IJC Metabolic & Endocrine 7 (2015) 3–9

Contents lists available at ScienceDirect

IJC Metabolic & Endocrine

journal homepage: http://www.journals.elsevier.com/ijc-metabolic-and-endocrine

Physiology of oxygen uptake kinetics: Insights from incremental cardiopulmonary exercise testing in the Study of Health in Pomerania

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ARTICLE INFO

Article history:
Received 6 August 2014
Received in revised form 31 January 2015
Accepted 21 February 2015
Available online 5 March 2015

Keywords:
Cardiopulmonary exercise testing
Oxygen uptake efficiency slope
Reference values
Study of Health in Pomerania

ABSTRACT

Background: Cardiopulmonary exercise testing allows for assessment of cardiac and respiratory limitation, but is often affected by patient effort. Indices of oxygen kinetics, including the oxygen uptake efficiency slope (OUES), oxygen uptake–work-rate slope (VO_2–WR slope) and the heart rate–oxygen uptake slope (HR–VO_2 slope) are relatively effort independent but may be affected by patient characteristics.
The objective of this study is to identify the impact of factors, such as age, gender, body size, respiratory function, smoking and beta-blockade on these parameters, as well as generate predictive equations.
Methods: 1708 volunteers from the population-based Study of Health in Pomerania underwent an incremental bicycle exercise protocol. Markers of oxygen kinetics were calculated. Participants with structural heart disease, echocardiographic or lung function pathology were excluded, leaving 577 males and 625 females. Age, height, weight, smoking, forced expiratory volume in 1 s (FEV_1) and beta-blockers were analysed for their influencing power by gender. Quantile regression analysis determined the reference equations for each parameter.
Results: Age, gender, height, weight and FEV_1 (but not percent predicted FEV_1) are strongly related to OUES. Participants using beta-blockers and male smokers had significantly lower OUES values. VO_2–WR slope was minimally affected by age, gender, weight and FEV_1. Gender, height, weight and beta-blocker use, but not FEV_1 and smoking status, were related to the HR–VO_2 slope whilst age was only related in females.
Conclusions: Markers of oxygen kinetics are differentially affected by patient characteristics. This study provides normal reference values for these variables thereby facilitating interpretation of oxygen uptake kinetics in health and disease.

1. Background

Recently new cardiopulmonary exercise test (CPET) parameters, beyond peak oxygen uptake (peakVO_2) have demonstrated an improved ability to predict mortality, in various forms of chronic circulatory (i.e. heart) failure [1–4].

The oxygen uptake efficiency slope (OUES) has greater prognostic power than the established parameters peakVO_2 and the minute ventilation to carbon dioxide production (VE/VCO_2) slope [1]. OUES is the slope of the relationship between oxygen uptake (VO_2) and minute ventilation logarithmically transformed ($\log_{10}$VE) [5,6]. Little is known about the impact of common clinical factors on OUES. Whilst OUES appears to be a simple ratio, it is, in reality, an absolute change in VO_2 during a relative change in ventilation (as this is logarithmically corrected) and therefore will be dependent on the absolute VO_2. OUES might therefore be related to variables like weight that affect resting and exercise VO_2.

The Study of Health in Pomerania (SHIP) is a large population cohort study and recently published the influence of factors such as age, gender, body size, smoking and beta-blockade on many of the more commonly used CPET parameters such as peakVO_2 [7,8]. A sample of participants within the SHIP population also provides predictive equations for a European population, and, unlike previous studies [9–11], the distribution of data was across both genders and a wide age range.

The objective of the present study is to identify the impact of factors, such as age, gender, body size, respiratory function, smoking and beta-blockade, on newer parameters of oxygen kinetics that can easily be

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http://dx.doi.org/10.1016/j.ijcme.2015.02.002

calculated from a standard incremental exercise test, as well as generate predictive equations. These parameters include the OUES, the slope of the relationship between oxygen uptake and work-rate (VO_2–WR slope) and the slope of the relationship between heart rate and oxygen uptake (HR–VO_2 slope).

2. Methods

2.1. Study population

SHIP is a population-based project in the north-east of Germany. Study details are given elsewhere [12,13]. In brief, a sample from 212,157 inhabitants living in the area was selected from the population registration offices, where all German inhabitants are registered. A two-stage cluster sampling method was adopted from the World Health Organization Monitoring Cardiovascular Disease Project in Augsburg, Germany. A representative sample, comprising 7008 adults aged 20–79 years with 292 persons of each sex in each of the twelve 5-year age strata, was drawn. The net sample (without migrated or deceased people) consisted of 6267 eligible subjects, of whom 4308 individuals participated in the baseline study of SHIP (SHIP-0). Data collection started in 1997 and finished in 2001, and from March 2003 until July 2006, a 5-year follow-up examination was performed (SHIP-1). The sample (without migrated, deceased or non-responding people) then comprised 3300 subjects (1589 males, 1711 females) aged 25–85 years. Of those, 1708 individuals (834 males and 874 females) volunteered for a standardised progressive incremental cycle exercise test. All participants gave written informed consent. The study conformed to the principles of the Declaration of Helsinki as reflected by an a priori approval of the Ethics Committee of the University of Greifswald (Greifswald, Germany).

2.2 . Pre-exercise diagnostics and exclusion criteria

The definition of cardiopulmonary disorders was based on self-reported physician's diagnosis, use of specific medication, electro- or echocardiographic pathological findings, and lung function abnormalities measured by spirometry and body plethysmography [14,15]. Reasons for exclusion are reported elsewhere [7]. Initial certification of all physicians and technicians involved in the study was awarded after a minimum of 3 months of training. The data collection phase was monitored by a Data Safety and Monitoring Committee.

Lung function testing was performed as part of the SHIP protocol, but only forced expiration in 1 s (FEV_1) was used in this analysis to assess impact on oxygen kinetic parameters.

2.3 . Exercise testing

A symptom-limited, physician supervised exercise test using one calibrated electromagnetically braked cycle-ergometer (Ergoselect100; Ergoline, Bitz, Germany) was performed according to a modified Jones protocol [9] (stepwise increase in work-rate of 16 W/min, starting with unloaded cycling). Gas exchange variables were analysed breath-by-breath using a VIASYS Healthcare system (Oxycon Pro or Rudolph's mask; VIASYS GmbH, Hoechberg, Germany). Prior to each test, equipment was calibrated in standard fashion with reference gas and volume calibration. Each test was preceded by a ≥3 min resting period. Participants were encouraged to reach maximal exhaustion. All tests were performed according to current guidelines [16,17], with continuous 12-lead ECG monitoring and blood pressure measurements with a standard cuff sphygmomanometer. Minute ventilation (VE), tidal volume (VT), VO_2 and VCO_2 were averaged over 10-second intervals.

Off-line calculations of OUES, VO_2–WR slope and HR–VO_2 slope were conducted using Matlab (Mathworks, Natick, Mass, USA) using only data points during exercise. OUES was defined as the slope of the regression line of VO_2 plotted against $\log_{10}$VE. VO_2–WR slope was defined as the slope of the regression line of VO_2 plotted against work-rate. HR–VO_2 slope was defined as the slope of the regression line of heart rate plotted against VO_2.

For OUES, the current predictive equations were compared to those previously published [6] using the median male and female within each 10-year age group and BMI ≤ 25 vs >25 kg/m^2.

2.4. Statistical analysis

Age, height, weight and BMI were assessed as the independent continuous variables using regression analysis with the CPET parameters as the dependent variables. The cohort was divided into 5 age ranges and 2 body mass index (BMI) groups for graphical data representation. ANOVA was used for categorical potential confounders such as gender, smoking and beta-blocker use. We used quantile regression to construct median, 5th and 95th percentile predictive equations [18]. Based on the results of the regression analysis for each parameter individually, age, gender, height and weight, beta-blocker use, smoking status (graded as current or non-smoker — former smokers are graded with non-smokers) and FEV_1 could be included as co-variates in the model (in keeping with the previous reference ranges published for peakVO_2, anaerobic threshold and O_2-pulse). Each variable was only added to the regression equation for each parameter individually following a significant contribution in the univariate analyses. These co-variates were also included in a multivariate model and the beta co-efficients calculated to show the impact of each co-variate on the model.

A p-value of <0.05 was considered significant throughout.

2.5. Results

Characteristics of study participants are shown in Table 1. There were 1203 participants following clinical exclusions, and one further participant's exercise data was non-interpretable. Age range was 25–84 years (males) and 25–80 years (females, n = 625).

Beta-blocker use is specifically indicated within the tables, however other anti-hypertensive agents were also used including ACE inhibitors or angiotensin-receptor blockers (13% of participants), calcium channel blockers (6%), diuretics (6%), alpha-blockers for hypertension (1%) and other agents (2%).

2.6. Confounding factors on cardiopulmonary exercise testing

The impact of gender, age and BMI is shown in Table 2.

Gender was a determinant of OUES ($R^2 = 0.38$, $p < 0.0001$) and HR–VO_2 slope ($R^2 = 0.30$, $p < 0.0001$), with a weaker interaction with VO_2–WR slope ($R^2 = 0.04$, $p < 0.0001$). Further determinants were assessed for males and females separately. The relationships between determinants and parameters are shown in Table 3.

In both males and females, age was strongly inversely related to OUES. The VO_2–WR slope was only weakly, though significantly, related to age; in males this relationship is positive and inverse in females. The HR–VO_2 slope had a weak, albeit significant, relation to age in females only.

Height had a strong, positive relationship to OUES in males and females. The VO_2–WR slope was not related to height. The HR–VO_2 slope was weakly, inversely related to height in both genders. Weight was strongly positively related to OUES. The VO_2–WR slope was weakly related to weight in both genders. The HR–VO_2 slope was strongly, inversely related to weight in males and females. Importantly BMI did not relate as strongly to any of the 3 parameters as height and weight as co-variates, and the addition of BMI to a simple model of height and weight did not increase the predictive power of the model (i.e. no change in R^2) suggesting that height and weight, but not BMI should be used in the more complex regression models.