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Original Article

Skeletal muscle contractility and fatigability in adults with cystic fibrosis

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Abstract

Background: Recent discovery of cystic fibrosis transmembrane conductance regulator expression in human skeletal muscle suggests that CF patients may have intrinsic skeletal muscle abnormalities potentially leading to functional impairments. The aim of the present study was to determine whether CF patients with mild to moderate lung disease have altered skeletal muscle contractility and greater muscle fatigability compared to healthy controls.
Methods: Thirty adults (15 CF and 15 controls) performed a quadriceps neuromuscular evaluation using single and paired femoral nerve magnetic stimulations. Electromyographic and mechanical parameters during voluntary and magnetically-evoked contractions were recorded at rest, during and after a fatiguing isometric task. Quadriceps cross-sectional area was determined by magnetic resonance imaging.
Results: Some indexes of muscle contractility tended to be reduced at rest in CF compared to controls (*e.g.*, mechanical response to doublets stimulation at 100 Hz: 74 ± 30 Nm *vs* 97 ± 28 Nm, $P = 0.06$) but all tendencies disappeared when expressed relative to quadriceps cross-sectional area ($P > 0.5$ for all parameters). CF and controls had similar alterations in muscle contractility with fatigue, similar endurance and post exercise recovery.
Conclusions: We found similar skeletal muscle endurance and fatigability in CF adults and controls and only trends for reduced muscle strength in CF which disappeared when normalized to muscle cross-sectional area. These results indicate small quantitative (reduced muscle mass) rather than qualitative (intrinsic skeletal muscle abnormalities) muscle alterations in CF with mild to moderate lung disease.

Keywords: Cystic fibrosis; Skeletal muscle function; Exercise tolerance; Neuromuscular fatigue

1. Background

Exercise has many positive effects on various health outcomes in cystic fibrosis (CF) and higher levels of physical fitness are associated with better quality of life [1] and better survival in this population [2, 3]. Although exercise intolerance is a hallmark of CF disease, the exact underlying mechanisms remain to be elucidated, in particular to optimize exercise rehabilitation programs. It is acknowledged that pulmonary factors alone are insufficient to explain exercise intolerance in CF, especially in

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CPET, cardiopulmonary exercise test; Db_{10}, potentiated doublets at 10 Hz; Db_{100}, potentiated doublets at 100 Hz; $Db_{10:100}$, ratio between potentiated doublets at 10 Hz and 100 Hz; FEV_1, forced expiratory volume in one second; FMNS, femoral magnetic nerve stimulation; Mmax, maximal M-wave; MVC, maximal voluntary contraction; PA, physical activity; qCSA, quadriceps cross-sectional area; Tw_p, potentiated twitch amplitude; VA, maximal voluntary activation; VA_{Db}, maximal voluntary activation from doublets at 100 Hz; VA_{Twp}, maximal voluntary activation from potentiated twitch.

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patients with mild to moderate lung disease. For example, inhaled bronchodilators improve lung function but not maximal exercise capacity in CF [4]. Recent evidence suggests that skeletal muscle dysfunction may play an important role regarding exercise intolerance in CF. Some studies demonstrated a reduction in maximal muscle strength which was related with exercise intolerance in both children and adults with CF [5–7]. This muscle weakness has been traditionally explained by physical inactivity and altered nutritional status. However, muscle weakness observed in a large sample of CF has been found to be in excess to that expected from physical inactivity alone [6]. Moreover, 6 months of endurance and/or resistance training failed to improve muscle strength despite normal nutritional status [8], questioning CF skeletal muscle trainability. Thus, the hypothesis of specific physiological impairments in the CF skeletal muscles can be raised. Wells et al. [9] found abnormalities in muscle metabolism in CF children as compared with age, sex and habitual physical activity (PA)-matched healthy controls, suggesting intrinsic dysfunction of skeletal muscle function. Lamhonwah et al. [10] recently demonstrated that CF transmembrane conductance regulator (CFTR) is expressed at the sarcoplasmic reticulum of human skeletal muscle. It has been proposed that sarcoplasmic reticulum CFTR Cl^- channels deficiency could perturb electrochemical gradient, leading to Ca^{2+} homeostasis dysregulation which could alter excitation–contraction coupling. These data suggest intrinsic CF-related skeletal muscle abnormalities, which may contribute to contractile impairments, increased muscle fatigability and reduced functional capacities in adults with CF.

Neuromuscular function can be assessed with artificial muscle stimulation, which allows differentiation between peripheral (*i.e.*, sarcolemmal action potentials propagation, excitation–contraction coupling, contractility) and central (*i.e.*, spinal and/or supraspinal activation of the skeletal muscles) factors accountable for reduced strength and increased fatigability. We recently developed an isolated muscle exercise test which combines voluntary and magnetically-evoked contractions [11]. This test permits to evaluate kinetics of changes in peripheral and central mechanisms of fatigue in a large muscle group (*i.e.*, quadriceps) and limits the influence of motivational factors using progressive loading, non-volitional contractions and multiple assessments. This test is reliable [11] and sensitive to small differences in muscle contractility and fatigability [11, 12]. We hypothesized that CF adults would have altered resting muscle contractility, even when normalized to muscle cross-sectional area, and increased muscle fatigability due to exaggerated alterations in excitation–contraction coupling, as compared to age, sex and habitual PA-matched healthy controls. We also hypothesized that these neuromuscular impairments would be associated with reduced exercise tolerance.

2. Methods

2.1. Study population

Fifteen adults with CF were recruited from two regional cystic fibrosis units (CRCM Grenoble and CRCM Giens). Main subjects' characteristics are presented in Table 1. Patients were not included if they were clinically unstable; had contraindications for maximal exercise testing or severe knee condition; had severe pulmonary disease (*i.e.*, forced expiratory volume in one second (FEV_1) < 50% of predicted values); were receiving long-term oxygen therapy or corticotherapy or were physically inactive (*i.e.*, less than 60 min of PA per week). Fifteen healthy subjects matched for age, sex and levels of PA were recruited from the hospital staff and visitors to constitute a control group. Written informed consent was obtained and the study was conducted according to the declaration of Helsinki and approved by the local Committee on Human Research (CPP Sud-Est V, Institutional Review Board number n° 1095538) (see Supplementary material for details).

2.2. Experimental design

All subjects answered questionnaires, performed a cardiopulmonary exercise test (CPET) and a quadriceps evaluation (*e.g.*, neuromuscular fatigue test and determination of quadriceps cross-sectional area, qCSA) in random order within two days. Habitual PA was measured using the Baecke questionnaire [13]. Health related quality of life was assessed by the French version of the CF questionnaire for adults (CFQ14+) [14]. CPET was performed using an electronically braked cycle ergometer with breath by breath gas exchanges measurement (see Supplementary material).

2.3. Quadriceps cross-sectional area

Subjects underwent magnetic resonance imaging assessment with a 3.0 T whole-body system (Achieva TX, Philips, Amsterdam, Netherlands) to determine qCSA (see Supplementary material).

2.4. Quadriceps neuromuscular evaluation

2.4.1. Experimental set-up

All measurements were performed on the right leg under isometric conditions, as previously described [11]. Briefly, subjects laid supine in a custom-built chair with knees at 90° of flexion and the hip angle at 130°. Knee extensor force was measured during voluntary and evoked contractions by calibrated force transducer. Surface EMG signals were recorded from the right vastus lateralis (as a surrogate for the whole quadriceps) according to SENIAM recommendations. Two magnetic stimulators (Magstim 200, The Magstim Company Ltd, Whitland, UK) linked by Bistim Module (Magstim) were used to stimulate the femoral nerve, as previously described [15]. Single (1 Hz, twitch) and paired (10 Hz and 100 Hz doublets) femoral magnetic nerve stimulations (FMNS) of 1-ms duration were delivered *via* a figure-eight of coil at the maximum stimulator output. The coil was positioned high in the femoral triangle in regard to the femoral nerve and manually controlled by an experienced investigator throughout the protocol (see Supplementary material).