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Chronic inflammation and infection associate with a lower exercise training response in cystic fibrosis adolescents

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Summary
Considerable heterogeneity among training-induced effects is observed in patients with cystic fibrosis (CF). We previously showed that longitudinal changes in exercise capacity in adolescents with CF were negatively associated with *Pseudomonas aeruginosa* (*P. aeruginosa*) colonization and total immunoglobulin G (IgG) levels, independent of age, pulmonary function and bodyweight. This is the first study investigating whether chronic inflammation and infection also associate with the exercise training response in adolescents with CF.

Participants performed a home-based exercise training program for 12 weeks. Pulmonary function, anthropometrics, exercise capacity, markers of inflammation and *P. aeruginosa* colonization status were measured at baseline. Exercise training-induced changes in pulmonary function and exercise capacity were compared between patients with a low and high inflammation–infection status.

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Participants with CF with high total IgG levels and *P. aeruginosa* colonization improved significantly less from the exercise training program, with regard to maximal oxygen consumption.

These observations support the hypothesis that chronic systemic inflammation and infection leads to devastating effects on skeletal muscles, hampering skeletal muscle tissue to improve from regular physical exercise. Data further suggest that patients with CF should preferentially be encouraged to engage in regular physical exercise when inflammation and infection status is low (e.g. at a young age).

Introduction

Patients with cystic fibrosis (CF) are encouraged to engage in regular physical exercise, since CF is associated with a reduced physical fitness and exercise capacity has been identified as an independent predictor of morbidity and mortality in these patients [1—4]. Regular physical exercise has been shown to improve pulmonary function, exercise capacity, muscle strength and quality of life in adults and children with CF, however considerable heterogeneity among training-induced effects is observed and, of which the underlying mechanisms are unknown [5].

Exercise intolerance in patients with cystic fibrosis (CF) is associated with a reduced pulmonary function [4,6—11], nutritional status [4,6—9], daily physical activity levels [12,13], chronic inflammation [4,14] and infection [4]. We previously showed that the exercise capacity declines 20% during adolescence in subjects with CF, of which *Pseudomonas aeruginosa* (*P. aeruginosa*) colonization status and total immunoglobulin G (IgG) levels were important determinants, independent of age, pulmonary function and bodyweight [4].

Enhanced circulating levels of pro-inflammatory mediators, such as TNF-α and interleukin (IL)-6, induce muscle cachexia [15,16] and have been associated with a reduced exercise capacity and skeletal muscle function in patients with CF and chronic obstructive pulmonary disease (COPD) [14,17]. Presence of such a catabolic state may affect the exercise training response in patients with CF and therefore be an explanation for the inconsistent results found by previous exercise training studies.

P. aeruginosa colonization is associated with a decline in pulmonary function [18], exercise capacity [4], increased morbidity and mortality [19,20] and is a main contributor to chronic inflammation in patients with CF [21]. However, whether chronic *P. aeruginosa* infection also contributes to differences in the exercise training response in patients with CF has never been studied.

Therefore, the aim of this study was to evaluate whether the exercise training response in adolescent with CF differed between those with a low or high inflammation or infection status.

Material and methods

Subjects

An open prospective intervention study involving adolescent (12—18-years-old) patients with CF was performed. Included patients had homozygous F508del mutations and were clinically stable, which meant no use of extra oral or intravenous antibiotics for at least four weeks prior to participation. Patients were excluded from participation when they used (inhaled) corticosteroids and/or immunosuppressive therapy, when they had CF-related diabetes mellitus and/or when they had undergone lung transplantation. Of 208 patients from the paediatric department of the CF-centre Utrecht (Netherlands), 60 patients were eligible for inclusion and 17 patients volunteered to participate. All participants, and if needed also their parents, gave written informed consent. The study was approved by the local medical ethics committee (UMC Utrecht).

Exercise training program

Participants executed a home-based exercise training program for 12 weeks [22]. The exercise training program was adjusted for children with CF by one of the exercise physiologists of our CF-centre. Briefly, the program is composed of six charts, which were arranged in increasing order of difficulty. The intensity was graded progressively by the patients based on their perceived exertion. Each session consisted of five basic exercises that had to be performed within 11 min for 5 days a week, without the need for specialized equipment. The first four exercises are callisthenic exercises (stretching, sit-ups, back extension, push-ups) and the fifth is an aerobic exercise (running). Individual starting levels of the exercise training program were based on measurement of physical fitness scores at the first visit. Patients were instructed how to perform the exercises at the start of the study. Progression was evaluated by telephone after three and nine weeks and a visit to the outpatient clinic after six weeks. Repetitive instructions were given, if needed. Furthermore, a diary was used by the participants to record exercise training progression. Detailed information of the study is visualized in Fig. 1.

Anthropometrics

Nutritional status was determined pre- and post-training by measurement of bodyweight, height, and body mass index (BMI), which were expressed as standard deviation score (SDS) based on reference values for healthy Dutch adolescents [23].