PERIPHERAL MUSCLE DYSFUNCTION IN IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION

Vincent MAINGUY M.Sc.¹, François MALTAIS MD¹, Didier SAHEY Ph.D.¹, Philippe GAGNON M.Sc.¹, Simon MARTEL MD¹, Mathieu SIMON MD¹ and Steeve PROVENCHER MD, M.Sc.¹

1Centre de recherche de l’Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Québec, Canada

Corresponding Author:  Steeve PROVENCHER
Centre de Recherche de l’Institut Universitaire de Cardiologie et de Pneumologie de Québec, Service de Pneumologie
2725, chemin Sainte-Foy
Québec (Québec)
Canada, G1V 4G5
Phone: 418-656-4747
Fax: 418-656-4267
Email: steve.provencher@criucpq.ulaval.ca

Steve Provencher is a clinical scientist of the Fonds de Recherche en Santé du Québec.
François Maltais is a research scholar of the Fonds de la Recherche en Santé du Québec.

Key Words: Hypertension Pulmonary, Muscles Skeletal, Exercise

Word count excluding title page, ref, fig and tables: 2551
ABSTRACT

Background: A majority of idiopathic pulmonary arterial hypertension (IPAH) patients display persistent exercise intolerance despite new specific therapies. Whether IPAH patients exhibit peripheral muscle dysfunction that may contribute to this limitation remains unknown. We tested the hypothesis that IPAH patients’ muscle is weaker and display morphological changes compared to control subjects and that those changes partly correlate with their exercise capacity.

Objective: To characterize quadriceps function, morphology and enzymatic profile of IPAH patients.

Methods: Exercise capacity, limb muscle cross sectional area by CT scan, quadriceps strength by maximal voluntary contraction (MVC) and non-volitional magnetic stimulation of the femoral nerve (TWq), and muscle morphology and enzymatic profile by quadriceps biopsy of 10 IPAH patients were compared to 10 matched controls subjects.

Results: IPAH patients displayed lower proportion of type I muscle fibres (p=0.05), a lower MVC (p=0.05) and TWq (p=0.01) and an increased muscular phosphofructokinase/3-Hydroxyacyl-CoA-dehydrogenase ratio (p=0.05). They also tended to have lower thigh muscle cross sectional area (p=0.15). Maximal oxygen uptake correlated with quadriceps strength ($R^2=0.42$, p=0.04) and oxygen uptake at anaerobic threshold correlated with muscle oxidative capacity assessed by oxidative enzyme level for Citrate synthase ($R^2=0.45$, p=0.05) and 3-Hydroxyacyl-CoA-dehydrogenase ($R^2=0.86$, p<0.01), and type I fibre capillarity ($R^2=0.57$, p=0.02).

Conclusion: IPAH patients present significant peripheral muscle changes that partly correlated with their exercise capacity.

Words: 214

Key Words: Hypertension Pulmonary, Muscles Skeletal, Exercise
INTRODUCTION

Idiopathic pulmonary arterial hypertension (IPAH) is characterized by the progressive increase in pulmonary vascular resistance ultimately leading to right heart failure and death. Until recently, the median survival in IPAH was less than three years.[1] New specific therapies have considerably improved long-term prognosis of IPAH patients, with recent studies describing a three-year survival higher than 80%.[2] However, a majority of patients display persistent dyspnea and significant exercise intolerance despite current therapies. Indeed, many patients remain in World Health Organization (WHO) functional class III, representative of marked exercise limitations and poor quality of life.[3]

This persisting exercise intolerance have been traditionally attributed to residual cardiac and respiratory impairment known to be involved in the exercise pathophysiology of IPAH.[4] However, as for other respiratory and cardiac diseases,[5;6] skeletal muscles abnormalities in IPAH may be implicated in the exercise limitation, leading to further worsening in functional status. This hypothesis has been reinforced by the recent description of respiratory [7] and forearm [8] muscle weakness in IPAH. Improvement in exercise capacity were also documented in patients with pulmonary hypertension undergoing pulmonary rehabilitation.[9] The main objective of this study was to characterize the peripheral muscle function, morphology and enzymatic profile of IPAH patients.

METHODS

Study subjects

Ten WHO functional class II-III subjects with IPAH were recruited at our institution from February 2007 to March 2008. The IPAH diagnosis was made according to recent guidelines.[10] All patients exhibited significant IPAH defined as a mean pulmonary artery pressure > 25 mmHg (range 29 to 69 mmHg) at rest with a pulmonary capillary wedge pressure < 15 mmHg.[11] Recent right heart catheterization (<6 months) performed as part of their routine follow-up was used to described hemodynamic severity. Also, only patients with no change in their IPAH therapy and in stable clinical condition over the last 6 months were eligible. None of them had participated in a rehabilitation program. Exclusion criteria were as follows: (1) recent syncope and WHO functional class IV; (2) left ventricular ejection fraction < 40% of predicted; (3) significant restrictive (more than minimal lung fibrosis on CT scan or total lung capacity < 70% of predicted) or obstructive (FEV₁/FVC < 70%) lung disease; (4) intrinsic musculoskeletal abnormality precluding exercise testing; (5) patients with a pacemaker. Ten sedentary healthy subjects individually matched for age (within 5 years), gender, height (within 10 cm) and weight (within 5 kg) were recruited by advertisement in the community and tested concomitantly. The research protocol was approved by the institutional ethics committee and both patients and control subjects gave written consent.
Study design

Measurements were performed by technicians blinded for patients’ condition and were completed during one visit to the laboratory.

Exercise capacity assessment
A six-minute walk test and an incremental exercise test were performed according to the recent American Thoracic Society recommendations. Subjects were seated on an electrically braked ergocycle (Quinton Corival 400; A-H Robins, Seattle, WA) and were connected to the respiratory circuit through a mouthpiece (Quinton Qplex; A-H Robins, Bothel, WA). After 3 minutes of rest and one minute of unloaded pedaling at a minimum rate of 60 rpm, a progressive RAMP protocol was performed until exhaustion. Increments were adjusted subjectively from 5 to 20 watts/min for a target exercise duration of 8 to 12 minutes. Five-breath averages of minute ventilation, O2 uptake and CO2 excretion were measured throughout the exercise.

Peripheral muscle morphology and enzymatic activity
Thigh muscle surface cross-sectional area A computed tomography of the dominant thigh halfway between the pubic symphisis and the inferior condyle of the femur was performed using a fourth-generation Toshiba Scanner 900S (Toshiba). Each image was 5-mm thick and was taken at 120 kV and 200 mA with a scanning time of 1 s while the subject was lying in the supine position. The thigh muscle cross-sectional area was obtained by measuring the surface area of the tissue with a density of 35 to 100 Hounsfield units, corresponding to the density of muscle tissue. Quadriceps biopsy Percutaneous biopsy specimens of the vastus lateralis muscle of the nondominant leg were taken at midthigh as described by Bergström. After local anaesthesia, a 5-8 mm skin incision was made and muscle samples were obtained using one or two passes with the Bergström needle. The sample was immediately frozen in liquid nitrogen and OCT, (Tissue-Tek, Miles Inc, Elkhart, IN, USA) embedded and frozen in cooled isopentane and stored at -80°C. Transverse sections of 10 μm were cut using a cryostat Leica Jung CM 3000 (Wetzlar, Germany). Each section was verified by light microscopy to ensure proper fibre orientation. Fibre Typing Muscle sections were stained to see myofibrillar adenosine triphosphatase activity according to the single step ethanol modified technique. For each subject, the proportion of types I (non-stained), Ila (lightly stained), and IIX (darkly stained) fibres was assessed and was calculated as the number of fibres of each type divided by the total number of muscle fibres. Fibre surface area and capillarity The surface of 40 randomly selected fibres of each type was measured and averaged for each fibre type. Muscle section were stained with the α-amylase-periodic acid shift method to visualize capillaries. Muscle capillarity was expressed by dividing the number of capillaries in direct contact with the outer fibre membrane with the number of fibres. Enzymatic Activity Quadriceps muscle activity of Citrate synthase (CS, EC 4.1.3.7), 3-hydroxyacyl CoA dehydrogenase (HADH, EC 1.1.1.3) and phosphofructokinase (PFK, EC 2.7.1.11) were assessed using the spectrophotometric technique. Discriminating enzyme ratios representing glycolysis to the citric acid cycle (PFK/CS) and the β-oxidation of the fatty acids (PFK/HADH) were assessed. For the 8 patients that were anti-coagulated, oral anticoagulants were stopped four days before, and INR was measured prior to muscle biopsy, according to recent guidelines.
Quadriceps muscle strength
Both non-volitional and volitional strength of the quadriceps was evaluated by a modified technique developed by Polkey et al.[22] adapted in our laboratory by Saey et al.[23] In recumbent position (N-K 330 Exercise Table, N-K Products, Elsinore CA), the dominant leg was stabilized with the knee flexed at 90°. The ankle was attached to a strain gauge (Hewlett-Packard, Palo Alto, CA, USA) through a non-elastic strap to measure isometric knee extension tension. Care was taken to ensure that ankle strap and transducer were perpendicular to the leg and the chair frame, and that standard position was kept identical throughout the protocol. During maximal voluntary contraction (MVC), patients maintained the highest isometric strength possible for 3 seconds. Verbal encouragements were provided throughout those manoeuvres. The obtained signal was amplified (8811A amplificator, Hewlett-Packard), then transformed by an analogue transducer (Biopac system, Santa Barbara, CA, USA) connected to a computer for further data analysis (Acknowledge software, Biopac). Non-volitional strength of the quadriceps was measured using two commercial magnetic stimulators both related by a BiStim (Magstim Co. Ltd., Whitland, Dyfed, Wales, UK). A 70-mm figure-of-eight coil was positioned over the femoral nerve at the position leading to the strongest muscle contraction. Because potentiated twitches (TWq) are more accurate,[24] TWq were obtained at 100% stimulator output 3 seconds after MVC manoeuvres. Three sets of MVC and TWq measurements were performed, separated by a one-minute resting period. In case of a variability of more than 5%, additional measurements were performed until the reproducibility criterion was met. Reported value for the MVC and TWq were the mean of the three strongest contractions.

Statistical methods
Values are reported as median (interquartile range) unless otherwise specified. Comparisons between groups were performed using Mann-Whitney U test. Categorical variable was analysed using the Fisher’s exact test. Based on normal TWq described in healthy subjects [25] and patients with other chronic respiratory diseases, [6] we estimated that quadriceps TWq would average 6.0 (2.0) kg in IPAH compared to 8.5 (2.0) kg for controls (primary outcome). Thus, we determined a priori that 10 IPAH patients and 10 controls would be necessary to detect a statistically significant difference in TWq with a type I error of 5 percent and a type II error of 20 percent. Pearson’s correlation coefficients were used to evaluate relationships between exercise capacity and quadriceps strength. Because the anaerobic threshold is representative of the oxidative capacity, correlations between the oxygen uptake at anaerobic threshold and markers of muscle aerobic characteristics (type I fibre proportion, capillarity, oxidative enzyme profile) were also assessed. A P<0.05 was considered statistically significant. Data were analysed using Statview v5.0.

RESULTS
Subjects characteristics
The characteristics of the study population are shown in Table 1.
<table>
<thead>
<tr>
<th>Demographics</th>
<th>IPAH (n=10)</th>
<th>Controls (n=10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40 (30-55)</td>
<td>38 (30-55)</td>
<td>0.88</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>(7/3)</td>
<td>(7/3)</td>
<td>1.00*</td>
</tr>
<tr>
<td>BMI (kg.m⁻²)</td>
<td>25 (23-28)</td>
<td>24 (21-29)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulmonary hemodynamic</th>
<th>IPAH (n=10)</th>
<th>Controls (n=10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP ( mmHg)</td>
<td>8 (7-8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>40 (33-60)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>CI (L.min⁻¹.m²)</td>
<td>3.2 (2.2-3.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVRi (WU.m⁻²)</td>
<td>14 (7-17)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exercise capacity</th>
<th>IPAH (n=10)</th>
<th>Controls (n=10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IET</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\dot{V}O_2$ max (ml. kg⁻¹.min⁻¹)</td>
<td>18.4 (14.8-22.3)</td>
<td>31.3 (28.3-34.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$\dot{V}O_2$ max (% pred)</td>
<td>55 (45-61)</td>
<td>100 (85-111)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$V_E/\dot{V}CO_2$ slope</td>
<td>43 (37-56)</td>
<td>31 (27-32)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>6MWT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distance (meters)</td>
<td>448 (401-456)</td>
<td>679 (619-690)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>% predicted (%)</td>
<td>70 (67-73)</td>
<td>106 (97-108)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values are median (interquartile range) *Analyzed by Fisher’s exact test

**Definition of abbreviation:** IPAH = idiopathic pulmonary arterial hypertension; F = female; M = male; BMI = body mass index; RAP = right atrial pressure; mPAP = mean pulmonary artery pressure; CI = cardiac index; PVRi = pulmonary vascular resistance index; WU = Wood units; IET = incremental exercise test; $\dot{V}O_2$ = oxygen uptake; % pred = percentage of predicted value; $\dot{V}CO_2$ = volume of carbon dioxide expired; $V_E$ = minute ventilation; 6MWT = six-minute walking test.
IPAH patients and controls were well-matched for age, gender and body mass index. Pulmonary functions tests were also comparable except for DLCO (67 (25) versus 89 (10) % of predicted, p=0.03). All IPAH patients displayed significant resting pulmonary hypertension and marked exercise intolerance. At the time of the study, mean symptoms duration was 55 (29) months and patients. All patients were in WHO functional III at the time of diagnosis. They had been treated for 35 (22) months with bosentan (n=6), sildenafil (n=1), calcium channel blockers (n=1) or epoprostenol (n=2). Seven patients were now classified as WHO functional class II, whereas 3 patients were in WHO functional class III.

**Quadriceps muscle morphology and enzymatic activity (Table 2)**

Compared to controls, IPAH patients displayed lower proportion of type I fibres and a higher overall proportion of type II fibres (p=0.05). Analysis of the type II fibres showed that the IIx fibres were responsible for the increase in the percentage of the type II fibres, although this did not reach statistical significance. Discriminating enzyme ratios revealed a higher PFK/HADH ratio, compatible with a relatively higher potential for anaerobic than for aerobic energy metabolism.
Table 2 – Peripheral muscle characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>IPAH (n=10)</th>
<th>Controls (n=10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thigh muscle CSA (cm²)</td>
<td>79 (69-82)</td>
<td>86 (74-96)</td>
<td>0.15</td>
</tr>
<tr>
<td>Fibre typing (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>34 (27-49)</td>
<td>50 (47-53)</td>
<td>0.05</td>
</tr>
<tr>
<td>Type IIa</td>
<td>27 (21-41)</td>
<td>29 (27-30)</td>
<td>0.81</td>
</tr>
<tr>
<td>Type IIx</td>
<td>31 (21-41)</td>
<td>21 (20-23)</td>
<td>0.18</td>
</tr>
<tr>
<td>Fibre type surface area (μm²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>5125 (3647-5492)</td>
<td>3811 (3401-6693)</td>
<td>0.92</td>
</tr>
<tr>
<td>Type II</td>
<td>4235 (3033-5262)</td>
<td>2702 (2606-3304)</td>
<td>0.06</td>
</tr>
<tr>
<td>Capillarity (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capillaries/fibres type I</td>
<td>2.16 (1.78-2.34)</td>
<td>2.35 (2.10-2.89)</td>
<td>0.24</td>
</tr>
<tr>
<td>Capillaries/fibres type II</td>
<td>1.85 (1.46-2.10)</td>
<td>1.75 (1.65-2.01)</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Enzymatic activity and discriminative ratios</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS (μmol/g/min)</td>
<td>11.8 (11.1-15.4)</td>
<td>13.3 (12.8-15.1)</td>
<td>0.13</td>
</tr>
<tr>
<td>HADH (μmol/g/min)</td>
<td>4.7 (3.6-5.7)</td>
<td>5.2 (4.5-6.3)</td>
<td>0.20</td>
</tr>
<tr>
<td>PFK (μmol/g/min)</td>
<td>62.5 (51.5-72.5)</td>
<td>51.5 (40.9-61.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>PFK/CS ratio</td>
<td>5.0 (3.9-6.2)</td>
<td>3.9 (2.5-4.6)</td>
<td>0.10</td>
</tr>
<tr>
<td>PFK/HADH ratio</td>
<td>15.0 (8.9-17.0)</td>
<td>9.1 (5.5-11.3)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Values are median (interquartile range).

Definition of abbreviation: IPAH = idiopathic pulmonary arterial hypertension; CSA = cross sectional area; CS = citrate synthase; HADH = 3-Hydroxyacyl CoA dehydrogenase; PFK = phosphofructokinase
**Quadriceps muscle function**

MVC (36 (10) versus 44 (7) kg, p=0.05) and TWq (6.8 (2.1) versus 9.4 (2.2) kg, p=0.01) were significantly lower in IPAH patients (Figure 1A). No difference was found when the quadriceps strength was normalized for thigh muscle cross-sectional area (0.49 (0.11) versus 0.50 (0.06) kg.cm\(^{-2}\), p=0.85). MVC moderately correlated with thigh muscle cross-sectional area (R\(^2\)=0.26; p=0.02).

**Correlates of peripheral muscle function in IPAH**

Among IPAH patients, exercise capacity in IPAH positively correlated with quadriceps strength (Figure 1B). Oxygen uptake at anaerobic threshold also positively correlated with the quadriceps oxidative characteristics assessed by two oxidative enzymes (citrate synthase and 3-hydroxyacyl CoA dehydrogenase) as well as with the capillaries/type I fibre ratio (Figure 2). Exploratory analyses suggested a negative correlation between disease duration and the proportion of type I fibre (R\(^2\)=0.45; p=0.03). Conversely, there was no correlation between maximal exercise capacity, the proportion of fibre types, muscle surface area, activity of oxidative and glycolytic enzymes, muscle strength and any pulmonary hemodynamic parameters at rest.

**DISCUSSION**

The present study documented significant morphological and functional quadriceps changes in IPAH including lower type I fibre proportion, a higher PFK/HADH ratio compatible with a relatively higher potential for anaerobic than for aerobic energy metabolism, as well as lower quadriceps strength. Non-volitional quadriceps strength correlated with maximal oxygen uptake, whereas quadriceps aerobic characteristics correlated with anaerobic threshold. Importantly, muscle characteristics were unrelated to the hemodynamic severity of IPAH. These observations suggest that peripheral muscle abnormalities may be implicated in exercise pathophysiology of IPAH.

In IPAH, exercise pathophysiology is characterized by disproportionate increase in pulmonary artery pressure, low stroke volume and chronotropic response and ventilation-perfusion mismatch.[26] These abnormalities presumably translate into low maximal oxygen uptake and oxygen pulse, early anaerobic threshold, excessive ventilation and exercise-induced hypoxemia.[4] Because baseline exercise capacity [4,26] or changes in exercise tolerance over time [26,27] only partly correlate with resting pulmonary hemodynamics in IPAH, others factors may contribute to exercise limitation in IPAH. More recently, respiratory and forearm muscle weakness were described in IPAH.[7,8] Interestingly, muscle weakness was independent from hemodynamic severity. Forearm strength also correlated to respiratory muscle strength and exercise capacity.[8] However, only volitional strength was assessed in these studies and thus, the validity of these observations was questioned.[28] The present study confirmed that lower limb muscles are functionally abnormal in IPAH, as evaluated by both volitional and non-volitional measurements. Moreover, muscle strength and quadriceps oxidative properties correlated with exercise capacity and anaerobic threshold, respectively, whereas muscle characteristics did not correlate with the hemodynamic severity of IPAH. This could be explained by the influence of...
muscle function on the perception of leg effort during exercise, which is the main limiting symptom in a significant proportion of IPAH patients.[4] Whether the functional improvement previously observed following pulmonary rehabilitation was related to changes in peripheral muscle function remains to be explored. [9]

These observations are consistent with the peripheral muscle abnormalities previously described in patients with congestive left heart failure and chronic obstructive pulmonary disease that include quadriceps muscle atrophy and weakness, relative increase in easily fatigable type IIx fibres, relative decrease in oxidative type I fibres, decreased oxidative enzymes and mitochondria, abnormal intracellular calcium profiles, slower restoration of muscle phosphocreatine stores after exercise and an increased lactate accumulation during exercise.[5;6] These muscle abnormalities also correlate with maximal exercise capacity but are discrepant with the traditional marker of disease severity.[5;6] Nevertheless, IPAH patients markedly differ from patients with congestive heart failure and chronic obstructive pulmonary disease: they are much younger and the disease duration is much shorter. Interestingly, the proportion of type I fibres negatively correlated with disease duration. Thus, one could not extrapolate data from other chronic cardiac and respiratory diseases to IPAH. Importantly, the observation that muscle abnormalities are a common final scenario of several chronic conditions suggests some similarities in the underlying mechanisms. The investigation of various disease models may thus help determining unifying mechanistic mechanisms involved in this dysfunction. Those may include presence of systemic and/or local inflammation,[29] low cardiac output and hypoxemia leading to impaired peripheral oxygen delivery,[1] sympathetic hyperactivity,[30] as well as deconditioning. Whether other factors such as endothelial dysfunction or interaction with molecules targeting the endothelin-1 and nitric oxide signalling pathways potentially influencing vascular responsiveness of skeletal muscle arterioles in IPAH remains unknown.[31;32]

The limitations of our study should be discussed. First, the proposed protocol was physically demanding and potentially led to some selection bias toward patients less severely impaired. Thus, our results may not be representative of peripheral abnormalities that would have been observed in the most severe patients and may have decreased the magnitude of differences in peripheral muscle characteristics between IPAH patients and healthy subjects. Furthermore, close correlations between muscle characteristics and exercise capacity do not imply causal relationships. Similarly, differences in muscle performance between groups were modest in comparison to the substantial differences in aerobic capacity. This suggests that muscle dysfunction, while potentially contributing to exercise intolerance, is unlikely to be the main limiting factor. Importantly, our limited sample size may have led to type I and type II errors, especially for secondary endpoints. However, the alterations in muscle characteristics observed in our study were of similar magnitude as in chronic obstructive pulmonary disease in which peripheral myopathy is clearly implicated in patients’ functional impairment. Further studies also are needed in the more heterogeneous population of patients with non-IPAH, in whom the primary disease could independently influence muscle characteristics. Finally, our study design precluded analyzing whether PAH-specific therapy influenced skeletal muscle function, morphology, enzymes activities and vascularisation.
CONCLUSION

The present study documented significant morphological and functional changes in the quadriceps of IPAH patients. Some of these abnormalities correlated with patients’ functional status. Whether improving peripheral muscle integrity will enhance functional status and quality of life in IPAH remains to be confirmed.
Acknowledgements: The authors would like to thank Annie Michaud, Louis Laviolette and Éric Nadreau for their technical assistance and Serge Simard for his statistical assistance, as well as the “Banque de tissue du Réseau en Santé Respiratoire du FRSQ, site de l’Institut Universitaire de Cardiologie et de Pneumologie de Quebec”.

Funding: The project has been supported by the Réseau en Santé Respiratoire du Fonds de Recherche en Santé du Québec and the Groupe de recherche en santé respiratoire de l'Université Laval (GESER).

Competing interests: None

Ethics approval: The research protocol was approved by the institutional ethics committee and subjects gave written consent.

License: «The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in [THORAX] editions and any other BMJPG Ltd products to exploit all subsidiary rights, as set out in our licence (http://thorax.bmj.com/ifora/licence.pdf).»

Figure legend:

Figure 1  (A) Non-volitional and voluntary strength of the dominant quadriceps in idiopathic pulmonary arterial hypertension patients (white bars) and matched sedentary controls (black bars) and (B) Correlation between non volitional strength of the quadriceps and maximal exercise capacity in idiopathic pulmonary arterial hypertension. Kg = kilogram; Twq = strength assessed by magnetic stimulation of the femoral nerve; MVC = maximal voluntary contraction; $\overset{\text{2}}{\text{VO}}_\text{max}$ = maximal oxygen uptake.

Figure 2  Correlation between oxygen uptake at anaerobic threshold and muscular morphology in idiopathic pulmonary arterial hypertension patients and (A) citrate synthase level (CS); (B) 3-Hydroxyacyl CoA dehydrogenase level (HADH) and (C) capillaries/type I fibre ratio (Cap/Type 1). Anaerobic threshold could not be determined in one patient. $\overset{\text{2}}{\text{VO}}_\text{AT}$ = oxygen uptake at anaerobic threshold.
References


Figure 1

A

Strength (kg)

TWq       MVC

P=0.05

p=0.01

B

\[ \text{\( \dot{\text{VO}_2\text{max}} \) (ml.kg\(^{-1}\).min\(^{-1}\)}} \]

Twq (Kg)

R\(^2\)=0.42

P=0.04
Figure 2

A

\[ \dot{V}O_2 \text{ AT} \quad (L/\text{min}) \]

\[ R^2 = 0.45 \]

\[ p = 0.05 \]

B

\[ \dot{V}O_2 \text{ AT} \quad (L/\text{min}) \]

\[ R^2 = 0.86 \]

\[ p < 0.01 \]

C

\[ \dot{V}O_2 \text{ AT} \quad (L/\text{min}) \]

\[ R^2 = 0.57 \]

\[ p = 0.02 \]