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Exercise-induced muscle oxygenation changes in fibrosing interstitial lung diseases: A near-infrared spectroscopy study

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Abstract. *Background:* The impact of fibrosing interstitial lung disease (F-ILD) on the oxygenation of peripheral and respiratory muscles during exercise remains poorly understood. Specifically, it's unclear whether regional blood flow influences exercise capacity in these patients, and if so, to what degree. *Objectives:* This study aimed to investigate changes in oxygenation and blood flow volume of the intercostal (IC) and quadriceps femoris (QF) muscles during exercise in patients with F-ILD. *Methods:* Muscle oxygenation (SmO_2) and total haemoglobin (tHb) changes of IC and QF were measured in 36 F-ILD patients using near-infrared spectroscopy (NIRS) during six-minute walking test (6MWT). Resting, minute-by-minute change, and average data were analyzed. *Results:* At rest, SmO_2 was significantly higher in IC compared to QF ($p<0.001$). When adjusted for SmO_2 at rest, SmO_2 at the different time points during 6MWT, average SmO_2 during 6MWT, and lowest SmO_2 during 6MWT did not differ between QF and IC muscles. Also, SmO_2 did not vary significantly during 6MWT in either QF ($F=2.193$) or IC muscle ($F=1.262$). THb increased more in QF than in IC. THb of IC inversely correlated to respiratory functions and 6MWT distance. *Conclusion:* Peripheral and respiratory muscle oxygenation in F-ILD seems to be normal. However, blood flow volume in exercising muscle, not muscle oxygenation, may be a contributing factor to exercise intolerance. Patients with poorer respiratory function may require excessive blood flow in their respiratory muscles which in turn may limit the blood flow available for exercising peripheral muscles.

Key words: fibrotic hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, near-infrared spectroscopy, nonspecific interstitial pneumonia, six minute walk test, exercise-induced oxygenation, interstitial lung disease exercise testing, fibrotic lung diseases

Introduction

Fibrosing Interstitial Lung Diseases (F-ILD) encompasses interstitial lung diseases (ILD) characterized by progressive scarring and fibrosis of the lung tissue, resulting in impaired lung function and exercise capacity (1, 2). Exercise intolerance is a common feature of F-ILD, which may be due to respiratory muscle weakness and/or the inability of the pulmonary circulation to meet the increased demand for oxygen during exercise (3, 4). While the use of

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near-infrared spectroscopy (NIRS) to measure muscle oxygenation during exercise has been widely studied in healthy individuals and in patients with chronic obstructive pulmonary disease (COPD) (5, 6), its use in F-ILD remains limited (7). The quadriceps femoris (QF) and intercostal (IC) muscles are two major muscle groups involved in exercise in patients with F-ILD. The quadriceps femoris muscle is primarily responsible for lower limb movement and is the largest muscle group in the body, while the intercostal muscles are responsible for breathing and are essential for ventilation during exercise. Studies have shown that the QF muscle is frequently affected by muscle atrophy and weakness in patients with F-ILD, leading to a decline in exercise capacity (8, 9). Similarly, respiratory muscle weakness is also common in these patients and may contribute to exercise intolerance and dyspnea (10, 11). Some studies have suggested that peripheral muscle muscle oxidative capacity could be one of the reasons for exercise limitation in respiratory patients (12, 13). Additionally, some studies have examined changes in regional blood flow of respiratory muscles during exercise (14, 15). However, it's important to note that the populations evaluated in these studies are either healthy individuals or patients with conditions other than F-ILD. In patients with F-ILD, who often exhibit severe lung restriction, diffusion impairment (16), frequent supplemental oxygen needs (17), and dramatic exercise limitations (18), the change in muscle oxygenation during exercise and its relationship with exercise capacity have not been investigated. Although studies on this topic in F-ILD cases are limited, there are several studies conducted on patients with COPD. In one study comparing changes in oxygenation of the Vastus Lateralis (VL) muscle during cycling exercise tests between COPD patients and healthy controls, no significant changes in muscle oxygenation were observed in either group (19). In another study, a decrease in VL oxygenation was found from pre-test to post-exercise, with a more pronounced decrease in the patient group (20). In a randomized controlled trial comparing two groups — one undergoing functional electrical stimulation combined with cycle training and the other receiving only cycle training — an increase in VL oxygenation was observed in both groups (21). Therefore, the change in muscle oxygenation during exercise in COPD patients remains a controversial topic. Understanding the effects of muscle oxygenation on exercise tolerance in F-ILD could fill a significant gap in the literature when compared to findings in similar conditions. The aim of this study is to use NIRS to measure the oxygenation and the regional blood volume of the QF and IC during exercise in patients with F-ILD. This will provide valuable information on the mechanisms underlying exercise intolerance in these patients and may help to identify new targets for therapeutic interventions.

Methods

This study was a prospective, single-centre, cross-sectional trial. It was carried out under the supervision of the local ethics committee (Protocol Number: 2/12 (2023)) and registered in the ClinicalTrial.gov website (registration number: NCT05855447). The study was conducted in accordance with the Helsinki Declaration. A written informed consent was obtained from each patient.

Participants

We recruited 36 patients with F-ILD who were referred to our outpatient clinic. The inclusion criteria were as follows: diagnosis of interstitial lung disease with fibrosis based on high-resolution computed tomography findings and pulmonary function tests, age between 18 and 75 years, and ability to perform the 6-minute walk test (6MWT). We excluded patients who had a history of acute exacerbation within the past 4 weeks, those with severe comorbid diseases (such as unstable coronary artery disease or collagen vascular diseases) that could potentially affect exercise capacity, individuals with a history of effort-related syncope or any other relevant comorbidity, as well as those who were unable to provide informed consent. *Sample size calculation:* A review of the literature revealed no studies examining the relationship between exercise capacity measured by the 6-minute walk test and muscle oxygenation (SmO_2) in individuals with progressive pulmonary fibrosis diseases. However, in patients with anemia, the correlation coefficient between exercise capacity measured by the 6-minute walk test and muscle oxygenation is reported as r=0.41 (22). Accordingly, to be able to detect a similar relationship in our study with a type 1 error rate of 5% and a power of 80%, it was calculated that minimum of 33 cases should be included in the study (23).

Study outcomes

Assessment of Muscle Oxygenation and regional blood volume: Muscle oxygenation and regional blood volume was measured using near-infrared spectroscopy (NIRS) technology with a Moxy (Fortiori Design LLC, Minnesota, USA) device during the 6-minute walk test. Measurements were taken from the vastus lateralis muscle in the dominant lower extremity for quadriceps muscle and from the intercostal muscles. The device was placed at the mid-thigh region between the anterior superior iliac spine reference point and the midpoint of the patella for measuring the vastus lateralis oxygenation, and at the intersection of the sixth and eighth intercostal spaces and the anterior axillary line for measuring the intercostal muscle oxygenation (15, 24) (Figure 1). For evaluating muscle oxygenation, SmO_2 at rest, SmO_2 at different time points during 6MWT, average SmO_2 during 6MWT and lowest SmO_2 during 6MWT were recorded for both vastus lateralis and intercostal muscles. Total haemoglobin (tHb) was considered as an estimate of regional blood volume and monitored and recorded alongside SmO_2 by the device during 6MWT. THb at rest, tHb at the end and average tHb during 6MWT were included in the analysis. Changes in muscle oxygenation regional blood volume were monitored and recorded with the manufacturer's software program (25, 26).

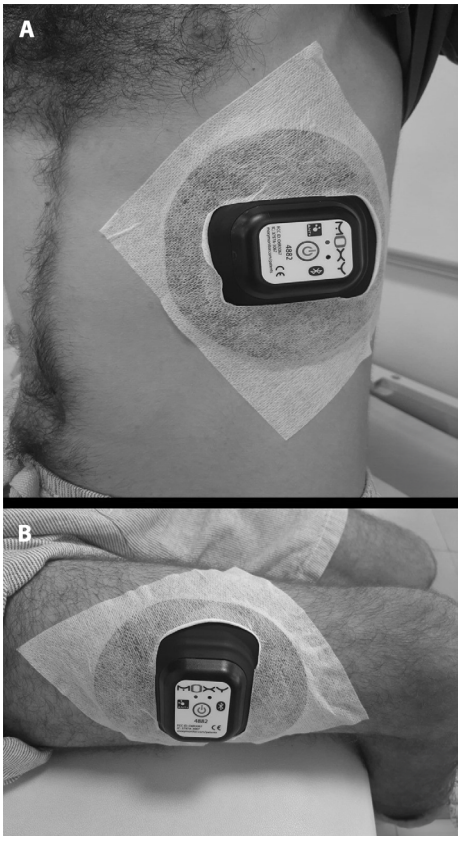

Figure 1. Near-infrared spectroscopy sensor placements on A) intercostal muscles, B) quadriceps muscle.

Six-minute walk test

After resting in a chair for a sufficient amount of time, patients were asked to walk to a turning point marked by a traffic cone in a straight corridor that was 30 meters long. Participants were instructed to walk as quickly as possible in the corridor without running for 6 minutes. In cases of extreme fatigue, participants were allowed to rest and encouraged to continue walking with standard commands. Before and after the test, patients were asked about their fatigue and dyspnea status using the Modified Borg Scale. Oxygen saturation was evaluated using a finger pulse oximeter before, during, and after the test. The walking distance covered in 6 minutes was recorded. (27, 28). Muscle Strength: Quadriceps femoris muscle strength were evaluated using the electronic hand dynamometer (Lafayette® 01165, USA). The force measurement was repeated three times and in each trial, the subject was asked to maintain muscle strength against the dynamometer for at least 5 seconds. The best value from the three tests will be recorded (29, 30). Pulmonary Function Test: It was conducted by using the Pony Fx instrument (Cosmed, Italy), and according to the American Thoracic Society (ATS) guidelines (31). Modified Medical Research Council (mMRC) Dyspnea Scale: The mMRC Dyspnea Scale was used to assess the degree of dyspnea experienced by patients during daily activities. This is a commonly used and validated tool in respiratory research (32). Patients were asked to rate their level of dyspnea on a scale from 0 to 4, where 0 represents no breathlessness and 4 represents severe breathlessness that prevents them from leaving the house or being breathless when dressing.

Data analysis

Data were analyzed using SPSS version 22.0 (IBM Corp., USA). Descriptive statistics were used to summarize the demographic and clinical

characteristics of the participants. Paired samples t-test was used to compare the SmO_2 measurements between two muscles. Since the SmO_2 at rest is significantly different between quadriceps and intercostal muscles, changes in SmO_2 during 6MWT was compared between two muscles after their means had been adjusted for SmO_2 at rest using analysis of covariance (ANCOVA). In order to analyze whether SmO_2 significantly varies during 6MWT in each muscle, repeated measures ANOVA test was used. Association of SmO_2 measurements with clinical and functional metrics was analyzed using Pearson correlation analysis. P<0.05 was considered statistically significance for all analyses.

Results

Demographics and clinical characteristics of patients were presented in Table 1. SmO_2 values of quadriceps and intercostal muscles during the 6MWT and their comparisons between the two muscles were shown in Table 2. SmO_2 at rest differed significantly between quadriceps and intercostal muscles (p<0.001). When adjusted for SmO_2 at rest, SmO_2 at different time points during the 6MWT, average SmO_2 during the 6MWT, pre- and post-6MWT SmO_2 changes, and the lowest SmO_2 during the 6MWT did not differ between quadriceps and intercostal muscles (p>0.05).

Repeated measures ANOVA showed no significant changes in SmO_2 over time for either the quadriceps (F = 2.193; p = 0.078) or intercostal muscles (F = 1.262; p = 0.291) during the 6MWT (Figure 2). THb values of quadriceps and intercostal muscles during the 6MWT and their comparisons between the two muscles were shown in Table 3. THb at rest did not differ between quadriceps and intercostal muscles; however, tHb at the end of the 6MWT, tHb increase during the 6MWT, and average tHb during the 6MWT were significantly higher in the quadriceps muscle (p<0.05). The association of SmO_2 and tHb of quadriceps and intercostal muscles with clinical and functional measurements is shown in Table 4. SmO_2 at rest and SmO_2 during the 6MWT did not correlate with any of the clinical or functional measurements including 6MWT distance, SpO_2 change during the 6MWT, spirometry, respiratory muscle strength, quadriceps strength, and mMRC dyspnea scale (p>0.05). However, tHb at rest and tHb at the end of the 6MWT significantly and inversely correlated with spirometric measures and respiratory muscle strength, having correlation coefficients ranging from -0.326 to -0.585 (p<0.05). THb at the end of the 6MWT also correlated with 6MWT (r= -0.419) and mMRC (r= 0.347) (p<0.05).

Table 1. Demographics and clinical characteristics of patients

Demographics	
Age (year)	64.50±10.40
Gender (male)	24 (67%)
BMI (kg/m^2)	27.48±4.23
MMRC dyspnea scale (n)	
0	4 (11%)
1	11 (31%)
2	10 (28%)
3	5 (14%)
4	6 (16%)
Pulmonary Function	
FVC (pred%)	67.89±24.85
FEV_1 (pred%)	67.66±22.19
FEV_1/FVC (%)	80.50±13.63
Respiratory muscle strength	
MIP (cmH_2O)	83.89±36.41
MEP (cmH_2O)	88.53±38.86
Quadriceps strength (kg)	30.58±8.94
6-min walk test	
Distance (m)	570±147
Resting SpO_2 (%)	94.36±3.58
Final SpO_2 (%)	88.86±6.19
SpO_2 change (%)	-5.50±5.07

Data is presented as X±SD or n (%). *Abbreviations:* BMI: Body Mass Index; FEV_1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; MMRC: Modified Medical Research Council; MIP: Maximum Inspiratory Pressure; MEP: Maximum Expiratory Pressure; SpO_2: oxygen saturation.

Discussion

Our results revealed that oxygenation of quadriceps and intercostal muscles did not change significantly during 6MWT in patients with F-ILD, even though their SpO_2 exhibited desaturation during exertion. Absolute value of resting SmO_2 was significantly different between two muscles; however, they responded the exertion in a similar way in terms of the SmO_2 changes. Neither resting SmO_2 nor the SmO_2 changes during 6MWT correlated to any of the clinical or functional indicators including pulmonary function, muscle strength and dyspnea severity. Our results suggest that the muscle oxygenation of patients with F-ILD is not significantly impaired, so it may not be among the major factors contributing to exercise intolerance in these patients. In addition,

Table 2. Muscle oxygenation of quadriceps and intercostal muscles during 6MWT.

	Quadriceps	Intercostal muscles	p value**
SmO_2 at rest (%)	41.47±19.49*	60.47±21.37*	
SmO_2 at 1st min. (%)	42.09±17.44	61.04±23.14	0.915
SmO_2 at 2nd min. (%)	40.85±17.86	58.84±23.89	0.971
SmO_2 at 3rd min. (%)	39.48±17.88	54.64±23.68	0.402
SmO_2 at 4th min. (%)	42.66±19.88	58.29±23.78	0.401
SmO_2 at 5th min. (%)	42.25±18.55	59.42±21.76	0.577
SmO_2 at the end (%)	41.56±19.90	56.92±23.45	0.933
Average SmO_2 during 6MWT (%)	42.64±18.86	57.82±20.49	0.847
Pre- and post-6MWT SmO_2 change (%)	0.08±8.18	-3.55±18.33	0.933
Lowest SmO_2 during 6MWT (%)	33.27±20.52	46.33±22.26	0.433

*"SmO_2 at rest" is significantly different between quadriceps and intercostal muscles (p<0.001). **Difference between quadriceps and intercostal muscles after adjusted for "SmO_2 at rest".
Abbreviations: 6MWT: 6-min walk test; SpO_2: oxygen saturation.

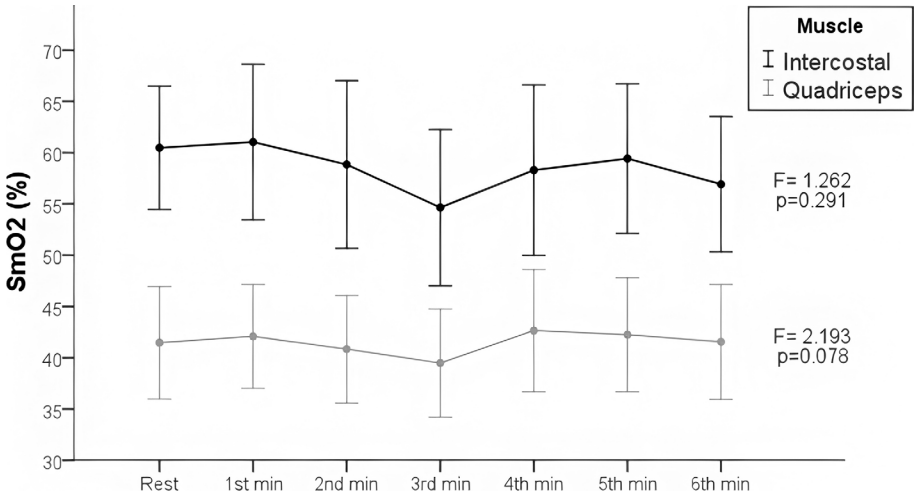

Figure 2. Changes in SmO_2 during 6MWT in each muscle. Error bars: 95% CI.

Table 3. Regional blood volume of quadriceps and intercostal muscles during 6MWT

	Quadriceps	Intercostal muscles	p value
tHb at rest (gr/dl)	12.23±0.26	12.09±0.36	0.065
tHb at the end of 6MWT (gr/dl)	12.40±0.26	12.10±0.33	<0.001
Pre- and post-6MWT tHb change (gr/dl)	0.16±0.29	0.01±0.33	0.042
Average tHb during 6MWT (gr/dl)	12.37±0.22	12.09±0.41	0.001

tHb: Total haemoglobin; 6MWT: 6-min walk test.

we found that increase of regional blood flow was greater in quadriceps muscle compared to intercostal muscles during exertion, which was not surprising since the quadriceps is the main exercising muscle during 6MWT. However, we also found that F-ILD patients with worse pulmonary function had higher blood flow in intercostal muscles during exertion, suggesting patients with more severely affected lungs demand higher blood flows for their respiratory muscles during exertion as the respiratory muscles have to work much harder. However, the observation

Table 4. Association of SmO_2 and tHb of quadriceps and intercostal muscles with clinical and functional measurements.

	6MWT	SpO_2 at rest	SpO_2 change	FVC	FEV_1	MIP	MEP	QS	MMRC
Quadriceps									
SmO_2 at rest	-0.034	0.123	0.146	0.028	0.042	0.063	-0.052	-0.029	-0.066
SmO_2 at the end of 6MWT	0.075	0.127	0.070	0.001	0.042	0.090	-0.079	0.127	-0.113
Average SmO_2 during 6MWT	0.023	0.144	0.055	0.052	0.063	0.086	-0.055	0.069	-0.110
tHb at rest	0.149	0.096	-0.008	0.109	0.069	0.113	0.116	0.063	-0.044
tHb at the end of 6MWT	-0.023	0.062	-0.299	-0.267	-0.188	-0.104	0.179	0.035	0.136
Average tHb during 6MWT	0.031	0.089	-0.034	-0.084	0.037	-0.026	0.177	0.059	0.016
Intercostal muscles									
SmO_2 at rest	-0.043	0.83	-0.147	-0.266	-0.211	-0.026	-0.001	0.006	0.250
SmO_2 at the end of 6MWT	0.051	0.23	0.120	-0.215	-0.165	-0.032	-0.101	-0.043	0.015
Average SmO_2 during 6MWT	0.031	0.126	0.146	-0234	-0.309	-0.046	-0.041	-0.154	0.062
tHb at rest	-0.313	-0.160	-0.080	**-0.326***	**-0.413***	**-0.376***	**-0.350***	-0.103	0.285
tHb at the end of 6MWT	**-0.419***	-0.250	-0.182	**-0.585****	**-0.511****	**-0.513****	**-0.396***	-0,323	**0.347***
Average tHb during 6MWT	-0.138	-0.100	-0.031	-0.255	-0.295	-0.216	-0.226	-0.025	0.034

Pearson correlation coefficients (r values) are presented.
*p<0.05; **p<0.01
FEV_1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; MMRC: Modified Medical Research Council; MIP: Maximum Inspiratory Pressure; MEP: Maximum Expiratory Pressure; SpO_2: oxygen saturation; QS: Quadriceps femoris muscle strength.

that patients with more severe pulmonary dysfunction exhibited higher blood flow in the intercostal muscles indicates that these patients require greater blood supply for respiratory muscles during exertion due to increased respiratory workload. This suggests that improving respiratory muscle efficiency through respiratory muscle training or similar interventions could potentially reduce the blood flow demand of respiratory muscles, thereby preserving more blood for the peripheral muscles and improving overall exercise tolerance. This strategy could be particularly beneficial for F-ILD patients with advanced lung disease who experience significant exertional dyspnea and muscle fatigue. Administering supplemental oxygen during exercise has been shown to increase leg muscle oxygenation and improve exercise tolerance in F-ILD patients (33). This aligns with our finding of increased oxygen demand during exertion and suggests that oxygen therapy could play a role in optimizing exercise performance. Tailoring oxygen therapy based on individual desaturation patterns, as identified by near-infrared spectroscopy (NIRS), could potentially enhance patient outcomes by preventing critical muscle deoxygenation during daily activities or exercise. Interstitial lung diseases represent a heterogeneous group of diseases primarily affecting the lung parenchyma. Patients with ILD often experience reduced lung volumes, impaired gas exchange, and decreased cardiovascular function (34). Exercise intolerance in chronic respiratory patients can vary depending on the type of disease. The underlying causes of exercise limitation can include an imbalance between ventilatory capacity and requirements, an imbalance between energy demands and supplies to working respiratory and peripheral muscles, and peripheral muscle weakness (35). In F-ILD patients, exercise limitation is primarily related to dyspnea (18) and exertional symptoms, and scientific evidence is increasing regarding the potential presence of respiratory and peripheral muscle dysfunction in these patients. Muscle dysfunction can lead to dyspnea, fatigue, and functional limitations. (10). In our study, more than half of the patients reported a perception of severe dyspnea. Peripheral and respiratory muscle dysfunction can arise from factors such as muscle weakness, circulation problems, neurological issues, and metabolic and inflammatory diseases (36, 37). In a cross-sectional study comparing muscle oxygenation and regional blood flow changes during isotonic concentric exercise testing between ILD patients and healthy individuals, (26) it was observed that SmO_2 of exercising lower limb was similar between healthy individuals and patients with mild ILD who are not dependent on oxygen, indicating muscle oxygenation is not significantly impaired in mild ILD. Considering our patients also have mild ILD, they may not have a severe impairment in muscle oxygenation as well, and this may explain lack of an association of SmO_2 with functional or clinical measures in our study. On the other hand, the authors also found that increase in the blood volume of lower limb in patients with "severe" ILD was much lower compared to that in healthy individuals and in patients with mild ILD. Authors hypothesized that a greater blood volume may have been distributed to the respiratory muscles in the severe ILD group, resulting in less blood volume for the lower limb. Our results support this hypothesis since there was an inverse relationship between tHb of intercostal muscles and respiratory measurements in our study; patients with worse pulmonary function or lower respiratory muscle strength required more blood volume for their intercostal muscles during exertion. Decreased blood flow to the exercising muscle, rather than the impaired muscle oxygenation, may be a contributing factor for exercise intolerance in ILD, since the increased demand of blood volume of respiratory muscles may result in less blood volume for the exercising muscles. Based on these results, it may be speculated that by improving respiratory muscle function via respiratory muscle training or such approaches, respiratory muscles may work more efficient and require less blood flow and thus the amount of blood directed to extremes may be increased, leading to an enhanced exercise performance. Based on these results, it may be speculated that by improving respiratory muscle function via respiratory muscle training or such approaches, respiratory muscles may work more efficiently and require less blood flow and thus the amount of blood directed to the extremities may be increased, leading to enhanced exercise performance. Administering supplemental oxygen to F-ILD patients during exercise was found to increase oxygenation in leg muscles and improve exercise tolerance (38). This finding underscores the close relationship between oxygen saturation and exercise tolerance. In our study, we observed fluctuations in both peripheral and respiratory muscle oxygenation during the first minute of the 6MWT, with a mild increase followed by a decrease and a subsequent rise

and final decline below the baseline level. Nevertheless, the alterations observed in SmO_2 did not reach statistical significance. While these fluctuations may seem inconsequential, they could offer valuable understanding regarding regions susceptible to significant muscle deoxygenation in individuals with more advanced illnesses. This suggests that exercise regimens could be tailored to these variations to preempt fatigue and mitigate its progression. This suggests that exercise regimens could be tailored to these variations to preempt fatigue and mitigate its progression. The near-infrared spectroscopy is a technique that is gaining increasing popularity and allows for the measurement of systemic and cerebral microcirculation (39). In a study comparing smokers with COPD and normal spirometry values, it was found that COPD patients had lower oxidative capacity in both upper and lower extremity muscles (12). Another study examining oxygenation changes in the vastus lateralis muscle during incremental cycling in hypoxemic fibrotic ILD patients, compared to healthy controls, found that fibrotic ILD patients had lower muscle oxygenation and exercise capacity, highlighting the potential usefulness of NIRS as a guiding method for interventions in F-ILD patients (40). In our study, we monitored both pulse oximetry for general oxygen saturation and muscle oxygenation. A decrease in general oxygen saturation was detected. Examination of the resting oxygenation levels of the quadriceps and intercostal muscles revealed significantly lower levels in the quadriceps compared to the intercostal muscles. However, the magnitude of the oxygen desaturation during exercise was similar and insignificant in both muscle groups. This insignificant change in the oxygen level in exercising muscles may be related to severity of the exercise test performed as well. Since 6MWT is a volitional test, it may not be able to exhaust patients to their limits and consequently results in no significant decrease in the oxygen level of the exercising muscles. This hypothesis may partially be supported by the study of Tabira et al. (13) who reports pronounced decrease in tissue oxygenation in quadriceps muscle during maximal exercise testing performed on a cycle ergometer in patients with COPD. In addition, considering legs are more strained during cycling compared to walking (41), oxygen desaturation may be experienced in quadriceps during cycle ergometer testing. Nevertheless, according to our results it seems that F-ILD patients will not be limited during their routine activities in daily life due to the muscle deoxygenation. Our study also has some limitations. We were only able to measure the oxygenation of the intercostal and quadriceps femoris muscles since we had only two devices for the NIRS for simultaneous measurement. A study reports that SCM may exhibit higher deoxygenation compared to intercostal, parasternal, and scalene muscles in healthy individuals and patients with various cardiopulmonary diseases (42). Evaluation of the oxygenation of accessory respiratory muscles may help better exploring the mechanisms of exercise limitation in F-ILD patients. Additionally, literature reports that ILD patients requiring oxygen supply has lower blood flow in their lower extremities which leads to the assumption that their respiratory muscles may be requiring excessive blood flow (26). Our study cohort did not include any ILD patient requiring oxygen supply. Evaluation of the SmO_2 and tHb of both peripheral and respiratory muscles of such patients may clarify whether excessive blood flow is required by the respiratory muscles. In conclusion, no relationship was found between exercise intolerance in F-ILD patients and oxygenation of peripheral and respiratory muscles. Oxygenation in respiratory muscles and lower extremity muscles showed variations at rest, but the differences in oxygenation response during exercise were similar in both muscle groups. Blood flow in the respiratory muscles was inversely associated with pulmonary function metrics, indicating as the severity of lung damage is increased, higher blood flows are required by the respiratory muscles, which may limit the blood flow of the exercising peripheral muscles. To build on these findings, future research should explore targeted interventions aimed at optimizing blood flow distribution during exercise. Potential areas for investigation could include the development of exercise programs that specifically address blood flow limitations or therapies designed to improve peripheral muscle performance. Additionally, further studies could evaluate how different exercise modalities impact muscle oxygenation and overall exercise tolerance in this patient population. NIRS technology was found to be an effective tool for investigating the relationship between muscle oxygenation and exercise performance in patients with F-ILD. We believe that this technology may contribute making exercise tests and exercise programs safer and more patient-friendly.

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Authors Contribution: EP: conceptualization, methodology data curation, project administration, writing - original draft; MZ: formal analysis, writing - review & editing; EÇ and BD: supervision, review & editing; ZBÖ, FSK, AA and Uİ: data curation.

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