CRC Project Proposal

Name: Joanna Kinney, MD

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Project Title: Cardiopulmonary Exercise Stress Testing in Obese Children and Adolescents

Principal Investigator: Aliva De, MD

Other Investigators: Robert Garofano, PhD; Aimee Layton, PhD

Scientific Abstract

In the United States, the rate of obesity continues to rise with implications across many if not all organ systems. Today, obesity alone affects 40% of US adults and 18% of US children, totaling 93.3 million adults and 19.7 million children, respectively.[1,2] The vast complications of obesity include strong associations with both the cardiovascular system and the pulmonary system including heart disease, dyslipidemia, asthma, chronic obstructive pulmonary disease, pulmonary embolism and more.[3] Cardiopulmonary exercise testing (CPET) is a useful tool for assessing functional status of the cardiopulmonary system. Several decades of epidemiologic findings have reported that quantified cardiorespiratory fitness (CRF) predicts a positive correlation with better health.[4] In clinical practice, CPET is often used to assess the outcome of various therapies (testing both before and after therapy) including patients with pulmonary hypertension, lung transplantation and lung reduction surgery, chronic obstructive pulmonary disease, congestive heart failure, and bariatric surgery. A cycle ergometer or a treadmill can be used for a CPET test. Among the obese population, the choice between cycle ergometer and treadmill may occur due to weight maximum of the cycle ergometer per the manufacturer instructions, with a treadmill often tolerating a higher weight-bearance.

Cooper *et.al.*[5] derived two separate equations to characterize peak VO2 in children on a cycle ergometer:

For normal boys:	Peak VO2 (mL/min) = 52.8 x W – 303.4	r = 0.94
For normal girls:	Peak VO2 (mL/min) = 28.5 x W + 288.2	r = 0.84

While CRF standards have been well characterized among the adult and obese adult population,[6] data are limited among the pediatric population with a paucity among the obese pediatric and adolescent population.[7]

At our institute, we have been performing CPET studies on the treadmill. Available reference equations for CPET are based on ergometer studies. As weight has an important bearing on CPET results from treadmill studies, the lack of available reference equations is limiting for interpretation of these studies in pediatric obese children and adolescents and use of known weight based equations from normal weight children as above can lead to underestimation of results. In the absence of appropriate reference equations among the pediatric obese population, the interpretation of oxygen uptake (peak VO2) is thus limited. As peak VO2 can be low secondary to suboptimal effort or physical deconditioning associated with obesity, or could also be secondary to cardiopulmonary limitations. Therefore an accurate set of physiological responses is paramount to interpretation of CPET studies. The traditional practice is to use a percent predicted value of the VO2 adjusted for body weight (VO2 in ml/min/kg or VO2/kg) reference value for interpretation of aerobic capacity and cardiopulmonary response to exercise, but in the absence of reference equations, arbitrary cut off parameters are used. Further, in obesity, excessive body fat can lead to a false underestimation of VO2/kg and results in a suboptimal value. Using ancillary parameters such as heart rate

response and ventilatory capacity can optimize the interpretation report. A hyper-efficient or altered ventilatory capacity has been anecdotally noted in our obese adolescents. Availability of more sophisticated estimates of lean body mass could give a more accurate estimate of oxygen uptake for a more accurate interpretation. The goal of this study is to review the CPET database of exercise studies from a large obese population prior to bariatric surgery and establish normative data for obese children. We would further like to study the utility of lean body mass data for estimating corrected peak VO2.

Pulmonary function test (PFT) data is available for our patients and correlating the PFT parameters with the exercise study parameters can help evaluate determinants of exercise capacity in obese children and adolescents.

AIMS

1. Establish normative data for treadmill studies for obese subjects and assess utility of lean body mass to interpret peak VO2 results.
2. Study correlation of pulmonary function parameters with exercise test parameters and the effect of obesity related comorbidities (such as diabetes and hypertension) on exercise stress testing.
3. Assess the ventilatory response to exercise of obese subjects, as a hyper-efficient ventilatory capacity has been anecdotally reported.

STUDY METHODS

The robust database of obese children who underwent comprehensive evaluations prior to bariatric surgery at the Center for Adolescent Bariatric Surgery (CABS) at New-York Presbyterian/ Morgan Stanley Children's Hospital, Columbia University Irving Medical Center (CUIMC), from January 1, 2006-December 31, 2019, will be accessed for this study. Comprehensive evaluation included cardiopulmonary exercise stress testing (CPET), pulmonary function testing, body mass densitometry measurements, and endocrine and metabolic evaluation studies. Additional information such as demographic variables, body mass densitometry measurements and pulmonary function testing were recorded. Diabetic and hypertensive diagnoses will be determined based upon chart review.

-Patients will be grouped into groups- those with maximal exercise response based on achievement of anaerobic threshold (AT), maximal heart rate response (>90% predicted) and a respiratory exchange ratio (RER) >1.1. We anticipate 100 patients in this group.

-The other group would include patients with submaximal exercise tests including about 200 patients.

STUDY PROCEDURES

Cardiopulmonary exercise stress testing (CPET)

Exercise testing was performed in the Exercise Laboratory at CUIMC in accordance with the American Thoracic Society guidelines. At the beginning of the test, subjects were asked to walk or run on a treadmill at an initial speed of 1.7 mph with no incline. The treadmill speed and incline were then increased according to the Bruce protocol. Subjects were encouraged to exercise until they were exhausted. Subjects breathed through a mouthpiece, and expired gas volumes and concentrations were continuously analyzed using a computerized breath-by-breath exercise system (Vyaire Vmax 22c Loma Linda, CA). Minute ventilation (V`E), volume of oxygen consumption (V`O2), carbon dioxide production (V`CO2), respiratory exchange ratio (RER=V`CO2/V`O2), and ventilatory equivalents for oxygen (V`E/V`O2), and carbon dioxide (V`E/V`CO2) were calculated on a breath-by-breath basis. Heart rate (HR) and oxygen saturation were continuously monitored by 12-lead electrocardiogram and pulse oximetry (Maximo Radical 7). Effort is considered to be maximal if the highest observed heart rate was >90% of the predicted value and the peak RER was ≥ 1.1. The V`O2 max was recorded as the highest V`O2 achieved during exercise. HR at V`O2 max and O2 pulse (V`O2 max/HR at V`O2 max) were also recorded. Anaerobic threshold (AT) was determined at the point at which V`CO2 increased non-linearly compared to V`O2. The V-Slope method was employed. V`E/V`CO2 at AT and V`E/V`O2 at maximum exercise (V`E/V`O2 max) were used for interpretation. The highest minute ventilation (V`E) during exercise was recorded as the V`E max. The maximum voluntary ventilation (MVV) was measured using a 6 second maneuver, and also calculated using the formula 35 × FEV1, the largest volume was used. Breathing reserve was calculated using the formula (MVV- V`E max)/MVV × 100. Pulmonary limitation to exercise was defined as an abnormal ventilatory response or an abnormal gas exchange.

Pulmonary function testing (PFT)

Some patients had PFT data. PFTs were performed at the PFT laboratory at Morgan Stanley Children's Hospital, CUIMC in accordance with the American Thoracic Society (ATS) guidelines. Testing was performed using CareFusion Vmax Encore 22 spirometer and CareFusion Vmax Autobox V62J (San Diego, California). PFT data collected included spirometry and lung volumes when possible. A flowsensor was used to obtain flow values, and lung volumes were determined by body plethysmography. Flows [forced expiratory volume in 1 second (FEV1) and forced expiratory flow between 25-75% of forced vital capacity (FEF25-75%)] and lung volumes [forced vital capacity (FVC), residual volume (RV), and total lung capacity (TLC)] were reported as raw values and as a percent of predicted based on standard reference values. Restrictive lung disease was defined as a TLC<80%pred. Obstructive lung disease was defined as an abnormal FEV1/FVC < 80% with or without an abnormal FEV1<80%, or an abnormal FEF25-75% < 68%. Hyperinflation was defined as a RV>120%pred or a RV/TLC ratio >28%.

Bioelectrical Impedance

Bioelectrical impedance is used to calculate lean body weight for all patients seen at the CABS Center at CUIMC. This data will be collected and used for development of regression equations.

STATISTICAL ANALYSIS

Patients will be categorized into 2 groups. For patients with a maximal exercise response based on attainment of AT and a RER> 1.1, we will use the distribution of data to calculate regression equations for VO2 for obese children a function of body weight as well as lean body weight (measured by body densitometry). These will be compared to calculated predicted values using reference equations from the normal population. The variation in results using the 2 methods will be analyzed.

For the second set of patients who did not meet maximal exercise parameters, the regression equation can be applied to assess their degree of severity.

PFT parameters such as FEV1, FVC, FEV1/FVC, TLC, ERV, and RV will be correlated with peak VO2 and ventilator parameters of CPET such as VE/VO2 at peak, VE/VCO2 at AT and breathing reserves. For normally distributed data, Pearson correlation coefficient will be used, and Spearman correlation coefficient will be used for non-normally distributed data.

We will further assess the ventilatory capacity and compare the differences between the 2 groups.

STUDY DRUGS AND ALTERNATIVES
Not Applicable

MEDICAL DEVICE
Not Applicable

POTENTIAL CONFLICTS OF INTEREST
No conflict of interest to declare.

POTENTIAL RISKS
This retrospective study does not involve risk to a patients' health or well-being.

POTENTIAL BENEFITS
Among the pediatric obese population, there is a paucity in the literature for validated methods to assess the cardiopulmonary system. Physicians are unable to accurately interpret CPET for these patients and appreciate the fitness and limitations in each of these patients. Our study can answer these questions by providing equations derived from our large data set to be used in the evaluation of adolescent obese patients in the future. This study will also provide insight into methods of using pulmonary data as a surrogate for CPET data in this population.

LIMITATIONS

The limitations of this study include its retrospective nature, and absence of information on patients' underlying physical fitness levels that can also have an impact on their CRF.

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