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Original Article

Absence of calf muscle metabolism alterations in active cystic fibrosis adults with mild to moderate lung disease☆

N. Decorte [a,b,*,1], M. Gruet [a,b,c,1], B. Camara [e], S. Quetant [e], L. Mely [c,d], J.M. Vallier [c], S. Verges [a,b,2], B. Wuyam [a,b,2]

[a] HP2 Laboratory, Grenoble-Alpes University, 38000 Grenoble, France
[b] INSERM, U1042, 38000, Grenoble, France
[c] LAMHESS EA 6312, Universities of Toulon and Nice Sophia–Antipolis, France
[d] Centre de ressources et de compétences de la mucoviscidose (CRCM), Hôpital Renée Sabran, Giens, France
[e] Centre de ressources et de compétences de la mucoviscidose (CRCM), Clinique Universitaire de Pneumologie, Pôle Thorax et Vaisseaux, CHU Grenoble, France

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Abstract

Background: Specific alterations in skeletal muscle related to genetic defects may be present in adults with cystic fibrosis (CF). Limb muscle dysfunction may contribute to physical impairment in CF.
Aims and objectives: We hypothesized that adults with CF would have altered calf muscle metabolism during exercise.
Methods: Fifteen adults with CF and fifteen healthy controls matched for age, gender and physical activity performed a maximal cycling test and an evaluation of calf muscle energetics by ^{31}P magnetic resonance spectroscopy before, during and after plantar flexions to exhaustion.
Results: Maximal cycling test revealed lower exercise capacities in CF (VO_{2peak} 2.44 ± 0.11 vs. 3.44 ± 0.23 L·Min^{-1}, $P = 0.03$). At rest, calf muscle phosphorus metabolites and pHi were similar in CF and controls ($P > 0.05$). Maximal power output during plantar flexions was significantly lower in CF compared to controls (7.8 ± 1.2 vs. 6.6 ± 2.4 W; $P = 0.013$). At exhaustion, PCr concentration was similarly reduced in both groups (CF −33 ± 7%, controls −34 ± 6%, $P = 0.44$), while PCr degradation at identical absolute workload was greater in CF patients ($P = 0.04$). These differences disappeared when power output was normalized for differences in calf size (maximal power output: 0.10 ± 0.02 vs. 0.10 ± 0.03 W/cm^2; $P = 0.87$). Pi/PCr ratio and pHi during exercise as well as PCr recovery after exercise were similar between groups.
Conclusion: Similar metabolic calf muscle responses during exercise and recovery were found in CF adults and controls. Overall, muscle anabolism rather than specific metabolic dysfunction may be critical regarding muscle function in CF.

Keywords: Cystic fibrosis; Muscle metabolism; Exercise tolerance; ^{31}P MR spectroscopy

1. Introduction

Indices of physical fitness are strong predictors of quality of life [1] and mortality [2] in patients with cystic fibrosis (CF). It is accepted that pulmonary factors alone are insufficient to entirely explain exercise intolerance in CF. There is now accumulating evidence that limb muscle function also plays a key role regarding functional limitations experienced by CF patients. For example, many patients rate scores of muscle effort higher than scores of dyspnea at peak cycling exercise [3]

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* Corresponding author at: HP2 Laboratory (INSERM U1042), Unité Sports et Pathologies, Hôpital Sud, Avenue Kimberley, 38434 Echirolles, France. Tel.: +33 6 23 37 58 57.
E-mail address: ndecorte@chu-grenoble.fr (N. Decorte).
[1] Both last authors share senior authorship.
[2] Both authors have contributed equally and share the first authorship.

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and, despite their ventilatory limitation, develop quadriceps fatigue after cardiopulmonary exercise test [4].

Different mechanisms may enhance muscle fatigability in CF. CF transmembrane conductance regulator (CFTR) is expressed in the sarcoplasmic reticulum of human skeletal muscles [5]. Sarcoplasmic reticulum CFTR Cl^- channels deficiency could perturb electrochemical gradient, leading to ionic homeostasis dysregulation [6]. In addition, CFTR has intrinsic ATPase activity [7] so that depleted or defective CFTR may result in inadequate energy production or utilization. As a consequence, alterations in high-energy phosphate metabolites and perturbation in Ca^{2+} homeostasis can be expected, leading to alteration in muscle oxidative capacity and excitation-contraction coupling, which in turn may contribute to increased muscle fatigability in CF. Using a neuromuscular approach, we recently reported no specific CF alterations in excitation–contraction coupling and sarcolemmal excitability [8].

^{31}P magnetic resonance spectroscopy (^{31}P MRS) is a powerful non-invasive method to assess muscle metabolism *in vivo*, both at rest and during exercise, by focusing on changes in concentrations of high-energy phosphate metabolites such as adenosine triphosphate (ATP), creatine phosphate (PCr) and inorganic phosphate (Pi). Using a localized muscle exercise within the magnet avoids large cardio-respiratory stimulation and permits to evaluate metabolic abnormalities in patients with severe lung diseases [9,10]. Few studies used ^{31}P MRS to evaluate muscle metabolism during exercise in CF [11–14] and all but one [14] found that CF patients exhibited higher intracellular pH (pHi) and reduced oxidative capacity during exercise. All these studies were conducted in adolescents and thus findings may not be extended in CF adults who, with their increasing age, may accumulate several pulmonary and extrapulmonary sequelae [15] potentially affecting CF muscle function. Furthermore, matching CF patients and controls for physical activity levels is critical when comparing muscle function and metabolic abnormalities previously reported in CF could be attributed, at least in part, to muscle deconditioning rather than specific CF muscle dysfunction [16]. Important methodological considerations also have to be considered when using ^{31}P MRS during exercise such as the effect of cytosolic pH and PCr consumption during exercise on measurements of muscle oxidative capacity during recovery [17]. Hence, further investigations using appropriate ^{31}P MRS variables [18] during standardized exercise protocol are needed to confirm the presence of specific muscle metabolic abnormalities in CF adults. This is an important question to be answered in order to design optimal interventions targeting the mechanisms underlying skeletal muscle dysfunction in CF.

The purpose of the present study was to determine whether adult CF patients have altered plantar flexor muscle (i.e. an important muscle group for daily life activities such as walking) metabolism during exercise and recovery, as compared to age, gender and habitual physical activity-matched healthy controls. We hypothesized that CF patients would have: (i) increased phosphorous metabolites degradation (PCr) during exercise; (ii) reduced oxidative capacity (as assessed by post-exercise PCr resynthesis) and (iii) higher end-exercise pHi, leading to reduced muscle exercise performance.

2. Material and methods

2.1. Participants

Fifteen CF patients from two regional CF units (CRCM Grenoble and Giens, France) and fifteen healthy subjects matched for age, gender and levels of physical activity were recruited. Patients were not included if they were clinically unstable; had contraindications for maximal exercise testing or severe limb joint condition; had $FEV_1 < 40\%$; were receiving long-term oxygen therapy or corticotherapy. Fifteen healthy subjects matched for age, gender and levels of physical activity were recruited to constitute a control group. The main subjects' characteristics are presented in Table 1. The experimental procedures and potential risks associated with participation in the study were explained, and informed consent was obtained from each subject. The study was approved by the local ethics committee (CPP Sud-Est V no. 1095538) and performed according to the Declaration of Helsinki. Data from the exercise cycling test have already been published elsewhere [8].

2.2. Study design

All subjects performed a maximal cardiopulmonary exercise cycling test (CPET) and two localized calf muscle tests (maximal incremental and constant-load) assessed by ^{31}P MRS in random order within two days. Habitual physical activity levels and quality of life were evaluated by questionnaires (see below).

2.3. Questionnaires

Habitual physical activity was measured using the Baecke questionnaire [19], which is recommended by the French Cystic Fibrosis Society [20]. This self-administered questionnaire has three scales: physical activity at work, sport during leisure time and physical activity during leisure time excluding sport. For each scale, higher scores denote higher level of habitual physical activity. Health-related quality of life (HRQoL) was assessed by the French version of the CF questionnaire for adults (CFQ14+) [21]. This is a validated, self-administered, multi-dimensional questionnaire which evaluates generic and disease-specific domains of HRQoL. For each of the 13 scales, higher scores (0- to 100-point scale) indicate higher HRQoL. The mean global score [22] was calculated from the scores of each scale.

2.4. CPET

Subjects performed a maximal incremental cycling test on an electronically braked cycle ergometer (Ergometrics 800, Ergoline, Bitz, Germany) with electrocardiogram, breath-by-breath ventilation and gas analysis (Medisoft, Dinant, Belgium) for the determination of maximal oxygen uptake. Warm-up workload (from 20 to 50 W) and increments (from 10 to 30 W/min) were adjusted according to disease severity (modified Godfrey protocol) with the aim of obtaining an exercise duration of 8–12 min. Subjects rated their perceived dyspnea and leg fatigue at peak exercise and lactate concentration 1 min after exhaustion