Clinical Correlates of Reduced Physical Activity in Idiopathic Pulmonary Fibrosis

Thomas Bahmer^{a, d} Anne-Marie Kirsten^{b, d} Benjamin Waschki^{a, d}
Klaus F. Rabe^{a, d} Helgo Magnussen^{b, d} Detlef Kirsten^{a, d} Marco Gramm^{b, d}
Simone Hummler^{c, e} Eva Brunnemer^{c, e} Michael Kreuter^{c, e} Henrik Watz^{b, d}

^aLungClinic Grosshansdorf, Pulmonology, Grosshansdorf, ^bPulmonary Research Institute at LungClinic Grosshansdorf, Grosshansdorf, ^cCenter for Interstitial and Rare Lung Diseases, Pneumology, Thoraxklinik at University of Heidelberg, Heidelberg, ^dAirway Research Center North (ARCN), German Center for Lung Research (DZL), and ^eTranslational Lung Research Center Heidelberg (TLRC), German Center for Lung Research (DZL), Germany

Key Words

Physical activity · Idiopathic interstitial pneumonia ·
Idiopathic pulmonary fibrosis · Fatigue · Exercise capacity

Abstract

Background: Little is known about the consequences of idiopathic pulmonary fibrosis (IPF) for physical activity (PA). **Objectives:** We aimed to investigate levels of PA in IPF and to study associations of PA with lung function, exercise capacity, symptoms, and quality of life. **Methods:** In stable patients with IPF we measured PA (steps per day, SPD; physical activity level, PAL; minutes of moderate activity, MMA) by accelerometry (SenseWear Armband) for 1 week. We also assessed lung function (forced vital capacity, FVC; diffusing capacity for carbon monoxide, DLCO); exercise capacity (6-minute walking distance, 6MWD); dyspnea (modified Medical Research Council, mMRC); fatigue (Multidimensional Fatigue Inventory, MFI-20), and generic (12-Item Short Form Survey, SF-12) and health-related quality of life (St. George's Respiratory Questionnaire) as further clinical variables. **Results:** We investigated 48 patients with IPF in two centers (mean age, 67 years; 75% male; 23% on long-term oxygen therapy; mean FVC 75%pred.; mean DLCO 43%pred.; mean

6MWD 355 ± 140 m; mean SPD $5,017 \pm 3,360$). On a bivariate level, all clinical variables were significantly associated with SPD ($p < 0.05$). The associations of mMRC, MFI-20, SF-12 (physical health), and 6MWD with SPD were independent of impaired lung function ($p < 0.05$). At multivariate analyses, either 6MWD (total explained variance of the model, total R^2 : 42%) or MFI-20 (total R^2 : 39%) were the strongest independent predictors of SPD. **Conclusion:** Fatigue and exercise capacity are strong and independent predictors of PA in patients with IPF, which suggests that both measures should be assessed when the consequences of IPF for PA in daily life are studied.

© 2016 S. Karger AG, Basel

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing interstitial pneumonia of unknown cause, characterized by progressive worsening of dyspnea and lung

T.B. and A.-M.K. are joint first authors. M.K. and H.W. contributed equally to this work.

function [1]. Forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO) are recommended measures to assess disease severity and progression [1]. The importance of exercise tolerance in the clinical assessment of IPF patients is not clear yet, even though it is increasingly investigated [2–4].

Physical activity (PA) in daily life is a significant clinical parameter related to morbidity and mortality in chronic obstructive pulmonary disease (COPD) [5]. The consequences of IPF for PA, however, have rarely been studied. Three previous studies measured PA in patients with IPF [6–8] and indicated that PA is reduced compared to healthy controls [7]. However, the clinical interpretation of these studies is limited, as either the majority of patients had minor dyspnea only [6], 40% of the study population had nonspecific interstitial pneumonia (NSIP) [7], or all patients were candidates for lung transplantation [8].

IPF profoundly affects patients' generic and health-related quality of life (QoL and HRQL) [9, 10]. HRQL measures may add clinically meaningful information on a patients' individual situation, as variability in HRQL is not fully explained by established measures of dyspnea or pulmonary function [9]. One aspect, partly reflected in quality of life measures, is fatigue [9, 11] – a debilitating and complex symptom. Although fatigue is increasingly recognized in IPF patients [9, 12], data on specific questionnaires investigating this multifactorial symptom in IPF are sparse [12, 13], and associations between PA and fatigue have not been studied so far.

In our study, we aimed to investigate the association between daily PA and lung function, exercise capacity, dyspnea, fatigue, and quality of life in a population of IPF patients of all severity grades at two specialized centers across Germany.

Methods

Study Population

We prospectively recruited patients with a proven diagnosis of IPF at the outpatient departments of two specialized tertiary care centers in northern and southern Germany (LungClinic and Pulmonary Research Institute Grosshansdorf, and Center for Interstitial and Rare Lung Diseases, Thoraxklinik at University of Heidelberg, respectively), between February 2013 and November 2013. The diagnosis of IPF at each center was established in an interdisciplinary discussion (Interstitial Lung Disease Board) and was based on current guidelines [1]. Exclusion criteria were respiratory tract infections or an exacerbation of IPF within the previous 4 weeks before study enrolment and extrapulmonary impairments that could interfere with PA (e.g. heart failure, arthrosis of hip or knee).

Physical Activity

We measured PA in IPF patients for 1 week by the use of the SenseWear Armband (BodyMedia Inc., Pittsburgh, Pa., USA), an activity monitor that has been widely used in patients with COPD [14] and IPF [7, 8]. Parameters of PA were steps per day (SPD), physical activity level (PAL; total daily energy divided by sleeping energy expenditure), and minutes of at least moderate activity per day (MMA; any PA >3 metabolic equivalents) [14]. Patients were instructed to wear the SenseWear Armband on 7 consecutive days for 24 h per day, except for the time spent on personal hygiene [14].

Lung Function and Functional Exercise Capacity

Spirometry, bodyplethysmography and DLCO (single-breath) were performed in line with current guidelines and established reference values [15–17]. Functional exercise capacity was assessed by the 6-minute walking distance (6MWD) according to previous guidelines [18].

Dyspnea, Quality of Life, and Fatigue

The participants completed questionnaires for dyspnea (modified Medical Research Council dyspnea scale, mMRC [19]); fatigue (Multidimensional Fatigue Inventory, MFI-20 [20]); QoL (12-Item Short Form Survey, SF-12 [21]), and HRQL (St. George's Respiratory Questionnaire, SGRQ [22]) during the study visit.

Statistical Analysis

Descriptive data are reported as mean and standard deviation (continuous variables), median and interquartile range (categorical variables and continuous variables with skewed distribution), or number and percent (dichotomous variables), as appropriate. Bivariate correlations between clinical parameters and SPD, PAL, and MMA were performed, reporting Spearman's rho or Pearson's correlation coefficient, depending on the scale. The distribution of SPD was analyzed in relation to the mMRC score (i.e. <2, =2, and >2) and to tertiles of MFI-20, SF-12 physical health, FVC %pred., DLCO %pred., and 6MWD.

Multivariate linear regression analyses were performed using SPD as dependent variable. In a first step, associations between SPD and lung function, exercise capacity, dyspnea, fatigue, QoL, and HRQL were analyzed after controlling for possible confounders, i.e. age, sex, and obesity (BMI ≥30), to identify the best single predictor. In a second step, we wanted to identify factors that are associated with PA in IPF, independent of lung functional impairment. Therefore, either FVC %pred. or DLCO %pred. were included in the model and the additional effect of exercise capacity, dyspnea, fatigue, QoL, and HRQL on PA was investigated.

A p value <0.05 was considered statistically significant. Data analysis was performed with the Statistical Package for Social Science, version 20.0 (SPSS, Chicago, Ill., USA).

Statement of Ethics

The study was approved by the local Ethics Committees of Schleswig-Holstein and of Heidelberg [ethics approval (AZ 038/12 II) and ethics approval S-200/2013, respectively; German Clinical Trials Register Number DRKS00006170]. Participants provided written informed consent.

Table 1. Patient characteristics

	n	IPF
Age, years	48	67.1 ± 7.5
Male	48	36 (75)
BMI	48	27.9 ± 4.5
Therapy		
Pirfenidone	48	13 (27.1)
Nintedanib	48	23 (47.9)
Clinical trial	48	4 (8.3)
Other/none	48	8 (16.7)
LTOT	47	11 (22.9)
PO ₂ at rest, mm Hg ^a	46	71.6 ± 8.7
FEV ₁ , liter	48	2.2 ± 0.6
FEV ₁ , %pred.	48	78.9 ± 22.1
FEV ₁ /FVC, %	48	83.2 ± 0.1
FVC, liter	48	2.7 ± 0.8
FVC, %pred.	48	75.4 ± 22.9
DLCO, %pred.	46	43.1 ± 14.6
6MWD, m	48	355.0 ± 140
mMRC	48	1.5 [1–2]
MFI-20 ^b	44	52.52 ± 14.75
SF-12 physical health	42	35.07 ± 10.92
SF-12 mental health	42	51.45 ± 9.93
SGRQ	41	49.74 ± 23.50
SPD	48	5,017 ± 3360
PAL	47	1.46 ± 0.23
MMA	47	90.43 [36.3–146]

Data are presented as mean ± SD, median [IQR] or n (%), depending on the scale and distributional characteristics. LTOT = Long-term oxygen therapy; FEV₁ = forced expiratory volume at 1 s; PO₂ = partial pressure of oxygen in capillary blood analysis. ^a In 3 cases, blood oxygen was measured with continuous nasal oxygen supplementation. ^b MFI-20 in males: 53.0 ± 14.9; in females: 51.2 ± 14.7.

Results

In total, we enrolled 51 patients in the study. Three patients were excluded from the final analyses, as they did not wear the accelerometer appropriately, resulting in just 1 evaluable day or less.

The remaining 48 IPF patients (75% male) of our study sample had a mean age of 67 years, a mean FVC of 75%pred., and a mean DLCO of 43%pred. IPF patients showed good compliance with wearing the SenseWear Armband (mean daily wearing time = 98%). Overall SPD was 5,017 ± 3,360 (table 1). On a bivariate level, mMRC, MFI-20, SF-12 physical health, SF-12 mental health, SGRQ, FVC %pred., DLCO %pred., and 6MWD were moderately associated with SPD in IPF patients (table 2).

Table 2. Bivariate correlations between clinical variables and steps per day in IPF

	r	p value
mMRC	–0.557	<0.001
MFI-20	–0.526	<0.001
SF-12 physical health	0.473	0.002
SF-12 mental health	0.370	0.016
SGRQ	–0.506	0.001
FVC, %pred.	0.526	<0.001
DLCO, %pred.	0.494	<0.001
6MWD	0.595	<0.001

Bivariate correlations with r reflecting Spearman's rho (for mMRC) or Pearson's correlation coefficient (for SGRQ, SF-12, MFI-20, FVC, DLCO, and 6MWD) between clinical parameters and daily PA in terms of SPD.

Replacing SPD by MMA, fatigue, QoL, HRQL, and lung function measures showed significant associations ($p < 0.05$), and replacing SPD by PAL, only lung function measures were significantly associated (data not shown). We further analyzed mean SPD according to mMRC score and tertiles of MFI-20, SF-12 physical health, FVC %pred., DLCO %pred., and 6MWD. According to tertile distribution, severely impaired IPF patients performed between 2,200 and 3,400 SPD (fig. 1). Dyspneic patients with an mMRC score >2 performed 1,900 SPD only (fig. 1).

In multivariate linear regression analyses adjusting for age, sex, and obesity, the observed associations between the clinical variables and SPD remained statistically significant ($p < 0.005$; online suppl. table E1, see www.karger.com/doi/10.1159/000446607). In these separate regression analyses, 6MWD and MFI-20 explained the highest proportion of variance for SPD as dependent variable (total R²: 42 and 39%, respectively). Lung function measures explained either 24% (FVC %pred.) or 28% (DLCO %pred.) of the variance for SPD in these separate models.

In a next step, we analyzed the association of dyspnea, fatigue, QoL, HRQL, and exercise capacity after adjusting for both basic confounders and lung function (either FVC %pred. or DLCO %pred., respectively). In these multivariate analyses, 6MWD, mMRC, MFI-20, and SF-12 physical health were significantly associated with SPD independent of FVC or DLCO (p values <0.05; table 3).

Fig. 1. Distribution of SPD in relation to MMRC score and tertiles of MFI-20, SF-12, FVC, DLCO, and 6MWD in patients with IPF. Distribution of SPD (mean: $5,017 \pm 3,360$) across mMRC scores [**a** <2 ($n = 24$), =2 ($n = 14$), and >2 ($n = 10$), respectively] and across tertiles for MFI-20 (**b**), SF-12 physical health (**c**), FVC %pred. (**d**), DLCO %pred. (**e**), and 6MWD (**f**) in patients with IPF. Severely impaired patients may either be represented in the highest category/highest tertile (mMRC, MFI-20) or in the lowest tertile (SF-12 physical health, FVC %pred., DLCO %pred., 6MWD) and in both

cases are displayed most right in the single graphs (**a–f**). Whiskers represent the mean of SPD $\pm$ standard error for each category of each parameter. ANOVAs were performed to compare SPD between these categories. For each parameter, severely impaired patients performed significantly less SPD compared to patients with mild impairment (**a–c** $p < 0.01$; **d–f** $p \leq 0.001$). Most severe and moderately impaired patients differed significantly for mMRC ($p = 0.024$), FVC ($p = 0.007$), DLCO ($p = 0.028$), and 6MWD ($p < 0.001$).

Discussion

The main findings of our study are that dyspnea, fatigue, and QoL are associated with physical activity in IPF patients and that these observed associations are independent of lung function. Furthermore, we demonstrate that exercise capacity and fatigue are the strongest independent predictors of reduced physical activity in this cohort of IPF patients.

Dyspnea is the cardinal symptom of IPF and has previously been suggested to be related to PA in IPF [6]. Patients in the previous study by Nakayama et al. [6], however, only had mild dyspnea as indicated by mMRC scores of 0 or 1 in more than 90% of the patients. Our results demonstrate a substantial contribution of dyspnea to impaired PA, as patients with an mMRC >2 walked approximately 1,900 steps per day only, which means a reduction

by approximately 70% compared to IPF patients with an mMRC <2. The simple assessment of both dyspnea and lung function could provide clinically meaningful insights into daily physical activity levels of IPF patients, as both measures were independently associated with PA in our study. Notably, a daily step count below 2,000 indicates dramatic physical inactivity and is even lower than physical inactivity of COPD patients in GOLD stage IV with an average step count of 2,800 [14].

Fatigue is increasingly recognized in IPF patients [9, 12], and the spectrum of consequences for this multifactorial symptom is broad. Our results show that fatigue is one of the strongest predictors of steps per day and that each point increase in MFI-20 is associated with a reduction of 120 steps. Interestingly, we can demonstrate these effects after adjustment for age, as MFI-20 scores in the general population show clear dependency on age with

Table 3. Separate multivariate regression analyses with clinical variables serving as independent predictors for SPD in IPF after adjustment for basic confounders and lung function

Model	Predictive parameter	Regression coefficient B	95% confidence interval	R ² change	p value
1.	6MWD				
	a	11	3 to 18	0.129	0.006
	b	10	2 to 18	0.103	0.013
2.	mMRC >2				
	a	-2,734	-5,230 to -238	0.079	0.033
	b	-2,597	-5,121 to -72	0.070	0.044
3.	MFI-20				
	a	-81	-150 to -12	0.097	0.023
	b	-78	-148 to -7	0.086	0.031
4.	SF-12 physical health				
	a	114	6 to 222	0.088	0.038
	b	112	7 to 217	0.088	0.037
5.	SF-12 mental health				
	a	69	-32 to 169	0.039	0.175
	b	64	-37 to 165	0.033	0.207
6.	SGRQ				
	a	-43	-95 to 10	0.056	0.111
	b	-34	-89 to 22	0.031	0.228

MMRC score was dichotomized: >2 vs. ≤2. p values <0.05 are marked in bold.

Interpretation: The additional effect of clinical parameters, independent of lung functional impairment was tested (1–6), either including FVC %pred. (a) or DLCO %pred. (b), and already adjusting for age, sex and obesity (BMI ≥30). R² change reflects the additional effect of exercise capacity (1a/1b), mMRC (2a/2b), fatigue (3a/3b), QoL (4a/4b and 5a/5b) and HRQL (6a/6b), beyond lung functional impairment.

higher values for older subjects [23]. Furthermore, fatigue scores remained independent predictors of PA, even after adjustment for lung function. Therefore, the level of fatigue might represent an important clinical aspect of IPF that limits daily PA in affected patients, independent of age and impaired lung function.

An association of generic quality of life and physical activity in IPF, to our knowledge, has previously just been indicated in a cohort of candidates for lung transplantation, including patients with both interstitial lung disease and COPD [8]. However, results may not be transferable to IPF patients due to the heterogeneous study sample and the expected lung transplantation. Our results demonstrate that HRQL and QoL are associated with PA in patients with IPF. After adjusting for lung function, however, only QoL remained a significant independent predictor.

Previously, an association between lung function and PA has been indicated for patients with fibrotic idiopathic interstitial pneumonias in the study by Wallaert et al. [7]. By contrast, Nakayama et al. [6] failed to demonstrate

a significant correlation between PA and lung function in patients with IPF who had relatively preserved lung function (mean FVC = 89 %pred., mean DLCO = 79 %pred.). In our study, associations between lung function and PA were moderate on a bivariate level and remained significant after adjustment for confounders. We can show that in IPF patients, 1% reduction in FVC %pred. was associated with 60 SPD less, and 1% reduction in DLCO %pred. was associated with 110 SPD less. These results demonstrate a close relationship between lung function and daily PA.

Irrespective of lung function impairment, exercise capacity turned out to be the strongest separate predictor of PA in IPF patients in our study, already explaining 42% of the variance of steps per day. The importance of exercise capacity as a strong determinant of PA in IPF patients was first suggested in the study by Langer et al. [8] in patients awaiting lung transplantation. The two studies by Wallaert et al. [6] and Nakayama et al. [7] also found exercise capacity to be related to PA, but associations were weak. In our study, exercise capacity and PA were sig-

nificantly associated on a bivariate level, and associations remained significant after adjustment for basic confounders and even after adjustment for lung function, indicating a substantial relationship.

Our results demonstrate that according to tertile distribution, patients with poor lung function or exercise performance execute similar SPD compared to patients with high fatigue or low QoL scores (fig. 1). This means that both functional measures and patient-centered questionnaire scores were equally able to identify patients with severely impaired daily PA. Total SPD in this population ranged between 2,200 and 3,400, which is as low as in pretransplant patients [8].

Conclusion

The results of our study suggest that PA in IPF is closely related to both patient-centered and functional measures in this progressive fibrotic lung disease. The study

sample of exclusively IPF patients of all severity grades may have caused the strong effects we could demonstrate in our multicenter study. Longitudinal studies will have to examine the development of this relationship under progressive disease conditions.

Acknowledgements

We are thankful to Beate Schaufler and Daniela Beissel for their excellent support. The work was supported by 'Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen' (WATL e.V.).

Financial Disclosure and Conflicts of Interest

The authors declare that there are no conflicts of interest to disclose.

References

- 1 Raghu G, Collard HR, Egan JJ, et al: An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824.
- 2 Nathan SD, du Bois RM, Albera C, et al: Validation of test performance characteristics and minimal clinically important difference of the 6-minute walk test in patients with idiopathic pulmonary fibrosis. *Respir Med* 2015;109:914–922.
- 3 du Bois RM, Albera C, Bradford WZ, et al: 6-Minute walk distance is an independent predictor of mortality in patients with idiopathic pulmonary fibrosis. *Eur Respir J* 2014;43:1421–1429.
- 4 Weir NA, Brown AW, Shlobin OA, et al: The influence of alternative instruction on 6-min walk test distance. *Chest* 2013;144:1900–1905.
- 5 Waschki B, Kirsten A, Holz O, et al: Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. *Chest* 2011;140:331–342.
- 6 Nakayama M, Bando M, Araki K, et al: Physical activity in patients with idiopathic pulmonary fibrosis. *Respirology* 2015;20:640–646.
- 7 Wallaert B, Monge E, Le Rouzic O, et al: Physical activity in daily life of patients with fibrotic idiopathic interstitial pneumonia. *Chest* 2013;144:1652–1658.
- 8 Langer D, Cebria i Iranzo MA, Burtin C, et al: Determinants of physical activity in daily life in candidates for lung transplantation. *Respir Med* 2012;106:747–754.
- 9 Swigris JJ, Kuschner WG, Jacobs SS, et al: Health-related quality of life in patients with idiopathic pulmonary fibrosis: a systematic review. *Thorax* 2005;60:588–594.
- 10 Swigris JJ, Brown KK, Behr J, et al: The SF-36 and SGRQ: validity and first look at minimum important differences in IPF. *Respir Med* 2010;104:296–304.
- 11 De Vries J, Seebregts A, Drent M: Assessing health status and quality of life in idiopathic pulmonary fibrosis: which measure should be used? *Respir Med* 2000;94:273–278.
- 12 Milioli G, Bosi M, Poletti V, et al: Sleep and respiratory sleep disorders in idiopathic pulmonary fibrosis. *Sleep Med Rev* 2015;26:57–63.
- 13 Mermigkis C, Stagaki E, Amfilochiou A, et al: Sleep quality and associated daytime consequences in patients with idiopathic pulmonary fibrosis. *Med Princ Pract* 2009;18:10–15.
- 14 Watz H, Waschki B, Meyer T, et al: Physical activity in patients with COPD. *Eur Respir J* 2009;33:262–272.
- 15 Macintyre N, Crapo RO, Viegi G, et al: Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005;26:720–735.
- 16 Wanger J, Clausen JL, Coates A, et al: Standardisation of the measurement of lung volumes. *Eur Respir J* 2005;26:511–522.
- 17 Miller MR, Hankinson J, Brusasco V, et al: Standardisation of spirometry. *Eur Respir J* 2005;26:319–338.
- 18 ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–117.
- 19 Nishiyama O, Taniguchi H, Kondoh Y, et al: A simple assessment of dyspnoea as a prognostic indicator in idiopathic pulmonary fibrosis. *Eur Respir J* 2010;36:1067–1072.
- 20 Lin JM, Brimmer DJ, Maloney EM, et al: Further validation of the Multidimensional Fatigue Inventory in a US adult population sample. *Popul Health Metr* 2009;7:18.
- 21 Han MK, Swigris J, Liu L, et al: Gender influences health-related quality of life in IPF. *Respir Med* 2010;104:724–730.
- 22 Swigris JJ, Esser D, Conoscenti CS, et al: The psychometric properties of the St George's Respiratory Questionnaire (SGRQ) in patients with idiopathic pulmonary fibrosis: a literature review. *Health Qual Life Outcomes* 2014;12:124.
- 23 Schwarz R, Krauss O, Hinz A: Fatigue in the general population. *Onkologie* 2003;26:140–144.