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Quantitative Functional Assessment of Ischemic Patients by Cardiopulmonary Exercise and Recovery Indices

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1. Introduction

Exercise stress testing is commonly used for assessing the presence and severity of coronary ischemia including heart rate (HR) and blood pressure (BP) responses as well as exertional symptoms estimation (Vivekananthan et al., 2000). Cardiopulmonary exercise test (CPET) indices, obtained by direct measurement of exercise respiratory gas exchange, may provide additional important clinical information for further and more quantitative evaluation of the ischemic response. Among these indices are the ventilatory anaerobic threshold (VAT), oxygen consumption (VO_2) and the oxygen pulse (O_2-P) measured during exercise. These indices mainly reflect cardiac problems (Milani et al., 1995, 2006). However, recovery cardiopulmonary indices have been found to be an important tool for assessing the overall exercise capacity in patients with chronic heart failure (CHF). These indices differ significantly from healthy subjects. The kinetics of post exercise VO_2 has been demonstrated to be delayed in relation to the severity of the disease and to be closely related to exercise capacity (Koike et al., 1998). Patients with severe CHF or dilated cardiomyopathy, demonstrated a prolonged recovery period to the baseline levels of VO_2 (Pavia et al., 1999; De Groot et al., 1999). Similar results were found in patients with mitral stenosis (Lim et al., 1998). This chapter is based on our five studies, and concerns a quantitative functional assessment of ischemic response in patients with documented coronary artery disease (CAD). The ischemic response was tested using various classic and novel cardiopulmonary indices. The first study demonstrates four O_2-P curve variables, achieved during exercise, which correlate well with different degrees of ischemic response. In the second study, the functional results following percutaneous transluminal coronary angioplasty (PTCA) were assessed in chronic CAD patients. In the third study there is a similar assessment of the effect of controlled exercise training in chronic CAD patients. In the fourth study the means by which ischemia can be improved, as a result of regular exercise training is explained. The most recent study deals with recovery indices of VO_2 kinetics and their contribution to quantitatively assessing varying degrees of CAD.

2. Assessment of the relationship between ischemic response by exercise multigated radionuclide test and the O2-P curve characteristics of the CPET

Four defined variable O_2-P curves were observed during CPET in different degrees of ischemic response in order to compare them with left ventricular ejection fraction (LVEF) [rest] **–** [exercise] response, as measured by multigated equilibrium 99mTc radionuclide cineangiography (MUGA) in ischemic patients. The hypothesis here was based on the direct relationship between the O_2-P and the stroke volume (SV) according to the Fick formula:

$$VO_2 = CO \times (a\text{-}v)\ O_2 \text{ content} \rightarrow O_2\text{-}P = SV \times (a\text{-}v)\ O_2 \text{ content}$$

$$\text{As } VO_2/HR = O_2\text{-}P; \text{ and } CO/HR = SV$$

The O_2-P response during exercise, represented by its curve, is expected to increase till its peak in healthy subjects. In patients with varying degrees of CAD, different quantitative ischemic responses may variate the curve shape accordingly. In the case of left ventricular (LV) dysfunction, a flat curve response is expected.

2.1 Methods

46 patients, 39 men and 7 women, mean age 59.2+/-11 years, with no hypertrophic, valvular or pericardial disease participated in this study. MUGA exercise tests were performed in all patients and followed by a CPET within 2-3 weeks under the same medical regimen while stopping medications like beta-blockers, calcium channel blockers or nitrates 24 hours prior to all tests.

2.1.1 MUGA test

Muga was performed to determine LV ejection fraction (EF) at rest and at peak exercise, using a supine bicycle ergometer with increments of 25W every 2 min. Patients were asked to continue until the predefined endpoint such as appearance of symptoms, volitional fatigue, significant ST changes on ECG or attainment of target HR. 10 mg of stannous pyrophosphate was injected prior to the study, followed 15 min later by 20-25 mCi of 99mTc. Data were recorded with a small-field-of-view scintillation camera and a digital processor. The camera was interfaced to an inter-technique cine data system (Apex-SP409; Elcint, Haifa, Israel). The detector was located at 45 degrees left anterior oblique projection. The cardiac cycle was divided into 24 frames yielding an average time per frame of 20-30 mins. Calibration was set to 4,000 kilo-counts for rest and exercise for all frames. 2,000 kilo-counts were used at exercise. After rest, the study was repeated during supine exercise until peak load was reached. The work load was then immediately decreased by 50% to allow the patient's upper body to remain as immobile as possible, with a stable uniform R-R interval on ECG. Following this, ventricular scintigraphy was started. This procedure was based on the assumption that if an ischemic response is observed during exercise, recovery is not expected within such a short time after peak exercise. According to the ischemic response degree, the patients were classified into four groups: Group 1 (n=10, control), normal findings, defined as LVEF**>**55% and LVEFexercise**–**LVEFrest $\geq$ 5%; Group 2 (n=10), mild ischemia, LVEF**>**55% and 0%**<**LVEFexercise**–**LVEFrest**<**5%; Group 3 (n=9), LV dysfunction, LVEF$\leq$35% at rest, and group 4 (n=17), significant ischemia, LVEF**>**55%, LVEFexercise**–**LVEFrest**<**0.

2.1.2 CPET

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 20W followed by increased stepwise of 10-20W every minute until a predefined end-point was reached (i.e., symptoms, volitional fatigue or attainment of target HR). Cardiopulmonary data were collected by an on-line metabolic chart (CPX Medical Graphics, Minn., USA). Patients 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 HR, minute ventilation (Ve), VO_2, carbon dioxide output (VCO_2) and O_2-P (=VO_2/HR). Peak- VO_2 and peak- O_2-P were related to normal predicted values (Wasserman et al., 1987). VAT was defined as the point at which the ventilatory equivalent of oxygen (Ve/VO_2) increases in the absence of such an increase of ventilatory equivalent of carbon dioxide (Ve/VCO_2); or as described for the V-slope method, which uses regression analysis to present the inflection point on a plot of VCO_2 vs. VO_2 (Beaver et al., 1986). BP was measured with a cuff sphygmomanometer at the test beginning, and at least twice during exercise and peak exercise. 12-lead ECGs were recorded at each one-minute interval throughout the test.

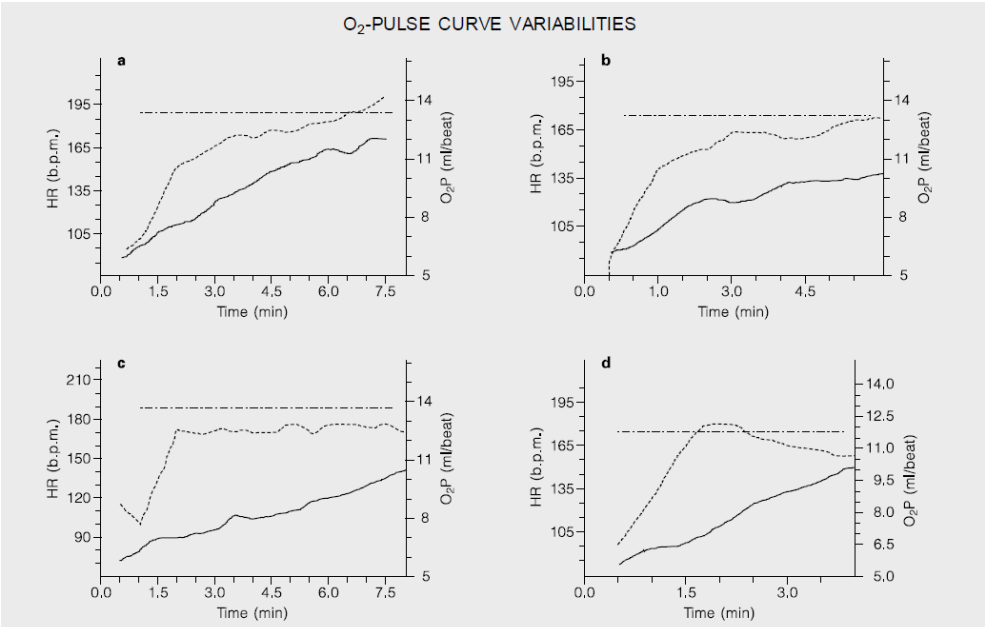

Fig. 1. The four O_2-P curve variables. Type A (top left): normal curve, 10 points; Type B (top right): normal curve, lower values, 8 points; Type C (bottom left): flat curve, low values, 5 points; Type D (bottom right): descending curve, 3 points. Dashed curve refers to O_2-P response. Continuous curve refers to the HR response. The dash-dot horizontal line refers to predicted O_2-P values.

The O_2-P curve appearance was scored on a 10-point scale as follows: Type A, a normal curve (10 points); Type B, a normal ascending curve with relatively low values, not reaching

the predicted value at peak exercise (8 points); Type C, an ascending curve reaching a low peak, then flattening through the remainder of exercise on a lower level than the predicted one (5 points), and type D, an ascending curve which may reach the predicted level briefly, then decreases towards the end of the exercise (3 points). These four curves are shown in Figure 1. The hypothesis was, as mentioned above, that type B correlates with mild to moderate ischemic response, curve D correlates with significant ischemia while curve C tends to correlate with LV dysfunction, since these curves reflect the SV dynamics during exercise.

2.2 Results

The peak-HR achieved was similar for both tests in all four groups. Since the supine MUGA was the first test done, in which patients usually achieve a lower sub-maximal HR, the CPET was limited to this peak-HR as well. A significant relationship between the MUGA grouping according to exercise response vs. the O_2-P-curve scoring were demonstrated (Table 1; $p<0.001$). Figure 2 shows the linear regression between these two factors, defined by the equation:

$$Y = -2.1X + 11.85$$

Where Y represents O_2-P-curve scoring and X represents MUGA grouping.

O_2-P-C Scores	MUGA Grouping				Total
	Group 1 (n=10)	Group 2 (n=10)	Group 3 (n=9)	Group 4 (n=17)	
10	9	2	0	0	11
8	1	6	1	1	9
5	0	2	8	3	13
3	0	0	0	13	13
Total	10	10	9	17	46

Table 1. Relationship between MUGA grouping and O_2-P-curve scoring

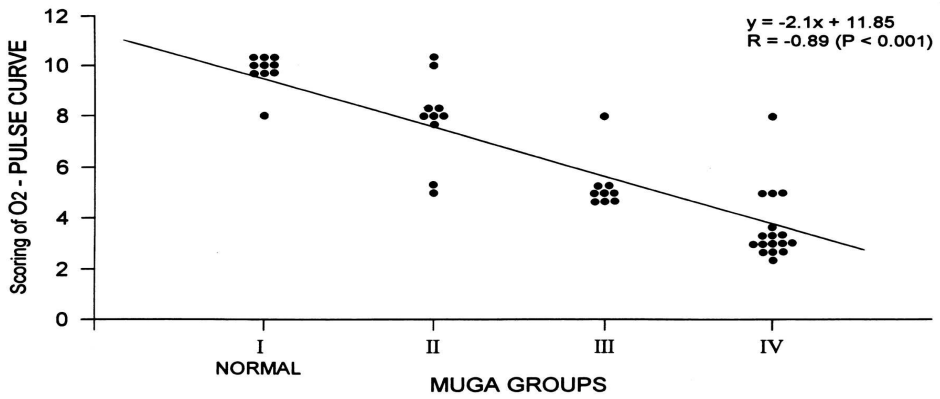

Fig. 2. Correlation between the MUGA grouping (X-axis) and the O_2-P-C score (Y-axis).

2.3 Conclusions

The present study demonstrates the physiological meaning of the O_2-P curve scoring which showed a significant correlation with the MUGA response during exercise. Thus, the exercise O_2-P-C and its scoring, which reflect the SV response during exercise, may serve as a good noninvasive, physiologically-based, parameter for quantitative assessment of ischemic patients and to distinguish between good or impaired LV function. This parameter was used in some of the following studies presented herein, among other indices, for further quantitative evaluation of ischemic patients.

3. Quantitative assessment of functional results after percutaneous transluminal coronary angioplasty by cardiopulmonary exercise indices

PTCA offers a means of improving the angiographic appearance of coronary arterial stenosis. Although a functional change is expected, owing to the augmented capacity of the dilated coronary artery to deliver blood to the previously ischemic myocardium, restenosis of the dilated vessel may occur. Thus, a recurrence of angina pectoris after successful PTCA is of major concern for both the patient and the clinician. Exercise stress testing has become a valuable clinical tool to assess myocardial efficacy and patient's prognosis following PTCA (Kent et al., 1982). As a result, traditional modalities are used before and after the PTCA procedure, including bicycle ergometer or treadmill exercise test, sequential isotopes myocardial perfusion or stress echocardiography (Fioretti et al., 1992), to assess persistence (dilated) or recurrence (stenosis) of the ischemic response. The success of PTCA may be manifested in global and regional cardiovascular function indices like reduced chest pain, increased ejection fraction, reduced abnormal ST segment morphology as well as improved wall motion and perfusion defects. Bengston et al., 1990 reported that since 20% of patients with restenosis following PTCA had neither recurrent angina nor exercise-induced ischemia, then regular exercise testing should be supplemented with more definite indices. This study was designed to investigate the potential importance of the CPET indices, such as VO_2, VAT, O_2-P and its curve appearance, on PTCA follow-up, while assessing the functional results of this procedure.

3.1 Methods

29 patients, candidates for PTCA, 26 men and 3 women aged 41-78 years (mean 63.24+/- 9) participated. All patients demonstrated good LV function by echo-Doppler tests, although 2 patients had suffered a recent non-Q-wave anterior wall myocardial infarction. All patients underwent a coronary angiography for further evaluation of ischemic heart disease (IHD) before the first CPET. The coronary angiography results are summarized in Table 2. The first CPET was performed within 1-2 weeks before PTCA and the second CPET within 2-4 weeks following PTCA. The same medication regimen was used on both tests, while stopping medications such as beta-blockers, calcium channel blockers and digitalis 24h before each test began. It was intended that similar peak-HRs would be achieved for each individual in both tests. The PTCA results are summarized in Table 3.

3.1.1 CPET protocol

The CPET protocol was performed as described in paragraph 2.1.2. Prior to PTCA, the CPET end-point of the patients was the appearance of angina or significant ST-segment

depression, fatigue or target HR. After the PTCA, the CPET was terminated at a similar peak-HR as in the first test, even in the absence of the above pre-PTCA end-points, in order to compare the CPET indices under similar conditions.

3.1.2 PTCA

PTCA was performed within 1-2 weeks after the first CPET if the coronary lesions showed a stenosis of > 70% diameter and were responsible for myocardial ischemia. Successful PTCA was defined as a reduction in stenosis to < 50%

Patient No.	Sex	Age years	Coronary angiography	
			diseased vessel(s)	respective stenosis diameter, %
1	m	78	LAD, CX, M1	90, 100, 80
2	m	64	RCA	100
3	f	69	SEPT, D1, CX, RCA	75, 85, 80, 95
4	f	64	D1, D2, PL	95, 85, 80
5	m	67	LAD, D2, RCA	85, 50, 60
6	m	67	CX, RCA	90, 100
7	m	72	RCA	99
8	m	70	LM, LAD, CX, LPD, M1	60, 100, 85, 70, 95
9	m	71	LAD, CX, RCA	100, 75, 70
10	m	60	LAD, D2, RAM	60, 100, 95
11	m	75	CX, LAD	80, 40
12	m	55	LAD (+ recent MI)	70
13	m	66	CX, M1, M2	50, 90, 99
14	m	62	LAD, CX, RCA	70, 75, 100
15	m	62	CX, RCA	75, 100
16	m	59	RCA (mid)	100
17	m	45	LAD, D2	80, 70
18	m	71	M3, RCA	100, 70
19	m	54	LAD, D1, D2, M1, RPD, PL	70, 90, 95, 90, 99, 90
20	m	76	LAD, CX, M1, Inter.	95, 50, 60, 90
21	m	57	LAD (+ recent MI)	95
22	f	75	RCA, LAD, CX	90, 100, 60
23	m	41	LAD	95
24	m	60	LAD	90
25	m	52	CX, LAD	95, 90
26	m	54	LAD, D1, D2, RPD, PL	70, 90, 95, 99, 90
27	m	61	LAD, M1, M2, RCA	90, 100, 90, 40
28	m	69	D1	95
29	m	61	M1	85

LAD = Left anterior descending; CX = circumflex; M1 = 1st marginal; M2 = 2nd marginal; SEPT = septal; MI = myocardial infarction; D1 = 1st diagonal; D2 = 2nd diagonal; PL = posterior lateral branch; LM = left main; RAM = ramus intermediate; RCA = right coronary artery; RPD = right posterior descending; LPD = left posterior descending.

Table 2. Patient basic data and coronary angiography findings prior to PTCA (n=29).

Patient No.	Vessel(s) subjected to PTCA	Stenosis of vessels, %	
		before PTCA	after PTCA
1	CX	100	100
2	RCA	100	100
3	RCA	95	20
4	D2	85	0
5	LAD	85	0
6	CX	90	10
7	RCA	99	10
8	CX	85	0
9	LAD	100	20
10	RAM	95	0
11	CX	80	0
12	LAD (+ recent MI)	70	20
13	CX, M1, M2	50, 90, 99	0, 0, 0
14	LAD	70	0
15	CX	75	10
16	RCA(mid)	100	0
17	LAD	80	10
18	RCA	70	0
19	M1	90	0
20	LAD	95	0
21	LAD (+ recent MI)	95	0
22	RCA	90	0
23	LAD	95	0
24	LAD	90	0
25	CX	95	0
26	LAD, RPD	70, 99	0, 0
27	M2, LAD	90, 90	20, 0
28	D1	95	35
29	M1	85	10

LAD = Left anterior descending; CX = circumflex; M1 = 1st marginal; M2 = 2nd marginal; D1 = 1st diagonal; D2 = 2nd diagonal; RAM = ramus intermediate; MI = myocardial infarction; RCA = right coronary artery; RPD = right posterior descending.

Table 3. PTCA results in all patients, individually (n=29).

Variables	**Before PTCA**	**After PTCA**	**p value**
Peak-HR, b.p.m.	128.7±16.9	132.0±17.2	NS
Peak-VO_2, ml/min	1,526.8±470	1,686.2±390.1	<0.0001
Peak-O_2-P , ml/beat	12.40±2.73	13.44±2.9	<0.0005
O_2-P -Curve, points	7.62±1.92	8.85±1.26	<0.001
VAT, ml/min	993.1±177.6	1,089.8±150.9	<0.0005

Table 4. Summarized CPET results before and after successful PTCA (n=27)

Patient No.	peak-HR, b.p.m		peak-VO_2, ml/min		Peak-O_2-P, ml/beat		O_2-P-C, points		VAT, ml/min	
	before PTCA	after PTCA	before PTCA	after PTCA	before PTCA	after PTCA	before PTCA	after PTCA	before PTCA	after PTCA
1	115	112	1,490	1,431	13	13	8	8	984	960
2	115	116	1,443	1,369	13	12	8	8	1,013	1,027
3	116	120	1,376	1,585	12	13.5	8	8	899	991
4	126	130	1,054	1,106	8	9	5	8	778	871
5	130	140	1,558	1,597	11	11	5	8	879	961
6	105	110	1,102	1,558	11	14	8	10	873	1,192
7	125	122	1,374	1,520	12	14	8	10	875	1,008
8	140	150	1,975	1,985	13	13	10	10	870	1,067
9	105	107	1,048	1,050	10	10	8	8	724	883
10	120	130	1,486	1,543	11	12	8	8	986	1,012
11	115	125	1,480	1,754	13	14	10	10	968	1,081
12	125	135	1,652	1,693	14	14	5	8	1,210	1,185
13	100	100	1,320	1,569	13	15	8	10	780	1,008
14	130	135	1,724	1,887	13	15	5	8	1,168	1,222
15	135	135	1,885	2,080	15	17	8	10	1,224	1,230
16	160	150	2,659	2,580	18	18	10	10	1,161	1,128
17	180	180	1,476	1,647	9	10	8	8	856	910
18	130	120	1,751	1,680	14	14	10	10	885	966
19	133	135	2,076	2,251	15	17	8	10	1,310	1,365
20	116	125	1,675	1,702	15	14	10	10	1,108	1,319
21	140	160	1,680	1,615	12	11	5	5	980	1,061
22	122	122	974	1,004	8	9	8	8	726	810
23	150	155	1,298	1,472	9	10	5	8	925	1,093
24	121	124	956	1,179	11	13	5	8	925	990
25	124	130	1,336	1,770	12	14	5	8	1,080	1,190
26	135	137	2,251	2,412	17	18.5	10	10	1,365	1,407
27	145	146	1,623	1,695	11	12	8	10	959	1,093
28	130	128	1,317	1,363	10	11	8	10	1,082	1,176
29	118	115	2,120	2,232	18	20	10	10	1,219	1,208
In patients 1 and 2, PTCA was unsuccessful.										

Table 5. Individual cardiopulmonary indices before and after PTCA (n=29).

3.2 Conclusions

After successful PTCA, patients generally showed improvement or absence of perfusion defects and thus achieved higher levels of exercise. The major findings of the present study, as summarized in tables 4 & 5, support this observation: 1) There was a significant functional aerobic improvement following a successful PTCA, as demonstrated by the CPET indices 2-4 weeks after the procedure and 2) This functional improvement occurred with

similar peak-HRs in both CPETs, inferring that an increase in O_2-P is responsible, since VO_2 = HR x O_2-P. It is concluded that CPET carried out following PTCA is an effective, short-term, noninvasive method for quantitative functional assessment of the PTCA results. Further studies are required to determine the long-term effects and prognostic-predicting value for restenosis or for acute coronary events.

4. Quantitative assessment of functional results following a controlled exercise training program in CAD patients by cardiopulmonary exercise indices

Aerobic exercise training is widely used in patients with CAD, with and without LV dysfunction. It is intended to improve physiological fitness, exercise threshold and anginal symptoms. As a result of exercise training, the maximal VO_2 may increase by 10-30% or more (Clausen & Trap-Jenaen, 1970; Redwood et al., 1972; & Sullivan et al., 1988a). However, not all patients experience improved exercise tolerance and for some there is a negative impact (O'Callaghan et al., 1984; Froelicher et al., 1984; & Grodzinski et al., 1987). One of the most challenging aspects of designing exercise programs for patients with CAD is the prescription of appropriate exercise intensity. It must be effective (not too low) yet not too intense as to be a cardiovascular risk (American College of Sports Medicine, 1990; Kohl et al., 1992). It has been shown that the HR at the VAT level is an optimal target HR for exercise (Gordon & Scott, 1995). This study evaluated the effect of an exercise program, prescribed on the basis of HR at the VAT, in patients with varying degrees of CAD, with good or impaired LV function, by CPET indices.

4.1 Methods

Over a 36-month period, 52 male patients, aged 38-75 years, with CAD, completed a 6-9 month supervised, telemetry-monitored, exercise training program. In all patients the CAD was chronic, without any recent coronary events. LV function (expressed by LVEF) was determined by a resting MUGA test. Good LV function was defined when LVEF>45% (32 patients), and LV dysfunction, when LVEF<35% (20 patients). The patients were divided into four groups on the basis of a coronary angiogram and the MUGA test. Groups 1-3 included those with a good LV function as follows: Group 1, 10 patients with single-vessel disease (excluding proximal LAD coronary artery obstruction); Group 2, 12 patients with two-vessel disease, and Group 3, 10 patients with 3-vessel disease. Group 4 included 20 patients with LV dysfunction. The CAD extent was determined by the number of vessels with >50% occlusion. All participants underwent a CPET before and after the exercise training program. The CPET protocol was as described above (paragraph 2.1.2) using the modified Balke treadmill protocol (Froelicher et al., 1974) instead of the bicycle.

4.1.1 Exercise training protocol

All participants completed the exercise program. Each participant was assigned two to three, 30- to 40-min sessions a week of continuous treadmill and bicycle exercise. The training HR was maintained at the VAT level as calculated from the CPET data. Each session was preceded and followed by warm-up and cool-down periods. During exercise, the patients were electrocardiographically monitored by single-lead telemetry (Nihon-Kohden; Life Scope 6).

4.2 Results

The variables at baseline and for the four groups are summarized in Table 6. There were no significant differences concerning age or LVEF among groups 1-3. Although the HR for group 3 (three-vessel disease) was lower than in the other groups, it was still relative to the VAT level. The CPET indices before and after the exercise program are summarized in Table 7. In groups 1 and 2, no significant changes occurred in the standard exercise variables; testing time, peak-HR, maximal ST segment depression and recovery time. Nevertheless, there were significant improvements in the cardiopulmonary indices; peak-VO_2, peak- O_2-P, O_2-P curve levels, and VAT levels. By contrast, group 3 showed significant changes only in the O_2-P curve, while group 4 (LV dysfunction), showed significant improvements in all cardiopulmonary indices except the standard exercise test variables (as did groups 1 and 2).

Variable	Group 1 *(1-vessel disease)*	Group 2 *(2-vessel disease)*	Group 3 *(3-vessel disease)*	Group 4 *(LV dysfunction)*
Number of cases	10	12	10	20
Age, years	53±10	57±8	58±7.5	60±6
Mean LVEF at rest, %	56±9	54±7	53±8	29±6
Mean training HR , beats/min	104	101	92	102
Training HR/peak-HR,%	60	63	59	65
Training HR/HR-max.-predicted,%	57	58	54	59

Table 6. Baseline variables and data from the exercise training program of the four groups

4.3 Conclusions

A 6-9 month exercise training program, determined by HR at the VAT, significantly improves the overall circulatory and cardiac function, as assessed by CPET indices, in CAD patients with one- or two-vessel disease as well as in patients with LV dysfunction, most probably by a peripheral circulatory mechanism in the latter ones. Such improvements were not achieved in patients with three-vessel disease and may be explained by the limitation of significant ischemia which occurred even at this relatively low intensity of exercise. Once again, the CPET was shown to be a sensitive and effective tool for quantitative assessment of exercise training results in CAD patients, in contrast to the routine exercise test variables. It appears, as the PTCA results also demonstrated, that patients with one- or two-vessel disease benefit from an exercise program. This leads us to the next study in which the functional cardiopulmonary indices are evaluated and compared in trained versus untrained CAD patients seeking further explanation of the beneficial effects of exercise for chronic CAD patients.

Index	Before training	After training	p
Group 1: One-vessel disease (n=10)			
ETT, min	7.6±1.3	8.1±1.1	NS
Peak-HR, beats/min	168±22	169±17	NS
Max ST ↓, mm	1.15±1.3	0.9±1.2	NS
Rec. time, min	3.1±4.1	3.2±4.2	NS
Max. load, W	148±37	180±36	<0.005
Peak-VO_2, ml/min/kg	20.5±3.9	25.7±4.6	<0.0001
Peak-O_2 pulse, ml/min/beat	12.4±2.1	15.9±2.5	<0.0005
O_2 pulse curve, points	7.2±2	9.3±1.6	<0.01
VAT, % of VO_2 max	40.3±6	51±11	<0.01
Group 2: Two-vessel disease (n=12)			
ETT, min	6.54±1.9	6.8±1.5	NS
Peak-HR, beats/min	157±20	153±21	NS
Max ST ↓, mm	1.92±1.1	1.5±1.1	<0.1(borderline)
Rec. time, min	7.9±3	8.3±5	NS
Max. load, W	109±35	127±29	<0.025
Peak-VO_2, ml/min/kg	16±5	19±4	<0.025
Peak-O_2 pulse, ml/min/beat	11.3±3.6	14.3±3.1	<0.0005
O_2 pulse curve, points	7.25±2.4	9.25±1.5	<0.005
VAT, % of VO_2 max	43±9.3	48±7	<0.1(borderline)
Group 3: Three-vessel disease (n=10)			
ETT, min	5.5±1.6	6.35±1.5	<0.1(borderline)
Peak-HR, beats/min	152±24	153±22	NS
Max ST ↓, mm	2.35±1	2.2±0.8	NS
Rec. time, min	10.3±4	9.7±3	NS
Max. load, W	110±28	103±22	NS
Peak-VO_2, ml/min/kg	16.7±2.4	15.9±2.2	NS
Peak-O_2 pulse, ml/min/beat	12.3±2.2	12.6±2.2	NS
O_2 pulse curve, points	5.4±1.5	8.2±1.9	0.005
VAT, % of VO_2 max	43±4.7	39±9.5	NS
Group 4: LV dysfunction CAD (n=20)			
ETT, min	7.4±3	8±2.2	NS
Peak-HR, beats/min	152±20	154±17	NS
Max ST ↓, mm	1±1.2	1.2±1.4	NS
Rec. time, min	2.5±3	2.7±2.8	NS
Max. load, W	131±27	155±40	<0.005
Peak-VO_2, ml/min/kg	19±3	22.5±5	<0.001
Peak-O_2 pulse, ml/min/beat	12.2±2.1	14±2.5	<0.0005
O_2 pulse curve, points	7.2±2.5	8.5±2.4	<0.05
VAT, % of VO_2 max	41±8	49±7	<0.05

ETT = exercise treadmill time; max HR = maximal heart rate; max ST ↓ = maximal ST segment depression; rec. time = time of recovery of ST changes; NS = non significant, statistically

Table 7. CPET indices before and after the exercise training program in the four groups.

5. Quantitative functional assessment and comparison of trained versus untrained CAD patients by combined CPET and 99mTC-Sestamibi myocardial imaging

Several studies, amongst many, have confirmed the overall benefit of exercise training in reducing the risk of CAD (Sesso et al., 2000; Blair et al., 1993). Additional studies have shown specific benefits of exercise training in CAD patients: Improved endothelial function with CHF (Hambrecht et al., 1998) or without CHF (Walther et al., 2004; Hambrecht et al., 2000); improved C-reactive protein values (Church et al, 2002); and increased cytokine- activity (Goldhammer et al., 2005). It has been established that exercising at the HR of the VAT level has a favorable effect (Gordon & Scott, 1995). However, the means by which exercise achieves this remains unclear. Does it enhance the development of collateral coronary blood supply to the ischemic myocardium? Or can the improvement in cardiopulmonary function be readily explained by other mechanisms such as a more "cost-effective" metabolic-physiologic demand-supply balance. According to the Fick formula (paragraph 2), O_2-P, which is simply VO_2 divided by HR, is directly related to SV. If O_2-P is significantly increased with exercise, it follows that exercise improves SV. Theoretically this could be induced by improved myocardial perfusion (e.g., by augmented collateral circulation). However, until now there is a lack of evidence to show that exercise training indeed, exerts such a beneficial effect on myocardial oxygen supply. Alternatively, the increase in SV, especially if accompanied by a decrease in HR at VAT level, could simply reflect an improved and a more effective myocardial VO_2 as a result of exercising, which may be accompanied by an objective evidence of reduced myocardial ischemia. This could occur simply as a result of a significant decrease in HR during exercise. In this study, an assessment and comparison of the functional CPET indices in trained vs. untrained CAD patients was carried out. The CPET was followed by evaluation of the degree of ischemia in every patient by ^{99m}TC sestamibi myocardial perfusion imaging (MIBI-SPECT), while using the same exercise testing for both studies. It was assumed that a decrease in myocardial oxygen demand could explain the improved functional capacity observed after exercise training in chronic CAD patients, irrespective of its possible effects on collateral blood flow.

5.1 Methods

44 men aged 40-83, a mean 62+/-12 years, with a recent coronary angiogram participated. They were divided into three age-coordinated groups: Group I, nine patients with normal coronary arteries at the coronary angiography (control group); Group II, 20 patients with significant 1-3 vessel disease who did not participate in any exercise training program (untrained group), and Group III, 15 patients also with significant 1-3 vessel disease, yet who completed a 3-6 month supervised, telemetry-monitored exercise training program prescribed by the HR at the VAT (trained group). All 35 CAD participants had chronic CAD, without any previous acute coronary events. All had normal LV function (LVEF>50%), documented by multigated acquisition angiography (MUGA) or LV angiography. All 44 participants underwent a CPET together with a MIBI-SPECT study using standardized techniques. A single exercise test was used for both studies. Beta-blockers and calcium channel antagonists were stopped 24 hours prior to testing.

5.1.1 CPET protocol

This test was performed as described in paragraph 2.1.1.

5.1.2 MIBI-SPECT protocol

MIBI myocardial perfusion tomography was performed with a same-day "rest-stress" imaging protocol (Tailefer, 1990). The first myocardial perfusion imaging was done at rest, one hour after the injection of MIBI 7-8 mc. The second imaging was done 1-2 hours later, after exercise and additional injection of MIBI 21-22 mc at peak-exercise. Tomographic imaging acquisition was performed over a 180-degree arc, from the -45-degree right anterior oblique to the +135-degree left posterior oblique with an S-P-4x digital camera (Elscint Ltd, Haifa, Israel) fitted with an all-purpose collimator. The degree of ischemia was scored on a 4-point scale as follows: 0-no ischemia; 1-mild; 2-moderate, and 3-severe ischemia. Only stress-imaging defects that showed partial or complete resolution on corresponding rest images were considered as "reversible ischemia".

5.2 Results

The basic data and summary of results for all three groups are shown in Table 8, and the extent of disease in the trained and untrained patients is shown in Table 9. There was an almost equal distribution of 1-, 2- and 3-vessel disease within groups II and III with no significant difference in the extent of disease between the groups (Table 9). Nevertheless, significantly less ischemia was observed in the trained patients (group III) in comparison to the untrained patients (group II) (0.8 ± 0.65 vs. 1.79 ± 0.95; $p<0.001$), as also demonstrated in Figure 3, along with a significantly greater peak-VO_2 (1989 ± 422 vs. 1608 ± 296 ml/min; $p<0.001$). Since peak-VO_2 equals peak-O_2-P x HR, and a highly significant increase in peak-O_2-P was observed in the trained vs. the untrained group (139 ± 29% vs. 94 ± 11% of predicted values; $p<0.001$) concomitantly with a significantly lower peak-HR (70 ± 11% vs. 84 ± 9% of predicted values; $p<0.001$), it indicates that the increase of peak-O_2-P contributes more to the increase of peak-VO_2 than the reduction of peak-HR deletes from its level. The Peak-VO_2 and O_2-P were not significantly different in the trained group (group III) vs. the control group (group I). The relationship between the peak-VO_2, peak-O_2-P and peak-HR within the three groups is demonstrated in Figure 4.

	Group I (n=9) (no disease)	Group II (n=20) (untrained)	Group III (n=15) (trained)
Age(yrs)	64±7	61±8	64±9
No. of occluded vessels	0	1.95±.83	1.93±.85
Ischemic degree (score)	0	1.79±.95‡	0.8±.65
Peak-VO_2 (ml/min)	2171±536†	1608±296‡	1989±422
Peak- O_2-P (%pred.)	125±24*	94±11‡	139±29
Peak-HR (%pred.)	89±7†	84±9‡	70±11

*p<0.05 group I vs. group II; † p<0.01 group I vs. group III; ‡ p<0.001 group II vs. group III.

Table 8. Basic data and summary of results.

	Group II (untrained)	Group III (trained)
1-vessel disease	7(35%)	6(40%)
2-vessel disease	7(35%)	4(27%)
3-vessel disease	6(30%)	5(33%)
Total	20(100%)	15(100%)

Table 9. Extent of coronary disease on angiography in trained and untrained patients.

5.3 Exercise training in chronic and stable CAD

Exercise training is a highly valuable non-pharmacological treatment for patients with chronic stable angina. It reduces myocardial ischemia and, on the clinical level, reduces the frequency of anginal attacks while also improving functional capacity and long-term outcomes (Nigam & Tardif, 2008). As regular exercise has been shown to improve myocardial perfusion and to retard disease progression in patients with stable CAD and even with ischemic cardiomyopathy (Belardinelli et al., 1998), a randomized study was conducted (Hambrecht et al., 2004) to compare the effects of exercise versus percutaneous coronary intervention with stenting on clinical symptoms, angina-free exercise capacity, myocardial perfusion and cost-effectiveness. It was concluded that a 12-month program of regular physical exercise in patients with stable CAD resulted in superior event-free survival and exercise capacity at a lower cost, due to reduced re-hospitalizations and repeated revascularizations. What is the contribution of our study?

What is not clear from previous studies is the dominant mechanism that underlies the cardiovascular improvement induced by an exercise program. Is the improvement mainly dominated by enhanced myocardial blood flow (by increased coronary collateralization for example, as well as by augmentation in endothelial function) or is it due to decreased myocardial oxygen demand and improved metabolic cost effect balance? (The improved ischemic burden evidenced by perfusion studies is compatible with either one of these possibilities). This study does not deny the former possibility of increased myocardial perfusion, since it does not address this issue. However, it does show that the reduced ischemic burden seen in perfusion studies can be attributed substantially, if not completely, to the improved metabolic-physiologic state of the myocardium that accrues from exercise training. It is shown here that SV (as indicated by O_2-P) is significantly higher in the CAD patients after a 3-6 month training program (group III) than in group II patients, who were not subjected to training yet had similar severity of CAD, and also similar to SV levels of subjects without CAD (group I, control). Furthermore, peak-VO_2 is also significantly higher in the trained group than in the untrained one, indicating an improvement in functional capacity. Simultaneously, peak-HR is also significantly lower in the trained group at a higher degree of exercise, as expressed by higher peak VO_2, than in the untrained group (Figure 4). This peak-HR decrease indicates that exercise training decreases myocardial oxygen demand, and the combination of this with the cardio-pulmonary data suggests that the beneficial effect of regular exercise is mediated, at least substantially, by a significant decrease in peak-HR along with the significant increase in peak-O_2-P (related to SV) and peak-VO_2 (functional capacity). This metabolic-physiological advantage to the myocardium

is expressed by the significant improvement of ischemia demonstrated by MIBI-SPECT imaging at the peak-HR that was simultaneously reached during the CPET. Thus, there is no need to invoke an improvement in myocardial blood flow to explain the beneficial effect of exercise training in chronic CAD. The results of this study need to be further validated by more extensive study.

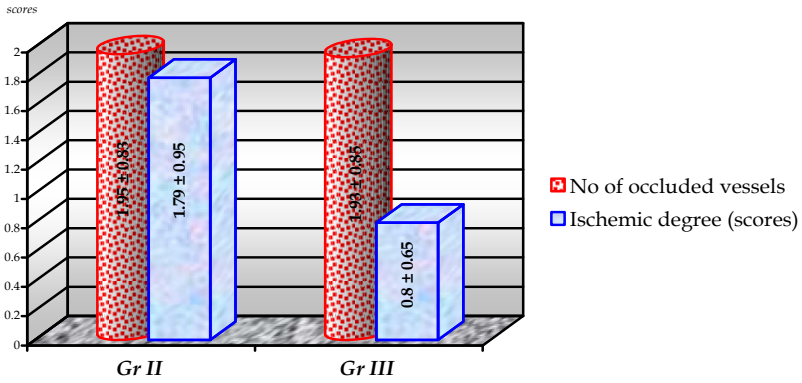

Fig. 3. Comparison of number of occluded coronary vessels and scoring of ischemic degree (Tecnetium-Sestamibi test) between groups II (untrained) and III (trained).

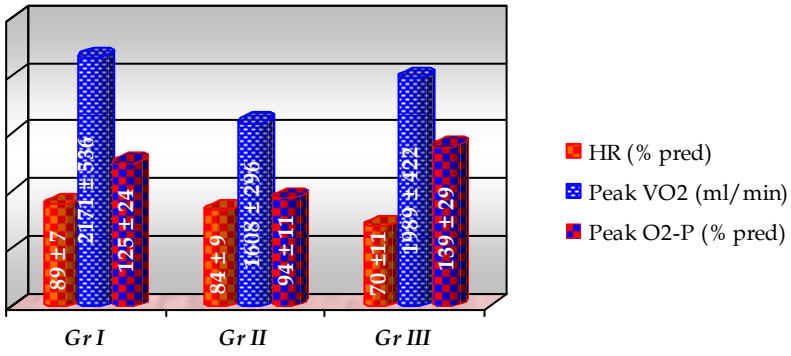

Fig. 4. Comparison of the relationship among peak- VO_2, peak- O_2-P and peak-HR within groups I (control), II (untrained) and III (trained).

6. Quantitative assessment of patients with varying degrees of coronary artery disease by cardiopulmonary exercise and recovery indices

Recovery indices of CPET are important tools for assessing the exercise capacity of patients with CHF, which differ significantly from healthy subjects, as shown in our former study (Klainman et al., 2004). The kinetics of post-exercise VO_2 is shown to be delayed in relationship to the severity of the disease and closely related to exercise capacity (Cerretelli et al., 1996; Hayashida et al., 1993; Sietsema et al., 1994). The ability to estimate quantitatively the severity of CAD by a non-invasive test, such as the CPET, might be of great value for directing further management of these patients. In this study we measured three recovery O_2 kinetic indices as detailed below, in order to compare patients with varying degrees of CAD.

6.1 Methods

62 ambulatory patients were selected in this study on the basis of the following criteria:

- All patients were men to avoid gender physiological discrepances.
- All patients have performed a coronary angiogram within two months prior or post a CPET (which has been done in all patients as well).
- All the CPETs were well qualified for collecting relevant data for the purpose of the study.
- No patients with a history of pulmonary, valvular or peripheral vascular diseases, CHF, left ventricular dysfunction, or chronic atrial fibrillation were selected.
- All patients stopped all relevant medications: beta-blockers, calcium channel antagonists and nitrates at least 24 hours prior to the CPET.

17 patients who demonstrated a normal coronary angiogram were defined as the control group (group A). The other 45 patients had documented CAD based on stenosis of 60% and above, in at least one major coronary artery, excluding the left main or proximal LAD stenosis. On the basis of the coronary angiogram results, patients were divided into three additional groups: B, 26 patients with mono-artery disease (1VD); C, 11 patients with two-vessel disease (2VD), and D, 8 patients with three-vessel disease (3VD).

6.1.1 CPET protocol

The exercise protocol was carried out as described in paragraph 2.1.1. Data were recorded during exercise and recovery periods until the respiratory exchange ratio (RER) of 1 or less was reached. 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, and 3) total-time recovery of VO_2 (TtRec- VO_2), which is the time, in minutes, from peak exercise end-point till obtaining an RER value of 1 or less.

6.1.2 Statistical analysis

Data were analyzed by the SAS system, using the Duncan's Multiple Range Test to compare the variables of each group. Values were calculated as mean +/- 1 standard deviation (SD). P values <0.05 were considered statistically significant. P values of 0.06-0.1 were considered as borderline. Values of > 0.1 were not significant.

6.2 Results

The mean age of all patients (n=62) was 65.75+/-9.85 years, and when divided into the four groups: A) 62.8+/-10.9 y (n=17); B) 67.5+/-9.5 y (n=26); C) 66.9+/-9.3 y (n=11), and D) 65+/-6.5 y (n=8). No statistical differences of age were found among the groups. Table 10 summarizes the group data of the CPET as mean +/-1 SD and shows the comparison of the exercise and recovery indices among the four groups. This table shows no significant differences of peak HR, % pred. HR, Ex. time and peak O_2-P among the four groups (lines 2, 3, 4 and 7 respectively). A significant difference of peak-VO_2 was observed only between groups A and D, while borderline differences were shown between groups A vs. B; A vs. C; D vs. B; and D vs. C (line 5). Similar differences among the groups were observed in peak O_2-P (% of predicted value) variable (line 8). Significant differences of peak VO_2 (% of predicted value) were observed between group D vs. A, B and C, but not among A, B and C themselves (line 6). Similar differences were shown in VAT variables (lines 9 and 10). Lines 2-10 summarize the exercise parameters, while lines 11-13 demonstrate the 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 11). Similar differences of the indices 1/2tRec- O_2-P and TtRec-VO_2 were demonstrated among the groups (lines 12 and 13): Significant differences were apparent between A or B vs. C or D, but not between A vs. B or C vs. D.

1	Group	A (N=17)	B (N=26)	C (N=11)	D (N=8)
2	Peak HR	146+/-17*	127+/-20*	131+/-15*	117+/-18*
3	% pred. HR	92+/-5*	84+/-13*	86+/-11*	76+/-12*
4	Ex. Time (min)	8.3+/-1.9*	7.8+/-1.9*	7.8+/-1.7*	6.8+/-1.9*
5	Peak-VO_2 (ml/kg/min)	25+/-6.4*	22.5+/-6.6¶	22+/-6.2¶	18.4+/-6.2†
6	Peak-VO_2 (% pred.)	109+/-13*	110+/-24*	99+/-18*	78+/-22†
7	Peak-O_2-P (ml/beat)	15.2+/-2.6*	16+/-5*	14.4+/-4.4*	12.5+/-3.2*
8	Peak-O_2-P (% pred.)	121+/-14*	132+/-32¶	115+/-26*	104+/-25†
9	VAT (ml of VO_2)	1170+/-182*	1161+/-234*	1027+/-172*	814+/-245†
10	VAT (% of VO_2-max)	56%+/-5*	62%+/-11*	55%+/-8*	44%+/-8†
11	1/2tRec-VO_2 (sec.)	84+/-20*	100+/-35‡	123+/-36§	134+/-18†
12	1/2tRec-O_2-P (sec.)	101+/-30*	123+/-34*	162+/-37†	174+/-40†
13	TtRec-VO_2 (min.)	7.6+/-1.3*	7.9+/-1.4*	9.1+/-1.9†	9.2+/-1.7†

Pred.=predicted; Ex.=Exercise; 1/2tRec=1/2 time recovery; TtRec=Total time recovery.
P values: Significance: * vs § or †; ‡ vs †.
Borderline: * vs ‡ or ¶; ‡ vs §; § vs †; and † vs ¶.
Not Significant: * vs *; † vs †; and ¶ vs ¶.

Table 10. Group comparison of CPET indices during exercise and recovery.

6.3 Post-exercise recovery period

Few data are available in regard to VO_2 kinetics in recovery among patients with CAD. Traditionally, the rate of VO_2 recovery from exercise indicates the oxidative capacity in healthy subjects, and its decrease has been related to the oxygen debt following exercise (Barstow, 1987; Di Prampero, 1970). This oxygen debt has been considered to involve a first, fast alactatic phase and a second, slow lactatic component (Margaria et al., 1933). 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 absolve this entity from a total dependence on anaerobic metabolism (Gaesser, 1984). A relatively fast recovery time of oxygen consumption has been demonstrated in athletes (McCully et al., 1992), while a delay of oxygen kinetics is shown in heart failure patients. The later may involve a delay of several factors, such as circulatory transport of oxygen to and from metabolizing tissue (Koike et al., 1989), pulmonary gas exchange (Sullivan et al., 1988b), or oxygen consumption of the exercising/recovering muscles themselves. One important factor, which contributes 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 (Chati et al., 1994; Sapega et al., 1987; Wiener et al., 1986). Other central factors, which may explain the slower VO_2 recovery in patients with heart failure, are higher cardiac output and increased SV during the early recovery period (Koike et al., 1990), which are directly related to VO_2 and O_2-P respectively, according to the Fick formula, as discussed previously. The arterio-venous oxygen difference, which appears in the formula, shows a rapid decline after exercise, thus supporting the direct relationship between the central factors to VO_2 and O_2-P (Sumimoto et al., 1991, 1993). Both healthy subjects and patients with CAD demonstrated elevated cardiac output and ejection fraction during early recovery (Plotnick et al., 1986), and the CAD patient levels were even higher. It is suggested that an existence of a transient mismatch between cardiac contractility and after-load reduction during recovery, even from mild-intensity exercise, in healthy subjects as well as in CAD patients, might be the mechanism of overshoot in cardiac function observed in the early-recovery phase (Kano et al., 1999). According to the above, we hypothesized that patients with CAD may also demonstrate similar changes in recovery indices since ischemic reaction during exercise might be considered as temporary LV dysfunction in correlation to the severity of the ischemic reaction. In our study, there are significant differences in the recovery VO_2 indices between the healthy group and the CAD groups, with a clear tendency of delayed recovery in parallel to the severity of the CAD. Our results demonstrate such differences, which are emphasized more in group D (3VD), where the sub-maximal exercise was mostly limited for the severity of the CAD. This supports other studies in which even mild-intensity or sub-maximal exercise was enough for showing slower recovery kinetics of VO_2 in CAD (Kano et al., 1999) and CHF patients (Cohen-Solal et al., 1995) compared to healthy subjects. Our findings do not concur with Pavia et al. which do not show significant differences between CAD and healthy subjects. In some patients the kinetics of VO_2 recovery may be complex and incorrectly described by a single exponential curve (Henry, 1951) as opposed to another later report (Hayashida et al., 1993). Thus, Cohen-Solal et al. characterized recovery kinetics by measuring the half-time of VO_2 recovery, while also measuring the time for RER to reach level 1 or less (Lim et al., 1998). In this study, the three recovery indices, mentioned above (paragraph 6.1.1) were measured. All three indices differ significantly among the four groups studied. The 1/2tRec- VO_2

shows a significant systematic progression of increased time from group A (control group) to group D, while the two other indices show only a tendency for such a progression. Moreover, these last two indices differ significantly between groups A or B vs. C or D. Group B appears closer to A while C appears closer to D, inferring that mono-artery disease should be considered for further conservative treatment rather than invasive procedures. Such significant differences were not demonstrated in most of the exercise indices (Table 1, lines 2-10). These findings validate the recovery indices as even more important than those in quantitative functional evaluation of varying degrees of CAD.

6.4 Conclusions

We have concluded that recovery cardiopulmonary indices of VO_2 kinetics are important in evaluating patients with CAD and may differ functionally according to the degree of disease. Thus, additional recovery measurement indices are recommended for the standard CPET in order to obtain a more comprehensive and quantitative assessment of the functional degree of CAD, which seems to correlate with the anatomical findings of the coronary angiogram. Additional studies are recommended to further establish these findings.

6.5 Clinical applications

The present study provides a simple, non-invasive physiological tool for evaluating the severity of ischemia in patients with CAD, following and in addition to the anatomical results of the coronary angiogram. Furthermore, this tool may be used for identifying patients with varying degrees of ischemia, prior to coronary angiogram and accordingly, indicate them for further treatment - conservative or invasive.

7. Summary

In the five studies reported in this chapter, we emphasize the important contribution of cardiopulmonary indices, during both exercise and recovery, for quantitative functional assessment of patients with CAD. The most important indices for measuring ischemic exercise responses were: Peak-VO_2; peak-O_2-P; VAT; O_2-P curve characteristics, all measured during exercise; and three relatively new indices, measured during the recovery period: total-time and half-time recovery kinetics of VO_2, and half-time recovery of O_2-P. Using these indices it was shown that it is possible to quantitatively assess the functional results following invasive procedures like PTCA in chronic CAD patients as well as exercise training results in similar patients. The results from these two groups support the assertion that benefits of regular exercise training are not inferior to the invasive procedure, at least in patients with one- or two-vessel CAD. Also illustrated here is a possible mechanism for better understanding the training effect in those patients. It is suggested that the increase in the O_2-P, which reflects an increase in SV following exercise training program, causes a gradual decrease in exercise HR, while maintaining the same or an even higher VO_2 level during exercising. As a consequence, there is a decrease in myocardial oxygen demand. This metabolic-physiologic advantage to the myocardium is expressed by significant improvement of ischemia as demonstrated by MIBI-SPECT imaging at peak-HR in trained patients compared to untrained ones. Finally, it has been

shown how the recovery O_2 kinetic indices may contribute, in addition to the exercise indices, to quantitative comparison among varying degrees of CAD, as expressed during CPET. All indices mentioned above, further validate the CPET as an effective, non-invasive, and essential tool for quantitative functional assessment of CAD patients and, accordingly, may even provide an indication of further treatment required – conservative or invasive, in chronic and stable patients.

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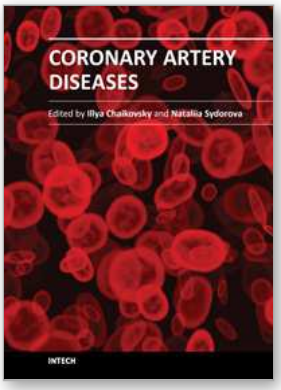

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This book has "wide geography" both literally and figuratively. First of all, this book brings together contributions from around the world, both from post-industrial countries and developing world. This is natural, because coronary artery disease is becoming pandemic worldwide. CAD is the single most frequent cause of death in developed countries, causes about 1 in every 5 deaths. Mortality from cardiovascular disease is predicted to reach 23.4 million in 2030. Moreover, in the developing world, cardiovascular disease tends to affect people at a younger age and thus could negatively affect the workforce and economic productivity. The morbidity, mortality, and socioeconomic importance of CAD make its diagnosis and management fundamental for all practicing physicians. On another hand, the book widely represents "geography" of CAD itself, i.e. many various aspects of its pathophysiology, epidemiology, diagnosis, treatment are touched in this book. This book does not pretend on complete and integral description of the Coronary artery disease. Rather, it contains selected issues on this complex multifactorial disease. Nevertheless, we hope that readers will find Coronary Artery Disease useful for clinical practice and further research.

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