Update on the role of exercise in cystic fibrosis
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Purpose of review
The role of exercise in patients with cystic fibrosis has been recognized for as long as cystic fibrosis has been identified as a clinical syndrome, as exercise intolerance has always been a hallmark of disease progression.

Recent findings
Work published in the past year has shed new light on several aspects of this field, including physiologic responses to exercise, responses to exercise programs, and the epidemiologic and prognostic implications of activity and exercise testing.

Summary
Barker's work is perhaps the most compelling, as it highlights the overwhelming interest and belief in the utility of exercise testing and prescription among cystic fibrosis physicians and the contrasting paucity of programs that test their patients and prescribe exercise for them. More studies are needed to identify the form of exercise programs and tests that are most likely to be effective and to be used by cystic fibrosis centers and patients.

Keywords
cystic fibrosis, exercise, exercise programs, exercise testing, physical activity

Introduction
The role of exercise in patients with cystic fibrosis has been recognized for as long as cystic fibrosis has been identified as a clinical syndrome, as exercise intolerance has always been a hallmark of disease progression. Physiologic responses to exercise have been studied since Godfrey and Mearns' work [1] in the early 1970s, and exercise programs have been undertaken since Keens et al. study [2] in the late 1970s.

The prognostic importance of exercise testing has been of interest for the past decade, and exercise testing has been incorporated in many cystic fibrosis centers' standard procedures. Exercise testing has also been employed as an outcome variable in some intervention studies.

In the past year, several interesting studies have appeared in the world literature, on various aspects of exercise and cystic fibrosis. This review highlights these studies, under the following categories: physiologic responses, epidemiology of physical activity and exercise, exercise training programs, the effect of medical intervention on exercise tolerance, and exercise testing in diagnosis and prognosis.

Physiologic responses
Cystic fibrosis patients waste much of their ventilation on dead space. Thin et al. [3*] studied six adults with cystic fibrosis with moderate to severe pulmonary disease severity and concluded that the problem is not so much increased dead space but rather the high respiratory rate (and correspondingly low tidal volume) the patients employ during exercise. With a low tidal volume, a greater proportion of each breath moves in and out of the airway dead space and does not participate in gas exchange. These investigators suggest that exercise tolerance would improve if patients with cystic fibrosis employed greater tidal volume and lower respiratory rate. It is not clear how this would be accomplished.

McKone et al. [4**] found cystic fibrosis patients to have decreased exercise tolerance if they exercised while breathing through 400 ml of added dead space. The patients then exercised with added dead space and 38% forced inspiratory oxygen and had increased peak exercise performance (VO2 and workload), minute ventilation, and arterial oxygen concentration. The patients' ability to increase their maximal ventilation in the presence of sufficient oxygen to prevent desaturation...
suggests hypoxemia, rather than ventilatory mechanics, as the limiting factor.

Several previous investigations have shown elevated resting energy expenditure in patients with cystic fibrosis. Energy expenditure almost certainly increases with pulmonary exacerbations and decreases after intravenous antibiotic treatment. Béghin et al. [5*] used indirect calorimetry and triaxial accelerometry as measures of energy expenditure at rest and during physical activity in 16 children with cystic fibrosis. After 14 days of intravenous antibiotics, the calculated energy expenditure was reduced, particularly with exercise. The investigators attribute this decrease in the energy cost of exercise to a decrease in the energy cost of breathing, as pulmonary function improved. We think the decrease could also be explained in part by less airway inflammation and its attendant energy cost.

Oxygen consumption (\(\dot{V}O_2\)) kinetics are classically described in three phases: \(\dot{V}O_2\) increases rapidly at the onset of exercise, as cardiac output and pulmonary blood flow increase (phase I). Phase II sees a further increase as deoxygenated blood returns to the lung from exercising muscle. Phase III is steady state. Hebestreit et al. [6*] examined the kinetics of oxygen uptake in 16 physically fit patients with cystic fibrosis. They found subtly but significantly slower phase II responses, compared with healthy control subjects. They speculate that the slower oxygen uptake kinetics in cystic fibrosis might be explained by a combination of peripheral muscle oxygen metabolism, oxygen delivery, and central mechanisms.

**Epidemiology of physical activity and exercise**

Using a self-report activity diary and an accelerometer, Selvadurai et al. [7**] examined habitual activity of 148 prepubescent and pubescent children with cystic fibrosis and matched healthy controls. There were no differences in activity levels between prepubescent boys and girls with the same severity of cystic fibrosis lung disease (forced expiratory volume in 1 second [FEV\(_1\)]). Overall, children with cystic fibrosis were as active as control subjects; however, both boys and girls with mild lung disease were more active than controls (\(P < 0.01\)). In the pubescent group, girls’ habitual activity levels were significantly lower than boys’ levels for cystic fibrosis patients with the same disease severity. The same gender difference in activity levels was found for the healthy controls. As a group, the pubescent children with mild cystic fibrosis were significantly more active than controls and those with moderate to severe cystic fibrosis were significantly less active. The innovative feature of this study was its secondary aim to determine correlations between patients’ physical activity and quality of life, aerobic capacity, anaerobic power, lung function, and nutritional status, assessed by body mass percentile (BMP) and pancreatic status. For the overall group of children with cystic fibrosis, significant relationships were found between activity levels and aerobic capacity (\(r^2 = 0.55, P < 0.01\)), anaerobic power (\(r^2 = 0.63, P < 0.01\)), and quality of wellbeing (\(r^2 = 0.61, P < 0.01\)). BMP correlated less well and lung function correlated poorly with activity levels. In the children with moderate to severe pulmonary disease, however, BMP correlated well with activity levels (\(r^2 = 0.45\)), suggesting the effects of poor nutrition on muscle mass and functional ability. Pancreatic-insufficient pubescent girls had significantly lower levels of activity, anaerobic power, aerobic capacity, and quality of life than girls with pancreatic sufficiency.

Buntain et al. [8*] examined the relation between bone mineral density (BMD) and several clinical parameters, including physical activity, in 153 pediatric and adult cystic fibrosis patients and 149 controls. The adults with cystic fibrosis reported significantly lower levels of physical activity than the control subjects. No significant differences in physical activity were found between the children and adolescents with cystic fibrosis and controls. For both the children and adolescents and the adult cystic fibrosis groups, there were significant associations between BMD and activity questionnaire scores. Positive correlations were also shown between hours of physical activity and lumbar spine BMD in the cystic fibrosis children and adolescents, and between the activity questionnaire score and physical/sedentary activity ratio and lumbar spine BMD in the adult cystic fibrosis subjects. The activity score was the only predictor of lumbar spine BMD in the regression model for adults.

Adequate muscle strength and function are vital components of physical activity. Sahlberg’s group [9*] compared muscle strength and function in 33 patients with cystic fibrosis (aged 16–35 years, with mild to moderate disease severity) with healthy controls matched for age and gender. The median physical activity score was similar for both groups. Female patients with cystic fibrosis had decreased maximal hand-grip strength, sustained hand-grip strength in the left hand, and leg muscle endurance, compared with healthy controls. Male patients with cystic fibrosis performed fewer sit-ups within 30 seconds and showed lower left leg isokinetic quadriceps strength than their healthy counterparts. No differences were related to pancreatic function and only sit-ups performed in 30 seconds in the male cystic fibrosis patients correlated with FEV\(_1\).

Barker et al. [10**] surveyed all cystic fibrosis centers in Germany to assess current practices and healthcare providers’ views on exercise. Fifty-nine percent of the cystic fibrosis centers responded. Overall, 60% of the responding centers performed exercise testing at a frequency of once
per 2.3 patient-years for those aged 8 years and above, yet fewer than half (42%) of the tests were performed according to standardized protocols. Thirty-one percent of the centers included exercise testing in their diagnostic routine. Nearly three-quarters of the centers did not discuss risks, benefits, or how to determine appropriate exercise intensities. Eighty-seven percent of the healthcare providers expressed interest in expanding the diagnostic and therapeutic applications of exercise in their own cystic fibrosis treatment programs.

**Exercise training programs**

Multiple studies conducted over the past three decades suggest that exercise training can improve aerobic fitness, maintain or slow decline in pulmonary function, possibly improve health-related quality of life, and perhaps even extend longevity in children with cystic fibrosis. Supervised programs spanning a variety of activities such as swimming, running, and cycling have had good regimen adherence and low dropout rates. Unsupervised exercise programs are dependent on intrinsic motivation, and few previous unsupervised exercise programs for patients with cystic fibrosis have been successful. Many of the training or follow-up periods have been shorter than 3 months, a time that is likely too short to demonstrate whether meaningful benefits could be sustained. If an exercise program maintains, or delays decline in, pulmonary function, this would be an important benefit. The expected decline in pulmonary function in patients with cystic fibrosis is likely between 2% and 3% per year [11]. This suggests that studies shorter than 12 months may be unable to detect a difference in pulmonary function between control and intervention subjects.

Five training studies have been published over the past year. Three research groups evaluated supervised programs of short duration (8–12 weeks), with short, or no, follow-up. Turchetta’s group [12*] found that 12 weeks of hospital-supervised treadmill exercise improved short-term cardiorespiratory fitness in adolescents and young adults with cystic fibrosis but did not affect FEV₁. This study did not include controls or randomization and used a small sample (n = 12) of highly selected children, who were sedentary and had mild to moderate lung impairment.

Enright *et al.* [13*] examined the effect of inspiratory muscle training (IMT) on lung function and exercise capacity in cystic fibrosis. Patients were randomly assigned to groups (training intensity of 80% of maximal inspiratory effort, 20% of maximal inspiratory effort, or control), but no follow-up was conducted after the 8-week, at-home, supervised training period. This study addressed inadequacies of previous IMT research by fixing the workload and resetting it (according to maximal inspiratory pressure generated) before each training session. High-intensity (80% of maximum) IMT significantly improved inspiratory muscle function, physical capacity, diaphragm thickness, lung volumes (vital capacity and total lung capacity), and anxiety and depression scores.

Klin *et al.* [14**••] found that after a 3-month supervised anaerobic training program, both anaerobic and aerobic performance, as well as quality of wellbeing scores, were increased in a sample of children with cystic fibrosis and mild-to-moderate pulmonary disease severity. No effects were evident for pulmonary function. Anaerobic performance and quality of wellbeing remained higher than pretraining values after an additional 3-month follow-up period. This study suggests that cystic fibrosis exercise prescriptions should include anaerobic components, which may more closely mirror children’s play activities and provide variation in training, which may in turn enhance adherence. Further, psychosocial changes found after exercise training [13•,14**••] continue to validate the multidimensional impact of exercise in cystic fibrosis.

The remaining two studies were randomized clinical trials that examined unsupervised exercise training over a 12-month period [15**,16*]. The length of both of these trials was sufficient to detect changes in fitness and lung function, although neither included follow-up after the 1-year training period. Moorcroft *et al.* [15**•] created individualized aerobic programs for 51 adult subjects by offering a choice of activities and attempted to track adherence through exercise diaries. Forty-two subjects completed the 12-month program; the exercise diaries were poorly kept and infrequently returned. A training effect (reduced blood lactate levels and heart rate for a constant submaximal work load) was achieved, however. There was a trend to preserving better pulmonary function in the training group compared with controls. This was the first home-based, unsupervised, randomized controlled exercise trial for adults with cystic fibrosis.

Our group [16*] conducted a home-based trial for children. We compared the effects of a semisupervised upper body strength training program with a similarly structured aerobic training program. Eighty-five percent of our subjects completed the program. Both strength and aerobic training procedures were associated with increased strength and physical working capacity. A no-training control condition would have improved the rigor of the design.

Because diverse activity modalities may increase interest and implementation of exercise, Barak *et al.* [17*] reviewed the literature examining use of trampolines in general and cystic fibrosis populations. Only two studies referred specifically to children with cystic fibrosis; the bulk of the articles reported injuries related to trampoline use. With trampoline use having a high risk of minor and major injuries, and the only apparent benefit for children
with cystic fibrosis being the choice of a different activity, the risks appear to outweigh the benefits.

We know with certainty that supervised exercise programs promote aerobic fitness in adults and children. Their long-term benefits, even 3 months after intervention, however, are not apparent. Recent studies [15**,16*] have shown that adherence to home-based, unsupervised or semi-supervised programs can be achieved and that improvements in fitness are possible. This raises the question about where future effort should focus. Should we attempt to fine-tune our techniques for home-based unsupervised programs or offer structured supervised programs, perhaps in community recreation facilities? Study of individually tailored programs that offer choices of physical activity, have long-term application, and promote adherence to make exercise an enjoyable lifestyle change is warranted.

Effect of medical intervention on exercise tolerance
DNase has been in widespread use in cystic fibrosis patients for over a decade and is generally thought to be useful in improving pulmonary function, but its effect on exercise tolerance had not been directly examined until Barker’s study [18•] from this year. Disappointingly, there was no discernable pattern among the 15 cystic fibrosis patients (age 9–28 years; FEV1 22–83% predicted). Some patients improved maximal oxygen uptake by as much as 20% after 8 weeks of first-time DNase, but nearly as many patients had lower exercise tolerance. Neither baseline pulmonary function nor patients’ subjective perception of the effects of DNase predicted performance on exercise testing.

Lung transplantation is a procedure of last resort for patients with end-stage lung disease from cystic fibrosis. Results have been spectacular in individual patients, but disappointing overall. Exercise tolerance has previously been evaluated, with variable results. Pinet et al. [19*] examined respiratory and leg muscle strength and size and peak oxygen uptake in 12 patients with cystic fibrosis 4 years after lung transplantation and compared them with healthy age-matched, sex-matched, and height-matched controls. Diaphragm and abdominal muscle strength were similar in the two groups, but quadriceps size and strength were reduced in the posttransplant patients. Cumulative steroid dose was an independent predictor of quadriceps atrophy. Peak oxygen uptake in the patients correlated with quadriceps strength and size and not with ventilatory muscle function. Unfortunately, the investigators did not quantify the amount of physical activity in which the patients engaged. Also unfortunately, the 12 patients tested were from a pool of 52 transplant patients. The other 40 subjects were either dead (25), had chronic rejection (five), other medical complications (three), or were unwilling to participate.

Exercise testing in diagnosis and prognosis
Pianosi et al. [20••] administered annual exercise tests to 28 children with cystic fibrosis over a 5-year period (1991–1996) and examined outcome in the ensuing 8 years. They found that peak VO2 fell by 2.1 ml/kg/min per year in their cohort and that the final peak VO2 in the 5 years of testing was predictive of subsequent 8-year mortality (defined as death or lung transplantation). Patients with peak VO2 less than 32 ml/kg/min had nearly 60% 8-year mortality, whereas none of those with peak VO2 greater than 45 ml/kg/min died in the follow-up period. The rate of decline in VO2 and FEV1 over the 5-year period when data were collected also correlated significantly with mortality. Although this study confirms earlier reports of the significant correlation of VO2 with subsequent survival, this is the first study to examine the rate of decline of VO2 as a predictor of mortality.

Conclusion
Several interesting and even important papers have been published within the past year on different aspects of exercise for patients with cystic fibrosis. The directions for future work are clear: there seems to be a need for physician education and motivation: we have known for years that exercise is safe and beneficial, and most cystic fibrosis physicians believe this, yet few prescribe specific exercise programs. Similarly, the usefulness of exercise testing is widely accepted, yet few centers employ this testing on a regular basis.

Studies are needed with longer follow-up, ideally with more patients, and with more emphasis on the best ways to ensure continued patient participation. This is not meant as a criticism of previous work: it is challenging to carry out exercise studies in cystic fibrosis; clinics have limited numbers of patients who are able – for logistical, financial, or geographic considerations – to attend exercise sessions. At the same time, clinics are faced with increasing numbers of clinical trials of promising new therapies based on the molecular/cellular underpinnings of cystic fibrosis. These trials compete with each other for patients willing and able to participate. Because of these constraints, the definition of ‘long term’ for clinical studies has steadily shortened. Yet, it is worth remembering in the face of multiple potential cellular and molecular approaches to cystic fibrosis, no therapy has yet appeared based on the basic defect that has shown anywhere near the promise of exercise programs, if we accept the strong correlation between fitness and survival and the ability exercise programs have shown to improve fitness.
be explained in part by less airway inflammation and its attendant energy cost. After 14 days of intravenous antibiotics, perhaps because of a decrease in the energy cost of ventilation.

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suggested that cystic fibrosis patients be taught to use larger tidal volumes and lower respiratory rates during exercise in order to reduce airway dead-space ventilation.


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This study showed evidence of slower phase II oxygen uptake kinetics in patients with cystic fibrosis, perhaps because of impaired oxygen delivery, perhaps peripheral muscle factors.


This group expanded previous research on habitual activity in children with cystic fibrosis by using a large sample (n = 148) of children with varying degrees of pulmonary disease severity and including accelerometers to validate self-report of activity. Pubertal activity levels were similar between genders of cystic fibrosis patients and between cystic fibrosis patients and controls. After puberty, girls with the same severity of cystic fibrosis disease were significantly less active than boys. The authors suggest that cystic fibrosis patients be taught to use larger tidal volumes and lower respiratory rates during exercise in order to reduce airway dead-space ventilation.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 555—556).


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This study of BMD in children, adolescents, and adults with cystic fibrosis revealed significant positive correlations between BMD and physical activity in all groups. Activity levels were lower for adults with cystic fibrosis than controls but were the same for children and adolescents and their respective controls.


The adolescent and adult subjects in this study reported similar activity level to matched controls. Patients showed muscle function and strength to controls. Slight muscular weakness was evident in the cystic fibrosis group split by sex, with the male cystic fibrosis patients differing from controls in quadriceps and abdominal endurance and the female cystic fibrosis patients differing from controls in hand and leg strength.


An interesting survey of German cystic fibrosis centers showing the gap between the degree of importance assigned to exercise and its actual application. Highlights an important disconnect that no doubt is seen the world over.


This uncontrolled, nonrandom study tested a 12-week supervised aerobic training program in a small sample of cystic fibrosis patients aged 15—22 years. The training improved cardiopulmonary fitness (peak VO2) in these children.


High-intensity (80% of max) IMT significantly improved inspiratory muscle function, physical working capacity, diaphragm thickness, lung volumes (vital capacity and total lung capacity), and anxiety and depression scores.


These authors are the first to show that children with cystic fibrosis can increase their aerobic and anaerobic capacity as well as their quality of wellbeing after a high-intensity anaerobic training program.


The study was the first randomized, controlled clinical trial to test a home-based, unsupervised aerobic training program for adults with cystic fibrosis. After 1 year, the subjects in the exercise group showed significant reductions in lactate concentrations and heart rates (during constant work rate bicycle ergometry) compared with controls. Trends were also seen for better preservation of pulmonary function in the training group.


We conducted a 1-year randomized clinical trial to compare the effects of strength versus aerobic training in children with cystic fibrosis. Both programs were associated with increased strength and physical work capacity.


Through a review of the literature, the authors assess the benefits and risks of trampoline use and do not recommend it as an exercise modality for patients with cystic fibrosis.


No consistent effect was found on exercise tolerance after 8 weeks of first-time DNase treatment, but some individual patients improved exercise tolerance by as much as 20%.


Four years after lung transplant, the few healthy survivors showed well preserved ventilatory muscle size and strength but smaller and weaker quadriceps. The effect of chronic steroid treatment might be a cause; habitual activity was not examined.


Interesting study showing annual decline of peak oxygen uptake over a 5-year period, and the utility of peak VO2 (oxygen consumption per unit time) in predicting subsequent mortality.