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Quadriceps weakness contributes to exercise capacity in nonspecific interstitial pneumonia

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Summary
Background and objective: It has been shown that peripheral muscle dysfunction is a critical factor in determining exercise intolerance in patients with several chronic lung diseases, including idiopathic pulmonary fibrosis. We hypothesized that exercise capacity would be, at least in part, determined by peripheral muscle dysfunction in patients with fibrotic nonspecific interstitial pneumonia (f-NSIP), another major subtype of fibrotic interstitial lung disease. The aim of the current study was to elucidate the relevance of peripheral muscle dysfunction and its contribution to exercise intolerance in f-NSIP.
Methods: The six-minute walk test was evaluated in 30 consecutive patients with f-NSIP along with potential determinants of exercise capacity, including respiratory muscle force and peripheral muscle force.
Results: Among 30 patients, the median age was 61 years, and 21 were female. Sixteen patients showed significantly decreased quadriceps force (QF), and 17 had significant decreases in maximum expiratory pressure. Exercise capacity and muscle power were clearly related to sex. Adjusted for sex, QF showed a significant relation to exercise capacity measured by six-minute walk distance (6MWD), whereas pulmonary function parameters such as vital capacity showed marginal correlations. In stepwise multiple regression analysis, only QF was an independent predictor of 6MWD.

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Conclusions: Quadriceps weakness is often observed in patients with f-NSIP. It seems that QF significantly contributes to exercise capacity in this population.

Introduction

The importance of evaluating exercise capacity is widely recognized in chronic lung diseases. Its clinical relevance has been intensely investigated especially in patients with chronic obstructive lung disease, and its impacts on their prognosis as well as their quality of life have been elucidated.[1] More recently, attention is also being directed to evaluation of exercise capacity in patients with interstitial lung diseases. Several recent studies have reported that six-minute walk distance (6MWD) is an independent and discriminating predictor of mortality among patients classified as having idiopathic pulmonary fibrosis (IPF).[2]

Fibrotic nonspecific interstitial pneumonia (f-NSIP) has been recognized, along with IPF, as one of the major types of chronic idiopathic interstitial pneumonias.[3–5] F-NSIP has come to be recognized as a distinct disease entity with characteristic clinical, radiologic, and pathologic features that differ from other idiopathic interstitial pneumonias.[5] However, the number of previous studies that have conducted exercise testing in f-NSIP patients is very limited.[2,6]

Previously, we reported factors related to exercise capacity in IPF and demonstrated that quadriceps weakness was related to exercise capacity.[7] However, the determinants of exercise tolerance in interstitial pneumonias other than IPF remain uncertain.

In considering the mechanisms of exercise limitation in patients with f-NSIP, we hypothesized that peripheral muscle weakness may exist in patients with f-NSIP and may contribute to exercise intolerance. We therefore assessed exercise tests and respiratory and peripheral muscle function of patients with f-NSIP along with tests of pulmonary function to explore the determinants of exercise capacity.

Materials and methods

Study subjects

Consecutive patients with f-NSIP diagnosed at Tosei General Hospital from April 2003 to March 2011, who consented to the study and underwent subsequent measurements in pulmonary function, exercise capacity and muscle strength, were retrospectively reviewed. During the study period a total of 257 cases of interstitial lung diseases were diagnosed by surgical lung biopsy at this hospital. One hundred and thirty patients were diagnosed as having fibrotic idiopathic interstitial pneumonia, and 38 of them were diagnosed with f-NSIP. The diagnosis of f-NSIP was confirmed by two lung pathologists. F-NSIP was newly diagnosed by a physician using the diagnostic criteria in the ATS/ERS consensus statement.[8] Patients who had received corticosteroids or similar medical treatment prior to the evaluation were excluded. Patients were also excluded if they had (1) clinically evident connective tissue disease (CTD), (2) cardiac disease, (3) obstructive lung disease such as COPD or asthma, and (4) other pathologic conditions (arthritis, malignancy, cerebrovascular disease).

This analysis was approved by our local institutional review board.

Exercise capacity

To evaluate exercise capacity, the current study adopted the six-minute walk test (6-MWT), a reliable, valid, and responsive measure of exercise tolerance in patients with interstitial lung diseases.[9] It also has major advantages over maximal exercise testing in terms of reproducibility in the routine evaluation of fibrotic interstitial pneumonias.[10]

The 6-MWT was conducted in all patients who participated in the study, according to the ATS statement.[11] Briefly, all patients were tested under standardized conditions by trained technicians. Baseline heart rate and oxygen saturation were measured. Patients were instructed to walk as far as possible in 6 min. The distance the patients could walk was recorded. Oxygen saturation was monitored and recorded continuously throughout the test by pulse oximetry. No supplemental oxygen was given during the test.

Pulmonary function tests and arterial blood gas tensions

All patients underwent pulmonary function testing including lung volumes and spirometry (CHESTAC-55V; Chest; Tokyo, Japan), according to the method described in the ATS 1994 update.[12] Single-breath diffusing capacity of carbon monoxide (DLco) was also measured (CHESTACV; Chest). The values for vital capacity (VC) and DLco were also related to predicted values. Arterial blood gas tensions were measured at rest.

Respiratory muscle force

Maximal inspiratory pressure (PI max) and maximal expiratory pressure (PE max) were determined in all patients. PI max was measured at residual volume, and PE max was measured near total lung capacity, according to the well-validated method proposed by Black and Hyatt (Vitalopower KH-101; Chest).[13] The highest value from at least three maneuvers was recorded. Reproducibility of the measurements was fairly good.

To determine patients with significant weakness in respiratory muscle power, the values were related to the predicted values[13] and those less than 80% of the prediction were considered to be significantly weak.[14]

Peripheral muscle force

The measurements of peripheral muscle forces were done with the methodologies well validated in the previous studies.[7,15]

Hand grip force (HF) was measured with a hydraulic hand dynamometer (Smedley's Dynamometer; TTM; Tokyo,

Japan). Peak HF (kg) was assessed with each hand with the shoulder, elbow and wrist in a neutral position.

Quadriceps force (QF) was measured using a dynamometer (Cybex II; Lumex; Bay Shore, NY). Peak torque (Newton-m) was measured in both legs during a maximal isokinetic knee extension maneuver with the hip in 90° flexion. The evaluation was performed in concentric mode with an angular speed of 60 s. After the practice session, each patient performed a series of four knee flexions/extensions on one side of the body and then the other, with a 15-s rest between the series.

The highest values for HF and QF from at least three respective maneuvers were recorded. Reproducibility of both measurements was good.

HF was related to age and sex specific predicted values,[16] and less than 80% of prediction was considered to be significantly weak.[17] QF was also related to normal values derived from healthy Japanese subjects, which were also age and sex specific.[18] QF less than 1.5 SD below norms were considered to be significant weakness, according to previous reports.[18]

Statistics

The data obtained from the 30 patients were analyzed statistically. All statistical analysis was performed using SPSS ver.17 (SPSS Inc., Chicago, IL).

The distribution of numeric data was stratified by sex and examined by Smirnov and Grubbs's test to detect possible significant (two-sided $p < 0.05$) outliers. To determine factors contributing to exercise performance in univariate analysis, linear regression models were assessed with raw 6MWD as the dependent variable and the model was adjusted for sex. Independent variables assessed in the model were age, height, weight, pulmonary function parameters (VC, DLco, PaO_2 and $PaCO_2$ assessed by arterial gas analysis), respiratory and peripheral muscle force (PI max, PE max, HF, and QF), and minimum SpO_2 observed in exercise testing. In the subsequent multivariate model, a stepwise multiple regression analysis was performed using 6MWD as a dependent variable, with adjustment either by sex only or by sex, age, height and weight. Any variable with $p < 0.2$ in univariate analysis were introduced in multivariable models as potential predictors. To avoid multicollinearity, only one of the highly correlated variables (coefficient of correlation ≥ 0.9) was entered in the multivariate model, if present.

In determining the factors contributing to QF, univariate analyses were conducted with all the variables except for 6MWD as independent variables. Subsequent multivariate analyses were conducted in a similar fashion. Comparisons between groups were performed using unpaired t-test.

A p value of <0.05 was considered to be significant. All values are presented as median (range), unless otherwise specified.

Result

Patient characteristics and anthropometric and pulmonary function data

Of 38 patients diagnosed with f-NSIP, six patients could not undergo exercise measurements because of a progressive clinical course, one had severe emphysematous change in lungs, and one had received corticosteroid therapy prior to the exercise measurement. These eight patients were excluded from the analysis. In the end, 30 patients with f-NSIP who fulfilled the full-set measurements were eligible for this study. All patients underwent all the measurements and there were no missing data. A majority of the patients were female and the median age was 61, although the ages were widely distributed. As shown in Table 1. There were significant differences in VC and DLco between males and females. However the prevalence of impaired VC (<80% predicted) or DLco (<70% predicted) did not differed significantly according to sex (male 4/9 versus female 14/21; $p = 0.43$ for VC, male 6/9 versus female 19/21; $p = 0.14$ for DLco). No patients showed resting hypoxemia in arterial blood gas analysis.

Exercise capacity

The exercise capacity of these patients is also shown in Table 1. Median 6-MWT distance was 560 m. Male patients walked longer than female patients ($p = 0.014$ in unpaired t-test). The median of the lowest SpO_2 during 6-MWT was 87.5%, showing hypoxemia on exercise. Of all patients, 50% (15/30 cases) showed exertional desaturation (SpO_2<88%) during 6-MWT. Although some of the patients showed remarkable desaturation measured by pulse oxymetry during exercise, all the patients completed the 6 min walking without any complication and the decreased SpO_2 and elevated pulse rate recovered quickly post test.

Muscle testing

Respiratory and peripheral muscle testing results are also shown in Table 1. There were significant differences between men and women in all muscle strength measurements ($p < 0.01$ for QF, HF, PEmax, and PImax). We defined the thresholds of significant muscle weakness as described in the Methods. According to these definitions, a majority of the patients showed significant weakness in PE max (17 of 30 patients) and QF (16 of 30 patients). Meanwhile, only a minority of the patients had significant weakness in HF (4 patients) and PI max (4 patients).

Explaining factors of exercise capacity

As shown in Table 1, 6MWD as well as muscle strength differed clearly by sex. Each of the possible contributing factors for 6MWD were then assessed by linear regression models adjusted for sex (Table 2). In this univariate analysis only QF showed a significant relation ($\beta = 1.030$, $p = 0.0282$) to 6MWD, whereas the following parameters showed marginal significance: PEmax, PaO_2 and DLco ($p < 0.1$); VC, HF and PImax ($p < 0.2$). A scatter diagram showing the correlation between 6MWD and QF is shown in Fig. 1.

To determine the independent predictors of exercise tolerance, we subsequently conducted a stepwise multiple regression analysis for 6MWD adjusted by gender. In this model, QF was the only independent determinant of 6MWD. The total variance explained by this model was 32% ($p < 0.01$) (Table 3, Model 1). In general, 6MWD is known to

Table 1 Patient characteristics.

	All	Men	Female
No	30	9	21
Age, yrs	61(34–75)	62(36–69)	59(34–75)
Height, cm	155.4(145.4–172.7)	166.5(159.7–172.7)	153.4 (145.4–159.2)
Weight, kg	59.9(41.5–84.4)	65(60.5–75)	54(41.5–84.4)
VC, L	1.96(1.03–4.48)	3.02(1.93–4.48)	1.70(1.03–2.91)
VC, %predicted	75.4(41.7–110.6)	87.5(57.1–110.6)	71.7(41.7–100.0)
DLco, mL/min/mmHg	8.8(2.4–28.8)	11.4(4.8–28.8)	8.4 (2.4–15.3)
DLco, % predicted	52.2(15.5–107.8)	63(25.9–107.8)	49.9 (15.5–87.6)
PaO_2, mmHg	81.4(62.4–96.8)	81.2(62.4–89.6)	81.4 (64.6–96.8)
$PaCO_2$, mmHg	40.8(34.1–49.4)	39.4(34.1–49.4)	41.0(35.9–44.7)
6MWD, m	560(333–710)	610(500–710)	545(333–660)
Lowest SpO_2 during test, %	87.5(58–97)	86.0(58–95)	88.0(70–97)
PI max, cmH_2O	95.1(34.1–181.2)	132.1(76.1–181.2)	82.5(34.1–151.5)
PI max, %predicted	117.0(51.5–194.3)	118.8(69.5–163.1)	115.2(51.5–194.3)
PE max, cmH_2O	123.3(53.4–243.8)	189.4(126.9–243.8)	105.2(53.4–190.2)
PE max, % predicted	75.3(40.8–141.2)	94.2(61.9–107.4)	74.8(40.8–141.2)
HF, kg	24.8(10.0–49.5)	39.3(32.5–49.5)	22.3(10–36.5)
HF, %predicted	96.6(50.5–131.1)	98.9(74.4–131.1)	94.7(50.5–114.2)
QF, Nm	83.3(45–236)	148.5(77.5–236)	74.5(45–110)
QF, %predicted	82.0(49.7–139.5)	106.2(55.4–139.5)	81.8(49.7–114.9)

Values are expressed as median (range) unless otherwise indicated.
SpO_2: percutaneous oxygen saturation. PI max: maximal inspiratory pressure, PE max: maximal expiratory pressure, HF: hand grip force, QF: quadriceps force, Nm: Newton-meter.

be related to age, height and weight. We subsequently assessed the multiple regression models with adjustment for sex, age, height and weight. In the latter model also, QF was proven to be the sole independent determinant of 6MWD among all the parameters. The total variance explained by this model was up to 55% ($p < 0.05$) (Table 3, Model 2).

Discussion

In the present study, we conducted simultaneous assessment of pulmonary function, exercise performance and muscle strength in 30 patients with f-NSIP to elucidate the determining factors for exercise capacity. We found that reduced PEmax and QF were often observed in patients with f-NSIP. Moreover, QF is the sole factor contributing significantly to exercise capacity according to our multivariate analysis. To our knowledge, this is the first report clarifying the relationship between peripheral muscle performance and exercise capacity in patients with f-NSIP.

Peripheral muscle dysfunction in COPD has been well characterized. Previous report by Gosselink et al. revealed

Table 2 Result of univariate analysis for factors relating to 6MWD.

	6MWD, m	
	β	p-Value
Age	−1.589	0.3372
Height	−3.622	0.3348
Weight	−1.680	0.2869
VC	48.188	0.1105
DLco	6.025	0.0975
PaO_2	3.303	0.0725
$PaCO_2$	4.151	0.4451
PI max	0.832	0.1127
PE max	0.704	0.0718
HF	4.452	0.1227
QF	1.030	0.0282
Lowest SpO_2 during test	2.250	0.2525

Models were adjusted for sex.

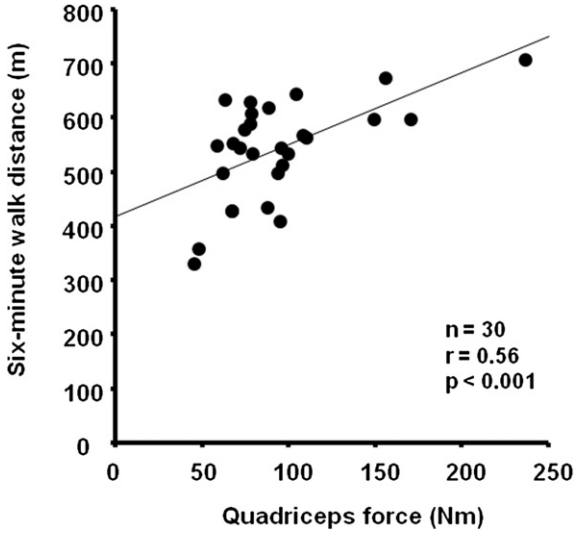

Figure 1 Correlations between six-minute walk distance and QF.

Table 3 Result of stepwise multiple regression analysis for determining factors of 6MWD.

	β	Standard errors	Standardized β	p
Model 1: Adjusted for sex				
QF, Nm	1.030	0.444	0.486	0.028
Sex, male	22.589	41.765	0.113	0.593
Model 2: Adjusted for sex, age, height and weight				
QF, Nm	1.771	0.505	0.835	0.002
Sex, male	118.371	53.124	0.594	0.035
Age	−0.988	1.644	−0.104	0.554
Height	−9.235	4.902	−0.743	0.033
Weight	−2.032	1.607	−0.245	0.218

Model 1: $R^2 = 0.32$, $p = 0.005$.
Model 2: $R^2 = 0.55$, $p = 0.01$.

that lower limb muscles are affected to a greater extent than are upper limb muscles. In their report, QF was correlated significantly with six-minute walking distance.[19] Recently, Mainguy et al. demonstrated that decreased quadriceps strength was correlated with impaired exercise capacity in patients with idiopathic pulmonary arterial hypertension.[20] We have previously reported on the relationship between exercise capacity and peripheral muscle performance of IPF.[7] Our current result in f-NSIP was consistent with these previous reports of other chronic lung diseases, suggesting a generalized process.

Determinants of exercise limitation in patients with interstitial lung diseases (ILD) have been explored. An early study by Burdon et al. reported that decreased exercise capacity was correlated with VC in patients with ILD.[21] Hansen and Wasserman reported that DLco was the best correlate of exercise capacity, from a retrospective review of 43 ILD patients.[22] In these studies, however, patients' diagnoses included IPF, sarcoidosis, hypersensitivity pneumonitis, and some other diseases.

Despite these previous studies, the pathophysiology of the exercise limitation in ILD has not been fully elucidated. Moreover, studies that investigated the mechanisms of exercise limitation in patients with ILD generally included a variety of diseases. It seems likely that the factors determining exercise limitation depend on the etiologies of ILD. In a study that enrolled only IPF patients, we previously revealed that QF is one of the main determinants of exercise capacity. Recently, Caminati et al. also reported moderate correlations between 6MWD and both percent predicted FVC and percent predicted DLco.[23]

To our knowledge, however, there has been no study on exercise capacity in patients with f-NSIP. Additionally, the evaluation of peripheral muscle strength in this study more clearly demonstrated the determinants of exercise capacity in f-NSIP. Thus, our current evaluation seems valuable.

Our current results revealed that quadriceps muscle weakness was frequently observed and related to exercise limitation in f-NSIP patients. This was consistent with previous observation in an IPF cohort. It is assumed that there are several possible factors and mechanisms that cause peripheral muscle dysfunction in ILD.

About half of the patients in this study showed exertional desaturation. Hypoxia is known to increase the oxidative stress that may adversely affect the performance of muscle.[24,25] Thus hypoxia might be a mechanism that adversely affects skeletal muscle and exercise capacity. To test this hypothesis, we also conducted an analysis to explore the determinants of QF (supplemental table). In univariate analysis there were several factors related to QF. In the subsequent stepwise multivariate analysis, DLco appeared to be one of the independent explaining factors for QF. It is supposed that dysfunction in lung parenchyma is relevant to peripheral muscle weakness in patients with f-NSIP; nevertheless, factors more directly related to hypoxia, such as PaO_2 and SpO_2 during exercise, did not show significant relations.

The inflammatory disease process is also thought to be related to quadriceps weakness, as NSIP is characterized by inflammatory cell infiltration in lung interstitium. Deconditioning due to limitation in activities of daily living might be another mechanism of impairment in the quadriceps muscles. Interestingly, aberrant TGF-β signaling was implicated in a model of atrophic muscle caused by hypoxia, inflammation and disuse.[26] TGF-β is known to play a critical role in the pathogenesis of fibrotic lung diseases, and it might be supposed that this molecule also affects peripheral muscles in this population. Unfortunately we did not perform muscle biopsy, but further insights will be obtained if this is done in future study.

In the current study we excluded patients with history of corticosteroid use to avoid possible effects on peripheral muscle weakness. Because CTD is a common complication in NSIP patients and may affect exercise performance as well as peripheral muscle weakness, patients with CTD were also excluded from the analysis. Moreover, patients with a coexisting disorder that might affect QF were excluded from the cohort in order to eliminate possible confounders.

Muscle weakness is known to be related to age, as a 25—30 percent decrease in muscle mass is observed in the seventh decade of life in humans.[24] Therefore we also assessed the multivariate model with the adjustment for age. Thus, we tried to eliminate possible confounding factors that would affect quadriceps weakness. However, the underlying pathophysiology of the weakness of the QF is unknown even in IPF. Clearly, additional research will be necessary to elucidate the pathophysiology of the muscle weakness in NSIP.

Measurement of pulmonary function and exercise indices is integral to the assessment and monitoring of patients with IPF and may also provide useful prognostic information and facilitate treatment decisions.[27,28]

The 6-MWT is a widely used measure of exercise tolerance in patients with various cardiac and pulmonary diseases. A couple of recent controlled trials provided support for the benefits of pulmonary rehabilitation in subjects with IPF and ILD.[29,30] We previously reported significant improvements in 6MWD in subjects with IPF.[29] Holland et al. also found significant improvements in 6MWD following rehabilitation, in a randomized controlled trial of 57 subjects with ILD.[30] The consistent finding that peripheral muscle strength was correlated with exercise capacity in patients with f-NSIP, as well as in IPF patients, raised an intriguing question. Will training of peripheral

muscles, especially in the lower extremities, increase the exercise capacity of patients with f-NSIP? Further study on exercise capacity is warranted in patients with f-NSIP.

Some limitations of this study should be mentioned. First, this was a retrospective and cross-sectional study. Second, the study involved a so small number of patients from one center that we could not make a definitive conclusion. Future study including larger sample size, if possible, may make the conclusion robust. In addition, the patients involved in the study consisted entirely of Japanese. It is unclear whether the present results can be adapted to other ethnic groups. Multiregional prospective studies would be able to eliminate ethnic bias and other possible bias. As there are no available normal values and/or lower limits for HF and respiratory muscle force in Japanese' subjects to our knowledge, it is possible that we did not evaluate the severity of muscle impairment observed in this cohort accurately, except for QF.

In conclusion, we explored the determinants of exercise capacity in 30 consecutive f-NSIP patients. Decreased QF was frequently observed and shown to be an independent predictor of exercise capacity in multivariate analysis. From the current results, it seems that peripheral muscle weakness may be related to exercise intolerance in this population. Further study regarding the therapeutic response to peripheral muscle training is warranted in this population.

Conflict of interest statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found in the online version at doi:10.1016/j.rmed.2012.12.013.

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