chronic Non-Communicable Diseases: An Integrated Approach for Personalized Management of Patients with COPD. *Clin. Res. Pulmonol.* 2015, 3, 1034.
15. Available online: https://www.viscovery.net (accessed on 26 December 2018).
16. de Torres, J.P.; Pinto-Plata, V.; Ingenito, E.; Bagley, P.; Gray, A.; Berger, R.; Celli, B. Power of outcome measurements to detect clinically significant changes in pulmonary rehabilitation of patients with COPD. *Chest* 2002, 121, 1092–1098. [CrossRef]
17. Holland, A.E.; Spruit, M.A.; Troosters, T.; Puhan, M.A.; Pepin, V.; Saey, D.; McCormack, M.C.; Carlin, B.W.; Sciurba, F.C.; Pitta, F.; et al. An official European Respiratory Society/American Thoracic Society technical standard: Field walking tests in chronic respiratory disease. *Eur. Respir. J.* 2014, 44, 1428–1446. [CrossRef] [PubMed]

18. Singh, S.J.; Puhan, M.A.; Andrianopoulos, V.; Hernandez, N.A.; Mitchell, K.E.; Hill, C.J.; Lee, A.L.; Camillo, C.A.; Troosters, T.; Spruit, M.A.; et al. An official systematic review of the European Respiratory Society/American Thoracic Society: Measurement properties of field walking tests in chronic respiratory disease. *Eur. Respir. J.* 2014, 44, 1447–1478. [CrossRef] [PubMed]

19. Laviolette, L.; Bourbeau, J.; Bernard, S.; Lacasse, Y.; Pepin, V.; Breton, M.J.; Baltzan, M.; Rouleau, M.; Maltais, F. Assessing the impact of pulmonary rehabilitation on functional status in COPD. *Thorax* 2008, 63, 115–121. [CrossRef]

20. Sewell, L.; Singh, S.J. The Canadian Occupational Performance Measure: Is it a Reliable Measure in Clients with Chronic Obstructive Pulmonary Disease? *Br. J. Occup. Ther.* 2001, 64, 305–310. [CrossRef]

21. Puhan, M.A.; Frey, M.; Buchi, S.; Schunemann, H.J. The minimal important difference of the hospital anxiety and depression scale in patients with chronic obstructive pulmonary disease. *Health Qual. Life Outcomes* 2008, 6, 46. [CrossRef]

22. Jones, P.W. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur. Respir. J.* 2002, 19, 398–404. [CrossRef]

23. Tsiligianni, I.; Kocks, J.; Tzanakis, N.; Siafakas, N.; van der Molen, T. Factors that influence disease-specific quality of life or health status in patients with COPD: A review and meta-analysis of Pearson correlations. *Prim. Care Respir. J.* 2011, 20, 257–268. [PubMed]

24. Huber, M.; Knottnerus, J.A.; Green, L.; van der Horst, H.; Jadad, A.R.; Kromhout, D.; Leonard, B.; Lorig, K.; Loureiro, M.I.; van der Meer, J.W.; et al. How should we define health? *BMJ* 2011, 343, d4163. [CrossRef] [PubMed]

25. Ziegelstein, R.C. Personomics. *JAMA Int. Med.* 2015, 175, 888–889. [CrossRef] [PubMed]

26. Wilson, T.; Holt, T.; Greenhalgh, T. Complexity science: Complexity and clinical care. *BMJ* 2001, 323, 685–688. [CrossRef]