Impact of Nocturnal Noninvasive Ventilation on Pulmonary Rehabilitation in Patients with End-Stage Lung Disease Awaiting Lung Transplantation

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Keywords

Pulmonary rehabilitation · End-stage lung disease · Lung transplantation · Noninvasive ventilation

Abstract

Background: Pulmonary rehabilitation (PR) in patients awaiting lung transplantation is crucial to ensure a transplant benefit. However, PR in patients with end-stage lung disease treated with noninvasive ventilation (NIV) remains an area of uncertainty. **Objectives:** The aim of the study was to assess the potential benefit of PR in patients awaiting lung transplantation treated with NIV. **Methods:** Patients awaiting lung transplantation who underwent comprehensive inpatient PR from 1998 to 2015 were retrospectively analyzed. Success of PR was assessed by comparing admission and discharge. Multivariate regression models were applied to assess the impact of long-term nocturnal NIV on PR success. **Results:** In total, 1,044 patients were included in the analysis.

Thereof, 296 patients (28%) were treated with NIV. PR in patients treated with NIV resulted in a significant increase in 6-min walk distance (6MWD; from 250 ± 117 to 309 ± 116 m; $p < 0.0001$) and in various items of the Short Form Health Survey (SF)-36 questionnaire. The increase in 6MWD was higher in patients treated with NIV than in patients without NIV (59 ± 63 vs. 48 ± 55 m; $p = 0.003$). Furthermore, improvements of various lung function variables were higher in patients with NIV. Finally, multivariate generalized regression analysis revealed that NIV therapy was associated with improvement of 6MWD ($p = 0.023$) while controlling for various baseline characteristics. **Conclusions:** PR in patients with end-stage lung disease awaiting lung transplantation on nocturnal NIV is feasible and is associated with improvements of exercise capacity and quality of life. Furthermore, despite more advanced lung disease, patients treated with NIV have an increased benefit of PR compared to patients without NIV while awaiting lung transplantation.

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Introduction

Pulmonary rehabilitation (PR) is recommended for patients with chronic respiratory diseases as an adjunct to standard pharmacologic therapy [1, 2]. Interest in the benefits of PR in patients with end-stage lung disease awaiting lung transplantation is increasing, since maintenance of exercise capacity and muscle mass are critical for survival on the waiting list and for transplant outcome [3–5].

Limited data demonstrate that PR is an effective treatment option for patients on the waiting list for lung transplantation and can improve quality of life and exercise capacity [6, 7]. There is increasing evidence that even patients with most advanced lung disease benefit from PR despite severely impaired functional status [8, 9]. Short-term comprehensive PR can significantly improve exercise capacity in lung transplant candidates to a clinically relevant extent [7].

Noninvasive ventilation (NIV) is used in many patients with end-stage lung disease. Long-term nocturnal NIV has been shown to improve hypercapnia and hypoxemia, quality of life, and neuropsychological function and to reduce hospital admissions and costs [10]. Data suggest that PR is feasible and effective in patients with chronic lung disease on NIV [11–14]. It has been proposed that NIV as an adjunct to PR improves exercise tolerance and respiratory and cardiovascular performance [15]. NIV augments the benefits of PR in patients with chronic obstructive pulmonary disease (COPD) with chronic hypercapnic respiratory failure as it improves several measures of health-related quality of life, functional status, and gas exchange [11]. Further, an individually tailored PR plus nocturnal NIV appears to be feasible even in hypercapnic patients with interstitial lung disease (ILD) and significantly improves exercise capacity and quality of life [14].

Currently, no data exist regarding the effect of NIV on PR success in patients with end-stage lung disease listed for lung transplantation. It remains unclear whether PR results in a clinically important benefit in these patients. The aim of the study was to assess the effect of PR in patients with end-stage lung disease awaiting lung transplantation on long-term nocturnal NIV.

Methods

Design

The study is designed as a retrospective analysis. All patients that were already listed or in evaluation for lung transplantation and underwent comprehensive inpatient rehabilitation between May 1998 and June 2015 were included in the study. All partici-

pants completed a multimodal inpatient PR program at the Schön Klinik Berchtesgadener Land (Schönau am Königssee, Germany). Scheduling for PR was elective in all patients, and only those patients were included for whom the 6-min walk distance (6MWD) at admission and discharge was documented during the hospitalization of at least 20 up to 90 days. No further exclusion criteria were specified.

Ethics approval was not indicated, as all of the tests were carried out as part of the clinical routine assessment and analyzed retrospectively out of the anonymized patients' records. The test and therapeutic methodologies used in this study did not change significantly over the study period.

Underlying diseases were categorized into ILD, COPD, cystic fibrosis (CF), and other diseases [16]. In all patients, long-term oxygen therapy and NIV, including NIV application time, inspiratory and expiratory pressures were recorded.

Intervention

The patients participated in a multimodal inpatient PR. This program included a total of 25–30 therapy sessions, which took place on 5–6 days per week. It consisted of an individualized exercise training program including aerobic exercise and strength training. For aerobic exercise, the patients trained between 10 and 20 min at 60% of the peak work rate derived from an initial cycle ergometer test or using an interval training approach exercising at 100% of the peak work rate and 30-s intervals [17]. Strength training was performed for 3–5 exercises of major muscle groups of the lower and upper extremities performing 3 × 20 repetitions with the maximum tolerated load. The intensity of the supervised endurance training sessions was adjusted continuously, with the aim of achieving the maximum tolerated exercise load during each training session [18]. When a drop in oxygen saturation was observed, oxygen was applied to keep oxygen saturation above 88%.

Respiratory physiotherapy consisted of teaching breath control (pursed lip breathing, secretion mobilization, and diaphragmatic breathing), energy saving techniques, and controlled coughing exercises along with activity-of-daily-living exercises. Twice a week (1 h each), all patients participated in educational sessions, which, in addition to self-management, included coping skills and nutrition interventions, self-medication, management of infections and exacerbations, dyspnea, use of oxygen, special lung transplantation-related topics, and activities of daily living. The indication for participating in this comprehensive inpatient PR was based on evaluation of the impact of the chronic respiratory disorder on different dimensions of health status (e.g., physiological functioning, symptoms, activities, quality of life, and health care utilization) as assessed by general practitioners or other pulmonary centers.

Exercise Capacity

Exercise capacity was measured at hospital admission and discharge using the 6-min walking test (6MWT), performed once at the beginning and once at the end of the PR program, according to the guidelines of the European Respiratory Society (ERS) [19] and carried out by experienced, well-instructed examiners. The minimal important difference of 30 m for the 6MWT compared between before and after PR was defined as the primary marker to differentiate between responders and nonresponders [9].

Table 1. Assessment of inpatient pulmonary rehabilitation in patients with end-stage lung disease awaiting lung transplantation (all) and patients requiring NIV and awaiting lung transplantation

	All patients (<i>n</i> = 1,044)				Patients with NIV (<i>n</i> = 296; 28.4%)			
	Admission	Discharge	Δ	<i>p</i> value	Admission	Discharge	Δ	<i>p</i> value
<i>Lung function testing</i>								
FEV1, % predicted	32.4±16.3	33.2±16.5	0.9±4.7	0.23	24.4±10.5	25.6±10.7	1.3±4.2	0.16
VCin, % predicted	51.1±17.9	53.3±18.1	2.2±10.2	0.012	45.2±13.8	48.7±14.4	3.6±10.1	0.006
FEV1/FVC, %	52.8±23.8	52.2±22.9	−0.6±9.8	0.59	46.9±20.2	45.4±19.7	−1.5±8.5	0.42
TLC, % predicted	114.9±41.8	114.3±40.9	−0.5±13.5	0.78	127.9±38.9	125.8±36.9	−2.1±15.7	0.50
RV, % predicted	238.2±114.3	233.8±112.0	−4.4±42.5	0.39	285.4±103.9	274.2±98.6	−11.1±51.0	0.2
RV/TLC, %	67.2±14.5	66.4±13.9	−0.8±7.6	0.20	74.4±11.3	73.1±10.5	−1.3±7.2	0.17
6MWD, m	285±127	336±126	51±57	<0.0001	250±117	309±116	59±63	<0.0001
<i>Health status (SF-36)</i>								
Physical functioning	14.3±12.4	16.8±12.9	2.5±9.4	<0.0001	12.3±12.3	14.4±12.5	2.2±8.7	0.065
Bodily pain	44.9±12.7	47.9±11.5	2.9±9.9	<0.0001	44.7±12.2	47.8±11.4	3.1±9.9	0.007
Physical role functioning	26.8±9.8	30.2±11.9	3.4±11.5	<0.0001	25.7±9.2	28.5±11.6	2.8±10.0	0.009
General health perceptions	30.6±8.7	32.8±9.4	2.3±7.6	<0.0001	30.8±8.5	32.4±9.6	1.7±7.6	0.061
Vitality	33.8±10.6	41.9±10.9	8.1±10.4	<0.0001	32.3±10.5	40.2±10.4	7.8±10.7	<0.0001
Social role functioning	27.8±17.2	35.0±16.5	7.2±16.5	<0.0001	24.7±17.2	31.8±17.9	7.1±16.9	<0.0001
Emotional role functioning	37.3±18.1	41.6±17.4	4.2±18.4	<0.0001	35.6±18.1	39.4±18.0	3.7±17.1	0.053
General mental health	41.1±12.8	47.3±11.6	6.2±10.0	<0.0001	39.2±12.3	45.3±11.5	6.1±10.8	<0.0001
Physical summary score	24.4±10.2	26.2±10.4	1.8±8.3	0.0019	23.7±10.3	25.2±10.3	1.5±7.1	0.20
Mental summary score	42.2±16.0	50.1±14.7	8.0±13.1	<0.0001	39.8±15.8	48.4±15.1	8.6±12.7	<0.0001

Data are presented as mean ± SD, unless stated otherwise. Bold type denotes significance. NIV, noninvasive ventilation; FEV1, forced expiratory volume in 1 s; VCin, inspiratory vital capacity; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; 6MWD, 6-min walk distance; SF-36, Short Form (36) Health Survey.

Quality of Life

As a standardized health-related quality of life measurement tool, the German version of the Short Form Health Survey (SF)-36 was used. The questionnaire measures 8 dimensions of health-related quality of life and allows calculation of 2 summary scales of physical and mental health. Each scale is directly transformed into a 0–100 scale on the assumption that each question carries equal weight. A lower score reflects more disability. The higher the score, the less disability, i.e., a score of 0 is equivalent to maximum disability and a score of 100 is equivalent to no disability [20]. Only those questionnaires which were filled in completely and valid were included in the final analysis.

Lung Function and Blood Gas Analysis

Spirometry and body plethysmography (Master Screen Body; Erich Jaeger GmbH, Höchberg, Germany) were performed on PR admission pursuant to the Guidelines of the American Thoracic Society [21, 22] with the use of reference values of the ERS [23]. Blood gases were taken at rest under room air condition (Radiometer ABL800; Radiometer GmbH, Willich, Germany).

Statistics

Data consistency was checked and the data were screened for outliers and normality by using quantile plots. Data are shown as mean values and standard deviation (SD). The Mann-Whitney U

test was used to test for continuous variables between groups and the χ^2 test for categorical variables. A generalized multivariate regression model was used to assess the association of NIV with success of PR based on the gamma distribution. A *p* value <0.05 was considered statistically significant. All analyses were done using Statistica 13 (StatSoft, Tulsa, OK, USA) and PASW 20 (IBM SPSS Statistics for Windows; IBM, Armonk, NY, USA).

Results

Study Population

In total, 1,044 patients were included in the analysis. The mean age was 51.6 ± 9.8 years, 585 patients (56%) were female, and the mean body mass index (BMI) was 23.7 ± 5.6. The underlying diseases were as follows: COPD, *n* = 608 (58%); ILD, *n* = 293 (28%); CF, *n* = 78 (7.5%); and other diseases, *n* = 65 (6.2%). Long-term oxygen therapy at rest was used by 912 patients (87%) and 296 patients (28%) were treated with long-term nocturnal NIV. The mean duration of PR was 33.4 ± 15.2 days.

Table 2. Characteristics of the patients with and those without NIV on admission to inpatient pulmonary rehabilitation ($n = 1,044$)

	NIV ($n = 296$; 28.3%)	No NIV ($n = 748$; 71.7%)	<i>p</i> value
Age, years	51.8±9.2	51.5±10.1	0.59
Female sex, <i>n</i> (%)	130 (43.7)	330 (44.2)	0.95
BMI	23.2±5.7	23.9±5.5	0.057
<i>Underlying disease, n (%)</i>			
COPD	222 (74.8)	386 (51.7)	<0.0001
ILD	37 (12.5)	256 (34.3)	<0.0001
CF	26 (8.8)	52 (7.0)	0.36
Others	11 (3.7)	54 (7.2)	0.033
<i>Lung function testing</i>			
FEV1, % predicted	24.5±10.8	35.7±17.2	<0.0001
VCin, % predicted	45.5±13.8	53.2±18.7	<0.0001
FEV1/FVC, %	46.9±20.2	55.7±24.8	<0.0001
TLC, % predicted	128.1±38.5	109.4±42.2	<0.0001
RV, % predicted	286.7±103.3	219.7±114.4	<0.0001
RV/TLC, %	74.4±11.3	64.3±14.6	<0.0001
DLCO, % predicted	23.2±13.7	29.1±15.8	<0.0001
pCO ₂ , mm Hg	48.9±8.1	40.4±6.1	<0.0001
6MWD, m	250±117	299±128	<0.0001
<i>Health status (SF-36)</i>			
Physical functioning	12.6±12.0	14.9±12.5	0.015
Bodily pain	45.2±12.3	44.8±12.9	0.70
Physical role functioning	26.1±9.3	26.9±9.8	0.31
General health perceptions	30.6±8.4	30.5±8.7	0.90
Vitality	32.6±10.6	34.3±10.6	0.037
Social role functioning	24.5±16.8	28.8±16.9	0.0008
Emotional role functioning	35.4±18.3	37.8±18.2	0.10
General mental health	39.2±12.3	41.8±12.9	0.006
Physical summary score	24.0±10.1	24.5±10.0	0.58
Mental summary score	40.2±16.2	42.9±16.0	0.039

Data are presented as mean ± SD, unless stated otherwise. Bold type denotes significance. NIV, noninvasive ventilation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; CF, cystic fibrosis; FEV1, forced expiratory volume in 1 s; VCin, inspiratory vital capacity; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; DLCO, diffusing capacity for carbon monoxide; pCO₂, partial pressure of carbon dioxide; 6MWD, 6-min walk distance; SF-36, Short Form (36) Health Survey.

Pulmonary Rehabilitation

The effect of PR was assessed by comparing lung function measures, 6MWD, and the SF-36 scores at admission and discharge. As shown in Table 1, PR resulted in an increase in predicted inspiratory vital capacity (VCin; +2.2%, from 51.1 ± 17.9 to 53.3 ± 18.1%; $p = 0.012$) and

Fig. 1. Increase in 6MWD in patients treated with NIV compared to patients without NIV. 6MWD, 6-min walk distance; NIV, non-invasive ventilation.

in 6MWD (+51 m, from 285 ± 127 to 336 ± 126 m; $p < 0.0001$). Further, PR resulted in a significant improvement in all SF-36 domains (Table 1).

PR in Patients Treated with NIV

To further assess the effect of PR in end-stage lung disease, a subgroup of patients with long-term nocturnal NIV treatment was analyzed. In total, 296 patients (28%) with NIV were identified. The mean time on NIV was 7.7 ± 2.6 h/day. The mean in- and expiratory pressures were 20.6 ± 4.8 and 5.3 ± 1.9 cm H₂O, respectively. The majority of the patients was female ($n = 167$; 56.4%). The mean age was 51.8 ± 9.1 years and the mean BMI was 23.2 ± 5.7. The diagnoses were as follows: COPD, $n = 222$ (75.0%); ILD, $n = 37$ (12.5%); CF, $n = 26$ (8.8%); and other diseases, $n = 11$ (3.7%) (Table 2).

PR in patients with NIV resulted in an increase in predicted VCin (+3.6%, from 45.5 ± 13.8 to 48.7 ± 14.4%; $p = 0.006$) and in 6MWD (+59 m, from 250 ± 117 to 309 ± 116 m; $p < 0.0001$). Additionally, PR resulted in a significant improvement in various items of the SF-36, as shown in Table 1.

Further, the effect of PR in patients treated with NIV was compared to that in patients without NIV (Table 2). Age, sex, and BMI were not different between the groups. However, the patients with NIV suffered more often from COPD (75 vs. 52%; $p < 0.0001$) and less often from ILD (13 vs. 34%; $p < 0.0001$) or other diseases (3.7 vs. 7.2%;

Table 3. Effects on pulmonary rehabilitation in patients treated with NIV compared to patients without NIV ($n = 1,044$)

	NIV ($n = 296$; 28.3%)	No NIV ($n = 748$; 71.7%)	<i>p</i> value
<i>Lung function testing</i>			
Δ FEV1, % predicted	1.3 $\pm$ 4.2	0.8 $\pm$ 4.9	0.12
Δ VCin, % predicted	3.6 $\pm$ 10.1	1.7 $\pm$ 10.1	0.014
Δ FEV1/FVC, %	-1.5 $\pm$ 8.5	-0.3 $\pm$ 10.2	0.11
Δ TLC, % predicted	-2.1 $\pm$ 15.7	0.1 $\pm$ 12.5	0.018
Δ RV, % predicted	-11.1 $\pm$ 51.0	-1.8 $\pm$ 38.3	0.002
Δ RV/TLC, %	-1.3 $\pm$ 7.2	-0.7 $\pm$ 7.1	0.27
Δ pCO ₂ , mm Hg	0.0 $\pm$ 5.2	0.3 $\pm$ 4.4	0.57
Δ 6MWD, m	59 $\pm$ 63	48 $\pm$ 55	0.003
<i>ΔHealth status (SF-36)</i>			
Physical functioning	2.2 $\pm$ 8.7	2.5 $\pm$ 9.6	0.66
Bodily pain	3.1 $\pm$ 9.9	2.9 $\pm$ 9.9	0.74
Physical role functioning	2.8 $\pm$ 10.0	3.6 $\pm$ 12.0	0.44
General health perceptions	1.7 $\pm$ 7.6	2.5 $\pm$ 7.5	0.19
Vitality	7.8 $\pm$ 10.7	8.2 $\pm$ 10.3	0.65
Social role functioning	7.1 $\pm$ 16.9	7.2 $\pm$ 16.3	0.94
Emotional role functioning	3.7 $\pm$ 17.1	4.4 $\pm$ 18.9	0.69
General mental health	6.1 $\pm$ 10.8	6.2 $\pm$ 9.7	0.93
Physical summary score	1.5 $\pm$ 7.1	1.9 $\pm$ 8.7	0.57
Mental summary score	8.6 $\pm$ 12.7	7.8 $\pm$ 13.2	0.48

Data are presented as mean $\pm$ SD, unless stated otherwise. Bold type denotes significance. NIV, noninvasive ventilation; FEV1, forced expiratory volume in 1 s; VCin, inspiratory vital capacity; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; 6MWD, 6-min walk distance; SF-36, Short Form (36) Health Survey.

$p = 0.033$). The partial pressure of carbon dioxide (pCO₂) was high in the patients treated with NIV compared to the patients without NIV (48.9 $\pm$ 8.1 vs. 40.4 $\pm$ 6.1 mm Hg; $p < 0.0001$). Additionally, several measures of severity of disease were more advanced in the patients treated with NIV, as shown in Table 2. On admission, the scores of various physical and mental health items from the SF-36 questionnaire were worse in the patients treated with NIV (Table 2).

The success of PR in the patients treated with NIV was compared to that in the patients without NIV. As shown in Figure 1 and Table 3, the increase in 6MWD was higher in the patients treated with NIV than in the patients without NIV (59 $\pm$ 63 vs. 48 $\pm$ 55 m; $p = 0.003$). Further, in the lung function test, the improvement in VCin, total lung capacity, and residual volume was higher in the patients with NIV than in the patients without NIV. No dif-

Table 4. Results of the generalized multivariate regression models on improvement in 6MWD

Input variables	<i>p</i> value
Age (years)	0.30
Sex (female)	0.58
Underlying disease	0.009
Duration of PR (days)	<0.0001
6MWD _{adm} (m)	<0.0001
VCin _{adm} (%)	0.008
FEV1 _{adm} (%)	0.62
Noninvasive ventilation	0.023

Bold type denotes significance. PR, pulmonary rehabilitation; 6MWD_{adm}, 6-min walk distance on admission; VCin_{adm}, inspiratory vital capacity on admission; FEV1_{adm}, forced expiratory volume in 1 s on admission.

ferences in the SF-36 outcomes between the groups were found, as shown in Table 3.

To assess the effect of NIV therapy on PR, a multivariate generalized regression model analysis was performed. As outcome variables, changes in 6MWD, VCin, forced expiratory volume in 1 s (FEV1), and physical and mental summary scores between admission and discharge were assessed. As input variables, age, sex, underlying disease, duration of PR, 6MWD, VCin, and FEV1 at admission were used. As shown in Table 4, NIV therapy was associated with significant improvement in 6MWD ($p = 0.023$) while controlling for the above-described confounding variables. No influences of NIV on the improvements in VCin, FEV1, and physical and mental summary scores were found (data not shown).

Patients treated with NIV were classified as responders ($n = 203$; 69%) or nonresponders ($n = 93$; 31%) according to the minimal important difference of 30 m in 6MWD, as shown in Table 5. Responders were more likely to be female (47 vs. 31%; $p = 0.009$). The predicted diffusing capacity for carbon monoxide (DLCO) was higher in the responders than in the nonresponders (25.2 $\pm$ 13.9 vs. 18.5 $\pm$ 12.2%; $p = 0.011$). There was no difference in the degree of hypercapnia (Table 5).

Discussion

PR in patients with end-stage lung disease awaiting lung transplantation on long-term nocturnal NIV is feasible and is associated with clinically important improvements in exercise capacity and quality of life. Further-

Table 5. Baseline characteristics of the patients treated with NIV classified as responders or nonresponders ($n = 296$)

	Responders ($n = 203$; 68.6%)	Nonresponders ($n = 93$; 31.4%)	<i>p</i> value
Age, years	51.4±9.4	52.8±8.6	0.23
Female sex, <i>n</i> (%)	96 (47.3)	29 (31.2)	0.009
BMI	23.3±5.9	22.8±5.4	0.51
<i>Underlying disease, n (%)</i>			
COPD	150 (73.9)	72 (77.4)	0.52
ILD	25 (12.3)	12 (12.9)	0.89
CF	20 (9.9)	6 (6.5)	0.34
Others	8 (3.9)	3 (3.2)	0.76
Duration of PR, days	36.6±14.8	37.6±26.3	0.66
<i>Lung function testing</i>			
FEV1, % predicted	24.5±10.6	24.5±11.2	0.95
VCin, % predicted	45.6±14.3	45.3±12.7	0.90
FEV1/FVC, %	47.1±20.6	46.3±19.3	0.77
TLC, % predicted	125.4±39.1	134.0±36.8	0.076
RV, % predicted	279.2±103.2	303.6±102.2	0.065
RV/TLC, %	73.9±11.5	75.5±10.8	0.28
DLCO, % predicted	25.2±13.9	18.5±12.2	0.011
pCO ₂ , mm Hg	48.9±8.0	48.9±8.4	0.98
6MWD, m	244±122	262±105	0.20

Data are presented as mean ± SD, unless stated otherwise. Bold type denotes significance. NIV, noninvasive ventilation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; CF, cystic fibrosis; FEV1, forced expiratory volume in 1 s; VCin, inspiratory vital capacity; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; DLCO, diffusing capacity for carbon monoxide; pCO₂, partial pressure of carbon dioxide; 6MWD, 6-min walk distance.

more, despite more advanced lung disease, patients treated with NIV experience a larger benefit from PR than patients without NIV while awaiting lung transplantation.

PR is highly recommended in patients with chronic lung disease as an adjunct to medical therapy [2, 24]. Several studies have proven benefits from PR concerning exercise capacity and quality of life [7, 9, 25]. Similarly, in our cohort of more than 1,000 patients awaiting lung transplantation, PR was associated with improvements in 6MWD and all SF-36 domains. Our results further support the usefulness of PR even in patients with end-stage lung disease. This is of particular interest for patients awaiting lung transplantation, since pretransplant functional status is closely related to transplant outcome [3]. Large studies of the UNOS database have shown that pre-

transplant 6MWD is a significant predictor of waitlist mortality [26] and is significantly associated with post-transplant survival [27, 28]. An improvement in 6MWD and functional status, respectively, by PR while awaiting lung transplantation might therefore directly impact outcome. Further, 6MWD and functional status are part of the lung allocation score to estimate the medical transplant benefit [29, 30].

Hypercapnia is common in patients with advanced lung disease and has several detrimental effects [31]. Severe breathlessness limits exercise capacity in patients with hypercapnia and might therefore reduce the benefits from PR. Studies have investigated the beneficial effect of NIV while exercising. NIV applied during walking prevents exercise-induced hypoxemia, improves exercise performance with an increased walking distance, and decreases dyspnea [32]. Therefore, it has been suggested that NIV in combination with PR is effective. The addition of NIV to outpatient PR for 2 years for severe COPD patients with chronic hypercapnic respiratory failure improved their quality of life, mood, dyspnea, gas exchange, exercise tolerance, and lung functional decline [12]. Further, NIV augments the benefits of PR in patients with COPD with chronic hypercapnic respiratory failure, as it improves several measures of health-related quality of life, functional status, and gas exchange [11].

Our data provide evidence that the beneficial effect of NIV on PR is notable already in the context of short-term inpatient rehabilitation. This is of particular interest for lung transplant candidates with an anticipated short waiting time for lung transplantation.

To assess the effect of NIV on PR success, multivariate regression analysis was performed. Despite controlling for age, sex, underlying diseases, lung function impairment, exercise capacity, and the duration of PR, treatment with NIV was independently associated with success of PR, underlining the impact of PR on patients with end-stage lung diseases on NIV.

Several factors might be responsible for the beneficial effect of nocturnal NIV on daytime training. NIV decreases hyperinflation and leads to recovery of the inspiratory muscle function, leading to an improvement in respiratory mechanics [12, 33, 34]. Further, NIV has been shown to improve sleep time and efficiency [35]. Nocturnal hypoventilation may be ameliorated, which allows the respiratory center to be reset, resulting in reduced daytime hypercapnia [33].

Daytime hypercapnia was assessed at admission to and at discharge from PR. As expected, the patients on NIV had significantly higher pCO₂ levels than the patients

without NIV. Despite improvements in 6MWD and lung volume, PR had no effect on pCO₂ level. Further, the pCO₂ levels at admission were not different between the responders and nonresponders to PR. Thus, an association between degree of hypercapnia and PR success seems unlikely. The nonresponders had a significantly lower DLCO and a trend for a higher residual volume and total lung capacity than the responders. This points towards a role of hyperinflation as a limiting factor for the success of PR in patients with NIV. Further, a reduced DLCO could also be a sign of associated pulmonary vascular disease, which might be another factor with an impact on PR success. Further studies will be needed to elucidate the pathophysiologic roles of these factors.

The results of our study should be interpreted in view of the study's limitations. First, it is retrospective, spanning a long time period. However, we provide data from

more than 1,000 patients with end-stage lung disease awaiting lung transplantation. Of these, approximately one-third were treated with long-term nocturnal NIV. Second, there is no control group of patients with chronic hypercapnic respiratory failure without NIV use in addition to PR. Therefore, multivariate regression analysis was used to assess the effect of NIV as an adjunct to PR while controlling for various confounding conditions. Third, the study did not research the mechanism providing the beneficial effect of NIV in addition to PR. This needs to be further investigated in more detail.

In conclusion, PR in patients with end-stage lung disease awaiting lung transplantation on long-term nocturnal NIV is beneficial and should be recommended to each of these patients. The effect of pretransplant PR waiting list and posttransplant outcome has to be further addressed in prospective controlled trials.

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