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EXERCISE TRAINING IN IDIOPATHIC PULMONARY FIBROSIS

Short- and long-term effects of a 12-week exercise program on clinical outcomes

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ABSTRACT

Background: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and fatal interstitial lung disease, which is characterized by restrictive pulmonary function, impaired gas exchange, dyspnea, exercise intolerance and poor quality of life. To date, an effective therapy for IPF remains elusive, and exercise pulmonary rehabilitation has weak recommendations for IPF.

Purpose: To examine the short-and long-term effects of an exercise training based pulmonary rehabilitation program on clinical outcomes in idiopathic pulmonary fibrosis patients.

Methods: A randomized controlled study was conducted with 34 IPF patients (68±8 yr) who took part in a 12-week intervention and were followed up until 15 months after completing the intervention. Exercise training (ET) group participated in a supervised outpatient exercise program, consisting of 60 minutes twice weekly group exercise sessions, while the control group continued with regular medical treatment alone. Socio-demographics, anthropometrics, blood samples and further determination of blood concentrations of biomarkers, Doppler-echocardiography, pulmonary function test, cardiopulmonary exercise test, 6 min walk test, senior fitness tests, modified Medical Research Council (mMRC) dyspnea scale, Saint Gorge Respiratory Questionnaire (SGRQ) and International Physical Activity Questionnaire (IPAQ) were assessed at baseline after 12 weeks and re-evaluated at 11 months time point (8 months from the end of the 12-week intervention). In addition, patients were followed up for 15 months from the end of 12-week intervention for hospitalizations, exacerbations and mortality.

Results: Thirty two IPF patients (E n=15; control n=17) completed the 12-week intervention period and 28 patients (14 in each group) was re-evaluated after at 11 months. At baseline the majority of patients presented moderate restrictive pulmonary pattern, impaired diffusion capacity, normal resting systolic heart function, moderately reduced aerobic capacity (VO_{2peak}≈60% predicted) with near normal functional capacity in walking. There were no differences between the groups at the beginning of the study. Following the 12-week intervention significant differences were observed between the ET and the control groups in raw mean deltas (Δ= post-pre intervention). Exercise capacity, pulmonary and ventilatory functions increased in the ET group while a trend of worsening was observed in the control group (mean difference between the groups ΔVO_{2peak}: 2.6 mL/kg/min, p=0.002, Δ6 minute walk distance (6MWD): 81 m, p<0.001, Δforced vital capacity (FVC) %predicted: 6%, p=0.038 respectively). The mMRC, SGRQ, ventilatory responses, senior fitness tests, body composition and IPAQ were also improved significantly following the exercise pulmonary rehabilitation program in the ET group, whereas the control group showed trend of deterioration. At 11 month time point the ET group lost the achieved improvements, and returned to baseline values in most outcomes, while the control group demonstrated only a slight trend of worsening. Raw mean deltas between the groups (ΔΔ=Follow up-post 12 weeks) $\Delta\Delta VO_{2peak}$: -2.9 mL/kg/min, p=0.001, ΔΔ6MWD: -25 m, p=0.285, ΔΔFVC %predicted: -4.7%, p=0.132, ΔΔmMRC: 0.5 units, p=0.055, ΔΔSGRQ: 7.9 units, p= 0.041. In addition, during the 15 months follow up period 4 patients experienced an acute exacerbation of IPF (2 patients in each group) and 3 patients (ET; n=1, 7% of the group and control; n=2, 11% of the group)

died during the follow-up period. Six patients (37%) from ET group and 8 patients (44%) from the control group were hospitalized during the follow up period. No significant differences were observed between the groups in hospitalizations ($\chi 2$= 0.16, p=0.68), exacerbations ($\chi 2$ = 0.005, p=0.943) and mortality rates ($\chi 2$ = 0.244, p=0.621).

Conclusions: Twelve-week supervised exercise training program in patients with IPF improves exercise tolerance and functional capacity, pulmonary and ventilatory functions, dyspnea, quality of life, body composition and physical activity levels. At short-term exercise training seems to be an effective treatment for clinical improvement, but the benefits were not preserved in the long-term after cessation of the supervised exercise program. Twelve-week supervised exercise program did not affect prognosis among IPF patients.

KEY WORDS: EXERCISE TRAINING, PULMONARY REHABILITATION, IDIOPATHIC PULMONARY FIBROSIS, EXERCISE TOLERANCE, FUNCTIONAL CAPACITY, PULMONARY FUNCTION, DYSPNEA, QUALITY OF LIFE.

RESUMO

Racional: A fibrose pulmonar idiopática é uma doença crónica, progressiva e fatal do grupo das doenças intersticiais pulmonares, caracterizada por um padrão pulmonar restritivo, reduzida capacidade de troca de gases, dispneia, intolerância ao exercício e reduzida qualidade de vida. Actualmente, não existe ainda uma terapêutica farmacológica de eficácia comprovada, e o nível das recomendações para a reabilitação pulmonar incluindo o exercício é fraca.

Objectivo: Avaliar os efeitos a curto e longo prazo de um programa reabilitação pulmonar baseado em exercício regular em indicadores clínicos de pacientes com diagnóstico de fibrose pulmonar idiopática.

Metodologia: Foi realizado um estudo randomizado com controlos, tendo nele participado um total de 34 pacientes diagnosticados com fibrose pulmonar idiopática (idade média de 68±8 anos). Foi realizada uma intervenção (programa de exercício) por período de 12 semanas, tendo os pacientes sido alvo de seguimento até aos 15 meses subsequentes ao final do período de intervenção. Os pacientes aleatoriamente alocados ao grupo de exercício (ET; n=15) participaram num programa de exercício supervisionado em regime de ambulatório, consistindo em duas sessões semanais de exercício, cada uma com duração de 60 minutos, enquanto os pacientes alocados ao grupo controlo (n=17) recebeu o seguimento médico habitual. No início da intervenção e após 12 semanas, para além do levantamento das características sócio-demográficas, todos os pacientes foram sujeitos a avaliações antropométricas, colheitas de sangue para determinação subsequente das concentrações séricas de biomarcadores, a testes de função pulmonar, a avaliação ecocardiografica bidimensional com Doppler, a teste de esgoespirometrico em exercício máximo ou limitado por sintomas, a avaliação da capacidade funcional utilizando o teste de marcha com duração de 6 minutos (6MWD) e a bateria *Senior Fitness Tests*, à avaliação da dispneia através da escala modificada *Medical Research Council* (mMRC), à avaliação da qualidade de vida relacionada com saúde recorrendo ao *Saint Gorge Respiratory Questionnaire* (SGRQ) e à avaliação dos níveis de actividade física por questionário (IPAQ). Ao décimo primeiro mês os pacientes foram reavaliados para os mesmos parâmetros e com os mesmos instrumentos. Adicionalmente, os pacientes foram seguidos até aos 15 meses, contados a partir do final das 12 semanas correspondentes ao período da intervenção, tendo sido registados os casos de hospitalização, exacerbação e de mortalidade.

Resultados: Trinta e dois pacientes (ET n=15; Control n=17) completaram as 12 semanas correspondentes ao período da intervenção e desses, 28 (14 em cada grupo) foram reavaliados após 11 meses. Em baseline a maioria dos pacientes apresentavam um padrão pulmonar restritivo moderado, capacidade de difusão reduzida, função sistólica do ventriculo esquerdo normal em repouso, capacidade aeróbia moderadamente reduzida (VO_{2pico} ≈ 60% do predito) e capacidade de marcha quase normal. Não se observaram diferenças significativas entre os grupos em baseline para as características dos pacientes e para as variáveis do estudo. Após as 12 semanas de intervenção foram observadas diferenças significativas entre grupos (ET *versus* controlo) nas médias das diferenças absolutas entre

momentos de avaliação (Δ= pós intervenção-baseline). No grupo ET observou-se o aumento da capacidade máxima de tolerância ao exercício e das funções pulmonar e ventilatória enquanto no grupo de controlo se observou uma tendência para agravamento (com as seguintes diferenças entre grupos das médias da variação entre momentos das seguintes variáveis: ΔVO_{2pico} = 2.6 mL/kg/min, p=0.002; Δ6MWD = 81 m, p<0.001; ΔCapacidade Vital Forçada (FVC) % do predito: 6%, p=0.038). No grupo ET registaram-se, também, alterações significativas nos níveis de dispneia (mMRC), na qualidade de vida (SGRQ), nas respostas ventilatórias, da capacidade funcional (*Senior Fitness tests*), da composição corporal e dos níveis de actividade física, enquanto no grupo de controlo se registou uma tendência para agravamento. Oito meses após o período da intervenção, as melhorias registadas às 12 semanas no grupo ET despareceram, com a reversão dos valores médios para níveis semelhantes aos registados no momento inicial do estudo, enquanto no grupo controlo se observou uma tendência ligeira de agravamento [com as seguintes diferenças entre grupos nas médias das diferenças absolutas entre momentos de avaliação (ΔΔ=Follow up-12 semanas): $\Delta\Delta VO_{2pico}$= -2.9 mL/kg/min, p=0.001; ΔΔ6MWD = -25 m, p=0.285; ΔΔFVC % do predito = -4.7%, p=0.132; ΔΔmMRC = 0.5 pontos, p=0.055; ΔΔSGRQ: 7.9 units, p= 0.041). Adicionalmente, durante o período de 15 meses de follow up para a realização do estudo ocorreram exacerbações agudas em 4 pacientes e 3 pacientes [ET n=1 (7%) and control n=2 (11%)] morreram durante o período de follow-up. Seis pacientes do grupo ET (37%) e 8 pacientes do grupo controlo (44%) foram hospitalizados durante o período de follow up. Não se observaram diferenças significativas entre grupos para hospitalizações, exacerbações e taxaNo significant differences were observed between the groups in hospitalizations ($\chi2$= 0.16, p=0.68), exacerbations ($\chi2$ = 0.005, p=0.943) e taxa de mortaslidade ($\chi2$ = 0.244, p=0.621). **Conclusões:** Em pacientes com fibrose pulmonar idiopática, doze semanas de exercício regular supervisionado melhoram as capacidades de tolerância ao exercício e funcional, as funções pulmonar e ventilatória, a dispneia, a qualidade de vida, a composição corporal e os níveis de actividade física. A curto termo reabilitação pulmonar com inclusão de exercício regular supervisionado parece ser uma forma de tratamento eficaz, mas os benefícios revertem longo prazo com a cessação da prática regular de exercício físico. A prática de exercício em programas da reabilitação pulmonar não afecta o prognóstico em pacientes diagnosticados com fibrose pulmonar idiopática .

PALAVRAS CHAVE: EXERCÍCIO REGULAR, REABILITAÇÃO PULMONAR, FIBROSE PULMONAR IDIOPÁTICA, TOLERÂNCIA AO EXERCÍCIO, CAPACIDADE FUNCIONAL, FUNÇÃO PULMONAR, DISPNEIA, QUALIDADE DE VIDA.

List of abbreviations

AACVPR: American Association of Cardiovascular and Pulmonary Rehabilitation

ACSM: American College of Sports Medicine

AT: Anaerobic Threshold

ATS: American Thoracic Society

BAL: Bronchoalveolar Lavage

BMI: Body Mass Index

BNP: Brain Natriuretic Peptide

BORG CR: Borg Category Ratio

CA: Carbohydrate antigen

COPD: Chronic Obstructive Pulmonary Disease

CPET: Cardiopulmonary Exercise Test

CRDQ: Chronic Respiratory Disease Questionnaire

CRP: C -Reactive Protein

DLCO: Diffusion Capacity for Carbon Monoxide

DNA: Deoxyribo-nucleic Acid

EBV: Epstein-Barr Virus

ERS: European Respiratory Society

ET: Exercise Training

FEV1: Forced Expiratory Volume in 1 second

FVC: Forced Vital Capacity

GER: Gastro-esophageal Reflux

HRCT: High Resolution Computed Tomography

ILD: Interstitial Lung Disease

IPF: Idiopathic Pulmonary Fibrosis

MCID: Minimal Clinical Important Difference

MET: Metabolic Equivalent Task

mPAP: mean Pulmonary Arterial Pressure

MVV: Maximal Voluntary Ventilation

mMRC: modified Medical Research Council

NT-proBNP: N-Terminal pro-Brain Natriuretic Peptide

PH: Pulmonary Hypertension

PR: Pulmonary Rehabilitation

QOL: Quality of Life

RHC: Right Heart Catheterization

SaO2: Oxygen saturation

SFT: Senior Fitness Test

sPAP: systolic Pulmonary Arterial Pressure

SpO_2: O_2 Saturation by Pulse Oxymeter

TLC: Total Lung Capacity

UIP: Usual Interstitial Pneumonia

V_A/Q: Alveolar Ventilation to Perfusion Ratio

V_E: Minute Ventilation

VD: Dead Space Ventilation

VT: Tidal Volume

VD/VT: Ratio Represents Physiological Dead Space

VO_2: Oxygen Consumption

WHO: World Health Organization

WR: Work Rate

6MWT: 6 Minutes Walk Test

6MWD: 6 Minutes Walk Distance

CHAPTER I

INTRODUCTION

INTRODUCTION

Pulmonary diseases are increasingly important causes of morbidity and mortality in the modern world [1]. Acute and chronic diseases of the upper and lower respiratory tract account for one third of all physicians' consultations. Estimates shows that one third of hospitalized patients have a problem with their respiratory system regardless of the immediate cause of admission [2]. In 2007 the World Health Organization (WHO) reported that 7% of the main reasons of death with approximately four million deaths annually worldwide, are attributable to chronic respiratory diseases. The global economic burden of chronic respiratory disease was estimated as 4% in general and 8.3% of the burden of all chronic diseases [3]. By definition pulmonary diseases affect the lungs, including their airways, blood vessels and parenchyma [2]. The common symptoms of pulmonary disease are shortness of breath, wheezing, cough, expectoration of sputum, chest pain or discomfort [2].

Idiopathic pulmonary fibrosis (IPF) is one of the most significant pathologies of the interstitial lung disease (ILD) group and the most common form of idiopathic interstitial pneumonias resulting in pulmonary fibrosis or scarring of the lung parenchyma [2, 4]. IPF is a rare disease which affects approximately 5 million persons worldwide [5]. It has an unpredictable clinical course but is usually a fatal lung disease characterized by progressive worsening of dyspnea and lung function and is associated with a poor prognosis [6-7]. The mortality rate in the United States in 2003 was 61.2 deaths per 1,000,000 in men and 54.5 per 1,000,000 in women. IPF is the most common cause of death in progressive lung disease (60% of deaths) [7]. The mortality burden attributable to IPF is higher than some cancers [7]. Mean survival rates vary and have been reported from 2-5 years from the time of diagnosis [4-5, 7-8]. IPF is manifest restrictive pulmonary function, impaired gas exchange and ventilatory capacity, hypoxemia and exercise intolerance [5, 7, 9]. Patients with IPF are more breathless and tend to be less physically active to avoid such symptoms [6, 10]. All these manifestations have a significant negative impact on functional capacity and quality of life (QOL) in IPF patients [5-6, 9-10]. Based on the evidence published to date, there is no proven pharmacological therapy for IPF [7]. Supplemental oxygen therapy for hypoxemic patients and early admission for lung transplantation candidature for selected patients are strongly recommended [7]. According the latest

American Thoracic Society/ European Respiratory Society (ATS/ERS) guidelines exercise-based pulmonary rehabilitation has only a "weak" level of recommendation for IPF patients [7].

Indeed, the effect of exercise training in pulmonary rehabilitation setting has not been studied extensively in IPF patients [10-13], although a growing body of evidence showed encouraging results with some health benefits following the participation in these programs. In the past few years several retrospective, prospective and randomized controlled trials have shown significant improvements in several outcomes after pulmonary rehabilitation among IPF patients [10-13].

Nevertheless, most these studies have methodological limitations [12-14]. The majority of those studies were uncontrolled [15-20] or non-randomized [15-21], were retrospective [22-23] and did not include follow-up data [15-19, 21-25]. Actually there are only three randomized controlled trials [24-26] in IPF patients. Furthermore, only two studies conducted a short (4-month) follow-up after a 6-8 weeks exercise program [20, 26].

IPF is a complex, progressive deadly lung disease with repercussions on other physiological systems and functions beyond the respiratory system. It is associated with other pathologies including: coronary arterial disease, lung cancer, pulmonary hypertension, emphysema, chronic inflammation [7] and skeletal muscle dysfunction [13]. Left ventricle dysfunction and development of pulmonary hypertension are also common among IPF patients, and are associated with more advanced disease-stages and poor prognosis [7, 27-28]. Data are somewhat equivocal with respect to the prevalence of pulmonary hypertension in IPF (32-85%) [27]. Since IPF is a progressive disease and over time patients tend to develop pulmonary hypertension especially at end-stage disease [7], echocardiography is justified as non-invasive method to evaluate the heart function and pulmonary pressures in patients with this disease especially in response to treatment [27]. Acute IPF exacerbation is also a significant event annually affecting 5-10% of IPF patients, usually with negative consequences on clinical course of the disease and survival [7].

Changes in blood biomarkers in response to exercise training have not been studied so far in IPF patients. Measuring pre-and post-exercise training program and at the end of follow up period of carbohydrate antigen (CA) 15-3, CA 19-9 [29-33], N-Terminal pro-Brain Natriuretic Peptide (NTpro-BNP) [34-35] and C-reactive protein (CRP) [36-37] which have been proposed as possible indicators for IPF severity, disease progression and prognosis of IPF [29-37] may provide important additional information for clinicians regarding the course of the disease, treatment efficacy and prognosis as well.

To the best of our knowledge there are no studies that have examined the effect of exercise training based-pulmonary rehabilitation on heart function and pulmonary pressures, exacerbation and survival rates, blood biomarkers and anthropometrics, physical activity and disease severity or prognosis in patients with IPF.

Furthermore, in the few existing short-term exercise pulmonary rehabilitation studies, typically 6 minutes walk distance (6MWD) was a primary end-point to assess exercise tolerance, and the usage of cardiopulmonary exercise test (CPET) was uncommon [15-19, 22-24]. Although 6 minute walking test (6MWT) was well established test to assess exercise capacity in pulmonary disease and heart failure patients [38-39], it is considered a sub-maximal test [40] providing only a performance information with many confounders that may have an impact on the results [38-39] and makes difficult to distinguish the mechanisms underlining the improvement [15-20, 22-24].

CPET is a gold-standard method for assessing cardio-respiratory capacity (VO_{2peak}), cardiovascular, ventilatory and gas exchange responses, which may provide information on the abnormalities and limiting factors in exercise, and physiological mechanisms' adaptation following exercise rehabilitation programs [41-44]. VO_{2peak} is objective indicator of aerobic exercise capacity directly measured during CPET, and has been strongly associated with survival and prognosis in heart and lung diseases patients [41-44] and IPF [45]. Since IPF patients presents restrictive pulmonary pathophysiology, impaired alveolar gas exchange and in many cases some degree of left ventricle diastolic and systolic dysfunction and development of pulmonary hypertension [7, 27-28], CPET is probably a superior method for assessing exercise tolerance and cardio-respiratory responses following exercise training intervention

among IPF. To the best of our knowledge, there are no studies showing an improvement in VO_{2peak} following exercise interventions in IPF patients [15-26]. In addition, significant lack of knowledge on physiological mechanisms exists with respect to the exercise component of pulmonary rehabilitation [15-26].

In our research we used both a lab test (cardiopulmonary exercise test) and field tests (6MWT and Senior fitness tests) to assess aerobic exercise capacity, aerobic endurance (VO_{2peak} and Anaerobic threshold respectively) and functional exercise capacity. These tools allow us to broadly evaluate exercise tolerance and physiological adaptations to the exercise pulmonary rehabilitation program. Moreover, with this approach we can explore some of the mechanisms underlying changes following the intervention, in order to target the exercise pulmonary rehabilitation programs for IPF more effectively. In addition, since part of the exercise clinical outcomes (VO_{2peak} and 6MWD) have a prognostic values for IPF patients, measuring these variables is important for following up on the progression of the disease and treatment implementation.

Taking into account the above mentioned methodological limitations – lack of strong comprehensive evidence regarding the benefit of exercise pulmonary rehabilitation for IPF, the "weak" level of recommendation for this therapy by ATS/ERS and the fact that IPF is a deadly lung disease for which efficient therapeutic options have remained elusive – exercise training as a core component of pulmonary rehabilitation can be a reasonable alternative medical care for most patients in order to maintain functional capacity and quality of life. Despite the positive results in recently published data about exercise pulmonary rehabilitation in IPF, knowledge gaps still exist regarding the chronic effect of exercise training on cardiopulmonary functions at rest and in response to exercise, blood biomarkers associated with the severity and progression of IPF, indicators of pulmonary hypertension, muscle strength and flexibility, body composition, physical activity, exacerbation and survival [7, 15-26].

Indeed, a deeper understanding of the short- and long-term effects of exercise training on clinical outcomes with their possible mechanistic adaptations will enable us to more efficiently target the pathophysiology of IPF and determine exercise programs for the optimal improvement of IPF patients.

AIMS

The aim of the present thesis was to examine the short- and long-term effects of an exercise training program on clinical outcomes including exercise tolerance and functional capacity, resting and exercise cardio-pulmonary functions, dyspnea, quality of life, blood biomarkers associated with disease severity and prognosis, anthropometrics and body composition, physical activity levels, exacerbations and hospitalizations and survival rates in patients with idiopathic pulmonary fibrosis.

HYPOTHESIS

Based on previous studies among patients with interstitial lung disease and particularly IPF, we hypothesized that exercise training will improve exercise tolerance and functional capacity, dyspnea levels and QOL in IPF patients [15-26]. We also expected to see enhancements in strength, body composition, inflammatory blood biomarkers, heart structure and left ventricle function and physical activity levels following our program [46-47]. In addition, taking into account that some of our outcomes (VO_{2peak}, 6MWD, and mMRC-dyspnea scale) have been proposed as prognostic parameters for increased risk of mortality in IPF patients [7, 36, 45, 48-49], and the fact that previous studies have already shown improvements in some of these outcomes (mainly 6MWD)[15-26], we hypothesized that the exercise training program will improve these outcomes with benefits on prognosis.

This dissertation contains 6 chapters which address the importance of our scientific clinical research question, justify the purposes and the hypothesis of the present work, the methodology that has been used to resolve the problem, and finally the findings and the scientific and clinical interpretation. Chapter I (Introduction) presents in brief the significant gap in the literature regarding the exercise component of pulmonary rehabilitation in IPF and clarifies the aims and hypothesis of our study. In Chapter II (Theoretical Background) we provide a broad review of the existent literature on IPF in terms of epidemiology, pathophysiology, prognosis and treatment options including exercise component of pulmonary rehabilitation. Chapter III (Methods) details the methodology applied in this study and the statistical analysis that was performed. In the "Results" section (Chapter IV) we present in figures, tables and text pertaining to

our findings. In the "Discussion" (Chapter V) we compared our results with previous reports, and try to determine some of the mechanisms underlying the changes we detected. Finally, in Chapter VI (Conclusions and Clinical Implications) we provide conclusions emerging from the present work and some clinical messages that arise from our findings.

CHAPTER II

THEORETICAL BACKGROUND

THEORETICAL BACKGROUND

1. Definitions and Epidemiology

1.1 Definition

In 2011, the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society and the Latin American Thoracic Association issued an evidence-based guideline statement proposing a new definition for IPF [7].

"IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP)" [7]. "The definition of IPF requires the exclusion of other forms of interstitial pneumonia including other idiopathic interstitial pneumonias and interstitial lung disease (ILD) associated with environmental exposure, medication, or systemic disease" [7].

1.2 Clinical presentation

IPF should be considered in all adults with unexplained chronic exertional dyspnea, and commonly presents with cough, bibasilar inspiratory crackles, and finger clubbing which is found in approximately 50% of IPF patients [5, 50-52]. The incidence of the disease increases with age, with presentation typically occurring in the sixth and seventh decades. Two-thirds of all cases arise in patients over 60 years of age and the mean age at presentation is 66 years old [5, 9] . Patients with IPF under the age of 50 are rare; such patients may subsequently manifest overt features of an underlying connective tissue disease that was subclinical at the time IPF was diagnosed. More men have been reported with IPF than women, and the majority of patients have a history of cigarette smoking [7, 9].

1.3 Incidence and prevalence

There are no large-scale studies of the incidence or prevalence of IPF on which to base formal estimates [7]. The incidence of IPF was estimated at 10.7 cases per 100,000 per year for men and 7.4 cases per 100,000 per year for women in a population-based study from the county of Bernalillo, New Mexico [53]. A study

from the United Kingdom reported an overall incidence rate of only 4.6 per 100,000 person-years, but estimated that the incidence of IPF increased by 11% annually between 1991 and 2003 [52]. A third study from the United States estimated the incidence of IPF to be between 6.8 and 16.3 per 100,000 persons using a large database of healthcare claims in a health plan [54].

Prevalence estimates for IPF have varied from 2 to 29 cases per 100,000 persons in the general population [7]. The wide range in these numbers is likely explained by the previous lack of a uniform definition for identifying cases of IPF, as well as by differences in study designs and populations [7]. A recent analysis based on healthcare claims data of a large health plan in the United States yielded a prevalence estimate of between 14.0 and 42.7 per 100,000 persons depending on the case definition used [54]. It is unclear if the incidence and prevalence of IPF are influenced by geographic, ethnic, cultural, or racial factors [7]. However, it also appears that during the last decade, the incidence of IPF has been on the rise [52].

1.4 Risk factors

Although idiopathic pulmonary fibrosis is, by definition, a disease of unknown etiology, a number of potential risk factors have been described [7]:

Cigarette smoking- Smoking is strongly associated with IPF, particularly for individuals with a smoking history of more than 20 pack-years [7]. Baumgartner KB et al [55] reported a correlation between smoking history (20–40 pack-years) and risk for IPF, with an odds ratio of 2.3 for smokers [55].

Environmental exposures- Increased risk for IPF has been found to be associated with a variety of environmental exposures [7, 9]. A significantly increased risk has been observed after exposure to metal dusts (brass, lead, and steel) and wood dust (pine) [56-58]. Farming, raising birds hair dressing, stone cutting/polishing, and exposure to livestock and to vegetable dust/animal dust have also been associated with IPF [55].

Microbial agents- Several studies have investigated the possible role of chronic viral infection in the etiology of IPF. Most research has been focused on Epstein-Barr virus (EBV) and hepatitis C. Both the protein and the deoxyribonucleic acid (DNA) of

EBV have been identified in lung tissue of patients with IPF, usually in the alveolar epithelial cells [7]. EBV genome rearrangement, which is associated with productive EBV replication, was found in 11 of 18 EBV DNA-positive IPF biopsies [59].
Variable results have emerged from studies of hepatitis C. Despite the large number of studies to date, definitive conclusions about the role of infection in IPF cannot be made [7].

Gastroesophageal reflux- Several studies have suggested that abnormal acid gastroesophageal reflux (GER) associated with microaspiration is a presumed risk factor for IPF. Abnormal GER is common in patients with IPF, nevertheless the exact mechanism still needs to be clarified [7].

Genetics and familial pulmonary fibrosis- Although accounting for less than 5% of total patients with IPF, familial forms of IPF (i.e., those affecting two or more members of the same primary biological family) have been reported [7]. The criteria used to define IPF in familial and sporadic cases are the same; familial IPF and sporadic IPF are clinically and histologically indistinguishable although familial forms may develop at an earlier age and seem to have different patterns of gene transcription. Several genes showed association with the familial form of IPF (ELMOD-2 located on chromosome 4q31 and surfactant protein C gene) [60-61], while others showed increased frequencies with a sporadic form of IPF (genes encoding for interleukin: 1,4,6,8,10 and tumor necrosis factor-α) [7]. However, at present research in this area is in an early phase and large cohorts are still needed [7].

2. Diagnosis and disease course

2.1 Usual interstitial pneumonia (UIP)

High-resolution computed tomography (HRCT) is an essential component of the diagnostic pathway in IPF. Usual interstitial pneumonia (UIP) is characterized on HRCT by the presence of reticular opacities, often associated with traction bronchiectasis and honeycombing which is critical for making a definite diagnosis [62-63]. Honeycombing is manifested on HRCT as clustered cystic airspaces, typically of comparable diameters on the order of 3–10 mm but occasionally as large as 2.5 cm. It is usually sub-pleural and is characterized by well-defined walls [63].

Ground glass opacities are common, but usually less extensive than the reticulation. The distribution of UIP on HRCT is characteristically basal and peripheral, though often patchy. The presence of coexistent pleural abnormalities (e.g., pleural plaques, calcifications, significant pleural effusion) suggests an alternative etiology for UIP pattern. Micronodules, air trapping, non-honeycomb cysts, extensive ground glass opacities, consolidation, or a peribronchovascular-predominant distribution should lead to consideration of an alternative diagnosis [7, 64].

Chest radiograph is less useful than HRCT in evaluating patients with suspected IPF. Several studies have documented that the positive predictive value of a HRCT diagnosis of UIP is 90 to 100%. These studies are affected by selection bias because they only included patients with biopsy-proven diagnoses. Nonetheless, a UIP pattern on HRCT is highly accurate for the presence of UIP pattern in surgical lung biopsy. If honeycombing is absent, but the imaging features meet criteria for UIP, suggesting possible UIP, then surgical lung biopsy is necessary to make a definitive diagnosis. In patients whose HRCT does not demonstrate a UIP pattern, the surgical lung biopsy may still demonstrate UIP pattern on histopathology [7].

2.2 Diagnostic criteria

The diagnostic criteria have been changed and updated since the last ATS/ERS statement from 2000 [7]. The new guidelines from 2011 emphasize the use of HRCT and the presence of UIP pattern as a primary diagnostic tool (Table 1). According to the new guidelines, surgical lung biopsy is now not essential for the diagnosis of IPF. In addition, the guidelines emphasize the importance of making a wide anamnesis including: medical, occupational/environmental and family history, physical examination, physiological testing and laboratory evaluation. Multidisciplinary decision making that includes pulmonologists, radiologists, and pathologists experienced in the diagnosis of ILD can increase the accuracy of IPF diagnosis [7].

The diagnosis of IPF requires the following:

1. Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease and drug toxicity).
2. The presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy.
3. Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy [7]. The diagnostic algorithm for IPF is presented in Figure 1, and the histological and radiological criteria for diagnostic of IPF are shown in Table 1.

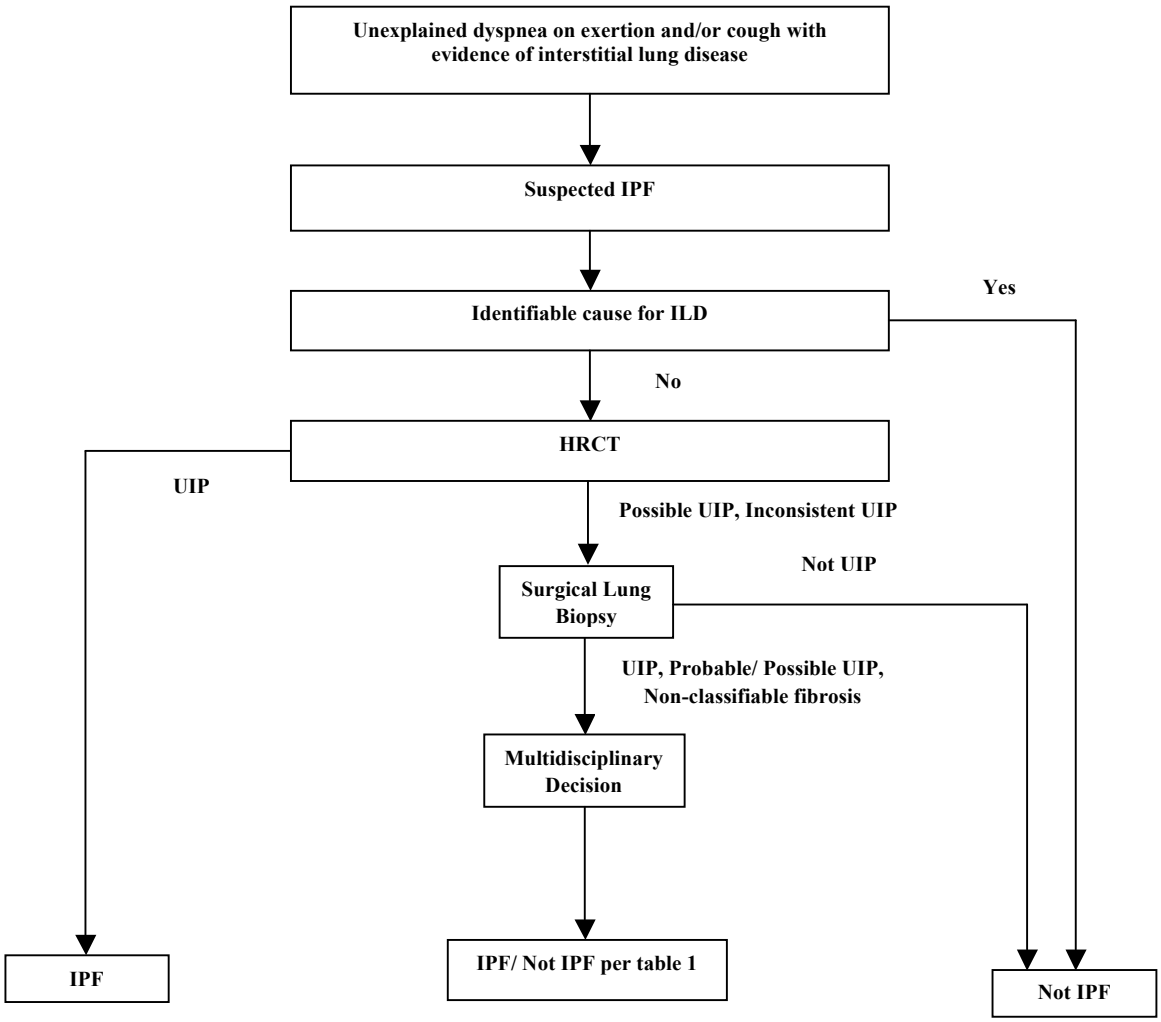


Figure 1. Diagnostic algorithm for idiopathic pulmonary fibrosis [7].

IPF; idiopathic pulmonary fibrosis, ILD; interstitial lung disease, HRCT; high-resolution computed tomography UIP; usual interstitial pneumonia.

Table 1. Summary of the histopathological and radiological criteria for the diagnosis of IPF.

HRCT	Lung biopsy (when performed)	Diagnosis of IPF
UIP pattern (all four) • **Evidence of marked fibrosis/architectural distortion, honeycombing in a predominantly subpleural/paraseptal distribution** • **Presence of patchy involvement of lung parenchyma by fibrosis.** • **Presence of fibroblast foci** • **Absence of features against a diagnosis of UIP suggesting alternative diagnosis**	• UIP • Probable UIP • Possible UIP • Nonclassifiable fibrosis	YES
Probable UIP pattern • **Evidence of marked fibrosis/architectural distortion, honeycombing** • **Absence of either patchy involvement or fibroblastic foci, but not both** • **Absence of features against a diagnosis of UIP suggesting alternative diagnosis** • **Honeycomb changes only**	• Not UIP • UIP, Probable UIP • Possible UIP, Nonclassifiable fibrosis	NO YES PROBABLE MDD
Possible UIP pattern • **Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation** • **Absence of other criteria for UIP** • **Absence of features against a diagnosis of UIP suggesting an alternate diagnosis**	• Not UIP • UIP, Probable UIP • Possible UIP, Nonclassifiable fibrosis	NO YES PROBABLE MDD
Not UIP pattern (any of the six) • **Hyaline membranes** • **Organizing pneumonia** • **Granulomas** • **Marked interstitial inflammatory cell infiltrate away from honeycombing** • **Predominant airway centered changes** • **Other features suggestive of an alternate diagnosis**	• Probable UIP • Possible UIP • Nonclassifiable fibrosis • Not UIP	NO

HRCT; high-resolution computed tomography UIP; usual interstitial pneumonia, IPF; idiopathic pulmonary fibrosis, MDD; multidisciplinary decision.

2.3 Acute exacerbation in IPF

Acute, unexpected deterioration in patients with IPF has usually been called the "acute exacerbation" or, more euphemistically, the "terminal complication" of IPF [5, 65]. Recent observations have suggested that the incidence of acute respiratory worsening occurs in a small minority of IPF patients (approximately 5–10% annually) [66] . These episodes may occur secondary to common conditions such as pneumonia, pulmonary embolism, pneumothorax, or cardiac failure [67]. When a cause cannot be identified for the acute respiratory decline, the term acute exacerbation of IPF has been used [7]. Historically, criteria for acute exacerbation of IPF have included an unexplained worsening of dyspnea within 1 month, evidence of hypoxemia as defined by worsened or severely impaired gas exchange, new radiographic alveolar infiltrates, and an absence of an alternative explanation such as infection, pulmonary embolism, pneumothorax or heart failure [66].

2.4 Clinical course of IPF

The natural history of IPF has been described as a progressive decline in subjective and objective pulmonary function until eventual death from respiratory failure or complicating co-morbidities [68-70]. Several retrospective longitudinal studies suggest a median survival time from 2 to 3 years from the time of diagnosis [71-74]. However, recent data from clinical trials in patient with preserved pulmonary function suggest that this statistics may be underestimated, and survival rates are higher [75-77].

There appear to be several possible natural histories for patients with IPF (Figure 2). For a given patient, the course of the disease is unpredictable at the time of diagnosis, and may influence the mean survival time of IPF patients [4, 7]. The majority of patients demonstrate a slow, gradual progression over many years. Some patients remain stable while others have an accelerated and rapid decline. A minority of patients may experience unpredictable acute worsening of their disease (lightning bolt), either from a secondary complication such as pneumonia, or for unrecognized reasons. This event may be fatal or may leave patients with substantially worsened disease. The relative frequency of each of these natural histories is unknown [4-5, 7].

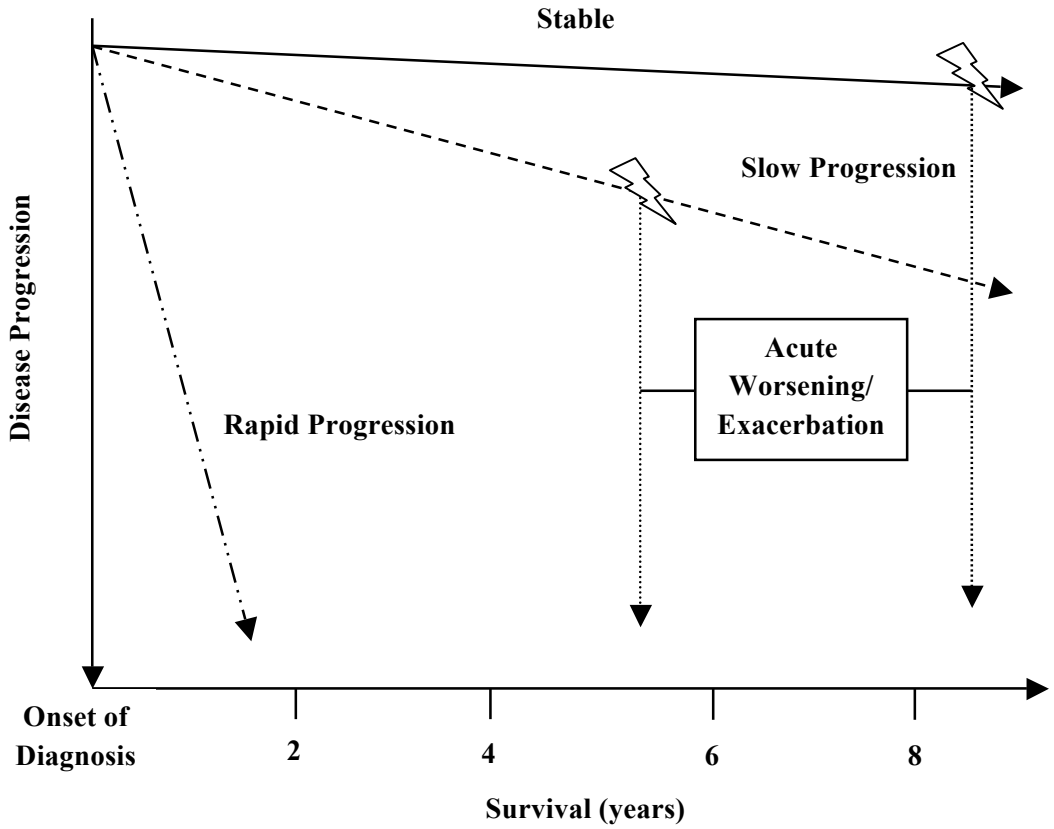


Figure 2. A graphical model of several clinical courses of IPF [7].

2.5 Staging and prognosis

The extent of disease and the severity of functional impairment of patients with IPF at the time of diagnosis are variable. The reasons for this are thought to be variation in subjective perception of symptoms and differences in providers' awareness [7]. Recent studies [4, 7, 34, 45, 48, 51, 78-79] have clarified predictors of survival in IPF (Table 2). However, the accuracy of these predictors is limited by the retrospective nature of some of these studies and differences in study designs. Terms such as ''mild,'' ''moderate,'' ''severe,'' ''early,'' and ''advanced'' have been suggested for staging the disease. Proposed stages are commonly based on resting pulmonary function test measurements and/or the extent of radiologic abnormalities. However, it is unknown if these staging approaches are relevant to clinical decision making. It is important to spot patient at high risk of 2 years mortality, and refer them to a lung transplantation candidate list [7].

Table 2. Selected parameters associated with increased risk for mortality in idiopathic pulmonary fibrosis [4, 7, 34, 45, 48, 51, 78-79].

Measurements at the time of diagnosis	Longitudinal measurements
MRC dyspnea score >3	**Increase in level of dyspnea**
DLCO < 40% predicted values	**Decrease in FVC by > 10% absolute value**
Desaturation < 88% during 6MWT	**Decrease in DLCO by > 15% absolute value**
Extent of honeycombing on HRCT	**Worsening of fibrosis on HRCT**
Presence of pulmonary hypertension, sPAP>50 mmHg	
Presence of finger clubbing	
Elevated BNP	
Peak VO_2 < 8.3 mL/kg/min	
6MWD<207-350 m	
DSP< 200 m%	

BNP; brain natriuretic peptide, DLCO; diffusion capacity for carbon monoxide, HRCT; high-resolution computed tomography, FVC; forced vital capacity, 6MWD; 6 minute walk distance, MRC; medical research council, sPAP; systolic pulmonary arterial pressure, Peak VO_2; peak oxygen consumption, DSP; distance saturation product.

3. Pathophysiology of IPF

3.1 Anatomical and structural changes

IPF is a chronic disease that manifests over several years and is characterized by scar tissue within the lungs and pulmonary structural remodeling leading to honeycombing, in the absence of known provocation. The process of remodeling in IPF is generally regarded as consisting of thickening of the alveolar walls. In addition, parenchymal damage, interstitial fibrosis, collapse and apposition of alveolar walls result in obliteration of alveolar lumina and distortion of normal lung architecture [5, 80]. The presence of honeycombing on HRCT is a consequence of dilatation of the remaining air spaces [80].

3.2 Pulmonary function at rest

Standard spirometry reveals decreased measures of forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) [5, 9]. The ratio of FEV_1/FVC

remains normal (or increased) in IPF, consistent with restrictive physiology as a consequence of reduced pulmonary compliance, which is confirmed by total lung capacity (TLC) in lung volume measurements [5, 9]. Gas exchange is impaired in IPF which can be demonstrated by reduced diffusion capacity for carbon monoxide (DLCO) [5, 9]. In some cases this impairment can precede the decline in lung volumes. The maximal breathing capacity is usually normal when measured by maximal voluntary ventilation (MVV) [5, 9].

In general, as the disease progresses, lung compliance decreases and lung volumes fall [9]. The resting arterial blood gas is usually normal or may reveal mild hypoxemia and respiratory alkalosis [9]. In addition patients with IPF are usually tachypeneic; they develop more rapid shallow breaths as the disease progresses, and therefore the work of breathing is increased [9].

3.3 Exercise capacity and limitations during exercise

Exercise intolerance is a cardinal feature of the ILDs and IPF patients which is often associated with significant exertional dyspnea and fatigue that may progress over time [81]. Patients with ILD and IPF typically exhibit reduced maximal or peak aerobic capacity (VO_{2peak}), peak work rate, and sub-maximal exercise endurance (anaerobic threshold compared with age- and sex matched normal subjects [82].

IPF patients usually exhibit rapid shallow breathing pattern that worsen with exercise [81]. At any given level of ventilation tidal volume (VT) is decreased and breathing frequency is increased [82]. Patients with IPF have less efficient patterns of breathing during exercise [9]. Ventilatory response is increased primarily by increasing their respiratory frequency. This pattern of increase differs from normal subjects in whom increased ventilation during mild exercise occurs by an increase in VT rather than in respiratory rate [9]. Despite this abnormal ventilatory pattern most IPF patients are not limited by ventilation and breathing reserve kept at normal levels [81-82]. Patients with IPF also have elevated minute ventilation during exercise that is in part related to the increase in dead space (VD) ventilation. The ratio of VD to VT is increased at rest and is maintained or decreases with exercise. In patients with IPF, an

increase in the VD/VT ratio should raise concern about pulmonary vascular disease, especially chronic pulmonary emboli, or associated emphysema [9].

In patients with IPF impaired pulmonary gas exchange and circulatory limitations are the main causes for exercise intolerance [81-82]. Abnormalities in gas exchange thought to occur due to alveolar ventilation-perfusion (V_A/Q) mismatching, oxygen diffusion limitation and low mixed venous oxygen content resulting in decrease in arterial O_2 pressure and arterial O_2 saturation (SaO_2) [81-82]. Although resting arterial oxygen saturation remains normal, oxygen desaturation is commonly found during exercise [5, 83]. With exercise, the alveolar-arterial O_2 gradient widens, and the arterial O_2 pressure and arterial O_2 saturation (SaO2) fall [9].

Circulatory limitations play also important role in the reduced aerobic capacity in IPF patients [81-82]. Arterial hypoxemia, pulmonary vascular damage and vasoconstriction, increased pulmonary vascular resistance and development of pulmonary hypertension can result in right and left ventricle dysfunctions [81-82].
Although dyspnea is predominant symptom of IPF patients, leg pain, chest discomfort and fatigue are common reasons for exercise test termination. Thus, exercise intolerance in ILD and IPF patients is multi-factorial, and skeletal and respiratory muscles dysfunction may have also be contributors [81-82].

Importantly, the abnormalities identified at rest do not accurately predict the magnitude of the abnormalities that may be seen during exercise [9]. Although these abnormalities can be assessed by oximetry saturation, it has been demonstrated that this method may not yield as dramatic or significant a change as that obtained by arterial blood gases [9]. Standard cardiopulmonary exercise test (CPET) is more sensitive for the detection of abnormalities in O_2 transfer and gas exchange compared to resting physiological measurements [9]. Furthermore, CPET can be used as an additional tool for monitoring the clinical course of the disease [9]. The six minute walk test (6MWT) is a simple and widely used tool in clinical practice [7]. Several studies indicated the 6 minute walk distance (6MWD) as a prognostic predictor for survival in IPF patients [48, 84].

Compared to the 6 minute walking test (6MWT) CPET has an advantage in assessing exercise tolerance by direct measure of cardio-respiratory responses during exercise in addition to measuring performance. Moreover, interpretation of ventilatory, gas exchange and cardiac capacities and responses to incremental exercise may provide important information on limiting factors during exercise which are lacking in the 6MWT.

3.4 Sign, symptoms, co-morbidities and quality of life in IPF

Classical signs during physical examinations in patients with IPF usually reveal early inspiratory crackles, predominantly located in the lower posterior lung zones upon auscultation of the lungs [5]. These show a fine acoustic character reminiscent of the sound made by Velcro. Finger clubbing is also a predominant sign which is found in approximately 50% of patients with IPF.[5] Oxygen desaturation during exercise is one of the significant clinical signs with powerful prognostic value in IPF patients [7]. Arterial desaturation <88% during 6MWT was documented as a marker for increased mortality [7].

There are no other physical manifestations, unless pulmonary hypertension has developed in association with end-stage disease. In that case, classic signs of right heart failure may be present [5].

Dyspnea during exertion is the most common symptom experienced by IPF patients [5]. In addition, they are also often bothered by a dry cough which interferes with daily activities. The onset of symptoms is slow, but symptoms become progressively worse over time [5].

Quality of life (QOL) is impaired in IPF patients with advanced symptoms and declined functional capacity [10]. Most health-related QOL domains are poor [10], and there are few therapies or other interventions that have shown efficacy to improve QOL in patients with IPF [6]. Swigris et al, [6] performed a systemic review of seven studies with 512 IPF patients examining the health-related QOL [6]. The results of this review showed that IPF patients have significantly reduced QOL with a more

pronounced repercussion in physical domains [6]. IPF patients suffer more breathlessness and tend to be less physical active to avoid such episodes which influences their mobility and independence [85]. Usually they need more rest periods and longer recovery time after exercise [85]. In addition, IPF patients also report higher degrees of fatigue, exhaustion, anxiety, depression and fear in their life [10].

3.5 Pulmonary hypertension in IPF patients

Pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure (mPAP) > 25 mmHg at rest or > 30 mmHg with exercise measured on right heart catheterization (RHC), usually for IPF patients referred to lung transplantation lists [86-89].

The complex pathophysiology of PH in IPF is not fully understood but it is believed that the mechanism is related to pulmonary artery vasoconstriction and pulmonary artery remodeling [27]. Both these mechanisms are most likely due to local-lung and systemic hypoxemia and the fibrosining process which causes damage to alveolar wall, connective tissue and blood vessels [27]. Since IPF is a progressive interstitial lung disease manifest in hypoxemia especially during physical effort, PH is frequently an accompanying co-morbidity in advanced IPF [7].

Although, RHC is the gold standard for the diagnosis and confirmation of pulmonary hypertension, this is an invasive procedure and is associated with some morbidity (1.1%) and mortality (0.055%) rates [90-91]. Doppler-echocardiography is a non-invasive and widely available tool that can be used not only for initial screening to estimate pulmonary pressures, but also for monitoring and following up disease progression over time [91]. Recently, in a large meta-analysis of 29 studies, Janda S et al [91] reported a moderate correlation coefficient (r=0.7) between sPAP on echocardiography and mPAP on RHC. In addition, the overall diagnostic power of Doppler-echocardiography for detecting PH was 83% for sensitivity and 72% for specificity [91]. The most common method to determine pulmonary pressures by Doppler-echocardiography is by measuring the velocity of the tricuspid regurgitated jet and adding estimated right atrial pressure (RAP) using the diameter and collapse of the inferior vena cava during spontaneous respiration. This method allows estimation

of systolic pulmonary arterial pressure (sPAP) [91]. During Doppler - echocardiography measures PH at rest is defined as sPAP >35 mmHg. Mild to moderate PH is defined as sPAP between 35 and 50 mmHg and severe PH as sPAP > 50 mmHg [92-93].

The presence of PH in patients with IPF has been associated with increased risk of mortality and poor prognosis [7, 86-89]. Reported estimates of the prevalence of PH in IPF patients have varied widely from 32% to 85% [5, 27, 94]. Two retrospective studies using RHC showed the presence of PH (mPAP >25 mmHg) in 31.6% [88] and 33.9% [95] of patients respectively, while in an echocardiography study a much higher prevalence of PH was found (sPAP>35 mmHg), namely 84% of 88 patients and 16% with sPAP >50 mmHg [96]. The differences in the prevalence of PH reflect variations in patient population, level of disease severity and different diagnostic modalities [94].

Diffusion capacity for carbon monoxide (DLCO), which is measured on pulmonary function tests, and profound desaturation during exertion have a strong inverse correlation with PH [88, 94, 96]. However, the severity of restrictive physiology has little bearing on the prevalence or degree of PH. Several studies had demonstrated a lack of correlation between pulmonary arterial pressure and forced vital capacity in IPF patients [5, 27, 88].

3.6 Emphysema combined with IPF

Several researchers have described a syndrome in which IPF coexists with pulmonary emphysema [97-98].This is not surprising as both diseases are associated with a history of exposure to cigarette smoke [5, 98]. Combined IPF and emphysema is characterized by upper lobe emphysema and lower lobe fibrosis. Physiologic testing of these patients reveals preserved lung volume indices contrasted by markedly impaired diffusion capacity [5, 98]. The incidence of combined IPF and emphysema remains unknown but smaller case series suggest that this subgroup may comprise up to 35% of patients with IPF [5, 98]. Combined IPF and emphysema is a strong determinant of secondary pulmonary hypertension and is more likely to require long-

term oxygen therapy [7, 97]. In addition, it has a major effect on measures of physiologic function, exercise capacity and prognosis [5].

3.7 Lung cancer and IPF

An association between IPF and lung cancer was theorized based on the simultaneous finding of IPF and lung cancer in autopsy studies dating back several decades [99]. A small number of epidemiologic reports helped to advance the notion that IPF is an independent risk factor for lung cancer [100].

The biological mechanisms underlying the association between IPF and lung cancer are not clearly understood but several explanations have been proposed. The fibrotic process that characterizes IPF is commonly considered the result of recurrent injury to the alveolar epithelium followed by uncontrolled proliferation of fibroblasts [101]. However, based on considerable scientific evidence, it has been recently hypothesized that IPF might be considered a neoproliferative disorder of the lung because this disease exhibits several pathogenic features similar to cancer [101]. Indeed, epigenetic and genetic abnormalities, altered cell-to-cell communications, uncontrolled proliferation, and abnormal activation of specific signal transduction pathways are biological hallmarks that characterize the pathogenesis of IPF and cancer [101].

Yet studies examining multiple causes of death, utilizing information obtained from death certificates, failed to confirm an association between pulmonary fibrosis and lung cancer [102]. A retrospective case-controlled study took advantage of the British general-practice database and identified 890 cases of IPF. Compared to 5,884 controls, a seven-fold increase in lung cancer was observed in IPF patients [103]. Based on large comprehensive data-bases from the United Kingdom and Japan, the overall relative risk for lung cancer in ILD patients is 5.3 to 14.1, although data from the United States of America are somewhat contradictive [104].

Several studies showed an association between IPF and lung cancer [104-107]. Nagai et al. [105] found a 31.3% prevalence of lung cancer among 99 IPF patients [105]. Park et al. [106] showed the presence of lung cancer in fibrotic regions of the lung in 37% of combined lung-cancer and IPF patients [106]. Males, cigarette smokers and

older age IPF patients are at higher risk for lung cancer [107]. Lower lobes, peripheral regions of the lung and squamous cell carcinoma type are more commonly involved with cancer in patients with IPF [107].

3.8 Blood biomarkers in IPF

Biomarkers act as surrogates for clinically meaningful outcomes and may or may not reflect the pathology underlying a disease. Examples of clinical utility include diagnosis, assistance in determination of disease severity, the prediction of disease progression or regression and prognostication of mortality [108]. A biomarker should be easily and reliably measured and available for serial monitoring in practice. Measuring peripheral blood biomarkers that reflect disease activity would provide an additional tool for monitoring prognosis and disease course, prediction markers of mortality, and treatment efficacy evaluation which would be valuable for both clinical care and research purposes [108]. Serum biomarkers have an advantage in that they can be measured in a minimally-invasively manner and are easily suitable for follow-up [109].

Biomarkers investigated in idiopathic fibrosing lung diseases reflect and perhaps broaden our current understanding of the events underlying the scarring of the lung [7, 108-109]. Research into the pathogenesis of IPF has advanced considerably in recent years and has shifted its focus from processes governing chronic inflammation with fibrosis as the end result, to alveolar epithelial dysfunction and injury with aberrant wound repair and disordered fibroproliferation [7, 108-109]. A range of molecules involved in epithelial damage and repair such as surfactant proteins –A and-D, Krebs von den Lungen 6, Clara cell secretory protein 16, matrix metalloproteinases 1 and 7 and CC Chemokine Ligand 18 are potential serum bronchoalveolar lavage (BAL) biomarkers [7, 108-109].

Data on the predictive value of these biomarkers in IPF are relatively scarce, and these markers are largely unavailable in routine clinical practice [7]. Several alternative biomarkers were proposed as candidates for monitoring the disease course and prognosis of IPF [29-33]. Carbohydrate antigens (CA) 15-3 and 19-9 levels were recently shown to have a significant association with IPF severity and prognosis indicating a lung injury [29-33]. The biological mechanisms of these markers related

to the development of pulmonary fibrosis are not fully understood and have been poorly investigated [29-30, 33].

CA15-3 has been implicated in cell adhesion, immunity and metastasis [29], and is a well-known marker for the early detection of breast cancer recurrence and for assessing the efficacy of treatment for metastatic breast cancer [110]. Elevated CA 15-3 serum levels have been previously reported in interstitial lung disease associated with collagen diseases, and may play a role in the fibrotic process of the lung and in disease progression [29-30].

Serum CA19-9 levels have been established as a useful tumor marker for gastrointestinal cancers, especially biliary tract and pancreas cancers [33]. Several investigators have reported that elevated serum levels of CA19-9 in patients with nonmalignant respiratory diseases, such as idiopathic interstitial pneumonia and pulmonary fibrosis, were associated with lower survival rates indicating poorer prognosis [31, 111].

Brain natriuretic peptide (BNP) is not mechanistically related to the pathogenesis of IPF. It is secreted by cardiac myocytes in response to volume or pressure overload. For patients with acute decompensated heart failure, elevated serum BNP levels are independently associated with mortality [108]. BNP levels have also been studied as markers of pulmonary hypertension and right ventricular dysfunction. Some IPF patients with advanced disease can develop pulmonary hypertension and right ventricular dysfunction [108].

Song et al [34] conducted a retrospective evaluation of the relationship between BNP and survival in 131 patients with IPF [34]. The prognosis of the subjects with increased BNP levels was poorer than of those with normal BNP levels (1-year mortality rate: 70.5% vs. 23.7%, mean survival: 11.0 months vs. 22.5 months; $p < 0.001$). In addition, multivariate analysis showed that increased BNP levels were an independent predictor of mortality (hazard ratio- 1.118) in IPF [34]. Corte et al [35] also demonstrated that BNP was a strong predictor biomarker for mortality in 90 ILD patients [35]. Patients with elevated BNP levels had 14-fold increased mortality compare to patients with normal values [35].

C-reactive protein (CRP) is a marker of systemic inflammation that has been the subject of considerable research for many years [112]. CRP is considered an important inflammatory biomarker for atherosclerosis and coronary artery disease [113]. Several studies in IPF patients demonstrated elevated CRP levels associated with poor prognosis suggesting some degree of inflammation [36-37].

4. Treatment for IPF

According to the latest ATS/ERS evidence-based guidelines, insufficient evidence has been found to support any specific pharmacologic therapy for patients with IPF [7]. Thus, to date there is no proven pharmacological treatment for IPF [7]. However, clinical trials of some agents have suggested a possible benefit, and may be a reasonable choice for a minority of IPF patients. These include: combined Acetylcysteine and Azathioprine and Prednisone, Acetylcysteine monotherapy, Anticoagulation and Pirfenidone [7].

Long-term oxygen supplementation therapy is strongly recommended for IPF patients with clinically significant resting hypoxemia [7]. For appropriate patients lung transplantation is recommended [7]. Mechanical ventilation for patients with respiratory failure has a "weak no" recommendation, while pulmonary rehabilitation has a "weak yes" recommendation [7].

5. Pulmonary rehabilitation

In 2006 the American Thoracic Society and the European Respiratory Society published a statement on pulmonary rehabilitation [114]. In 2007 the American Association of Cardiovascular and Pulmonary Rehabilitation and the American

College of Chest Physicians published evidence-based guidelines for pulmonary rehabilitation [1]. Both of these documents adopted the following definition of pulmonary rehabilitation: *"Pulmonary rehabilitation is an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualized treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, increase participation, and reduce health-care costs through stabilizing or reversing systemic*

manifestations of the disease. Comprehensive pulmonary rehabilitation programs include patient assessment, exercise training, education, nutritional intervention and psychosocial support" [1, 114]. Recently the ATS/ERS published a new document of *"Key Concepts and Advances in Pulmonary Rehabilitation"* [13]. This position stand proposes a new definition of pulmonary rehabilitation: *"Pulmonary rehabilitation is a comprehensive intervention based on a thorough patient assessment followed by patient tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors"*[13].

Pulmonary rehabilitation is a standard of care for patients with COPD [1, 13, 114]. Exercise training is a core-stone component of these comprehensive programs [1, 13, 114]. Many clinical trials have shown the beneficial effect of pulmonary rehabilitation programs on clinical outcomes [13, 115]. In 2007 Lacasse et al [116] in a meta-analysis of 31 randomized controlled trials demonstrated significant improvements in exercise and functional capacity, dyspnea and quality of life in COPD patients [116]. Furthermore, several studies reported significant reduction in hospitalization and other health care use, and improvement in cost-effectiveness [1, 13, 115]. In addition, reductions in depression and anxiety and improvements in cognitive function and self-efficacy have been also reported [115, 117].

5.1 Pulmonary rehabilitation in IPF patients

Exercise training at pulmonary rehabilitation program has not been studied extensively in IPF patients [10-14]. However, a growing body of evidence has shown encouraging results with some health benefits following participation in these programs. In the past few years several retrospective, prospective and randomized controlled trials have demonstrated significant improvements in some outcomes after short-term exercise programs among IPF patients [10-14].

Table 3 summarizes exercise-based pulmonary rehabilitation studies in patients with IPF.

Table 3. Exercise-based pulmonary rehabilitation studies in IPF patients.

Study	Number of IPF patients	Research mode	Pulmonary rehabilitation program	Type of exercise training	Outcomes
Jastrzebski 2006	13	Prospective	Twice weekly 4-week inpatient + 4 week home-based	Leg cycling and respiratory muscle training	Borg dyspnea scale and SGRQ
Holland 2008	34	RCT	Twice weekly 8-week outpatient	Walking +cycling and resistance training for lower body	6MWD and CRDQ
Nishiyama 2008	28	RCT	Twice weekly 10-week outpatient	Walking + cycling and resistance exercises for peripheral muscles	6MWD and SGRQ
Ferreira 2009	50	Retrospective	2-3 sessions a-week, 6-8 weeks outpatient	Walking +cycling, resistance and respiratory muscle training	6MWD +Borg dyspnea scale
Ozalevli 2010	17	Prospective	Daily home-based sessions 12-weeks	Walking, functional resistance training and breathing exercise	6MWD +MRC dyspnea scale
Swigris 2011	14	Prospective	2-3 sessions a-week, 6-8 weeks outpatient	Walking, cycling and resistance training	6MWD +FSS
Kozu 2011	65	Prospective	2 sessions a-week 8 weeks outpatients/ home-based	Leg cycling and strength training walking and resistance training	6MWD +SF-36
Rammaert 2011	13	Prospective	Daily home-based, 8-weeks	Leg cycling	Endurance time, steps per day and dyspnea.
Huppmann 2013	202	Retrospective	Inpatient 5 days/week, 4 weeks	Walking, cycling and resistance training	6MWD + SF-36
Arizono 2013	48	Prospective	2 sessions a week, outpatient, 10 weeks	Leg cycling, resistance training and respiratory muscle training	Endurance time, 6MWD, VO_{2peak}, Peak work rate, shuttle walk distance, strength
Ryerson 2014	22	Prospective	2 sessions a week, outpatient, 6-8 weeks	Walking, leg cycling and sitting eliptical	6MWD+SGRQ, dyspnea, depression and physical activity levels
Jackson 2014	21	RCT	2 sessions a week, outpatient, 12 weeks	Walking, leg cycling, resistance and flexibility	Endurance time, MIP

SGRQ; Saint George Respiratory Questionnaire, CRDQ; Chronic Respiratory Disease Questionnaire, 6MWD; 6 minute walk distance, MRC; Medical Research Council, FSS; Fatigue Severity Scale, SF-36; Short Form 36 quality of life questionnaire, VO_{2peak}; Peak oxygen consumption, MIP; maximal inspiratory pressure.

Jastrzebski et al [15] conducted a prospective study to examine the effect of a combined 4-week inpatient and 4-week home-based pulmonary rehabilitation program on dyspnea levels and quality of life in 13 IPF patients among 31 ILD patients. The inpatient exercise training program consisted of 30 min aerobic bicycle riding and respiratory muscle training on a daily basis. The home-based program included twice weekly aerobic and breathing exercises for 30 min. The results of the study showed a significant decline in the Borg dyspnea scale (-0.78 units) and a 5 unit decrease in the Saint George Respiratory Questionnaire following the pulmonary rehabilitation, suggesting an improvement in dyspnea and QOL [15].

A landmark randomized controlled study was conducted by Holland et al [26] on 34 IPF out of 57 ILD patients to examine the effect of an 8-week twice-weekly combined aerobic and functional resistance exercise training program as part of a pulmonary rehabilitation program on safety and efficacy. The group demonstrated a significant increase in 6MWD (35m), a decrease in dyspnea Medical Research Council (MRC) score (-0.7 units) and an improvement in QOL according to the Chronic Respiratory Disease Questionnaire (CRDQ). The authors concluded that exercise training is safe and efficient for IPF and ILD patients but the enhancements were not sustained at a 6 month follow-up [26].

Nishiyama et al [24] also conducted a randomized controlled trial to examine the effect of a 10-week twice-weekly pulmonary rehabilitation program on exercise capacity, dyspnea and QOL in 28 IPF patients. The program consisted of aerobic (walking on treadmill and bike cycling) and resistance exercises for peripheral muscles. The results showed significant improvements in 6MWD (46m) and QOL after completing the program, suggesting that pulmonary rehabilitation is effective for improving exercise capacity and QOL in IPF patients [24].

Ferreira et al [23] conducted a retrospective multi-central study with 50 IPF out of 99 ILD patients. The study addressed the effectiveness of pulmonary rehabilitation on functional status and dyspnea. The pulmonary rehabilitation program included 2-3 weekly sessions of aerobic, resistance and respiratory muscles training for 6-8 weeks.

The study showed significant improvements in 6MWD (56m) and Borg dyspnea (-1 unit) after the program, leading to the conclusion that pulmonary rehabilitation statistically and clinically improved functional status and dyspnea in ILD and IPF patients [23].

In a prospective study, Swigris et al [18] demonstrated the beneficial effect of 18 exercise sessions during 6-8 weeks of a standard pulmonary rehabilitation program in 14 IPF patients. The program included walking, cycling and resistance training 2-3 times a week. The results showed a significant increase in 6MWD (202 feet) and a decline in severity of fatigue scale (-1.5 points) compared to baseline measures [18].

Rammaert et al [19] tested the impact of an 8-week home-based walking pulmonary rehabilitation program on exercise capacity, symptoms and QOL in 13 IPF patients. The results showed improvements in endurance time and steps per day, dyspnea and physical limitations. The authors concluded that these programs are feasible and can significantly improve functional parameters [19].

Ozalevli et al [17] also conducted a prospective study aimed at examining the effect of a 12-week home-based pulmonary rehabilitation program in 17 IPF. The study showed significant improvement in 6MWD (40 m), MRC dyspnea scale (-0.9 points) and leg fatigue following the program [17].

Huppmann et al [22] retrospectively examined the effect of an inpatient pulmonary rehabilitation program on exercise capacity and QOL in 202 IPF of 402 ILD patients. The program consisted of 5 sessions/week walking, cycling and resistance training for 4 weeks. The authors demonstrated significant improvement in 6MWD (46m) and QOL following the participation in the program [22].

Kozu et al [16] prospectively examined the effect of an 8-week twice-weekly pulmonary rehabilitation program on exercise capacity and QOL among 65 IPF patients of different severity. The results showed that patients with high degree medical research council (MRC) dyspnea scale (4,5) had significant lower improvements compared to patients with MRC-2,3 following pulmonary

rehabilitation. The authors concluded that disease severity has a negative impact on the level of improvement following pulmonary rehabilitation program in IPF patients [16].

Arizono et al [21] conducted a prospective-controlled study with 48 IPF patients (24 in pulmonary rehabilitation group and 24 in the control group) who were admitted for a 10-week twice-weekly pulmonary rehabilitation program. The exercise program consisted of leg cycling, resistance training and respiratory training. The investigators showed significant differences between the groups and improvements in endurance time, 6MWD, shuttle walk distance and peak work-rate after the intervention. The authors concluded that endurance time is the most responsive exercise measurement following pulmonary rehabilitation among IPF [21].

Reyrson et al [20] prospectively examined the short-term and long-term effects of a 6-8 week pulmonary rehabilitation program in 22 IPF of 50 ILD patients. The results of the study immediately after the intervention demonstrated significant improvements in 6MWD (57.6 m), QOL, depression, dyspnea and physical activity levels. Moreover, the improvements were still significant at 6 months follow up for QOL, depression and physical activity [20].

Recently, Jackson et al [25] performed a pilot randomized controlled study of pulmonary rehabilitation with 21 (pulmonary rehabilitation group n=11, control group n=10) IPF patients. The exercise program consisted of 60-75 minutes, twice weekly aerobic, resistance and flexibility training sessions for 12 weeks. The study showed significant improvements only in endurance time on constant load cycle exercise test and maximal inspiratory pressure on pulmonary function test [25].

In overall, the existing literature demonstrates a beneficial effect of exercise-based pulmonary rehabilitation programs on exercise functional capacity (6MWD), symptoms and quality of life in IPF patients [15-26], although these studies have several limitations. The majority of studies conducted were based on short-term exercise training programs and were non-randomized and uncontrolled. Hence, a significant gap in the scientific knowledge exists regarding the cardiopulmonary and metabolic effects of exercise-based pulmonary rehabilitation in IPF. In addition, the

mechanisms underlying the improvements and the impact on IPF pathophysiology manifested in these studies are unknown, which makes it difficult to target exercise pulmonary rehabilitation treatments effectively for IPF patients. Moreover, the gold standard measurement of cardio-respiratory capacity (VO_{2peak}) was not tested in most of these studies and no long-term outcomes of exercise pulmonary rehabilitation on exacerbations and prognosis in IPF are available at the present.

6. Summary

Pulmonary diseases are increasingly important causes of morbidity and mortality in the modern world [1]. Chronic respiratory diseases account for 7% of worldwide mortality with approximately four million deaths annually and a significant global economic burden [3]. By definition pulmonary diseases affect the lungs, including their airways, blood vessels and parenchyma [2]. The common symptoms of pulmonary disease are shortness of breath, wheezing, cough, expectoration of sputum, chest pain or discomfort [2]. IPF is a chronic and progressive interstitial lung disease occurring primarily in older adults with a presence of pulmonary fibrosis or scarring of the lung parenchyma [7]. IPF's etiology is unknown, its clinical course is unpredictable and it usually has a poor prognosis [7]. IPF is considered a fatal lung disease with mean survival rates ranging from 2-5 years from the time of diagnosis [4-5, 7-8]. Estimates of IPF prevalence have varied from 2 to 29 cases per 100,000 in the general population [7]. To date, an effective treatment for IPF remains elusive [7]. Several risk factors are associated with IPF including smoking history, environmental exposures, microbial agents, gastroesophageal reflux and genetics and familial pulmonary fibrosis [7]. Patients with IPF have a significantly higher prevalence of other chronic conditions such as: pulmonary hypertension (32-84%) [7, 27-28] and lung cancer (7-fold increased risk) [103]. Five to ten percent of IPF patients annually experience acute exacerbation which causes significant deterioration of the disease or death [7]. IPF is characterized by progressive worsening of dyspnea and lung function, impaired gas exchange and ventilatory capacity, hypoxemia, exercise intolerance all of which have a negative impact on quality of life [7]. Pulmonary rehabilitation is an evidence-based standard of care for patients with chronic obstructive pulmonary diseases [1, 13, 114]. Exercise training plays a major role in these programs, since significant improvements have been reported in exercise and

functional capacities, level of dyspnea and quality of life [116]. A literature review of the effect of exercise pulmonary rehabilitation on IPF revealed some positive results with respect to exercise capacity, symptoms and quality of life outcomes, although strong evidence from randomized controlled trials are still warranted and the level of recommendations for this therapy in patients with IPF is weak at present [7, 10-14].

CHAPTER III

METHODS

METHODS

1. Patient recruitment and selection

A randomized controlled trial was conducted at the Rabin Medical Center, Beilinson Hospital, Petach Tikva, Israel. The study was approved by the local ethics committee (Approval number-6531) and was registered in Clinicaltrials.gov (NCT01499745). Patients were recruited by invitation and volunteered to take part in the study. Written informed consent was obtained from all patients prior to participation. Clinical assessment included medical history, risk factors for IPF and a physical examination for all participants.

Patients were included if they had been diagnosed with IPF according to accepted clinico-radiological criteria of the latest established guidelines of the American Thoracic Society and the European Respiratory Society [7].

Exclusion criteria were: severe co-morbid illnesses; unstable cardiac disease; any neurological or orthopedic contraindications for exercise training; need for oxygen supplementation >4 L/min at rest, exacerbations and participation in a pulmonary rehabilitation program in the 12 months prior to recruitment.

2. Study design

A study coordinator uninvolved in patient assessment or treatment performed randomization. Patients' names were drawn from an envelope containing all the patients' names, and randomly allocated to the exercise training (ET) or the control group envelope. The ET group participated in a 12-week, twice-weekly 60-minute supervised group exercise training program in addition to usual care in an outpatient pulmonary rehabilitation program, while the control group continued with usual care alone (an appointment with a Pulmonologist and medication) (Figure 3). Patients allocated to the control were allowed to participate in the exercise pulmonary rehabilitation program after the 12-week study period. At baseline and within one-week post intervention, all participants were assessed as described below:

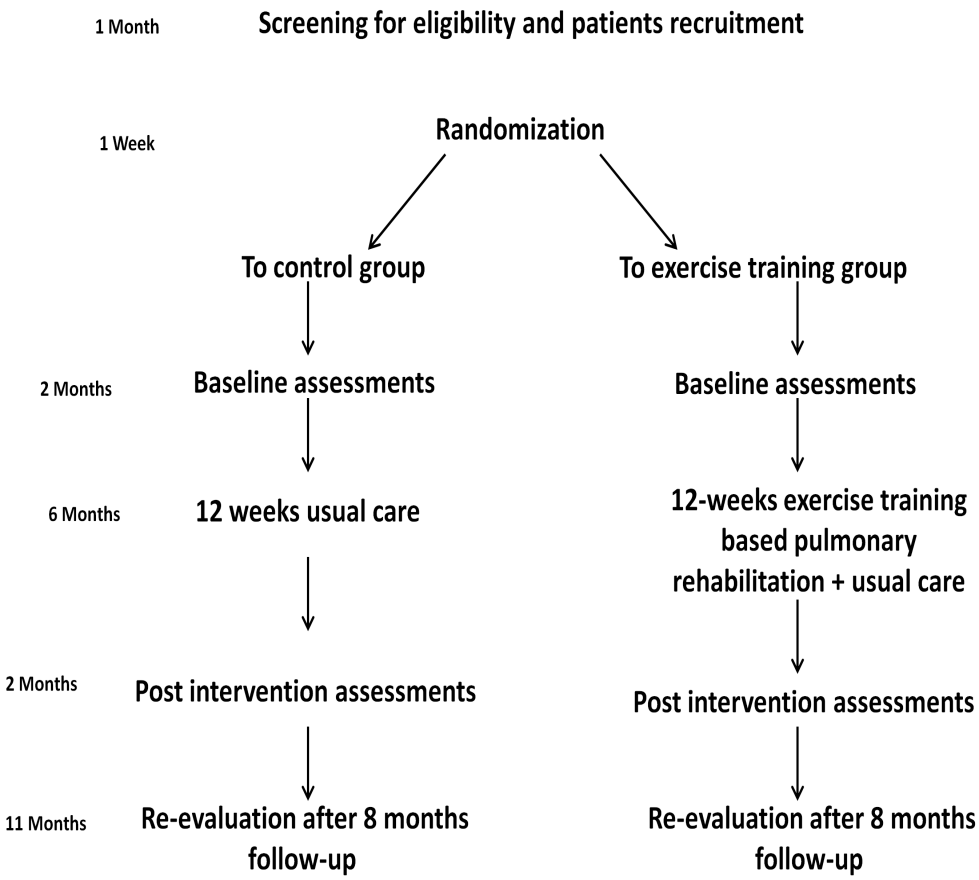


Figure 3. Flowchart describing study stages.

2.1 Socio-demographics, anthropometrics and body composition measures

Socio-demographics data was collected during the first visit and weight and height were measured for all patients. Body mass index (BMI) was calculated by dividing the patients' weight (kg) by their height squared (m^2). Body fat% was assessed using Lange skin-fold caliper (Beta technology, Santra Cruz, California). The sum of 4 measured anatomical cites (biceps, triceps, suprailiac and subscapular) was calculated and converted to % fat as previously proposed by Durnin and Womersley [118]. The average of three samples was taken from all 4 sites which were measured 1 cm below the finger grip on the right side of the body in relaxed standing position [118]. Waist circumference was measured by standard fiber glass centimeter. A duplicate horizontal measure of the abdominal obesity, 2.5 cm above the umbilicus in standing and abdomen in relaxed position was taken [42].

2.2 Blood collection and analysis of biomarkers

At rest venous blood samples were collected and serums were further analyzed for the determination of concentration levels of the following biomarkers with standard techniques: C-reactive protein (CRP) (Beckman Coulter Biomedical Ltd. Lismeham, Callagham Mills, Co. Clare Ireland, Olympus AU 2700 analyzer) [37], carbohydrate antigen (CA) 15-3 [29-30] and 19-9 [33], (Roche immunoassay Cobas E analyzer (Roche Diagnostics GmbH, Mannheim, Germany, Roche Hitachi Cobas 6000, 601E module). N-terminal pro-brain natriuretic peptide (NT-proBNP) [108] was assessed with a whole blood drop of 15 μL by Elecsys NT-proBNP assay, (Cardiac Reader, Roche, Germany).The cut-off levels for CA 15-3 and CA 19-9 were 0-30 U/mL and 0-37 U/mL, respectively [32].

2.3 Doppler-Echocardiography- left ventricle dimensions and diastolic and systolic function

Two-dimension echocardiography was performed at rest (Vivid 7 Dimension, General Electric, USA). Systolic pulmonary arterial pressure (sPAP) was estimated from the maximal tricuspid regurgitated jet velocity adding estimated right atrial pressure [119]. Pulmonary hypertension (PH) was defined as sPAP > 35 mm Hg. Mild to moderate PH was defined as sPAP between 35 and 50 mm Hg and severe PH as sPAP > 50 mm Hg [92]. Left ventricular dimensions and function were determined using standard techniques [120]. Measurements included left atrium diameter and area, left ventricle posterior wall and intra-ventricular septum wall thickness, left ventricle end-systolic and end-diastolic diameter indices, stroke volume, cardiac output, cardiac index, ejection fraction, fractioning shortening, earlier transmitral velocity (E), late transmitaral velocity (A), E/A ratio, isovolumic relaxation time, deceleration time, systolic pulmonary arterial pressure (sPAP).

2.4 Pulmonary function tests (PFT)

PFT including spirometry and total lung capacity (TLC), maximal voluntary ventilation (MVV) and diffusion capacity for carbon monoxide (DLCO) were performed by experienced respiratory technicians who were blinded to study allocation, according standard techniques and ATS/ERS guidelines (Zan 530 Oberthulba, Germany) [121-124]. All the measured parameters were presented as

percent of predicted (% predicted) values of the European Community for Coal and Steel [125].

2.5 Cardiopulmonary exercise test (CPET)

CPET was performed according to established guidelines [41-44]. All tests were supervised by a physician, and were held between 8:30 am and 12:30 pm. Patients were instructed to take their usual medications as prescribed. A 10-15watts/min ramp protocol was performed on an electromagnetically braked cycle ergo-meter (Ergoline-800S) to the patient's maximal subjective exertion level and respiratory exchange ratio (RER≥1.1) [41]. During the test, 12-lead electrocardiogram, blood pressure, pulse oximetry (SpO_2) and breath-by-breath respiratory gas exchange were recorded and monitored (ZAN 600, Oberthulba, Germany). Patients were tested without supplemental oxygen during the test, and oxygen was provided immediately after the CPET as needed. All peak cardio-pulmonary data were calculated and analyzed based on average of the last 30 seconds of the test. The anaerobic threshold (AT) was determined by the dual methods approach, using the V-slope method combining ventilatory equivalents (V_E/VO_2 and V_E/VCO_2) [41]. Breathing reserve was calculated in absolute values and expressed also in percentages of MVV [41]. Predicted values of peak oxygen consumption ($VO_{2\ peak}$) and peak work rate (WR) were determined according to Jones et al. [126] based on prospective data of 100 subjects (50 males and 50 females) from the general population aged 15-71 [126].

2.6 6-minute walk test (6MWT)

Participants were given 30 minutes of rest after CPET before performing the 6MWT in a 35-meter corridor at the pulmonary unit within the hospital. The 6MWT was set according to ATS guidelines [39], prior and immediately post, perceived exertion Borg category ratio (CR) 10 dyspnea scale [39] (see in Appendix), heart rate and SpO_2% (Pulse Oximeter 2500 30 EM, Nonim Medical Minneapolis MN, USA) were obtained. The minimal clinical important difference (MCID) was set at 25 m based on previously published data by du Bois et al [127].

2.7 Senior fitness tests (SFT)

At least 20 minutes of rest were allowed after completing the 6MWT and before performing a battery of tests according to the "senior fitness tests" guidelines [128].

30-second chair-stand test- for leg strength evaluation: The subject was encouraged to complete as many full stands as possible from the sitting position on the (43 cm height) chair within the 30 seconds of test duration [128].

8-foot-up-and –go- for agility and mobility evaluation: The test began with the participant fully seated in the chair (43 cm height), hands on thighs and feet flat on the floor. On the signal "go" the subject got up from the chair, walked as quickly as possible around a cone (placed 8 feet/2.40 m from the chair) and returned to a seated position on the chair. Scoring of the performance was the time in seconds for completing the task [128].

Chair sit-and- reach- for lower body flexibility: Starting position is sitting on the front edge of the chair, left leg bent at the knee joint with foot flat on the floor and the right leg straight and extended in front of the hip with heel on the floor and foot flexed (at approximately 90^{o}). The subject slowly bends forward at the hip joint sliding the hands with middle finger on the ruler (20 inch) in an attempt to touch the toes for 2 sec in the extended leg. The score was recorded by the number of inches reached before (minus score) or behind the toes (plus score). The middle of the toes at the end of the shoe represents a zero score [128].

Back stretch- for upper body flexibility: In standing position, the patients placed the preferred hand behind the head and the other hand behind the back, trying to reach up as far as possible in an attempt to touch or overlap the extended middle fingers of both hands. The distance between the fingers was measured with ruler and scored for upper body flexibility[128].

2.8 Quality of life, dyspnea and physical activity levels

At baseline, after 12-week intervention and after 8 months post intervention, prior to the exercise examinations all patients completed the following questionnaires: The

mMRC dyspnea scale, is a simple grading system from 0-4 to assess a patient's level of breathlessness. Grade=0 means feeling breathless only with strenuous exercise, while grade=4 indicates breathlessness when leaving the house (see example in Appendix) [129-130]. In addition, a validated Saint George's Respiratory Questionnaire (SGRQ) for IPF was also completed for quality of life evaluation [131-133]. SGRQ is an instrument designed to measure the impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease. Recently, it was also validated for assessment of QOL in IPF patients (see example in Appendix) [131-133]. The questionnaire contains 50 items divided into three domains ("symptoms", "impact" and "activity") and the total score ranges from 100 (the most disabled condition and the value of QOL) to 0 (no limitations with best QOL) [133]. Each item in the questionnaire is scored according to the severity and prevalence of discomfort, and an overall score as well as scores for each domain are calculated [133]. For IPF, changes of 5-8 points in the SGRQ were proposed to indicate differences of minimal clinical importance [131-132]. Physical activity levels were assessed by the self-report 7-day short form International Physical Activity Questionnaire (IPAQ) (see example in Appendix) [134-135]. IPAQ has been accepted as a reliable and validated tool for measuring physical activity in many settings, in different languages and countries around the world, especially in repeated measures settings for observing changes [135-136]. The questionnaire comprises 9 items to assess the amount of physical activity at moderate and vigorous intensities, walking time and sitting time. The score of overall physical activity is calculated in MET-minutes/week units of the sum of each mode of activity multiplied by the constant level of energy (metabolic equivalent task=MET) required for the task by number of minutes performed per day and by the number of time performed per week [135-136].

3. Exercise-training at outpatient pulmonary rehabilitation

The program was conducted according proposed recommendations for respiratory disease patients [1, 13, 42, 114, 137] with twice-weekly 60-minute group exercise sessions in the pulmonary unit. The exercise sessions were instructed by a clinical exercise physiologist, a physiotherapist and supervised by a respiratory nurse and study physician.

The exercise-training program consisted of two progressive 6-week blocks (Table 4). In the first block participants exercised using interval training methods with increasing duration of work to rest ratio. Each session started with 5-8 minutes of warm-up exercises (calisthenics), short active stretching and deep breathing exercises for thoracic expansion. The main part of the exercise session contained 30 minutes of aerobic interval training (treadmill walking, leg-cycling and step climbing). The program began with bouts of 5 minutes duration followed by 1 minute of passive rest (interval). The progression of the training program included adding 1 minute to each bout duration in each session, until reaching 15 minutes of continuous exercise. Exercise intensity in the first block for cycling was set at 50-60% of peak work-rate achieved during the CPET, and 70-80% of individual average walking speed measured during the 6MWT. In addition, during the first sessions the workload was adjusted individually on 3-5 dyspnea and exertion levels using the Borg CR 10 scale (see in Appendix) [42]. Furthermore, a specific bout of self-paced walking for 5-8 minutes in a 35 m corridor within the pulmonary unit was conducted in each session for functional transfer adaptation. Ten minutes of resistance training with dumbbells and body weight for upper and lower body were also included. One set of 12-15 repetitions at moderate intensity (3-5 on Borg CR 10 scale) with 1 minute of rest between the sets for 4-6 exercises (wall push-ups, chair squat, dumbbell shoulder press, dumbbell bicep curls, dumbbell arm extension and abdominal curl-ups) was performed. In addition, 5 minutes of flexibility training was conducted at the end of each session. One set of 4-5 stretching exercises for 15-30 seconds (one-leg seated hamstring stretch, standing quadriceps stretch, chest stretch, overhead reach stretch and wall cat stretch) were performed [42].

In the second block the duration of the exercise bouts was maintained and further increased up to 20 minutes of continuous aerobic endurance training. Intensity was increased up to 60-70% of peak work-rate in cycling and 80-90% of individual average walking speed for treadmill walking and corridor walking. Stair climbing for 3-5 minutes within the hospital was added to each session. In addition, resistance and flexibility training were maintained and overall load was increased. Two sets of 10-12 repetitions with 45 seconds rest between the sets for resistance and 2 sets of 15-30

seconds for stretching exercises at Borg 4-6 perceived exertion level were conducted [42].

During all exercise sessions patients were monitored for blood pressure, oxygen saturation by pulse oximeter (SpO2), heart-rate and symptoms. Oxygen supplement was provided for patients who requested or desaturated (SpO2<88%) during exercise. Patients were also educated for symptoms management and encouraged to increase their physical activity levels out of the program on other days of the week.

Table 4 Exercise training program.

Phase	Type		Intensity		Duration
1st 6-Week Block ***2 Sessions/Week***	*Aerobic- Interval* Treadmill and Corridor Walking, Leg Cycling	*Resistance and Flexibility* 1 Set of 4-6 Exercises for Major Muscle Groups 10-15 Repetitions (Dumbbells and Body-Weight)	*Aerobic- Interval* Cycling: 50-60% of Peak Work-Rate. Walking: 70-80% of Individual Average Waking Speed Borg Scale 3-5	*Resistance* and Flexibility Moderate Borg scale 3-5	*60 minutes* *5-8 Min Warm-Up* 30 Min Aerobic Training Bouts of 5-15 min Work Following 1 Min Rest Interval. 6-8 Min Corridor Walking 10 Minutes Resistance Training and Flexibility
2nd 6-Week Block ***2 Sessions/Week***	*Aerobic- Interval Endurance* Treadmill and Corridor Walking, Leg Cycling, Stair Climbing	*Resistance* and Flexibility 2 Sets of 4-6 Exercises for Major Muscle Groups with 10-15 Repetitions (Dumbbells and Body-Weight)	*Aerobic- Interval Endurance* Cycling: 60-70% of Peak Work-Rate. Walking: 80-90% of Individual Average Waking Speed Borg Scale 4-6	*Resistance* and Flexibility Moderate Borg scale 4-6	*60 minutes* *5-8 Min Warm-Up* 30 Min Aerobic Training Bouts of 15-20 min Work Following 1 Min Rest Interval. 6-8 Min Corridor Walking 10-15 Minutes Resistance Training and Flexibility

4. Follow-up

Patients from both groups were re-evaluated at 11 months time point (8 months from completion of the 12-week intervention). Pulmonary function test, cardiopulmonary exercise test, 6MWT, 30-sec chair stand test, blood biomarkers, anthropometrics and body composition, mMRC, SGRQ and IPAQ were assessed. In addition, follow up for hospitalizations, exacerbations and mortality for 15 months after the end of 12-week intervention was conducted.

5. Primary and secondary outcomes

Primary outcomes were changes in exercise tolerance: VO_{2peak}, peak work-rate, anaerobic threshold and 6MWD. Secondary outcomes were change in pulmonary and ventilatory functions, echocardiography, anthropometrics, CPET parameters, mMRC, physical activity levels (IPAQ), senior fitness tests, blood biomarkers and SGRQ.

6. Statistical analysis

All clinical and physiological parameters were presented as mean ± SD (standard deviations). Patients' baseline characteristics, all primary and secondary parameters, delta changes from baseline (Δ= post-pre intervention) and delta changes from post 12-week to follow up (ΔΔ= follow up-post intervention) were compared between the ET and control group by two independent samples, *t*-test and χ^2 test for non-parametric variables. In addition, comparison between the follow up and baseline results for each group was performed by paired *t*-test. Exploratory data analysis using stepwise linear multiple regression was performed for deltas between primary and secondary outcomes in the ET group and Pearson correlation was calculated between selected parameters. Furthermore, intervariability observation in the ET group was performed to define the responsiveness to exercise pulmonary rehabilitation program within patients. Responders were defined as patients who reached the criteria of improvement above the minimal clinical important difference for Δ6MWD (>25m), ΔSGRQ (> -5 points). Cox regression analysis was performed to determine survival rates in the cohort, and χ^2 test for comparison of exacerbations and hospitalizations

between the groups. Statistics were analyzed using SPSS v.17 software. Significance level was set at $p < 0.05$.

6.1 Power analysis

Only one randomized control study that assessed the effect of exercise training in ILD and IPF patients calculated a sample size according to the 6MWD [26]. However, the minimal clinical important difference (MCID) for 6MWD ranged from 24-45 m with a large distribution (standard deviation 108-139 m) among IPF patients [24, 26, 127]. Moreover, our group previously showed a significant mean difference between the exercise and control groups in VO_{2peak} and 6MWD (1.6 mL/kg/min and 58 m respectively) after an exercise training program in pulmonary hypertension patients, suggesting that it was clinically significant [138]. Peak oxygen consumption is a highly accurate, valid and reliable measure and is considered a gold-standard assessment for cardio-respiratory capacity [43-44]. In addition, VO_{2peak} usually distributes with low range numbers as was demonstrated by our group [138].

In the present work we performed a power analysis to calculate the sample size with 95% probability and 80% power for detecting mean difference ≥ 2 mL/kg/min in one primary outcome ($VO_{2\ peak}$) between the groups and time effect. The analysis revealed that a total of 28 participants (14 in each group) was needed [139].

CHAPTER IV

RESULTS

RESULTS

1. Patients' characteristics

Between January 2012 and November 2013 the study was conducted in the Pulmonary Institute. Thirty eight IPF patients were screened and 34 were recruited and randomly assigned to ET group (n=16) or control group (n=18) (Figure 4). During the 12-week intervention, one patient in the ET group dropped out due to an acute exacerbation. In the control group, one patient withdrew consent. Thirty-two patients completed the study with baseline and post measurements. All patients in ET group completed at least 75% (18 sessions) of the exercise program (mean 22.5±2.2 sessions) with overall adherence rate of 90%.

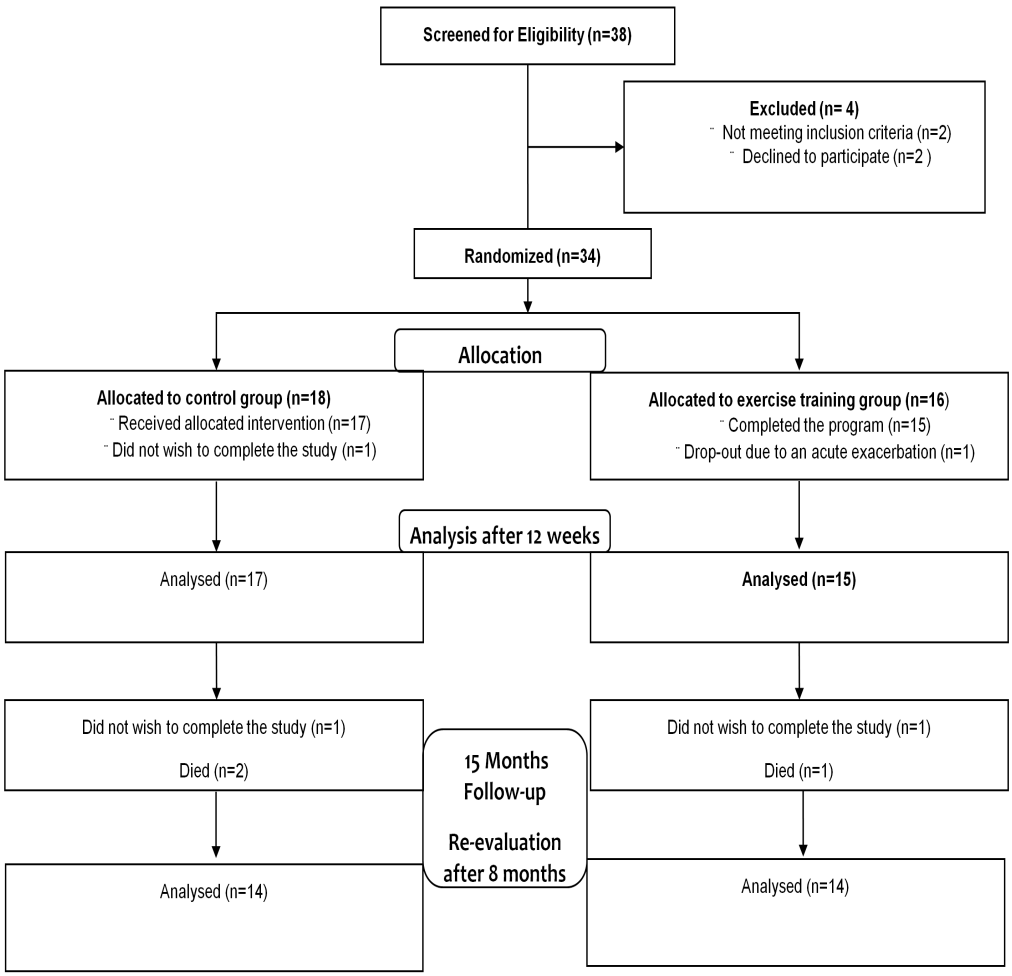


Figure 4. Study design flowchart.

No serious adverse events were observed during the exercise sessions. Patients attended twice weekly group exercise training sessions for 12 weeks at the hospital pulmonary unit. Five patients from the ET group were oxygen supplemented (2-4 L/min) during the sessions. Baseline characteristics and clinical and physiological data of the ET (n=15) and the control groups (n=17) are shown in Tables 5-16. At baseline there were no differences between groups in terms of characteristics (age, sex, and supplemental oxygen use), co-morbidities, physiological and clinical parameters and medication. All patients were hemodynamically stable with near-normal resting SpO_2 values. In addition, no changes were made in medication during the study period.

Table 5 Baseline characteristics of study population (n=32).

	Control group (n=17)	ET group (n=15)	p -value
Age (yr)	66±9	68.8±6	.337
Male/Female (n/%)	11/6 (65/35%)	10/5 (67/33%)	.907
Time from diagnosis of IPF (yr)	1.9±3.1	3±3.7	.379
Patients with smoking history (n/%)	9 (53%)	10 (67%)	.430
Supplemental oxygen users			
Rest (n/%)	1(6%)	2 (13%)	.471
Exertion (n/%)	4 (24%)	5 (33%)	.538
***Co-morbidities* (n/%)**			
Pulmonary hypertension according to echocardiography	6(35%)	5(33%)	.907
CAD	6(35%)	7(47%)	.513
Systemic hypertension	11(65%)	12(80%)	.337
COPD (Emphysema)	5(29%)	2(13%)	.272
Diabetes mellitus	4(24%)	7(47%)	.169
Osteoporosis	3(18%)	2(13%)	.093
***Medications* (n/%)**			
Steroidal therapy	13(77%)	9(60%)	.316

ET; exercise training. n/%; absolute number of patients and % of the group, CAD; coronary artery disease, COPD; chronic obstructive pulmonary disease.

At baseline most patients presented normal hemodynamic values and oxygen saturation. No significant differences were detected between the exercise training and control groups (Table 6).

Table 6 Baseline resting hemodynamics and oxygen saturation of study population (n=32).

	Control group (n=17)	ET group (n=15)	p -value
Resting hemodynamics and oxygen saturation			
HR (beat/min)	70.4±15	74.8±12	.373
SBP (mmHg)	112.8±17.5	113.4±13.7	.911
DBP (mmHg)	78.3±10.6	70.7±11	.054
SpO_2 (%)	97.1±1.7	96.5±2.3	.419

ET; exercise training. HR; heart rate, SBP; systolic blood pressure, DBP; diastolic blood pressure, SpO_2; oxygen saturation by pulse oximeter.

After the intervention there were no significant differences in resting hemodynamics and SpO_2 in our patients, although a trend of decrease in resting heart rate was observed among the ET group and of increase in the controls (Table 7).

Table 7 Mean changes from baseline to 12-week (raw differences) and mean differences of changes between the ET and the control groups in resting hemodynamics and oxygen saturation in IPF patients.

	Control group (n=17)	ET group (n=15)	Mean difference (CI 95%)	p-value
Resting hemodynamics and oxygen suturation				
ΔHR (beat/min)	4.4±10	-2.4±9.1	-6.8 (-13.8- -0.16)	.055
ΔSBP (mmHg)	-1.3±19.2	-2.9±13.6	-1.6 (-13.9-10.6)	.786
ΔDBP (mmHg)	1±14.4	1.5±7.1	0.5 (-7.8-8.9)	.897
ΔSpO_2 (%)	-0.9±1.6	0.13±1.7	1 (-0.17-2.2)	.092

Values presented as means ± SD. CI; confidence interval. ET; exercise training. * Significant differences between the groups; $p< 0.05$. ** Significant differences between the groups; $p< 0.001$. HR; heart rate, SBP; systolic blood pressure, DBP; diastolic blood pressure, SpO_2; oxygen saturation by pulse oximeter.

2. Anthropometrics and body composition

At baseline, most our patients showed overweight conditions according to BMI category with high percentage of body fat (33%±6, 61%±18 of predicted). There were no differences between the ET and the control groups in body composition, weight, BMI and waist circumference prior to the program (Table 8).

Table 8 Baseline anthropometrics and body composition of study population (n=32).

	Control group (n=17)	ET group (n=15)	p -value
Anthropometrics			
BMI (index)	28.8±3.8	28.3±3.5	.686
Weight (kg)	81.8±16.6	77.4±12.8	.251
Fat (%)	33.4±5.3	33.4±6.9	.172
Waist circumference (cm)	102.4±13.9	103.7±10.6	.269

ET; exercise training. BMI; body mass index.

Following the 12-week intervention significant mean differences were observed between the groups in weight, body fat% and waist circumference (Table 9). The ET group decreased and the control group increased values in these parameters.

Table 9 Mean changes from baseline to 12-week (raw differences) and mean differences of changes between the ET and the control groups in anthropometrics and body composition in IPF patients.

	Control group (n=17)	ET group (n=15)	Mean difference (CI 95%)	p-value
Anthropometrics				
ΔBMI (index)	0.4±0.9	-0.3±1.1	-0.7(-1.4-0.5)	.065
ΔWeight (kg)	0.9±2.4	-1±2.7	-2(-3.8 - -0.1)	.037*
ΔFat (%)	0.8±2.2	-1.9±1.3	-2.7(-4 - -1.3)	<.001**
ΔWaist circumference (cm)	1.6±4.1	-2.7±3.4	-4.4(-7.1- -1.6)	.003*

Values presented as means ± SD. *Significant difference between the groups, $p<0.05$, ** Significant differences between the groups; $p< 0.001$, ET; exercise training.

3. Blood biomarkers

There were no differences between the groups at the beginning of the study in blood biomarkers except for CA 15-3. Patients from both groups presented mildly elevated NT-proBNP and CA 15-3 levels with increased level of CRP only in the ET group (Table 10).

Table 10 Baseline blood biomarkers of study population (n=32).

	Control group (n=17)	ET group (n=15)	p -value
Blood biomarkers			
CA 15-3 (U/ml)	49.9±22.4	72.8±40.4	.019*
CA 19-9 (U/ml)	35±38.1	17.8±33.8	.287
CRP (mg/dL)	0.5±0.6	1.1±2.4	.118
NT-proBNP (pg/ml)	167±101	165±134	.225

Values presented as means ± SD. *Significant difference between the groups, p<0.05. ET; exercise training. CA; carbohydrate antigen, CRP; c- reactive protein, N-terminal pro-brain natriuretic peptide.

Following the 12-week intervention CA 15-3 and CRP showed a trend of decline but did not reach statistical significance (Table 11). Other biomarkers did not change in both groups after the intervention.

Table 11 Mean changes from baseline to 12-week (raw differences) and mean differences of changes between the ET and the control groups in blood biomarkers in IPF patients.

	Control group (n=17)	ET group (n=15)	Mean difference (CI 95%)	p-value
Blood biomarkers				
ΔCA 15-3 (U/ml)	-0.7±18.8	-14±21.9	-13.3(-28-1.7)	.080
ΔCA 19-9 (U/ml)	10.8±34.8	-0.4±3.1	-11.2(-29.7-7.3)	.226
ΔCRP (mg/dL)	0.71±2	-0.73±2.4	-1.4(-3-1.2)	.083
ΔNT-proBNP (pg/ml)	-165±541	15±129	-150(-444-144)	.304

Values presented as means ± SD. CI; confidence interval. ET; exercise training. * Significant differences between the groups; p< 0.05. ** Significant differences between the groups; p< 0.001. CA; carbohydrate antigen, CRP; c- reactive protein, N-terminal pro-brain natriuretic peptide.

4. Doppler-Echocardiography-left ventricle dimensions and diastolic and systolic function

In most patients baseline echocardiography demonstrated mild hypertrophy of the left ventricle posterior wall and intra-ventricular septum thickness, normal systolic function and grade-1 impairment of diastolic function (Table 12). Most patients presented normal systolic pulmonary arterial pressure. Mild to moderate pulmonary hypertension was detected in 5 patients from the ET group and 5 patients from the control group. Severe pulmonary hypertension was observed in one patient from the control group. There were no differences between the groups in all echocardiographic parameters at the beginning of the study.

Table 12 Baseline Doppler-Echocardiography measures.

	Control group (n=17)	ET group (n=15)	p- value
Left ventricle size and geometry			
Left atrium diameter (mm)	3.6±0.5	3.7±0.3	.105
Left atrium area (mm^2)	20.4±3.9	18.6±4	.881
Left ventricle posterior wall thickness (cm)	1±0.1	1±0.1	.158
Intra-ventricular septum thickness (cm)	1.1±0.2	1.1±0.1	.744
Left ventricle end diastolic diameter index (cm/m^2)	2.3±0.2	2.4±0.2	.347
Left ventricle end systolic diameter index (cm/m^2)	1.5±0.2	1.5±0.3	.546
Left ventricle systolic functions			
Stroke volume (ml/beat)	78.7±16.6	68.4±13.6	.255
Cardiac output (L/min)	5.1±0.9	4.8±0.8	.382
Cardiac index ($L/min/m^2$)	2.6±0.5	2.5±0.4	.478
Ejection fraction (%)	58.7±3.4	58.9±4.4	.875
Fractioning shortening (%)	35.7±5.8	38±7.4	.194
Left ventricle diastolic functions			
Earlier transmitral velocity (E) (ms)	66.3±22.9	66.3±16.2	.393
Late transmitaral velocity (A) (ms)	77.2±25.8	76.2±13.7	.148
E/A ratio	0.9±0.4	0.9±0.2	.241
Isovolumic relaxation time (ms)	86.5±25.4	90.7±33.6	.924
Deceleration time (ms)	167.9±74.2	162.2±45.9	.244
Pulmonary pressure			
Systolic pulmonary arterial pressure (mmHg)	32.4±9.2	32.5±7	.994

Values presented as means ± SD, ET; exercise training.

After the intervention small but significant changes were found in end diastolic diameter index and septum thickness, without changes in other echocardiography variables in both groups of the study (Table 13).

Table 13 Mean changes from baseline to 12-week (raw differences) and mean differences of changes between the ET and the control groups in Doppler-echocardiography parameters in IPF patients.

	Control group (n=17)	ET group (n=15)	Mean difference (CI 95%)	p-value
Left ventricle size and geometry				
ΔLeft atrium diameter (mm)	0.2±0.5	0.02±0.5	-0.2(-0.5-0.2)	.307
ΔLeft atrium area (mm^2)	-0.2±4.6	0.2±2.7	0.4(-2.6-3.3)	.809
ΔLeft ventricle posterior wall thickness (cm)	-0.03±0.1	0.03±0.1	0.06(-0.04 - -0.2)	.240
ΔIntra-ventricular septum thickness (cm)	-0.03±0.1	0.06±0.1	0.1(0 -0.2)	.042*
ΔLeft ventricle end diastolic diameter index (cm/m^2)	0.07±0.2	-0.14±0.3	-0.2 (-0.4- -0.02)	.032*
ΔLeft ventricle end systolic diameter (cm/m^2)	0.03±0.2	-0.12±0.3	-0.16 (-0.3- 0.2)	.087
Left ventricle systolic functions				
ΔStroke volume (ml/beat)	-3.9±14.4	-4.5±13.4	-0.7 (-11.2-9.9)	.900
ΔCardiac output (L/min)	0±0.65	-0.4±0.8	-0.4(-0.9-0.2)	.167
ΔCardiac index ($L/min/m^2$)	-0.01±0.3	-0.2±0.4	-0.2 (-0.4-0.1)	.261
ΔEjection fraction (%)	-0.2±4.2	0.8±3	1 (-0.9-3)	.280
ΔFractioning shortening (%)	1.1±6.2	0.9±6.2	-0.1 (-4.6-4.4)	.957
Left ventricle diastolic functions				
ΔEarlier transmitral velocity (E) (ms)	-1.8±21.2	0.8±16.9	2.6 (-12.2-17.5)	.719
ΔLate transmitaral velocity (A) (ms)	-1.7±28.2	5.1±20.7	6.8 (-12.4-26.1)	.473
ΔE/A ratio	0.1±0.9	0±0.4	-0.1 (-0.6-0.4)	.643
ΔIsovolumic relaxation time (ms)	-4.3±32	9.1±32.1	13.4 (-12.2-38.9)	.292
ΔDeceleration time (ms)	16.7±72.4	11±52.7	-5.7(-55-43.6)	.815
Pulmonary pressure				
ΔSystolic pulmonary arterial pressure (mmHg)	-0.3±5.1	-0.5±6.8	-0.2(-4.8-4.3)	.919

Values presented as means ± SD. CI; confidence interval. ET; exercise training.* Significant differences between the groups; $p< 0.05$.

5. Pulmonary function tests

Patients in both groups demonstrated a moderate pulmonary restrictive pattern with moderate to severe diffusion impairments. No differences were observed at baseline between the groups in all lung function parameters (Table 14).

Table 14 Baseline pulmonary function test of study population (n=32).

	Control group (n=17)	ET group (n=15)	p -value
Pulmonary function test			
FVC %predicted	70.1±17.4	66.1±14.8	.487
FEV_1 % predicted.	71.8±20.1	68.5±15.8	.607
FEV_1/ FVC % predicted	107.5±11.4	109.3±10.5	.635
TLC % predicted	68.5±14	64.3±13	.231
DLCO % predicted	53.2±12.2	48.6±17.2	.393
MVV (L/min)	78.9±28.6	69.8±18.3	.301

Values presented as means ± SD, FVC; forced vital capacity, FEV_1; forced expiratory volume in 1 sec, TLC; total lung capacity DLCO; diffusion capacity for carbon monoxide, MVV; maximal voluntary ventilation.

Following the intervention significant mean differences between the groups was observed in FVC% predicted; p=0.038 and MVV; p=0.003 (Table 15).

Table 15 Mean changes from baseline to 12-week (raw differences) and mean differences of changes between the ET and the control groups in pulmonary function among IPF patients.

	Control group (n=17)	ET group (n=15)	Mean difference (CI 95%)	p-value
Pulmonary function test				
ΔFVC %predicted	-3±7.6	3±8.4	6 (0.35-11.9)	.038*
ΔFEV_1 %predicted	-0.9±11.5	6.3±11.3	7.2 (-1-15.5)	.085
ΔFEV_1/ FVC %predicted	0.12±6	0.66±6.1	0.55 (-3.8-4.9)	.799
ΔTLC %predicted	-0.2±83	2.4±10	2.6 ((-4.1-9.3)	.439
ΔDLCO %predicted	-1.5±10.6	-0.1±6.8	1.38 (-5.3-8.1)	.676
ΔMVV (L/min)	-6±11.5	8.2±13.9	14.2 (5-23.4)	.003*

Values presented as means ± SD. CI; confidence interval. ET; exercise training. * Significant differences between the groups; $p< 0.05$. ** Significant differences between the groups; $p< 0.001$. FVC; forced vital capacity, FEV_1; forced expiratory volume in 1 sec, TLC; total lung capacity DLCO; diffusion capacity for carbon monoxide, MVV; maximal voluntary ventilation.

6. Cardiopulmonary exercise test

Baseline exercise tolerance was moderately reduced with a marked desaturation during peak exercise in both groups of patients. Most patients demonstrated inefficient breathing pattern with normal breathing reserve. All cardiopulmonary data showed no differences between the groups at the beginning of the study (Table 16).

Table 16 Baseline cardiopulmonary exercise test parameters.

	Control group (n=17)	ET group (n=15)	p-value
Peak VT (L/breath)	1.37±0.6	1.16±0.4	.233
Peak Bf (breath/min)	39.8±8	37.9±6.6	.473
V_E peak (L/min)	50.5±15.9	42.5±13	.136
BR (MVV- V_E peak) (L)	28.4±20.4	27.3±12.6	.853
BR% (V_E peak/MVV)	67.2±17.8	61.9±13.6	.353
Peak WR (watts/min)	83.7±33.1	71.5±27.9	.265
Peak WR %predicted	59.7±17.5	53.7±19.9	.348
VO_2 Peak (mL/kg/min)	14.3±3.1	13.6±3.4	.539
VO_2 Peak %predicted	62.3±15.4	61±16.2	.815
AT (mL/kg/min)	10.9±2.1	9.7±2.2	.127
AT % predicted peak VO_2	45.9±14.9	44.6±13.1	.793
Peak O_2 pulse (ml/beat)	10.7±3.4	9.1±2.8	.181
Peak V_E/VO_2 (ratio)	41±7.9	37.7±9.5	.294
Peak V_E/VCO_2 (ratio)	34.9±6.3	33.9±6.1	.637
Peak VD/VT (%)	33.2±3.6	34.5±3.8	.334
Peak HR (beat/min)	113.2±22.8	117.5±20.1	.573
Peak SBP (mmHg)	157.4±30.5	155.3±31.2	.854
Peak DBP(mmHg)	77.9±17.7	74.9±11.4	.585
Peak SpO_2 (%)	91.2±5.2	88.7±6.4	.231

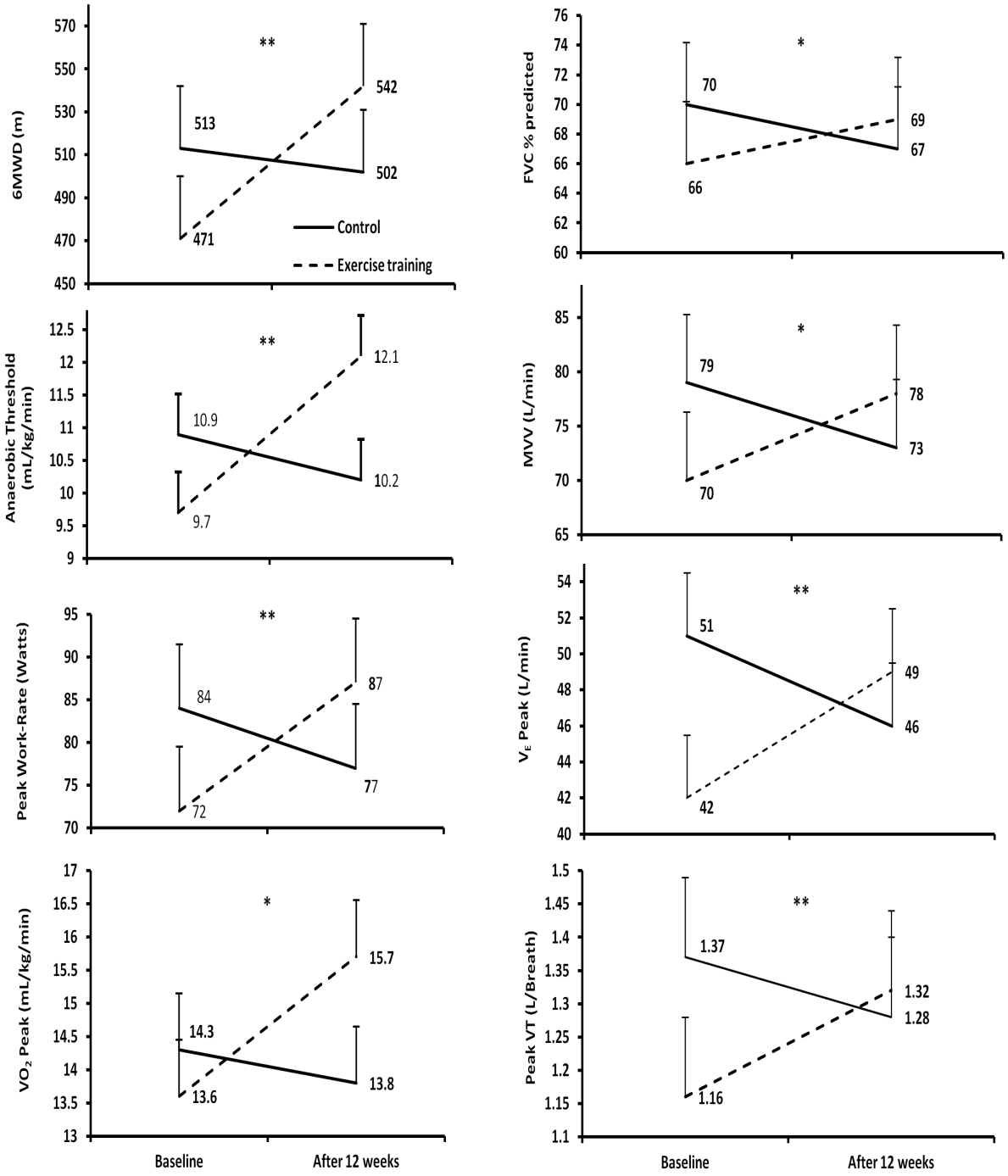
Values presented as means ± SD. ET; exercise training. VT; tidal volume, Bf; breathing frequency, V_E; minute ventilation, MVV; maximal voluntary ventilation, BR; breathing reserve, WR; work rate, VO_2 peak: peak oxygen consumption, AT; anaerobic threshold, V_E/VO_2; ventilatory equivalent for oxygen consumption, V_E/VCO_2; ventilatory equivalent for carbon dioxide, VD/VT; dead space to tidal volume ratio, HR; heart rate, SBP; systolic blood pressure, DBP; diastolic blood pressure, SpO_2; oxygen saturation by pulse oximeter.

After the intervention significant mean differences were observed in ΔVO_{2peak}: 2.6 mL/kg/min, p=0.002; Δpeak work-rate: 22.1 watts, p<0.001; Δanaerobic threshold: 3.1 mL/kg/min p<0.001, Δpeak minute ventilation: 11.6 L/min, p<0.001; Δpeak tidal volume (VT): 0.25 L/breath, p<0.001 and O_2 pulse: 1.1 ml/beat, p=0.028 (Table 17, Figure 5). Patients in the ET group improved significantly their exercise capacity and ventilatory response to exercise, whereas the control group deteriorated.

Table 17 Mean changes from baseline to 12-week (raw differences) and mean differences of changes between the ET and the control groups in exercise cardiopulmonary parameters among IPF patients.

	Control group (n=17)	ET group (n=15)	Mean difference (CI 95%)	p-value
ΔPeak VT (L/breath)	-0.94±0.1	0.16±0.2	0.25 (0.13-0.37)	<.001**
ΔPeak Bf (breath/min)	0.35±5.9	1.4±6.2	1 (-3.3-5.4)	.629
ΔV_E peak (L/min)	-4.5±6.7	7±6.9	11.6 (6.7-16.5)	<.001**
ΔBR (MVV- V_E peak) (L)	-1.4±11.8	1.2±14.7	2.6 (-6.9-12.2)	.580
ΔBR% (V_E peak/MVV)	0.3±13.7	3.4±15.7	3.1 (-7.5-13.7)	.558
ΔPeak WR (watts/min)	-6.7±9.5	15.4±9.8	22.1 (15.1-29.1)	<.001**
ΔPeak WR %predicted	-5±7.2	12.2±6.2	17.2 (12.3-22.1)	<.001**
ΔVO_2 Peak (mL/kg/min)	-0.5±2	2.1±2.3	2.6 (1-4.1)	.002*
ΔVO_2 Peak %predicted	-1.8±9.2	8.9±9.3	10.7 (4-17.4)	.003*
ΔAT (mL/kg/min)	-0.72±1.8	2.4±2.4	3.1 (1.6-4.6)	<.001**
ΔAT % predicted peak VO_2	-0.64±9.9	9.7±10.7	9.7 (2.3-17.1)	.012*
ΔPeak O_2 pulse (ml/beat)	-0.18±1.2	.93±1.5	1.1 (0.12-2.1)	.028*
ΔPeak V_E/VO_2 (ratio)	-2.2±5.7	3.2±6.2	5.5 (1.2-9.7)	.014*
ΔPeak V_E/VCO_2 (ratio)	0.5±3.6	0.4±4.8	-0.1 (-3.1-2.9)	.947
ΔPeak VD/VT (%)	0.76±3.2	-0.7±2.2	-1.4 (-3.4-0.6)	.155
ΔPeak HR (beat/min)	0.7±9.1	4.2±9.3	3.6 (-3.1-10.2)	.283
ΔPeak SBP (mmHg)	-5±23	7.3±24.6	12.3 (-4.9-29.5)	.154
ΔPeak DBP(mmHg)	5.6±21.6	5.9±14.4	0.3 (-13.1-13.8)	.959
ΔPeak SpO_2 (%)	-1.4±5.4	-.0.73±4.3	0.7 (-2.9-4.2)	.700

Values presented as means ± SD. CI; confidence interval. ET; exercise training. * Significant differences between the groups; p< 0.05. ** Significant differences between the groups; p< 0.001, VT; tidal volume, Bf; breathing frequency, V_E; minute ventilation, MVV; maximal voluntary ventilation, BR; breathing reserve, WR; work rate, VO_2 peak: peak oxygen consumption, AT; anaerobic threshold, V_E/VO_2; ventilatory equivalent for oxygen consumption, V_E/VCO_2; ventilatory equivalent for carbon dioxide, VD/VT; dead space to tidal volume ratio, HR; heart rate, SBP; systolic blood pressure, DBP; diastolic blood pressure, SpO_2; oxygen saturation by pulse oximeter.



Data presented as means and standard errors of means (SEM). * Significant differences between the groups; $p< 0.05$. ** Significant differences between the groups; $p< 0.001$. $VO_{2\ peak}$; peak oxygen consumption, AT; anaerobic threshold, WR; work-rate, MVV; maximal voluntary ventilation, and V_E ; minute ventilation, VT; tidal volume, FVC; forced vital capacity, 6MWD; 6 minutes walk distance.

Figure 5. Exercise tolerance and functional capacity, pulmonary and ventilatory capacities after 12-week intervention in idiopathic pulmonary fibrosis patients.

7. Functional capacity, dyspnea, quality of life and physical activity levels.

Most patients in the current study showed preserved functional capacity, mild to moderate dyspnea levels, reduced quality of life and mild to moderate patterns of physical activity. Both groups were similar in terms of baseline values except for upper body flexibility which was slightly lower in the ET group (Table 18).

Table 18 Baseline functional capacity tests, dyspnea, quality of life and physical activity levels.

	Control group (n=17)	ET group (n=15)	p-value
Functional capacity			
6MWD (m)	513±108	471±108	.283
SpO2 after 6MWT (%)	85.2±8.4	83.7±8	.609
Borg dyspnea scale after 6MWT (0-10)	4.3±1.9	4.4±2.5	.864
30 sec chair stand (num of stands)	13.7±4.5	11.5±2.8	.117
Chair- sit& reach (inch)	-1.7±3.2	-1.5±2.8	.584
Back stretch (inch)	-4.9±2.5	-6.4±5.2	.010*
8 feet-up-& go (sec)	6.7±1.6	7.4±1.7	.711
Dyspnea and quality of life			
mMRC dyspnea scale (0-4)	1.7±0.9	1.9±0.9	.684
SGRQ- total score	18±4.8	20.6±6.7	.204
SGRQ- symptoms	29±17.3	34.3±25.2	.494
SGRQ- impact	17.9±4.5	20.9±5.9	.115
SGRQ- activity	12.1±1.9	12.6±0.6	.294
Physical activity levels			
IPAQ (MET-minutes/week)	2102±3016	955±989	.170

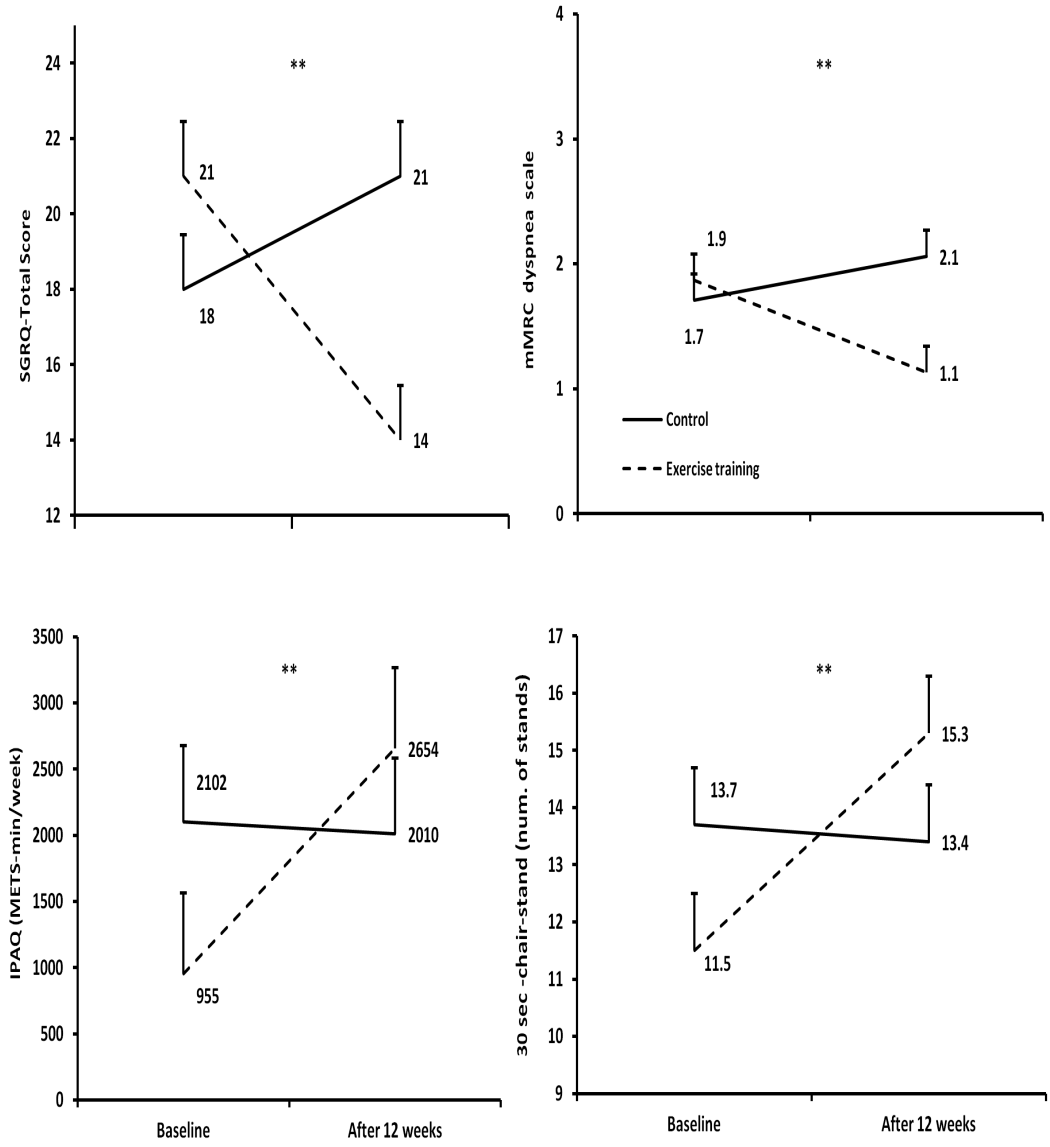
Values presented as means ± SD ET; exercise training. *Significant difference between the groups, p<0.05. 6MWT; 6 minutes walk test, 6MWD; 6 minutes walk distance, mMRC; modified medical research council. SGRQ; Saint' George respiratory questionnaire, IPAQ; international physical activity questionnaire.

After the 12-week intervention significant differences were observed between the groups in functional tests, dyspnea, quality of life and physical activity levels. The ET group improved significantly while the control showed a trend of deterioration. Mean differences between the groups: Δ6MWD: 81.1 m, p<0.001; Δ30 sec chair stand: 4.1 stands, p<0.001; ΔmMRC: -1.1 units, p<0.001; ΔSGRQ total score: -9.7 units, p<0.001 and ΔIPAQ: 1791 MET-min/week, p<0.001 (Table 19, Figures 5, 6).

Table 19 Mean changes from baseline to 12-week (raw differences) and mean differences of changes between the ET and the control groups in dyspnea, functional capacity tests, quality of life and physical activity level in IPF patients.

	Control group (n=17)	ET group (n=15)	Mean difference (CI 95%)	p-value
Functional capacity				
Δ6MWD (m)	-10.6±35.4	70.4±77	81.1 (38.7-123.5)	<.001**
ΔBorg dyspnea scale after 6MWT (0-10)	0.47±2	0.4±1.7	-0.7 (-1.4-1.3)	.916
ΔSpO_2 after 6MWT (%)	-0.3±6	-1.6±3.6	-1.3 (-4.9- -2.3)	.465
Δ30 sec chair stand (number of stands)	-0.4±2.5	3.7±2.6	4.1 (2.3-5.9)	<.001**
ΔChair- sit& reach (inch)	-1±3.8	2.2±	3.2(1-5.4)	.007*
ΔBack stretch (inch)	-1.2±3.2	1.4±3.1	2.6(0.3-4.9)	.029*
Δ8 feet-up-& go (sec)	0.6±1.6	-1.3±1.3	-1.9(-2.9- -0.8)	.001*
Dyspnea levels and Quality of life				
ΔmMRC dyspnea scale (0-4)	0.35±0.7	-0.73±0.8	-1.1 (-1.62- -0.54)	<.001**
ΔSGRQ- total score	2.8±3.6	-6.9±6.5	-9.7 (-13.4- -5.9)	<.001**
ΔSGRQ- symptoms	8.9±15	-14.7±22.8	-23.5 (-37.4- -9.7)	.002*
ΔSGRQ- impact	2.5±3.7	-7.6±5.4	-10.1 (-13.7- -6.5)	<.001**
ΔSGRQ- activity	-0.04±1.4	-1.4±3.3	-1.34 (-3.1-0.45)	.137
Physical activity levels				
ΔIPAQ (MET-minutes/week)	-92 ±1136	1699±1427	1791 (864-2717)	<.001*

Values presented as means ± SD. CI; confidence interval. ET; exercise training. * Significant differences between the groups; p< 0.05. ** Significant differences between the groups; p< 0.001. 6MWD; 6 minute walk distance, SpO_2; oxygen saturation by pulse oximeter, mMRC; modified medical research council, SGRQ; Saint' George respiratory questionnaire, IPAQ; international physical activity questionnaire.



Data presented as means and standard errors of means (SEM). * Significant differences between the groups; p< 0.05. ** Significant differences between the groups; p< 0.001. mMRC; modified medical research council, SGRQ; Saint' George respiratory questionnaire, IPAQ; international physical activity questionnaire.

Figure 6. Dyspnea, quality of life, leg strength and physical activity level after 12-week intervention in idiopathic pulmonary fibrosis patients.

Within subject observations among the ET group showed that 10 patients decreased, 4 patients maintained and 1 increased their dyspnea levels, while in the control group 13 patients maintained and 4 increased the mMRC (χ^2=16.5, p<0.001). Significant differences were observed between the ET and control groups with respect to the minimal clinical important difference (MCID) for 6MWD and SGRQ. Thirteen patients (87%) in the ET group versus 4 (24%) patients in the control group improved 6MWD above the MCID (χ^2=12.8, p<0.001), and only in the ET group 9 patients (60%) improved SGRQ above MCID (χ^2=14.2, p<0.001) (Figures 7, 8).

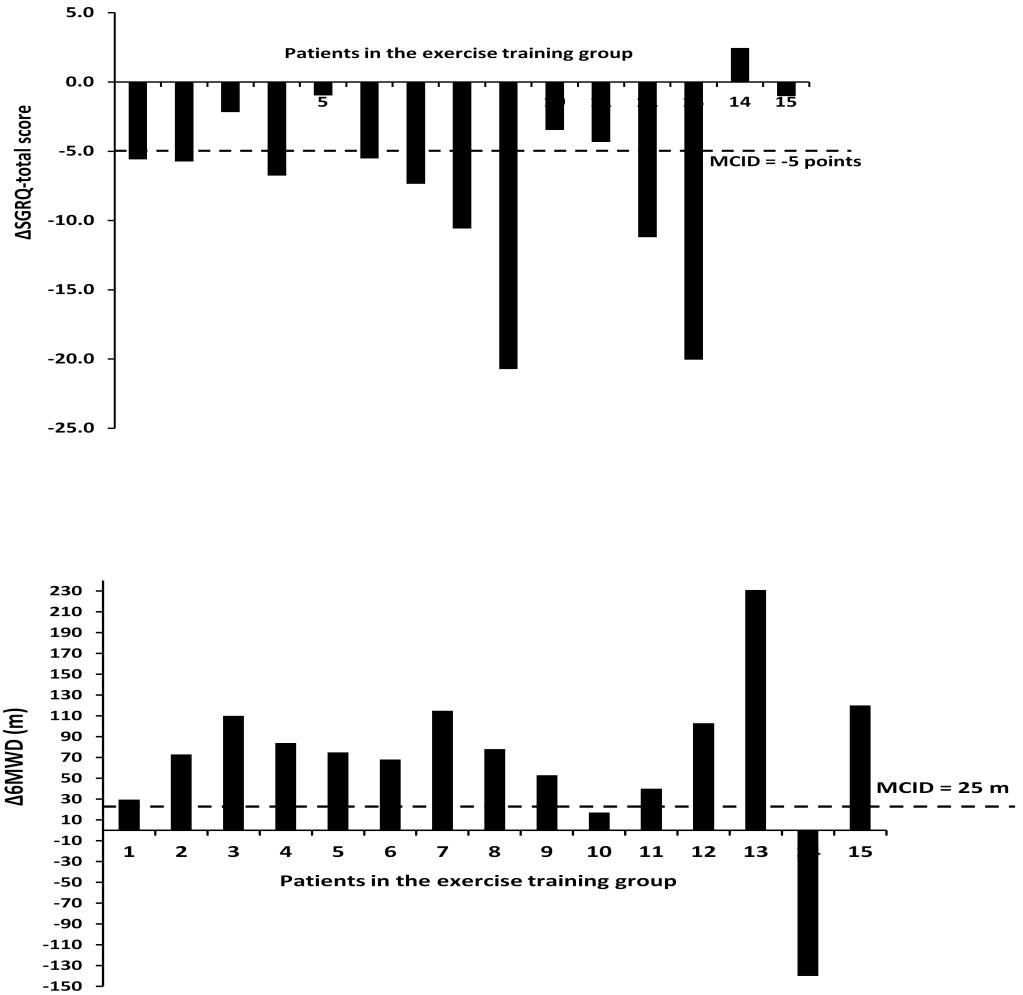


Figure 7. Intervariability responses in 6 minute walk distance and Saint George Respiratory Questionnaire with respect to minimal clinical important difference (MCID) among exercise training group.

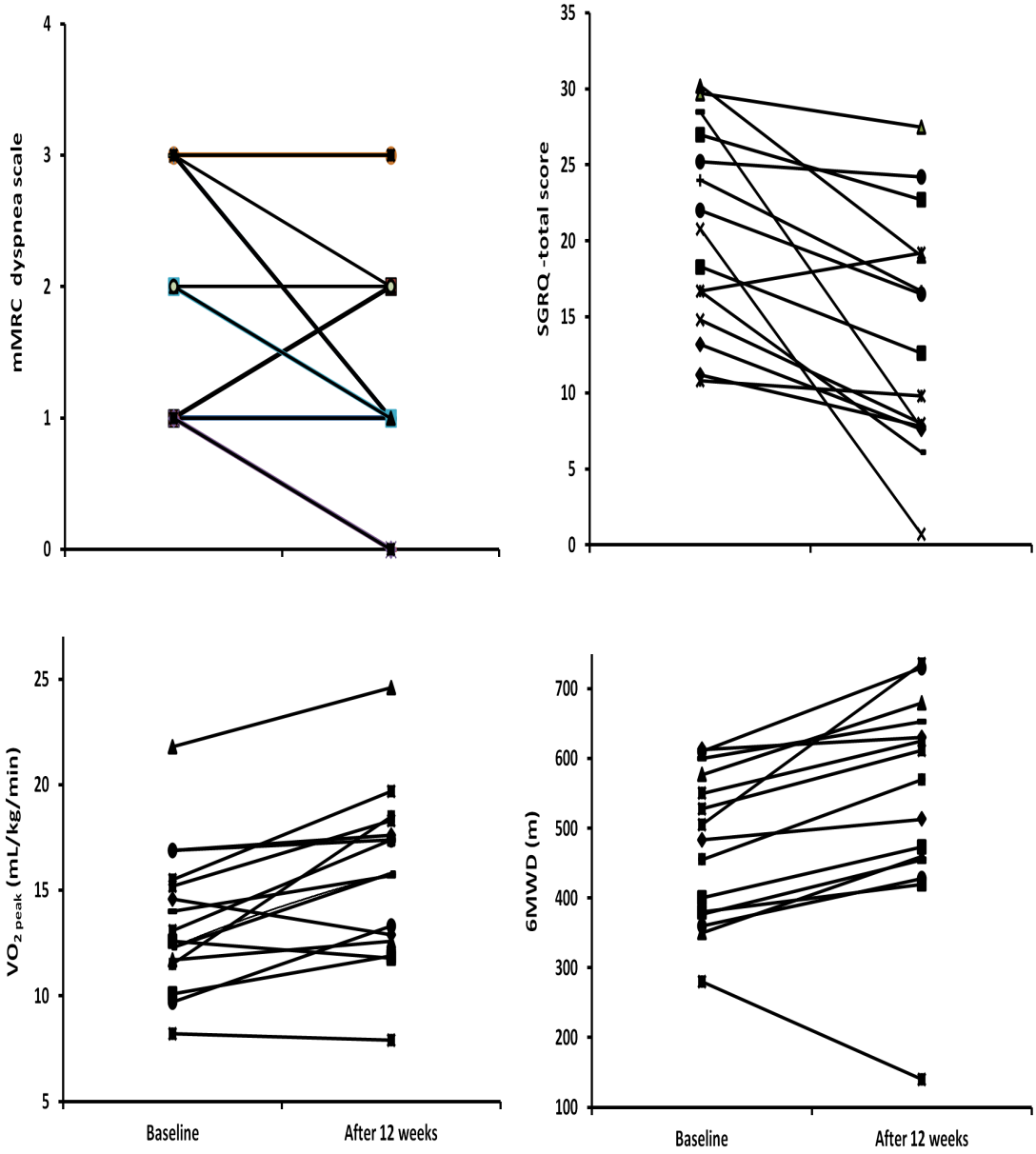


Figure 8. Intervariability adaptations of selected outcomes to exercise pulmonary rehabilitation program among exercise training group.

Table 20. Baseline selected individual characteristics among exercise training group.

Patient num.	Age (years)	Gander (male/female)	FVC %predicted	DLCO %predicted	TLC %predicted	mMRC	6MWD (m)	SpO_2 post 6MWT (%)	VO_{2peak} (mL/kg/min)	SGRQ-total score
1	76	male	62	48	63	1	483	87	14.6	13.2
2	68	female	84	42	81	1	400	89	10.1	18.3
3	65	male	76	30	76	3	350	68	11.7	29.7
4	67	male	37		35	1	528	85	13.1	14.8
5	65	female	76	34	66	1	550	68	15.2	10.8
6	68	male	50	37	54	3	360	84	9.7	22.0
7	64	male	60	66	54	3	455	89	11.5	24.0
8	80	male	63	50	63	1	377	93	12.3	16.7
9	61	female	88	47	72	3	600	82	14.0	28.5
10	77	male	63	54	62	1	613	85	16.9	11.2
11	76	female	51	49	42	2	380	78	12.6	27.0
12	62	male	90	66	93	2	577	95	21.8	30.2
13	68	male	60	91	62	1	505	89	15.5	20.8
14	72	female	61	23	51	3	280	76	8.2	16.7
15	63	male	70	44	61	1	610	87	16.9	25.2

VO_2 peak: peak oxygen consumption, 6MWT; 6 minute walk test, 6MWD; 6 minute walk distance, SGRQ; Saint' George respiratory questionnaire, FVC; forced vital capacity , TLC; total lung capacity DLCO; diffusion capacity for carbon monoxide SpO2; oxygen saturation by pulse oximeter, mMRC; modified medical research council

Table 21. Intervariability changes of selected outcomes after 12-week exercise pulmonary rehabilitation program among exercise training group (n=15).

Patient Num./ delta outcomes	Num. exercise sessions	ΔVO$_{2peak}$ (mL/kg/min)	Δ6MWD (m)	ΔAT (mL/kg/min)	ΔWR (watts/min)	Δ30 sec-chair-stand (num)	ΔFVC% predicted	ΔPeak VT (L/breath)	ΔV$_{E\ peak}$ (L/min)	ΔmMRC	ΔSGRQ total score	ΔSGRQ symptoms	Δ% Fat	WS(cm)	IPAQ (Mets-min/week)
1	20	-1.7	29.6*	0.3	3	5	1	0.07	2	0	5.6*	15*	0	5	423
2	23	1.8	73*	1.4	10	9	2	0.17	14	1	5.7*	3.5	1.5	0	678
3	19	0.9	110*	0.4	16	4	-1	0.12	17	1	-2.2	3.8	2.2	4	2010
4	25	4.3	84*	2.80	34	3	4	0.07	15	-1	-6.8*	18*	1.3	0	1722
5	24	3.1	75*	2.2	11	7	6	0	0	0	1	13.5	5	-12	2160
6	22	3.6	68*	3.1	9	3	2	0.47	17	0	5.5*	31.2*	2	1	347
7	24	7	115*	7.7	40	4	14	0.64	4	2	-7.4*	31*	2	2	1557
8	24	3.5	78*	1.6	22	4	2	0.38	10	1	10.6*	21*	1	3	862
9	21	1.7	53*	2.3	15	5	7	0.17	-4	-2	20.7*	60.2*	2	7	1506
10	25	0.7	17	1.7	12	3	-4	-0.03	2	-1	3.5	6.8*	1.7	2	5845
11	18	0.8	40*	0.4	13	3	4	0.03	2	-2	4.3	14.3*	2	1	960
12	24	2.8	103*	5.8	10	4	7	0.13	12	-1	11.2*	32.4*	1	-4	1489
13	24	4.2	231*	5.9	10	2	26	0.22	6	-1	20*	41.4*	2.5	0	3777
14	24	-0.3	140	0.04	11	3	7	0.07	7	0	2.5	13.1	0.1	0	852
15	21	0.5	120*	-0.1	15	3	1	0.12	6	-1	-1	24.4	4	-2	1297

Result presented in Δ (post –pre rehabilitation). *Above the minimal clinically improvement difference. V_E; minute ventilation, VT; tidal volume, WR; work rate, VO_2 peak: peak oxygen consumption, AT; anaerobic threshold. FVC; forced vital capacity, 6MWD; 6 minute walk distance, mMRC; modified medical research council, SGRQ; Saint' George respiratory questionnaire, WS; waist circumference, IPAQ; international physical activity questionnaire.

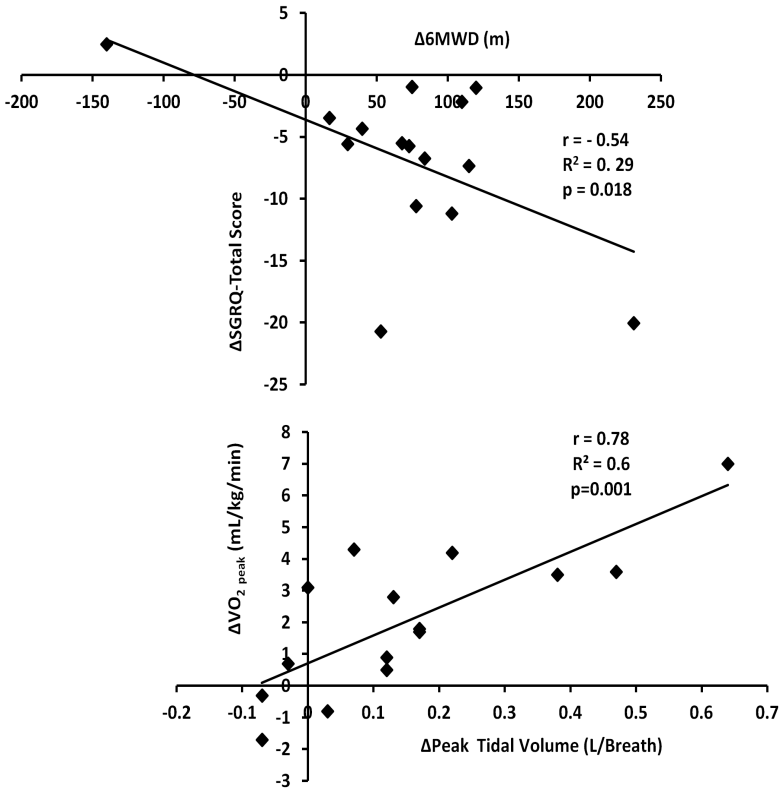
8. Exploratory analysis

Exploratory analysis using a stepwise linear multiple regression including exercise, pulmonary and QOL parameters of the ET group revealed several models with significant associations between the outcomes (Table 22). Changes in aerobic exercise capacity (ΔVO_{2peak}) after the intervention were significantly explained (57%) by changes in ΔVT peak, whereas changes in functional capacity (Δ6MWD) were mainly explained (75%) by changes in pulmonary and ventilatory parameters (ΔFVC %predicted, ΔMVV, ΔVE peak). Changes in pulmonary function (ΔFVC %predicted) were mainly explained (77%) by changes both in exercise parameters (Δ6MWD and ΔAT) and ventilation (ΔVE peak). Changes in quality of life (ΔSGRQ-total score) were partially explained (43%) by ΔFVC %predicted. In addition, Pearson correlations analysis in the ET group revealed significant associations between ΔVO_{2peak} and Δpeak VT (r=0.78, p=0.001), between ΔSGRQ-total score and Δ6MWD (r= -0.54, p=0.018) (Figure 9, Table 23), and between ΔFVC %predicted with Δ6MWD and SGRQ as well (Table 23).

Table 22 Stepwise linear multiple regression models for exercise capacity, pulmonary function and quality of life among exercise training group patients.

Depended Variables	Independent Variables Entered to the Model	Adjusted R^2	B	Constant	P value
ΔVO_{2peak}	ΔVT peak	0.57	8.8	0.7	.001*
Δ6MWD	ΔFVC %predicted, ΔMVV, ΔV_E peak,	0.75	2.1	5.3	<.001**
ΔFVC% predicted	Δ6MWD, ΔV_E peak, ΔAT	0.77	1.6	-1.4	<.001**
ΔSGRQ-total score	ΔFVC %predicted	0.43	-0.5	-5.2	.005*

Δ=post –pre intervention, VO2 peak; peak oxygen consumption, 6MWD; 6 minutes walk distance, FVC; forced vital capacity, SGRQ; Saint George's Respiratory Questionnaire. * Significant differences between the groups; p< 0.05. ** Significant differences between the groups; p< 0.001.



Δ; post-pre intervention among exercise training group, VO_{2peak}; peak oxygen consumption, 6MWD; 6 minutes walk distance, SGRQ; Saint' George respiratory questionnaire.

Figure 9. Correlation between changes in primary and secondary outcomes in the exercise training group.

Observation of inter-variability responses within the ET group showed most patients improved exercise functional capacity and quality of life following the program. Only one patient deteriorated after the intervention, presenting impaired baseline levels of 6MWD=280 m and severe dyspnea effort mMRC=3 (Tables 20, 21, Figures 7, 8). In addition, 9 of 15 patients in the ET group improved both VO_{2peak} and mMRC (Tables 20, 21).

Table 23 Correlations between the changes from baseline to 12-week in the primary and secondary outcomes in the exercise training group.

	Δ6MWD (m)	ΔVO_{2peak} (mL/kg/min)	Δ30 s chair stand test (num. of stands)	ΔSGRQ-total score	ΔIPAQ (MET-minutes/week)	ΔFVC %predicted	ΔpeakVT (L/breath)
Δ6MWD (m)	1	r = 0.534*	r= 0.411	r = -0.543*	r = 0.223	r = 0.722*	r = 0.444
		p = 0.04	p = 0.128	p = 0.018	p = 0.423	p = 0.002	p = 0.097
ΔVO_{2peak} (mL/kg/min)	r = 0.534*	1	r = 0.145	r =-0.067	r = 0.103	r = 0.513	r = 0.775*
	p = 0.04		p = 0.605	p = 0.407	p = 0.716	p = 0.051	p = 0.001
Δ30 s chair stand test (num. of stands)	r= 0.411	r = 0.145	1	r = -0.175	r = - 0.09	r = 0.094	r = 0.132
	p = 0.128	p = 0.605		p = 0.532	p = 0.126	p = 0.739	p = 0.639
ΔSGTQ-total score	r = -0.543*	r =-0.067	r = -0.175	1	r = - 0.146	r =- 0.683*	r =- 0.334
	p = 0.018	p = 0.407	p = 0.532		p = 0.302	p = 0.005	p = 0.223
ΔIPAQ (MET-minutes/week)	r = 0.223	r = 0.103	r = - 0.09	r = - 0.146	1	r = 0.251	r =- 0.204
	p = 0.423	p = 0.716	p = 0.126	p = 0.302		p = 0.367	p = 0.465
ΔFVC %predicted	r = 0.722*	r = 0.513	r = 0.094	r =- 0.683*	r = 0.251	1	r =0.404
	p = 0.002	p = 0.051	p = 0.739	p = 0.005	p = 0.367		p = 0.135
ΔpeakVT (L/breath)	r = 0.444	r = 0.775*	r = 0.132	r =- 0.334	r =- 0.204	r =0.404	1
	p = 0.097	p = 0.001	p = 0.639	p = 0.223	p = 0.465	p = 0.135	

Δ; post-pre intervention among exercise training group. * Significant correlation at $p< 0.05$. VO_2 peak: peak oxygen consumption, 6MWD; 6 minute walk distance, SGRQ; Saint' George respiratory questionnaire, IPAQ; international physical activity questionnaire, FVC; forced vital capacity, VT; tidal volume.

9. Follow-up evaluation

Twenty eight patients (ET; n=14, control; n=14) were re-evaluated at 11-month time point from baseline. During the 15 months follow up period 4 patients experienced an acute exacerbation of IPF (2 patients in each group), ($\chi 2$ = 0.005, p=0.943) and 3 patients (ET; n=1, 7% of the group and control; n=2, 11% of the group) died during the follow-up period. Group allocation did not affect survival and time to event in our study ($\chi 2$ = 0.244, p=0.621). Six patients (37%) from ET group and 8 patients (44%) from the control group were hospitalized during the follow up period ($\chi 2$= 0.16, p=0.68). No significant differences were observed between the groups in hospitalizations, exacerbations and mortality rates (Table 24).

Table 24. Patients' characteristics at follow up time.

New events and co-morbidities	**Control group**	**ET group**	**p -value**
Death (n/%)	2(12%)	1 (7%)	.621
Acute exacerbations (n/%)	2(12%)	2(13%)	.943
Hospitalization (n/%)	8 (44%)	6 (37%)	.680
New supplemental oxygen users			
Rest (n/%)	1(6%)	2 (13%)	.471
Exertion (n/%)	4 (24%)	5 (33%)	.538
Acute cardiovascular event (n/%)	1(7%)	1(7%)	1
Lung Transplanted (n/%)	1(7%)	0	.340
Continued or started pulmonary rehabilitation (n/%)	2(13%)	3(21%)	.564

At 11-month time point (8 months after the end of 12-week intervention), significant differences in mean raw deltas (ΔΔ= follow up-post intervention) between the groups were observed in exercise tolerance, ventilatory responses and quality of life (Tables 25, 26 Figures 10, 11, 12).

Table 25 Mean changes from post 12-week intervention to 11 months follow-up (raw differences) and mean differences of changes between the ET and the control groups in anthropometric, pulmonary function and blood biomarkers in IPF patients.

	Control group (n=14)	ET group (n=14)	Mean difference (CI 95%)	p-value
Anthropometrics				
ΔΔWeight (kg)	-0.2±3.6	-0.9±2	-0.6(-2.9-1.6)	.566
ΔΔFat (%)	-0.3±2.7	1.4±3.1	1.7(-0.6-4)	.131
ΔΔWaist circumference (cm)	-4.9±11.4	-1.2±4	3.7 (-2.9-10.3)	.263
Pulmonary function test				
ΔΔFVC %predicted	0.07±8	-4.5±7.2	-4.6 (-10.5-1.3)	.124
ΔΔFEV_1 %predicted	0.1±8.8	-3.4±7	-3.5 (-9.7-2.7)	.256
ΔΔFEV_1/ FVC %predicted	0.5±4.4	2±5.4	1.6 (-2.2-5.4)	.405
ΔΔTLC %predicted	-0.5±7.7	-3.5±9.4	-3(-9.9-3.9)	.379
ΔΔDLCO %predicted	-3.7±10.3	-0.9±8.9	3.7 (-4.9-10.4)	.459
ΔΔMVV (L/min)	-1.5±9.2	-13.6±9.6	12.1 (-19.4- -4.7)	.002*
ΔΔSpO_2 (%)	-0.9±1.6	0.13±1.7	1 (-0.17-2.2)	.092
Blood biomarkers				
ΔΔCA 15-3 (U/ml)	1.4±22.2	20.1±32.6	18.8 (-6-44)	.130
ΔΔCA 19-9 (U/ml)	-3.1±44.2	-1.7±21.9	1.4 (-27-30)	.922
ΔΔCRP (mg/dL)	-0.6±2.8	-0.002±0.2	0.6 (-1-2.2)	.440
ΔΔNT-proBNP (pg/ml)	-3±401	17±180	-19 (-228-266)	.873

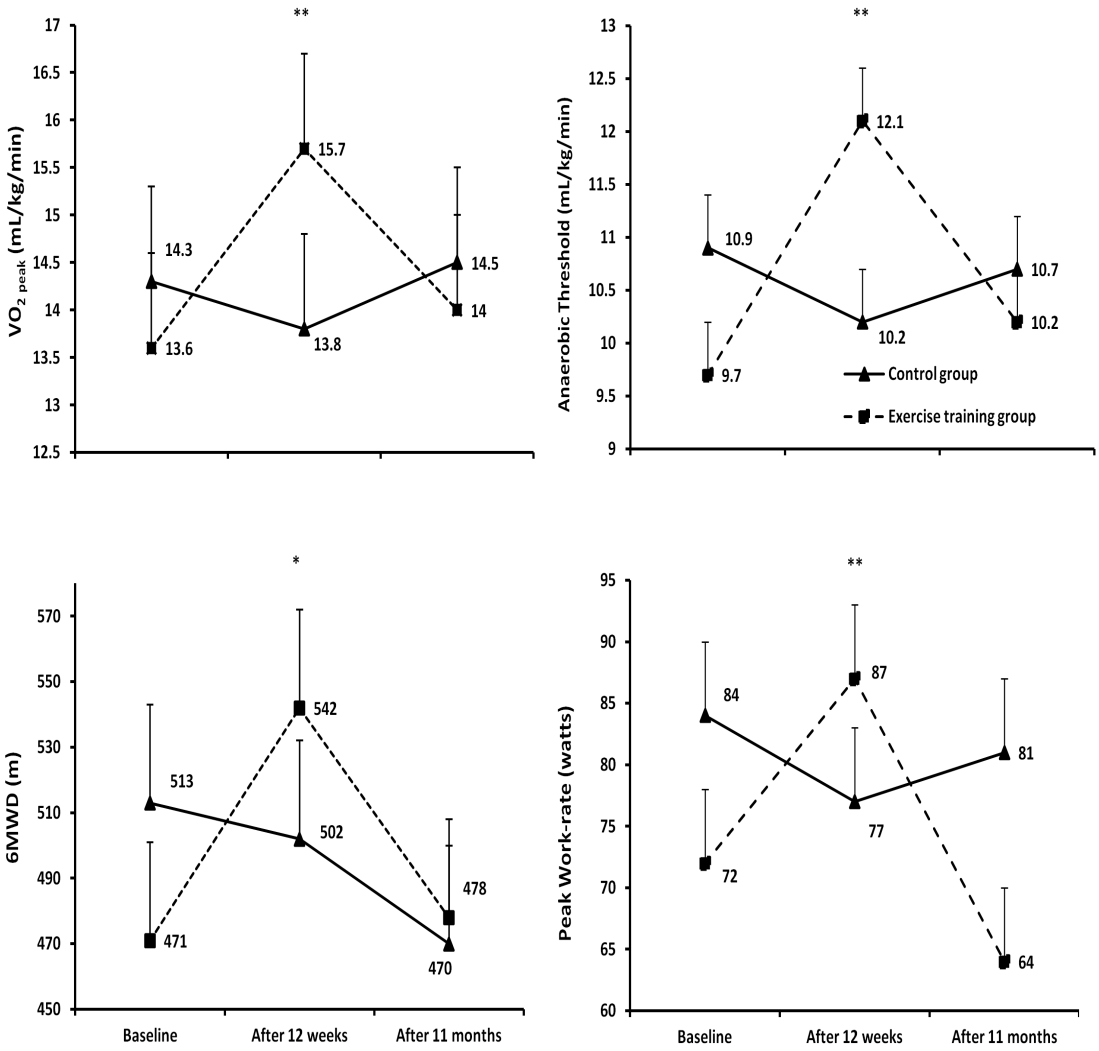
Values presented as means ± SD. CI; confidence interval. ET; exercise training. * Significant differences between the groups; $p< 0.05$. ** Significant differences between the groups; $p< 0.001$. FVC; forced vital capacity, FEV_1; forced expiratory volume in 1 sec, TLC; total lung capacity DLCO; diffusion capacity for carbon monoxide, MVV; maximal voluntary ventilation BMI; body mass index, HR; heart rate, SBP; systolic blood pressure, DBP; diastolic blood pressure, SpO_2; oxygen saturation by pulse oximeter, CA; carbohydrate antigen, CRP; c- reactive protein, N-terminal pro-brain natriuretic peptide.

Table 26 Mean changes from post 12-week intervention to 11 month follow-up (raw differences) and mean differences of changes between the ET and the control groups in exercise tolerance and ventilatory responses, dyspnea, functional capacity, quality of life and physical activity level in IPF patients.

	Control group (n=14)	ET group (n=14)	Mean difference (CI 95%)	p-value
Exercise tolerance and ventilatory responses				
ΔΔPeak VT (L/breath)	-0.05±0.2	-0.2±0.2	-0.15 (-0.3- -0.003)	0.046*
ΔΔV_E peak (L/min)	3.8±8.3	-8.9±7.7	-12.7 (-18.9 - -6.5)	<.001**
ΔΔPeak WR (watts/min)	-3±10	-25±10	-22 (-29.8- -14.2)	<.001**
ΔΔVO_2 Peak (mL/kg/min)	0.9±1.7	-1.9±2.2	-2.8 (-4.4- -1.3)	.001*
ΔΔAT (mL/kg/min)	1.1±2.4	-1.9±2.1	-3.1 (-4.8- -1.3)	.001*
Functional capacity				
ΔΔ6MWD (m)	-44±59.6	-71.7±55.9	-27.7 (-72.5-17.2)	.216
ΔΔSpO_2 after 6MWT (%)	-0.8±3	1.7±5.3	2.5(-0.8 - 5.8)	.135
ΔΔ30 s chair stand (number of stands)	-1.1±2.3	-1.9±2.1	-0.7 (-2.6-1.1)	.435
Dyspnea levels and Quality of life				
ΔΔmMRC dyspnea scale (0-4)	-0.1±0.8	0.4±0.5	0.5(-0.003 -1)	.052
ΔΔSGRQ- total score	-4.3±12.5	3.6±7.4	7.9 0.4 -15.4)	.041*
ΔΔSGRQ- symptoms	-3±31.2	13.5±20.1	16.5 (-2.7- 35.8)	.090
ΔΔSGRQ- impact	-3.9±11.4	2.7±9	-6.6(-0.9-14)	.082
ΔΔSGRQ- activity	-2.3±5.2	-0.08±4.1	2.2 (-1.2-5.6)	.200
Physical activity levels				
ΔΔIPAQ (MET-minutes/week)	-256 ±1392	-1432±1913	-1175 (2474-123)	.074

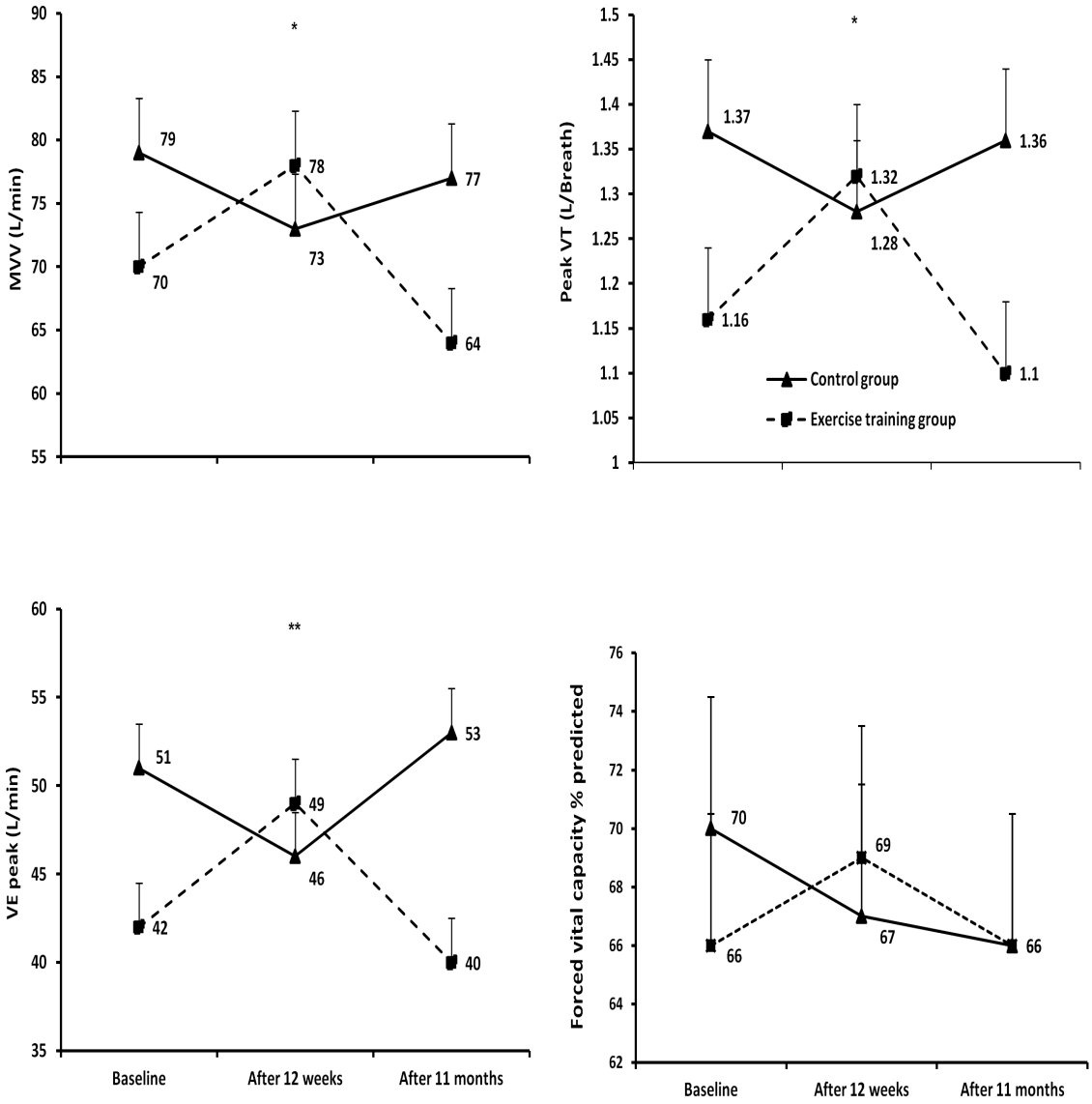
Values presented as means ± SD. CI; confidence interval. ET; exercise training. * Significant differences between the groups; p< 0.05. ** Significant differences between the groups; p< 0.001. VT; tidal volume, V_E; minute ventilation, WR; work rate, VO_2 peak: peak oxygen consumption, AT; anaerobic threshold, 6MWD; 6 minute walk distance, SpO_2; oxygen saturation by pulse oximeter, mMRC; modified medical research council, SGRQ; Saint' George respiratory questionnaire, IPAQ; international physical activity questionnaire.

The ET group deteriorated in cardiopulmonary exercise parameters, 6MWD, dyspnea leg strength, pulmonary function, SGRQ and physical activity levels from post 12-week intervention, but remained at the level of baseline values (Figures 10-12). The control group maintained with a slight trend of decline in most parameters from post 12-week intervention, although a trend of worsening was shown compared to baseline values. No significant changes in mean raw deltas were seen for anthropometrics, blood biomarkers, pulmonary functions, functional capacity and physical activity levels. No significant differences were observed between the groups at the end of the study except for peak minute ventilation that was significantly reduced in ET group only (53 versus 40 L/min, p= 0.037).



Data presented as means and standard errors of means (SEM). * Significant differences between the groups; $p< 0.05$. ** Significant differences between the groups; $p< 0.001$. $VO_{2\ peak}$; peak oxygen consumption, AT; anaerobic threshold, WR; work-rate, 6MWD; 6 minutes walk distance.

Figure 10. Changes in exercise tolerance and functional capacity from baseline to 11 months follow-up in idiopathic pulmonary fibrosis patients.



Data presented as means and standard errors of means (SEM). * Significant differences between the groups; $p< 0.05$. ** Significant differences between the groups; $p< 0.001$. MVV; maximal voluntary ventilation, and V_E ; minute ventilation, VT; tidal volume.

Figure 11. Changes in pulmonary and ventilatory functions from baseline to 11 months follow-up in idiopathic pulmonary fibrosis patients.

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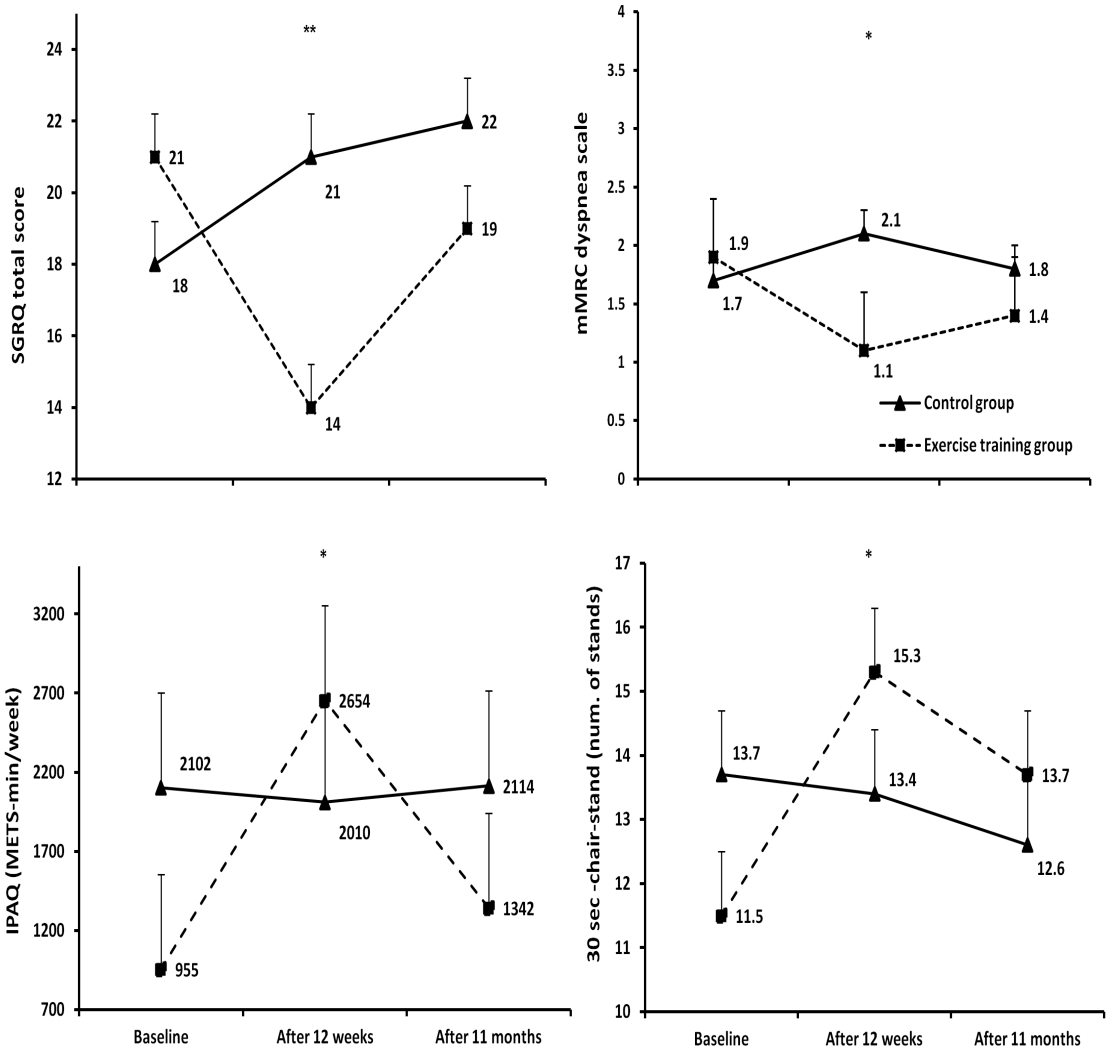

Data presented as means and standard errors of means (SEM). * Significant differences between the groups; p< 0.05. ** Significant differences between the groups; p< 0.001. mMRC; modified medical research council, SGRQ; Saint' George respiratory questionnaire, IPAQ; international physical activity questionnaire.

Figure 12. Changes in dyspnea, quality of life, leg strength and physical activity level from baseline to 11 months follow-up in idiopathic pulmonary fibrosis patients.

CHAPTER V

DISCUSSION

DISCUSSION

In the present investigation using a randomized controlled study we examined the effect of outpatient supervised group exercise training at pulmonary rehabilitation on numerous short and long term clinical and physiological outcomes in patients with idiopathic pulmonary fibrosis. We showed that a 12-week exercise training based-pulmonary rehabilitation program improves exercise tolerance, functional capacity, pulmonary function, ventilatory responses, physical activity levels, dyspnea and quality of life in patients with IPF, while a trend for worsening was observed in the control group. We demonstrated that 12-week exercise training program is an effective treatment for clinical improvements in IPF patients but these benefits were unpreserved in the long-term and did not affect prognosis.

1. Methodological - discussion

Pulmonary rehabilitation including exercise training is a standard of care for patients with chronic obstructive pulmonary disease with strong evidence of health outcomes [1, 13, 114-115]. Although exercise-based pulmonary rehabilitation has not been studied extensively in IPF patients a growing body of emerging evidence offers encouraging results with some health benefits following participation in these programs [10-13]. However, most these studies have significant limitations regarding the methodology or protocol used [12-14]. The majority of studies were uncontrolled [15-20] and non-randomized [15-21], retrospective [22-23] and measured only a few outcomes without including follow-up data [15-19, 22-25]. Only two studies conducted a short 4-month follow-up post 6-8 week program with only a few outcomes [20, 26].

Taking into account the above-mentioned limitations we conducted a comprehensive randomized controlled trial in an attempt to resolve and overcome the gaps.
The present study was randomized and controlled, which is considered the gold-standard in clinical trials to ascertain the effectiveness of treatments and to establish causality relationships between treatment and outcome [140-141].

The patients were randomly allocated to ET or control groups by the study-coordinator who was uninvolved in patient treatment or testing to avoid bias. In this

study 34 IPF patients were included. The sample size was estimated prior the recruitment through a power-analysis, with 95% probability and 80% power for detecting mean difference ≥ 2 mL/kg/min in one primary outcome ($VO_{2\ peak}$ based on previous published data [138]) between the groups and time effect. The analysis revealed that a total of 28 participants (14 in each group) was needed [139]. We recruited 20% above the needed number of patients due to an expected 5-20% drop-out rate based on previous studies [24, 26]. We tested our patients at baseline, after a 12-week intervention and 8 months after the completion of the intervention (11 months from baseline). Using this methodology we were able to evaluate the short and long-term effects of a 12-week exercise training program on clinical outcomes in IPF patients (in comparison to one randomized controlled study that included only a 4-month follow up period) [26]. Moreover, most previous studies included both IPF and ILD patients [15-17, 19-20, 22-23, 26]. This approach is somewhat questionable. Although IPF is a part of the ILD group, IPF has a different pathophysiology with severer clinical conditions, higher levels of symptoms and disability and different clinical course and prognosis [7, 26]. In addition, the number of IPF patients was sufficiently reduced in these studies due to adoption of this kind approach by including IPF as part of ILD patients [20, 26].

In our study we enrolled only IPF patients according clinico-radiological criteria of the latest established ATS/ERS guidelines [7]. Patients were excluded if they had left-side heart failure, any contra-indication for exercise training and participation in pulmonary rehabilitation program during the 12 months prior to enrolment.

In addition, we re-evaluated our patients at 11-month time point, and followed for 15 months from the end of 12-week intervention for exacerbations, hospitalizations and mortality, to assess the long-term impact on clinical outcomes of short-term exercise program. Only two previous studies conducted a short follow up period (4 months) following the exercise intervention [20, 26], and only one study was a randomized controlled trial (RCT) [26]. To the best of our knowledge there are no studies showing the effect of exercise training on exacerbations, prognosis and mortality in IPF. The methodology we used including RCT, short and long-term examinations and sufficient follow-up period after the intervention, allowed us to provide answers for the above gap in the literature.

In the present investigation we tested comprehensively both resting and exercise cardiopulmonary functions, including: Doppler-Echocardiography and pulmonary function test and CPET respectively. Since exercise intolerance and dyspnea-effort are significant manifestations of IPF, assessing cardiac and pulmonary responses and functions during exercise might be more sensitive for monitoring disease progression and treatment benefits. Furthermore, we evaluated exercise tolerance and functional capacity using both a lab test (CPET) and functional field tests (6MWT and senior fitness tests). This approach provides a broader picture of aerobic capacity, walking functional capacity, strength, agility and flexibility, all of which are related to activity of daily living [47]. Moreover, we assessed anthropometrics and body composition, blood biomarkers, quality of life, symptoms and physical activity level questionnaires to evaluate the impact of our exercise program on other health-related outcomes.

Over time, as disease progresses, a significant percentage of IPF patients (32-85%) develop pulmonary hypertension as accompanying co-morbidity [5, 27, 94] and consequently left ventricle dysfunction [28]. The presence of these co-morbidities was associated with a severer clinical condition and poorer prognosis among IPF patients [7]. Measuring left ventricle structure and function and evaluating pulmonary pressures by means of Echocardiography are important for assessing the treatment efficacy of exercise training for the cardiopulmonary system and for IPF manifestations. Although echocardiography has some limitations compared to right heart catheterization (RHC) in terms of accuracy in detecting pulmonary hypertension [90-91], a meta-analysis from 29 studies showed a good correlation (r=0.7) between sPAP on echocardiography and mPAP on right heart catheterization [91]. In addition, Doppler-echocardiography is a non-invasive and widely available instrument with good overall diagnostic power for detecting PH, with 83% for sensitivity and 72% for specificity [91].

Furthermore, based on previous extensive data on the effect of exercise pulmonary rehabilitation on respiratory disease patients, the expected improvements in exercise capacity following an exercise program were usually associated with enhancements in cardiac function and peripheral skeletal muscles [10, 115]. In our research we also hypothesized that some cardiac ameliorations would occur in the exercise training

group which could be assessed by Doppler-echocardiography, and might explain, at least partially, the expected improvements in exercise tolerance.

The primary outcome in our study was exercise tolerance, which was measured by cardiopulmonary exercise test (CPET) on a bicycle ergo-meter, and 6MWT. In addition senior fitness tests (SFT) were also performed to assess functional capacity related to activities of daily living (ADL).

In the majority of previous studies exercise capacity was measured only by 6MWD [15-20, 22-24], which is considered a sub-maximal test [40] with many confounders that may have an impact on the results [38-39], and making it difficult to distinguish the mechanisms underlying the improvement [15-20, 22-24]. CPET is a highly accurate, valid and reliable test, and is considered a gold-standard for assessing cardio-respiratory capacity [41-44]. In addition, CPET may indicate the limiting factors in exercise intolerance and the possible mechanisms underlying improvements following an exercise training program [41-44]. In the present investigation we took advantage of CPET as a laboratory test and also performed well established functional field exercise capacity test (6MWT) [39] and battery of SFT related to ADL [128]. With this innovative methodology we extended existing data on exercise capacity by more broadly covering the evaluation of exercise tolerance. Moreover, with this approach we enhance our understanding on the chronic adaptation of IPF patients to an exercise training, and can more efficiently target the variables of the exercise program.

In our research we also assessed anthropometrics (weight, BMI, waist circumference) and body composition (body-fat %) using skin-fold measures with Caliper, an accepted and validated tool for fat% evaluation [118]. It is well established that excessive body weight; especially abdominal obesity and fat%, are significant cardio-metabolic risk factors [47, 142]. Since most of our patients at baseline showed increased levels of body fat% and waist circumference indicating abdominal obesity, improvement in these variables might decrease the risk for coronary artery disease which is highly prevalent and constitutes a significant cause for complications and mortality among IPF [7, 142-143]. This is a novel approach that has not been previously studied among IPF patients.

In addition, as part of the research we measured 4 blood biomarkers (CA 15-3, CA 19-9, CRP, and NT-proBNP) in all three time points of the study (baseline, after 12-week intervention and 11 months after baseline). The rationale for the selection of these biomarkers was recent data associating them with disease severity and prognosis and the relation of some of these biomarkers to IPF pathophysiology such as CRP as an inflammatory marker and NT-proBNP as an indicator of the development of pulmonary hypertension and left ventricle dysfunction (wall stress) [29-33]. Although CA 15-3 and CA 19-9 are not direct mechanistic biomarkers for lung fibrosis, recent data including our group have demonstrated that these markers are sensitive to changes in IPF severity and improve following lung transplantation, and were proposed as alternative biomarkers for monitoring IPF progression [29-33].

We hypothesized that these markers could be an additional tool for monitoring disease progression or delay in disease progression after the exercise training intervention. CRP was selected as a standard and well-accepted biomarker of systemic inflammation [112]. Since part of IPF pathophysiology is related to inflammation [5], and several studies among IPF patients have demonstrated elevated CRP levels associated with poor prognosis [36-37], measuring CRP in our study can provide important information on the effect of rehabilitative exercise training on part of the pathophysiology and prognosis of IPF. This information is novel and has not been tested so far in other exercise training studies in IPF patients.

In our study we also measured the NT-proBNP biomarker as an additional tool for detecting and monitoring pulmonary hypertension. As described above, as the disease progresses a significant proportion of IPF patients (32-85%) over time develop pulmonary hypertension, which is related to a severer clinical condition and poorer prognosis [5, 7, 27, 94]. Moreover, left ventricle dysfunction, which is secondary to pulmonary hypertension, is also common in IPF, which can progress to heart failure, further impair exercise tolerance and affect prognosis [28]. Therefore, we thought that using this biomarker would give important information to clinicians about any possible impact of exercise training on NT-proBNP levels as an indirect indicator of pulmonary hypertension and maladaptive cardiac function, as well as for prognosis.

Quality of life, dyspnea and physical activity levels were assessed by SGRQ, mMRC and IPAQ respectively. SGRQ was chosen since the instrument was designed to measure impact on overall health, daily life, and perceived well-being, and recently was also validated for assessment of QOL in IPF patients [131-133]. The mMRC dyspnya scale is a simple grading system from 0-4 to assess a patient's level of breathlessness [129-130] and was widely used in previous studies of exercise training in ILD and IPF patients [16-18, 26]. We considered using this tool to evaluate the level of dyspnea in our patients based on previous data and its simplicity of implementation within the study.

Physical activity levels in IPF patients were not evaluated at the time we conceived our research plan, and this outcome was only examined recently by Ryerson et al [20], using the Rapid Assessment of Physical Activity (RAPA) questionnaire [20]. To the best of our knowledge there are no validated physical activity questionnaires for IPF. Despite the fact that physical activity was not set as a primary outcome in the present study, and recognizing the limitations of using IPAQ to assess physical activity, we thought that this additional information would be useful and clinically relevant because increasing habitual physical activity levels is one of aims of rehabilitation programs [1, 13, 114] and can be related with exercise-induced increases in exercise capacity [135-136, 144].

To detect the long-term effect of a 12-week exercise program we re-evaluated our patients with: CPET, 6MWT, 30-sec chair stand test, pulmonary function test, anthropometrics, blood biomarkers, dyspnea scale, QOL and physical activity levels at 11-month time point from baseline. In addition, we also followed up for exacerbations, hospitalizations and mortality for 15 months after the end of 12-week intervention. This comprehensive approach improves on the methodology of previous shorter follow-up periods following exercise programs [20, 26] and provides some presently unknown information on the effect of exercise training on prognosis and survival.

Taken together, the above described comprehensive approach demonstrates a broader picture with causality effects for the impact of exercise training on numerous short- and long-term clinical and physiological outcomes, with possible effects on the

prognosis for IPF patients. Furthermore, broad observation of different physiological systems may provide cues for further studies investigating the mechanisms underlying exercise-induced changes on pathology, signs and symptoms.

The exercise training program that was used for the present study was designed according to the guidelines for respiratory disease patients proposed by the American College of Chest Physicians/ American Association of Cardiovascular and Pulmonary Rehabilitation [1], the American Thoracic Society/European Respiratory Society [13, 114], the American College of Sports Medicine [42] and other professional groups [137]. Although these world-leading scientific and clinical organizations established a general framework for the exercise program in their "evidence-based guidelines" mainly on COPD patients, they also strongly recommended exercise pulmonary rehabilitation for other respiratory diseases such as ILD [1, 13, 42, 114, 137].

We performed a 12-week, twice-weekly 60 minute outpatient, supervised group exercise training program within the pulmonary unit in the hospital. The exercise training consisted of aerobic, resistance and flexibility components in each session. We divided our program into 2 six-week blocks, in which we progressively increased the overload as patients' tolerance increased. In each exercise session we included several breathing exercises for thoracic expansion and stretching of these muscles, which it was proposed would be effective for IPF [12]. We also attempted to improve the most researchable and functional-related exercise outcome of 6MWD among respiratory disease patients [1, 12-13, 114]. In each exercise session we conducted 5-8 minutes of self-paced walking in the hospital corridor specifically targeted to improve 6MWD. The rationale for using this method is based on the physiological principle of specificity in exercise training [145]. According to this principle physiological adaptation to exercise training is also specific to the stimulus that was applied, and greater adaption can be expected if the exercise stimulus is more specific to the performance that is measured [145].

In the first program block our goal was to build basic aerobic endurance, muscle strength and basic flexibility. For the aerobic component we applied progressive interval training at moderate intensity. The ratio of work to rest was gradually increased in each session until patients were able to maintain continuous aerobic

exercise for 15-20 minutes. For the resistance component we gradually increased the overload with accepted variables (increased number of repetitions in each set, increased number of sets for each exercise and increased weight). For the flexibility component we gradually increased the duration of muscle stretch in each exercise.
In the second block we wanted to further improve our patients in all components of the exercise program. We continued to gradually increase the overload based on performance in the first block. We also added 3-5 minutes of stair climbing within the hospital during the exercise sessions. This was the most difficult exercise for the patients and was intended to target the specific important component of functional capacity and activity of daily living, stair climbing [42].

In summary, we conducted a randomized control study using a strong comprehensive methodology to assess the short- and long-term effects of a 12-week supervised exercise training program on exercise tolerance, functional capacity, cardio-pulmonary functions, blood biomarkers, anthropometrics, quality of life and physical activity levels among IPF patients. We also intended to evaluate the prognostic effect and the impact of our treatment on the course of the disease. The tests we used in our study were well accepted, reliable and validated, and the exercise program used was set according to the proposed guidelines as mentioned above.

2. Results – discussion

2.1 Patients' baseline characteristics

In this study we recruited 34 IPF patients who were randomly assigned to exercise training (ET) or control group. Patients from both groups were medically treated with standard care, including low dose steroid therapy among 2/3 of patients. At baseline both groups of patients presented: moderate restrictive pulmonary pattern, normal left ventricle size and function with border-line systolic pulmonary arterial pressures, moderate to severe pulmonary diffusion abnormalities, impaired gas exchange, moderate exercise intolerance (VO_{2peak}: 60% predicted) dyspnea related physical effort, substantial hypoxemia during exercise and preserved functional capacity in most subjects. Based on objective parameters (FVC %predicted=68±16, the level of desaturation post 6MWT (SpO2=84±8%), DLCO %predicted= 51±15, level of dyspnea (mMRC=1.8±0.9), and functional exercise capacity of 6MWD (493±108m)

result) [7] and the subjective clinical impression of the study's pulmonologist, most patients in our study were classified as having moderate disease severity. In addition, most patients were overweight with high body fat percentage and a somewhat elevated CA 15-3 blood biomarker. No significant differences between the groups were detected at baseline for a great majority of variables. Only CA 15-3 and back stretch flexibility values were different between the groups at the beginning of the study.

2.2 Effect of exercise training in the pulmonary rehabilitation program

Our primary outcomes were changes in exercise tolerance in response to exercise training within pulmonary rehabilitation. To the best of our knowledge this is the first randomized controlled study of exercise training with IPF patients showing significant improvements in VO_{2peak}, anaerobic threshold and ventilatory responses, measured by CPET, which is considered the gold-standard measurement for cardio-respiratory capacity [43-44]. These are novel and unexpected findings among IPF subjects, especially because pulmonary function and gas exchange do not typically improve with exercise interventions in other respiratory diseases, such as chronic obstructive pulmonary disease [115]. Moreover, although enhancements inVO_{2peak} might be considered *per se* a strong result, our findings also demonstrated a cluster of exercise parameters assessed during CPET that also improved significantly. Since these parameters are objective and valid parameters of exercise tolerance both at maximal (VO_{2peak}, peak work-rate) and sub-maximal (anaerobic threshold) levels of exertion, we can be more confident regarding the efficacy of our treatment on the true improvement in exercise tolerance at different levels of exertion [41].

Furthermore, 6MWT was used in many previous studies [15-20, 22-24, 26] and also recommended by the American Thoracic Society as a valid and well-accepted tool to assess exercise capacity in lung disease patients [39]. Recently this test was also validated for IPF and the minimal clinical important difference (MCID) was established as 24-45m [127]. Following our exercise training program the ET group increased performance in 6MWD by 70±77m while the control decreased by 11±35 m, with a mean difference of changes between the groups of 81m CI (39-124) ($p<0.001$) (Figures 8, 9,). The magnitude of improvement in the ET is well above the MCID for 6MWD in IPF and presents a large and meaningful effect of this therapy

[127]. Moreover, in the within group analysis of the ET group we found that 13 out of 15 patients improved their performance in the 6MWD above the MCID (Figures 8, 9, Table 19). These results clearly indicate the efficacy of our 12-week supervised exercise training program for clinical improvement of IPF patients.

Previous studies with interstitial lung disease and IPF patients using an exercise-training program showed an improvement in 6MWD [24, 26], which is a test performed at sub-maximal intensity [40]. In the present study, patients were tested with cardiopulmonary exercise test, 6 minutes walk test, 30-second chair-stand test and 8- feet-up- and- go test, and those exposed to supervised exercise training improved both their sub-maximal (anaerobic threshold, 6MWD) and maximal exertion (VO_{2peak} and peak work-rate) levels, functional leg strength and functional agility- mobility. Our findings are consistent with Holland et al [26], but extend further with additional outcomes they did not observe such as improved VO_{2peak} and pulmonary function, possibly because of some differences in programs' length and the study populations. In Holland's study [26] the exercise training program endured for 8 weeks versus 12 weeks in our study, at baseline the patients had more severe levels of dyspnea symptoms (mMRC=3 versus less than 2 among our patients) and lower functional capacity (6MWT=354 m versus 493 m respectively) [26]. Probably shorter program's duration and the severity of the IPF patients in Holland's study had an impact on IPF's trainability, and lower level of adaption after exercise training program. These were previously demonstrated among COPD and ILD patients suggesting greater improvement in longer pulmonary rehabilitation programs [1, 12], and supported by Kuzo et al [16], who showed that the dyspnea severity and disability level of IPF patients has a negative impact on the degree of improvement following pulmonary rehabilitation [16]. Our findings are also in concordance to a recent report by Arizono et al [21], who also showed significant improvements of CPET parameters in IPF patients but not VO_{2peak} [21].

Our intervention also demonstrated significant improvements in pulmonary function and ventilatory responses, which are also novel in IPF. Patients allocated to the ET group showed resting and exercise pulmonary enhancements with respect to restrictive pathophysiology. Forced vital capacity %predicted, maximal ventilatory ventilation, peak minute ventilation and peak tidal volume were all improved following the 12-week intervention in the ET group. In previous randomized

controlled study the authors did not demonstrate changes in pulmonary function after an exercise training program in ILD and IPF patients [26]. Furthermore, in a large recent retrospective study the group reported a modest but statistically significant improvement in FVC following 5 weeks of an inpatient pulmonary rehabilitation program among ILD and IPF [22]. It is possible that differences in exercise training program construction and length have an impact on pulmonary system adaptation as a result of the program. In Holland's [26] and Huppmann's [22] studies program duration was significant shorter compared to our program, and the applied exercise training mode was standard exercise pulmonary rehabilitation for COPD patients, which may be less effective for ILD and IPF [12]. In our program we used specific exercise modes during each session including deep breathing for lung expansion and flexibility of the trunk to stimulate the restrictive pathophysiology of IPF. Since progression of IPF has a negative effect on pulmonary compliance, lung volumes, ventilatory responses and inefficient breathing pattern [5, 9, 82], it is reasonable to assume that specific exercises targeting this restrictive pathophysiology may enhance some of these functions as evidenced by significant improvements in these pulmonary and ventilatoty parameters [12].

Our exercise training program was also effective in improving dyspnea and quality of life, which is consistent with previous reports in IPF and ILD patients [17-19, 22-24, 26]. Dyspnea is the most common and predominant symptom bothering IPF patients, it progressively worsens over time and has significant negative impact on QOL [5, 7]. IPF patients experiencing dyspnea tend to be less physically active in order to avoid such episodes which influence their mobility and independence [85]. In addition, IPF patients also report higher degrees of fatigue, exhaustion, anxiety, depression and fear in their lives [10]. In our investigation, we measured the level of dyspnea by the mMRC scale, which was also used in previous studies with ILD and IPF patients [16-18, 26]. We showed significant improvement in mMRC following the intervention, mean difference of changes between the groups of -1.1 CI (-1.6- -0.5) units, $p<0.001$.

Quality of life is significantly impaired in IPF patients [10] and more pronounced in the physical domain [6]. Recently the MCID for changes in quality of life according to SGRQ was set at 5-8 points in IPF patients [132]. Our findings showed a significant improvement in QOL after a 12-week exercise program, based on SGRQ-total score, which is above the accepted MCID for IPF [132]. Following our exercise

pulmonary rehabilitation program the ET group decreased SGRQ by -6.9±6.5 points while the control increased by 2.8±3.6 points, with a mean difference of changes between the groups of -9.7 CI(-13.4- -5.9) ($p<0.001$) (Figures 8, 9,). Moreover, within group analysis among the ET group showed that 9 of 15 patients improved in SGRQ above the MCID (Figures 8, 9, Table 19). Our results are statistically significant and clinically important for improving dyspnea and QOL in IPF patients, consistent with previous studies which also showed the efficacy of exercise pulmonary rehabilitation on these outcomes [17-19, 22-24, 26]. Thus, the results suggest that supervised exercise training is clinically beneficial for improving dyspnea and QOL in IPF.

In addition, we demonstrated significant improvements in health-related fitness components associated with activities of daily living (ADL) [47]. We showed strength, agility-mobility and flexibility performance enhancement, body fat%, waist circumference and weight reduction and increase in physical activity levels in patients who participated in the supervised exercise training program. These results are novel and of clinical importance since excess body fat, particularly abdominal fat, and inactivity are major cardiovascular risk-factors among the older population [47, 142]. Because patients showed increased levels of body fat% and waist circumference at baseline, indicating abdominal obesity, amelioration of these conditions may decrease the risk of coronary artery disease which is highly prevalent and constitutes a significant cause of complications and mortality among IPF [7, 142-143]. Furthermore, IPF patients usually have some degree of disability and poor quality of life [6, 10, 146]. The enhancement of functional fitness components and increase in physical activity levels which occurred following our exercise training program can have significant impact on independence, activities of daily living and quality of life. Taken these components together, we showed significant improvements following our treatment in physiological health-related outcomes which are novel among IPF and may have clinical importance.

Our secondary outcomes in the present work were measures of additional physiological systems, which are stimulated by exercise training and may provide information about some of the mechanisms that explain the enhancements in exercise tolerance following the treatment. Echocardiography tests showed no significant differences between the groups or time effect on left ventricle size, geometry and function, except for intra-ventricular septum thickness, left ventricle end diastolic

diameter index. Both were changed and decreased following the intervention in the ET group. To the best of our knowledge there are no published studies of echocardiography in response to exercise training among IPF. Nevertheless, in pulmonary hypertension patients data showed no effect of exercise pulmonary rehabilitation on systolic pulmonary arterial pressure or cardiac output [138, 147]. With our resting echocardiography measures we were unable to demonstrate cardiac ameliorations that might explain the improvement in VO_{2peak}. It is possible that resting echocardiogram is a less sensitive tool for detecting changes following short-term exercise training programs in IPF. Perhaps stress-echocardiography could have shown more sufficient cardiac changes related to the enhanced cardio-respiratory capacity that was presented in the ET group. More research is warranted to study heart function in response to exercise training in IPF.

In the present investigation we used several blood biomarkers to identify the molecular indicators of IPF severity and disease progression in response to exercise training. Although the biomarkers we tested are less "classical" in IPF research, several previous studies support their use, and their high availability in daily practice make them preferred candidates [29-32]. Following the intervention we found a trend of decline in CA 15-3 and CRP blood biomarkers among the ET group, although the results did not reach statistical significance, probably due to small sample size. Previous reports demonstrated a negative relationship between exercise parameters and CA 15-3, and a significant reduction in the marker following lung transplantation among IPF patients [32]. The remodeling of fibrotic lung includes thickening of the alveolar wall, parenchymal damage and distortion of normal lung architecture which is related with inflammatory processes [5, 80]. CRP is a marker of systemic inflammation [112] and is considered an important inflammatory biomarker for atherosclerosis and coronary artery disease [113]. Several studies of IPF patients demonstrated elevated CRP levels associated with poor prognosis suggesting some degree of inflammation [36-37]. Although CRP is not a specific local biomarker of lung inflammation, the decline of this marker following exercise program may indicate an improvement of this pathologic mechanism in IPF patients.

We speculate that among the ET group after exercise pulmonary rehabilitation, some histological changes within the lung tissue may have occurred based on the physiological improvements in pulmonary and ventilatory functions that were

detected. However, in the present study this was not measured directly, and should be ascertained in future research. Therefore, our data do not support the enhancement in blood biomarkers associated with IPF severity and progression.

During the follow-up period no significant differences between the ET and the control group were observed with respect to IPF exacerbation, hospitalization and mortality rates, which is consistent with previous reports in ILD and IPF patients [26]. Our results of short-term supervised exercise training based pulmonary rehabilitation did not demonstrate a beneficial effect on the disease course in IPF. Future research should address the question of whether long-term programs have any impact on the prognosis of IPF.

After an average 8 months post 12-week intervention the improvements in exercise tolerance and functional capacity, pulmonary and ventilatory functions, dyspnea, quality of life, anthropometric changes and physical activity levels were no longer sustained among the ET group. A significant deterioration was observed which was more pronounced in the ET group. At the 11 month time-point from baseline, there were no significant differences in any outcomes between the groups. The ET group returned to baseline values in most outcomes, while the control group showed a trend of slow decline in the outcomes. Despite this, after 11 months from the beginning of the study the results for the ET group remained similar to baseline values. We can speculate that if the patients had not attended exercise pulmonary rehabilitation a trend of deterioration would probably have been seen, as in the control group. We believe this is also an important clinical benefit of our program in which the patients' condition did not worsen as the disease took its course. Only two studies with exercise training and ILD patients reported follow-up data [20, 26]. Our results aligns with Holland et al's [26] study which also did not find any preserved benefits of an 8-week exercise pulmonary rehabilitation program at a 6-month follow-up [26]. But in contrast to Reyrson et al [20] who had show a preserved improvement for QOL, depression and physical activity at a 6-month follow-up [20]. Among COPD patients studies showed that short-term (6-12 week) exercise pulmonary rehabilitation resulted in prolonged benefits for some outcomes (dyspnea symptoms and quality of life) up to 12-18 months after completing the program [1]. However, Otsuka et al [148] found significant deterioration in physiological responses measured during CPET at 5 months post exercise training program among COPD patients [148]. It is possible that

despite an objective decline in physiological functions as a detraining effect, some subjective benefits such as dyspnea perception or quality of life might be preserved in COPD patients. Nevertheless, our results showed significant decline both in objective physiological functions (VO_{2peak}, $V_{E\ peak,}$ peak work rate, peak VT) and subjective reports of dyspnea and quality of life. Probably the pathophysiology in ILD and IPF is different from that in COPD in terms of preservation of the achieved benefits following exercise pulmonary rehabilitation, and other approaches are required to sustain the clinical benefits for a longer duration.

We conducted a randomized controlled study of short-term supervised exercise training based pulmonary rehabilitation with a sufficient period of follow-up among IPF patients. Although we were unable to demonstrate any benefits of our treatment regarding hospitalizations, exacerbations of IPF and mortality, it is unclear whether a long-term program might have some benefits on these outcomes in IPF. We can speculate that long-term supervised exercise training might have an additional benefit on the prognosis for IPF, since FVC %predicted, VO_{2peak}, 6MWD and dyspnea levels (mMRC) have been proposed as prognostic parameters for increased risk of mortality in those patients [7, 36, 45, 48-49]. It is presumptive to assume that improvements and maintenance of those parameters may increase long-term physiological reserves, delay the clinical course and slow the progression of the disease. This issue must be ascertained in long-term exercise program studies.

The effect of exercise training on improving physiological and clinical outcomes in IPF can be explained by several mechanisms. IPF patients usually present impaired lung compliance and low efficiency breathing patterns as part of their restrictive pathophysiology [5, 9, 82]. It is possible that repetitive stimulus of high ventilatory demands during exercise sessions, chest expansion during deep-breathing exercises and stretching of the thoracic muscles that we used in our program, resulted in a more efficient breathing pattern adaptation, improved strength of respiratory muscles, enhanced pleural elasticity and pulmonary compliance within the lung tissue, and decreased rigidity in rib cage structures and dyspnea perception after the exercise training program [9, 12, 82]. This aligns with recently reports showing beneficial effects of thoracic expansion and stretching on pulmonary restriction in IPF [12]. Part of these physiological changes may have occurred as a result of our treatment since improvements in pulmonary function (FVC %predicted), ventilatory responses (peak

VT, V_{Epeak}, MVV), gas exchange (VO_{2peak}, AT) mMRC dyspnea scale, exercise (peak WR, 6MWD, and quality of life (SGRQ) were indeed demonstrated among the ET group, although pulmonary morphological adaptations were not tested objectively in the current study and need to be ascertained in future studies.

Most patients in the ET group presented improvements in exercise tolerance, ventilatory capacities and mMRC which are strengthened by the relationship between exercise and ventilatory capacities and exertion dyspnea respectively. This is consistent with Manali et al [79] who reported a significant correlation between mMRC and VO_{2peak} in IPF patients [79]. The enhancement in ventilatory responses that occurred after the exercise program could have increased alveolar oxygen tension and improvements in alveoli ventilation to perfusion (V_A/Q) mismatch, resulting in an increase in VO_{2peak} [5, 9, 82]. This was partially supported by the trend of decline in dead space/tidal volume (VD/VT) in the ET group. Although most of our patients were not limited by ventilation and presented a normal breathing reserve, ventilatory enchantments seem to be closely related to the improvements in exercise capacity.

In the exploratory analysis using stepwise linear multiple regression models and Pearson correlations between the variables we noted that improvements in exercise capacity (VO_{2peak} and 6MWD) were highly correlated with ventilatory and pulmonary enhancements among the ET group which explains 57% and 75% of changes in these variables respectively (Table 21). Improvement in VO_{2peak} was closely related to improvement of peak VT in the ET group (Tables 22, 23, Figure 9). Furthermore, improvement in FVC in the ET group was largely explained (77%, $p<0.001$) by improvements in 6MWD, $V_{E\ peak}$, and AT by the linear regression model (Table 21). Changes in QOL (SGRQ-total score) were partially explained by changes in FVC (Table 22), consistent with the results of Tzanakis et al [149] who also demonstrated a significant correlation between FVC and SGRQ [149]. In addition, a moderate correlation was seen between SGRQ and 6MWD (Table 23), which was also supported previously by Nishiyama et al [24].

Surprisingly, our results showed that improvement in exercise capacity (VO_{2peak} and 6MWD) was not associated with improvement in leg strength in the 30-second chair-stand test (Table 23). Our data indicate that most of the improvement in exercise tolerance occurred due to ventilatory factors for VO_{2peak}, and ventilatory and

pulmonary enhancements for 6MWD, although it is also likely that cardiovascular adaptations contributed to some extent to the increase in exercise capacity evident by some improvement in O_2 pulse and trend of decline in resting heart rate after the exercise training program [10]. Furthermore, our data indicate that improvement in FVC is a potential mediator for other clinical outcomes (both exercise and QOL) in IPF which should be further explored in future studies.

Despite the fact that our program was sufficient to increase leisure time physical activity, this achievement lacked any relationship to improvement in exercise tolerance or functional capacity (Table 23), probably because this physical activity was performed below the intensity threshold for improving exercise capacity and function. Thus, our data suggest that most improvements in symptoms and quality of life occurred due to changes in exercise functional capacity (Δ6MWD) and pulmonary function (ΔFVC %predicted), and these clinical and physiological benefits were achieved primarily by the supervised exercise training program.

The changes in body composition that the ET group demonstrated following a 12-week intervention probably occurred due to a negative caloric balance [142]. The patients increased their energy expenditure by 2-week supervised sessions in our unit and home-based physical activity. These might have caused the reductions in body fat%, weight and waist circumference that were observed in our study.

The fact that the majority of benefits achieved after the 12-week exercise pulmonary rehabilitation were lost by the ET group during the follow-up examinations may suggest that IPF patients need long-term, rather than short-term, medically supervised exercise training programs. IPF is a heterogenic and fatal lung disease with severe presentation of clinical signs and symptoms especially during physical exertion [7]. In addition, patients with IPF frequently demonstrate mood disturbances such as depression, anxiety, sadness, fear, worry and panic [6, 10, 146]. It might be that the severe symptoms and accompanying psychological disorders among IPF have an impact on maintenance of home-based exercise training, and avoidance of sufficient exercise intensity stimulus. Thus, we hypothesize that IPF patients should be referred for long-term exercise pulmonary rehabilitation program and future research should address this question. Despite the financial burden on health systems of such programs and lack of evidence at present to support the recommendation for long-

term exercise pulmonary rehabilitation, it should be taken into account that IPF is deadly lung disease with a mean survival 2-5 years [7]. Moreover, currently there is no effective treatment except lung transplantation for the majority of IPF patients. For most patients lung transplantation is unfeasible, due to their advanced age, which excludes them from the transplant-list, and lack of lung organs [7, 12]. Taking these facts together, our data and previous reports suggesting that supervised exercise training based pulmonary rehabilitation is a safe and efficient treatment for clinical improvements with very few possible adverse events, and since to date a cure for IPF has remained elusive, it seems reasonable to recommend this therapy for long-term use [12, 24, 26].

Our results strengthen the evidence for the role of exercise training in pulmonary rehabilitation for IPF patients. The data have significant clinical and practical implications for IPF patients. Supervised group exercise training based pulmonary rehabilitation clearly showed the potential to improve several outcomes and few concerns about safety and side effects. In addition, our data emphasize the clinical significance of long-term exercise pulmonary rehabilitation programs in IPF.

3. Study limitations

Our study has several limitations. First, sample size was relatively small for each group of patients and somewhat heterogeneous, nevertheless a power analysis for the required sample size was calculated and recruited. A sufficient number of participants yielded enough power for detecting significant changes in primary and secondary outcomes. Second, the primary outcomes measured from the cardiopulmonary exercise test and 6MWT were non-blinded, due to lack of qualified medical personal for exercise testing and exercise training in our institute, although no differences were found between the groups in self-report Borg dyspnea post 6MWT (Table 11), and RER levels in CPET which supports that both groups reached the same level of exertion during these tests. In addition, pulmonary function assessments which were performed blinded to group allocation and time of the study clearly showed significant mean differences between the groups in FVC and MVV, reflecting true changes that occurred following our intervention. In retrospect, we probably should have used stress-echocardiography instead of resting measures, since no significant

differences were detected in resting echocardiography examination following the intervention.

4. Perspectives for future research

Our study revealed some unresolved research directions that should be addressed in the future. First, the effect of supervised exercise training on disease progression, exacerbations and survival in IPF is unclear from our results and need to be clarified in well-designed longer-term studies. The second direction for future is morphological and histological adaptation to exercise pulmonary rehabilitation of the lung tissue, which is also unknown at the moment. Future works should use low-dose high-resolution computed tomography (HRCT) in pulmonary rehabilitation studies to detect changes within the lungs. At present only short-term exercise pulmonary rehabilitation studies exist in IPF. In the future long-term programs need to be evaluated in terms of mortality, exacerbations, exercise tolerance, dyspnea symptoms and quality of life. More research is also warranted for examining the psychological health effect of these programs.

The effect of exercise pulmonary rehabilitation programs is also important for evaluating health related risk factors, co-morbidities, peripheral muscle function and cardiac function. Finally, future researches should try to identify the optimal exercise pulmonary rehabilitation program for IPF using different exercise modalities from COPD programs. Such training should stimulate the restrictive pathophysiology of IPF, for instance by using swimming or water gymnastics.

CHAPTER VI

CONCLUSIONS AND CLINICAL IMPLICATIONS

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1. Conclusions

Considering the purposes of the present study we conclude the following:

i. Short-term outpatient supervised group exercise training based-pulmonary rehabilitation programs improve exercise tolerance, functional capacity, pulmonary function, ventilatory responses, physical activity levels, body composition, dyspnea and quality of life in patients with IPF.

ii. Ventilatory enhancements seem to be a primary contributing mechanism in improved cardio-respiratory capacity (VO_{2peak}) of IPF, while amelioration in quality of life was closely related to improvement of forced vital capacity and the improvement in 6MWD was highly associated with ventilatory enhancement and forced vital capacity. The finding of ventilatory enhancement as a possible primary mechanism for amelioration of exercise capacity is the opposite of our original hypothesis. We thought cardiovascular and muscle systems would be the mechanistic source of the improvement in exercise capacity; however, the results indicate that ventilatory enhancement is the primary contributor to this adaptation.

iii. The increased physical activity levels following the 12-week intervention among the ET group were not associated with any exercise, functional or clinical outcomes, suggesting that home-based physical activity are probable less effective for eliciting improvements in clinical outcomes in IPF.

iv. Short-term exercise training in a pulmonary rehabilitation program was unable to show any long-term benefits in exacerbations, hospitalizations and mortality.

v. The improvements achieved in the clinical outcomes following a 12-week supervised exercise training program were not-sustained after 8 months post intervention. However, at the follow-up, patients in the ET group returned to baseline, and maintained their beginning values.

In summary, the finding of this randomized controlled study strengthens the evidence for the beneficial effect of supervised exercise training-based pulmonary rehabilitation on clinical outcomes in IPF patients, although short-term improvements were unpreserved for long-term.

2. Clinical implications

1) Exercise training based pulmonary rehabilitation in IPF patients is a safe practice with low concern of side-effects.
2) Exercise pulmonary rehabilitation is an effective treatment for clinical improvement and should be considered as standard care for IPF.
3) Since idiopathic pulmonary fibrosis is a deadly lung disease and has few efficient therapeutic options, exercise-based pulmonary rehabilitation may be an alternative care for improving and maintaining function in daily tasks and quality of life.
4) Although according to a latest American Thoracic Society/European Respiratory Society evidence-based guidelines on IPF, pulmonary rehabilitation has only a "weak" level of recommendation [7], our findings strengthen the evidence for the clinical benefits of exercise training-based pulmonary rehabilitation, which should be considered in clinical decisions to recommend exercise pulmonary rehabilitation for IPF patients.
5) Our data also emphasize the clinical significance of conducting long-term exercise pulmonary rehabilitation programs for IPF patients, since most benefits were not sustained after 8 months post intervention.

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APPENDIX

Academic activity related to this dissertation

Published papers:

Vainshelboim B. and Kramer MR. The Role of Pulmonary Rehabilitation in Idiopathic Pulmonary Fibrosis. Harefua; 151, 4, 2012.

Accepted for publication:

Submitted to journals:

Baruch Vainshelboim, Jose Oliveira, Liora Yehoshua, Israela Weiss, Benjamin Daniel Fox , Oren Fruchter and Mordechai R. Kramer. "Exercise Training Based Pulmonary Rehabilitation Program is Clinically Beneficial for Idiopathic Pulmonary Fibrosis". "Respiration".

Accepted abstracts and presented posters and oral presentations in international conferences:

Baruch Vainshelboim, Jose Oliveira, Alexander Sagie, Gila Ruth, Mali Mantzur, Liora Yehoshua, Israela Weiss and Mordechai R. Kramer**. Oral presentation:** "Effect of Exercise Training on Left Ventricle Systolic Function, Exercise Tolerance and Prognostic Predictors in Idiopathic Pulmonary Fibrosis Patients". The 60th International Conference of Israel Heart Society. 22-23 April 2013, Jerusalem, Israel.

Mordechai R. Kramer, Baruch Vainshelboim, Jose Oliveira, Liora Yehoshua1, Israela Weis1, Victoria Rusanov, Oren Fruchter. **Poster presentation**: "Pulmonary Rehabilitation Improves Exercise Capacity and Function in Patients with Idiopathic Pulmonary Fibrosis" American Thoracic Society International Conference May 17-22, 2013, Philadelphia, Pennsylvania , USA.

Baruch Vainshelboim, Jose Oliveira, Liora Yehoshua, Israela Wais, Mordechai R. Kramer. **Poster presentation:** "Effect of Pulmonary Rehabilitation Program on Exercise Tolerance and Functional Capacity in Patients with Idiopathic Pulmonary Fibrosis. 60th Annual Meeting of American College of Sports Medicine, May 28-1 June 2013, Indianapolis, Indiana, USA.

Baruch Vainshelboim, Jose Oliveira, Liora Yohoshua, Israela Wais and Mordechai R. Kramer. **"Accepted for oral presentation"** "Exercise Training in Pulmonary Rehabilitation Program is Beneficial for Idiopathic Pulmonary Fibrosis". 2013 Congress of the European College of Sport Sciences, 26-29 June 2013, Barcelona, Spain.

Baruch Vainshelboim, Jose Oliveira, Liora Yehoshua, Israela Wais, Mordechai R. Kramer. **Poster discussion presentation:** "The Effect of Pulmonary Rehabilitation on Exercise Tolerance Pulmonary Function Dyspnea and Quality of Life in Patients with Idiopathic Pulmonary Fibrosis". European Respiratory Society Annual Congress 7-11 September 2013, Barcelona, Spain.

Baruch Vainshelboim, Jose Oliveira, Benjamin D. Fox, Liora Yehoshua, Mordechai R. Kramer. **Oral presentation**: "Effect of Exercise Pulmonary Rehabilitation on Long-Term Outcomes in Idiopathic Pulmonary Fibrosis". American Thoracic Society International Conference May 16-21, 2014, San Diego, California, USA.

Baruch Vainshelboim, Jose Oliveira, Benjamin D. Fox, Liora Yehoshua, Mordechai R. Kramer. **Poster presentation**: "Effect of Exercise Pulmonary Rehabilitation on Long-Term Outcomes in Idiopathic Pulmonary Fibrosis". 61th Annual Meeting of American College of Sports Medicine, May 27-1 June 2014, Orlando, Florida, USA.

Baruch Vainshelboim, Jose Oliveira, Benjamin D. Fox, Liora Yehoshua, Oren Fruchter and Mordechai R. Kramer. **Oral presentation**: "Exercise Training Based Pulmonary Rehabilitation Program in Idiopathic Pulmonary Fibrosis" The 2014 Wingate Congress of Exercise and Sport Sciences, 12-15 June, Netanya, Israel.

QUESTIONNAIRES

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

St. George's Respiratory Questionnaire
PART 1

Questions about how much chest trouble you have.

Please select **ONE** box for each question:

Question 1. I cough:

- most days a week ..... ☐ a
- several days a week ..... ☐ b
- only with chest infections ..... ☐ c
- not at all ..... ☐ d

Question 2. I bring up phlegm (sputum):

- most days a week ..... ☐ a
- several days a week ..... ☐ b
- only with chest infections ..... ☐ c
- not at all ..... ☐ d

Question 3. I have shortness of breath:

- most days a week ..... ☐ a
- several days a week ..... ☐ b
- not at all ..... ☐ c

Question 4. I have attacks of wheezing:

- most days a week ..... ☐ a
- several days a week ..... ☐ b
- a few days a month ..... ☐ c
- only with chest infections ..... ☐ d
- not at all ..... ☐ e

Question 5. How many attacks of chest trouble did you have during the last year?

3 or more attacks ..... ☐ a

1 or 2 attacks..... ☐ b

none ..... ☐ c

Question 6. How often do you have good days (with little chest trouble)?

no good days..... ☐ a

a few good days..... ☐ b

most days are good ..... ☐ c

every day is good..... ☐ d

Question 7. If you have a wheeze, is it worse in the morning?

no ..... ☐

yes..... ☐

St. George's Respiratory Questionnaire
PART 2

8. ***How would you describe your chest condition?***

Please select ***ONE***:

Causes me a lot of problems or is the most important problem I have	☐ a
Causes me a few problems	☐ b
Causes no problem	☐ c

9. ***Questions about what activities usually make you feel breathless.***

For each statement please select ***the box*** that applies to you **these days**:

	True	False
Getting washed or dressed.....	☐	☐ a
Walking around the home.....	☐	☐ b
Walking outside on the level.....	☐	☐ c
Walking up a flight of stairs.....	☐	☐ d
Walking up hills.....	☐	☐ e

St. George's Respiratory Questionnaire
PART 2

10. ***Some more questions about your cough and breathlessness.***

For each statement please select ***the box*** that applies to you **these days**:

	True	False	
My cough hurts	☐	☐	a
My cough makes me tired	☐	☐	b
I am breathless when I talk	☐	☐	c
I am breathless when I bend over	☐	☐	d
My cough or breathing disturbs my sleep	☐	☐	e
I get exhausted easily	☐	☐	f

11. ***Questions about other effects that your chest trouble may have on you.***

For each statement please select ***the box*** that applies to you **these days**:

	True	False	
My cough or breathing is embarrassing in public	☐	☐	a
My chest trouble is a nuisance to my family, friends or neighbours	☐	☐	b
I get afraid or panic when I cannot get my breath	☐	☐	c
I feel that I am not in control of my chest problem	☐	☐	d
I have become frail or an invalid because of my chest	☐	☐	e
Exercise is not safe for me	☐	☐	f
Everything seems too much of an effort	☐	☐	g

St. George's Respiratory Questionnaire
PART 2

12. ***These are questions about how your activities might be affected by your breathing.***

For each statement please select ***the box*** that applies to you **because of your breathing**:

	True	False	
I take a long time to get washed or dressed	☐	☐	a
I cannot take a bath or shower, or I take a long time	☐	☐	b
I walk slower than other people, or I stop for rests	☐	☐	c
Jobs such as housework take a long time, or I have to stop for rests	☐	☐	d
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐	e
If I hurry or walk fast, I have to stop or slow down	☐	☐	f
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐	g
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	☐	☐	h

13. ***We would like to know how your chest trouble <u>usually</u> affects your daily life.***

For each statement please select ***the box*** that applies to you **because of your breathing**:

	True	False	
I cannot play sports or games	☐	☐	a
I cannot go out for entertainment or recreation	☐	☐	b
I cannot go out of the house to do the shopping	☐	☐	c
I cannot do housework	☐	☐	d
I cannot move far from my bed or chair	☐	☐	e

St. George's Respiratory Questionnaire

14. ***How does your chest trouble affect you?***

Please select ***ONE***:

It does not stop me doing anything I would like to do ..... ☐ a

It stops me doing one or two things I would like to do..... ☐ b

It stops me doing most of the things I would like to do..... ☐ c

It stops me doing everything I would like to do..... ☐ d

Thank you for filling in this questionnaire.

Before you finish, would you please check to see that you have answered all the questions.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (IPAQ)

(August 2002)

SHORT LAST 7 DAYS SELF-ADMINISTERED FORMAT

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ

The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ

Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation

Translation from English is supported to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ

International collaboration on IPAQ is on-going and an ***International Physical Activity Prevalence Study*** is in progress. For further information see the IPAQ website.

More Information

More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective*. Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

_____ days per week

☐ No moderate physical activities → ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ hours per day

_____ minutes per day

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ days per week

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

Modified Medical Research Council (mMRC)

Table 1. Modified Medical Research Council Questionnaire for Assessing the Severity of Breathlessness

Scale	
mMRC Grade 0	I only get breathless with strenuous exercise.
mMRC Grade 1	I get short of breath when hurrying on the level or walking up a slight hill.
mMRC Grade 2	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.
mMRC Grade 3	I stop for breath after walking about 100 meters or after a few minutes on the level.
mMRC Grade 4	I am too breathless to leave the house or I am breathless when dressing or undressing.

Borg Category Ratio (CR) 10

rating	description
0	NOTHING AT ALL
0.5	VERY, VERY LIGHT
1	VERY LIGHT
2	FAIRLY LIGHT
3	MODERATE
4	SOMEWHAT HARD
5	HARD
6	
7	VERY HARD
8	
9	
10	VERY VERY HARD (MAXIMAL)