Muscle Size and Cardiorespiratory Response to Exercise in Cystic Fibrosis

CHUANPIT MOSER, PORNCHAI TIRAKITSOONTORN, ELIEZER NUSSBAUM, ROBERT NEWCOMB, and DAN M. COOPER

Department of Pediatrics, University of California Irvine Medical Center, Irvine; and Division of Pediatric Pulmonology, Miller Children’s at Long Beach Memorial Medical Center, Long Beach, California

The mechanism responsible for diminished exercise performance in cystic fibrosis (CF) is not clear. We hypothesized that reduced muscle size, rather than an intrinsic muscle defect, was the primary factor in such diminished exercise performance. Twenty-two subjects with CF (14 females and eight males, aged 6.5 to 17.7 yr, with FEV \(_1\) of 46% to 111% predicted) participated in a study of this hypothesis, and were compared with healthy children tested in the same laboratory. Muscle size was estimated from midthigh muscle cross-sectional area (CSA) obtained by magnetic resonance imaging, and fitness was determined by progressive cycle ergometer exercise testing with breath-by-breath measurements of gas exchange. Peak oxygen consumption \(\dot{V}O_2\) was reduced in CF subjects (956 ± 81 [mean ± SEM] ml/min, as compared with 1,473 ± 54 ml/min in controls; \(p < 0.00001\)). Surprisingly, CF subjects had a lower peak \(\dot{V}O_2\) per CSA (mean for CF subjects 70 ± 3% predicted, \(p < 0.0001\)) than did controls, whereas muscle CSA in CF subjects was not significantly smaller than in controls. The scaling parameters of peak \(\dot{V}O_2\) and muscle CSA did not differ significantly between healthy controls (0.80 ± 0.16) and CF subjects (1.03 ± 0.12). Indexes of aerobic function that are less effort-dependent \(\dot{V}O_2\) and work rate \(\dot{W}\) (\(\dot{V}O_2\)/\(\dot{W}\)) were also lower in the CF subjects (e.g., the slope of \(\dot{V}O_2\) versus work rate [\(\dot{W}\)] \((\Delta\dot{V}O_2/\Delta\dot{W})\) was 68 ± 2% predicted; \(p < 0.005\)). The study data did not support the initial hypothesis, and suggest a muscle-related abnormality in oxygen metabolism in patients with CF.

Children and adolescents with cystic fibrosis (CF) are known to have reduced exercise tolerance, but despite this there appear to be therapeutic benefits of exercise in these subjects. Indeed, more fit CF patients may have improved outcomes (1). The precise mechanism of the exercise impairment in CF remains largely unknown, but nutritional and cardiorespiratory factors clearly play a role in it (2). In the study reported here we focused on structure–function interactions during exercise in CF as a means to determine the extent to which muscle function and gas transport may contribute to the overall exercise impairment in this disease.

In previous studies in healthy children, we used cross-sectional magnetic resonance imaging (MRI) of muscle, along with measurements of gas exchange during exercise, to gain insight into the process of muscle maturation in children (3). A similar approach was used in the present study to determine the relationship between muscle size and cardiorespiratory function in subjects with CF. We hypothesized that the exercise impairment in CF is primarily due to a reduced overall muscle mass rather than to an abnormality in muscle metabolism. The latter hypothesis was proposed by de Meer and coworkers, who published data suggesting abnormal oxidative phosphorylation in CF on the basis of \(^{31}\)P–magnetic resonance spectroscopy (4).

Specifically, we predicted that in CF subjects: (1) oxygen uptake \((\dot{V}O_2)\) would correlate with muscle mass in a manner similar to that observed in healthy children; (2) muscle is smaller per body size; and (3) the relationship between \(\dot{V}O_2\) and work rate \((\dot{W}; an indicator of muscle metabolic efficiency) is the same as in control subjects.

METHODS

Subjects

Twenty-two subjects (14 females and eight males) ranging in age from 6 to 18 yr and cared for at the Cystic Fibrosis Center of Miller Children’s at Long Beach Memorial Medical Center (a CF Foundation-accredited center) volunteered for the study (Table 1). All subjects had CF diagnosed according to acceptable criteria (sweat chloride greater than 60 mEq/L, two copies of the CF DNA mutation, and signs of pulmonary disease). All were outpatients and free of pulmonary exacerbations or concurrent illness. Patients with overt hyperglycemia or liver disease were excluded. The treatment regimen for the study subjects was consistent with current standards of care for CF. Informed consent and assent were obtained from each subject. The study was approved by the Institutional Review Boards of the University of California Irvine College of Medicine and the Long Beach Memorial Medical Center.

MRI

We chose to examine the musculature of the left thigh, since these muscles would be largely involved in the cycle ergometer exercise protocols used in the study. In this way, the metabolic response obtained could easily be related to the size of the working muscle. MRI was performed with a 1.5-Tesla, whole-body MRI system (General Electric, Schenectady, NY). A body coil was used for both signal detection and for radio frequency transmission for imaging. Each subject was positioned with the lower extremities at the isocenter of the magnet bore of the MRI scanner. Pilot-image coronal slices of the left thigh were obtained in order to select an image that included the distal femur. Twelve axial slices from above the knee to below the femoral neck were obtained. These axial slices were 20-mm thick, with no gap between them, and were obtained with a T1-weighted sequence with a time to echo of 12 ms and repetition time of 400 ms. The matrix was 192 × 256 pixels, with two acquisitions at each phase-encoding step.

The muscle cross-sectional area (CSA) was determined first, from the longitudinal image of the thigh. The midthigh region was measured, and the appropriate image was then used for subsequent analysis. Roman and colleagues (5) demonstrated the close relationship between MRI determination of muscle CSA and muscle volume. In the present study MRI was done before exercise testing in order to avoid the acute effect of exercise on muscle image. Images were digitized and scanned with commercially available software (SigmaScan; SPSS, Inc., Chicago, IL) to measure the midthigh muscle CSA.

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Correspondence and requests for reprints should be addressed to Dan Michael Cooper, M.D., Professor of Pediatrics, Clinical Research Center, Bldg. 25, ZOT 4094-03, 101 The City Drive, Orange, CA 92868. E-mail: dcooper@uci.edu

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is easily calculated with standard linear regression techniques. To determine the slope of the relationship between exercise variables (E) and carbon dioxide production (V\textsubscript{CO2}) during a progressive exercise test, standard linear regression analysis was used to calculate the slope of the E–V\textsubscript{CO2} relationship. The slope of the E–V\textsubscript{CO2} relationship has been previously published (11).

Normal Values

Exercise data from 54 healthy children (37 females and 17 males) who had been recently tested under the supervision of one of the authors (D.M.C.) were used to establish normal values for gas exchange relationships between E and CO\textsubscript{2} during a progressive exercise test on an electronically braked cycle ergometer (Vmax 229; SensorMedics, Yorba Linda, CA). The work rate was increased by 10 W/min, and each subject was instructed to exercise to the limit of his or her tolerance. Gas exchange was measured on a breath-by-breath basis (6), and Sa\textsubscript{O2} was measured continuously. This approach has been used extensively in children and adolescents (7).

In addition to peak VO\textsubscript{2}, we determined several dynamic variables indicative of the cardiorespiratory response to exercise, as previously done in our laboratory (8–10). Standard linear regression analysis was used to determine the slope of the relationship between (1) VO\textsubscript{2} and WR; (2) VO\textsubscript{2} and heart rate (HR); and (3) minute ventilation (VE) and carbon dioxide production (V\textsubscript{CO2}). An example of the data used to determine the slope of VE versus VCO\textsubscript{2} for a CF subject is shown in Figure 1.

Normal Values

Exercise data from 54 healthy children (37 females and 17 males) who had been recently tested under the supervision of one of the authors (D.M.C.) were used to establish normal values for gas exchange responses to exercise and CSA of the thigh musculature. The age range of the normal subjects was similar to that of the CF subjects. The MRI data from one group of these healthy children (adolescent females) has been previously published (11).

Table 1

| Age (yr) | Weight (kg) | Height (cm) | BMI (kg/cm\textsuperscript{2}) | % IBW |
|---------|-------------|-------------|---------------------------------|-------|
| Control (n = 54) | 9.3 ± 0.1 | 33.8 ± 1.2 | 137 ± 1 | 17.9 ± 0.5* | 103 ± 3 |
| CF (n = 22) | 10.3 ± 0.7 | 30.2 ± 2.4 | 134 ± 4 | 16.2 ± 0.5 | 99 ± 3 |

* Data are expressed as mean ± SEM (range).
† p < 0.05.

Table Definition of abbreviations: BMI = body mass index; CF = cystic fibrosis; IBW = ideal body weight.

Spirometry and Exercise Testing

Each subject underwent standard spirometry before exercise testing. To measure cardiorespiratory responses to exercise, we used a ramp-type progressive exercise test on an electronically braked cycle ergometer (Vmax 229; SensorMedics, Yorba Linda, CA). The work rate was increased by 10 W/min, and each subject was instructed to exercise to the limit of his or her tolerance. Gas exchange was measured on a breath-by-breath basis (6), and Sa\textsubscript{O2} was measured continuously. This approach has been used extensively in children and adolescents (7).

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Data Analysis

Data are presented as mean (with 95% confidence interval [CI]) and percent of predicted values. Two-tailed unpaired t tests were used to compare differences between the two study groups. Linear regression analysis was used to assess relationships between gas exchange parameters, midthigh muscle CSA, anthropometric data, and pulmonary function values. We also tested whether or not these regressions differed for the CF and control populations. This was done by determining whether an improvement in fit was obtained by fitting the two data sets with separate regression lines as compared with fitting them with a single regression line. Statistical significance was tested with the F test statistic (12).

In addition to linear regression analysis, we used allometric (or power function) approaches. Such an approach has gained widespread use in gauging the effect of size on metabolic function during growth (13, 14). Allometric equations have the general form

\[ q = a \cdot M^b \]

where q indicates a metabolic rate (e.g., VO\textsubscript{2}), M is a parameter related to body dimension (e.g., mass), a is the mass coefficient, and b is the dimensionless mass exponent or the scaling factor (15).

RESULTS

Peak Values

As expected, peak VO\textsubscript{2} was reduced in CF subjects both in terms of absolute levels (956 ± 81 [mean ± SEM] ml/min compared with 1,473 ± 54 ml/min in controls; p < 0.00001) and when peak VO\textsubscript{2} was normalized to body weight (Figure 2). A reduced peak or maximal VO\textsubscript{2} is commonly observed in the CF population. In contrast to the low peak VO\textsubscript{2}, peak HR and the respiratory exchange ratio (R) were comparable to those seen in controls (peak HR 170 ± 5 beats/min; R = 1.27 ± 0.03). Sa\textsubscript{O2} was 97.5 ± 0.4% before exercise, and was not influenced by exercise (97.0 ± 0.5%, after exercise, p = NS).

Relationship between VO\textsubscript{2}, Body Size, and Muscle CSA

The linear regression of VO\textsubscript{2} on muscle CSA in CF subjects and healthy controls is shown in Figure 3. In both groups, the correlation was significant (control group r = 0.57, p < 0.001; CF group r = 0.89, p < 0.001). However, CF subjects had a lower peak VO\textsubscript{2} at a given CSA (mean for CF subjects = 70 ± 3% predicted, p < 0.001). We found a statistically significant difference between the regression equations for the two groups (p < 0.05), most likely due to the y intercept (129 in the CF group versus 305 in the control group) rather than to the slope (16.9 in the CF group versus 16.2 in the control group). In accord with this, the peak VO\textsubscript{2}-to-CSA ratio (Figure 2) was significantly lower in the CF group versus the control group.
lower in the CF patients (14.8 ± 0.7 ml V\textsubscript{O2}/min/cm\textsuperscript{2}) than in the controls (20.6 ± 0.6 ml V\textsubscript{O2}/min/cm\textsuperscript{2}, p < 0.001).

**Height, Weight, and Muscle CSA**

There were no significant differences in height or weight between the CF subjects and controls (Table 1). Unlike the reduced ratio of peak V\textsubscript{O2} to muscle CSA, the ratio of muscle CSA to body weight did not differ between CF and control subjects (Figure 2). In addition, body mass index, a quantification of the relationship between height and weight, was significantly lower in the CF subjects, but we found no differences between CF and control subjects in ideal body weight (Table 1). Absolute muscle CSA and the ratio of muscle CSA to height were to a small but significant degree lower in the CF subjects (muscle CSA in the CF group: 64 ± 4 cm\textsuperscript{2}, versus the control group: 72 ± 2 cm\textsuperscript{2}; p < 0.05; CSA-to-height ratio in the CF group: 0.47 ± 0.02 cm, versus the control group: 0.53 ± 0.01 cm; p < 0.02). Further, muscle CSA in CF subjects was 91 ± 3% predicted (p < 0.02) based on height. Muscle CSA in CF subjects was 93 ± 3% predicted based on body weight, and this difference was not statistically significant.

**Dynamic Exercise Variables**

CF subjects had significantly different dynamic cardiorespiratory responses to progressive exercise. In CF subjects, the slope of V\textsubscript{O2} versus WR (\(\Delta V\text{O2}/\Delta WR\)) was 8.7 ± 0.26 ml/min/W, which was significantly lower than in controls (13.2 ± 0.22 ml/min/W, p < 0.001) (Figure 4). CF subjects had an average \(\Delta V\text{O2}/\Delta WR\) that was 68 ± 2% predicted. \(\Delta V\text{E}/\Delta V\text{CO2} \) was increased in CF subjects (36.8 ± 1.3, versus 23.4 ± 0.4 in controls, p < 0.001) (Figure 4). CF subjects had an average \(\Delta V\text{O2}/\Delta V\text{CO2} \) of 144 ± 5% predicted. In addition, \(\Delta V\text{O2}/\Delta HR\) in the CF subjects was 8.6 ± 0.7 ml O\textsubscript{2}/beat, which was 87 ± 3% predicted (p < 0.001). We found no significant correlations between variables reflecting exercise capacity (e.g., peak V\textsubscript{O2}) and measurements of lung function (e.g., FEV\textsubscript{1}, FVC), even when these were normalized to body size or expressed as percent predicted values. There was, however, a weak but significant correlation (r = 0.30, p < 0.018) between CSA/height and FVC % predicted.

**Scaling Factors**

The scaling factor b, relating peak V\textsubscript{O2} to CSA (V\textsubscript{O2peak} ∝ CSA\textsuperscript{b}), was 0.80 ± 0.16 (p < 0.001) in healthy controls, and was 1.03 ± 0.12 in CF subjects. These values did not significantly differ from each other or from the expected scaling factor of 1.0.

**DISCUSSION**

As expected, peak V\textsubscript{O2} both in absolute terms and when normalized to body weight, was low in CF subjects, but this could not be explained solely by a specific reduction in muscle size.

A novel finding of this study was that the reduction in peak V\textsubscript{O2} was observed even when this measure was normalized to muscle CSA, whereas muscle CSA was only slightly smaller in CF than in control subjects (Figures 2 and 3). Thus, reduced muscle mass alone could not account for all of the impairment of peak V\textsubscript{O2} observed in subjects with CF. These observations tended to disprove one of our key hypotheses, and they may indicate impaired oxygen delivery or intrinsic abnormality of muscle function during exercise in CF subjects.

A number of previous investigators have examined muscle function and strength in CF patients. Interestingly, respiratory muscles in these subjects seem “trained,” probably in response to the increased work of breathing associated with CF (16). A major confounding factor recognized by many of the investigators who have examined muscle function and strength in CF patients was that muscle size was probably altered in CF, which in and of itself would influence exercise performance (17). A variety of attempts have been made to appropriately normalize exercise function to some estimate of muscle size. Indeed, a major goal of our research effort was to directly measure muscle size in CF patients, rather than to rely on indirect approaches based on body height and weight.

Previous investigators have also examined the potential role of nutritional factors in determining exercise function in CF. Skeie and coworkers (18) reported that total parenteral nutrition led to increased ability to participate in activities of daily living and improved V\textsubscript{O2} during exercise in CF patients, and Hanning and associates (19) showed that skeletal muscle strength was a function of nutritional status in CF. Boucher and coworkers (20) showed that habitual physical activity was significantly correlated with nutritional status, and Boas and colleagues (21) found that nutritional factors accounted for 70% to 80% of the variability in anaerobic power in their CF patients. Shah and associates (2) similarly concluded that nutritional status rather than pulmonary function was the major determinant of anaerobic exercise capacity in CF.

Thus, an important finding in the present study was that the impairment in exercise V\textsubscript{O2} in CF patients occurred not only with highly effort-dependent measures of exercise such as peak V\textsubscript{O2}, for which the absolute muscle mass is critical, but also with dynamic exercise variables such as \(\Delta V\text{O2}/\Delta WR\) (Figure 4). The latter was determined from the slope of the regression of V\textsubscript{O2} on WR throughout the exercise test, and was not dependent on whether or not the subject achieved maximal levels of either variable. The physiologic meaning of a reduced oxygen cost of exercise in CF is not readily apparent. Indeed,
one interpretation might be that CF subjects had an increased work efficiency that permitted them to perform the work required during exercise by utilizing less oxygen than did healthy controls.

Alternatively, the oxygen cost of exercise may have been lower in CF subjects because anaerobic pathways contributed to energy metabolism throughout the exercise test to a greater extent in these subjects than in healthy controls. Indeed, the slope of the regression of VO2 on WR is known to be reduced in a number of conditions, such as certain congenital heart diseases (22), in which oxygen transport to muscle is reduced. In the present study, however, oxygen saturation in the CF patients was 97% before exercise, and did not change significantly during exercise. However, without direct measurements of arteriovenous oxygen content across the exercising muscle tissue, it is impossible to rule out abnormalities of oxygen delivery as a potential mechanism for reduced oxygen cost of exercise.

There is much interest in the mechanism of reduced oxygen cost of exercise in patients with chronic diseases, but no clear explanation for this reduction has emerged. Current explanations are varied and range from alterations in muscle fiber type to fundamental changes in adenosine triphosphate (ATP) metabolism in skeletal muscle (23). Whether the reduced oxygen cost of exercise in patients with chronic diseases occurs because of an adaptation of anaerobic muscle metabolic pathways is not yet known.

The hypothesis that the mechanism for the reduced oxygen cost of exercise in CF patients is related to intrinsic muscle function is supported by a number of studies. Kusenbach and coworkers (24) recently demonstrated that with relatively low levels of exercise, the kinetic VO2 responses to exercise were slower in CF patients, but were not altered by supplemental oxygen. Slower responses indicate peripheral muscle abnormalities, as reflected by recent studies done with 31P-magnetic resonance spectroscopy, suggesting that kinetic responses to exercise are governed largely by intracellular ATP dynamics. It is possible that ATP metabolism is influenced by the effect on energy metabolism in muscle cells of the abnormality in the cystic fibrosis transmembrane regulator.

In another study supporting a specific muscle metabolic derangement in CF, De Meer and coworkers (4) examined high-energy phosphate metabolism in muscle noninvasively, using 31P-magnetic resonance spectroscopy during relatively low-intensity handgrip exercise in eight subjects with CF. A reduced metabolic efficiency (i.e., less oxidative ATP turnover for muscle mechanical work) was noted in the CF subjects than in controls. Precisely why CF patients might have intrinsic changes in muscle that lead to a reduced oxygen cost of exercise is unknown. As noted earlier, some studies suggest that nutrition may play a role in this. In addition, inflammatory mediators are increased in patients with CF (25–27), and these agents might impair muscle function directly (28).

Inferences about whether or not the VO2 abnormality in CF worsens with age in children and adolescents with CF can be made from the regression of muscle size on peak VO2. Larger muscle size will generally be associated with older subjects. In the healthy children in our study, the slope of the regression of peak VO2 on muscle CSA was 16.9 ml/min/cm2, and did not differ from that found in CF subjects. Moreover, the scaling factors relating peak VO2 to muscle CSA were not statistically different in CF subjects and healthy controls. These data therefore suggest that although peak VO2 was lower for muscle CSA in CF subjects, the abnormality causing this did not progressively worsen in older subjects, who tended to have greater muscle CSA.

Maximal or peak exercise tests are highly effort dependent, and rely on the willingness of the subject to endure muscle fatigue and the sensation of dyspnea. In patients with CF, the presence of lung disease and general deconditioning might lessen the tolerance of uncomfortable sensations and therefore the ability to achieve true maximal exercise or even peak levels comparable to those found in healthy subjects. Our data suggest that this was probably not the case in our subjects. We found no significant difference between the CF subjects and controls in peak HR and peak RER (respiratory exchange ratio), suggesting that the CF subjects, like the controls, had stopped exercising only when they had reached the physiological limit of their tolerance.

Two other indexes of cardiorespiratory responses to exercise were abnormal in our CF subjects, and might contribute to a greater understanding of the mechanism of gas exchange impairment in these individuals. ΔVO2/ΔHR was lower in CF subjects, and ΔVE/ΔVCO2 was high (Figure 4). The slope of the VO2–HR relationship is determined by the stroke volume and the arteriovenous difference in oxygen content. This slope is typically reduced when the stroke volume response to exercise is impaired, such as in children with single-ventricle lesions corrected surgically by the Fontan procedure (22). Although left ventricular dysfunction is not typically found in mild to moderate CF, stroke volume during exercise has been shown to be reduced in adults with CF who have severe lung disease (FEV1 < 55% predicted) (29). The mildly reduced ΔVO2/ΔHR in the present study may reflect very early abnormalities in cardiac function during exercise in CF subjects.

A much more substantial abnormality was the large increase in the slope of ΔVE/ΔVCO2 (Figures 1 and 4). The increased slope suggests excessive ventilation in CF subjects as compared with controls, as shown by the modified alveolar gas equation: $VE = \left[863 \times P_{acO2}^{-1} \times (1 - Vd/VT)^{-1}\right] \times VCO2,$ where $P_{acO2}$ is arterial CO2 tension and $Vd/VT$ is the dead space-to-tidal volume ratio. The two most likely explanations for excessive ventilation are increased Vd/VT and changes in the chemoreceptor set point for $PacO2.$ In CF patients, previous investigators, using other approaches, have found exercise abnormalities in both chemoreceptor set point (30) and increased ventilatory deadspace (31, 32). The measurement of ΔVE/ΔVCO2 during exercise may prove to be a noninvasive, relatively effort-independent, and useful means for gauging dynamic respiratory function in these patients.

It is becoming increasingly apparent that individuals with CF benefit from exercise in terms of improved lung function and longevity (1, 33). However, the problem for the clinician remains how to determine an exercise intervention that is appropriate for the individual cardiorespiratory and metabolic limitations imposed by the CF patient’s underlying disease. Our data show that there probably exists a muscle-related impairment in oxygen uptake in these patients, and this should be considered when establishing fitness goals and expectations for children with CF, their families, and their school environment. A judicious use of exercise testing, along with estimates of muscle size, might provide a means of realistically optimizing the exercise prescription for children and adolescents with CF.

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