Respiratory Medicine (2015) 109, 463–474

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/rmed

Effects of exercise intensity compared to albuterol in individuals with cystic fibrosis

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Received 24 September 2014; accepted 4 December 2014
Available online 18 December 2014

KEYWORDS
Albuterol;
Bronchodilation;
Submaximal exercise;
Cycle ergometer;
Catecholamines;
Diffusion capacity of the lungs for nitric oxide

Summary
Background: Although exercise is a vital component of the therapy prescribed to individuals with cystic fibrosis (CF), it is not a priority due to a finite amount of treatment time and the view that exercise is not as beneficial as pharmacological treatments by many individuals with CF. We sought to compare the therapeutic benefits of exercise and their prescribed bronchodilator albuterol.
Methods: CF ($n = 14$) and healthy ($n = 16$) subjects completed three visits, a baseline screening with VO_2 max test and two treatment visits. On the two treatment visits, subjects completed spirometry and diffusing capacity of the lungs for nitric oxide (DLNO) maneuvers either at baseline, 60, and 110 min post-albuterol administration, or at baseline and the midway point of three separate 15 min exercise bouts at low, moderate and vigorous intensity (25, 50 and 65% of the maximum workload, respectively).
Results: With moderate exercise the increase in DLNO was double (39 ± 8 vs 15 ± 6% change) and the level of bronchodilation similar (23% change) when compared to 110 min post-albuterol in individuals with CF. During exercise FVC became reduced (−309 ± 66 mL with moderate

Abbreviations: ASL, airway surface liquid; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; Cl^-, chloride; DLNO, diffusion capacity of the lung for nitric oxide; ENaC, epithelial sodium channel; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; FEF_{25-75}, forced expired flow at 25–75% of FVC; MEFV, maximal expiratory flow volume; Na^+, sodium; Q, cardiac output; SpO_2, peripheral oxygen saturation; RR, respiratory rate; V_T, tidal volume; VCO_2, carbon dioxide production; VO_2, oxygen consumption; V_E, minute ventilation; V_A, alveolar volume.

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http://dx.doi.org/10.1016/j.rmed.2014.12.002

exercise) and the increase in FEV_1 was attenuated (103 ± 39 vs 236 ± 58 mL, exercise vs. albuterol) when compared with the response to albuterol in individuals with CF. Epinephrine (EPI) release increased 39, 72 and 144% change with low, moderate and vigorous intensity exercise respectively for individuals with CF, but this increase was blunted when compared to healthy subjects.

Conclusion: Our results suggest that moderate intensity exercise is the optimal intensity for individuals with CF, as low intensity exercise increases EPI less than 50% and vigorous intensity exercise is over taxing, such that airflow can be restricted. Although the duration of the beneficial effect is uncertain, exercise can promote greater improvements in gas diffusion and comparable bronchodilation when compared to albuterol.

Background

Research investigating the effects of exercise as therapy in cystic fibrosis (CF) has demonstrated that exercise can increase aerobic capacity (VO_2peak) and exercise tolerance [1], facilitate sputum clearance [2,3], and that individuals with CF with better aerobic fitness have better survival [4]. Although exercise is a vital component of the therapy regimen prescribed to individuals with CF, Myers et al. demonstrated that adherence is poor, finding only 24% of adults with CF are completing their exercise program [5]. Reasons individuals with CF may not make exercise a priority are the belief that exercise is not as beneficial as pharmacological treatments, and not feeling they have the time and/or energy to engage in physical activity [6—9].

In the CF lung the abnormal or absent cystic fibrosis transmembrane conductance regulator (CFTR) chloride (Cl^-) channel results in reduced or absent Cl^- secretion and hyperabsorption of sodium (Na^+) due to the loss of the CFTR-mediated inhibition of epithelial sodium channels (ENaC), with water being reabsorbed as it follows the osmotic gradient, or salt. This improper ion transport, causes a drastic depletion of the airway surface liquid (ASL) and compression of the cilia that impairs mucociliary clearance leaving thick, stagnant mucus to obstruct the distal airways and submucosal glands and becomes a stagnant breeding ground for infection. The therapeutic goals of the treatment of CF are to prevent the annual decline in pulmonary function and to improve ion regulation in the lung. With habitual exercise demonstrating the ability to attenuate the expected 2—3% annual decline in pulmonary function, exercise as a treatment achieves one of these goals [10]. Additionally, exercise can activate two pathways that could potentially improve ion regulation and thus hydration of the lung and subsequently facilitate improvements in mucus clearance. Exercise activates both the adrenergic pathway, through endogenous release of catecholamines, and the purinergic pathway, through sheer stress on the airway epithelia as a result of increases in ventilation. Stimulation of the β-$_2$ adrenergic receptor will result in activation of ENaC and CFTR [11,12], stimulate an increase in ciliary beating [11,13—15], and promote bronchodilation [16—20]. Activation of the purinergic pathway will activate the CFTR-independent calcium-activated chloride channels and inhibit ENaC [21,22]. Recent work has demonstrated that exercise can inhibit ENaC function in individuals with CF [23,24], which suggests that exercise may have beneficial effects on ion regulation in CF, but further investigation is needed. Therefore, exercise through activation of the adrenergic and purinergic pathways can provide a mechanism for Cl^- secretion that is CFTR-independent and inhibit hyperabsorption of Na^+ helping to ameliorate the two ion regulation deficiencies plaguing individuals with CF, and facilitate improvements in mucus clearance directly through stimulation of ciliary beating and as an airway clearance technique and secondary to improved hydration of the lungs. These improvements in ion regulation along with mediating bronchodilation collectively have the potential to improve airflow and provide better ventilation and perfusion matching to improve gas distribution, diffusion, and spirometry during and post an exercise bout.

Exogenous stimulation of the adrenergic pathway by a bronchodilator, β_2-adrenergic agonist, is commonly found in the therapy regimen for individuals with CF, prescribed in over 80% of individuals with CF, primarily to treat the symptoms of wheezing and breathlessness and preemptively combat airway hyperreactivity that can result as a consequence of other medications [25,26]. A goal of this study was to compare the systemic effects of submaximal exercise, at varying intensities, to that of the short-acting β_2-adrenergic agonist, albuterol, which is a standard medication for individuals with CF taken 3—4 times daily for its bronchodilatory benefits.

Through this study we first, wanted to determine the intensity of exercise necessary to beneficially activate the adrenergic and purinergic pathways, but not limit pulmonary function in individuals with CF. Second, we sought to compare the therapeutic benefits between exercise and a prescribed pharmacologic bronchodilator, albuterol. We evaluated changes in airflow and ability to mediate bronchodilation through basic spirometry and the potential improvements in mucus hydration, facilitation of mucus clearance and better gas distribution through assessment of the diffusion capacity of the lungs for nitric oxide (DLNO), a measure of alveolar-capillary membrane conductance. Healthy control subjects also completed the study to provide a measure of the normal response to these treatments and allow for a comparison to the response observed in our CF population. We hypothesized that vigorous intensity exercise (60—65% maximum workload) would allow for