Skeletal Muscle Mass Is Linked to Cardiorespiratory Fitness in Youth

SAMUEL G. WITTEKIND[1,2], ADAM W. POWELL[1,2], ALEXANDER R. OPOTOWSKY[1,2], WAYNE W. MAYS[2], SANDRA K. KNECHT[2], GREGORY RIVIN[2], and CLIFFORD CHIN[1,2]

[1]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH; and [2]The Heart Institute, Cincinnati Children's, Cincinnati, OH

ABSTRACT

WITTEKIND, S. G., A. W. POWELL, A. R. OPOTOWSKY, W. W. MAYS, S. K. KNECHT, G. RIVIN, and C. CHIN. Skeletal Muscle Mass Is Linked to Cardiorespiratory Fitness in Youth. *Med. Sci. Sports Exerc.*, Vol. 52, No. 12, pp. 2574–2580, 2020. **Introduction:** Cardiorespiratory fitness (CRF) measured by oxygen consumption ($\dot{V}O_2$) during exercise is an important marker of health. The traditional method of indexing $\dot{V}O_2$ to total body mass is suboptimal because skeletal muscle mass (SMM), rather than fat and extracellular fluid, is the main contributor to CRF. The traditional estimating equations for peak $\dot{V}O_2$ in youth do not account for this. Bioelectric impedance analysis (BIA) is a noninvasive method to accurately measure body composition. The objectives of this study were to 1) examine the relationship of body composition indices and peak $\dot{V}O_2$ in healthy children, adolescents, and young adults, and 2) derive an optimized estimating equation incorporating BIA and compare its performance with traditional estimating equations. **Methods:** A retrospective, cross-sectional, single-center study of patients <21 yr old referred for exercise testing who did not have underlying cardiovascular disease. All patients underwent BIA immediately before exercise testing. Univariable and multivariable linear regression models were constructed and tested for model performance. **Results:** A total of 165 young healthy people (mean age 14 yr, 48% male) were studied. There was a strong and linear relationship between peak $\dot{V}O_2$ and SMM ($R^2 = 0.79$). The sex difference in SMM explained the most variability in CRF between boys and girls. A generalized equation using SMM (peak $\dot{V}O_2 = 302 - (23.7 \times \text{age}) - (50.3 \times [\text{female} = 1, \text{male} = 0]) + (81.8 \times \text{SMM})$) had superior performance ($R^2 = 0.80$) compared with estimating equations currently used in clinical practice ($R^2 = 0.67$). **Conclusions:** SMM is a stronger correlate of CRF than is total body mass in youth and may be a better scaling variable to estimate expected peak $\dot{V}O_2$. **Key Words:** OXYGEN CONSUMPTION, $\dot{V}O_2$, BODY COMPOSITION, BIOELECTRIC IMPEDANCE ANALYSIS, PREDICTION, ESTIMATING, EQUATION

During aerobic exercise, multiple-organ systems and physiologic mechanisms work in concert to deliver oxygen to exercising tissue, predominately skeletal muscle. Cardiorespiratory fitness (CRF) is a summary variable that captures the strength of these components and their coupled interactions. Peak oxygen consumption ($\dot{V}O_2$), assessed during cardiopulmonary exercise testing (CPET), is considered the gold standard measure of CRF (1). In recent years, CRF has received significant attention as a robust independent predictor of mortality and numerous clinical outcomes in apparently healthy young adults (2,3) as well as those with cardiovascular disease (CVD) including heart failure (4,5). As such, peak $\dot{V}O_2$ is used in management decisions regarding advanced heart failure therapy (6) and is increasingly followed as an outcome in clinical research trials. The prognostic utility of CRF extends to young patients with CVD including congenital heart disease (7,8) and cardiomyopathy (9,10).

CRF normally increases during development from childhood through puberty (11,12), then slowly declines beginning in the fourth decade of life (13,14), with males generally having higher peak $\dot{V}O_2$ at any given age. To account for differences in maturity and body size, peak $\dot{V}O_2$ is most commonly scaled to total body mass in units of milliliters per kilogram per minute. However, the linear relationship between peak $\dot{V}O_2$ and total body mass is quite weak, especially in overweight patients (15) in whom the standard indexed peak $\dot{V}O_2$ systemically underestimates CRF and can lead to inappropriate assignment of disease risk. It has been suggested that normalizing peak $\dot{V}O_2$ to fat-free mass provides the most accurate expression of CRF (16). Recently, Imboden et al. (17) demonstrated in a large cohort of apparently healthy adults that peak $\dot{V}O_2$ normalized to fat-free mass had superior ability to predict all-cause, CVD, and cancer mortality compared with $\dot{V}O_2$ indexed to total body mass. Calculating fat-free mass in the clinical setting can be cumbersome and error prone. Fortunately, body composition can now be measured accurately and rapidly without irradiation through bioelectric impedance analysis (BIA), which has been validated against dual-energy x-ray absorptiometry (DXA) in adults (18) and children (19) including those with obesity (20–22).

Address for correspondence: Samuel G. Wittekind, M.D., MSc., F.A.C.C., Heart Failure & Transplant Heart Institute, Cincinnati Children's Hospital, 3333 Burnet Ave, MLC 2003, Cincinnati, OH 45229; E-mail: samuel.wittekind@cchmc.org.
Submitted for publication March 2020.
Accepted for publication June 2020.

0195-9131/20/5212-2574/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0000000000002424

APPLIED SCIENCES

Estimating equations for peak $\dot{V}O_2$ in children were developed in the 1980s by Cooper et al. (23) with different equations based on total body weight for boys versus girls, but not correcting for overweight/obese status. These are still widely used in pediatric exercise laboratories. For those ≥18 yr of age, a set of six estimating equations based on sex and weight status (underweight/normal weight/overweight) developed by Wasserman (24) are commonly used. Thus, the traditional method of calculating percent-predicted peak $\dot{V}O_2$ in youth is complicated by multiple estimating equations that variously take into account age, sex, total body mass, and body mass index (BMI) class.

The primary purpose of this study was to explore the relationship of different indices of body composition and peak $\dot{V}O_2$ in a cohort of children, adolescents, and young adults completing a CPET at our institution. It was hypothesized that skeletal muscle mass (SMM) would be the strongest predictor of CRF in this population and thus could be a preferred candidate normalizing variable. The secondary aim was to derive and test a new estimating equation in youth using SMM.

METHODS

Patient cohort. All patients referred to our center's exercise laboratory for clinical CPET between April and December 2019 were reviewed. Those who fit the following criteria were included in the analysis: A) age <21 yr, B) completed a symptom-limited maximal CPET, and C) were healthy without CVD. Patients were considered healthy without CVD if they A) were referred for common indications including chest pain, palpitations, syncope, evaluation of possible long-QT syndrome, premature ventricular contractions, or a family history of sudden cardiac death; B) had a normal heart rate (HR) and blood pressure (BP) response to exercise with normal oxygen saturation and no pathologic electrocardiographic changes; C) had normal related cardiology test results (e.g., echocardiography, genetic testing); and D) were not taking cardiovascular medication. This research was approved for conduct as exempt from the requirement for obtaining written informed consent from the institutional review board at Cincinnati Children's.

BIA. Per our exercise laboratory standard, patients were instructed to not eat or drink for at least 3 h and to use the restroom before their exercise test. Body composition was measured by BIA (InBody370; InBody, Cerritos, CA) immediately before CPET per our current standard. All patients stood on the scale unsupported, with bare hands and feet making contact with the eight total electrodes (two palms, two thumbs, two toes, and two heels). Total body weight and the BIA indices were automatically calculated. The test took approximately 30 s. Output variables from the InBody software included total lean body mass (LBM), LBM of both the upper and lower extremities (summed together as appendicular lean mass), LBM of the trunk, SMM (SMM = appendicular lean mass/0.75), skeletal muscle index (SMI = appendicular lean mass/height^2), body fat mass (BFM), and percent body fat (PBF). Details of this technology have been published (18–22). SMM is estimated from appendicular lean mass based on previous data showing that approximately 75% of total SMM is carried in the extremities (25).

CPET. All patients underwent standardized CPET on a cycle ergometer using a ramp protocol with the goal of reaching exhaustion after 10 min of exercise. The ramp protocol consisted of an initial work rate determined by an exercise physiologist based on the patient's expected fitness level. A 12-lead ECG was recorded during the test (GE Medical Case 8000, Milwaukee, WI). Arm BP was measured at rest, once during the 3-min unloaded warm-up, every 2 min during ramping, and during recovery using auscultation with an appropriately sized manual sphygmomanometer. $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$), and minute ventilation ($\dot{V}_E$) were assessed continuously using breath-by-breath gas analysis with a metabolic cart (Ultima Cardi02; Medgraphics MGC Diagnostics, Saint Paul, MN). Pulse oximetry was measured continuously via a forehead probe (Radical-7; Masimo Corporation, Irvine, CA). The test was judged to be maximal if two of the following three criteria were met: A) RER ≥1.1, B) maximal HR ≥85% of age-predicted maximal HR (24), or C) maximal perceived exertion ≥18/20 on the Borg scale (26). The $\dot{V}O_2$ at RER = 1.0 was defined as the $\dot{V}O_2$ equivalent after which the RER never dropped below 1.0; it was used as a reliable surrogate for anaerobic threshold (27). The predicted peak $\dot{V}O_2$ for children (<18 yr old) was calculated using one of the two estimating equations described by Cooper et al. (23):

$$\text{peak } \dot{V}O_2 \text{ for boys} = (52.8 \times \text{weight}) - 303.4$$

$$\text{peak } \dot{V}O_2 \text{ for girls} = (28.51 \times \text{weight}) + 288.2$$

where the predicted peak $\dot{V}O_2$ for adults was calculated using one of the six estimating equations from Wasserman (24):

$$\begin{aligned}&\text{peak } \dot{V}O_2 \text{ for underweight adult men}\\ &\quad = ([\text{predicted weight} + \text{actual weight}]/2)\\ &\qquad \times (50.72 - [0.372 \times \text{age}])\end{aligned}$$

$$\begin{aligned}&\text{peak } \dot{V}O_2 \text{ for normal weight adult men}\\ &\quad = \text{measured weight} \times (50.72 - [0.372 \times \text{age}])\end{aligned}$$

$$\begin{aligned}&\text{peak } \dot{V}O_2 \text{ for overweight adult men}\\ &\quad = \text{predicted weight} \times (50.72 - [0.372 \times \text{age}])\\ &\qquad + (6 \times [\text{actual weight} - \text{predicted weight}])\end{aligned}$$

where predicted weight for adult men = (0.79 × height) − 60.7.

$$\begin{aligned}&\text{peak } \dot{V}O_2 \text{ for underweight adult women}\\ &\quad = ([\text{predicted weight} + \text{actual weight} + 86]/2)\\ &\qquad \times (22.78 - [0.17 \times \text{age}])\end{aligned}$$

$$\begin{aligned}&\text{peak } \dot{V}O_2 \text{ for normal-weight adult women}\\ &\quad = (\text{measured weight} + 43) \times (22.78 - [0.17 \times \text{age}])\end{aligned}$$

APPLIED SCIENCES

$$\text{peak }\dot{V}O_2\text{ for overweight adult women} = (\text{predicted weight} + 43) \times (22.78 - [0.17 \times \text{age}]) + (6 \times [\text{actual weight} - \text{predicted weight}]),$$

where predicted weight for adult women = (0.65 × height) − 42.8.

$\dot{V}O_2$ is in units of milliliters per minute, age is in years, weight is in kilograms, and height is in centimeters.

The $\dot{V}_E/\dot{V}CO_2$ slope was measured from rest to peak exercise. As part of the CPET, all patients underwent baseline spirometry in a standing position; the best result of three trials was used for analysis per standards from the American Thoracic Society (28). Predicted spirometry variables were based on sex, age, and height (29). Maximal voluntary ventilation (MVV) was calculated from forced expiratory volume in 1 s (FEV_1) × 40 (30). Breathing reserve was defined as follows: peak $\dot{V}_E$/MVV × 100 (27).

Statistical analysis. Data were summarized as mean ± SD for normally distributed continuous variables, median (interquartile range, Q_1–Q_3) for continuous variables with skewed distributions, and proportions with percentages for categorical variables. Relationships between variables were assessed using univariable linear regression models. Significant predictors of peak $\dot{V}O_2$ at the univariable level were considered as candidate variables in multivariable general linear models, which were fit by the method of least squares. Model variable selection was based on 1) traditional variables in the widely used prediction equations from Cooper et al. (23), Wasserman (24), and the FRIEND registry (31); 2) our study hypothesis that SMM would be a strong predictor; and 3) published evidence that adiposity exerts a negative effect on CRF (32,33). The models were reduced using parsimony and model stability as goals. Partial correlation analysis was used to examine the relationship between each variable and peak $\dot{V}O_2$ controlling for the other variables in each model. Analysis of covariance was used to compare regression line slopes and intercepts. All tests were two-tailed, and the significance level was set at 0.05. Statistical analyses were performed using JMP 14 (SAS Institute Inc., Cary, NC).

RESULTS

A total of 165 patients were included in the analysis, and their baseline characteristics are shown in Table 1. The mean age was 14.4 ± 2.5 YR (total range, 8–20 yr). Forty-eight percent were male, and MOST were white. Median BMI was 20.8 (Q_1–Q_3, 19.4–23.6) kg·m^{-2}, with 15% underweight and 15% overweight/obese. The measures of muscularity included a mean LBM of 46.6 ± 12.0 kg, mean SMM of 25.8 ± 7.3 kg, and mean SMI of 6.7 ± 1.2 kg·m^{-2}. Adiposity measures included a median BFM of 11.8 (Q_1–Q_3, 8.0–17.9) kg and mean PBF of 22.4% ± 9.6%.

Cardiopulmonary exercise test measurements are summarized in Table 2. The mean resting and peak HR and systolic BP were normal for age, and all patients had normal oxygen saturation. The mean peak work rate was 167 ± 58 W. The median peak RER was 1.24 (Q_1–Q_3, 1.19–1.29). The median peak absolute $\dot{V}O_2$ was 1914 (Q_1–Q_3, 1586–2493) mL·min^{-1} corresponding to a mean percent predicted $\dot{V}O_2$ of 88% ± 17% based on the traditional estimating equations described in the Methods section. The mean peak $\dot{V}O_2$ values indexed to total body mass versus SMM were 34 ± 8 and 80 ± 12 mL·kg^{-1}·min^{-1}, respectively. The median $\dot{V}_E/\dot{V}CO_2$ slope was 30 (Q_1–Q_3, 28–34). Resting spirometry indices were largely normal, and the mean breathing reserve was normal (62% ± 15%) consistent with no significant pulmonary limitation to exercise capacity in this cohort.

TABLE 1. Baseline patient characteristics.

	Study Cohort (*N* = 165)
Demographics	
Age, mean (SD), range, yr	14.4 (2.5), 8–20
Age <18 yr, *n*/*N* (%)	153/165 (93)
Male, *n*/*N* (%)	79/165 (48)
Race	
White, *n*/*N* (%)	138/165 (84)
Black, *n*/*N* (%)	21/165 (13)
Anthropometrics	
Height, mean (SD), cm	166 (13)
Total body weight, median (Q_1–Q_3), kg	59.5 (52.0–69.7)
BMI, median (Q_1–Q_3), kg·m^{-2}	20.8 (19.4–23.6)
BMI class	
Normal, *n*/*N* (%)	115/165 (70)
Underweight, *n*/*N* (%)	25/165 (15)
Overweight, *n*/*N* (%)	15/165 (9)
Obese, *n*/*N* (%)	10/165 (6)
Body surface area, mean (SD), m^2	1.66 (0.26)
Total LBM, (mean (SD), kg	46.6 (12.0)
LBM of the right upper extremity, (mean (SD), kg	2.4 (0.9)
LBM of the left upper extremity, (mean (SD), kg	2.3 (0.8)
LBM of the trunk, (mean (SD), kg	20.5 (5.3)
LBM of the right lower extremity, (mean (SD), kg	7.2 (2.1)
LBM of the left lower extremity, (mean (SD), kg	7.1 (2.1)
SMM, (mean (SD), kg	25.8 (7.3)
SMI, mean (SD), kg·m^{-2}	6.7 (1.2)
BFM, median (Q_1–Q_3), kg	11.8 (8.0–17.9)
PBF, mean (SD), %	22.4 (9.6)

The relationships of peak $\dot{V}O_2$ to total body mass and SMM were first examined in male versus female patients. Simple linear regression of peak absolute $\dot{V}O_2$ as a function of total body mass demonstrated a weak to moderate relationship (R^2 = 0.49), especially in the typical adult weight range >60 kg. This relationship was less strong for female patients (R^2 = 0.33) compared with male patients (R^2 = 0.50); however, the slopes of the regression lines were not significantly different (P = 0.13) as shown in Figure 1A. The linear relationship between peak $\dot{V}O_2$ and SMM was much stronger (R^2 = 0.79) and similar between the sexes (R^2 for female vs male = 0.63 vs 0.74; slope difference, P = 0.75) as shown in Figure 1B.

The relationships were next examined across the different BMI classes. Linear regression of peak $\dot{V}O_2$ by total body mass revealed a difference in the intercepts, but no significant difference in slopes (P = 0.51) between the BMI classes as shown in Figure 2A. The linear relationship with SMM was much stronger in all BMI classes with less dispersion of the intercepts (slope difference, P = 0.25; Fig. 2B).

Multivariable regression models were constructed to test the hypothesis that SMM is a superior and independent predictor of peak $\dot{V}O_2$ in our cohort of healthy youth. First, the variables included in the standard estimating equations for peak $\dot{V}O_2$ were entered in the model, which yielded a model R^2 = 0.62. All variables were significant predictors; weight (partial R^2 = 0.29) and

APPLIED SCIENCES

TABLE 2. Cardiopulmonary exercise test variables.

	Study Cohort (*N* = 165)
Workload	
<20 W·min^{-1} ramp, *n*/*N* (%)	68/165 (41)
20–25 W·min^{-1} ramp, *n*/*N* (%)	81/165 (49)
>25 W·min^{-1} ramp, *n*/*N* (%)	16/165 (10)
Peak work rate, mean (SD), W	167 (58)
Noninvasive hemodynamic data	
Resting HR, (mean (SD), bpm	82 (5)
Peak HR, (mean (SD), bpm	184 (12)
% Predicted peak HR, median (Q_1–Q_3), %	92 (88–95)
Resting SBP, mean (SD), mm Hg	114 (10)
Peak SBP, mean (SD), mm Hg	175 (22)
Resting DBP, mean (SD), mm Hg	67 (7)
Peak DBP, mean (SD), mm Hg	64 (11)
Resting SpO_2, median (Q_1–Q_3), min–max, %	100 (100–100), 98–100
Peak exercise SpO_2, median (Q_1–Q_3), min–max, %	98 (97–99), 91–100
Metabolic data	
Peak RER, median (Q_1–Q_3), %	1.24 (1.19–1.29)
$\dot{V}O_2$ at RER = 1.0, median (Q_1–Q_3), mL·min^{-1}	1289 (1037–1539)
Peak $\dot{V}O_2$, median (Q_1–Q_3), min–max, mL·min^{-1}	1914 (1586–2493), 796–3714
% Predicted peak $\dot{V}O_2$ based on Cooper–Wasserman equations, mean (SD), min–max, %	88 (17), 52–137
Peak $\dot{V}O_2$ indexed to total body weight, mean (SD), min–max, mL·kg^{-1}·min^{-1}	34 (8), 19–60
Peak $\dot{V}O_2$ indexed to SMM, mean (SD), min–max, mL·kg^{-1}·min^{-1}	80 (12), 50–113
Peak O_2 pulse, median (Q_1–Q_3), mL per beat	10 (9–14)
% Predicted peak O_2 pulse based on Cooper–Wasserman equations, median (Q_1–Q_3), %	95 (82–100)
Peak $\dot{V}_E$, mean (SD), L·min^{-1}	80 (23)
$\dot{V}_E$/MVV, mean (SD), %	62 (15)
$\dot{V}_E$/$\dot{V}O_2$ slope, median (Q_1–Q_3)	30 (28–34)
Spirometry data	
FVC, mean (SD), L	3.92 (1.08)
% Predicted FVC, median (Q_1–Q_3), %	100 (93–100)
FEV_1, mean (SD), L	3.33 (0.95)
% Predicted FEV_1, median (Q_1–Q_3), %	100 (90–100)
FEV_1/FVC, mean (SD), %	85 (9)
% Predicted FEV_1/FVC, median (Q_1–Q_3), %	98 (91–100)
$FEF_{25\%–75\%}$, mean (SD), L	3.62 (1.21)
% Predicted $FEF_{25\%–75\%}$, median (Q_1–Q_3)	95 (79–100)

DBP, diastolic BP; $FEF_{25\%–75\%}$, midexpiratory flow rate; FEV_1/FVC, ratio of FEV_1 and forced vital capacity; FVC, forced vital capacity; SBP, systolic BP; SpO_2, oxygen saturation; $\dot{V}_E$/$\dot{V}CO_2$ slope, slope of the best fit line of $\dot{V}_E$ vs carbon dioxide production from rest to peak exercise; $\dot{V}_E$/MVV, ratio of $\dot{V}_E$ and MVV.

sex (partial $R^2 = 0.28$) were the dominant predictors in this traditional variable model (Table 3A). When SMM was added to the model, it became the dominant predictor (partial $R^2 = 0.50$), sex became nonsignificant, and the model characteristics improved substantially ($R^2 = 0.81$ with a lower Bayesian information criterion (BIC)) as shown in Table 3B. Addition of BFM provided no model improvement ($R^2 = 0.81$ with slightly higher BIC), and the very low partial R^2 values suggested multicollinearity (Table 3C). Limiting the variables to just age, sex, and SMM simplified the model while maintaining excellent explanatory power ($R^2 = 0.80$) as shown in Table 3D. Importantly, although SMM was the dominant (partial $R^2 = 0.62$) and independent predictor in this model, age and sex were retained because of the biological plausibility that these variables exert an effect on CRF during maturity from childhood to young adulthood. This model yielded a multivariable regression equation:

$$\text{peak } \dot{V}O_2 = 302 - (23.7 \times \text{age}) - (50.3 \times [\text{female} = 1, \text{male} = 0]) + (81.8 \times \text{SMM}),$$

where $\dot{V}O_2$ is in units of milliliters per minute, age is in years, and SMM is in kilograms.

The performance of this derived multivariable prediction equation was compared with that of the traditional estimating equations from Cooper and Wasserman in this cohort. A plot of actual versus predicted peak $\dot{V}O_2$ from the traditional equations demonstrated a moderately strong linear relationship ($R^2 = 0.67$, Fig. 3A) with the residual plot shown in Figure 3B. The proposed prediction equation using SMM had more explanatory power ($R^2 = 0.80$) as shown in Figures 3C and 3 D. A sensitivity analysis in which patients 18 yr or older were excluded from the analysis did not change the model performance ($R^2 = 0.80$), which supports its robustness across the age spectrum of childhood to young adulthood.

DISCUSSION

Previous reports suggest that indexing peak $\dot{V}O_2$ to LBM rather than total mass more accurately represents CRF, especially in obese people (16,34,35). Accuracy in CRF is important for prognosis as shown in the recent study by Imboden et al. (17) in which peak $\dot{V}O_2$ normalized to fat-free mass (estimated from triceps skin fold thickness) in middle age was more predictive of mortality over a 20-yr follow-up. Studies

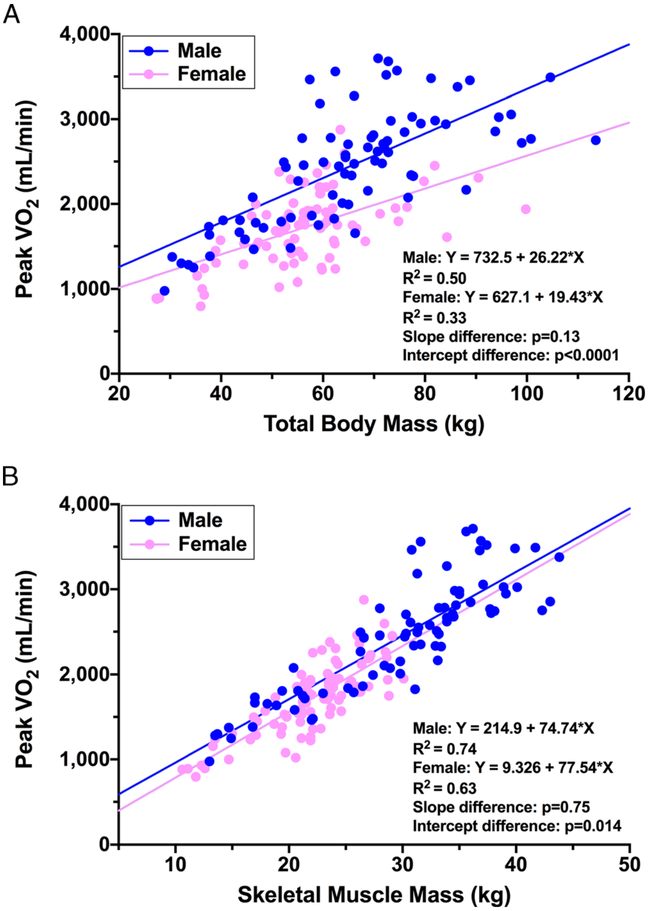

FIGURE 1—Peak $\dot{V}O_2$ as a function of total body mass (TBM) vs SMM stratified by sex. A, The linear relationship of peak $\dot{V}O_2$ with TBM is modest, especially in female patients, and weakens in the adult weight range >60 kg. B, The linear relationship with SMM is stronger for both sexes. Individual data point and fit line colors: blue, male; pink, female.

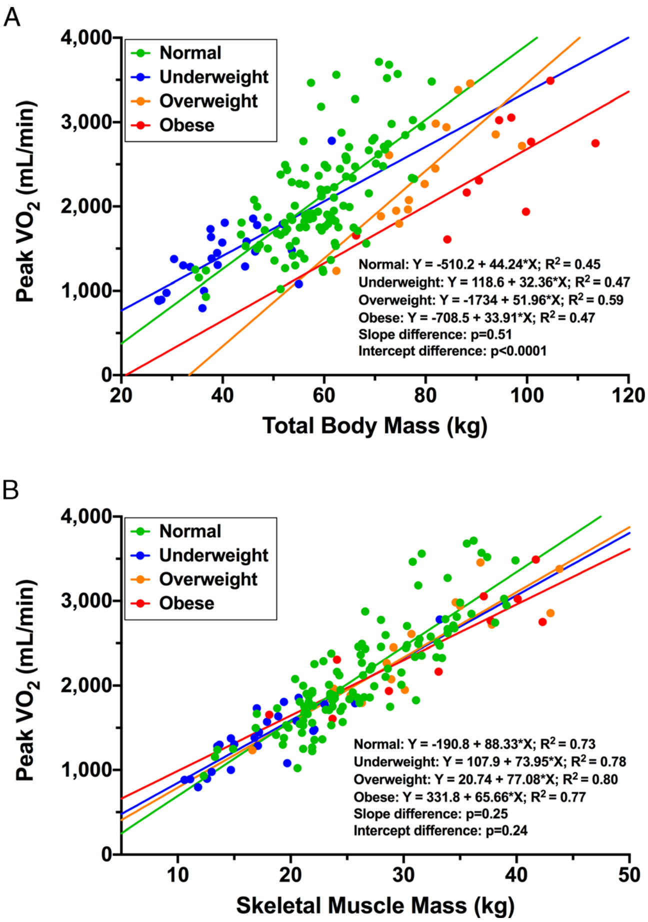

FIGURE 2—Peak $\dot{V}O_2$ as a function of total body mass (TBM) vs SMM stratified by BMI class. A, The linear relationship of peak $\dot{V}O_2$ with TBM is modest with differences in the intercepts (P < 0.0001) between the BMI classes, but similar slopes. B, The linear relationship with SMM is stronger across BMI classes with less dispersion of the intercepts (P = 0.24). Individual data point and fit line colors: green, normal; blue, underweight; orange, overweight; red, obese.

in various patient populations including adult heart failure (36), coronary artery disease (37), and childhood obesity (34) have identified a strong relationship between SMM, in particular, and fitness. The use of DXA in these studies limits clinical application; however, available BIA scales that perform segmental lean analysis make it feasible to measure SMM quickly and easily.

A recent study by Cooper et al. (35) highlights the need to index CRF to an estimate of SMM in youth. They observed a similar, strong linear relationship of peak $\dot{V}O_2$ and LBM (measured by DXA) in normal- and high-BMI but otherwise healthy children. Access to DXA is a limitation acknowledged by those investigators; the present study used BIA to address this limitation. Other studies (32,33) have also suggested that body fat exerts a negative effect on CRF independent of SMM. Although neither BFM nor PBF was a significant predictor of peak $\dot{V}O_2$ in multivariable models in the current analysis, future studies with more overweight/obese youth should explore the association of adiposity and CRF.

To our knowledge, this is the first study to examine the relationship of BIA-measured body composition with CRF in healthy youth. We used these data to develop a new prediction equation including age, sex, and SMM with improved explanatory power compared with traditional estimating equations used in pediatric exercise testing. Whether referencing peak $\dot{V}O_2$ to SMM provides improved value in terms of prognosis in youth with CVD or other diagnoses is an area of future research.

Study limitations. The present study has a number of limitations. First, the sample size is modest; however, it is in line with previous studies exploring the relationship of baseline patient characteristics and CRF in youth. For example, Cooper et al. (23) studied a similar sample size of 109 normal-weight children age 6–17 yr. Still, larger prospective studies are required to confirm these findings and examine the interaction of SMM with other patient factors including age and adiposity. Another limitation is that the proposed prediction equation was derived and tested in the same group of subjects, whereas the traditional models to predict peak $\dot{V}O_2$ were derived decades ago in other contexts. It is unclear whether validation in an independent cohort would confirm the dramatically better correlation between predicted and actual values using SMM compared with total body mass as was seen in the current study. That said, even using a newly derived equation from the current cohort using total body mass was substantially less robust in terms of predicting actual peak $\dot{V}O_2$. Next, the traditional estimating equations used to calculate percent-predicted $\dot{V}O_2$ were different for children and adults in this study, which parallels real-world practice. When patients in this study were stratified

TABLE 3. Multivariable regression models.

Term	Parameter Estimate, mL·min^{-1}	Partial R^2	P
A. Peak $\dot{V}O_2$ as function of traditional variables			
Intercept	253.48		
Age	42.21	0.04	0.007
Female sex	−261.12	0.28	<0.0001
Weight	20.06	0.29	<0.0001
Model R^2	0.62		<0.0001
BIC	2475.43		
B. Peak $\dot{V}O_2$ adding SMM			
Intercept	360.84		
Age	−25.57	0.03	0.04
Female sex	−13.46	0.001	0.66
Weight	−9.11	0.06	0.002
SMM	101.92	0.50	<0.0001
Model R^2	0.81		<0.0001
BIC	2367.53		
C. Peak $\dot{V}O_2$ adding skeletal muscle and BFM			
Intercept	667.72		
Age	−26.69	0.03	0.04
Female sex	−4.83	0.0001	0.87
Weight	−88.69	0.01	0.15
SMM	234.00	0.03	0.02
BFM	80.36	0.01	0.20
Model R^2	0.81		<0.0001
BIC	2370.90		
D. Proposed multivariable regression model for estimating peak $\dot{V}O_2$ from baseline demographics and SMM in youth			
Intercept	301.82		
Age	−23.72	0.02	0.06
Female sex	−50.29	0.02	0.09
SMM	81.82	0.62	<0.0001
Model R^2	0.80		<0.0001
BIC	2372.14		

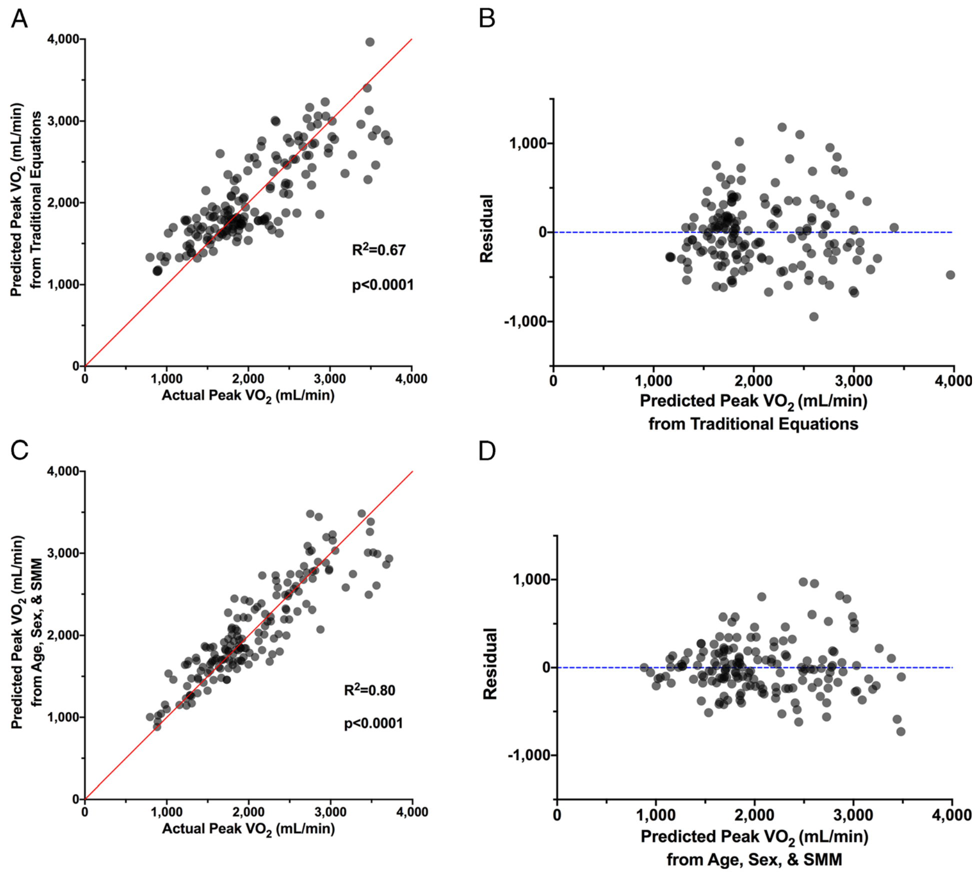

FIGURE 3—Performance comparison of the traditional equations vs the proposed estimating equation incorporating SMM. Plots of the actual by estimated peak $\dot{V}O_2$ from the traditional estimating equations (A) and from the new estimating equation (C) are shown along with the respective residual plots (B and D).

by age <18 or ≥18 yr, the results were unchanged: SMM drove the association with CRF. The more contemporary, multivariable reference equation for CRF in adults 20–79 yr of age from the FRIEND Registry (31) illustrates the desire for a unified prediction equation from youth to old age. That reference equation was not applied in the present study because of the age cutoff. Lastly, SMM reflects muscle hypertrophy and does not correspond directly to strength. Physiologic processes in skeletal and cardiac muscle associated with disease and advancing age (e.g., inflammation, mitochondrial dysfunction, and cellular senescence) (38) may contribute to declines in strength and CRF beyond the degree of change in SMM. Further investigation exploring the association of body composition and CRF into adulthood is needed.

CONCLUSIONS

Incorporating BIA estimates of body composition into the standard workflow of a CPET informed an expected exercise capacity. We observed a strong linear relationship between SMM and peak $\dot{V}O_2$ in youth across the age, sex, and BMI spectra. Furthermore, differences in SMM explain the majority of variability in CRF between the sexes. A novel prediction equation using age, sex, and SMM has superior explanatory power compared with traditional peak $\dot{V}O_2$ prediction equations that are in current clinical use. These data support SMM as a preferred scaling variable compared with the traditional method of scaling to total body mass. Whether SMM is also a strong predictor of CRF and prognosis in youth with heart disease and other diseases warrants further research.

The authors would like to thank the staff of the Exercise Laboratory at the Heart Institute at Cincinnati Children's for their effort in collecting the data used in this study.

No funding was provided for this study. The authors declare no conflict of interest. The results of the present study do not constitute endorsement by the American College of Sports Medicine. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

APPLIED SCIENCES

REFERENCES

1. Ross R, Blair SN, Arena R, et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. *Circulation*. 2016;134:e653–99.
2. Artero EG, Jackson AS, Sui X, et al. Longitudinal algorithms to estimate cardiorespiratory fitness: associations with nonfatal cardiovascular disease and disease-specific mortality. *J Am Coll Cardiol*. 2014;63(21):2289–96.

3. Cao C, Yang L, Cade WT, et al. Cardiorespiratory fitness is associated with early death among healthy young and middle-aged Baby Boomers and Generation Xers. *Am J Med*. 2020;S0002-9343(20):30054–1.
4. Farrell SW, Finley CE, Radford NB, Haskell WL. Cardiorespiratory fitness, body mass index, and heart failure mortality in men: Cooper Center Longitudinal Study. *Circ Heart Fail*. 2013;6(5):898–905.
5. Osman AF, Mehra MR, Lavie CJ, Nunez E, Milani RV. The incremental prognostic importance of body fat adjusted peak oxygen consumption in chronic heart failure. *J Am Coll Cardiol*. 2000;36(7):2126–31.
6. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds L Jr, Wilson J. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation*. 1991;83(3):778–86.
7. Diller G-P, Dimopoulos K, Okonko D, et al. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation*. 2005;112(6):828–35.
8. Cunningham JW, Nathan AS, Rhodes J, Shafer K, Landzberg MJ, Opotowsky AR. Decline in peak oxygen consumption over time predicts death or transplantation in adults with a Fontan circulation. *Am Heart J*. 2017;189:184–92.
9. den Boer SL, Flipse DH, van der Meulen MH, et al. Six-minute walk test as a predictor for outcome in children with dilated cardiomyopathy and chronic stable heart failure. *Pediatr Cardiol*. 2017;38(3):465–71.
10. Coats CJ, Rantell K, Bartnik A, et al. Cardiopulmonary exercise testing and prognosis in hypertrophic cardiomyopathy. *Circ Heart Fail*. 2015;8(6):1022–31.
11. Cooper DM, Weiler-Ravell D, Whipp BJ, Wasserman K. Growth-related changes in oxygen uptake and heart rate during progressive exercise in children. *Pediatr Res*. 1984;18(9):845–51.
12. Pate RR, Wang C-Y, Dowda M, Farrell SW, O'Neill JR. Cardiorespiratory fitness levels among US youth 12 to 19 years of age: findings from the 1999–2002 National Health and Nutrition Examination Survey. *Arch Pediatr Adolesc Med*. 2006;160(10):1005–12.
13. Fleg JL, Morrell CH, Bos AG, et al. Accelerated longitudinal decline of aerobic capacity in healthy older adults. *Circulation*. 2005;112(5):674–82.
14. Jackson AS, Sui X, Hebert JR, Church TS, Blair SN. Role of lifestyle and aging on the longitudinal change in cardiorespiratory fitness. *Arch Intern Med*. 2009;169(19):1781–7.
15. Savonen K, Krachler B, Hassinen M, et al. The current standard measure of cardiorespiratory fitness introduces confounding by body mass: the DR's EXTRA study. *Int J Obes (Lond)*. 2012;36(8):1135–40.
16. Buskirk E, Taylor HL. Maximal oxygen intake and its relation to body composition, with special reference to chronic physical activity and obesity. *J Appl Physiol*. 1957;11(1):72–8.
17. Imboden MT, Kaminsky LA, Peterman JE, et al. Cardiorespiratory fitness normalized to fat-free mass and mortality risk. *Med Sci Sports Exerc*. 2020;52(7):1532–7.
18. Ling CH, de Craen AJ, Slagboom PE, et al. Accuracy of direct segmental multi-frequency bioimpedance analysis in the assessment of total body and segmental body composition in middle-aged adult population. *Clin Nutr*. 2011;30(5):610–5.
19. Chiplonkar S, Kajale N, Ekbote V, et al. Validation of bioelectric impedance analysis against dual-energy x-ray absorptiometry for assessment of body composition in Indian children aged 5 to 18 years. *Indian Pediatr*. 2017;54(11):919–24.
20. Kriemler S, Puder J, Zahner L, Roth R, Braun-Fahrlander C, Bedogni G. Cross-validation of bioelectrical impedance analysis for the assessment of body composition in a representative sample of 6- to 13-year-old children. *Eur J Clin Nutr*. 2009;63(5):619–26.
21. Seo YG, Kim JH, Kim Y, et al. Validation of body composition using bioelectrical impedance analysis in children according to the degree of obesity. *Scand J Med Sci Sports*. 2018;28(10):2207–15.
22. Thivel D, Verney J, Miguet M, et al. The accuracy of bioelectrical impedance to track body composition changes depends on the degree of obesity in adolescents with obesity. *Nutr Res*. 2018;54:60–8.
23. Cooper D, Weiler-Ravell D, Whipp BJ, Wasserman K. Aerobic parameters of exercise as a function of body size during growth in children. *J Appl Physiol Respir Environ Exerc Physiol*. 1984;56(3):628–34.
24. Wasserman K. *Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications*. Philadelphia (PA): Lippincott Williams & Wilkins; 2005.
25. Gallagher D, Visser M, De Meersman RE, et al. Appendicular skeletal muscle mass: effects of age, gender, and ethnicity. *J Appl Physiol*. 1997;83(1):229–39.
26. Borg G. *Borg's Perceived Exertion and Pain Scales*. Champaign (IL): Human Kinetics; 1998.
27. Chin C, Kazmucha J, Kim N, Suryani R, Olson I. VO2@RER1.0: a novel submaximal cardiopulmonary exercise index. *Pediatr Cardiol*. 2010;31(1):50–5.
28. Culver BH, Graham BL, Coates AL, et al. Recommendations for a standardized pulmonary function report. An official American Thoracic Society technical statement. *Am J Respir Crit Care Med*. 2017;196(11):1463–72.
29. Goldman H, Becklake MR. Respiratory function tests; normal values at median altitudes and the prediction of normal results. *Am Rev Tuberc*. 1959;79(4):457–67.
30. Campbell SC. A comparison of the maximum voluntary ventilation with the forced expiratory volume in one second: an assessment of subject cooperation. *J Occup Med*. 1982;24(7):531–3.
31. Myers J, Kaminsky LA, Lima R, Christle JW, Ashley E, Arena R. A reference equation for normal standards for VO_2 max: analysis from the Fitness Registry and the Importance of Exercise National Database (FRIEND Registry). *Prog Cardiovasc Dis*. 2017;60(1):21–9.
32. Moliner-Urdiales D, Ruiz JR, Vicente-Rodriguez G, et al. Associations of muscular and cardiorespiratory fitness with total and central body fat in adolescents: the HELENA study. *Br J Sports Med*. 2011;45(2):101–8.
33. Lee S, Arslanian S. Body composition and cardiorespiratory fitness between metabolically healthy versus metabolically unhealthy obese black and white adolescents. *J Adolesc Health*. 2019;64(3):327–32.
34. Bhammar DM, Adams-Huet B, Babb TG. Quantification of cardiorespiratory fitness in children with obesity. *Med Sci Sports Exerc*. 2019;51(11):2243–50.
35. Cooper DM, Leu S-Y, Taylor-Lucas C, Lu K, Galassetti P, Radom-Aizik S. Cardiopulmonary exercise testing in children and adolescents with high body mass index. *Pediatr Exerc Sci*. 2016;28(1):98–108.
36. LeMaitre JP, Harris S, Hannan J, Fox KA, Denvir MA. Maximum oxygen uptake corrected for skeletal muscle mass accurately predicts functional improvements following exercise training in chronic heart failure. *Eur J Heart Fail*. 2006;8(3):243–8.
37. Nichols S, O'doherty AF, Taylor C, Clark AL, Carroll S, Ingle L. Low skeletal muscle mass is associated with low aerobic capacity and increased mortality risk in patients with coronary heart disease—a CARE CR study. *Clin Physiol Funct Imaging*. 2019;39(1):93–102.
38. Li H, Hastings MH, Rhee J, Trager LE, Roh JD, Rosenzweig A. Targeting age-related pathways in heart failure. *Circ Res*. 2020;126(4):533–51.