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Predictive Significance of the Six-Minute Walk Distance for Long-Term Survival in Chronic Hypercapnic Respiratory Failure

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Key Words

Cardiopulmonary exercise test · Chronic obstructive pulmonary disease · Chronic respiratory failure · Non-invasive mechanical ventilation · Prognostic factor · Respiratory diseases

Abstract

Background: The 6-min walk distance (6-MWD) is a global marker of functional capacity and prognosis in chronic obstructive pulmonary disease (COPD), but less explored in other chronic respiratory diseases. ***Objective:*** To study the role of 6-MWD in chronic hypercapnic respiratory failure (CHRF). ***Methods:*** In 424 stable patients with CHRF and non-invasive ventilation (NIV) comprising COPD (n = 197), restrictive diseases (RD; n = 112) and obesity-hypoventilation-syndrome (OHS; n = 115), the prognostic value of 6-MWD for long-term survival was assessed in relation to that of body mass index (BMI), lung function, respiratory muscle function and laboratory parameters. ***Results:*** 6-MWD was reduced in patients with COPD (median 280 m; quartiles 204/350 m) and RD (290 m; 204/362 m) compared to OHS (360 m; 275/440 m; $p < 0.001$ each). Overall mortality during 24.9 (13.1/40.5) months was 22.9%. In the 424 patients with CHRF, 6-MWD independently predicted mortality in addition to BMI, leukocytes and forced expiratory volume in 1 s ($p < 0.05$ each). In COPD, 6-MWD was strongly associated with mortality using the median [$p < 0.001$, hazard ratio (HR) = 3.75, 95% confidence interval (CI): 2.24–6.38] or quartiles as cutoff levels. In contrast, 6-MWD was only significantly associated with impaired survival in RD patients when it was reduced to 204 m or less (1st quartile; p = 0.003, HR = 3.31, 95% CI: 1.73–14.10), while in OHS 6-MWD had not any prognostic value. ***Conclusions:*** In patients with CHRF and NIV, 6-MWD was predictive for long-term survival particularly in COPD. In RD only severely reduced 6-MWD predicted mortality, while in OHS 6-MWD was relatively high and had no prognostic value. These results support a disease-specific use of 6-MWD in the routine assessment of patients with CHRF.

Introduction

The availability of noninvasive ventilation (NIV) techniques has evoked a large increase in the number of patients treated with home mechanical ventilation due to chronic hypercapnic respiratory failure (CHRF) [1]. Owing to improved survival achieved in many diseases, the prevalence of these patients is expected to rise progressively [2]. Most patients treated with home NIV suffer from either severe chronic obstructive pulmonary dis-

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ease (COPD), restrictive disorders (RD) or obesity-hypoventilation syndrome (OHS) [1–5]. Until now, international guidelines for the specific assessment of patients with CHRF undergoing NIV have not been firmly established and only few studies focused on clinical measures that could be important for monitoring or estimation of survival [3, 6].

The 6-min walk distance (6-MWD) is well established as a global marker of functional capacity in the cardiorespiratory domain, having the advantage of integrating diverse physiological components [7, 8]. Most of the evidence favoring 6-MWD in the evaluation of treatment effects [9–12] and prediction of survival has been obtained in COPD [8, 13, 14], consistent with the fact that COPD exhibits multiple systemic manifestations beyond the respiratory impairment itself [14–18], e.g. reductions in body mass index (BMI) and fat-free mass [4, 18], which affect 6-MWD [19].

Low BMI and nutritional depletion are also not uncommon in patients with RD and CHRF [4] and predictive for survival [3, 6]. Moreover, chronic or intermittent hypoxia could evoke functional changes in skeletal or respiratory muscles similar to COPD [20–23] and, together with a reduction in lung volume, affect exercise capacity. Indeed, the 6-MWD has already been used as outcome parameter in determining the efficacy of NIV in CHRF and RD [9, 24–27]. Despite that, the clinical significance (especially the prognostic value) of 6-MWD in patients with CHRF without obstruction is not well explored [28]. Owing to differences in the pathophysiology of diseases leading to CHRF, a separate evaluation of patients with COPD, OHS and RD might provide further insights.

Based on this background, we analyzed the association between 6-MWD and long-term survival in the presence of CHRF and NIV in patients with RD and OHS compared with COPD. To facilitate the comparison with previous data, we also evaluated established risk factors, e.g. lung function, BMI and laboratory parameters.

Patients and Methods

Study Population

Consecutive patients treated with NIV due to CHRF, who were regularly admitted for follow-up to the Center of Pneumology, Donaustauf Hospital, University of Regensburg, between March 2000 and December 2005, were selected retrospectively from a survey data base. Patients were in a stable clinical condition of either COPD, OHS or RD comprising chest wall diseases (CWD), non-progressive neuromuscular disorders (NMD) or interstitial lung diseases (ILD).

The diagnosis of COPD was based on clinical history, symptoms and airway obstruction, i.e. forced expiratory volume in 1 s (FEV_1) to vital capacity <70% predicted after bronchodilator inhalation [29]. OHS was defined by a BMI >30, daytime arterial carbon dioxide tension ≥45 mm Hg prior NIV therapy and clinical symptoms of CHRF in the absence of other known causes of hypoventilation [30]. Patients with clinical signs of airway infection, current exacerbation, unstable cardiac arrhythmia or patients with invasive ventilation were excluded. Additionally, duration of nocturnal home NIV of ≥3 months was required. The study was approved by the local Ethics Committee.

Assessments

On the day of admission, blood gases (Rapidlab; Bayer; East Walpole, Mass., USA) were analyzed at rest from the hyperemic earlobe. Samples were taken in the daytime during spontaneous breathing of room air, if possible, or otherwise during the patients' usual oxygen flow. Spirometry and body plethysmography (MasterScreen, Viasys, Würzburg, Germany) were performed following guidelines of the American Thoracic Society [31], using reference values of the European Respiratory Society [32]. For measurement of inspiratory mouth occlusion pressure at 100 ms, plateau values from five qualitatively acceptable attempts were taken. Maximal inspiratory pressure (PI_{max}) was measured from residual volume at maximal inspiratory effort [33], and the best value of at least three reproducible attempts was documented [34]. Additionally an electrocardiogram was recorded.

After a phase of recovery, 6-MWD was determined based on the guidelines of the American Thoracic Society [8] while patients had their usual oxygen flow. The test was performed on a 30-meter corridor by nurses with specific experience, and its result was recorded in absolute values and in percent of predicted (%pred) [35]. Hemoglobin and leukocyte levels were measured using conventional procedures (Micros 60-CT, ABX, Montpellier, France). Additionally, BMI calculated as weight/height^2 and comorbidities were documented.

Follow-Up

All patients were routinely readmitted to the hospital every 6 months for reevaluation of clinical state and treatment efficacy of NIV. During these visits, adherence to NIV was assessed via the time counter of the ventilator, and ventilation parameters were adjusted according to nocturnal capillary blood gases and oxygen saturation. For survival analysis, patients were followed until death or until the end of the study period in January 1st, 2006, but at least 3 months after discharge. Information on cardiopulmonary or all-cause mortality was obtained from the patients' relatives and/or family doctors.

Statistical Analysis

For data description, continuous variables are shown as median values and quartiles. The presence of normal distribution was assessed by the Shapiro-Wilk test. Baseline characteristics of groups were compared using the Mann-Whitney U test for quantitative variables or Fisher's exact test for binary variables. Survival was calculated by Kaplan-Meier analysis, starting the day of assessment of 6-MWD to the closing date (January 1st, 2006). Cutoff values were derived from rounded median values, or from the 25th or 75th population percentiles. The predictive value of each single variable for all-cause mortality was analyzed by uni-

Table 1. Baseline characteristics of the patients with RD, COPD or OHS

Characteristics	COPD (n = 197)	RD (n = 112)	OHS (n = 115)
Sex, females/males	58/139	60/52[a]	44/71[b]
Age, years	66.7 (59.7; 72.6)	66.9 (58.8; 74.4)	58.1 (50.3; 67.5)[b, c]
BMI, kg/m^2	28.6 (23.4; 32.8)	28.3 (23.9; 31.8)	43.3 (36.8; 47.6)[b, c]
6-MWD, m	280.0 (204.0; 350.0)	290.0 (204.0; 362.0)	360.0 (275.0; 440.0)[b, c]
6-MWD, %pred	58.6 (40.5; 70.7)	61.3 (44.7; 78.6)	76.6 (61.6; 90.4)[b, c]
Hemoglobin, g/dl	13.6 (12.4; 14.8)	13.4 (12.4; 14.3)	13.5 (12.5; 15.3)
Leukocytes, $10^3/\mu l$	8.5 (7.0; 10.5)	7.2 (6.0; 8.6)[a]	8.3 (6.7; 9.8)[b]
FEV_1, liters	0.85 (0.70; 1.17)	0.97 (0.76; 1.23)	2.0 (1.6; 2.5)[b, c]
VC, liters	2.0 (1.6; 2.4)	1.4 (0.98; 1.7)[a]	2.7 (2.2; 3.6)[b, c]
sR_{aw}, kPa × s	3.8 (2.7; 6.3)	0.98 (0.7; 1.5)[a]	1.3 (0.9; 1.7)[b, c]
RV/TLC, %	69.8 (63.2; 76.9)	58.1 (53.5; 63.6)[a]	46.0 (42.0; 54.8)[b, c]
$P_{0.1}$, kPa	0.50 (0.39; 0.62)	0.39 (0.27; 0.50)[a]	0.36 (0.24; 0.45)[c]
PI_{max}, kPa	4.2 (3.1; 5.8)	3.7 (2.5; 5.0)[a]	5.3 (4.0; 8.0)[b, c]
pH	7.42 (7.40; 7.44)	7.42 (7.40; 7.44)	7.43 (7.41; 7.45)[c]
PaO_2, mm Hg	64.0 (55.0; 71.0)	65.0 (59.0; 72.0)[a]	64.0 (58.5; 70.5)[c]
$PaCO_2$, mm Hg	44.0 (40.0; 47.0)	44.0 (40.0; 47.8)[a]	40.0 (38.0; 43.0)[b, c]
BE, mmol/l	4.3 (2.1; 7.0)	3.7 (1.6; 5.4)	2.5 (0.5; 4.3)[b, c]
pH[1]	7.43 (7.40; 7.45)	7.42 (7.40; 7.44)	7.43 (7.41; 7.45)
PaO_2, mm Hg[1]	56.0 (51.0; 53.0)	62.0 (57.0; 68.0)[a]	62.0 (57.0; 68.8)
$PaCO_2$, mm Hg[1]	44.0 (40.0; 47.0)	44.0 (40.0; 47.0)	40.0 (38; 43.0)[b, c]
BE, mmol/l[1]	4.1 (2.2; 6.0)	4.0 (1.7; 5.5)	2.3 (0.7; 4.1)[b, c]

Data are shown as median values and quartiles (in parentheses), except for sex. Characteristics of the groups were compared using the non-parametric Mann-Whitney U test. [a] $p < 0.05$ vs. COPD, [b] $p < 0.05$ vs. RD, and [c] $p < 0.05$ vs. COPD. VC = Vital capacity; sR_{aw} = specific airway resistance; RV = residual volume; TLC = total lung capacity; $P_{0.1}$ = mouth occlusion pressure at 100 ms; PaO_2 = arterial oxygen tension; $PaCO_2$ = arterial carbon dioxide tension; BE = base excess. Blood gas values of all patients were obtained either with oxygen (median 2.0, quartiles: 1.0, 2.0 l/min) or without.

[1] Values were obtained only without oxygen (191 RD patients and 118 with COPD).

variate regression using the log-rank test. Variables significant in univariate analyses were entered into a stepwise multivariate Cox regression analysis to identify independent predictors, using an entry level of $p < 0.05$ and a removal level of 0.10. For all tests, p values <0.05 were considered statistically significant. Data were analyzed using a statistical software package (version 12.0; SPSS, Chicago, Ill., USA).

Results

Study Population

The study population comprised 424 patients (262 males and 162 females) with CHRF due to either severe COPD (n = 197; stage IV according to the Global Initiative for Chronic Obstructive Lung Disease) [36], OHS (n = 115) or RD (n = 112). In the group with RD, 68.8% (n = 77) had CWD, 17.9% (n = 20) NMD and 13.4% (n = 15) ILD.

Nocturnal NIV had been initiated 5.6 (median; quartiles: 3.6; 24.5) months prior to enrolment in patients with RD/OHS and 7.0 (3.7; 14.4) months in patients with COPD; these values did not significantly differ between groups. Patients were ventilated either in volume- or pressure-cycled assist-controlled mode with an expiratory airway pressure of 4 (3; 5) cm H_2O, an inspiratory airway pressure of 22 (18; 24) cm H_2O and a respiratory frequency of 18 (16; 22) per minute. The daily duration of ventilator use was 6.8 (4.8; 8.3) h/day. Ventilation parameters did not significantly differ between groups. 74.0% of the patients with RD/OHS and 96.5% of the patients with COPD were on long-term oxygen therapy ($p < 0.001$).

6-MWD in absolute values and %pred, as well as age, BMI, lung function, mouth occlusion pressures, arterial carbon dioxide tension and base excess of patients with OHS differed significantly compared to those with COPD and RD (table 1). However, no significant differences in

Table 2. Significant prognostic factors according to univariate survival analyses in the total group of patients (n = 424)

Variable	Median (quartiles)	p value	HR	95% CI of HR
6-MWD, m	303.0 (232.3; 373.0)	<0.0001	2.567	1.701–3.804
6-MWD, %pred	64.8 (47.6; 80.0)	<0.0001	2.561	1.682–3.755
Age, years	65.2 (57.1; 71.6)	0.0204	0.622	0.418–0.928
BMI, kg/m^2	30.9 (25.3; 37.8)	<0.0001	2.518	1.636–3.643
Leukocytes, $10^3/\mu l$	8.0 (6.7; 10.0)	0.0081	0.560	0.360–0.859
FEV_1, liters	1.1 (0.8; 1.6)	<0.0001	2.440	1.553–3.449
VC, liters	2.0 (1.5; 2.6)	0.0323	1.554	1.038–2.304
sR_{aw}, kPa × s	2.0 (1.1; 3.7)	0.0391	0.651	0.440–0.979
RV/TLC, %	60.7 (52.3; 70.4)	0.0006	0.480	0.331–0.739
$P_{0.1}$, kPa	0.43 (0.31; 0.54)	0.0252	0.612	0.404–0.942

p values were according to univariate survival analysis (log-rank test) using the respective median value for survival predictors. For abbreviations, please see table 1 and the text.

6-MWD (absolute values and %pred) between patients with COPD and RD were observed, while sex, leukocyte levels, mouth occlusion pressures and lung function were different between these groups (table 1). When comparing single diagnoses within RD, only 6-MWD of patients with ILD (median 195 m; quartiles 100, 295 m, or 42.0; 20.7, 70.4%pred) was shorter ($p < 0.05$) compared to patients with CWD (300 m; 231, 360 m, or 64.2; 50.8, 79.1%pred) or NMD (290 m; 240, 408 m, or 64.2; 48.5, 87.1%pred).

Predictors of Long-Term Survival in the Total Population

Overall (n = 424), the mean observation time between the end of the study period or until patients died was 24.9 (13.1; 40.5) months. Within this period, 59 patients with COPD and 38 patients with RD/OHS died, corresponding to an overall mortality of 22.9%. Deaths resulted predominantly from respiratory causes (n = 75; 77.3%), including respiratory or right heart failure, pulmonary embolism or pneumothorax. The other patients died from non-respiratory (n = 15; 15.5%) or unknown causes (n = 7; 7.2%).

In univariate analyses of the total population, using median values as cutoff, 6-MWD (absolute and %pred; $p < 0.001$ each; table 2; fig. 1), age, BMI, leukocytes, specific airway resistance, residual volume to total lung capacity, FEV_1, vital capacity and mouth occlusion pressure at 100 ms (table 3) predicted long-term survival. Similar associations were found using the %pred values. There were no significant associations of survival with hemoglobin (p = 0.119), pH (p = 0.948), arterial oxygen (p = 0.756) and carbon dioxide tension (p = 0.558), base excess (p = 0.203) and PI_{max} (absolute and %pred; p = 0.071 and 0.137). In a stepwise multivariate Cox regression analysis, only 6-MWD, BMI, leukocyte number and FEV_1 remained as independent predictors of mortality ($p < 0.05$ each; table 3).

Prognostic Value of 6-MWD in Different Diseases

6-MWD was a strong predictor of long-term survival in COPD (n = 197) using the respective median values (280 m or 58.6%pred) as cutoff [$p < 0.001$, hazard ratio (HR) 3.75, 95% confidence interval (CI) 2.24–6.38; or $p < 0.001$, HR 3.48, 95% CI 2.06–5.85]. Using quartiles of 6-MWD, increasing 6-MWD was associated with stepwise improved survival (comparison between quartiles: $p < 0.001$; fig. 2).

In contrast, 6-MWD was not predictive for survival in patients with RD using the median values (290 m or 61.3%pred) as cutoff. However, using quartiles of 6-MWD demonstrated that 6-MWD was significantly associated with impaired survival in RD patients when it was reduced to 204 m or less (1st quartile; p = 0.003, HR 3.31, 95% CI: 1.73–14.1) compared with subjects with a 6-MWD of more than 204 m (p = 0.003, fig. 3). The 2nd, 3rd and 4th quartiles of 6-MWD did not significantly differ regarding survival. In patients with OHS, 6-MWD did not have any prognostic value using either the median value of this population (360 m) or the quartiles (fig. 4) as cutoff values.

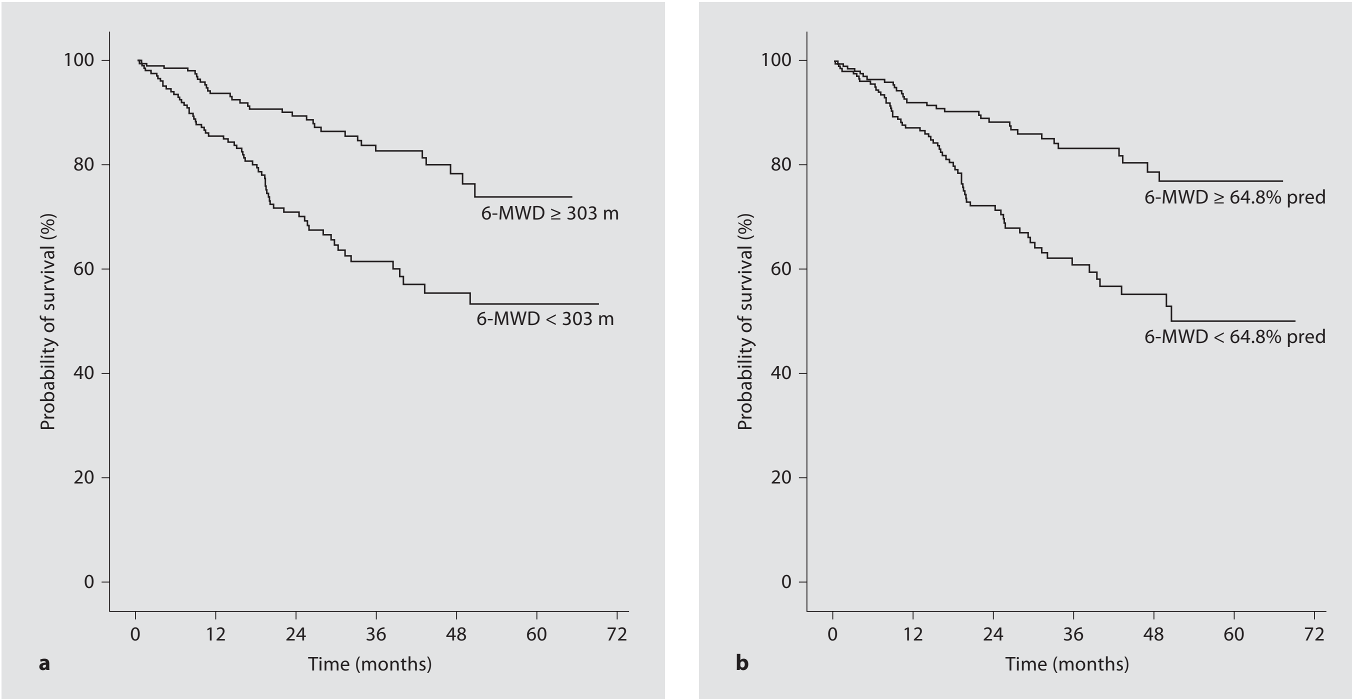


Fig. 1. Prognostic value of either absolute (**a**) or %pred (**b**) values of 6-MWD in CHRF patients (n = 424) using the respective median values as cutoff (303 m; $p < 0.001$, and 64.8%pred; $p < 0.001$).

Table 3. Prognostic value of baseline parameters in the total group of patients (n = 424) according to a stepwise Cox multivariate regression analysis

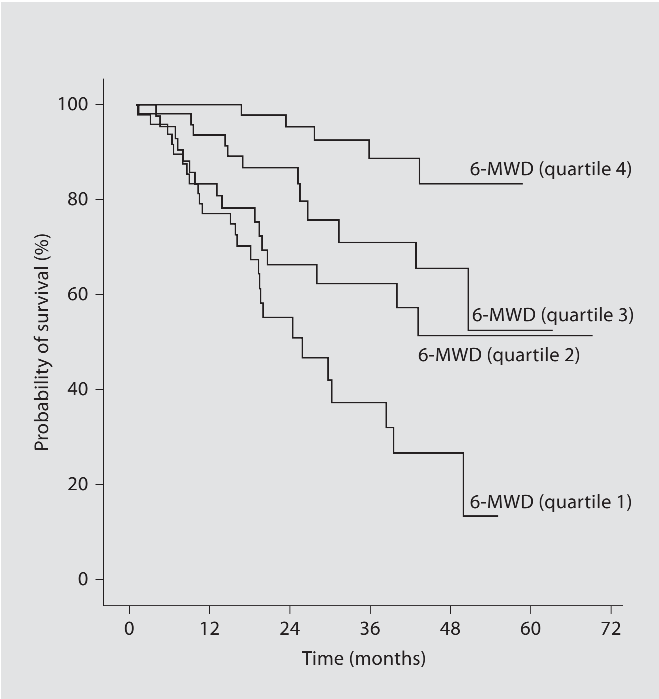
Parameter	Cutoff	B	SE	Exp (B)	95% CI of Exp(B)	p value
6-MWD, m	303.0	–0.609	0.246	0.544	0.336–0.880	0.013
BMI, kg/m^2	30.9	–0.731	0.263	0.481	0.287–0.807	0.005
Leukocytes, $10^3/\mu l$	8.0	0.572	0.229	1.773	1.131–2.773	0.013
FEV_1, liters	1.1	–0.603	0.282	0.547	0.315–0.951	0.032

B = Estimate of regression coefficient; SE = standard error of estimate.

Discussion

The present study aimed to evaluate the prognostic value of 6-MWD in patients with CHRF treated with NIV. Within the total population, 6-MWD was an independent predictor of mortality in addition to known risk factors such as BMI and FEV_1 or leukocyte count. This result was mainly attributable to the patients with COPD in whom 6-MWD was highly predictive for long-term survival throughout the whole range of values. In contrast, in patients with RD and CHRF, only a markedly decreased 6-MWD predicted increased mortality, while any association with OHS was lacking. Thus the prognostic role of 6-MWD depended on the underlying disease and could not be extrapolated from the results obtained in COPD.

Patients with CHRF are commonly considered to be at high risk for death and hospitalization [3, 37] and NIV is often used in the various underlying disorders. As reflected in our population, many patients are characterized by a restrictive ventilatory pattern resulting predominantly from chest wall deformations, post-tuberculosis syndrome or neuromuscular disorders [38]. More recent-



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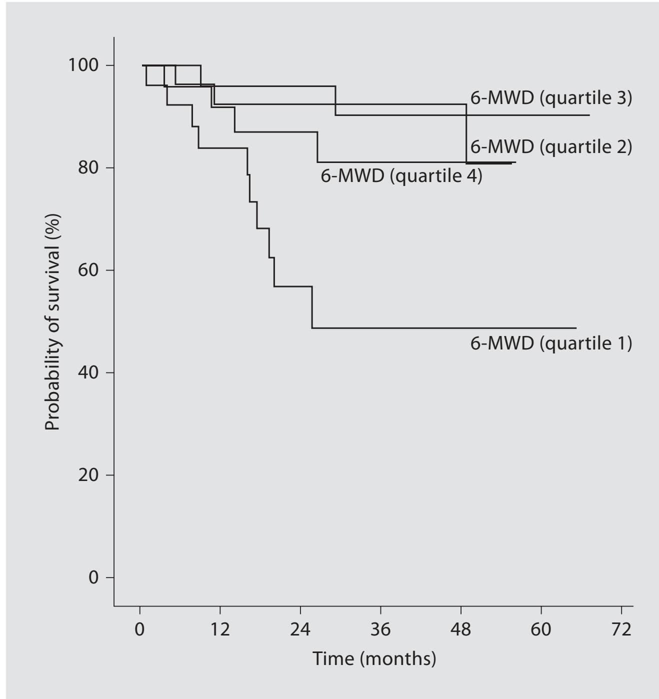

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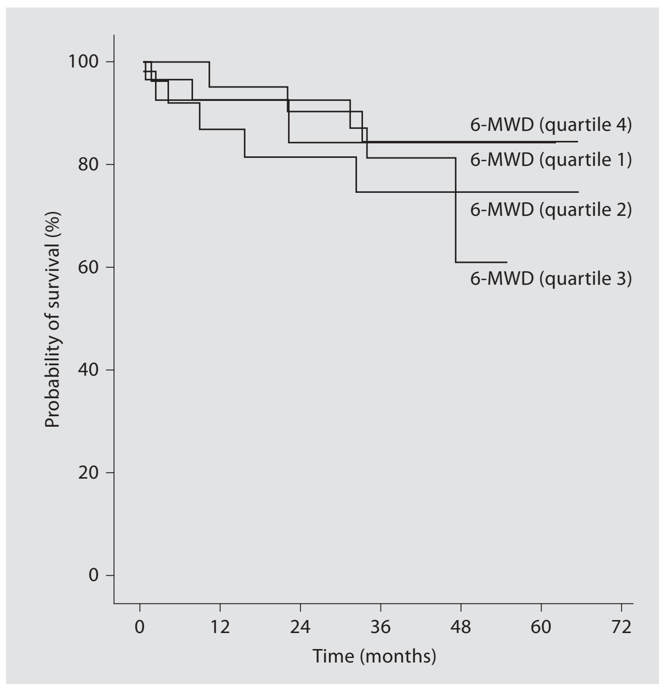

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Fig. 2. Prognostic value of 6-MWD in patients with COPD (n = 197) comparing the quartiles of 6-MWD (0–204, quartile 1; 205–280, quartile 2; 281–350, quartile 3, and >350 m, quartile 4; log-rank test; $p < 0.001$). Significant differences in long-term survival were present between quartile 1 and 2 ($p = 0.015$), 3 ($p < 0.001$) and 4 ($p < 0.001$), quartile 2 and 4 ($p < 0.001$), quartile 3 and 4 ($p = 0.047$), but not between quartile 2 and 3 ($p = 0.207$).

Fig. 3. Prognostic value of 6-MWD in patients with RD (n = 112) comparing the quartiles of 6-MWD (0–204, quartile 1; 205–290, quartile 2; 291–362, quartile 3, and >362 m, quartile 4; log-rank test; $p = 0.003$). Significant differences in long-term survival were obtained when comparing quartile 1 to each of the other quartiles ($p < 0.05$ each). Survival was not significantly different between the 2nd, 3rd and 4th quartile.

Fig. 4. Prognostic value of 6-MWD in patients with OHS (n = 115) comparing the quartiles of 6-MWD (0–275, quartile 1; 276–360, quartile 2; 361–440, quartile 3, and >440 m, quartile 4; log-rank; $p = 0.783$). Survival was not significantly different between each of the quartiles.

ly, OHS also became a major indication [1, 5]. Recent findings have indicated that long-term NIV has an impact on survival in many of these diseases [39–41], consequently knowledge of outcome parameters is essential to best utilize the potential of NIV therapy.

In the present study, BMI, leukocyte counts and FEV_1 were found to be major predictors for long-term survival in CHRF patients. Evidence has already been provided that nutritional depletion and systemic inflammation are common in patients with respiratory failure and, therefore, represent important risk factors beyond the respiratory impairment [3, 6]. In previous analyses partially including the same patients, we also found associations between survival, inflammatory markers and BMI [41, 42]. Based on the concept that 6-MWD is an integrative measure comprising different physiologic components, it seems plausible that 6-MWD was an independent predictor of long-term mortality within the total group of patients with CHRF and NIV.

To further elucidate this novel finding, we separately analyzed patients with either COPD, RD or OHS, revealing that the associations of 6-MWD with long-term survival observed in the overall population were to a great extent due to the COPD subgroup. In line with this, 6-MWD in COPD is known to be valuable for clinical assessment, monitoring and prediction of survival [10–14, 43–45]. Recent data even suggest that 6-MWD can indicate clinical changes not detectable in the sequential evaluation of pulmonary impairments alone [44]. Our findings additionally elucidated 6-MWD as a sensitive measure with regard to long-term survival in patients with COPD and CHRF. As shown by the analysis of quartiles, 6-MWD was highly predictive of mortality throughout its rather small range independent of lung function impairment.

Associations of 6-MWD with mortality have also been detected in primary pulmonary hypertension [46], chronic heart diseases [47] or, more recently, idiopathic pulmonary fibrosis [48], but knowledge on the role of 6-MWD in other, particularly restrictive, chronic respiratory disorders is rather limited. Our data indicated that the median 6-MWD in RD (290 m) was as low as in COPD (280 m) and that the two groups did not significantly differ in BMI, although BMI might obscure a loss of fat-free mass [4]. Nevertheless, compared to COPD, the prognostic value of 6-MWD was lower in RD and present only when using the 1st quartile as cutoff. In OHS, knowledge on the significance of 6-MWD is scarce, and we could not reveal any prognostic value. These patients showed a relatively high 6-MWD, which seemed plausible in view of the low age but high BMI, lung volumes and PI_{max}, all of which predict high exercise capacity in chronic respiratory diseases [7, 49]. Of course, our data do not implicate that 6-MWD has no value in the assessment of treatment effects in OHS or RD, as particularly these patients showed improved walking distances after initiation of NIV [9].

Different factors might explain the weaker impact of 6-MWD on survival in RD or OHS compared to COPD. As recent data suggest, patients with RD or OHS have a favorable prognosis while using NIV [39–41], which might have rendered it more difficult to reveal an association with 6-MWD. This argument does, however, not invalidate our conclusion, as a weaker statistical association also implies a lower predictive power in practice. Secondly, systemic inflammation is thought to play a role in nutritional depletion, skeletal muscle dysfunction and mortality [16]. Correspondingly, leukocyte numbers were highest in COPD. Thirdly, most of the patients with RD suffered from CWD with large skeletal deformities which may affect 6-MWD without being reflected in survival.

To our knowledge, there is one comprehensive study of similar size (n = 446) considering the relationship between 6-MWD and long-term survival in patients with chronic respiratory diseases receiving long-term oxygen therapy and/or home mechanical ventilation [6]. 6-MWD turned out as a prognostic factor in univariate analyses but was no independent predictor, possibly due to the lower proportion of COPD (42.8 vs. 53.5% in the present study). The study did not report data on restrictive and obstructive disorders separately. A previous study comprising 149 patients with chronic respiratory diseases after pulmonary rehabilitation (89% COPD, 8% asthma, 2% CWD and 1 patient with ILD) demonstrated 6-MWD to be strongly related to survival, again supporting its role particularly in COPD [45]. Our data extend these findings by demonstrating that in CHRF 6-MWD has prognostic value mainly in COPD or in severe RD.

While our study had the advantage of comprising large patient cohorts with RD or COPD, some aspects require attention in interpretation. Limitations of our study were the retrospective design and the fact that all patients were under NIV treatment. We only included patients who continuously used NIV documented in regular follow-up visits. It is thus not possible to compare our findings with that of a control group without NIV. As the great majority of patients with CHRF is treated with NIV, we thus assured a rather homogeneous condition with regard to the treatment considered most effective in CHRF. The data obtained in COPD also served to assess the validity of the analysis. Indeed, they turned out to be fully consistent with previously published reports.

In summary, the present study comprising patients with CHRF under NIV treatment demonstrated 6-MWD to be an independent predictor of long-term survival. This result was mainly attributable to COPD, while in RD the prognostic value of 6-MWD was limited to severely impaired patients. In OHS, 6-MWD was rather high and not predictive of mortality. In conclusion, our data suggest a disease-specific use of 6-MWD to assess and monitor NIV-treated patients with CHRF.

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