CLINICAL SCIENCE

Long-term stability of the oxygen pulse curve during maximal exercise

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INTRODUCTION: Exercise oxygen pulse (O2 pulse), a surrogate for stroke volume and arteriovenous oxygen difference, has emerged as an important variable obtained during cardiopulmonary exercise testing.

OBJECTIVES: We hypothesized that the O2 pulse curve pattern response to a maximal cycling ramp protocol exhibits a stable linear pattern in subjects reevaluated under the same clinical conditions.

METHODS: We retrospectively studied 100 adults (80 males), mean age at baseline of 59 ± 12 years, who performed two cardiopulmonary exercise testings (median interval was 15 months), for clinical and/or exercise prescription reasons. The relative O2 pulse was calculated by dividing its absolute value by body weight. Subjects were classified into quintiles of relative O2 pulse. Cardiopulmonary exercise testing results and the O2 pulse curve pattern, expressed by its slope and intercept, were compared among quintiles of relative O2 pulse at both cardiopulmonary exercise testings.

RESULTS: After excluding the first minute of CPX (rest-exercise transition), the relative O2 pulse curve exhibited a linear increase, as demonstrated by high coefficients of determination (R² from 0.75 to 0.90; p<0.05 for all quintiles). Even though maximum oxygen uptake and relative O2 pulse were significantly higher in the second cardiopulmonary exercise testing for each quintile of relative O2 pulse (p<0.05 for all comparisons), no differences were found when slopes and intercepts were compared between the first and second cardiopulmonary exercise testings (p>0.05 for all comparisons; except for intercept in the 5th quintile).

CONCLUSION: Excluding the rest-exercise transition, the relative O2 pulse exhibited a stable linear increase throughout maximal exercise in adults that were retested under same clinical conditions.

KEYWORDS: Stroke Volume; Coronary Artery Disease; Cardiopulmonary Exercise Testing, Heart Rate; Ramp Protocol.

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INTRODUCTION

The stroke volume (SV) response to exercise is considered one of the most important indices of heart function. Unfortunately, its direct measurement during exercise requires intravascular catheterization, and therefore is rarely performed in the clinical setting. Consequently, several non-invasive methods to estimate exercise SV have been developed. Recently, attention has been given to the oxygen pulse (O2 pulse), a readily available variable obtained during cardiopulmonary exercise testing (CPX), calculated by the ratio of oxygen uptake (VO2) and heart rate (HR). The O2 pulse has been demonstrated to be a powerful predictor of mortality in patients with cardiovascular diseases and it has been associated to the onset of exercise-induced ischemia. Although clinically useful, the O2 pulse is not a simple variable to consider, since it is influenced by many factors that can confound its interpretation, including the presence of diastolic dysfunction, valvular regurgitation, fitness level (athletes may exhibit a pulse at both cardiopulmonary and CV levels). Recently, attention has been given to the O2 pulse curve pattern, when plotted as a function of HR, the O2 pulse equals the slope of the VO2-HR relationship. This
relation of pulse oximetry during steady-state and O₂ pulse curve pattern during progressive pulse desaturation (more than 30 kg/m²) and physiological studies during serial testing under the same clinical conditions and exercise, expressed by its slope and intercept, remains stable during exercise. To our knowledge, the O₂ pulse curve pattern during the now-commonly used non-steady-state (ramp protocol) incremental exercise test has not been well described.

In addition, since SV is directly influenced by body dimensions and O₂ pulse is related to the SV response to exercise, adjustments for body dimensions or weight should be included in studies aiming to evaluate the O₂ pulse response to exercise. If only maximal values are considered, overweight or obese subjects would have a superior O₂ pulse response, which is likely misleading considering the higher prevalence of cardiovascular disease in this particular group. This aspect has been an important limitation of both clinical and physiological studies and requires further exploration.

In the present study, we tested the hypothesis that O₂ pulse corrected for body weight (hereafter termed relative O₂ pulse) in response to non-steady-state incremental exercise testing demonstrates a linear pattern in a well controlled data set of subjects referred for exercise testing at our institution. In addition, we tested the hypothesis that the relative O₂ pulse curve pattern during progressive exercise, expressed by its slope and intercept, remains stable during serial testing under the same clinical conditions and similar drug regimens.

MATERIALS AND METHODS

Study Population

We retrospectively studied a sample consisting of 502 adult non-athletes referred, at least twice, for exercise testing for clinical and/or exercise pre-participation reasons at our clinic from January 02, 2001 to October 31 2009. The study was designed to conform to the Declaration of Helsinki and approved by the Institutional Ethics Committee. Inclusion criteria consisted of patients who: a) performed two maximal cycling ramp protocol CPX at least 3 months apart; b) did not change clinical status and regular use of medications that might have affected the cardiovascular response to exercise (such as beta-blockers) at both CPXs. Subjects with valvular heart disease, lung disease, anemia and those who exhibited O₂ desaturation (more than 4% at maximal effort) during exercise were excluded from the study. In addition, all CPXs stopped early for clinical indications were not considered maximal and were excluded. After applying all inclusion and exclusion criteria, 100 subjects were considered for final analyses (80 men), of whom 50% had coronary artery disease. Baseline clinical characteristics are shown in Table 1. After undergoing the first CPX, 75% of the subjects attended a supervised exercise program at our clinic at least three times a week, while the remaining 25% received advice regarding exercise.

Cardiopulmonary Exercise Testing (CPX)

After providing written informed consent, all subjects underwent a symptom-limited CPX using an electronically-braked cycle ergometer (EC-1600; Cat Eye, Japan or CG-04, Inbraspport, Brazil), according to an individualized ramp protocol designed to allow patients to reach maximum exercise within the desirable range of 8 to 12 minutes. The patients were verbally encouraged to exercise to volitional fatigue, regardless the maximal HR attained. No medications were stopped before the CPX. The electrocardiogram (ECG) (Cardiolife TEC 7100; Nihon-Kohden, Japan; or Elite Ergo PC 3.2.1.5; Micromed, Brazil) was continuously monitored via a single lead (CC5 or CM5). Ventilatory expired gas analysis was obtained by a metabolic system (VO2000; MedGraphics, US). The air flow and oxygen and carbon dioxide sensors were calibrated before each test using 2-liter syringes and gases with known volumes of oxygen, nitrogen, and carbon dioxide concentrations. No test results were classified as indeterminate. All exercise tests were performed, analyzed and reported according to a standardized protocol by a single experienced physician.

Hemodynamic and Ventilatory Assessments

The HR was analyzed beat-by-beat and expressed every 10-s. Maximum HR was considered as the highest 10-s average obtained during the CPX. The age-predicted

| Table 1 - Baseline clinical characteristics by quintiles of maximum relative O₂ pulse. |
|---------------------------------------------------------------|
| All (n = 100) | Q1 | Q2 | Q3 | Q4 | Q5 |
|----------------|----|----|----|----|----|
| **Medications** | | | | | |
| Beta blockers | 41 | 5/20 | 10/50 | 5/20 | 12/60* | 9/45 |
| Calcium channel blockers | 16 | 4/20 | 4/20 | 4/20 | 3/15 | 1/5 |
| Nitrates | 10 | 2/10 | 2/10 | 1/5 | 4/20 | 1/5 |
| ACE-inhibitors | 14 | 2/10 | 3/15 | 7/35 | 2/10 | 0 |
| Diuretics | 12 | 6/30 | 2/10 | 3/15 | 0 | 1/5* |
| Statins | 63 | 12/60 | 16/80 | 13/65 | 13/65 | 9/45* |
| **Risk factors** | | | | | |
| Hypertension | 43 | 8/40 | 10/50 | 9/45 | 9/45 | 7/35 |
| Dyslipidemia | 50 | 9/45 | 12/60 | 10/50 | 11/55 | 8/40 |
| Diabetes | 13 | 1/5 | 4/20 | 3/15 | 5/25 | 0 |
| Obesity (BMI ≥ 30 kg/m²) | 14 | 3/15 | 3/15 | 3/15 | 3/15 | 2/10 |
| **Medical history/Procedures** | | | | | |
| Apparently healthy | 29 | 7/35 | 2/10 | 5/25 | 6/30 | 9/45* |
| Coronary Artery Disease | 50 | 8/40 | 13/65 | 10/50 | 12/60 | 7/35 |
| CABG | 26 | 4/20 | 9/45 | 6/30 | 5/25 | 2/10* |
| PTCA | 26 | 3/15 | 6/30 | 7/35 | 6/30 | 4/20 |

CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; Q, quintile; * p < 0.05 vs. Q1; † p<0.05 vs. Q2; ‡ p<0.05 vs. Q3.
maximum HR was also calculated by the equation \[210 - (0.65 \times \text{age})\]. \(^{19}\) Expired ventilatory data were analyzed and expressed at each 10-s. Maximum \(\text{VO}_2\) (\(\text{VO}_2\text{max}\)) was expressed as the highest 60-s average value obtained during the CPX. The age-predicted \(\text{VO}_2\text{max}\) was also calculated according to standard equations. \(^{19}\) Delta \(\text{VO}_2/\text{workload}\) was calculated as: \(\text{VO}_2\text{max} - \text{resting VO}_2\) divided by maximum workload and expressed in \(\text{mL.min}^{-1}.\text{watts}^{-1}\). For practical purposes, the resting \(\text{VO}_2\) while sitting on the cycle ergometer was considered to be 3.5 \(\text{mL.kg}^{-1}.\text{min}^{-1}\) for all subjects. \(\text{O}_2\) pulse was calculated by dividing \(\text{VO}_2\) by HR obtained every 10-s during CPX. Maximum \(\text{O}_2\) pulse was expressed as the highest 60-s average value and was expressed in milliliters per beat. In addition, this value was expressed as a percentage of age-predicted achieved, which corresponds to the ratio between the predicted values for maximum \(\text{VO}_2\) and maximum HR. In order to remove the influence of body weight on the magnitude of \(\text{O}_2\) pulse response during CPX, its values were then divided by weight in kilograms (relative \(\text{O}_2\) pulse). In order to make the mathematical manipulations of the study easier, all results related to the relative \(\text{O}_2\) pulse were multiplied by 100.

### Data management and statistical analyses

One of the strategies for testing our hypothesis was to divide the sample into quintiles, according to the results of maximum relative \(\text{O}_2\) pulse obtained during the first CPX. Dividing the sample by quintiles allowed us to compare the stability of relative \(\text{O}_2\) pulse in subjects with different fitness levels and values of maximum relative \(\text{O}_2\) pulse. Paired students t-tests were used to assess the differences for key variables between the first and second CPX, when comparisons were made for the entire sample. A \(\chi^2\) statistics was used for comparisons of categorical variables among quintiles of relative \(\text{O}_2\) pulse. For comparisons made on key variables among quintiles of maximum relative \(\text{O}_2\) pulse, a repeated-measures two-way ANOVA with Greenhouse-Geisser correction \(^{20}\) was performed, in which CPX (i.e., first versus second CPX) and quintiles of maximum relative \(\text{O}_2\) were the main factors. After excluding the first minute (rest-exercise transition) of the CPX, Pearson’s product-moment correlations between relative \(\text{O}_2\) pulse and CPX duration were performed for each CPX, in order to test the linearity of the relative \(\text{O}_2\) pulse curve during progressive exercise. After testing the adequacy of linear regression by the magnitude of coefficient of determination of the relative \(\text{O}_2\) pulse, we then calculated the slopes and intercepts among quintiles for both CPX. To compare the slopes and intercepts, a paired student t-test was performed. All continuous data were reported as mean \(\pm\) SEM or as otherwise indicated. NCSS statistical software (Kaysville, UT) was used to perform all analyses. Statistical significance was set at \(p<0.05\) for all calculations.

### RESULTS

The median time between the first and second CPX was 15 months (minimum and maximum of 5 and 62 months, respectively). Table 1 presents the baseline clinical characteristics of all patients divided by quintiles of maximum relative \(\text{O}_2\) pulse. Except for the higher proportion of apparently healthy subjects and lower proportion of coronary artery bypass surgery in the 5th quintile compared to the 2nd quintile \((p<0.05)\), clinical characteristics were homogeneously distributed among all groups. The proportion of subjects taking beta-blockers differed only between the 4th quintile versus 1st and 3rd quintiles \((p<0.05\) for both comparisons).

Demographic characteristics and exercise responses for both CPX are shown in Table 2 for the entire sample. No significant differences were found for body weight \((p=0.76)\). Except for maximum HR \((p=0.53)\), diastolic blood pressure \((p=0.53)\) and delta \(\text{VO}_2/\text{workload}\) \((p=0.14)\), significant differences were found for all other maximum results when the first and second CPXs were compared; the average increases were 11% and 10% for \(\text{VO}_2\text{max}\) and maximum relative \(\text{O}_2\) pulse, respectively.

### Table 2 - Demographic characteristics and exercise test responses.

| VARIABLE | N = 100 | First CPX | Second CPX | p-value |
|----------|---------|-----------|------------|---------|
| **Demographic characteristics** | | | | |
| Age (yr) | 59 ± 1.2 | 60 ± 1.3 | <0.001 |
| Body mass index (kg/m²) | 26.9 ± 0.4 | 26.9 ± 0.4 | 0.82 |
| Height (cm) | 170.4 ± 0.9 | 170.5 ± 0.9 | 0.14 |
| Weight (kg) | 78.4 ± 1.3 | 78.3 ± 1.4 | 0.76 |
| **Resting Values** | | | | |
| Heart rate (beats/min) | 63 ± 1.1 | 60 ± 1.3 | 0.01 |
| Blood pressure (mm Hg) | | | | |
| Systolic | 133 ± 1.5 | 127 ± 2.3 | 0.02 |
| Diastolic | 77 ± 1.0 | 72 ± 1.4 | <0.001 |
| **Maximum Values** | | | | |
| Heart rate (beats/min) | 144 ± 2.6 | 144 ± 2.5 | 0.53 |
| Blood pressure (mm Hg) | | | | |
| Systolic | 201 ± 3.1 | 207 ± 2.6 | 0.009 |
| Diastolic | 91 ± 1.3 | 91 ± 1.3 | 0.53 |
| \(\text{VO}_2\) (mL.kg\(^{-1}.\text{min}^{-1}\)) | 25.1 ± 1.0 | 28.2 ± 1.0 | <0.001 |
| \(\text{O}_2\) pulse (mL.beat\(^{-1}\)) | 13.7 ± 0.5 | 15.2 ± 0.5 | <0.001 |
| Relative \(\text{O}_2\) pulse (mL.beat\(^{-1}.\text{kg}^{-1}\)) | 17.4 ± 0.5 | 19.3 ± 0.5 | <0.001 |
| % achieved age predicted \(\text{O}_2\) pulse | 110 ± 3.2 | 128 ± 3.3 | <0.001 |
| Workload (watts) | 133 ± 6.1 | 150 ± 6.7 | <0.001 |
| Delta \(\text{VO}_2/\text{workload}\) (mL.min\(^{-1}.\text{watts}^{-1}\)) | 12.9 ± 0.22 | 13.2 ± 0.31 | 0.14 |
| Exercise duration (minutes) | 10 ± 0.2 | 11 ± 0.2 | <0.001 |

Values are mean \(\pm\) SEM. \(\text{VO}_2\), oxygen uptake; \(\text{O}_2\), oxygen.
Table 3 - Cardiopulmonary exercise testing results by quintiles of maximum relative O₂ pulse.

| Quintile (Q) (n=20) | Body Weight (kg) | Maximum VO₂ (mL.kg⁻¹.min⁻¹) | Maximum heart rate (beats.min⁻¹) | Maximum O₂ pulse (mL.beat⁻¹) | Maximum relative O₂ pulse (mL.beat⁻¹.kg⁻¹) | Delta VO₂/workload (mL.min⁻¹.watts⁻¹) |
|---------------------|------------------|-------------------------------|---------------------------------|-----------------------------|------------------------------------------|--------------------------------------|
| Q1 (n=20)           |                  |                               |                                 |                             |                                          |                                      |
| First CPX           | 74.2 ± 3.6       | 16.4 ± 0.6                    | 143 ± 4                         | 8.6 ± 0.4                   | 11.6 ± 0.3                               | 12.1 ± 0.6                           |
| Second CPX          | 74.1 ± 3.7       | 20.2 ± 1.0                    | 143 ± 4                         | 10.6 ± 0.6                  | 14.3 ± 0.6                               | 13.3 ± 0.7                           |
| Q2 (n=20)           |                  |                               |                                 |                             |                                          |                                      |
| First CPX           | 75.2 ± 3.3       | 19.5 ± 1.0                    | 138 ± 7                         | 10.8 ± 0.5                  | 14.3 ± 0.1                               | 12.5 ± 0.4                           |
| Second CPX          | 74.9 ± 3.6       | 24.3 ± 1.3                    | 140 ± 6                         | 13.2 ± 0.8                  | 17.6 ± 0.7                               | 12.9 ± 0.5                           |
| Q3 (n=20)           |                  |                               |                                 |                             |                                          |                                      |
| First CPX           | 82.3 ± 2.7       | 22.9 ± 0.7                    | 142 ± 6                         | 13.4 ± 0.4                  | 16.3 ± 0.2                               | 13.0 ± 0.4                           |
| Second CPX          | 81.5 ± 3.0       | 26.4 ± 1.3                    | 143 ± 5                         | 15.1 ± 0.6                  | 18.7 ± 0.7                               | 12.7 ± 0.4                           |
| Q4 (n=20)           |                  |                               |                                 |                             |                                          |                                      |
| First CPX           | 82.2 ± 2.6       | 27.1 ± 1.5                    | 139 ± 6                         | 16.2 ± 0.6                  | 19.7 ± 0.2                               | 12.8 ± 0.4                           |
| Second CPX          | 82.6 ± 5.3       | 29.6 ± 2.2                    | 139 ± 6                         | 17.8 ± 1.1                  | 21.4 ± 1.1                               | 12.6 ± 0.4                           |
| Q5 (n=20)           |                  |                               |                                 |                             |                                          |                                      |
| First CPX           | 78.2 ± 2.4       | 39.9 ± 2.5                    | 159 ± 5                         | 19.5 ± 1.0                  | 24.9 ± 1.0                               | 13.9 ± 0.5                           |
| Second CPX          | 79.6 ± 2.5       | 40.3 ± 2.6                    | 160 ± 6                         | 19.5 ± 1.1                  | 24.4 ± 1.2                               | 14.8 ± 1.1                           |

p value

| Quintile factor | 0.018 | <0.001 | 0.002 | <0.001 | <0.001 |
| CPX factor      | 0.949 | 0.004  | <0.843| 0.002  | <0.001 |
| Interaction     | 0.998 | 0.740  | 0.999 | 0.001  | 0.113  |

Values are mean ± SEM. VO₂, oxygen uptake; O₂, oxygen; Q, quintile. * All results of maximum relative O₂ pulse were multiplied by 100.

Table 4 - Linear regression results by quintiles of maximum relative O₂ pulse.

| Quintile (Q) | R² | Slope* (95% CI) | Slope p-value versus Q5 | Slope p-value 1st vs 2nd CPX | Intercept (95% CI) | Intercept p-value 1st vs 2nd CPX |
|--------------|----|-----------------|--------------------------|-----------------------------|--------------------|-------------------------------|
| Q1           |    |                 |                          |                             |                    |                               |
| First CPX    | 0.78 | 0.61 (0.47 - 0.76) | <0.001                   | 0.57                        | 6.9 (5.8 - 8.0)     | 0.22                          |
| Second CPX   | 0.79 | 0.68 (0.50 - 0.85) | 0.04                     |                            | 8.1 (9.1 - 12.3)    |                               |
| Q2           |    |                 |                          |                             |                    |                               |
| First CPX    | 0.75 | 0.62 (0.43 - 0.80) | 0.003                    | 0.37                        | 9.4 (8.3 - 10.5)    | 0.13                          |
| Second CPX   | 0.78 | 0.73 (0.56 - 0.90) | 0.34                     |                            | 10.7 (9.11 - 14.0)  |                               |
| Q3           |    |                 |                          |                             |                    |                               |
| First CPX    | 0.82 | 0.68 (0.51 - 0.85) | 0.009                    | 0.27                        | 10.3 (9.1 - 11.5)   | 0.82                          |
| Second CPX   | 0.86 | 0.79 (0.63 - 0.95) | 0.61                     |                            | 10.5 (8.7 - 12.4)   |                               |
| Q4           |    |                 |                          |                             |                    |                               |
| First CPX    | 0.84 | 0.88 (0.70 - 1.05) | 0.36                     | 0.54                        | 11.1 (9.7 - 12.5)   | 0.10                          |
| Second CPX   | 0.85 | 0.81 (0.62 - 1.01)| 0.79                     |                            | 12.6 (11.0 - 14.2)  |                               |
| Q5           |    |                 |                          |                             |                    |                               |
| First CPX    | 0.90 | 0.99 (0.82 - 1.15) | -                        | 0.12                        | 12.8 (10.9 - 14.6)   | 0.007                         |
| Second CPX   | 0.89 | 0.85 (0.66 - 1.03)| -                        |                            | 15.4 (13.6 - 17.1)  |                               |

R², coefficient of determination for correlation between Relative O₂ Pulse and CPX duration; CI, Confidence interval; Q, quintile. * Slopes significantly different from zero (p<0.05).
compared separately in men (p = 0.75) and women (p = 0.24); among subjects taking beta-blockers (p = 0.78) and in subjects with known coronary artery disease (p = 0.31).

Figure 1 shows the relative O$_2$ pulse curves as a function of percentage time during first and second CPX for 1$^{st}$ and 5$^{th}$ quintiles. No differences were found between CPXs for each quintile (p > 0.05). The vertical line highlights the linearity of the curves after exclusion of the first 10% of the CPX time.

**DISCUSSION**

The results of the present study add to the existing body of research showing a linear increase in O$_2$ pulse throughout maximal incremental non-steady-state exercise testing. In addition, to our knowledge, this is the first study to demonstrate the stability of the O$_2$ pulse curve pattern in a large group of subjects under identical clinical status, who served as their own control in a test-retest design.

Our results are in agreement with previous studies in that VO$_{2\text{max}}$ and maximum O$_2$ pulse were within normal limits and were significantly higher in the second CPX (p < 0.05; Table 2 and 3). Even though the purpose of our study was not to assess the influence of exercise training, the higher values observed for VO$_{2\text{max}}$ and maximum O$_2$ pulse between tests probably occurred because of the training influence, since almost all the subjects increased their physical activity levels. In addition, an effect due to counseling may have occurred since the remaining 25% of the patients were underwent activity counseling after undergoing their initial CPX.

A strong debate regarding the behavior of the SV response to progressive maximum exercise still exists. Variations in these studies include a decrease, a plateau or an increase in SV when approaching volitional exhaustion, when untrained, moderately trained or heart disease patients are considered. The prospective design and complexity of methods for measuring SV in most studies has generally limited sample sizes, and thus limited the external validity of the results. In addition, different testing protocols (graded or constant), type of ergometer (treadmill or cycle), criteria for termination of the test (exhaustion or pre-determined % of age-predicted maximum HR) and also the lack of control of confounding variables such as body weight have limited the interpretation of previous results.

Our results support the concept that SV, estimated by relative the O$_2$ pulse response to maximum exercise, increases in a linear fashion throughout exercise in non-athletes as shown by the high R$^2$ (Table 4). A decrease or a plateau in relative O$_2$ pulse would lead to a reduced R$^2$ which was not the case in our results. Our approach was novel in that we excluded the first minute of CPX to calculate the linearity and slopes of relative O$_2$ pulse. At the onset of a ramp protocol, the lack of linearity in the intensity increment affects the linear increase of HR as a function of VO$_2$ (average R$^2$ = 0.53 for both CPX). As a consequence, an artificial upward shift in O$_2$ pulse slope occurs at the onset of exercise, as seen in Figure 1 during the first 10% of the test (the slopes are visually different before and after the vertical line). Thus, excluding the first minute of the CPX has an advantage in that it allows the direct use of the O$_2$ pulse slope, obviating the need to calculate the VO$_2$ and HR slopes. Although linearity was present irrespective of quintile of maximum relative O$_2$ pulse (high R$^2$ in all quintiles) it is clear that the higher the slope of the relative O$_2$ pulse, the higher will be its linearity, as demonstrated by the positive trend shown in the results of R$^2$ among quintiles of relative O$_2$ pulse (Table 4).

Data have recently emerged in regard to the association between the O$_2$ pulse pattern during CPX and the presence of ischemia during exercise. Belardinelli et al. studied 202 patients with known coronary heart disease who underwent both myocardial scintigraphy and cycle CPX. By logistic regression analysis, the only independent predictors of a positive myocardial scintigraphy were O$_2$ pulse flattening duration (calculated from the inflection point occurring in VO$_2$ as related to work) and the slope of VO$_2$/workload. The slope of VO$_2$/workload was within normal limits from the start of exercise to a point corresponding to the onset of myocardial ischemia. However, as work rate increased further, an inflection point was evident in most patients with detectable myocardial ischemia, with the cutoff of 3.9 mL.min$^{-1}$watts$^{-1}$ being the strongest independent predictor according to a hierarchical model. Supporting these results, Chaudhry et al., showed that at the onset of myocardial ischemia, a decrease in the O$_2$ pulse with increasing work rate and a abrupt decrease in the slope of VO$_2$/workload occurred in a 68 year old woman referred for CPX as part of a preoperative evaluation. The O$_2$ pulse patterns observed in these studies are most likely explained by reduced stroke volume at higher intensity exercise due to myocardial ischemia. In contrast, this was not the case in our relatively normal subjects, since delta VO$_2$/workload was within normal limits in all quintiles of maximum relative O$_2$ pulse (Table 3) and the slopes were significantly different from zero (Table 4). A novel finding shown by the present study was that, after a median time of 15 months in between first and second CPXs, the relative O$_2$ pulse curve pattern remained unchanged as demonstrated by the lack of significant differences in slopes and intercepts regardless the maximum relative O$_2$ pulse presented in each quintile (Table 4). The slopes and intercepts were similar despite the significantly higher values of VO$_{2\text{max}}$ in second CPX in each
that arterio-venous oxygen difference increases in a predictable way with respect to workload, reaching an approximate constant peak value at close to maximal intensity.

Therefore, after the point where arterio-venous oxygen difference tends to reach its maximum value, any further increase in $O_2$ pulse will reflect changes in SV. Finally, although the aim of the present study was not to assess the influence of exercise training of key dependent variables, we cannot exclude the possible influence of the supervised exercise program or counseling on our results. Considering all the above, some caution should be made when interpreting the results of the present study.

Clinical implications

The novelty of our study lays in the fact that it was the first study to demonstrate the stability of $O_2$ pulse. By showing the $O_2$ pulse curve stability after a median time of 15 months in subjects under similar clinical conditions and drug regimens, we reject the hypothesis that factors such as measurement variability inherent to any test (in our case CPX), could affect the $O_2$ pulse pattern. This increases in importance considering the established association between $O_2$ pulse curve pattern and myocardial ischemia. In other words, if such variability in the $O_2$ pulse curve pattern was present, rejecting our hypothesis, it could be difficult to discriminate those with a flat $O_2$ pulse curve truly caused by myocardial ischemia from those with a flat curve caused just by variations in measurements inherent to CPX.

CONCLUSIONS

After excluding the first minute of CPX (rest-exercise transition), the relative $O_2$ pulse exhibited a linear increase throughout maximum exercise. In addition, in a test-retest design, where subjects served as their own controls, the pattern of relative $O_2$ pulse remained stable.

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REFERENCES

1. Astrand PO, Cuddy TE, Saltin B, Stenberg J. Cardiac Output during Submaximal and Maximal Work. J Appl Physiol. 1964;19:268-74.
2. Linton DM, Gilson D. Advances in noninvasive cardiac output monitoring. Am Card Anaesth. 2002;14:1-8.
3. Oliveira RB, Myers J, Araújo CG, Abella J, Mandic S, Froelicher V. Maximal exercise oxygen pulse as a predictor of mortality among male veterans referred for exercise testing. Eur J Cardiovasc Prev Rehabil. 2009;16:358-64, doi: 10.1097/HJR.0b013e3282392de8.
4. Oliveira RB, Myers J, Araújo CG, Arena R, Mandic S, Bensimhon D, et al. Does peak oxygen pulse complement peak oxygen uptake in risk stratifying patients with heart failure? Am J Cardiol. 2009;104:554-8, doi: 10.1016/j.amjcard.2009.04.022.
5. Belardinelli R, Lacaaprice F, Carle F, Minucci A, Cianci G, Perna N, et al. Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing. Eur Heart J. 2003;24:1304-13, doi: 10.1016/S0195-668X(03)00210-0.
6. Munhoz EC, Hollanda R, Vargas JP, Silveira CW, Lemos AL, Hollanda RM, et al. Flattening of oxygen pulse during exercise may detect extensive myocardial ischemia. Med Sci Sports Exerc. 2007;39:1221-6, doi: 10.1249/mss.0b013e3180601136.
7. Lim JC, McAvaney TJ, Fleg JL, Shapiro EP, Turner KL, Bacher AC, et al. Oxygen pulse during exercise is related to resting systolic and diastolic left ventricular function in older persons with mild hypertension. Am Heart J. 2005;150:941-6, doi: 10.1016/j.ahj.2004.12.021.
8. Tada H, TamajI, Takaki H, Ohnishi E, Okano Y, Yoshioka T. Mild mitral regurgitation reduces exercise capacity in patients with idiopathic dilated cardiomyopathy. Int J Cardiol. 1997;58:41-5, doi: 10.1016/s0167-5273(96)02389-2.
9. Rowland T. Endurance athletes’ stroke volume response to progressive exercise: a critical review. Sports Med. 2009;39:687-95, doi: 10.2165/0000305-000000000-00000.

10. Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ. Principles of exercise testing and interpretation. Baltimore: Lippincott, Williams & Wilkins, 2004. p. 151.

11. Whipp BJ, Higgenbotham MB, Cobb FC. Estimating exercise stroke volume from asymptotic oxygen pulse in humans. J Appl Physiol. 1996;81:2674-9.

12. Collis T, Devereux RB, Roman MJ, de Simone G, Yeh J, Howard BV, et al. Relations of stroke volume and cardiac output to body composition: the strong heart study. Circulation. 2001;103:820-5.

13. de Simone G, Devereux RB, Daniels SR, Mureddu G, Roman MJ, Kimball TR, et al. Stroke volume and cardiac output in normotensive children and adults. Assessment of relations with body size and impact of overweight. Circulation. 1997;95:1837-43.

14. Laukkanen JA, Kurl S, Salonen JT, Lakka TA, Rauramaa R. Peak oxygen pulse during exercise as a predictor for coronary heart disease and all cause death. Heart. 2006;92:1219-24, doi: 10.1136/hrt.2005.077487.

15. Babb TG, Korzick D, Meador M, Hodgson JL, Buskirk ER. Ventilatory response of moderately obese women to submaximal exercise. Int J Obes. 1991;15:59-65.

16. Bambhani Y, Norris S, Bell G. Prediction of stroke volume from oxygen pulse measurements in untrained and trained men. Can J Appl Physiol. 1994;19:49-59.

17. Myers J, Buchanan N, Smith D, Neutel J, Bowes E, Walsh D, et al. Individualized ramp treadmill. Observations on a new protocol. Chest. 1992;101:2369-241S.

18. Myers J, Buchanan N, Walsh D, Kraemer M, McAuley P, Hamilton-Wessler M, et al. Comparison of the ramp versus standard exercise protocols. J Am Coll Cardiol. 1991;17:1334-42, doi: 10.1016/S0735-1097(10)80143-6.

19. Jones N. Clinical Exercise Testing. Philadelphia, PA: WB Saunders Company, 1997. p. 167.

20. Ludbrook J. Repeated measurements and multiple comparisons in cardiovascular research. Cardiovasc Res. 1994;28:303-11, doi: 10.1093/cvr/28.3.303.

21. Bambhani YN. Prediction of stroke volume during upper and lower body exercise in men and women. Arch Phys Med Rehabil. 1995;76:713-8, doi: 10.1016/S0003-9995(95)80244-9.

22. Lucia A, Foster C. Decrease or no decrease in the stroke volume of healthy humans approaching volitional exhaustion during large muscle mass exercise. J Appl Physiol. 2006;104:284-5; author reply 284-5, doi: 10.1152/japplphysiol.01073.2007.

23. Vella CA, Robergs RA. A review of the stroke volume response to upright exercise in healthy subjects. Br J Sports Med. 2005;39:190-5, doi: 10.1136/bjsm.2004.013037.

24. Warburton DE, Gledhill N. Counterpoint: Stroke volume does not decline during exercise at maximal effort in healthy individuals. J Appl Physiol. 2008;104:276-8; discussion 278-9, doi: 10.1152/japplphysiol.00595.2007a.

25. Proctor DN, Beck KC, Shen PH, Eickhoff TJ, Halliwill JR, Joyner MJ. Influence of age and gender on cardiac output-VO2 relationships during submaximal cycle ergometry. J Appl Physiol. 1998;84:599-605.

26. Hagberg JM, Allen WK, Seals DR, Hurley BF, Elsnser AA, Holloszy JO. A hemodynamic comparison of young and older endurance athletes during exercise. J Appl Physiol. 1985;58:2041-6.

27. Gledhill N, Cox D, Jammik R. Endurance athletes’ stroke volume does not plateau: major advantage is diastolic function. Med Sci Sports Exerc. 1994;26:1116-21.

28. Palange P, Ward SA, Carlsson KH, Casaburi R, Gallagher CG, Gosselink R, et al. Recommendations on the use of exercise testing in clinical practice. Eur Respir J. 2007;29:185-209, doi: 10.1183/09031936.0004906.

29. Chaudhry S, Arena R, Wasserman K, Hansen JE, Lewis GD, Myers J, et al. Exercise-induced myocardial ischemia detected by cardiopulmonary exercise testing. Am J Cardiol. 2009;103:615-9, doi: 10.1016/j.amjcard.2008.10.034.

30. Hsi WL, Wong PL, Lai JS. Submaximal oxygen pulse divided by body weight during incremental exercise test. Am J Phys Med Rehabil. 1997;76:297-303, doi: 10.1097/00002060-199707000-00008.

31. Lavie CJ, Milani RV, Mehra MR. Peak exercise oxygen pulse and prognosis in chronic heart failure. Am J Cardiol. 2004;93:588-93, doi: 10.1016/j.amjcard.2003.11.023.

32. Salvadori A, Fanari P, Fontana M, Buontempi L, Saezza A, Baudo S, et al. Oxygen uptake and cardiac performance in obese and normal subjects during exercise. Respiration. 1999;66:25-33, doi: 10.1139/n00029333.

33. Klimann E, Fink G, Lebzelter J, Krebbaum T, Kramer MR. The relationship between left ventricular function assessed by multigated radionuclide test and cardiopulmonary exercise test in patients with ischemic heart disease. Chest. 2002;121:841-5, doi: 10.1378/chest.121.3.841.

34. Klimann E, Kusniec J, Stern J, Fink G, Farbeinstein H. Contribution of cardiopulmonary indices in the assessment of patients with silent and symptomatic ischemia during exercise testing. Int J Cardiol. 1996;53:257-63, doi: 10.1016/0167-5273(95)02551-0.

35. Stringer W, Wasserman K, Casaburi R, Porszasz J, Maehara K, French W. Lactic acidosis as a facilitator of oxygen hemoglobin dissociation during exercise. J Appl Physiol. 1994;76:1462-7, doi: 10.1152/1.357720.