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Preface

The book contains the articles related to the clinical advances in the regulation of the respiratory system. The research presented herein was communicated and discussed at the International Conference 'Advances in Pneumology,' which was held in Bonn, Germany, on June 17–18, 2011. The articles are a selection of peer-reviewed manuscripts to demonstrate the scope of the issues tackled at the conference. The conference is thought as a merger between basic and clinical research concerning respiratory medicine, neural and chemical respiratory regulation, and the mutual relationship between respiration and other neurobiological functions. Clinical pathophysiology of the respiratory system is always at the core of these meetings. The topics included lung function, hypoxic lung pathologies, pharmacotherapy, epidemiology, and cardiovascular-respiratory interactions, particularly during sleep. Other essential topics of interest were infections and inflammatory conditions exemplified by asthma and chronic obstructive pulmonary disease (COPD), respiratory allergy and cough, and also psychosomatic issues which broadened the scope of the conference. In the articles presented in this volume, the cutting-edge knowledge is communicated and discussed by prominent experts in the areas of science outlined above. I want to thank all the speakers at the conference and the authors and reviewers of the articles; their contributions certainly will enhance the value of this volume.

The 'Advances in Pneumology' is an annual conference organized alternately in Poland and Germany. It refers to the long-standing contacts between Polish and German clinicians and researchers in the field of respiration. The contacts have begun decades ago from the common interest in prophylaxis and treatment of respiratory ailments in coal miners and in populations inhabiting the mining regions of both countries. Nowadays, the coal mining is limited, but the diseases and clinical problems persist.

The 2011 conference was the fruit of many collaborative efforts. The Local Organizing Committee was headed by Dr. Rüdiger Siekmeier of the Federal Institute for Drugs and Medical Devices (BfArM) in Bonn, Germany. I am indebted to him for his efforts and to all those who extended a helping hand and advice in the organization, particularly Prof. Dr. med. Kurt Rasche of HELIOS Klinikum Wuppertal Lungenzentrum, Klinik für Pneumologie, Allergologie, Schlaf- und Beatmungsmedizin and Ms. Anke Hastenrath of Wuppertal, and Dr. Tadeusz M. Zielonka of Warsaw Medical University and the Polish Respiratory Society in Warsaw, Poland.

I also want to thank the non-profit research and academic institution which kindly cooperated and supported the organization of the conference and the publication of this book, particularly the Medical Research Center of the Polish Academy of Sciences in Warsaw, the Polish Respiratory Society, and the Rhein-Ruhr-Stiftung in Essen. Finally, I am also grateful to Mr. Max Haring, Ph.D., and Ms. Tanja van Gaans of Springer for their expert management of the production process of this book.

Due to the efforts of all involved in the conference, the participants could not only benefit from scientific knowledge and contacts but also could enjoy the vibrant Bonn's life. It had been decided at the conference that the next conference of this series will be held in the city of Wroclaw in southwest Poland on October 5–6, 2012; details can be accessed at http://www.pneumology.pl.

Warsaw, Poland Mieczyslaw Pokorski

Contents

Chapter 1
Assessment of Airway Hyperresponsiveness: Comparison of Spirometry and Body Plethysmography

F. Nensa, N. Kotschy-Lang, H.-J. Smith, W. Marek, and R. Merget

Abstract While methacholine (MCH) testing is commonly used in the clinical diagnosis of asthma, the detection of airway narrowing often relies on either spirometry or body plethysmography, however comparative studies are rare. In this study we performed MCH testing in 37 patients with variable shortness of breath at work and in 37 patients with no history of airway disease. The inclusion criteria were: no acute respiratory infection within 6 weeks, no severe diseases, normal baseline specific airway resistance (sR_{aw}), normal baseline forced expiratory volume in 1 s (FEV_1), Tiffeneau index >70%, no previous treatment with steroids within 14 days and no short acting bronchodilators within 24 h. Cumulative doses of 0.003, 0.014, 0.059, 0.239 and 0.959 mg MCH were inhaled by a dosimeter method. A FEV_1 decrease of ≥20% from baseline and a 100% increase of sR_{aw} to ≥2.0 kPa/s was defined as end-of-test-criterion. Provocation doses were calculated by interpolation. Performance of lung function parameters was compared using receiver-operating-characteristic (ROC) analysis. ROC analysis resulted in an area under the ROC curve (AUC) of 0.74 for FEV_1 *vs.* 0.82 for sR_{aw}. The corresponding Youden Indices (J) were 0.46 for FEV_1 and 0.57 for sR_{aw}. The Youden Index of sR_{aw} was higher and sensitivity and specificity (73%/84%) were rather well-balanced, in contrast to FEV_1 (54%/92%). In conclusion, in cumulative MCH challenges sR_{aw} was found to be the overall most useful parameter for the detection of bronchial hyperresponsiveness. Body plethysmography yielded a balanced sensitivity-specificity ratio with higher sensitivity than spirometry, but comparable specificity.

Keywords Airway hyperresponsiveness • Asthma • Bronchodilation • Body plethysmography • Methacholine • Spirometry • Airway resistance

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1.1 Introduction

Airway hyperresponsiveness is defined as an exaggerated bronchoconstrictive response to a number of inhaled physical, chemical or pharmacologic stimuli that occurs in patients with asthma, but not or rarely in healthy subjects. As a distinctive characteristic of asthma it regularly appears earlier (at lower doses) and is more intensive in patients with asthma and therefore underlies the rationale for bronchial challenge testing (Crapo et al. 2000; Cockcroft et al. 1977; Juniper et al. 1981). Both the American Thoracic Society (ATS) (Crapo et al. 2000) and the European Respiratory Society (ERS) (Sterk et al. 1993) recommend challenge tests by inhalation of aerosolized methacholine (MCH).

Spirometry being technically simple, cheap and highly reliable is currently the most commonly used method of indirect airway narrowing detection. A fall of the forced expiratory volume in 1 s (FEV_1) of at least 20% from baseline following MCH inhalation is widely used to determine airway hyperresponsiveness. However, FEV_1 largely depends on the subject's cooperation, which especially has to be considered in the context of pediatric examinations and medical opinions. Furthermore, FEV_1 maneuvers require maximal inspiration that has been shown to reduce bronchoconstriction induced by histamine or methacholine (Cockcroft and Davis 2006; Nadel and Tierney 1961). Slats et al. (2007) showed that airways inflammation plays an essential role in the bronchoprotective effects of deep inhalations in healthy subjects and patients with bronchial asthma. Bronchoprotection by deep inhalation may however be of only minor importance in patients with chronic obstructive pulmonary disease (COPD) and increased levels of airway resistance (Slats et al. 2007).

In contrast, body plethysmographic measurements of specific airway resistance (sR_{aw}) are performed under tidal breathing conditions, requiring only a minimum of the subject's cooperation. A ≥100% increase of sR_{aw} from baseline to a minimum absolute value of 2.0 kPa/s is a commonly used threshold to determine airway hyperresponsiveness (Baur et al. 2005; Criée et al. 2011). Comparative studies between spirometry and body plethysmography as effect parameters are rare. Hence both methods were compared in order to evaluate the concordance of spirometry and body plethysmography concerning their clinical value during MCH testing.

1.2 Methods

1.2.1 Subjects

MCH testing was performed in 74 patients (Table 1.1) during their stay at Berufsgenossenschaftliche Klinik für Berufskrankheiten, Falkenstein, Germany. Subjects were assigned to two groups. The asthma group consisted of 37 (20 males) patients who reported variable shortness of breath at work in recent years. Subjects with isocyanate exposure and subjects with COPD-like disease were excluded. The control group consisted of 37 (22 males) patients with unrelated diagnoses that are not known to cause airway hyperresponsiveness, but no history of airway diseases.

All subjects met the following criteria: no acute respiratory infection or exacerbation within the preceding 6 weeks; no severe accompanying diseases; normal baseline sR_{aw} and FEV_1, FEV_1/FVC >70%, no previous treatment with oral or inhaled steroids within 14 days, and no short acting bronchodilators within 24 h before MCH testing. Also patients were asked to refrain from using caffeine containing beverages. A paradoxical increase in FEV_1 >5% of baseline during methacholine testing was regarded as a sign of unstable breathing control and those tests (n = 8) were subsequently excluded from the study for quality assurance. All patients were over 18 years

Table 1.1 Demographic and pulmonary baseline data of subjects included in the study

Group	N (males)	Age (year)	Weight (kg)	Height (cm)	sR_{aw} (kPa/s)	FVC (L)	FEV_1 (L)	FEV_1/FVC (%)
Normal	37 (20)	48 ± 13	78 ± 15	171 ± 9	0.70 ± 0.2	4.1 ± 0.9	3.3 ± 0.8	82 ± 6
Asthmatic	37 (22)	47 ± 14	83 ± 18	170 ± 10	0.85 ± 0.2	4.2 ± 0.9	3.4 ± 0.7	82 ± 5

Table 1.2 Methacholine testing protocol

Step	Concentration	Dose (mg)	Cumulative dose (mg)	Substance	Procedure
B	0.9%	0.072	0.072	Saline	8 breaths
1	3.3 mg/mL	0.003	0.003	Methacholine	1 breath
2	16.5 mg/mL	0.011	0.014	Methacholine	1 breath
3	16.5 mg/mL	0.045	0.059	Methacholine	3 breaths
4	16.5 mg/mL	0.180	0.239	Methacholine	10 breaths
5	16.5 mg/mL	0.720	0.959	Methacholine	16.36 s inspiration

of age (range 22–74, average 47 years) and informed written consent was obtained from each subject. The study protocol was approved by a local Ethics Committee.

1.2.2 Methacholine Testing

An ATS-adapted dosimeter method was used, with minor modifications as described recently (Merget et al. 2009). Briefly, methacholine chloride (Provokit, Lindopharm, Hilden, Germany) was dissolved in sterile water supplied with the product to a concentration of 3.3 mg/mL for the first very low dose provocation step and 16.5 mg/mL for all following steps (Table 1.2). After measuring baseline values and an initial inhalation of aerosolized isotonic saline, MCH was administered in up to five steps (0.003, 0.011, 0.045, 0.180, and 0.720 mg) aerosolized by a MedicAid nebulizer (mass median aerodynamic diameter of particles of 3.2 μm) and dosimetrically applied by the APS provocation system (CareFusion, Höchberg, Germany).

The cumulative inhaled doses after each step of inhalation (0.003, 0.014, 0.059, 0.239, and 0.959 mg MCH) were obtained by taking one breath (3.3 mg/mL) at step one, one breath (16.5 mg/mL) at step two, three breaths (16.5 mg/mL) at step three and ten breaths (16.5 mg/mL) at step four. At step five patients took multiple breaths until a total inspiration time of 16.36 s was accumulated.

1.2.3 Lung Function Measurements

sR_{aw} and intrathoracic gas volume (FRCpleth) were recorded by body plethysmography (MasterScreen, CareFusion, Höchberg, Germany). Spirometry was performed after sR_{aw} tidal breathing analysis and linked to FRCpleth in the sitting position. Body plethysmography and forced spirometric maneuvers were performed at rest and 2 min after inhalation of saline and each MCH dose, with the measurements of sR_{aw}, FRCpleth, and FEV_1.

A fall of FEV_1 ≥20% from baseline together with an sR_{aw} increase of ≥100% from baseline to ≥2 kPa/s or application of the maximum MCH dose was defined as end-of-test-criterion. Because most thresholds in MCH testing are defined relative to the baseline values and therefore the accuracy of these are critical to the whole test, baseline measurements without any prior inhalation were repeated several times. From three spirometric measurements that fulfilled acceptability criteria the best was identified by the maximal sum of FEV_1 and forced vital capacity (FVC). Calculating the median of

five airway resistance and three FRCpleth measurements reduced artifacts in body plethysmographic baseline values. While body plethysmography was performed in an identical way after each intermediate MCH inhalation step, spirometry was done only once. After the end-of-test-criterion was reached measurements were performed as during baseline measurements.

1.2.4 Data Analysis

It was the aim of this study to compare body plethysmographic and spirometric parameters not only regarding the dose response at discrete steps of provocation levels, but to perform statistical data analysis over a continuous dose interval. Using regression analysis of the recorded lung function parameters with the applied MCH doses as the covariates the corresponding MCH provocation doses or concentrations (PD or PC) at arbitrary thresholds could be estimated by interpolation. An interpolated MCH dose that was needed to cause a fall of FEV_1 of 20% (10%) from baseline was called $PD_{20}FEV_1$ ($PD_{10}FEV_1$). $PD_{100}sR_{aw}$ was defined as the interpolated MCH dose needed to cause an increase in sR_{aw} of 100% from baseline, $PD_{+100}sR_{aw}$ with the additional increase of sR_{aw} to ≥2 kPa/s.

Performance of lung function parameters in binary classification of patients into asthmatic and non-asthmatic groups was compared using receiver-operating-characteristic (ROC) analysis taking the MCH dose as the varying discrimination threshold. For comparison of the ROC curves the area-under-the-ROC-curve (AUC), a robust measure for the overall quality of a classifier, was calculated. In contrast to the AUC being a summary statistic for test comparison the maximum test performance was quantified by estimating the Youden Index $J = max(sensitivity + specificity - 1)$ (Schisterman et al. 2005), which also provides a criterion for choosing an 'optimal' threshold value (Greiner et al. 2000).

To investigate the impact of the definition of the reactive thresholds on the tests' ability to discriminate subjects with and without asthma, ROC analysis was performed iteratively over broad intervals of reasonable threshold definitions and summarized by plotting these thresholds against their corresponding AUC values (Fig. 1.2). According to O'Connor et al. (1987), the dynamics of the dose–response curves were summarized by a measure defined as the slope of a line extending from baseline to the last data point obtained from provocation. FEV_1 and sR_{aw} were again compared by ROC analysis using this alternative approach.

All calculations were done using an Oracle© 10 g XE database, custom Java© code (Java Development Kit 1.6) and the R software environment for statistical computing (Ihaka and Gentleman 1996). ROC analysis was facilitated by the ROCR (Sing et al. 2005) package.

1.3 Results

Normal and asthmatic subjects were comparable in terms of demographic and pulmonary baseline characteristics (Table 1.1). Baseline sR_{aw} was significantly ($p<0.05$) higher in the asthmatics group but still within normal limits due to inclusion criteria used.

1.3.1 ROC Analysis

When applying $PD_{20}FEV_1$ for spirometry and $PD_{+100}sR_{aw}$ including an absolute threshold of ≥2.0 kPa/s for body plethysmography (Fig. 1.1), ROC analysis resulted in AUC of 0.74 for FEV_1 *vs.* 0.82 for

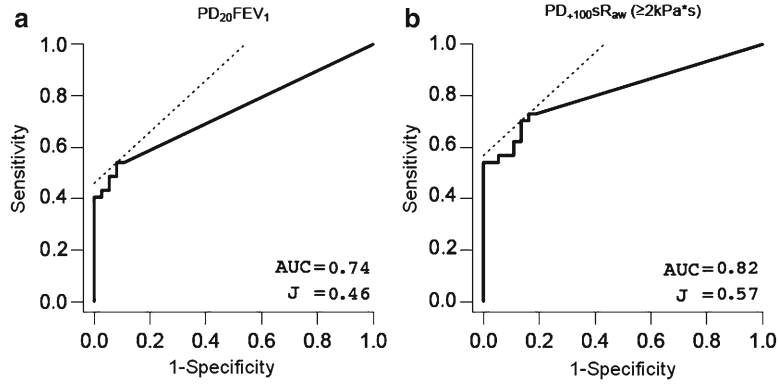

Fig. 1.1 Comparison of FEV_1 and sR_{aw} using ROC analysis. The intersections of the *dashed line* with the ROC curves represent the Youden Indices (J). *AUC* area under the curve

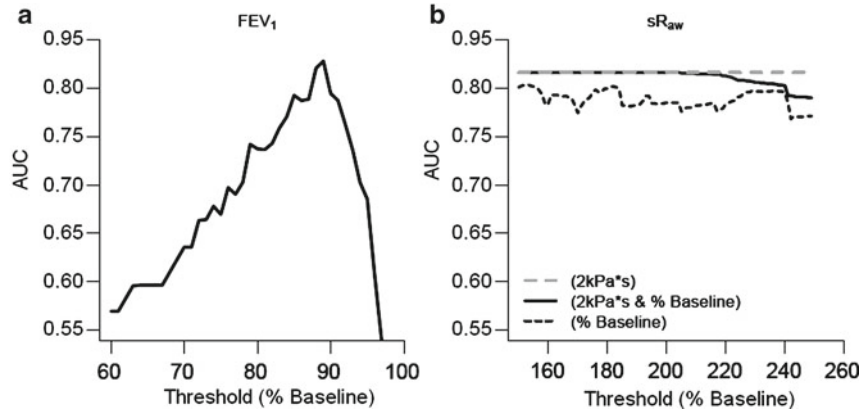

Fig. 1.2 Effect of the definition of reactive thresholds on test performances measured as areas under the curves (*AUC*)

sR_{aw}. The corresponding Youden Indices (J) were 0.46 for FEV_1 and 0.57 for sR_{aw}. The Youden Index in sR_{aw} was not only higher, but sensitivity and specificity (73%/84%) were rather well-balanced, in contrast to FEV_1 (54%/92%).

1.3.2 Threshold Optimization

By iterative threshold variation, FEV_1-based MCH testing was found to perform best at thresholds near 90% ($PD_{10}FEV_1$) of baseline value (Fig. 1.2, left part) being significantly better than that at 80% ($PD_{20}FEV_1$). Evaluating threshold definitions for body plethysmography was more complex because two synergistic thresholds, relative increase (% baseline) and 2.0 kPa/s absolute value, and their logical "AND" combination had to be analyzed. The performance of sR_{aw} based MCH testing was completely determined by the absolute threshold of 2.0 kPa/s. Variation of the relative threshold did not improve the performance of the test but instead resulted in a test performance decline for thresholds ≥200% (Fig. 1.2, right part).

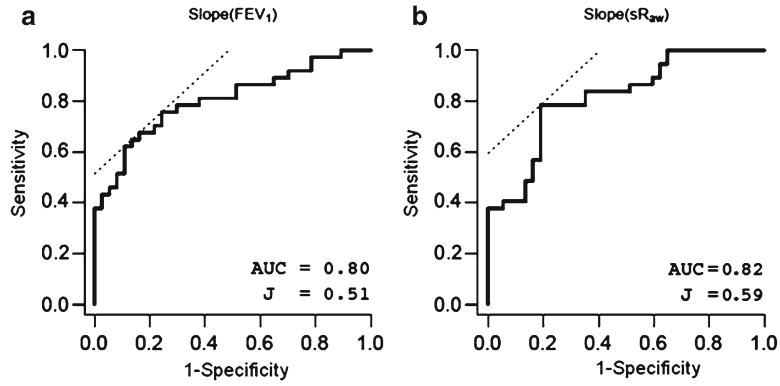

Fig. 1.3 ROC analysis of dose–response curve slopes. The intersections of the *dashed line* with the ROC curves represent the Youden Indices (J). *AUC* area under the curve

1.3.3 Slopes as Alternative Measures

The discrimination between both groups based on slopes of both FEV_1 and sR_{aw} were comparable. ROC analysis of sR_{aw} slopes resulted in a slightly higher AUC (0.82 sR_{aw} *vs.* 0.80 FEV_1) and a higher Youden Index (0.59 sR_{aw} *vs.* 0.51 FEV_1), but FEV_1 slopes produced a more uniform and stable ROC curve with several alternative maxima suitable as Youden Indices (Fig. 1.3). Both parameters provide well balanced sensitivity and specificity ratios (78%/81% sR_{aw} *vs.* 76%/76% FEV_1).

1.4 Discussion

It was the aim of the present study to assess the diagnostic value of spirometry and body plethysmography in MCH testing. We chose a case–control design, which has also been used for the same purpose by Cockcroft and Berscheid (1983) almost 30 years ago. In that study the authors compared $PC_{20}FEV_1$ and $PC_{35}sG_{aw}$ (provocation dose at a 35% fall of specific airway conductance from baseline) in 16 asthmatic and 27 normal subjects. The major result of that study was that $PC_{20}FEV_1$ was about fourfold larger than $PC_{35}sG_{aw}$, but the authors recommended to use FEV_1 because of better separation of both groups. The study was criticized some years later by Popa and Singleton (1988) because of the ceiling method that was used to define the cut-offs. The ceiling method selects the highest provocation dose in the asthmatic group as the cut-off value consequently leading to poor specificity if provocation doses overlap between normal and asthmatic groups, which appears to be the situation in the general population (Cockcroft et al. 1983; Hendrick et al. 1986; Tiffeneau 1957; van der Lende et al. 1973; Woolcock et al. 1987). There was very little overlap between groups in Cockcroft and Berscheid's (1983) study, possibly due to selection of the subjects. In the study by Popa and Singleton (1988), $PD_{20}FEV_1$ was about threefold higher than $PD_{40}sG_{aw}$ and the authors recommended using $PD_{20}FEV_1$ because this parameter produced lower misclassification rates due to lower variability of the endpoint. However, as it was obviously not the primary goal of that study to compare spirometry and body plethysmography and no threshold variations of sG_{aw} besides the $PD_{40}sG_{aw}$ (40% fall without an additional absolute threshold) were considered, this result is threading on thin ice.

Whereas both studies considered only one, Khalid et al. (2009) compared $PC_{20}FEV_1$ with three different body plethysmographic parameter variations (45%, 52%, and 56% fall). That study was

performed retrospectively in subjects with suspected asthma. However, because $PD_{20}FEV_1$ was used as the gold standard for ROC analysis, it could not answer the question whether one method was superior to the other and thus the authors could not explain the high number of subjects with significant responsiveness in sG_{aw} without reaching the spirometric criterion. All available studies had used the spirometric end-of-test-criterion because of the much lower threshold doses of body plethysmography. Although it is a plausible assumption that subjects with a 20% fall of FEV_1 will all show a significant fall in sG_{aw}, this has never been demonstrated by using two combined end-of-test-criteria, i.e., to terminate the test when both end-of-test criteria are reached.

When we designed this study, firstly, we wanted to avoid limitations of earlier studies by comparing spirometry and body plethysmography over continuous threshold intervals. Secondly, our study was designed as a systematic comparison of FEV_1 and sR_{aw} with both spirometric and body plethysmographic parameters as end-of-test criteria without the need for extrapolation to missing values. Third, we wanted to test a second body plethysmographic criterion that is widely used in Germany. As it may not be relevant to produce a relative change within reference limits, it is plausible to add an absolute criterion of a clinically relevant airway obstruction (at a sR_{aw} of about 2 kPa/s subjects experience dyspnea).

It is essential for case control studies to clearly define cases and controls. In this study we used subjects with suspected occupational asthma, i.e., variable shortness of breath at work. This may be considered as a weakness of the present study explaining its relatively low sensitivities (e.g., with the 20% fall of FEV_1 criterion merely 20 asthmatics were considered hyperresponsive). However, low sensitivities within a similar range as in our study were reported in a recent cohort study (Anderson et al. 2009). In order to avoid misclassification in future studies, further information should be included in the case definition.

The main conclusion of our study is that sR_{aw} is the overall most useful parameter for the detection of airway hyperresponsiveness. sR_{aw} yielded a more balanced sensitivity-specificity ratio with higher sensitivity than FEV_1, but comparable specificity. With a threshold at 80% of baseline the FEV_1-based test may not be tuned to produce optimal results. Optimization of reactive thresholds showed a distinct absolute peak near 90% of baseline ($PD_{10}FEV_1$) for FEV_1 that indicates that the often-used $PD_{20}FEV_1$ might not always be ideal, particularly as lower thresholds (closer to baseline) decrease false negative test rates. It must be considered though, that our study group was assembled to meet criteria like normal baseline FEV_1 as well as Tiffeneau index >70%, which subsequently reduced variance in airway obstruction and therefore shifted optimal thresholds closer to the baseline. Furthermore, by not including those patients in the study that showed mild airway obstruction at baseline, and consecutively in most cases a strong airway response to MCH, the sensitivity of both FEV_1 and sR_{aw}, was artificially reduced. FEV_1 tends to be more specific than sensitive and therefore yields more false negative test results, which is not a desirable feature of early screening tests. In fact MCH testing should be adjusted to provide low false negative rates, which of course requires high sensitivities.

Threshold optimization of sR_{aw} showed the test performance to be completely determined by the absolute 2.0 kPa/s threshold, which might as well be attributed to our concrete study group that did not include patients with non-asthmatic obstructive pulmonary diseases. Relative thresholds avoid the misclassification of subjects with those diseases, such as silicosis. These obstructive diseases are characterized by high absolute baseline resistance and therefore might cross the 2.0 kPa/s boundary prematurely without originating in airway hyperresponsiveness.

Apart from describing hyperresponsiveness with static absolute or relative thresholds there are alternative approaches that focus on the dynamics of the dose–response curve. Lötvall et al. (1998) proposed different pathophysiological mechanisms that lead to differently shaped curves. The authors separated hypersensitivity characterized by a general left-shift from hyperreactivity characterized by a steeper slope of the dose–response curve. The slope of the dose–response curve provides additional valuable information that prospectively should be integrated into the diagnosis of airway hyperresponsiveness. The slope-based test performances were comparable to those of the threshold-based

analyses, which suggests that the dynamics of the dose–response curve may be regarded as an alternative or additional measure to effectively separate asthmatics from normal subjects.

In summary, this study indicates that body plethysmography adds valuable information to the question whether a subject has airway hyperresponsiveness. Its most important advantage is the reduction of false negative tests which may occur with spirometry. This is important especially in the diagnosis and compensation of occupational asthma. While we are still waiting for optimal threshold definitions based on credible normative data and reliable statistical methods, a combination of both, spirometry and body plethysmography, should offer the best information.

Conflicts of Interest: The authors declared no conflicts of interest in relation to this article.

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Chapter 2
Hospital Management of Patients with Exacerbation of Severe Chronic Obstructive Pulmonary Disease

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Abstract The article assesses the originally developed criteria of clinical stability and treatment protocol in the hospital management and discharge procedures of patients with exacerbations of severe chronic obstructive pulmonary disease (COPD). The study included 34 patients (26 males, 8 females), aged 58–80 years, hospitalized due to exacerbation of severe (23 patients) and very severe (11 patients) COPD. On admission, the mean FEV1 was 0.78 ± 0.22 L (31.7% ± 8.2% of predicted), FVC 2.52 ± 0.87 L (77.9% ± 9.8% of predicted) and FEV1/FVC 33.17% ± 10.84%. Before hospitalization, 10 out of the 34 patients were diagnosed with chronic respiratory failure. All patients were treated according the same treatment protocol which included the developed criteria of clinical stability. Meeting all these criteria in a 24-h observation period was the basis to slash the dose of systemic glucocorticosteroids by half. The maintenance of the stability criteria through the subsequent 24 h allowed discharging a patient from the hospital. Every patient was supplied with a detailed plan of out-of-hospital treatment. The results show that the mean duration of hospitalization was 6.4 ± 4.8 days. Only one patient required readmission within 4 weeks after discharge. Two patients died; one during the hospitalization time and the other after discharge. In the latter case, death was not directly related to the COPD exacerbation. In conclusion, the protocol of treatment and the criteria of stability used for patients with COPD exacerbation enabled to optimize the hospitalization time. A shortening of hospitalization was not associated with increased risk of readmission within 4 weeks after discharge.

Keywords COPD exacerbation • Clinical stability • Length of hospitalization • Chronic respiratory failure • Treatment protocol

2.1 Introduction

Exacerbations of chronic obstructive pulmonary disease (COPD) are a substantial burden for healthcare systems. The hospitalization rate due to COPD exacerbation is rising worldwide. Patients suffering from severe COPD experience, on average, 3.5 exacerbations per year, out of which about 52% require hospitalization. It has been estimated that hospitalizations constitute up to 60% of direct costs of

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COPD treatment (Hillman et al. 2000; Miravitlles et al. 2002) and up to 90% of the costs of treatment of severe exacerbations (Oostenbrink and Rutten-van Molken 2004). In addition to a considerable financial burden, hospital treatment is associated with a high risk for nosocomial infections. A key issue is to recognize the early phase of COPD exacerbation and to initiate treatment. The issue also is a proper qualification of patients either for hospitalization or outpatient treatment. COPD exacerbations result in deterioration of lung function and can be accompanied by respiratory and circulatory failure, and by impaired consciousness. Patients with respiratory failure often require non-invasive or invasive mechanical ventilation. COPD exacerbations constitute a risk of death, especially in patients with severe and very severe chronic obstructive pulmonary disease.

Clinical presentations of COPD exacerbation depend on disease severity, cause of exacerbation, its dynamics, and co-morbidities. Therefore, a definition of clinical stability should take into account a number of parameters and the natural daily variability of symptoms. It is essential to recognize that lung function, health related quality of life, and often blood gases remain abnormal after resolution of COPD exacerbation. In addition, clinical status of an individual prior to COPD exacerbation often times is unknown, making it difficult to judge whether the therapy of exacerbation brought about the optimal improvement. Thus, only some of exacerbation indicators are reliable and can be useful in clinical practice. Criteria of clinical stability should take into consideration all limitations and should reflect the variable and dynamic presentation of a patient.

Likewise, it is difficult to qualify a patient for treatment of COPD exacerbation on the outpatient or hospital basis. That mainly applies to patients suffering from severe (stage III according to GOLD) and very severe (stage IV according to GOLD) COPD. The current GOLD guidelines (2010) recognize an exacerbation of severe and very severe COPD as the indication for hospitalization. In some cases, however, alternative programs of home hospitalization (hospital at home) or support programs of early discharge home (early supported discharge) are acceptable. The GOLD guidelines do not specify the clinical and/or laboratory criteria which would help to assess the risk of failure of home-based management programs. In some countries (especially Spain and Scandinavia), the programs of early supported discharge are becoming more popular as they shorten hospital stay even twice. Such programs have been shown not to increase either the death rate or the need for additional and unexpected medical interventions when compared with exclusively hospital based management (Cotton et al. 2000; Sala et al. 2001; Hernandez et al. 2003; Ram et al. 2004; Davison et al. 2006; Salazar et al. 2009). Patients included into the programs of home hospitalization presented a significantly better quality of life, a higher degree of satisfaction, and a greater sense of safety, which was related to better education of patients (Gravil et al. 1998; Ojoo et al. 2002; Casas et al. 2006). Despite that the hospital-at-home programs are already recommended by the British Thoracic Society (BTS) guidelines of 2007, the criteria of clinical stability have not yet been clearly defined. Accordingly, the early discharge from hospital remains difficult and questionable. The average time of hospitalization due to exacerbations of COPD is long as it reaches 11–15 days worldwide.

The objectives of the present study were twofold: (1) development and assessment of the protocol of treatment and discharge from the hospital of patients with exacerbations of severe and very severe COPD and (2) development and assessment of the criteria of clinical stability, essential for the decision-making on discharge.

2.2 Methods

The study was performed in conformity with the Declaration of Helsinki for Human Experimentation and the protocol was approved by the Ethics Committee of Wroclaw Medical University (No. 157/2003). All patients gave informed written consent to participate in the clinical experiment.

Table 2.1 Pulmonary function, blood gas content, and Borg score on the first and last day of hospitalization, and 4 weeks afterward

	First day of hospitalization	Last day of hospitalization	Follow-up of 4 weeks
FEV1pre (L)	0.78 ± 0.22	0.79 ± 0.23	0.88 ± 0.26
FEV1pre (% pred)	31.7 ± 8.2	32.3 ± 8.9	34.9 ± 8.2
FVCpre (L)	2.52 ± 0.87	2.54 ± 0.77	2.89 ± 1.1
FVCpre (% pred)	77.9 ± 19.8	79.2 ± 17.9	88.4 ± 24.4
FEV1/FVCpre (%)	33.2 ± 10.8	32.7 ± 9.9	32.5 ± 11.1
FEV1post (L)	0.86 ± 0.28	0.89 ± 0.26	0.98 ± 0.29
FEV1post (% pred)	35.1 ± 10.4	36.37 ± 9.8	39.0 ± 9.4
FVCpost (L)	2.55 ± 0.87	2.74 ± 0.83	2.96 ± 0.93
FVCpost (% pred)	79 ± 20.2	85.6 ± 20.0	91.7 ± 24.0
FEV1/FVCpost (%)	36.0 ± 12.2	33.9 ± 9.5	34.9 ± 11.9
pH	7.40 ± 0.07[a]	7.43 ± 0.04[b]	7.42 ± 0.04[b]
PO_2	60.2 ± 11.7[a]	61.1 ± 11.6[b]	65.4 ± 13.0[b]
PCO_2	45.4 ± 12.0[a]	42.8 ± 8.2[b]	41.2 ± 8.1[b]
HCO_3^-	27.2 ± 5.02[a]	28.2 ± 5.2[b]	26.0 ± 4.7[b]
BE	2.1 ± 4.1[a]	3.9 ± 4.2[b]	1.8 ± 4.0[b]
SaO_2	88.9 ± 6[a]	90.3 ± 5.5[b]	91.2 ± 5.8[b]
Borg scale	5.9 ± 1.7	–	1.4 ± 0.9

Data are means ± SD; pre-post, before and after administration of a bronchodilator
[a]Arterialized blood gas analysis on optimal oxygen therapy
[b]Arterial blood gas analysis on room air

The study included 34 patients (26 males, 8 females), aged 58–80 (mean 72 ± 7SD years), admitted to the Department of Internal Medicine, Geriatrics and Allergology of Wroclaw Medical University in Wroclaw, Poland. The patients were hospitalized due to exacerbation of severe (23 patients) and very severe (11 patients) COPD. All patients were past or current cigarette smokers (10–150 pack-years, mean 60.7 ± 31.2 pack-years; 28 ex-smokers, 6 active smokers) and were diagnosed with COPD, without accompanying asthma or any other lung disease. Ten patients (29%) were previously diagnosed with chronic respiratory failure and seven patients were subjected to long-term oxygen therapy. On admission, central cyanosis was recorded in 17 patients (50%), whereas orthopneic position was recorded in 22 out of the 34 patients (65%). According to the Borg scale, the patients assessed the severity of dyspnea from moderate (3 points) up to very severe, almost the maximum (9 points). The mean Borg score was 5.9 ± 1.7 points. Pulmonary function tests performed on the first day of hospitalization showed severe airflow limitation in all individuals. Before administration of a bronchodilator, the mean group FEV1 was 0.78 ± 0.22 L (31.7% ± 8.2% predicted), FVC was 2.52 ± 0.87 L (77.9% ± 19.8% predicted), and FEV1/FVC was 33.2% ± 10.8%. After bronchodilation, the mean FEV1 was 0.86 ± 0.28 L (35.1% ± 10.4% predicted), FVC 2.55 ± 0.87 L (79.0% ± 20.2% predicted), and FEV1/FVC 36.0% ± 12.2%. On admission, all subjects were sampled for arterialized blood gas content and 17 patients (50%) were found hypoxemic (PaO_2 38.6–59.3 mmHg), 14 patients had hypercapnia ($PaCO_2$ 46–66.8 mmHg), and 5 patients had respiratory acidosis (minimum pH 7.24). Selected parameters of pulmonary function, blood gas content, and Borg score on the first day of hospitalization are summarized in Table 2.1.

All patients were subjected to the same protocol of treatment and received: (1) nebulizations with ipratropium bromide 250 μg every 6 h; (2) additional nebulizations with salbutamol 2.5 mg on demand (each administration was preceded by a physician's examination); (3) hydrocortisone hemisuccinate 100 mg i.v. every 12 h; (4) optimal oxygen therapy *via* nasal catheter, and if necessary *via* non-invasive ventilation with a BiPAP device (Bi-level positive airway pressure); (5) antibiotics and cardiovascular drugs according to indications; and (6) methylxanthines orally at previously prescribed doses, only if used on a regular basis before exacerbation. When antibiotic therapy was indicated, empirical therapy

Table 2.2 Protocols of in-hospital and out-of-hospital treatment of COPD exacerbation

In-hospital treatment	Out-of-hospital treatment
Ipratropium bromide 250 μg every 6 h (nebulization)	Ipratropium bromide 40 μg every 6 h (spacer)
Salbutamol 2.5 mg on demand (nebulization)	Salbutamol 200 μg on demand (spacer)
Hydrocortisone hemisuccinate 100 mg every 12 h (i.v.)	Prednisone 20 mg with reduction of the dose by 5 mg every 7 days (orally)
Optimal oxygen therapy (nasal catheter or BiPAP)	Methylxanthines at the previously used doses (orally)
Antibiotic and/or cardiovascular drugs according to indications	Fluticasone propionate 500 μg every 12 h (DPI-Discus or MDI-spacer)
Methylxanthines at the previously used doses (orally)	Long-acting β_2-agonist 1 dose every 12 h (inhalation)

with amoxicillin combined with clavulanic acid was given. In case of contraindications to penicillin, ciprofloxacin was administered as a second line therapy. Non-invasive mechanical ventilation using BiPAP was applied to the patients fulfilling the following criteria of arterialized blood gas content: respiratory acidosis (pH < 7.3) and/or hypercapnia (PCO_2 > 55 mmHg), and/or increase in PCO_2 by more than 20% compared with baseline. The treatment protocol was summarized in Table 2.2.

In case of reported shortness of breath, at patient's demand, it was allowed to advance a planned dose of ipratropium bromide and hydrocortisone hemisuccinate, but for no more than 1 h. In other cases of intensification of dyspnea, the patient was given extra doses of salbutamol 2.5 mg in nebulization and hydrocortisone 100 mg i.v., if required. Every extra dose of bronchodilator or glucocorticosteroid was recorded in the study documentation. All patients were continually monitored for the stability criteria which included the following elements:

1. stable vital signs for 24 h:
   (a) respiratory rate <20/min
   (b) heart rate <100/min
2. body temperature <37°C for at least 2 consecutive days
3. stable arterialized blood gases for 24 h (on optimal oxygen therapy), defined as a maximum increase in PCO_2 in the morning by less than 10% of the PCO_2 measured in the preceding evening.
4. no night-time awakenings due to dyspnea
5. necessity to use rescue β2-agonist (Salbutamol) up to 4 times/day and no extra doses of hydrocortisone hemisuccinate
6. leukocytosis <13,000
7. absence of clinical symptoms of pneumonia and resolution of COPD exacerbation cause
8. unassisted food intake and the ability to walk 10 m
9. mastery in the correct technique of drug inhalation
10. adequate nursing care at home

If a given patient fulfilled all the stability criteria above outlined, the dose of hydrocortisone hemisuccinate was reduced by 50% from 100 to 50 mg b.i.d. If these criteria were maintained through the subsequent day, the patient was administered 20 mg of prednisone orally and discharged home. All subjects continued treatment of COPD exacerbations at home in accordance with the out-of-hospital treatment protocol as shown in Table 2.2. In addition, the patients received cardiovascular and other concomitant treatment as indicated. On the day of discharge, the arterial blood gas content was checked and in the case of hypoxemia, the patient was recommended to use oxygen therapy at home. The diagnosis of chronic respiratory failure was verified at the follow-up visit.

The patients and their families were educated in regard to home management of dyspnea attacks. The choice of a dry powder inhalation system was based on the value of the peak inspiratory flow (PIF) rates related to the resistance measured with In-Check Inhaler Assessment Kit (Clement Clark

International Ltd.). The ability to use inhalers was strictly monitored and if the use was improper, the patient was instructed in the correct technique of inhalation. Once a week, a referring doctor telephoned the patient in order to assess the results of COPD treatment. When in doubt, the patients could contact the doctor 24 h a day. Four weeks after the discharge, there was a follow-up visit on site. The patients were examined, including a lung function test and sampled for arterial blood gas analysis. Based on the examination, severity of COPD and the previous diagnosis of chronic respiratory failure were verified. The need for emergency room visits due to dyspnea, hospital readmissions, or modifications of the out-of-hospital treatment protocol within 1 month after discharge were regarded as a failure and were thoroughly analyzed.

2.3 Results

The mean hospitalization time was 6.4 ± 4.8 days. Two patients died. The first patient died at the hospital on the 26th day of hospitalization. The decease was due to *enterococcal* pneumonia and was directly related to the exacerbation of COPD. The patient had right ventricular failure and deep vein thrombosis in a proximal part of the left lower extremity. The second patient died at home due to extensive myocardial infarction. The family reported that since discharge the patient felt quite well, had improved of exercise tolerance, and there were no episodes of nocturnal dyspnea. Based on this, no direct link between the death of the patient and the early discharge from the hospital after COPD exacerbation was recognized.

The 4-week follow-up visit covered 30 out of the 34 patients. Two patients refused to attend the follow-up visit on site due to a long distance between the hospital and patients' home and difficulty in moving. During a substitute phone follow-up visit, both declared satisfaction with the participation in the program and claimed satisfactory control of COPD and the stability of the disease. All remaining 30 patients also declared satisfaction with the results of the early-supported discharge program. Most patients emphasized the role of education in providing the sense of security and finally in improving the control of COPD. On the follow-up visit, all patients were examined including the lung function tests and arterial blood gas analysis. The severity of chronic obstructive pulmonary disease and previous diagnosis of chronic respiratory failure were verified. It was confirmed that all study participants manifested severe airflow limitations (stage III and IV by GOLD). In the whole group, before administration of a bronchodilator, the mean FEV1 was 0.88 ± 0.26 L (34.9% ± 8.2% predicted), the mean FVC was 2.90 ± 1.1 L (88.4% ± 24.4% predicted), and the mean FEV1/FVC was 32.5% ± 11.1%. The corresponding values after a bronchodilator were 0.98 ± 0.29 L (39.0% ± 9.4% predicted), 2.96 ± 0.93 L (91.7% ± 24.0% predicted), and 34.9% ± 11.9%, respectively. In nine individuals, the previous diagnosis of chronic respiratory failure was confirmed.

2.4 Discussion

Exacerbations of severe and very severe chronic obstructive pulmonary disease usually afflict people at old age and suffering from chronic co-morbid conditions. Due to severe airflow limitation and possible concurrent respiratory failure, prognosis at the initial phase of COPD exacerbation is difficult and uncertain. It is accepted that advanced age, FEV1 ± 35% of predicted, long-term history of the disease, male sex, chronic respiratory failure, chronic heart failure, crippling and disabling diseases (e.g., cancers), and frequent (3 or more a year) exacerbations are risk factors for unfavorable course of COPD exacerbation (Almagro et al. 2002; Plant et al. 2001; Chu et al. 2004; Patil et al. 2003). For this reason and in accordance with the GOLD guidelines, patients suffering exacerbation of severe

and very severe COPD require medical evaluation at the emergency unit of the nearest hospital regardless of the severity of exacerbation (Global Initiative for Chronic Obstructive Lung Disease 2010). There is an urgent need for further studies in this group of patients to define the safety criteria for the out-of-hospital treatment following the initial hospital-based treatment. There are new programs – 'home hospitalization' and 'early supported discharge' - to meet these needs. Based on the results of home hospitalization programs, the British Thoracic Society guidelines (BTS Guideline 2007) allow the continuation of the treatment of exacerbation of severe and very severe COPD in an out-of-hospital setting. However, treatment protocols and clinical stability criteria for early discharge are still under discussion.

In this study we present a uniform protocol of treatment of patients with severe and very severe COPD exacerbation, and new clinical stability criteria for early discharge from the hospital. The treatment regimen offered the patient-oriented flexibility of therapy by controlled increases of bronchodilator and systemic glucocorticosteroid dosing. In contrast to previously published clinical trials, our protocol did not determine in advance the number of treatment days according to a specified plan. The glucocorticosteroid dose tapering, reflecting the shortening of hospitalization duration was based on the patient's clinical status. The criteria of clinical stability presented covered respiratory and circulatory variables, resolution of COPD exacerbation cause, basic life activity assessment, and the ability for proper inhalation of a drug. We emphasize the importance of respiratory rate which reflects the severity of dyspnea and $PaCO_2$ which is an indicator of respiratory failure. The value of PaO_2 seems to be less useful due to the need for oxygen therapy. It is worth noting that current guidelines do not include gasometry parameters as the qualifying criteria for the home hospitalization procedures. Lung function parameters – FEV1 and FVC – are poor predictors of clinical status in COPD, and were not included in the stability criteria. We conclude that potential clinical predictors of clinical stability are the need for rescue medication (no more than four occasions) and no night-time awakenings caused by dyspnea. The criteria also included the resolution of COPD exacerbation cause and the absence of pneumonia. Pneumonia is an indication for hospitalization regardless of the stage and severity of COPD exacerbation. The British Thoracic Society guidelines (2007) do not recommend outpatient treatment of COPD exacerbation in patients with pneumonia confirmed by X-ray examination. The other criteria such as unassisted food intake, the ability to walk 10 m, mastery in the proper technique of drug inhalation, and adequate nursing care at home all seem to play a key role in daily practice.

The presented protocol for treatment of COPD exacerbations and the criteria for clinical stability were shown to be effective tools in the optimization of hospitalization duration. The mean hospitalization time was shortened to 6.4 ± 4.8 days. Application of both tools in clinical practice allows for safe and efficacious continuation of treatment of exacerbations of severe and very severe COPD in out-of-hospital settings. The results of this study create the rationale for further development of programs of early supported discharge from the hospital.

Conflicts of Interest: The authors declare no conflicts of interest in relation to this article.

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Chapter 3
Pulmonary Rehabilitation in Patients Referred for Lung Transplantation

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Abstract Effectiveness of pulmonary rehabilitation in patients with chronic obstructive lung diseases, cystic fibrosis, and interstitial lung disease is well documented but little is known about the results of pulmonary rehabilitation in patients referred for lung transplantation. The purpose of this study is to prospectively examine the efficacy of Nordic walking, a low cost, accessible, and proven beneficial form of physical exercise, as a form of pulmonary rehabilitation in patients referred for lung transplantation. Twenty-two male patients referred for lung transplantation at the Department of Lung Diseases and Tuberculosis in Zabrze, Poland, were invited to take part in the study. The rehabilitation program, which was conducted for 12 weeks, was based on Nordic walking exercise training with ski poles. Lung function tests (FVC, FEV1), mobility (6 min walking test (6MWT)), rating of dyspnea (Oxygen Cost Index, MRC and Baseline Dyspnea Index), and quality of life assessments (SF-36) were performed before and after the completion of the exercise program. No adverse events were observed after completing the pulmonary rehabilitation program in patients referred for lung transplantation. After 12 weeks of pulmonary rehabilitation with Nordic walking we observed a significant increase in the mean distance walked in the 6MWT (310.2 m *vs.* 372.1 m, $p<0.05$). The results of lung function tests also showed improvement in FVC. There were no significant differences in the perception of dyspnea before and after completing the rehabilitation program. General health and quality of life questionnaire (SF-36) showed improvement in the domain of social functioning ($p<0.05$). In conclusion, pulmonary rehabilitation with a Nordic walking program is a safe and feasible physical activity in end-stage lung disease patients referred for lung transplantation and results in improvements in patients' mobility and quality of life.

Keywords Interstitial lung disease • Lung transplantation • Pulmonary rehabilitation • Nordic walking • Six-minute walking distance

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3.1 Introduction

Effectiveness of pulmonary rehabilitation in patients with COPD is well documented (Troosters et al. 2000). According to growing evidence, in patients with interstitial lung diseases, pulmonary rehabilitation is associated with a significant improvement in dyspnea and functional status (Holland and Hill 2008). Little is known about the impact of such medical intervention in patients with end-stage lung diseases who are referred for lung transplantation. The Silesian Center for Heart Disease in Zabrze is the only medical center in Poland which performs lung transplantations. Patients who are on the waiting list for lung transplantation often deteriorate in mobility and health status and have more pronounced dyspnea. The question arises of whether pulmonary rehabilitation could be beneficial in patients with end-stage lung diseases waiting for lung transplantation. To the best of our knowledge, there is lack of controlled studies on pulmonary rehabilitation program in patients referred for lung transplantation. In this study, therefore, we attempted to address this issue by prospectively examining the efficacy of Nordic walking, a low cost, accessible and proven beneficial form of physical exercise, as a form of pulmonary rehabilitation in patients referred for lung transplantation.

3.2 Methods

3.2.1 Patients

The study was approved by the Bioethics Committee of the Medical Academy of Silesia. Thirty patients with end-stage lung disease were referred for lung transplantation in the Department of Lung Diseases and Tuberculosis in Zabrze between November 2009 and September 2010. All of them fulfilled the ISH lung transplantation criteria for lung transplantation (Orens et al. 2006). Those without exclusion criteria for pulmonary rehabilitation were invited to take part in the study. A total of 26 male patients aged 50.4 year gave written informed consent to participate in the study. Two patients were excluded from the study because of lung transplantation, and two patients withdrew consent for participation in the study during the pulmonary rehabilitation program because of general weakness due to disease progression. The diagnoses included end-stage COPD (n = 7), idiopathic pulmonary fibrosis (IPF) (n = 3), and other than IPF forms of idiopathic interstitial pneumonia (IIP) (n = 12).

3.2.2 Physiological Measurements

Physiological testing was completed on the same day as informed consent was obtained. Spirometry was performed using Jaeger-Masterlab (Erich Jaeger GmbH, Wurtzburg, Germany). Two lung function parameters were measured: forced vital capacity (FVC) and forced expiratory volume in one second (FEV1). Results were normalized to the reference values proposed by the European Community for Coal and Steel and presented as percentage of the predicted value (% pred.). Mobility was presented as the distance covered in the 6-min walking test (6MWT). The test was performed according to the guidelines of the modified Bruce protocol (American Thoracic Society Statement 2002). The use of oxygen during the test was standardized, and all follow-up walking tests were conducted using the same flow rate supplemental oxygen that had been used at baseline. Dyspnea before and after 6MWT on Borg's scale, arterial oxygen saturation (SaO_2) before and after 6MWT, and the time and distance to desaturation <80% were also recorded.