eCysticFibrosis Review Volume 3 Issue 7

The Role of Exercise and Physical Activity in Optimizing Outcomes Among Patients With Cystic Fibrosis

In this Issue...

Despite advances in clinical care, life expectancy in patients with cystic fibrosis (CF) remains shortened. It has been well documented that exercise capacity in this population is limited by impaired lung function, peripheral skeletal muscle function, and nutritional status, as well as the inability of the cardiorespiratory system to meet the metabolic demands associated with exercise. Interestingly, the physiologic consequences observed in patients with CF are similar to the effects of deconditioning, including poor cardiovascular function, reduced muscle mass, and impaired strength and power. Further, children with CF may be more physically inactive because of the burden of their chronic disease and thus may be at risk for compounding the combined effects of chronic disease and physical inactivity. Exercise and physical activity are key factors in the management of patients with CF, as such markers of physical fitness as aerobic capacity are related to pulmonary function and may be associated with mortality.

In this issue, we review the pathophysiology of exercise intolerance in patients with CF, and discuss new research on how clinicians can incorporate physical activity into the treatment plan for their patients with CF, with the expectation that exercise can improve outcomes in this population.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Describe the pathophysiology of exercise intolerance in patients with cystic fibrosis (CF)
- Discuss the research on the relationship between exercise function/capacity and longitudinal clinical outcomes in patients with CF
- Summarize how to implement exercise and physical activity recommendations to optimize clinical outcomes in patients with CF
for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s Commission on Accreditation.

The Institute for Johns Hopkins Nursing and the American Nurses Credentialing Center do not endorse the use of any commercial products discussed or displayed in conjunction with this educational activity.

CREDIT DESIGNATIONS

Physicians
Newsletter: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 1.0 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses
Newsletter: This 1 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each Newsletter carries a maximum of 1 contact hours or a total of 7 contact hours for the seven newsletters in this program.

Respiratory Therapists
For United States: Visit this page to confirm that your state will accept the CE Credits gained through this program.

For Canada: Visit this page to confirm that your province will accept the CE Credits gained through this program.

INTENDED AUDIENCE

This activity has been developed for pulmonologists, pediatric pulmonologists, gastroenterologists, pediatricians, infectious disease specialists, respiratory therapists, dieticians, nutritionists, nurses, and physical therapists.

LAUNCH DATE

This program launched on September 7, 2011, and is published monthly; activities expire two years from the date of publication.

HARDWARE & SOFTWARE REQUIREMENTS

Pentium 800 processor or greater, Windows 98/NT/2000/XP or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, Windows Media Player 9.0 or later, 128 MB of RAM Monitor settings: High color at 800 x 600 pixels, Sound card and speakers, Adobe Acrobat Reader.

DISCLAIMER STATEMENT

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only. Use of Johns Hopkins University School of Medicine name implies review of educational format design and approach. Please review the complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings and adverse effects before administering pharmacologic therapy to patients.

FACULTY DISCLOSURE

As a provider approved by the Accreditation Council for Continuing Medical Education (ACCMCE), it is the policy of the Johns Hopkins University School of Medicine Office of Continuing Medical Education (OCME) to require signed disclosure of the existence of financial relationships with industry from any individual in a position to control the content of a CME activity sponsored by OCME. Members of the Planning Committee are required to disclose all relationships regardless of their relevance to the content of the activity. Faculty are required to disclose only those relationships that are relevant to their specific presentation. The following relationships have been reported for this activity:

- Michael P. Boyle, MD, FCCP discloses that he has received grant/research support from Vertex Pharmaceuticals, Inc. and is a consultant to Genentech, Inc., Gilead Sciences, Inc. and Bayer.

the requested information when prompted. Otherwise, complete the registration form to begin the testing process. A passing grade of 70% or higher on the post-test/evaluation is required to receive CE credit.

There are no fees or prerequisites for this activity.

STATEMENT OF RESPONSIBILITY

The Johns Hopkins University School of Medicine takes responsibility for the content, quality and scientific integrity of this CME activity.

CONFIDENTIALITY DISCLAIMER FOR CME CONFERENCE ATTENDEES

I certify that I am attending a Johns Hopkins University School of Medicine CME activity for accredited training and/or educational purposes.

I understand that while I am attending in this capacity, I may be exposed to “protected health information,” as that term is defined and used in Hopkins policies and in the federal HIPAA privacy regulations (the “Privacy Regulations”). Protected health information is information about a person’s health or treatment that identifies the person.

I pledge and agree to use and disclose any of this protected health information only for the training and/or educational purposes of my visit and to keep the information confidential.

I understand that I may direct to the Johns Hopkins Privacy Officer any questions I have about my obligations under this Confidentiality Pledge or under any of the Hopkins policies and procedures and applicable laws and regulations related to confidentiality. The contact information is: Johns Hopkins Privacy Officer, telephone: 410-735-6509, e-mail: HIPAA@jhmi.edu.

“The Office of Continuing Medical Education at the Johns Hopkins University School of Medicine, as provider of this activity, has relayed information with the CME attendees/participants and certifies that the visitor is attending for training, education and/or observation purposes only.”

For CME Questions, please contact the CME Office at (410) 955-2959 or e-mail cmenet@jhmi.edu.

For CME Certificates, please call (410) 502-9634.

Johns Hopkins University School of Medicine Office of Continuing Medical Education
Turner 20/720 Rutland Avenue
Baltimore, Maryland 21205-2195

Reviewed & Approved by:
General Counsel, Johns Hopkins Medicine (4/1/03)
Updated 4/09

INTERNET CME/CE POLICY

The Office of Continuing Medical Education (CME) at the Johns Hopkins University School of Medicine is committed to protecting the privacy of its members and customers. The Johns Hopkins University SOM CME maintains its Internet site as an information resource and service for physicians, other health professionals and the public.

Continuing Medical Education at the Johns Hopkins University School of Medicine will keep your personal and credit information confidential when you participate in a CME Internet-based program. Your information will never be given to anyone outside the Johns Hopkins University School of Medicine’s CME program. CME collects only the information necessary to provide you with the services that you request.
No other planners have indicated that they have any financial interests or relationships with a commercial entity.

Guest Author’s Disclosures

IN THIS ISSUE

- **COMMENTARY** From Our Guest Author
- CYSTIC FIBROSIS TRANSMEMBRANE REGULATOR EXPRESSION IN HUMAN SKELETAL MUSCLE
- METABOLIC PATHOPHYSIOLOGY OF SKELETAL MUSCLE DYSFUNCTION IN ADOLESCENTS WITH CYSTIC FIBROSIS
- FEV₁ AND VO₂PEAK AS PREDICTORS OF MORTALITY IN PATIENTS WITH CYSTIC FIBROSIS
- LONG-TERM EFFECTS OF TRAINING PROGRAMS FOR PATIENTS WITH CYSTIC FIBROSIS
- ANAEROBIC TRAINING IN CHILDREN WITH CYSTIC FIBROSIS

Program Directors

Michael P. Boyle, MD, FCCP
Associate Professor of Medicine
Director, Adult Cystic Fibrosis Program
The Johns Hopkins University
Baltimore, MD

Peter J. Mogayzel, Jr., MD, PhD
Associate Professor of Pediatrics
Director, Cystic Fibrosis Center
The Johns Hopkins University
Baltimore, MD

Donna W. Peeler, RN, BSN
Pediatric Clinical Coordinator
Cystic Fibrosis Center
The Johns Hopkins University
Baltimore, MD

Meghan Ramsay, MS, CRNP
Adult Clinical Coordinator
Cystic Fibrosis Center
The Johns Hopkins University
Baltimore, MD

GUEST AUTHOR OF THE MONTH

In This Issue & Reviews:

Greg D. Wells, PhD
Associate Scientist in Physiology and Experimental Medicine
The Hospital for Sick Children
Toronto, Ontario, Canada

Guest Faculty Disclosure

Greg D. Wells has indicated that he has no financial interests or relationships with a commercial entity.

Unlabeled/Unapproved Uses

The author indicates that there will be no reference to unlabeled/unapproved uses of drugs or products in the presentation.

Program Directors’ Disclosures

COMMENTARY

Long-term prognosis and survival remain significant issues among patients with cystic fibrosis (CF), despite advances in treatment and care. Exercise capacity in this group is limited by impaired pulmonary function, peripheral skeletal muscle function, and nutritional status, as well as by the capacity of the cardiorespiratory system to endure the metabolic demands of exercise. Although observed intolerance has been reported among this population, higher levels of exercise and habitual physical activity have been shown to be important for the health and quality of life (QOL) of patients with CF. Unfortunately, however, exercise and physical activity remain underutilized in the clinical management of the disease. Recent research has provided a new perspective on the pathophysiology of
Recent research has provided a new perspective on the pathophysiology of exercise intolerance in individuals with CF and the specific benefits of exercise in terms of improved pulmonary function. These new data can provide patients, families, clinicians, and scientists the necessary rationale for the inclusion of exercise and physical activity in the daily management of CF to improve clinical outcomes and survival among patients with the disease.

Significant challenges exist with respect to the use of exercise and physical activity as therapy for chronic diseases, particularly CF. Boas reported that parents of children with CF perceive fewer benefits from exercise and greater barriers to physical activity than do parents of healthy children, with this view being more prevalent among parents of girls than of boys. In addition, the author found that fewer than half of the parents of children with CF knew that exercise performance was related to long-term prognosis or that exercise could be beneficial even among those with the most severe forms of CF. Further, in patients with CF, such issues as fatigue and the time required for treatments (ie, drug regimens and physiotherapy) make incorporating exercise into daily life even more challenging.

In addition to the challenges faced by patients with CF and their families regarding exercise as therapy, the medical and scientific communities have been engaged in a "chicken vs egg" type of debate. Simply stated, uncertainty exists as to whether exercise intolerance in patients with CF is primary or secondary to the disease. More specifically, the debate centers on whether exercise intolerance is due to impaired oxygen delivery or to intrinsic abnormalities in muscle function itself. Lamhonwah and colleagues (reviewed in this issue) have recently provided several lines of evidence demonstrating that the CF transmembrane conductance regulator (CFTR) is expressed in human skeletal muscle, and that CFTR dysfunction may contribute to the observed skeletal muscle weakness and exercise intolerance in patients with CF. These mechanistic observations are a crucial advance, as CF can now be considered a muscle disease, in addition to its previously defined effects on epithelial cells in the lung, pancreas, and digestive systems.

To build on the mechanistic observations that CF disease has a primary impact on skeletal muscle function and that skeletal muscle function is impaired in children with CF, it is important to recognize the established link between exercise capacity and lung function. Researchers have shown that a relationship exists between aerobic capacity, as assessed by traditional cardiopulmonary exercise testing, and survival in patients with CF. Additionally, exercise training programs are effective in improving both exercise capacity and, in some cases, lung function in patients with CF. Interestingly, the positive benefits of exercise training programs appear to have long-lasting effects and are not limited to just aerobic training. Anaerobic and strength training programs have been shown to be effective as well. It is critical that the scientific and medical communities work toward developing clear exercise recommendations for patients with CF and that these recommendations are implemented as part of routine clinical practice.

Exercise training programs, although effective, may not always be easy to implement, supervise, and sustain. The current trend in health promotion is to encourage a lifestyle change of increased habitual physical activity, which refers to the level of activity incorporated into a person's daily life. Changes in habitual physical activity represent a lifestyle modification that results in long-lasting benefits. Habitual physical activity presents an interesting possibility for patients with CF to help incorporate daily exercise into their lives, thus improving their health and QOL. Evidence suggests that habitual physical activity is positively associated with lung function (forced expiratory volume in 1 second; FEV1). Schneiderman and coworkers reported a positive relationship between habitual physical activity and FEV1 in girls when studied over a 2-year period. This study is ongoing, and a recent update over a longer evaluation period has confirmed the relationship between FEV1 and habitual physical activity, also demonstrating that the relationship exists for males as well as for females.

In summary, regular exercise and habitual physical activity are important for a patient with CF. Research has demonstrated the benefits of aerobic, anaerobic, and strength exercise training programs for health and QOL; however, patients with CF are faced with unique barriers and challenges to participation. In a recent review, Wilkes and co-workers have summarized research that has shown that increased levels of habitual physical activity slow lung function decline in patients with CF and that regular participation in a variety of activities may result in greater adherence in the long term. Research is now available to justify the incorporation of exercise into the routine care of patients with CF. Education of
health care providers on the importance of exercise and habitual physical activity for patients with CF is needed, in order for exercise and physical activity to become key components of clinical practice and of the daily lives of patients with CF.

Commentary References


back to top

CYSTIC FIBROSIS TRANSMEMBRANE REGULATOR EXPRESSION IN HUMAN SKELETAL MUSCLE


(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)

View journal abstract  View full article

The objective of the current study by Lamhonwah and associates was to examine cystic fibrosis transmembrane conductance regulator (CFTR) expression in human skeletal muscle. Previous research has shown that patients with CF experience exercise intolerance and skeletal muscle weakness, although the pathophysiology of these observations was poorly understood. Western blot analysis, confocal microscopy, and reverse transcription polymerase chain reaction (RT-PCR) were used to determine if CFTR is expressed in human skeletal muscle. Localization of CFTR in skeletal muscle was performed by immunoelectron microscopy.

The principal discovery by the authors is that CFTR is present in human skeletal muscle and that dysfunctional CFTR in human skeletal muscle has measurable pathophysiology. Specifically, the authors studied CFTR expression in human skeletal muscle by Western blot with anti-CFTR antibody L12B4, and demonstrated a single band with a molecular weight of 168 kDa. They then isolated the cDNA by RT-PCR and directly sequenced a 975bp segment that was identical to the human CFTR sequence. The cellular distribution of CFTR was localized to the sarcoplasmic reticulum, sarcotubular network, and sarcolemma. The investigators demonstrated staining of CFTR in the sarcolemma and sarcoplasm with the use of immunofluorescence microscopy. In a final set of experiments, the authors reported that they were able to activate CFTR chloride channels of wild-type isolated muscle fibers but were unable to do so in mutant F508del-CFTR muscle. These data in aggregate suggest a functional role of CFTR in the regulation of human skeletal muscle contraction.

The results of this study provide evidence for the expression of functional CFTR chloride channels in human skeletal muscle, with strong expression in the sarcotubular network. The authors speculate that CFTR dysfunction in skeletal muscle interferes with calcium regulatory channels or calcium adenosine triphosphatases (ATPases), which may contribute to the skeletal muscle weakness and exercise intolerance reported among patients with CF. Most importantly, the studies reported in this paper provide a mechanistic and metabolic rationale
METABOLIC PATHOPHYSIOLOGY OF SKELETAL MUSCLE DYSFUNCTION IN ADOLESCENTS WITH CYSTIC FIBROSIS


The objective of this study was to identify and quantify muscle metabolic abnormalities in patients with CF compared with a respiratory disease control group with similar patterns of inflammation, infection, and bronchiectasis (primary ciliary dyskinesia [PCD]) and matched healthy control (HC) participants. The authors sought to differentiate the specific impact of CF on muscle metabolism from inflammatory factors associated with lung disease in general. The researchers used $^{31}$P-magnetic resonance spectroscopy ($^{31}$P-MRS) to assess muscle metabolism in vivo, and to evaluate the function of creatine kinase, oxidative phosphorylation, and anaerobic glycolysis pathways during exercise and recovery. The use of $^{31}$P-MRS, in conjunction with specifically designed exercise protocols, allowed for the noninvasive analysis of skeletal muscle metabolism in patients with CF.

The results suggested abnormalities in muscle bioenergetics both during rest (lower resting adenosine triphosphate [ATP] concentrations) and during short bouts of high-intensity exercise (higher end-exercise pH values) in patients with CF that are not observed in respiratory disease controls and in matched HCs. Since ATP is the primary energy source for muscle contraction, lower resting ATP levels might be indicative of a lower energy reserve available for exercise. Alternatively, low resting ATP levels might mean that ATP is being used at a higher rate at rest in patients with CF compared with HCs. Higher end-exercise pH could be interpreted as an impaired glycolytic capacity in the muscle. Both CF and PCD patients demonstrated delayed postexercise phosphocreatine recovery times compared with HCs, suggesting a nonspecific effect of respiratory disease on mitochondrial function.

In this research, the authors discuss the mechanistic pathophysiology of CF as it relates to skeletal muscle function in vivo. They described differences in resting energy levels, as well as in the metabolic pathways that provide energy during exercise. It appears as if some of these differences may be primary to the CF disease process itself. This is the first research paper that describes the intramuscular mechanisms of exercise intolerance in patients with CF. The results provide a rationale for the use of exercise therapies in this population, as physical activity and exercise have been shown to improve resting energy stores, as well as aerobic and anaerobic energy metabolism, in both healthy individuals and in patients with CF.
however, a dearth of longitudinal data are available on the assessment of VO2peak in children. Pianosi and colleagues claim that longitudinal tracking of VO2peak might be of interest, as it may offer some insight into understanding the relationship between fitness and survival in patients with CF. In the current study, the authors sought to analyze VO2peak data and mortality over a 10-year period to determine if VO2peak is a good predictor of mortality and, if so, if the rate of change in VO2peak or the VO2peak level is the more important variable. To this end, the research team performed annual spirometry per standard protocols, as well as exercise testing and tracking of disease outcomes (mortality or lung transplantation). Lung transplantation was interpreted as an endpoint, as the patients would not have survived without the procedure. VO2peak was determined using a standard incremental step exercise protocol. Statistical analyses were performed to evaluate the influence of VO2peak and FEV1 on mortality.

Pulmonary function in the study population ranged from normal to severe airway obstruction. The overall decline in FEV1 during the study period averaged 2.5% predicted. Similarly, the statistical model demonstrated that VO2peak decreased 0.17 mL/min/kg per month. In both cases, the analysis showed that the rate of decline was more rapid in children who were older. For FEV1, either a low initial FEV1 with little change thereafter or a high FEV1 with a significant rate of decline were both associated with mortality. The same pattern was apparent for VO2peak.

The longitudinal analysis reported herein confirmed earlier findings that VO2peak is a prognostic indicator of outcome in children with CF.1 In the current research, patients in the lower tertile had a mortality rate of 60% in the subsequent 8 years. The statistical analysis showed that the effects of FEV1 and VO2peak on survival were of similar magnitude, although consideration of initial values and rates of decline supported the superiority of FEV1 as a prognostic indicator. This study provides clear evidence for the value of physical fitness, participation in physical activities and regular exercise, in patients with CF. Further, establishing a foundation of aerobic fitness as early as possible may also be important, as the prognostic value of VO2peak became more apparent when a patient's rate of lung function decline increased. The authors even hypothesized that patients with similar degrees of lung disease, as estimated by FEV1, have different prospects for survival depending on their VO2peak. Exercise testing delivers a comprehensive functional assessment of cardiovascular capacity, and is influenced by age, lean body mass, gender, genetics, and subjective effort. As such, exercise assessments may provide the clinician with valuable information on the overall health and function of their patients, and can be considered in light of specific pulmonary assessments as part of the clinical monitoring of patients with CF.


LONG-TERM EFFECTS OF TRAINING PROGRAMS FOR PATIENTS WITH CYSTIC FIBROSIS


(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)

View journal abstract  View full article

Studies investigating the effects of exercise programs in children and adults with CF have shown an increase in exercise capacity, a sustainment or increase in lung function, and enhanced QOL. Supervised and home-based programs have been studied, with both proving effective in improving the exercise capacity and health status of the participants. The primary objective of this study was to determine the effects of a home-based, partially supervised conditioning program on exercise capacity 12 to 18 months after the intervention program had ended. The variables of interest included VO2peak, maximal work rate, physical activity levels
The variables of interest included VO\textsubscript{2peak}, maximal work rate, physical activity levels (assessed by accelerometry), pulmonary function (spirometry), and QOL (questionnaire). Participants were assessed at 3, 6, 12, 18, and 24 months. The participants in the intervention group were counseled and supported to increase their exercise and physical activity by a minimum of 3 x 60 minutes per week for the first 6 months of the study. Participants elected to engage in endurance-type sports, ball games, and/or strength training exercises, per personal preference. After the first 6 months, participants were counseled to maintain or increase their physical activity. Those in the control group were asked to maintain their current activity levels for the same period of time (12 months). During the second year of the study, all participants were free to change their physical activity behavior as they chose.

The intervention group increased their physical activity participation by 2.16 hours per week, of which about 1 hour was vigorous exercise. Participants in the intervention group had an increase in VO\textsubscript{2peak} at 6 months, as well as during the open follow-up period at 12 to 18 months. Throughout the study, physical activity levels in the intervention group were significantly higher than in the control group. For pulmonary function, only forced vital capacity (FVC) was significantly higher (6%) in the intervention group compared with the control group (P<.05).

The primary finding of this study was that the positive health effects of a 6-month, home-based, partially supervised conditioning program can be observed for up to 12 months or longer after the end of the intervention. Beneficial effects were noted in terms of exercise capacity, physical activity participation, and FVC, all of which are relevant and important determinants of health in patients with CF.

ANAEROBIC TRAINING IN CHILDREN WITH CYSTIC FIBROSIS


(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)

Regular aerobic exercise has positive effects on the aerobic capacity of patients with CF, and has also been associated with prolonged survival and enhanced QOL. To date, limited research has focused on the effects of anaerobic fitness in the CF population. This is disappointing, as children's natural pattern of play is characterized by short bursts of intense activity interspersed with periods of low-intensity exercise or even rest. Therefore, anaerobic training programs may be highly suitable for children with CF. Further, children with CF have been shown to have reduced anaerobic performance. The aim of this research was to investigate the effects of an anaerobic training program on exercise performance, lung function, and QOL in children with CF.

Participants were assessed at baseline, within 7 days after completing a 12-week supervised training program, and once again after a 12-week period in which the children were able to participate in physical activity as they wished. Measurements included anthropometry, pulmonary function, anaerobic exercise performance using the traditional 30-second Wingate cycling test, and aerobic performance using a standard incremental ramp protocol. The anaerobic training program consisted of a 30- to 45-minute training session that was performed 2 times per week for 12 weeks (the program can be downloaded at http://www.chestjournal.org/cgi/content/full/125/4/1299/DC1).

Perhaps the most interesting result of this study was the fact that adherence to the training program was 98%. This is an excellent rate for a training intervention study. Pulmonary function was unchanged in both the intervention and control groups, although the training group demonstrated significant improvements in both aerobic (+5.7% predicted, P<0.05) and absolute anaerobic (+11% to +12%, P<0.001) exercise performance. QOL in the physical functioning domain, as assessed by questionnaire, was improved in the training group only. Anaerobic performance and markers of QOL, but not aerobic fitness, remained elevated during the follow-up period.
These results demonstrate that children with CF can improve their aerobic and anaerobic exercise capabilities, as well as their perception of physical functioning, in as few as two 30-minute anaerobic training sessions per week. The authors suggest that anaerobic training programs may have higher rates of participation and compliance, as anaerobic exercise is similar to the nature of children’s play. Interestingly, anaerobic function and perceived QOL remained elevated up to 12 weeks after completion of the formal training program. It is also interesting to note that the anaerobic training program had a positive effect on aerobic capacity as well. Unfortunately, an improvement in pulmonary function was not observed in the training group. The direct effects of training programs on pulmonary function in patients with CF remain equivocal, with some studies demonstrating positive effects and others showing no improvement. To date, no studies have demonstrated adverse effects from exercise on pulmonary function in patients with mild to moderate CF.