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Skeletal Muscle Oxidative Capacity in Patients with Cystic Fibrosis

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Abstract

Introduction—Exercise intolerance predicts mortality in patients with cystic fibrosis (CF); however, the mechanisms have yet to be fully elucidated. Using near infrared spectroscopy (NIRS), this study compared skeletal muscle oxidative capacity in patients with CF to healthy controls.

Methods—Thirteen patients and 16 demographically-matched controls participated in this study. NIRS was utilized to measure the recovery rate of oxygen consumption (musVO_2max) of the vastus lateralis muscle after 15 s of electrical stimulation (4 Hz) and subsequent repeated transient arterial occlusions.

Results— musVO_2max was reduced in patients with CF ($1.82 \pm 0.4 \text{ min}^{-1}$) compared to controls ($2.13 \pm 0.5 \text{ min}^{-1}$, $p = 0.04$). A significant inverse relationship between age and musVO_2max was observed in patients ($r = -0.676$, $p = 0.011$), but not controls ($r = -0.291$, $p = 0.274$).

Discussion—Patients with CF exhibit a reduction in skeletal muscle oxidative capacity compared to controls. It appears as the reduced skeletal muscle oxidative capacity is accelerated by age and could likely contribute to exercise intolerance in patients with CF.

Keywords

cystic fibrosis; near-infrared spectroscopy; skeletal muscle oxidative metabolism; mitochondria

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Introduction

Cystic fibrosis (CF) is a genetic disease that affects multiple organ systems. There is currently no cure for CF, so increasing longevity and enhancing quality of life are important clinical goals (Williams *et al.*, 2014). Exercise is a recommended tool that can be used to achieve these goals (Schneiderman *et al.*, 2014). Exercise capacity has clinical appeal as a marker of health because VO_2 peak has also been shown to predict mortality in patients with CF (Nixon *et al.*, 1992). A common phenotype observed in CF is exercise intolerance (reduced VO_2 peak) (Pianosi *et al.*, 2005) and this occurs even in patients with normal lung function (FEV_1). Thus, there is a growing interest in understanding physiological responses to exercise in patients with CF.

Investigations of exercise intolerance have contributed to increased interest in the understanding the pathophysiology of the musculature. Patients with CF have been reported to have intrinsic skeletal muscle defects (Lamhonwah *et al.*, 2010). Excessive muscle weakness is prevalent in patients with CF, thought to be caused by factors other than physical activity status (Troosters *et al.*, 2009). Reductions in muscle force and strength, as well as differences in metabolism in female athletes have also been reported (Selvadurai *et al.*, 2003). In addition, using culture studies, there has been a report of mitochondrial defects in patients with CF (Shapiro, 1989). Another study reported a reduction in mitochondrial function using the recovery rate of phosphocreatine (PCr) measured by ^{31}P -MRS (Wells *et al.*, 2011).

Near-infrared spectroscopy (NIRS) offers a novel way to non-invasively assess skeletal muscle oxidative metabolism. NIRS has several advantages over MRS and muscle biopsies due to greater accessibility, lower cost, and the ability to conduct repeated measures with minimal burden to participants. NIRS has been used previously to measure skeletal muscle oxidative capacity in a variety of populations (Brizendine *et al.*, 2012; Erickson *et al.*, 2013; Ryan *et al.*, 2014), and findings have been shown to be similar to MRS (Ryan *et al.*, 2013). Accordingly, NIRS is a promising tool that can be applied to the CF population.

The purpose of the present study was to evaluate skeletal muscle oxidative capacity using NIRS in patients with CF. It was hypothesized that patients with CF would have reduced skeletal muscle oxidative capacity when compared to demographically-matched healthy controls.

Materials and Methods

Study Design and Participants

Employing a cross-sectional experimental design, skeletal muscle oxidative capacity was measured in 13 patients with CF (age range 7–42 years) and 16 demographically-matched controls (age range 7–59 years). Data from 7 matched controls have previously been published (Erickson *et al.*, 2013). Patients with CF were instructed to adhere to the timing of their daily treatments and come to the lab following their morning airway clearance technique and inhaled medicines. Additionally, lung function and exercise capacity was only determined in patients with CF due to the experimental scope of this investigation. All NIRS

testing and analyses were performed by the same investigator. Testing occurred in the Laboratory of Integrative Vascular and Exercise Physiology at Georgia Regents University and the Exercise Muscle Physiology Laboratory at the University of Georgia.

Ethical Approval—All study protocols conformed to the Declaration of Helsinki and were approved by the Human Assurance Committee at Georgia Regents University or by the Institutional Review Board at the University of Georgia. Written and verbal assent/consent was obtained from all subjects and parents prior to participation in this study.

Experimental Procedures

Skeletal Muscle Oxidative Capacity—Near infrared spectroscopy (NIRS) was used to assess skeletal muscle oxidative capacity as previously described (Ryan *et al.*, 2012). Both hemoglobin and myoglobin chromophores contribute to changes in the NIRS signals (Lutjemeier *et al.*, 2008). Accordingly, the NIRS technique assumes that the signal changes are proportional to mitochondrial oxygen consumption due to relative changes in hemoglobin and myoglobin. NIRS testing was performed with the PORTAMON device (Artinis Medical Systems, The Netherlands), which is a portable, continuous wave NIRS device. The PORTAMON consists of 3 channels with separation distances consisting of 30, 35 and 40 mm. B-mode ultrasound imaging (LOGIQ 7; GE HealthCare, USA) was used to measure adipose tissue thickness (ATT) at the site of NIRS assessments to ensure that NIRS penetration depth was deep enough to reach active skeletal muscle.

Three consecutive recovery kinetics tests were conducted on the vastus lateralis with approximately 15 seconds between each test. A rate constant (noted as $\text{musVO}_{2\text{max}}$) was calculated and the mean of all three tests was reported. For each recovery kinetics test, resting muscle metabolic rate was measured using three resting arterial occlusions (10 seconds in duration). The average of all three occlusions was reported. Figure 1 illustrates a representative tracing of an oxygen recovery kinetics test in a patient with CF. Metabolic rate of the muscle was increased using 15 seconds of continuous electrical stimulation (4 Hz, highest tolerable current, pulse duration/interval = 200/50 μs), which has been used previously to activate mitochondrial oxygen consumption (Walter *et al.*, 1997; McCully *et al.*, 2011; Ryan *et al.*, 2012). It is important to note that the $\text{musVO}_{2\text{max}}$ is not dependent on frequency of electrical stimulation (Ryan *et al.*, 2012). Immediately after electrical stimulation, repeated short duration arterial occlusions were used to assess changes in metabolic rate. The initial 1–4 arterial occlusions were 5 seconds in duration followed by 5 seconds of rest. The subsequent 5–6 occlusions were 10 seconds in duration followed by 10 seconds of rest, and the remaining 7–15 occlusions were 10 seconds in duration followed by 20 seconds of rest. NIRS signals were corrected for blood volume shifts as previously described (Ryan *et al.*, 2012). The rate of oxygen consumption during each arterial occlusion was calculated by linear regression and the slope of this line was assumed to represent muscle oxygen consumption (mVO_2). Slopes from each measurement of mVO_2 were fit to an exponential curve and time constants were calculated using the following equation:

$$y = \text{End} - \text{Delta} \times e^{-1/Tc}$$

For this equation, y represents relative mVO_2 during the arterial occlusion, End is the mVO_2 immediately after electrical stimulation, Δ is the change in mVO_2 from rest to end exercise, and Tc is the fitting time constant. Matlab v. 7.13.0.564 (The Mathworks, Natick, MA) was used to analyze all the NIRS signals. Once determined, time constants were converted to rate constants to represent skeletal muscle oxidative capacity using the following equation:

$$k = (1/Tc) \times 60$$

For this equation, k represents rate constant and Tc represents the time constant calculated from the exponential curve. A higher rate constant (k) is proportional to better muscle oxidative capacity and is reported here as $musVO_{2max}$, analogous to V_{max} reported for phosphocreatine rate constants (McCully *et al.*, 2003). Conversely, a higher time constant (Tc) is inversely proportional to muscle oxidative capacity. Data are reported as both $musVO_{2max}$ and time constants for convenience.

For measurements of resting metabolic rate, a physiological calibration was used to normalize the NIRS signal for each subject's complete NIRS test. This involved electrically stimulating the vastus lateralis for 15 seconds followed by a long (3–5 minutes) arterial cuff occlusion at 250–280 mmHg of pressure. Minimum oxygen levels during the long arterial cuff occlusion and maximum oxygen levels during reactive hyperemia following cuff release were determined and NIRS values obtained during each kinetics test were scaled within this range.

Exercise Testing—All patients with CF performed a maximal exercise test using the Godfrey protocol on an electronically braked cycle ergometer (Lode Corival or Lode Corival Pediatric, Groningen, Netherlands), which maintains work rate (watts) independent of revolutions per minute. After a 1 minute unloaded warm-up, exercise intensity started to increase 15–20 watts depending on the height of the patient (S., 1974). Expired gases were analyzed breath by breath by a TruOne® 2400 metabolic cart (ParvoMedics, Sandy, UT) and analyzed as 30 second averages. In addition to reporting oxygen consumption controlling for body mass (kg), VO_2 was normalized to fat-free mass (kg-FFM), which helps adjust for nutritional status in patients with CF (Gulmans *et al.*, 1997). Peak oxygen consumption (VO_{2max}) was verified using the American College of Sports Medicine exercise testing criteria (ACSM, 2005): 1) volitional fatigue (> 17 on RPE), 2) a plateau in oxygen uptake, 3) achieving 85% of predicted heart rate max, and 4) a respiratory exchange ratio (RER) greater than 1.1. A test was considered maximal effort if the patient met 3 out of the 4 following criteria. Tests that met less than 3 of the criteria were considered to be peak tests.

Pulmonary Function Test—A pulmonary function test (PFT) using closed circuit spirometry (ParvoMedics, Sandy, UT) was performed in all patients with CF according to the American Thoracic Society standards (American Thoracic Society, 1995). Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and forced expiratory flow (FEF_{25-75}) were determined. The national health and nutrition examination survey

(NHANES) III spirometric reference standards were used to determine the % predicted data set.

Statistical Analysis

All analyses were performed using SPSS, version 19.0 (IBM, Armonk, NY). Data are presented as means $\pm$ SD unless otherwise noted. $\text{musVO}_{2\text{max}}$ were compared between CF patients and healthy controls using a Student's unpaired *t*-test. Regression and partial correlation analyses were performed to identify relationships among $\text{musVO}_{2\text{max}}$, lung function, and exercise capacity. Significance was accepted when $p < 0.05$.

Results

Subject Characteristics

Characteristics of patients and controls are presented in Table 1. No differences in age (yrs), sex (m/f), height (cm), weight (kg), or BMI (kg/m^2) were observed between patients and controls (all $p > 0.05$). The range in age was similar between patients with CF (7–42 years) and controls (7–59 years). In addition, vastus lateralis ATT was similar ($p = 0.528$) between patients and controls.

Skeletal Muscle Oxidative Capacity measured with NIRS

Resting skeletal muscle oxygen consumption was similar between groups (CF: $-0.60 \pm 0.3 \text{ min}^{-1}$ vs. control: $-0.57 \pm 0.59 \text{ min}^{-1}$, $p = 0.422$). Figure 2 displays $\text{musVO}_{2\text{max}}$ calculated from the recovery of oxygen consumption for patients with CF and controls. The $\text{musVO}_{2\text{max}}$ was significantly lower in patients with CF compared to controls ($1.8 \pm 0.4 \text{ min}^{-1}$ vs. $2.1 \pm 0.5 \text{ min}^{-1}$, respectively, $p = 0.04$). $\text{musVO}_{2\text{max}}$ is proportional to skeletal muscle oxidative capacity and time constants are inversely proportional to oxidative capacity. For convenience, values expressed as time constants are as follows: CF: $35.2 \pm 8.0 \text{ sec}$ vs. control: $29.9 \pm 7.7 \text{ sec}$, $p = 0.04$.

Pulmonary Function and Exercise Testing

Pulmonary function and VO_2 peak were only determined in patients with CF. Values for spirometric lung function in patients were: FVC ($3.27 \pm 0.95 \text{ L}$), FEV_1 ($2.40 \pm 0.74 \text{ L}$), FEV_1 ($84.6 \pm 22.1 \%$ predicted, range 54 – 123% predicted), FEV_1/FVC ($73.5 \pm 9.1 \%$), FEF_{25-75} ($2.03 \pm 0.97 \text{ L/s}$). Because only 12 out of 13 patients achieved a true maximal test, values are expressed as VO_2 peak. Values for exercise testing in patients were: absolute VO_2 peak ($1.57 \pm 0.62 \text{ L/min}$), relative VO_2 peak ($30.6 \pm 6.5 \text{ ml/kg/min}$), normalized to FFM VO_2 peak ($43.3 \pm 6.6 \text{ ml/kg-FFM/min}$), $\text{VO}_2 \%$ predicted (78.2 ± 15.6), maximal heart rate ($166 \pm 14 \text{ bpm}$), and peak work rate ($115 \pm 49 \text{ watts}$).

Relationship between Skeletal Muscle Oxidative Capacity and Age

Combining patient and controls, $\text{musVO}_{2\text{max}}$ was significantly greater ($p = 0.021$) in young (2.22 ± 0.49 , ages 7–17 years; $n = 13$) compared to old (1.81 ± 0.42 , ages > 18 years; $n = 16$) participants. Figure 3 illustrates the relationship between $\text{musVO}_{2\text{max}}$ and age in patients with CF (panel A) and controls (panel B) separately. A significant inverse relationship

between $\text{musVO}_{2\text{max}}$ and age was observed in patients with CF ($r = -0.676$; $p = 0.011$); however, this same relationship was absent in controls ($r = -0.291$; $p = 0.274$).

Relationships between Skeletal Muscle Oxidative Capacity, Lung Function, and VO_2 Peak in CF

There was an inverse relationship between FVC (L) and $\text{musVO}_{2\text{max}}$ ($r = -0.671$; $p = 0.012$). The statistical value for the relationship between FEV_1 (L) and $\text{musVO}_{2\text{max}}$ was $r = -0.545$; $p = 0.054$. There was no relationship between $\text{musVO}_{2\text{max}}$ and FEV_1 % predicted ($r = 0.018$; $p = 0.953$) observed in patients with CF. The partial correlation between $\text{musVO}_{2\text{max}}$ and VO_2 peak normalized for fat-free mass (ml/kg-FFM/min) when controlling for age and sex was $r = 0.602$; $p = 0.05$.

Discussion

In this study, we identified that patients with CF exhibit an impairment in skeletal muscle oxidative capacity, measured with NIRS, compared to demographically-matched controls. In addition, a significant inverse relationship between skeletal muscle oxidative capacity and age was observed in patients, but not in controls, indicating that muscle impairment may be accelerated by age in patients with CF. Exercise plays an important role in the assessment and treatment of patients with CF (Williams *et al.*, 2014). Exercise intolerance that is observed in patients with CF has led to an increased interest in the pathophysiology of the musculature and there are limited data to support skeletal muscle abnormalities in CF (Shapiro, 1989; Selvadurai *et al.*, 2003; Lamhonwah *et al.*, 2010).

Skeletal Muscle Oxidative Capacity in patients with CF

Near infrared spectroscopy (NIRS) is a non-invasive tool that has been utilized by our group and others to evaluate skeletal muscle oxidative capacity, an index of mitochondrial function, in different groups and patient cohorts (Brizendine *et al.*, 2012; Erickson *et al.*, 2013; Ryan *et al.*, 2014). To our knowledge, this is the first study to document a deficit in skeletal muscle oxidative capacity, using NIRS, in patients with CF compared to controls (Figure 2). Findings from the current study have identified a 15% reduction in skeletal muscle oxidative capacity in patients with CF compared to healthy demographically-matched controls. The deficit we have observed using the NIRS methodology is similar to findings of a previous report of skeletal muscle metabolism in adolescents with CF (Wells *et al.*, 2011). Utilizing the rate of phosphocreatine re-synthesis after exercise, Wells and colleagues documented a 19% lower mitochondrial capacity in patients with CF compared to controls (Wells *et al.*, 2011). Although mean lung function appears to be preserved in patients, the range in FEV_1 was between 54 and 123 % predicted. We did not observe a relationship between FEV_1 (% predicted) and $\text{musVO}_{2\text{max}}$ ($r = 0.018$; $p = 0.953$) which suggests that skeletal muscle oxidative capacity may be impaired even in patients with the highest lung function. Nonetheless, due to the relatively small sample sizes of the two studies, additional investigations with larger patient cohorts are needed to further classify the magnitude of deficit of skeletal muscle oxidative exhibited in patients with CF.

The present study identified a deficit in skeletal muscle oxidative capacity in patients with CF. Lung function was not assessed in controls; however, it is unlikely that any undiagnosed lung pathophysiology was present in our healthy comparator group. All controls reported to be apparently healthy and free of any overt cardiovascular, pulmonary, or metabolic disease. The advantage of using the NIRS method for measuring skeletal muscle oxidative capacity, however, is that it does provide a quantifiable measure of *in vivo* muscle oxidative capacity that is not confounded by prior bouts of maximal exercise. In addition, the NIRS method compared to ^{31}P -magnetic resonance spectroscopy is inexpensive, non-invasive, and can be repeated as often as necessary to investigate changes in muscle oxidative capacity over time (Wolf *et al.*, 2007; Hamaoka *et al.*, 2011; Ryan *et al.*, 2013). It is important to accept that NIRS measurements of oxidative capacity cannot distinguish between a lower mitochondrial number and/or a decline in mitochondrial function. In addition, we have chosen to present the NIRS measurements as skeletal muscle oxidative capacity rather than skeletal muscle mitochondrial capacity to include the possibility that factors outside of mitochondria (such as intramuscular oxygen diffusion rates) may influence results. Thus, these data should be interpreted as an index of intact whole-tissue oxidative capacity. Further investigation of mitochondrial site-specific defects or impairments would require a more invasive technique. Use of the NIRS method is limited to investigation of limb muscles due to the methodological involvement of arterial occlusion. Additionally, excessive adipose tissue thickness (> 2 cm) will impede NIRS light penetration which limits this method to non-obese populations. Nonetheless, it is reasonable to suspect that the localization of cystic fibrosis transmembrane conductance regulator (CFTR) on the skeletal muscle (Fiedler *et al.*, 1992) is contributing to impaired muscle oxidative capacity in CF, although future studies are warranted to investigate this phenomenon.

Age Associated Changes in Skeletal Muscle Oxidative Capacity

A notable strength of the current study was the use of a cross-sectional approach to evaluate the impact that age has on skeletal muscle oxidative capacity in patients with CF. Age in CF is typically associated with disease severity and therefore represents another potential factor that may contribute to the skeletal muscle oxidative capacity deficit we observed in patients with CF. In the present study, no relationship between NIRS and FEV_1 % predicted was observed, likely due to relatively healthy cohort of patients and the preserved spirometric function. Additionally, the present study identified a significant inverse relationship between skeletal muscle oxidative capacity and age in the patients with CF that was not observed in the controls (Figure 3). The control participants were selected to match the patients with CF, and therefore, it is plausible that a significant relationship in controls would have been observed in a cohort that included more older participants (i.e. between 50–70 yrs). Moreover, it is likely that the significantly lower rate constant that was observed in older (1.81 ± 0.42 , ages > 18) compared to younger subjects (2.22 ± 0.49 , ages 7–17 years) overall was primarily driven by patients with CF. These data indicate that patients with CF experience an approximate 2.5% decline in skeletal muscle oxidative capacity per year that is not evident in healthy controls. To our knowledge, this is the first study to report an age-related decline in skeletal muscle oxidative capacity in CF. These data suggest that future investigations of skeletal muscle oxidative capacity should take age into account.

VO₂ peak drops 5–8% each year (Pianosi *et al.*, 2005) in CF so it is possible that the age-associated decline in muscle oxidative capacity in CF contributes to the accelerated decline in VO₂ peak. Controlling for age and sex, we observed an almost significant relationship ($r = 0.602$; $p = 0.05$) between VO₂ peak and skeletal muscle oxidative capacity (musVO_{2max}). However, the patient cohort tested in this study was relatively healthy, as evidenced by their lung function. It is possible that a stronger relationship between VO₂ peak and skeletal muscle oxidative capacity may be seen in CF patient cohorts with increased disease severity. Longitudinal studies will be needed to further document patient-specific temporal changes and determine what additional factors contribute to the age-related reductions in skeletal muscle oxidative capacity and VO₂ peak.

In conclusion, this is the first study that utilized NIRS to conduct a noninvasive recovery kinetics test for evaluation of skeletal muscle oxidative capacity in patients with CF. Findings from this study indicate that patients with CF exhibit a deficit in skeletal muscle oxidative capacity compared to demographically-matched controls. Based on the present data we propose that patients with CF experience an age-related reduction in skeletal muscle oxidative capacity. This may, in part, contribute to exercise intolerance in patients with CF. However, future research is needed to provide mechanistic insight into the impairment of skeletal muscle oxidative capacity and exercise capacity in CF.

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References

- ACSM. ACSM's guidelines for exercise testing and prescription. Vol. 6. Lippincott Williams and Wilkins; New York: 2005.
- American Thoracic Society. Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med*. 1995; 152:1107–1136. [PubMed: 7663792]
- Brizendine JT, Ryan TE, Larson RD, McCully KK. Skeletal Muscle Metabolism in Endurance Athletes with Near-Infrared Spectroscopy. *Med Sci Sports Exerc*. 2012; 14:14.
- Erickson ML, Ryan TE, Young HJ, McCully KK. Near-infrared assessments of skeletal muscle oxidative capacity in persons with spinal cord injury. *Eur J Appl Physiol*. 2013; 113:2275–2283. [PubMed: 23703066]
- Fiedler MA, Nemecz ZK, Shull GE. Cloning and sequence analysis of rat cystic fibrosis transmembrane conductance regulator. *Am J Physiol*. 1992; 262:L779–784. [PubMed: 1377454]
- Gulmans VA, de Meer K, Brackel HJ, Helden PJ. Maximal work capacity in relation to nutritional status in children with cystic fibrosis. *Eur Respir J*. 1997; 10:2014–2017. [PubMed: 9311494]
- Hamaoka T, McCully KK, Niwayama M, Chance B. The use of muscle near-infrared spectroscopy in sport, health and medical sciences: recent developments. *Philos Transact A Math Phys Eng Sci*. 2011; 369:4591–4604.
- Lamhonwah AM, Bear CE, Huan LJ, Kim Chiaw P, Ackerley CA, Tein I. Cystic fibrosis transmembrane conductance regulator in human muscle: Dysfunction causes abnormal metabolic recovery in exercise. *Ann Neurol*. 2010; 67:802–808. [PubMed: 20517942]

- Lutjemeier BJ, Ferreira LF, Poole DC, Townsend D, Barstow TJ. Muscle microvascular hemoglobin concentration and oxygenation within the contraction-relaxation cycle. *Respir Physiol Neurobiol*. 2008; 160:131–138. [PubMed: 17964228]
- McCully KK, Mulcahy TK, Ryan TE, Zhao Q. Skeletal muscle metabolism in individuals with spinal cord injury. *Journal of Applied Physiology*. 2011; 111:143–148. [PubMed: 21512153]
- McCully KK, Smith S, Rajaei S, Leigh JS Jr, Natelson BH. Blood flow and muscle metabolism in chronic fatigue syndrome. *Clin Sci (Lond)*. 2003; 104:641–647. [PubMed: 12589704]
- Nixon PA, Orenstein DM, Kelsey SF, Doershuk CF. The prognostic value of exercise testing in patients with cystic fibrosis. *N Engl J Med*. 1992; 327:1785–1788. [PubMed: 1435933]
- Pianosi P, LeBlanc J, Almudevar A. Peak oxygen uptake and mortality in children with cystic fibrosis. *Thorax*. 2005; 60:50–54. [PubMed: 15618583]
- Ryan TE, Erickson ML, Brizendine JT, Young HJ, McCully KK. Noninvasive evaluation of skeletal muscle mitochondrial capacity with near-infrared spectroscopy: Correcting for blood volume changes. *J Appl Physiol*. 2012
- Ryan TE, Erickson ML, Verma A, Chavez J, Rivner MH, McCully KK. Skeletal muscle oxidative capacity in amyotrophic lateral sclerosis. *Muscle Nerve*. 2014
- Ryan TE, Southern WM, Reynolds MA, McCully KK. A cross-validation of near-infrared spectroscopy measurements of skeletal muscle oxidative capacity with phosphorus magnetic resonance spectroscopy. *J Appl Physiol* (1985). 2013; 115:1757–1766. [PubMed: 24136110]
- SG. Exercise Testing in Children. London: W.B. Saunders Company Ltd; 1974. p. 1-168.
- Schneiderman JE, Wilkes DL, Atenafu EG, Nguyen T, Wells GD, Alarie N, Tullis E, Lands LC, Coates AL, Corey M, Ratjen F. Longitudinal relationship between physical activity and lung health in patients with cystic fibrosis. *Eur Respir J*. 2014; 43:817–823. [PubMed: 24176992]
- Selvadurai HC, Allen J, Sachinwalla T, Macauley J, Blimkie CJ, Van Asperen PP. Muscle function and resting energy expenditure in female athletes with cystic fibrosis. *Am J Respir Crit Care Med*. 2003; 168:1476–1480. [PubMed: 14500260]
- Shapiro BL. Evidence for a mitochondrial lesion in cystic fibrosis. *Life Sci*. 1989; 44:1327–1334. [PubMed: 2654530]
- Troosters T, Langer D, Vrijzen B, Segers J, Wouters K, Janssens W, Gosselink R, Decramer M, Dupont L. Skeletal muscle weakness, exercise tolerance and physical activity in adults with cystic fibrosis. *Eur Respir J*. 2009; 33:99–106. [PubMed: 18715878]
- Walter G, Vandenborne K, McCully KK, Leigh JS. Noninvasive measurement of phosphocreatine recovery kinetics in single human muscles. *Am J Physiol*. 1997; 272:C525–534. [PubMed: 9124295]
- Wells GD, Wilkes DL, Schneiderman JE, Rayner T, Elmi M, Selvadurai H, Dell SD, Noseworthy MD, Ratjen F, Tein I, Coates AL. Skeletal muscle metabolism in cystic fibrosis and primary ciliary dyskinesia. *Pediatr Res*. 2011; 69:40–45. [PubMed: 20938370]
- Williams CA, Saynor ZL, Tomlinson OW, Barker AR. Cystic fibrosis and physiological responses to exercise. *Expert Rev Respir Med*. 2014; 8:751–762. [PubMed: 25395018]
- Wolf M, Ferrari M, Quaresima V. Progress of near-infrared spectroscopy and topography for brain and muscle clinical applications. *J Biomed Opt*. 2007; 12:062104. [PubMed: 18163807]

New Findings

- What is the central question of the research study? Do patients with cystic fibrosis have reduced skeletal muscle oxidative capacity, measured with near infrared spectroscopy, compared to demographically-matched controls?
- What is the main finding and what is its importance? Patients with cystic fibrosis have impairments in skeletal muscle oxidative capacity. This Reduced skeletal muscle oxidative capacity not only appears to be accelerated by age, it may also contribute to exercise intolerance in patients with CF.

Figure 1.

Representative raw NIRS data during a single recovery kinetics test. Electrical stimulation (15 sec, 4 Hz) was used to increase muscle metabolic rate which was followed by a series of repeated arterial occlusion cuffs. The red signal represents oxyhemoglobin (O_2Hb), the blue signal represents deoxyhemoglobin (HHb), and the green signal represents total hemoglobin (tHb). Slopes of the NIRS signal during the repeated arterial occlusions were measured and fit to an exponential curve. Rate constants were calculated to represent skeletal muscle oxidative capacity.

Figure 2. Individual data and mean difference in $\text{musVO}_{2\text{max}}$ between patients with CF (CF) and healthy controls (HC). *Significant difference between groups.

Panel A: CF

Panel B: Controls

Figure 3.

Association between $\text{musVO}_{2\text{max}}$ and age in patients with CF (Panel A) and healthy controls (Panel B).

Table 1

Characteristics of Patients and Controls

	Cystic Fibrosis	Controls	p-value
N	13	16	
Age (yrs)	20.2 ± 11.2	21.6 ± 13	0.750
Sex (M/F)	6/7	7/9	0.901
Height (cm)	154.8 ± 15.5	160.4 ± 18.1	0.382
Weight (kg)	51.3 ± 15.9	54.6 ± 21.1	0.643
BMI (kg/m ²)	20.9 ± 3.3	20.4 ± 4.4	0.732
Adipose Tissue Thickness (cm)	0.72 ± 0.27	0.80 ± 0.30	0.528

Values are mean ± SD. BMI = body mass index.