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Early View

Research letter

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The relationship between perceived and performance fatigability in severe fibrotic interstitial lung disease: a prospective, cross-sectional study

Mathieu Marillier[1,2], Mathieu Gruet[3], Anne-Catherine Bernard[1,2], Samuel Verges[2], Onofre Moran-Mendoza[4], J. Alberto Neder[1]

[1]Laboratory of Clinical Exercise Physiology, Queen's University and Kingston General Hospital, Kingston, ON, Canada.

[2]HP2 Laboratory, INSERM U1300, Grenoble Alpes University, Grenoble, France

[3]IAPS Laboratory, University of Toulon, Toulon, France

[4]Interstitial Lung Disease Program, Queen's University and Hotel Dieu Hospital, Kingston, ON, Canada.

Correspondence to:

Mathieu Marillier, PhD

Laboratoire HP2 (INSERM U1300), Université Grenoble Alpes

UM Sport & Pathologies, Hôpital Sud, Avenue de Kimberley, 38 434 Echirolles, France

E-mail: mmarillier@chu-grenoble.fr

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Take-home message: Our study suggests that interventions geared to improve peripheral factors of performance fatigability during exercise in interstitial lung disease may prove valuable to decrease patients' perceived fatigability, since both seem closely related.

Dear Editor,

A sizeable fraction (~70%) of patients with fibrotic interstitial lung disease (*f*-ILD) suffer from and seek medical advice due to debilitating symptoms of fatigue.[1] Broadly, fatigue can be defined as an unrelenting feeling of tiredness or lack of energy that is not improved by rest. Fatigue is, however, a complex symptom thus remaining poorly understood and appropriately treated in *f*-ILD.[2]

Fatigue is thought to originate from predisposing, precipitating, and perpetuating factors that are not necessarily specific to *f*-ILD, although most factors may be applicable to the disease (as reviewed in [2]). In this letter, we reason using the recent and renowned framework for fatigue offered by Enoka and Duchateau [3] in which "perceived" and "performance" fatigability interact to limit one's physical (and cognitive) functioning.

Perceived fatigability refers to an individual's sensations about fatigue.[4] Of note, it can be assessed as a trait characteristic (i.e. the amount of fatigue faced by patients over a prolonged period of time) or as a state level (i.e. the amount of fatigue faced at a specific moment in time, such as physical tasks).[4] Performance fatigability corresponds to the objective changes in performance relative to the requirements brought by a specific task. This component depends on the ability of the neuromuscular system to meet such specific requirements and may be divided in central (e.g. voluntary activation) and peripheral (e.g. tissue O_2 delivery) factors.[4]

It is, however, unknown whether sensations of fatigue relate, at least in part, to alterations in neuromuscular mechanisms in patients with severe *f*-ILD. In this context, we aimed to offer a comprehensive assessment of fatigue in patients with *f*-ILD comprising both perceived (trait/state level) and performance fatigability and assess relationships between these two components.

Sixteen patients (13 men, 73±8 years, 10 with idiopathic pulmonary fibrosis, total lung capacity= 63±15% predicted, lung transfer for carbon monoxide= 42±10% predicted) were recruited from the ILD clinic (Division of Respirology, Kingston, Canada) between November 2018 and February 2020. They first performed an incremental (typically 5-15 W increment every 2 min [5, 6]) exercise test on a bicycle ergometer to determine peak work rate (WR_{peak}). All patients had severe exertional hypoxaemia (room air nadir of O_2 saturation by pulse oximetry <88%[7]). On a different day, they performed a constant-load, bicycle exercise test (60% WR_{peak}) to symptom limitation.[8] Magnetic femoral nerve stimulation assessed quadriceps neuromuscular fatigability.[8] Peripheral and central components of performance fatigability were measured as the pre- to post-exercise reduction in the potentiated quadriceps twitch amplitude (ΔTw) and voluntary activation (ΔVA, interpolated twitch technique [9]), respectively.[10] ΔTw and ΔVA were also expressed as a function of the external work (kJ= work rate (W) × exercise time (s)/1000) performed during constant-load exercise test. The state level of perceived fatigability was assessed using the Rating-of-Fatigue (ROF) scale, a valid tool to measure the intensity of fatigue in various contexts, such as whole-body exercise.[11] Perceived fatigability as a trait was assessed with the Fatigue Severity Scale (FSS) [12], a tool validated in a large sample to assess and quantify this outcome for clinical and research purposes [13] and previously used in *f*-ILD [14]. Patients were then discriminated according to their FSS (trait) and ROF (state) scores as "less fatigued" or "more fatigued", using a cut-off of 38 points (FSS) and 0.14 units/kJ (ROF). These cut-off scores corresponded to the median sample score for both scales. This prospective study was approved by the Queen's University (Kingston, Canada) Research Ethics Board (DMED-2150-18). Written informed consent was obtained from each participant prior to their participation.

Moderate and severe perceived fatigability as a trait (FSS) was reported by 12/16 (75%) and 6/16 (38%) of patients with *f*-ILD, respectively [15]; specifically, less fatigued patients had FSS scores of 29±10 and more fatigued patients had a score of 48±5 points (p<0.001). On average, patients exercised at 43±13 W for 17.0±4.0 min, leading to 44.4±19.0 kJ of work (with no difference according to FSS subgroups). Indices of performance fatigability [Δ maximal voluntary contraction (MVC), ΔTw and ΔVA, both absolute and work corrected values] did not differ between FSS subgroups nor correlated with FFS scores (p>0.05). Similarly, perceived fatigability as a state (i.e. on exercise: ROF scores, both absolute and work corrected) did not differ between less *vs* more fatigued patients: 6.3±2.1 *vs* 6.0±1.7 ROF units, and 0.20±0.12 *vs* 0.14±0.06 ROF units/kJ at exercise cessation, respectively (both p>0.05); there was no correlation between trait and state levels of perceived fatigability (p>0.05).

Considering perceived fatigability as a state, less and more fatigued patients had ROF scores of 5.6±1.9 *vs* 6.6±1.8 ROF units (p>0.05) and 0.10±0.03 *vs* 0.24±0.08 ROF units/kJ (p=0.001) at exercise cessation, respectively. This was due to less external work performed in more fatigued patients: 29.7±12.1 *vs* 59.0±11.6 kJ (p<0.001). When ROF scores were work adjusted, Δ Tw did not differ between less and more fatigued patients: -21.3±10.2 *vs* -20.9±7.6% drop from baseline, respectively (p>0.05). However, ΔTw/work was larger in more fatigued patients: -0.72±0.13 *vs* -0.38±0.20%/kJ (p=0.001; **Figure 1**, ***panel A***). In fact, ROF and ΔTw strongly correlated (r= -0.80; p<0.001) when adjusted for external work (***panel B***). Other indices of performance fatigability (ΔMVC and ΔVA, both absolute and work corrected) did not differ between ROF subgroups nor correlated with ROF scores (p>0.05; ***panels C-D***).

Fatigue assessment in *f*-ILD has so far been restricted to a trait characteristic.[2] The present study is innovating because it offers a thorough assessment of fatigue, comprising both components of perceived (trait and state levels) fatigability and directly measured performance fatigability. We found that i) trait level of perceived fatigability was not linked to performance fatigability but, in contrast, ii) state level of perceived fatigability and performance fatigability elicited by exercise significantly correlated when corrected external work performed in *f*-ILD. Our approach seems particularly relevant when considering the multidimensional facets of a complex symptom, which can hardly be captured by a single measure.

Paneroni and colleagues recently found a similar mismatch between trait level of perceived fatigability and performance fatigability on exercise in severe to end-stage chronic obstructive pulmonary disease.[16] They, in fact, reported that FSS was inversely related to forced expiratory volume in 1 sec, that is, perceived fatigability was associated with the severity of airflow obstruction. Applying such reasoning, we found that FSS inversely correlated with forced vital capacity (r= -0.52; *p*=0.038), suggesting that greater perceived fatigability was associated with the severity of lung restriction in our sample. However, perceived fatigability did not correlate with other relevant variables such as exercise tolerance (peak O_2 uptake or work rate) or the extent of exertional hypoxemia (*p*>0.05). Owing to the fact that fatigue in *f*-ILD is multifactorial, its management may likely require a comprehensive approach comprising, for instance, optimised treatment of the underlying disease and other associated comorbidities (e.g. sleep apnea or obesity) or supportive measures (e.g. cognitive behavioral therapy) [2].

Importantly, perceived fatigability and the peripheral component of performance fatigability during exercise were strongly associated in *f*-ILD. In this context, acute and chronic interventions aiming at lessening peripheral impairments underlying fatigability might translate into beneficial effects on perceived fatigability during physical exertion in this population. Specifically, in such patients with severe exercise-related hypoxemia, acute strategies targeting enhancement of muscle O_2 delivery (e.g. supplemental O_2 [8] or nitrate intake [17]) may be of strong interest. From a chronic standpoint, rehabilitative exercise training producing favourable changes in muscle structure and function has been related to improved muscle fatigability in other respiratory disorders [18]. The corollary is that lessening exercise-related fatigability may help patients being more active [14], physical inactivity being itself a perpetuating factor for fatigue in *f*-ILD [2]. Of note, we only enrolled a small sample of patients with severe *f*-ILD (mostly idiopathic pulmonary fibrosis). It is unknown whether similar results would be observed in milder form or other etiologies of *f*-ILD.

In conclusion, we found no association between trait level of perceived fatigability and performance fatigability in patients with severe *f*-ILD. Conversely, state level of perceived fatigability and the peripheral component of performance fatigability for a given amount of work were strongly associated in this patient population. Interventions improving peripheral factors associated with performance fatigability during physical exertion (e.g. O_2 supplementation or exercise training) may prove valuable to decrease patients' symptoms, such as heightened perceived fatigability.

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Author contribution. MM and ACB collected the data. MM analyzed the data. MM, MG, ACB, SV, OMM, and JAN were involved in the interpretation of the results. MM, MG and JAN drafted the first version of the manuscript and all authors provided critical feedback to shape the final version of the manuscript. All authors approved the final version of the manuscript to be published and agree to be accountable for all aspects of the present work.

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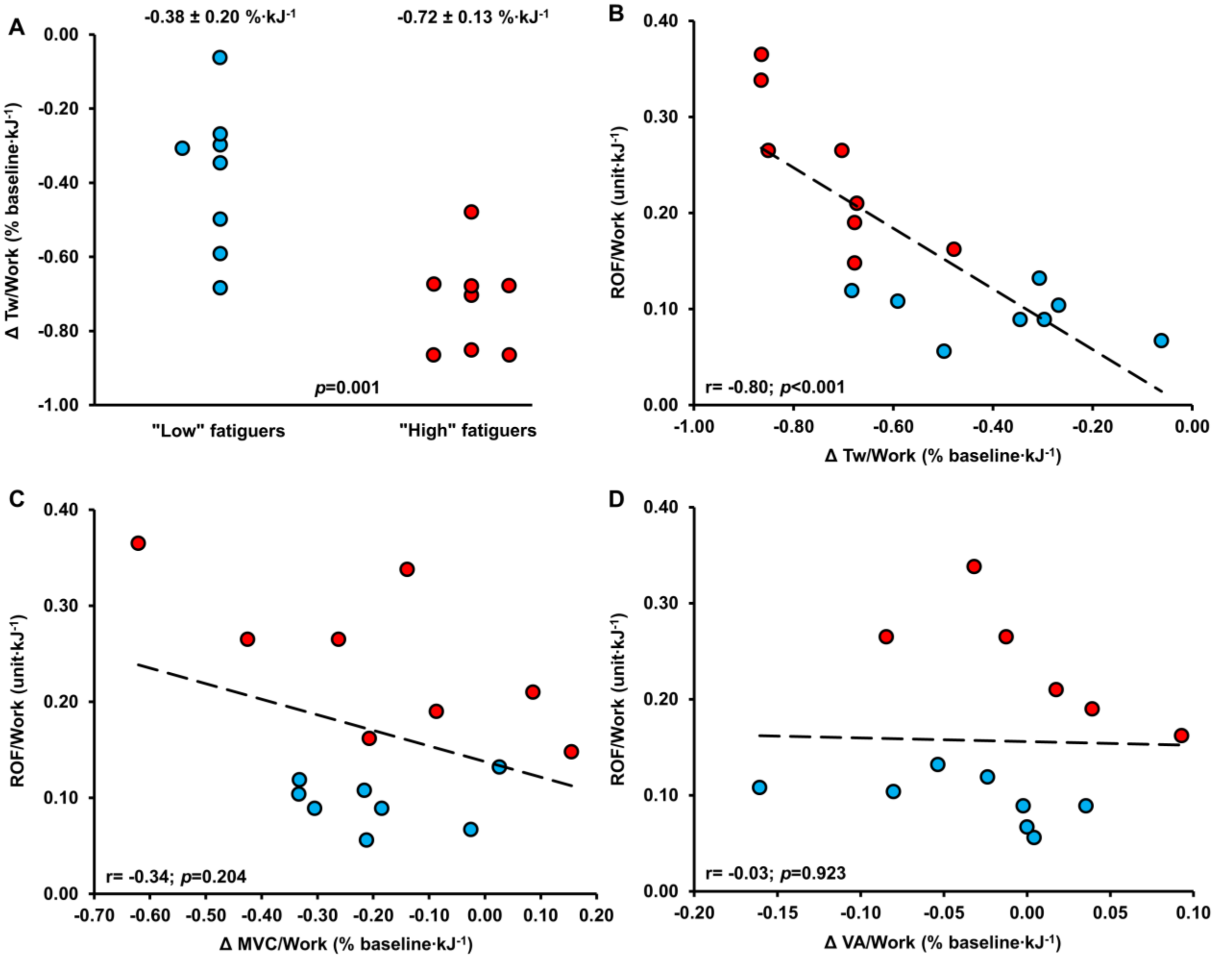
FIGURE LEGEND

Figure 1. Comparison of performance fatigability indices according to patients' state level of perceived fatigability during exercise and their corresponding relationships in fibrotic interstitial lung disease.

Variables were adjusted for the external work performed during a bicycle, constant-load exercise test. Patients were discriminated according to their state level of perceived fatigability [Rating-Of-Fatigue (ROF) scores] as "low" fatiguers (blue) or "high" fatiguers (red) using a cut-off of 0.14 ROF units/kJ (median sample score).

Panel A depicts exercise-induced changes in potentiated quadriceps twitch (ΔTw) in the two subgroups of patients. ***Panels B, C*** and ***D*** depict relationships between ΔTw, exercise-induced changes in maximal voluntary contraction (ΔMVC) and voluntary activation (ΔVA) with patients' state level of perceived fatigability, respectively.



A
-0.38 ± 0.20 %·kJ-1
-0.72 ± 0.13 %·kJ-1
Δ Tw/Work (% baseline·kJ-1)
p=0.001
"Low" fatiguers
"High" fatiguers
B
ROF/Work (unit·kJ-1)
r= -0.80; p<0.001
Δ Tw/Work (% baseline·kJ-1)
C
ROF/Work (unit·kJ-1)
r= -0.34; p=0.204
Δ MVC/Work (% baseline·kJ-1)
D
ROF/Work (unit·kJ-1)
r= -0.03; p=0.923
Δ VA/Work (% baseline·kJ-1)