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

Klainman E, Yosefy C, Caspi A, Landau A, Vishnitzer R
Fink G

Homepage:

www.kup.at/jcbc

Online Data Base Search
for Authors and Keywords

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

E. Klainman[1, 2], C. Yosefy[3], A. Caspi[2], A. Landau[1], R. Vishnitzer[2], G. Fink[2]

*Background: Recovery indices of oxygen-consumption (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-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 (VD); (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 VO$_2$; (2) 1/2tRec of oxygen pulse (O$_2$P); (3) Total time recovery of VO$_2$ (TtRec-VO$_2$), until RER reached value of 1 or less. Results: 1/2tRec-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-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 vs B and C vs D. The TtRec-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 ± 1.9 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 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.***

Key words: oxygen consumption in recovery kinetics, oxygen consumption in coronary artery disease, cardiopulmonary exercise test

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 (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 VO$_2$ [6–7]. Similar results were found in pts with mitral stenosis [8].

There is a lack of data regarding 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 O$_2$ kinetics indices including half-time recovery of O$_2$ pulse (1/2tRec-O$_2$P); half-time recovery of VO$_2$ (1/2tRec-VO$_2$); and total-time recovery of VO$_2$ (TtRec-VO$_2$) in order to compare these values among groups of pts with various degrees of CAD.

Methods

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 betablockers, 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).

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 (Ve), oxygen uptake (VO$_2$), carbon dioxide output (VCO$_2$) and oxygen pulse (VO$_2$/HR). Ventilatory anaerobic threshold (VAT) was defined as the point at which the ventilatory equivalent of oxygen (Ve/VO$_2$) increased in the absence of a ventilatory equivalent of carbon dioxide (Ve/VCO$_2$) as described by Beaver et al [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 VO$_2$ (1/2tRec-VO$_2$), which is the time (in seconds) of peak-VO$_2$ reaching half of its value;

2. half-time recovery of oxygen pulse (1/2tRec-O$_2$P), which is the time (in seconds) of peak-O$_2$P 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$_2$P 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$_2$P (% pred.) variable (line 7).

Significant differences of peak VO$_2$ (% pred.) were observed between group D and the others, but 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-VO$_2$ 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).

Similar differences of 1/2tRec-O$_2$P 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$_2$P 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-lactatic and a second slow-lactatic 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 absolve 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$_2$-pulses, 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

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

		A (n = 17)	B (n = 26)	C (n = 11)	D (n = 8)
1	Peak HR	146 ± 17*	127 ± 20*	131 ± 15*	117 ± 18*
2	% predicted HR	92 ± 5*	84 ± 13*	86 ± 11*	76 ± 12*
3	Exercise time (min.)	8.3 ± 1.9*	7.8 ± 1.9*	7.8 ± 1.7*	6.8 ± 1.9*
4	Peak VO$_2$ (ml/kg/min.)	25 ± 6.4*	22.5 ± 6.6¶	22 ± 6.2	18.4 ± 6.2†
5	Peak VO$_2$ (% predicted)	109 ± 13*	110 ± 24*	99 ± 18*	78 ± 22†
6	Peak O$_2$P (ml/beat)	15.2 ± 2.6*	16 ± 5*	14.4 ± 4.4*	12.5 ± 3.2*
7	Peak O$_2$P (% predicted)	121 ± 14*	132 ± 32	115 ± 26*	104 ± 25†
8	VAT (ml of VO$_2$)	1170 ± 182*	1161 ± 234*	1027 ± 172*	814 ± 245†
9	VAT (% of VO$_2$-max.)	56 ± 5*	62 ± 11*	55 ± 8*	44 ± 8†
10	1/2tRec-VO$_2$ (sec.)	84 ± 20*	100 ± 35‡	123 ± 36§	134 ± 18†
11	1/2tRec-O$_2$P (sec.)	101 ± 30*	123 ± 34*	162 ± 37†	174 ± 40†
12	TtRec-VO$_2$ (min.)	7.6 ± 1.3*	7.9 ± 1.4*	9.1 ± 1.9†	9.2 ± 1.7†

HR = Heart Rate; VAT = Ventilatory Anaerobic Threshold; 1/2tRec = 1/2time recovery;
TtRec = Total time recovery.
p-values: significant: * vs § or †; ‡ vs †; borderline: * vs ‡ or ¶; ‡ vs §; § vs †; and † vs ¶;
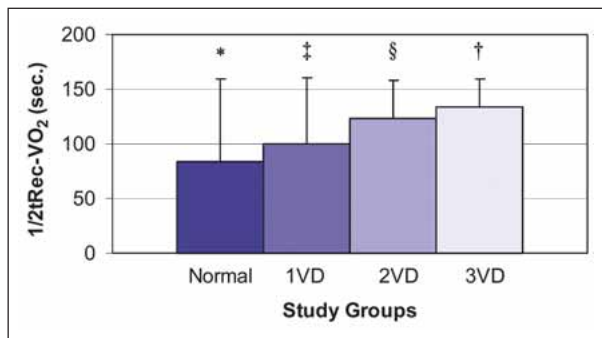not significant: * vs *; † vs †; and ¶ vs ¶.

Figure 1. Half-time recovery of VO$_2$ kinetics (1/2tRec-VO$_2$) in various degrees of CAD, in comparison to normal pts. VD = vessel disease. p-values: significant: * vs § or †; ‡ vs †; borderline: * vs ‡ or ¶; ‡ vs §; § vs †; and † vs ¶; not significant: * vs *; † vs †; and ¶ vs ¶.

Figure 2. Half-time recovery of O$_2$P kinetics (1/2tRec-O$_2$P) in various degrees of CAD, in comparison to normal pts. VD = vessel disease. p-values: significant: * vs § or †; ‡ vs †; borderline: * vs ‡ or ¶; ‡ vs §; § vs †; and † vs ¶; not significant: * vs *; † vs †; and ¶ vs ¶.
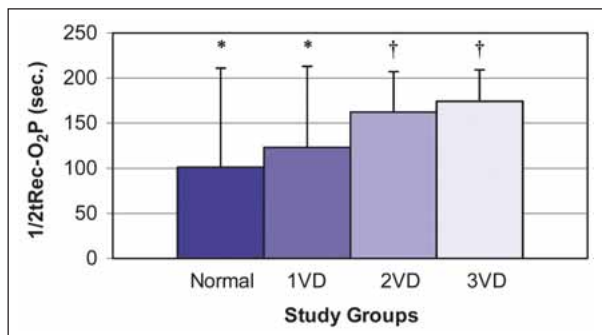

Figure 3. Total time recovery of VO$_2$ kinetics (TtRec-VO$_2$) in various degrees of CAD, in comparison to normal pts; VD= vessel disease. p-values: significant: * vs § or †; ‡ vs †; borderline: * vs ‡ or ¶; ‡ vs §; § vs †; and † vs ¶; not significant: * vs *; † vs †; and ¶ vs ¶.
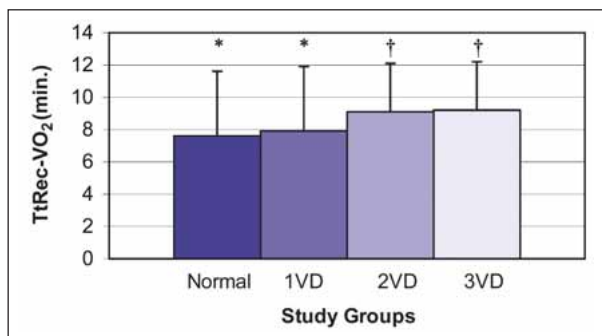
healthy group and CAD groups are shown, with a clear tendency of delayed recovery in parallel to the severity of CAD.

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 VO$_2$ 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 VO$_2$ 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 VO$_2$ 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 VO$_2$- and O$_2$-pulses, i. e., the time required for a 50 % fall in the peak of these two peak values, and the total recovery time of VO$_2$ in which RER reached a value of 1 or less. All three indices differ significantly among our four groups. The 1/2tRec-VO$_2$ 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 VO$_2$ 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:

1. Klainman E, Lebzelter J, Fink G, Kramer MR. Significance of post exercise oxygen consumption kinetics in the evaluation of patients with congestive heart failure. J Heart Disease 2004; 2: 123 (Abstract).
2. Cerretelli P, Sikand R, Farhi LE. Readjustment of cardiac output and gas exchange during onset of exercise and recovery. J Appl Physiol 1996; 21: 1355–60.
3. Hayashida W, Kumada T, Kohno F. Post exercise oxygen uptake kinetics in patients with left ventricular dysfunction. Int J Cardiol 1993; 38: 63–72.
4. Sietsema KE, Ben Dov I, Zhang YY, Sullivan C, Wasserman K. Dynamics of oxygen uptake for submaximal exercise and recovery in patients with chronic heart failure. Chest 1994; 105: 1693–700.
5. Koike A, Hiroe M, Marumo F. Delayed kinetics of oxygen uptake during recovery after exercise in cardiac patients. Med Sci Sports Exerc 1998; 30: 185–9.
6. Pavia L, Myers J, Cesari R. Recovery kinetics of oxygen uptake and heart rate in patients with coronary artery disease and heart failure. Chest 1999; 116: 808–13.
7. De Groote P, Millaire A, Decoulx E, Nugue O, Guimier P, Ducloux P. Kinetics of oxygen consumption during and after exercise in patients with dilated cardiomyopathy. J Am Coll Cardiol 1999; 28: 168–75.
8. Lim H, Lee CW, Park SW, Kim JJ, Song JK, Hong MK, Jin YS, Park SJ. Effect of percutaneos balloon mitral valvuloplasty and exercise training on the kinetics of recovery oxygen consumption after exercise in patients with mitral stenosis. Eur Heart J 1998; 19: 1865–71.
9. Beaver WL, Wasserman K, Whipp B. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 1986; 60: 2020–7.

10. Di Prampero P, Davies CT, Cerretelli P, Marqaria R. An analysis of the oxygen debt contracted in submaximal exercise. J Appl Physiol 1970; 29: 547–51.

11. Barstow TJ, Mole PA. Stimulation of pulmonary O2 uptake during exercise transients in human. J Appl Physiol 1987; 63: 2253–61.

12. Margaria R, Edwards HT, Dill DB. The possible mechanisms of contracting and paying the oxygen debt and the role of lactic acid in muscular contraction. Am J Physiol 1933; 106: 689–715.

13. Gaesser GA, Brooks GA. Metabolic bases of excess post-exercise oxygen consumption: a review. Med Sci Sport Exerc 1984; 16: 29–43.

14. McCully KK, Vandenborne K, DeMeirleir K, Posner JD, Leigh JS Jr. Muscle metabolism in track athletes using 31P magnetic resonance spectroscopy. Can J Physiol Pharmacol 1992; 70: 1353–9.

15. Koike A, Itoh H, Taniguchi K, Hiroe M. Detecting abnormalities in left ventricular function during exercise by respiratory measurements. Circulation 1989; 80: 1737–46.

16. Sullivan MJ, Higginbotham MB, Cobb FR. Increased exercise ventilation in patients with chronic heart failure: intact ventilatory control despite hemodynamic and pulmonary abnormalities. Circulation 1988; 77: 552–9.

17. Chati Z, Zannad F, Robin-Lherbier B, Jeandel C, Escanye JM, Robert J, Aliot E. Contribution of specific skeletal metabolic abnormalities to limitation of exercise capacity in patients with chronic heart failure: a 31P nuclear magnetic resonance study. Am Heart J 1994; 128: 781–92.

18. Sapega AA, Sokolow DP, Graham TJ, Chance B. Phosphorous nuclear magnetic resonance: a noninvasive technique for the study of muscle bioenergetics during exercise. Med Sci Sports Exerc 1987; 19: 410–20.

19. Wiener DH, Fink LI, Maris J, Jones RA, Chance B, Wilson JR. Abnormal skeletal muscle bioenergetics during exercise in patients with heart failure: role of reduced muscle blood flow. Circulation 1986; 73: 1127–36.

20. Koike A, Itoh H, Doi M, Taniguchi K, Marumo F, Umehara I, Hiroe M. Beat-to-beat evaluation of cardiac function during recovery from upright bicycle exercise in patients with coronary artery disease. Am Heart J 1990; 120: 316–23.

21. Sumimoto T, Sugiura T, Takeuchi M, Yuasa F, Hasegawa T, Nakamura S, Iwasaka T, Inada M. Oxygen utilization, carbon dioxide elimination and ventilation during recovery from supine bicycle exercise 6 to 8 weeks after acute myocardial infarction. Am J Cardiol 1991; 67: 1170–4.

22. Sumimoto T, Sugiura T, Takeuchi M, Yuasa F, Iwasaka T, Inada M. Overshoot in mixed venous oxygen saturation during recovery from supine bicycle exercise in patients with recent myocardial infarction. Chest 1993; 103: 514–20.

23. Plotnick GD, Becker LC, Fisher ML. Changes in left ventricular function during recovery from upright bicycle exercise in normal persons and in patients with coronary artery disease. Am J Cardiol 1986; 58: 247–51.

24. Kano H, Koike A, Yajima T, Koyama Y, Marumo F, Hiroe M. Mechanism of overshoot in cardiac function during recovery from submaximal exercise in man. Chest 1999; 116: 868–73.

25. Henry FM. Aerobic oxygen consumption and alactic debt in muscular work. J Appl Physiol 1951; 3: 427–38.

26. Cohen-Solal A, Laperche T, Morvan D, Geneves M, Caviezel B, Gourgon R. Prolonged kinetics of recovery of oxygen consumption after maximal graded exercise in patients with chronic heart failure. Circulation 1995; 91: 2924–32.