Comparison of the respiratory and hemodynamic responses of healthy subjects to exercise in three different protocols

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Although the importance of exercise testing has been well established, standardization of protocols is lacking. In the current study three protocols were compared with respect to respiratory and hemodynamic variables at submaximal and peak exercise. Fifteen healthy young men underwent three maximal exercise tests using the following protocols: (I) an increase of 30 Watt, every three minutes; (II) an increase of 10 Watt, every minute; (III) a continuous load increase of 10 Watt/min. Respiratory measurements were made of oxygen uptake (VO₂), carbon dioxide output (VCO₂), minute ventilation (V̇e) and tidal volume (VT). Hemodynamic measurements were made of ECG, heart rate (HR), blood pressure and stroke volume (SV). The latter variable was measured by means of electrical impedance cardiography (EIC). There were no differences in mean maximum load or peak-VO₂ between protocols I, II and III. The course of SV was similar in all protocols, i.e. an increase of about 30% until 100 Watt, with a subsequent stabilization until maximum load. All other hemodynamic measurements were similar in both protocols, too. Significant differences were found in submaximal values of VO₂ and VCO₂. There were no differences in other gas-exchange variables at any moment during exercise. With respect to the VO₂max or the hemodynamic response to exercise, any protocol can be used. For the evaluation of submaximal exercise, the protocol that has been used has to be taken into account. Differences at these levels are not related to differences in hemodynamic response.

Key words: Cardiopulmonary exercise testing; hemodynamics; impedance cardiography; oxygen uptake; protocol.

INTRODUCTION

Although cardiopulmonary exercise (CPX) testing has acquired an important role in occupational medicine, standardization of exercise protocols is lacking. Some exercise laboratories use protocols in which load is increased stepwise, whereas others use protocols with a ramping load increment. Previous research suggests that when the duration of a test remains constant, no large differences in gas-exchange will be found at peak-exercise. However, especially when simulating working situations, accurate interpretation of submaximal-exercise data is warranted, too. Little is known about the comparability of different exercise protocols at these levels. From results of studies concerning gas-exchange kinetics, it can be hypothesized that differences at these levels will be found.

Since in healthy subjects exercise is considered to be mainly limited by the central circulation, evaluation of the hemodynamic response during CPX-testing would be very useful. Unfortunately, the evaluation of this response poses practical problems. The course of heart rate (HR) is monitored as the primary hemodynamic variable, although those of stroke volume (SV), cardiac output (CO, SV ± HR), and systemic vascular resistance (SVR) would give more valuable information about the cardiac status. Invasive techniques for continuous measurement of SV imply unacceptable risks for routine use. Noninvasive techniques are frequently considered to be invalid or impractical during
exercise testing. One of these techniques is Electrical Impedance Cardiography (EIC), and although its validity has been extensively shown,7,8 its use has been limited. This may be related to the fact that it has always been very laborious to acquire noise-free signals and, subsequently, to interpret them. Recently, development of computer averaging techniques9-11 and improvements in electrode positioning12,13 have yielded new possibilities for the use of EIC during exercise.

In this study, three different exercise protocols (routinely used in European exercise laboratories) were compared in 15 healthy male adults. Two of the protocols (one of which was proposed by the ECSC15) had a stepwise load increment, and one had a ramping load increment. In addition to standard CPX measurements, hemodynamic function was evaluated. Aim of this study was the assessment of possible differences in gas exchange or hemodynamic performance between exercise protocols, especially at submaximal exercise-levels. This should provide a contribution to the standardization of CPX-testing.

SUBJECTS AND METHODS

Fifteen healthy non-smoking male volunteers participated in the study. Their characteristics are shown in Table 1. In order to calculate fat free mass, total body impedance was measured (IPG-104 impedance MiniLab, RJI Systems, Detroit, USA and Akern, Florence, Italy).14 After physical examination, blood pressure measurement and ECG-recording, pulmonary function was evaluated by assessment of static and dynamic lung volumes, single breath carbon monoxide diffusing capacity (Masterlab, Jaeger, Würzburg, Germany), plethysmographic airway resistance (BodyScreen II, Jaeger) and maximal expiratory and inspiratory pressures (Dataspot, converted in our own laboratory). The lung function data are shown in Table 2. Reference values are those from Quanjer,15 Cotes16 and Black.17 The exercise tests were performed on a bicycle ergometer (Ergoline 900, Blitz, Germany) in the upright position. Subjects completed a series of three protocols in random order. Subjects were familiarized with the testing method by performing one maximal test in advance. This test was not included in the analysis. Subjects were requested not to participate in vigorous exercise the day before the test and to refrain from food or drinks in the two hours preceding the test. Between two tests a period of at least 24 hours was taken as recovery period. After three minutes of unloaded pedalling, one of three protocols was used:

I: an increase of 30 Watt, every three minutes.

II: an increase of 10 Watt, every minute.

III: a continuous load increase of 10 Watt/min ('ramp' pattern).

The subjects were stimulated to exercise to exhaustion. Measurements were continued during recovery, which comprised 5 minutes of cycling at 50 Watt and 5 minutes of upright rest.

Measurements of oxygen uptake (VO2), carbon dioxide output (VCO2), minute ventilation (VE) and tidal volume (VT) were made breath-by-breath using an open system (Oxycon Gamma, Mijnhardt, Bunnik, The Netherlands). Calculations were made of breathing frequency (f), respiratory exchange ratio (RER, VCO2 divided by VO2) and respiratory equivalents for O2 and CO2 (eqO2 and eqCO2, VE divided by VO2 and VCO2 respectively). Electrocardiographic measurements (Hellige, Freiburg, Germany) were performed continuously and blood pressure was determined by sphygmomanometry every three minutes.

SV measurements were performed by means of EIC (IPG-104). This technique relates changes in thoracic impedance to changes in thoracic blood volume. A constant sinusoidal alternating current of 0.8 mA and 60 kHz is introduced through spot electrodes (Red Dot, 3M, St Paul, USA) on the forehead and lower abdomen (see Figure 1). Two pairs of electrodes in the mid-axillary lines at the base of the neck and at the level of the xiphoid of the sternum detect changes in voltage. This electrode configuration has been developed and validated in our own laboratory.12 It is a modification of the Kubicek18 electrode configuration and gives comparable results.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± standard deviation</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>23.3 ± 2.5</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.86 ± 0.08</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.1 ± 6.3</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>22.6 ± 1.5</td>
</tr>
<tr>
<td>Hb (mmol/l)</td>
<td>9.3 ± 0.6</td>
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<tr>
<td>FFM (kg)</td>
<td>67.9 ± 4.3</td>
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<tr>
<td>FFM (%)</td>
<td>87.5 ± 6.2</td>
</tr>
</tbody>
</table>

BMI = body mass index, [weight/(height)²];
FFM = fat free mass [3.04 + (0.85 x height²)/resistance], assessed by whole body impedance measurement;
FFM (%) = FFM as percentage of body weight.
SV was calculated according to the formula of Kubicek:

\[ SV = \rho \times \left( \frac{L}{Z_0} \right)^2 \times \frac{dZ}{dt_{\text{max}}} \times \text{LVET}, \]

where \( \rho \) = resistivity, calculated as 53.2 \( \times 10^{-22} \) \( \text{m}^2 \text{kg}^{-1} \text{sec}^{-1} \text{C} \text{m}^{-1} \), \( L \) = distance between the two levels of detection electrodes, \( Z_0 \) = baseline thoracic impedance, \( \frac{dZ}{dt_{\text{max}}} \) = maximum of the first derivative of the change in thoracic impedance, and \( \text{LVET} \) = left ventricular ejection time. \( ^{14} \) SV was expressed per m\(^2 \) body surface area (stroke index, SI). Subsequently, calculations were made of cardiac index (CI, SI \( \times \text{HR} \)), \( C_{\text{a,}O_2} \) (VO\(_2\)/CO), mean arterial pressure (MAP, \( \frac{1}{3} \) diastolic pressure + \( \frac{1}{3} \) systolic pressure) and systemic vascular resistance index (SVRI, 80 \( \times \) MAP/CI, expressed as dynes sec/cm\(^5\)/m\(^2\)).

Statistical analysis (using the SPSS-Advanced Statistics package\(^{26} \)) included regression analysis for the detection of relationships between variables, and Friedman analysis of variance (non-parametric) or repeated measurements analysis of variance (parametric) to assess changes in measured variables between the tests. A \( p \)-value less than 0.05 was considered significant. After detection of an overall difference between the protocols, specific differences between protocols were searched for using the Difference Contrast and the Helmert's Contrast. Parameters were considered significant if the joint univariate Bonferroni confidence intervals didn't comprise 0.

The investigation was approved by the Ethical Committee of the University Hospital VU, Amsterdam and informed consent was obtained from all participants.

RESULTS

There were no differences in mean maximum load 338 ± 51 (I), 339 ± 43 (II) and 340 ± 48 (III) Watt, respectively) or peak oxygen uptake (see Table 3) between the three protocols. In all protocols significant \( (p < 0.001) \) correlations were found between load and \( \text{VO}_2 \). The slopes of the regression lines didn't differ significantly among the protocols (11.4, 11.6 and 11.7 ml/min/watt, respectively). No differences were found in any of the hemodynamic variables either during submaximal or at peak-exercise. To illustrate the hemodynamic measurements during CPX-testing, the mean courses of SI, HR, CI, MAP, \( C_{\text{a,}O_2} \) and SVRI in protocol II are shown in Figures 2-7.

There were no differences in mean responses of \( VT_3 \), \( \dot{f} \) or eq\( O_2 \) (see Table 3). However, at all submaximal levels there were significant differences in \( \text{VO}_2 \) and VCO\(_2 \) between the three protocols. Differences were not noted for any of the measured variables at either peak-exercise or during recovery.

DISCUSSION

The slopes of the relationships between \( \text{VO}_2 \) and work rate in the three standard protocols agreed well with the study of Hansen and coworkers for a ramping protocol with a relatively slow increase of load. \( ^{21} \) The relationship between load and \( \text{VO}_2 \) has also been shown to be independent of pattern of work rate increase (ramping or stepwise) during rapid-increment exercise, provided that the mean load increase is kept constant. \( ^{22} \)
Figure 4. Cardiac index (mean ± 95% confidence-interval) during incremental exercise in 15 healthy subjects.

![Cardiac index graph](image)

Figure 5. Mean arterial blood pressure (MAP, mean ± 95% confidence-interval) during incremental exercise in 15 healthy subjects.

![Mean arterial pressure graph](image)

Figure 6. Systemic vascular resistance index (mean ± 95% confidence-interval) during incremental exercise in 15 healthy subjects.

![Systemic vascular resistance graph](image)

Figure 7. Arterio-venous oxygen difference (Ca-vO₂, mean ± 95% confidence-interval) during incremental exercise in 15 healthy subjects.

![Arterio-venous oxygen difference graph](image)

Table 3. Comparison of three protocols

<table>
<thead>
<tr>
<th>Protocol</th>
<th>60 Watt</th>
<th>90 Watt</th>
<th>120 Watt</th>
<th>150 Watt</th>
<th>180 Watt</th>
<th>210 Watt</th>
<th>Peak exercise</th>
</tr>
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<tbody>
<tr>
<td>VCO₂ (l/min)</td>
<td>0.93 ± 0.10&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1.21 ± 0.08&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1.51 ± 0.09&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1.81 ± 0.14&lt;sup&gt;†&lt;/sup&gt;</td>
<td>2.20 ± 0.18&lt;sup&gt;†&lt;/sup&gt;</td>
<td>2.57 ± 0.21&lt;sup&gt;†&lt;/sup&gt;</td>
<td>4.45 ± 0.62</td>
</tr>
<tr>
<td>VO₂ (l/min)</td>
<td>1.10 ± 0.11&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1.41 ± 0.10&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1.70 ± 0.08&lt;sup&gt;†&lt;/sup&gt;</td>
<td>2.02 ± 0.18&lt;sup&gt;†&lt;/sup&gt;</td>
<td>2.20 ± 0.18&lt;sup&gt;†&lt;/sup&gt;</td>
<td>2.75 ± 0.15&lt;sup&gt;†&lt;/sup&gt;</td>
<td>4.28 ± 0.67</td>
</tr>
<tr>
<td>V̇E (l/min)</td>
<td>30.1 ± 4.3</td>
<td>36.5 ± 4.1</td>
<td>43.3 ± 5.0</td>
<td>50.1 ± 5.6</td>
<td>59.5 ± 8.1</td>
<td>69.4 ± 8.3</td>
<td>142 ± 31</td>
</tr>
<tr>
<td>V̇R (l/min)</td>
<td>28.9 ± 4.4</td>
<td>35.8 ± 3.0</td>
<td>41.8 ± 4.6</td>
<td>49.8 ± 4.2</td>
<td>57.3 ± 5.2</td>
<td>66.1 ± 6.1</td>
<td>146 ± 26</td>
</tr>
<tr>
<td>f&lt;sub&gt;r&lt;/sub&gt;</td>
<td>1.14 ± 0.23</td>
<td>1.73 ± 0.28</td>
<td>1.93 ± 0.31</td>
<td>2.15 ± 0.33</td>
<td>2.38 ± 0.31</td>
<td>2.45 ± 0.33</td>
<td>3.00 ± 0.45</td>
</tr>
<tr>
<td>eqCO₂</td>
<td>32.4 ± 2.44</td>
<td>30.1 ± 2.28</td>
<td>28.7 ± 2.36</td>
<td>27.7 ± 2.00</td>
<td>26.9 ± 1.76</td>
<td>27.0 ± 1.58</td>
<td>31.8 ± 3.77</td>
</tr>
<tr>
<td>eqO₂</td>
<td>27.3 ± 3.20</td>
<td>25.9 ± 2.28</td>
<td>25.4 ± 2.53</td>
<td>24.9 ± 2.90</td>
<td>25.1 ± 3.37</td>
<td>25.2 ± 2.76</td>
<td>33.1 ± 4.22</td>
</tr>
</tbody>
</table>

Overall significance between protocols: * p<0.05; † p<0.01; ‡ p<0.001.
Specific significant parameters: a I vs. II; b I vs. II+III; c II vs. III; d III vs. I+II
The only differences that were noted between the three protocols, concerned the submaximal values of VO$_2$ and VCO$_2$. The differences between protocol were systematic: protocol I, with the largest load-steps, yielded much higher values than the other two protocols. The overall significance for the difference between protocols, obtained with the repeated-measurements statistic, owned its significance largely to protocol I. During a ramp test, the actual VO$_2$ achieved at a particular load will lag the steady state VO$_2$ requirement by a constant amount, equal to the time constant of the system. After a change in load, it takes between 3 and 6 minutes for the respiratory variables to attain a new steady state. This steady state can only be attained below an individually fixed threshold load level. The time constant of this response depends on the magnitude of the change in load as well as on the absolute load. After training an individual adapts to a new steady state more rapidly. Although the 3 minutes in protocol I are too short for a steady state to be reached, higher values were found here than in protocols II and III.

The differences between protocols were not related to differences in hemodynamic response. As it takes much less time for HR to increase to a new steady state, no differences in this variable were found between protocols. Differences in SV were not found either, as it reached its maximal value already at a load of about 100 Watt. The rise in SV is mainly dependent on the change in preload at the start of exercise, when the leg muscle pump comes into play. Another important factor influencing SV is afterload, which is reflected by MAP. This variable didn’t differ between protocols.

As decreased exercise capacity can have its origin in a wide range of systems (cardiovascular, pulmonary, locomotor), direct measurement of hemodynamic function by means of EIC could prove to be a valuable addition to stress testing in occupational medicine. Addition of this technique to standard cardiopulmonary exercise testing gives a better understanding of pathology and creates possibilities for rational interventions (training, drug therapy, etc.). Although EIC is not familiar to many scientists or clinicians involved in exercise testing, its measurement of SV has been validated by comparison with a wide range of invasive techniques (e.g. direct Fick method, dye-dilution and with the technique of CO$_2$- rebreathing). The validity and accuracy of EIC during moderate exercise have been clearly shown. In the mentioned studies the correlation coefficients between SV measurement using EIC and the reference method ranged from 0.87-0.94. During strenuous exercise, however, motion and respiratory artifacts can become a large technological impediment. We made a computer averaging of 20 consecutive cardiac cycles, which removes random artefacts and improves signal to noise ratio. Further improvement was obtained by replacing band electrodes by spot electrodes. Using this strategy, we have found an intra- and interobserver variability of less then 5%, even during exercise in patients with respiratory disease (submitted for publication).

The lack of differences between protocols with respect to hemodynamic and maximal gas-exchange data is reassuring and indicates that results from different laboratories should be comparable, as long as the mean load increase is kept constant. However, when analyses are made using submaximal gas-exchange variables, e.g. calculation of the anaerobic threshold (AT), the protocol that is used should be taken into account. In fact, calculation of the AT should only be performed in protocols it was developed for: those using a ramping load increase.

In conclusion, for the evaluation of hemodynamic function and maximal exercise performance, stepwise and ramping protocols (with equal mean load increase) are comparable. In contrast, submaximal gas-exchange data of different patients or laboratories can only be compared using similar protocols.

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