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Fink G

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Recovery Kinetics of Oxygen Uptake in Patients with Various Degrees of Coronary Artery Disease

E. Klainman\textsuperscript{1,2},  C. Yosefy\textsuperscript{3}, A. Caspi\textsuperscript{2}, A. Landau\textsuperscript{1}, R. Vishnitzer\textsuperscript{2}, G. Fink\textsuperscript{2}

\textbf{Background:} Recovery indices of oxygen-consumption (\( \text{VO}_2 \)) kinetics have been observed as an important factor to evaluate and differentiate patients (pts) with various degrees of chronic heart failure (CHF) and less for pts with coronary artery disease (CAD). Objectives: To find the significance of recovery-\( \text{VO}_2 \) kinetics indices in differentiating pts with various degrees of CAD as compared to normal individuals. Methods: 62 male pts were studied. They were divided into four groups according to their CAD degree: (A) 17 normal subjects (control); (B) 26 pts with one-vessel disease (1VD); (C) 11 pts with 2VD; (D) 8 pts with 3VD. All pts underwent a cardiopulmonary exercise test (CPET). The recovery indices measured were: (1) Half-time recovery (1/2tRec) of \( \text{VO}_2 \); (2) 1/2tRec of oxygen pulse (\( \text{O}_2 \)P); (3) Total time recovery of \( \text{VO}_2 \) (TtRec-\( \text{VO}_2 \)), until RER reached value of 1 or less. Results: 1/2tRec-\( \text{VO}_2 \) differs significantly between groups A vs C and D (84 ± 20 vs 123 ± 36 and 134 ± 18); groups B vs D (100 ± 35 vs 134 ± 18) (\( p < 0.05 \)). 1/2tRec-\( \text{O}_2 \)P differs significantly between groups A or B vs C or D (101 ± 30 or 123 ± 34 vs 162 ± 37 or 174 ± 40) (\( p < 0.05 \)), while no significant differences are observed between groups A and B vs C and D. The TtRec-\( \text{VO}_2 \) index shows similar differences between the groups as the former one (7.6 ± 1.3 or 7.9 ± 1.4 vs 9.1 ± 1.7 or 9.2 ± 1.7, in respect to groups A, B, C and D; \( p < 0.05 \)). Conclusions: Significant differences in the recovery indices of \( \text{VO}_2 \) kinetics were observed among pts with various degrees of CAD. Such findings validate the recovery indices as important for better quantitative assessment of CAD pts. J Clin Basic Cardiol 2007; 10 (online): 16–9.

\textbf{Key words:} oxygen consumption in recovery kinetics, oxygen consumption in coronary artery disease, cardiopulmonary exercise test

\textbf{Recovery indices of the Cardiopulmonary Exercise Test (CPET) are important tools for the assessment of the overall exercise capacity in patients (pts) with chronic heart failure (CHF), which differ significantly from normal subjects [1]. The kinetics of post-exercise oxygen consumption (\( \text{VO}_2 \)) have been demonstrated to be delayed in relation to the severity of the disease and to be closely related to exercise capacity [2–5]. Pts with severe CHF or dilated cardiomyopathy demonstrated a prolonged recovery period to the baseline levels of \( \text{VO}_2 \) [6–7]. Similar results were found in pts with mitral stenosis [8].

There is a lack of data regarding \( \text{O}_2 \) kinetics during recovery in various degrees of severity of coronary artery disease (CAD). The ability to estimate the severity of CAD by a non-invasive test such as the CPET might be of great value in the further management of these pts.

In the present study, we measured the recovery \( \text{VO}_2 \) kinetics indices including half-time recovery of \( \text{O}_2 \) pulse (1/2tRec-\( \text{O}_2 \)P); half-time recovery of \( \text{VO}_2 \) (1/2tRec-\( \text{VO}_2 \)); and total-time recovery of \( \text{VO}_2 \) (TtRec-\( \text{VO}_2 \)) in order to compare these values among groups of pts with various degrees of CAD.

\textbf{Methods}

\textbf{Patients}

Sixty-two ambulatory pts were selected in this retrospective study based on the following criteria:

- to avoid gender-physiological discrepancies all pts selected were men;
- all pts underwent a coronary angiogram within two months before or after CPET which was performed in all pts;
- all CPETs were well-qualified for collecting relevant data for the study purpose;
- pts with a history of pulmonary diseases, valvular diseases, CHF, left ventricular dysfunction, chronic atrial fibrillation or peripheral vascular disease were not selected;
- all pts selected stopped all relevant medications such as beta-blockers, calcium channel antagonists or nitrates at least 24 hours prior to CPET.

17 pts who demonstrated a normal coronary angiogram were defined as control group (group A). The other 45 pts demonstrated CAD based on a stenosis of ≥ 60 % in at least one major coronary artery, except left-main or proximal LAD stenosis.

Based on the coronary angiogram results, pts were divided into three additional groups: B: 26 pts with mono-artery disease (1VD); C: 11 pts with two-vessel disease (2VD); D: 8 pts with three-vessel disease (3VD).

\textbf{CPET Protocol}

An upright symptom-limited test was performed on an electronically braked cycle ergometer (Ergoline-800). After two minutes of free pedaling, exercise was initiated at 20 W, followed by a stepwise increase of 10–20 W every minute until a predefined end-point was reached (i. e., symptoms, volitional fatigue or attainment of target heart rate).

Cardiopulmonary data were collected using an online metabolic chart (CPX Medical Graphics, MN, USA). Pts breathed through a low-resistance, two-way valve (Hans-Rudolph, MO, USA) connected to the expiratory limb. The breath-by-breath signals were integrated by a computer to yield 30-second averages of heart rate (HR), minute ventilation (V\( \text{e} \)), oxygen uptake (\( \text{VO}_2 \)), carbon dioxide output (\( \text{VCO}_2 \)) and oxygen pulse (\( \text{VO}_2/\text{HR} \)). Ventilatory anaerobic threshold (VAT) was defined as the point at which the ventilatory equivalent of oxygen (V\( \text{e} \)/\( \text{VO}_2 \)) increased in the absence of a ventilatory equivalent of carbon dioxide (V\( \text{e} \)/\( \text{VCO}_2 \)) as described by Beaver et al \cite{9}.

Data were recorded during exercise and recovery periods until reaching a respiratory exchange ratio (RER) of 1 or less, which is done routinely in our laboratory.

Three recovery indices were defined as follows:

1. Half-time recovery of \( \text{VO}_2 \) (1/2tRec-\( \text{VO}_2 \)), which is the time (in seconds) of peak-\( \text{VO}_2 \) reaching half of its value;

2. Total-time recovery of \( \text{VO}_2 \) (TtRec-\( \text{VO}_2 \)), which is the time (in seconds) at which peak-\( \text{VO}_2 \) is reached; and

3. Half-time recovery of \( \text{O}_2 \) pulse (1/2tRec-\( \text{O}_2 \)P), which is the time (in seconds) of peak-\( \text{O}_2 \) pulse reaching half of its value.

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From the “Gefen” Cardiac Health Center, Givatayim and Sakler School, Tel. Aviv University, \textsuperscript{2}Cardiac Institute and Cardiopulmonary Unit, Pulmonology Institute, Kaplan Medical Center, Rehovot, and \textsuperscript{3}Department of Cardiology, Barzilai Medical Center, Ashkelon, Israel.

\textbf{Correspondence to:} Prof. Eliezer Klainman, MD, “Gefen” Cardiac Health Center, 1, Korazin St., Givatayim, Z. C. 53583, Israel; e-mail: klainman@zahav.net.il
2. half-time recovery of oxygen pulse (1/2tRec-O_2P), which is the time (in seconds) of peak O_2P reaching half of its value;
3. total time recovery of VO_2 (TtRec-VO_2), which is the time (in minutes) from peak exercise end-point until reaching RER value of 1 or less.

Statistical Analysis
Data were analyzed by the SAS system, using the Duncan’s Multiple-Range Test for comparison among the groups for each variable. Values were calculated as mean ± 1 standard deviation. P-values of less than 0.05 were considered statistically significant.

P-values of 0.06–0.1 were considered as borderline. Values of above 0.1 were not significant.

Results
The mean age of all pts (n = 62) was 65.75 ± 9.85 years, and breaks down into the four groups as follows:
A) 62.8 ± 10.9 y (n = 17)
B) 67.5 ± 9.5 y (n = 26)
C) 66.9 ± 9.3 y (n = 11)
D) 65.0 ± 6.5 y (n = 8)

No statistical differences were found among the groups.

Table 1 summarizes the whole group data of the CPET as mean ± 1 SD and shows the comparison among the four groups. Table 1 shows no significant differences of peak HR, % pred. HR, exercise time and peak O_2P among all four groups (lines 1–3 and 6, respectively). A significant difference of peak VO_2 was observed only between groups A vs D, while borderline differences were shown between groups A vs B; A vs C; D vs B; and D vs C (line 4). Similar differences among the groups were observed in peak O_2P (% pred.) variable (line 7).

Significant differences of peak VO_2 (% pred.) were observed between group A vs D, while not among these very three (line 5). Similar differences were shown in VAT variables (lines 8 and 9). Lines 1–9 summarize exercise parameters, while lines 10–12 demonstrate recovery indices.

Significant differences of 1/2tRec-V_O2 were observed between the following groups: A vs C; A vs D; and B vs D, while borderline differences were shown between groups A vs B; B vs C; and C vs D (line 10).

Table 1. Group comparison of CPET indices during exercise and recovery

<table>
<thead>
<tr>
<th></th>
<th>A (n = 17)</th>
<th>B (n = 26)</th>
<th>C (n = 11)</th>
<th>D (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Peak HR</td>
<td>146 ± 17*</td>
<td>127 ± 20*</td>
<td>131 ± 15*</td>
<td>117 ± 18*</td>
</tr>
<tr>
<td>2 % predicted HR</td>
<td>92 ± 5*</td>
<td>84 ± 13*</td>
<td>86 ± 11*</td>
<td>76 ± 12*</td>
</tr>
<tr>
<td>3 Exercise time (min.)</td>
<td>8.3 ± 1.9*</td>
<td>7.8 ± 1.9*</td>
<td>7.8 ± 1.7*</td>
<td>6.8 ± 1.9*</td>
</tr>
<tr>
<td>4 Peak VO_2 (ml/kg/min.)</td>
<td>25 ± 6.4*</td>
<td>22.5 ± 6.6*</td>
<td>22 ± 6.2</td>
<td>18.4 ± 6.2*</td>
</tr>
<tr>
<td>5 Peak VO_2 (% predicted)</td>
<td>109 ± 13*</td>
<td>110 ± 24*</td>
<td>99 ± 18*</td>
<td>78 ± 22*</td>
</tr>
<tr>
<td>6 Peak O_2P (ml/beat)</td>
<td>15.2 ± 2.6*</td>
<td>16 ± 5*</td>
<td>14.4 ± 4.4*</td>
<td>12.5 ± 3.2*</td>
</tr>
<tr>
<td>7 Peak O_2P (% predicted)</td>
<td>121 ± 14*</td>
<td>132 ± 32</td>
<td>115 ± 26*</td>
<td>104 ± 25*</td>
</tr>
<tr>
<td>8 VAT (ml of VO_2)</td>
<td>1170 ± 182*</td>
<td>1161 ± 234*</td>
<td>1027 ± 172*</td>
<td>814 ± 245*</td>
</tr>
<tr>
<td>9 VAT (% of VO_2-max)</td>
<td>56 ± 5*</td>
<td>62 ± 11*</td>
<td>55 ± 8*</td>
<td>44 ± 8*</td>
</tr>
<tr>
<td>10 1/2tRec-VO_2 (sec.)</td>
<td>84 ± 20*</td>
<td>100 ± 35*</td>
<td>123 ± 36*</td>
<td>134 ± 18*</td>
</tr>
<tr>
<td>11 1/2tRec-O_2P (sec.)</td>
<td>101 ± 30*</td>
<td>123 ± 34*</td>
<td>162 ± 37*</td>
<td>174 ± 40*</td>
</tr>
<tr>
<td>12 TtRec-VO_2 (min.)</td>
<td>7.6 ± 1.3*</td>
<td>7.9 ± 1.4*</td>
<td>9.1 ± 1.1*</td>
<td>9.2 ± 1.7*</td>
</tr>
</tbody>
</table>

HR = Heart Rate; VAT = Ventilatory Anaerobic Threshold; 1/2tRec = 1/2time recovery; TtRec = Total time recovery.

Similar differences of 1/2tRec-O_2P and TtRec-VO_2 indices were demonstrated among the groups (lines 11 and 12): significant differences between A or B vs C or D, but not significant ones between A vs B or C vs D.

Figures 1–3 demonstrate graphically the differences in the recovery indices among the four groups. Figure 1 shows the differences in the 1/2tRec-VO_2 index; Figure 2 shows those of the 1/2tRec-O_2P index, and Figure 3 demonstrates the differences in the TtRec-VO_2 index.

Discussion
Few data are available on VO_2 kinetics in recovery among pts with coronary artery disease. Traditionally, the rate of VO_2 recovery from exercise indicates the oxidative capacity in healthy subjects, and its decrease has been related to oxygen debt after exercise [10, 11]. This very oxygen debt has been considered to involve first fast-lactic and a second slow-lactic components [12]. More recently, the term “excess post-exercise oxygen consumption” has been used to express more complex mechanisms which mediate the post-exercise VO_2 recovery and to absorb this entity from a total dependence on anaerobic metabolism [13]. A relatively fast recovery time of oxygen consumption has been demonstrated in athletes [14], while a delay of oxygen kinetics is shown in heart failure. The latter may involve a delay of several factors such as circulatory transport of oxygen to and from metabolizing tissue [15], pulmonary gas exchange [16] or oxygen consumption of the exercising/recovering muscles themselves.

One important factor contributing to the delayed recovery of VO_2 is the prolonged recovery of the muscle phosphate/phosphocreatine ratio which is determined by the blood flow as well as by the oxidative capacity of the exercising muscles [17–19]. Other central factors which may explain the slower VO_2 recovery in pts with heart failure are higher cardiac output and increased stroke volume during the early recovery period [20], which are directly related to VO_2- and O_2-pulse, respectively, according to the fick formula where VO_2 equals to cardiac output multiplied by arterio-venous oxygen difference. The arterio-venous oxygen difference shows a rapid decline after exercise and supports the direct relationship between the above central factors to VO_2- and O_2-pulse (defined as VO_2 divided into heart rate and, therefore, related to stroke volume) [21, 22].

Elevated cardiac output and ejection fraction during early recovery are demonstrated by Plotnick et al [23] in both healthy subjects and pts with CAD, while those two groups differed due to higher values measured in CAD pts. Kano et al [24] suggest the existence of a transient mismatch between cardiac contractility and after-load reduction during recovery even from mild-intensity exercise in normal subjects as well as in CAD pts as the mechanism of overshoot in cardiac function observed in the early recovery phase.

According to the above, we hypothesized that pts with CAD may also demonstrate similar changes in recovery indices since ischaemic reaction during exercise might be considered as temporary left ventricular dysfunction in correlation to the severity of the ischaemic reaction.

In our study, significant differences in the VO_2 recovery indices between
and healthy subjects [6].

which do not show significant differences between CAD pts

Figure 3. Half-time recovery of VO2 kinetics (1/2tRec-VO2) in various
degrees of CAD, in comparison to normal pts. VD = vessel disease.
p-values: significant: * vs § or †; ‡ vs †; § vs †; and † vs ¶; not significant: * vs †; † vs †; and ¶ vs ¶.

healthy group and CAD groups are shown, with a clear tendency of delayed recovery in parallel to the severity of CAD.

Our results demonstrate such differences more emphasized in group D (3VD) where the sub-maximal exercise was mostly limited due to the severity of CAD. It supports other studies in which even mild-intensity or sub-maximal exercise was enough for showing slower recovery kinetics of VO2 in CAD pts [24] and in CHF pts [25] as well as in normal subjects.

Our findings do not support the findings of Pavia et al, which do not show significant differences between CAD pts and healthy subjects [6].

In some pts, the kinetics of VO2 recovery may be complex and incorrectly described by a single exponential curve [25] in opposition to another later report [3]. Thus, Cohen-Solal et al characterized recovery kinetics by simply measuring the half-time of VO2 recovery [26], while measuring of recovery until RER reaching level 1 or less is described by Lim et al [8].

In the present study, we simply measured three recovery indices: half-time recovery of VO2- and O2-pulses, i.e., the time required for a 50 % fall in the peak of these two peak values, and the total recovery time of VO2 in which RER reached a value of 1 or less. All three indices differ significantly among our four groups. The 1/2tRec-VO2 shows a significant systematic progression of time prolongation from group A (control group) to group D, while the two other indices show only a tendency for such a progression. On the other hand, these last two indices differ significantly between groups A or B vs groups C or D. Group B seems to be closer to A while C is closer to D denoting that mono-artery disease might be considered for further conservative treatment rather than invasive procedures. Such significant differences were not demonstrated in most exercise indices (lines 1–9, Table 1). These findings validate the recovery indices as important even more than the exercise ones in the evaluation of various degrees of CAD.

Conclusions

We conclude that recovery cardiopulmonary indices of VO2 kinetics are important for evaluation of pts with CAD and may differ functionally in various degrees of their disease. Thus, additional recovery index measurements are recommended for standard CPET for more intensive and quantitative assessment of at least the functional degree of CAD, which seems to correlate well with the anatomical findings of the coronary angiogram. More studies are recommended to further establish the present study’s findings.

Clinical Applications

The present study provides a simple non-invasive physiological tool for evaluation of the severity of ischaemia in pts with CAD, following and in addition to the anatomical results of the coronary angiogram. Furthermore, this very tool may identify pts with various degrees of ischaemia prior to undergoing a coronary angiogram and, accordingly, may indicate further treatment – conservative or invasive.

References:

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