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Noninvasive assessment of peripheral skeletal muscle weakness in idiopathic pulmonary fibrosis: a pilot study with multiparametric MRI of the rectus femoris muscle

Wagner Diniz de Paula,[1] Marcelo Palmeira Rodrigues,[2] Nathali Mireise Costa Ferreira,[2] Viviane Vieira Passini,[2] César Augusto Melo-Silva[2]

[1]Department of Radiology, Brasilia University Hospital, University of Brasilia
[2]Department of Pulmonology, Brasilia University Hospital, University of Brasilia, Brazil
Institution where the work was done: Hospital Universitário de Brasília / Universidade de Brasília, Brazil

ABSTRACT

Background: To investigate differences in magnetic resonance imaging (MRI) features of rectus femoris muscle between idiopathic pulmonary fibrosis (IPF) patients and healthy volunteers.

Methods: Thirteen IPF patients with GAP Index stage II disease were subjected to pulmonary function tests, 6-minute walk test (6MWT), quadriceps femoris muscle strength measurement and MRI of the thigh at rest. At MRI, muscle cross-sectional areas, T2 and T2* relaxometry, and 3-point Dixon fat fraction were measured. The results were compared to those of eight healthy sedentary volunteers.

Results: IPF patients had significantly lower %predicted FVC, FEV_1 and DL_{CO} (p<0.001 for the three variables) and walked significantly less in the 6MWT (p=0.008). Mean quadriceps femoris muscle strength also was significantly lower in IPF patients (p=0.041). Rectus femoris muscle T2* measurements were significantly shorter in IPF patients (p=0.027). No significant intergroup difference was found regarding average muscle cross-sectional areas (p=0.790 for quadriceps and p=0.816 for rectus femoris) or rectus femoris fat fraction (p=0.901). Rectus femoris T2 values showed a non-significant trend to be shorter in IPF patients (p=0.055).

Conclusions: Our preliminary findings suggest that, besides disuse atrophy, other factors such as hypoxia (but not inflammation) may play a role in the peripheral skeletal muscle dysfunction observed in IPF patients. This might impact the rehabilitation strategies for IPF patients and warrants further investigation.

Key words: Interstitial lung disease; idiopathic pulmonary fibrosis; skeletal muscle; magnetic resonance imaging.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause, which occurs primarily in older adults [1]. Limited to the lungs, it is the most common of the idiopathic interstitial pneumonias and carries the worst prognosis, with median survival ranging from 2.5 to 3.5 years prior to the advent of antifibrotic drugs [2]. Progressive dyspnea is the hallmark symptom and causes exercise limitation. Exertional dyspnea and exercise limitation lead to difficulties in performing daily activities and are major contributors to impairments in health-related quality of life [3].

The presence of exercise limitation and significant disability suggests that individuals with IPF are likely to be appropriate candidates for pulmonary rehabilitation. However, although there is evidence of short-term benefits [4,5], other investigators have shown that these gains are short-lived and only modest when compared to patients with chronic obstructive pulmonary disease (COPD) [3] and other interstitial lung diseases [6]. In COPD, reduced respiratory and lower extremity muscle strength are associated with decreased exercise and functional capacity, and muscle weakness is likely an important component of impairment and disability [7-9].

Previous research has shown that quadriceps femoris muscle weakness is related to exercise intolerance also in IPF [9,10], but the underlying pathophysiology remains unknown. Possible mechanisms include deconditioning (disuse atrophy), decreased levels of anabolic hormones, an IPF-specific inflammatory myopathy, sarcopenia, hypoxemia, and oxidative stress, among others [9,11,12].

Magnetic resonance imaging (MRI) can non-invasively detect pathological changes at the cellular and tissue level in skeletal muscle by probing different aspects of hydrogen nuclear magnetic properties that are affected by physiological and pathological features of the tissue [13]. Transverse magnetization relaxation time (T2) is increased in idiopathic inflammatory myopathies, and has been advocated to objectively gauge disease activity [14]. Transverse relaxation in gradient echo (GRE) pulse sequences is subject to bulk field dephasing effect caused by local magnetic field inhomogeneities, and its characteristic time is referred to as T2* relaxation. T2*-weighted sequences are used to depict paramagnetic deoxyhemoglobin, methemoglobin, or hemosiderin in lesions and tissues [15]. Diffusion-weighted MRI is sensitive to molecular motion of water in tissues [13], and may reflect microscopic architectural changes in diseased muscle [16]. MRI also allows measurement of muscle volume [17,18], fat content [18,19], and oxygenation [20,21]; and may provide valuable insight into muscle abnormalities observed in IPF patients.

The aim of our study was to investigate differences in morphologic and resting nuclear magnetic resonance properties of the rectus femoris muscle between patients with idiopathic pulmonary fibrosis and sedentary healthy controls.

Design and Methods

Participants

This prospective study was approved by our institutional review board and informed consent was obtained from all participants. From November 2016 to February 2019, we enrolled consecutive patients with IPF and healthy volunteers of comparable age, nonsmokers and not physically active.

Inclusion criteria in the study group were: diagnosis of idiopathic pulmonary fibrosis as per official guidelines in effect at the time of enrollment [22]; stage II disease based on the GAP (Gender, Age, lung Physiology) index [23]; and absence of other coexisting pulmonary diseases. Patients currently enrolled or previously subjected to pulmonary rehabilitation were excluded. We specified stage II disease (GAP index 4 or 5) in order to obtain a more homogeneous sample, devoid of mild or severe cases. Eight patients were being treated with pirfenidone and four with nintedanib, and one had not initiated antifibrotic treatment yet. No patients received corticosteroids.

As controls, we enrolled healthy volunteers with a sedentary lifestyle and no regular physical activity for at least six months, without respiratory symptoms or clinical diagnosis of any pulmonary disease, in the same age range of the IPF patients.

Musculoskeletal, neurological and cardiovascular disorders that might compromise locomotion or exercise capacity, including conditions known to cause sarcopenia, such as active malignancies, were regarded as exclusion criteria for both groups.

We recorded participants' age (yr), sex, body mass (kg) and height (m), and calculated the body mass index (BMI, defined as the body mass divided by the square of the body height), and the body surface area (BSA) [24].

Functional characterization

We documented the mMRC Dyspnea Scale [25] scores, the six-minute walk test [26] distances and the results of standardized pulmonary function tests [27], comprising spirometry and diffusing capacity for carbon monoxide (DL_{CO}). Spirometric parameters recorded were forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1), both absolute and as percentage of predicted for age and sex. The Tiffeneau-Pinelli index (FEV_1/FVC ratio) was then calculated and expressed as percentage. Quadriceps muscle strength was measured using maximal voluntary isometric contraction [28].

MRI acquisition

MR imaging was performed on a clinical closed-bore 1.5 T scanner with 33 $mT.m^{-1}$ gradient and 120 $T.m^{-1}.s^{-1}$ slew rate (Signa HDxt, GE Healthcare, Milwaukee MI, USA), with the participant in dorsal decubitus, using a phased-array 8-channel cardiac coil. Images of the right thigh were obtained in the transverse plane, at mid-femoral level (at 50% of femoral length), with 24 cm field of view and 5 mm slice thickness. Additional acquisition parameters are shown in Table 1.

Table 1. MRI pulse sequences and acquisition parameters.

Pulse sequence design	TR/TE (ms)	FA/TI (° / ms)	Matrix dimensions (frequency x phase)	Slice thickness / interslice gap (mm)
STIR	4000 / 38.9	180/90 / 150	320 x 192	5 / 1
T2 Map	1000 / 7.4 – 59.1	90 / –	320 x 256	5 / 1
T2* Map	39 / 1.2 – 10.2	25 / –	64 x 64	5 / 1
IDEAL	10.6 / 6.0	10 / –	256 x 256	5 / -2.5

TR, repetition time; TE, echo time; FA, flip angle; TI, inversion time; STIR, short tau inversion recovery; IDEAL, iterative decomposition of water and fat with echo asymmetry and least-squares estimation.

The fat-suppressed, T2-weighed STIR (**s**hort **t**au **i**nversion recovery) pulse sequence is sensitive to free water and was used to visually assess imaging signs of muscle inflammation and damage [14]. We used fast multi-echo sequences for relaxometric quantification of T2 and T2* transverse magnetization times (T2 and T2* mapping). The T2 mapping pulse sequence was acquired with higher spatial resolution to be used also for morphological evaluation and muscle outlining. The IDEAL (Iterative Decomposition of water and fat with Echo Asymmetry and Least-squares estimation) sequence is a 3-point Dixon technique for water/fat separation and was used to compute muscle fat fraction [29].

Continuous composite Bézier regions of interest (ROI) outlining the rectus femoris muscle [12], quadriceps femoris muscle and thigh contour were manually drawn by a radiologist (WDP) with more than 10 years of experience, to obtain the respective absolute cross-sectional areas (CSA_{abs}) on the central image in each series. To exclude variation in body size as a confounding factor, we performed allometric scaling of CSA_{abs} using BSA, with a scaling exponent of 2/3 ($CSA_{corrected} = CSA_{abs} \div BSA^{2/3}$).[30] For signal intensity (SI) measurements on T2 and T2* maps, we used the largest possible elliptical ROIs in the rectus femoris muscle, avoiding artifacts and excluding vessels and any other macroscopic non-muscle tissue. The rectus femoris muscle was selected for displaying the lowest coefficient of variation in a subsample of our SI measurements, for being readily separable from the remaining components of the quadriceps muscle, and for having been assessed in previous studies [12]. Fat fraction was calculated as the ratio of average SI on fat-only images and average SI on in-phase (water plus fat) images, expressed as percentage, in continuous composite Bézier ROI encompassing the entire cross-section of the rectus femoris muscle. Image analysis was performed with OsiriX MD (Pixmeo) and Advantage Windows Workstation FuncTool (GE Healthcare).

Statistical analyses

IBM SPSS Statistics for Mac version 26 (International Business Machines Corp.) was used for statistical analyses. Distribution of the interval and ratio variables were assessed with the Shapiro-Wilk normality test. Categorical variables were compared with Fisher's exact test. Interval and ratio variables were statistically compared using the t-test for independent samples or the independent-samples Mann-Whitey U test as appropriate. The tests were two-tailed and statistical significance was established at $\alpha < 0.05$.

Results

The demographic and clinical variables are shown in Table 2. There was no intergroup difference in median age (p=0.245), sex distribution (p=0.673), mean BMI (p=0.342) or mean BSA (p=0.855). No participants in the control group complained of dyspnea (mMRC dyspnea scale score of zero) and all IPF patients had a non-zero mMRC score (p<0.001). The mean distance covered in the 6MWT was significantly shorter in the IPF group (-32.1%, p=0.008), and the IPF patients also showed significantly lower mean quadriceps femoris muscle strength measurements than sedentary healthy controls (-28%, p=0.041). Participants in the IPF group had significantly lower mean %predicted FVC (-36%, p<0.001), FEV_1 (-26%, p<0.001) and DL_{CO} (-52%, p<0.001). Average FEV1/FVC ratio was significantly higher in IPF patients than in controls (+9%, p=0.027). Baseline SpO_2 in the IPF group was 93.0% ±3.9 (ranging from 84% to 98%). During the 6MWT, the SpO_2 decreased from 92.8% ± 3.1 to 82.5% ± 8.1, with absolute decrease of 10.3% ± 6.9 (p=0.004).

MRI assessment

Main results are shown in Table 3. No participant had overt muscle edema or otherwise visually abnormal muscle SI on STIR images. Intergroup difference in mean corrected cross-sectional muscle area was less than 3% and non-significant for both the quadriceps femoris muscle (p=0.790) and the rectus femoris muscle (p=0.816). Rectus femoris muscle T2 values ranged from 44.4 ms to 55.2 ms in the IPF group and from 47.9 ms to 59.6 ms in the control group, without reaching statistically significant difference in the mean value (lower in the IPF group by 6%, p=0.055). T2* values ranged from 25.2 ms to 33.2 ms in the IPF group and from 30.7 ms to 37.1 ms in the control group, with a significant difference in the mean value (lower in the IPF group by 8%, p=0.027). Figure 1 shows two examples of T2* maps. Fat fraction measurements ranged from 5.1% to 17.7% in the IPF group and from 5.6% to 10.3% in the control group, without significant intergroup difference (p=0.901).

Table 2. Demographics and clinical variables.

	IPF patients (n=13)	Control group (n=8)	p
Age, yr	77.0 (66.0, 81.5)	67.0 (65.3, 73.3)	0.245
Male	8 (62)	4 (50)	0.673
BMI, kg.m^{-2}	27.3±2.6	29.5±6.0	0.342
BSA, m^2	1.86±0.20	1.90±0.31	0.768
PFT			
FVC, L	2.22±0.81	2.84±0.34	0.025
FVC, % predicted	65.8±14.8	102.9±12.3	<0.001
FEV_1, L	1.90±0.56	2.23±0.37	0.155
FEV_1, % predicted	74.7±13.2	101.0±8.7	<0.001
FEV_1/FVC ratio, %	84.8±6.7	78.0±5.1	0.027
DL_{CO}, mmol.min^{-1} . kPa^{-1}	3.04±1.21	5.99±0.69	<0.001
DL_{CO}, % predicted	38.6±8.7	80.9±5.2	<0.001
Quadriceps strength, kgf	30.9±13.1	42.9±6.8	0.041
6MWT, m	346±114	510±49	0.008
mMRC score (0/1/2/3)	0/3/2/8	8/0/0/0	<0.001

IPF, idiopathic pulmonary fibrosis; BMI, body mass index; BSA, body surface area; PFT, pulmonary function tests; FVC, forced vital capacity; DL_{CO}, diffusion capacity for carbon monoxide; FEV_1, forced expiratory volume in one second; 6MWT, six-minute walk test; mMRC, modified Medical Research Council Dyspnea Scale. Data are presented as mean ± SD for normally distributed data, median (interquartile range) for non-normally distributed data, or n (%) for categorical data.

Table 3. Comparison of groups for MRI assessment.

	IPF patients (n=13)	Control group (n=8)	p
Quadriceps muscle cross-sectional area			
Absolute, cm^2	49.0 (45.5, 59.0)	43.5 (39.0, 71.5)	0.737
Corrected, cm^2.m^{-2}	33.7±6.1	34.6±8.6	0.790
Rectus femoris muscle cross-sectional area			
Absolute, cm^2	5.3±1.7	5.5±2.1	0.762
Corrected, cm^2.m^{-2}	3.5±1.0	3.6±1.1	0.816
Rectus femoris muscle SI measurements			
T2, ms	49.3±2.8	52.6±4.4	0.055
T2*, ms	30.2±2.5	32.7±2.0	0.027
Fat fraction, %	7.3 (5.6, 10.9)	6.7 (5.8, 9.0)	0.901

IPF, idiopathic pulmonary fibrosis; SI, signal intensity. Data are presented as mean ± SD for normally distributed data, or median (interquartile range) for non-normally distributed data.

Discussion

Muscle dysfunction may be assessed through a variety of invasive and non-invasive methods. Muscle strength can be measured by means of isokinetic or isometric dynamometry, but it does not provide insight into pathophysiological mechanisms. Muscle structure and composition can be directly examined by tissue sampling techniques, but their invasive nature and low availability hinder their widespread use. Imaging modalities allow non-invasive evaluation of morphological aspects, including volume-related measurements (*e.g.*, cross-sectional area and thickness), and presence and degree of myosteatosis. MRI, in particular, can also extract metabolism-related features. To the best of our knowledge, this is the first study to address MRI-specific features of skeletal muscle in IPF patients.

We found significantly shorter T2* values in the rectus femoris muscle of IPF patients compared to sedentary healthy controls. Shorter T2* values suggest larger local magnetic field inhomogeneities, and we hypothesize this could be related to higher concentration of paramagnetic substances in skeletal muscle tissue, such as deoxyhemoglobin or deoxymyoglobin [31-33]. Whether this is in fact the case remains an open question, and further investigation is warranted to directly evaluate the potential role of an ischemic/hypoxic factor in the pathogenesis of the skeletal muscle dysfunction observed in IPF patients. This could not only improve our understanding of the mechanisms underlying the impaired response to rehabilitation in this condition but also ultimately modify therapeutic approaches.

We found neither visual signs of muscle edema nor longer T2 values in IPF patients, arguing against the assumption of a diffuse inflammatory myopathy in IPF. In fact, T2 values tended to be lower in the IPF group, albeit not reaching statistical significance. Muscle cross-sectional area and fat fraction in IPF patients were also not statistically different from sedentary healthy controls, findings that are in line with the role of physical inactivity in exercise intolerance, but the significant intergroup difference in quadriceps strength measurements supports the notion of a multifactorial nature of muscle dysfunction in IPF [34], as one would expect a greater degree of muscle atrophy or myosteatosis should disuse atrophy being the sole causative mechanism. As expected, pulmonary compliance was lower in IPF patients, as evinced by the significantly lower FVC values in this group. The preferential decrease of FVC over FEV_1 accounts for the significantly increased Tiffeneau-Pinelli index in IPF patients, a marker of disease severity. The substantially reduced pulmonary diffusing capacity in the IPF group was also anticipated. Both pulmonary functional abnormalities and quadriceps muscle weakness may contribute to the observed intergroup difference in 6MWT performance.
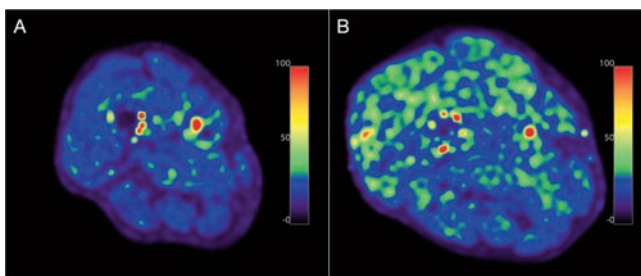
Figure 1. T2* maps in a patient with idiopathic pulmonary fibrosis (A) and in a sedentary healthy volunteer (B).

Our work had some limitations. Owing to the prospective nature of the study, the sample size was relatively small, being especially difficult to enroll healthy participants with a sedentary lifestyle in the age range of the IPF patients. The small sample size limits the power of the study, so small differences may have remained uncovered. Besides, the small sample size also precluded the employment of correlation analysis. Furthermore, due to the cross-sectional design of the study, we did not evaluate the effect of rehabilitation on the measured MRI parameters. Lastly, some derangements in skeletal muscle may not be apparent at rest, requiring exercise or ischemia to be disclosed.

Conclusions

This pilot study showed significantly shorter T2* in the rectus femoris muscle of IPF patients at rest, without significant difference in T2, fat fraction or cross-sectional area, in comparison with sedentary healthy volunteers. These findings support the notion that disuse atrophy is involved in the skeletal muscle dysfunction observed in IPF, but in addition suggest that other factors, such as hypoxia, may also play a role, without evidence of an inflammatory component. This may have potential clinical value in the rehabilitation of IPF patients and warrants further investigation.

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