International Journal of Cardiology 174 (2014) 337–342

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Cardiopulmonary exercise testing is more accurate than ECG-stress testing in diagnosing myocardial ischemia in subjects with chest pain

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ARTICLE INFO

Article history:
Received 4 November 2013
Received in revised form 10 March 2014
Accepted 6 April 2014
Available online 15 April 2014

Keywords:
Cardiopulmonary exercise stress testing
Chest pain
Obstructive coronary artery disease

ABSTRACT

Background: Cardiopulmonary exercise stress testing (CPET) is used to grade the severity of heart failure and to assess its prognosis. However it is unknown whether CPET may improve diagnostic accuracy of standard ECG stress testing to identify or exclude obstructive coronary artery disease (O-CAD) in patients with chest pain.
Methods: We prospectively studied 1265 consecutive subjects (55 ± 8 years, 156 women) who were evaluated with ECG stress testing (ET) for chest pain. No one had a documented O-CAD. All patients performed an incremental CPET with ECG recordings on an electronically braked cycle ergometer.
Results: Of 1265 patients, 73 had a positive CPET and 1192 had a negative CPET. Seventy-three patients with a positive CPET and 71 patients with a negative CPET agreed to undergo nuclear SPECT imaging and coronary angiography. Follow-up lasted 48 ± 7 months. As compared with ET, sensitivity, specificity, PPV and NPV were all improved significantly (ET: 48%, 55%, 33%, 95%; CPET: 88%, 98%, 73%, 99%, respectively, $P < 0.001$). Patients with both peak VO_2 > 91% of predicted VO_2 max and absence of VO_2-related signs of myocardial ischemia had no evidence of O-CAD in 100% of cases. Cardiac events occurred in 32 patients with a positive CPET and 8 patients with a negative CPET (log rank 18.2, $P < 0.0001$).
Conclusions: In patients with chest pain, CPET showed a better diagnostic and predictive accuracy than traditional ET to detect/exclude myocardial ischemia. Its use should be encouraged among physicians as a first line diagnostic tool in clinical practice.

1. Introduction

Cardiopulmonary exercise testing (CPET) is used in clinical practice to grade the severity of heart failure and to assess its prognosis, [1] to determine the timing of heart transplantation, [2] to evaluate the efficacy of therapeutic interventions, [3] to prescribe the intensity of exercise training programs, and to identify the pathophysiological causes of exercise limitation in patients with depressed functional capacity [4]. Despite the increased spectrum of clinical applications in recent years, CPET is still less popular than the "traditional" ECG stress test and it is routinely performed in a minority of centres in the western countries. Limitations are the need to calibrate before each test, the use of a mouthpiece or facial mask, the insecurity of the examiner in interpreting the results, and the cost of equipment. Moreover, current guidelines do not consider CPET as a diagnostic tool for diagnosing myocardial ischemia in documented as well as suspected coronary artery disease cases.

Chest pain is one of the most common symptoms yielding to medical consultation. However, objective electrocardiographic evidence of myocardial ischemia at rest and during exercise is not possible in all cases. Almost three/fourth of patients with chest pain visited at the emergency units have no detectable ECG abnormalities [5,6]. According to a metanalysis, the sensitivity and specificity of exercise-induced ST segment depression are 66% and 84%, respectively, with a range of 40% for one-vessel disease and 90% for 3-vessel disease [7]. Recent evidence suggests that CPET improves the diagnostic accuracy of ECG-stress test in patients with documented coronary artery disease (CAD) [8]. When gas exchange analysis is added to ECG stress testing, sensitivity improves by 89%, from 46% to 87%, and specificity also improves from 66% to 74%. In light of this result, it would be of potential clinical value to prove the diagnostic accuracy of CPET in subjects with suspected CAD.

The primary objective of the present study was to determine if the analysis of gas exchange during an increasing work rate exercise test may improve the diagnostic accuracy of standard ECG stress test for

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http://dx.doi.org/10.1016/j.ijcard.2014.04.102
0167-5273/

identifying or excluding myocardial ischemia in subjects referred for chest pain of unknown origin and suspected CAD. Another objective was to determine whether CPET may predict the outcome.

2. Methods

We prospectively studied a group of patients with chest pain referred to exercise testing core laboratory at the Lancisi Heart Institute. Of 1345 patients, 1289 were considered eligible and enrolled in the study (Table 1). We collected clinical data from patients during a preliminary visit: age, height, weight, body mass index, family history and other cardiovascular risk factors including cigarette smoking (current or prior), hypertension, hypercholesterolemia, diabetes, obesity (BMI > 30) and estrogenic status (negative or positive). Chest pain was classified according to Diamond categories: typical angina, atypical angina and no angina [9]. Pre-test score was calculated according to Morise and Jalisi: low (0 to 8 points), intermediate [9–15] and high (>15) [10]. Exclusion criteria were: history of coronary artery disease, chronic heart failure, uncontrolled hypertension or diabetes, anemia, respiratory disease and inability to exercise.

2.1. Protocol

The protocol was approved by the internal Ethical Committee. All patients signed an informed consent form. All tests were performed in the morning in the fasting state. Medications were stopped before each test for 4 times their half-lives. Tea, coffee, cola-drinks, chocolate and smoking were not allowed for 24 hours before the evaluation. In order to satisfy the primary objective we compared CPET results from 144 patients (73 positive vs 71 negative) with coronary angiography as gold standard for O-CAD. Briefly, after their written consent, we randomized 71 patients with a negative CPET consecutively chosen on the basis of sex, age, height, weight, chest pain characteristics, peak heart rate and peak VO_2 as a percentage of VO_2 max with similar clinical characteristics as the 73 patients with a positive CPET.

In order to satisfy the secondary objective we followed up all patients for 48 ± 7 months to compare cardiovascular event rate.

2.2. Cardiopulmonary exercise testing

After a familiarization test, a symptom-limited cardiopulmonary exercise test was performed on an electronically-braked cycle-ergometer using a ramp-pattern increase in work rate, as previously described [8]. Peak oxygen uptake was the average oxygen uptake during the last 15 s of exercise. $\Delta VO_2/\Delta WR$ slope was automatically calculated as: peak VO_2-unloaded VO_2 / T − 0.75 × S, where peak VO_2 is VO_2 at peak exercise, T is the time of incremental exercise, and S is the slope of work rate increment in watts per minute [1]. In healthy subjects, $\Delta VO_2/\Delta WR$ slope is approximately 10 ml/min/W, and the increase in VO_2 is linear with the increase in work rate until peak exercise is reached. The diagnosis of myocardial ischemia by CPET was made using the model previously described [7]. Briefly, the coexistence of an inflection in $\Delta VO_2/\Delta WR$ slope with O_2 pulse flattening duration calculated from the inflection point to peak exercise of similar duration as that calculated in $\Delta VO_2/\Delta WR$ slope was considered as an evidence of myocardial ischemia (Fig. 1). Criteria to exclude myocardial ischemia were: 1) the absence of inflection in $\Delta VO_2/\Delta WR$ slope; 2) the lack of a similar duration in flattening from inflection point to peak exercise between $\Delta VO_2/\Delta WR$ slope and O_2 pulse; and 3) peak VO_2 above 90% of VO_2 max (AUC 0.84). All three criteria had to coexist.

Table 1
Study population.

Men/Women (*n*)	1109/156
Age (yrs)	59 ± 9
Height (cm)	165 ± 9
Weight (kg)	76.6 ± 14
Occupation (*n*)	
-White collar	234
-Blue collar	244
-Retired	787
Cardiovascular risk factors, *n* (%)	
-family history	139 (11)
-hypercholesterolemia	368 (33)
-hypertension	271 (25)
-smoking	705 (65)
-diabetes mellitus	174 (16)
-obesity	63 (5)
No. of risk factors (0/I/2/3/>3)	165/345/421/154
Medications, *n*	-Betablockers, 168 -ACE-inhibitors, 98 -Angiotensin II blockers, 55 -Antiplatelets, 225 -Statins, 298 -Antidiabetics, 131

The evidence of an inflection in VO_2 during the last 30 s of exercise was not considered as abnormal, because it could be the result of a plateau in VO_2 frequently occurring in normal fit subjects. Tests were interpreted by 2 experienced evaluators who were blinded to the names of the patient, results of other studies, clinical history and physical findings. For CPET parameters selected in the model, intra-observer and inter-observer variability were assessed in 50 patients with documented ischemic heart disease (40 men, 10 women, mean age 55 ± 10) and 50 healthy subjects matched for age, sex, race, height and weight. Intra-observer variability was 3.5 ± 6% and interobserver variability was 4.8 ± 5%.

2.3. Myocardial scintigraphy

A nuclear imaging study was performed in 73 patients with a positive CPET and 71 patients with a negative CPET over 2 weeks from CPET. At the end of the exercise stress test, or at 85% of predicted maximal heart rate, 500 MBq tetrofosmin was injected into an antecubital vein and myocardial scintigraphy was then performed using a dual-head gated-SPECT system (ADAC Vertex,CA). The day after, 500 MBq tetrofosmin was reinjected at rest, and acquisition started 1 hour later (2-day stress/rest protocol). A gated-SPECT acquisition results in a standard SPECT data set from which perfusion was assessed, and a larger gated SPECT data set, from which function was evaluated. Three summed scores were automatically derived: summed stress score (SSS = sum of the stress scores); summed rest scores (SRS = sum of the rest scores); and summed difference score (SDS = the difference between SSS and SRS). The severity of myocardial ischemia was defined on the basis of summed difference score: <3, no reversibility; 3–7, mild ischemia; 7–12, moderate ischemia; >12, severe ischemia [11].

2.4. Coronary angiography

Coronary angiography was performed by Judkins' technique. A stenosis was considered hemodynamically significant if a ≥50% reduction in luminal diameter was measured. Quantitative analysis was performed in each angiogram with a computer-assisted edge detection system (Digital Cardiac Imaging, Philips) by two experienced cardiologists unaware of clinical picture and each other's interpretation

2.5. Follow-up

Follow-up started the day after the CPET and lasted 48 ± 7 months. Follow-up ended with an adverse event or at 48-month in those without events. Measures of outcome were prospectively defined as mortality from all causes and cardiovascular morbidity (acute coronary syndrome, coronary angioplasty, or coronary artery by-pass surgery).

3. Statistical analysis

Statistical analysis was performed using SPSS statistical software version 17 (SPSS Inc., Chicago Ill). Unpaired Student's *t* tests (2-sided) was used to compare means of ECG stress test variables and means of CPET variables between groups of patients with positive or negative myocardial scintigraphy and with or without evidence of coronary artery disease on coronary angiography. One way ANOVA was used to compare clinical, hemodynamic and metabolic variables among groups of patients stratified according to SDS score and to one, two or three vessel disease. Two-by-two tables were built to estimate sensitivity, specificity, predictive values and 95% confidence intervals of ECG stress tests and CPET, using myocardial scintigraphy and coronary angiography as a gold standard for both. Kaplan Meier survival curves were then plotted to compare patients with and without evidence of myocardial ischemia on CPET. Differences were considered significant at $P < 0.05$. Data are mean ± SD.

4. Results

Of 1289 subjects enrolled, 24 (1.86%) had uninterpretable ECG and were excluded. Four patients had hypotension during recovery and 80 had minor arrhythmias. There were no myocardial infarctions or deaths resulting from CPET and no significant morbidity resulted from the test. Electrocardiographic and CPET parameters are shown in Table 2. Of 1265 subjects, 73 (6%) had a positive CPET and 1192 (94%) had a negative CPET. Of 73 patients with a positive CPET, 40 (30 M,10 W) showed significant ST abnormalities (55% agreement between CPET and ECG), while 33 subjects did not. Of 1192 subjects with a negative CPET (141 women), 1174 (98.5%) had a negative ECG stress testing (98% agreement), while 18 (1.5%) had ST abnormalities (positive ECG stress test). Of them, 15 were women (83%).

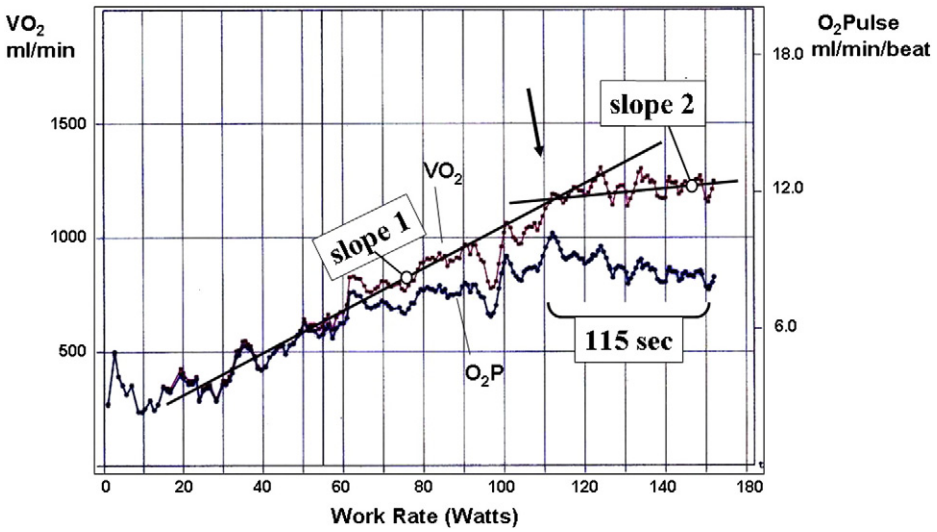

Fig. 1. An example of a postive CPET according to the method of identification of myocardial ischemia described in R. Belardinelli et al, Eur Heart J 2003; 24: 1304–13. Two markers should be considered: A. an "inflection point" in DVO2/DWR slope ("double slope sign"); B. similarity in the time from the inflection point to peak exercise between DVO2/DWR slope and O2pulse. Oxygen uptake (VO2) as a function of work rate (W) during a progressively increasing work rate test is linear, with a normal value of 10ml/min/W. The transition from normal increase in VO2 as related to work rate (slope 1) to a slow increase in VO2 (slope 2) has been considered the onset of myocardial ischemia. Slope 2 should be <4 ml/min/W. In this case slope 1 is 9.7 ml/min/W and slope 2 is 2.8 ml/min/W. The duration of flattering in slope 2 is similar in O2pulse (115 s in this case).

Obstructive coronary artery disease was diagnosed in 64 out of 73 subjects with a positive CPET (88%) and in 3 out of 71 patients with a negative CPET (4%). In the 64 patients with a positive CPET, 1 vessel disease was present in 9 subjects (14%), 2-vessel disease in 24 (38%) and triple vessel disease in 31 (48%). In the 3 patients with a negative CPET, 1-vessel disease was present in 1 patient and triple vessel disease in two. Nuclear imaging revealed a reversible defect in 59 out of 73 subjects with a positive CPET (81%) and in 2 patients with a negative CPET. In 40 patients with a positive CPET and a positive SPECT imaging there was a direct correlation between VO_2-related model and severity of myocardial ischemia ($r = 0.82$, $P < 0.0001$). Patients with a SSS > 12 and a SWTI > 2 had a $\Delta VO_2/\Delta WR$ slope 2 significantly flatter than patients with a SSS < 7 and SWTI <1 (2.5 ± 0.9 vs 3.7 ± 0.5, $P < 0.0001$).

As shown in Table 3, of 15 women with a positive CPET who underwent coronary angiography and nuclear imaging, 13 had a perfusion defect (86%) and 9 a significant coronary artery stenosis on angiography (60%). Of 58 men with a positive CPET, 55 had coronary artery stenosis on angiography (95%) and 46 had a reversible perfusion defect (79%). Traditional ECG stress testing was considered positive in 30 men and 10 women, while it was negative in 28 men and 5 women.

Follow-up—Cardiac events occurred in 32 patients with a positive CPET and 8 patients with a negative CPET (positive predictive accuracy (PPV): 76%; negative predictive accuracy (NPV): 95%) (Table 4). Kaplan Meier analysis revealed a significant lower event rate in patients with a negative CPET (log rank 18.2, $P < 0.0001$) (Fig. 3). As compared with ECG stress testing, sensitivity, specificity, PPV and NPV were all improved significantly with CPET (ET: 48%, 75%, 33%, 95%; CPET: 88%, 98%, 73%, 99%, respectively, $P < 0.001$ for all). Patients with a peak VO_2 > 91% of predicted VO_2 max and absence of VO_2-related signs of myocardial ischemia had no evidence of IHD in 100% of cases.

5. Discussion

The results of the present study demonstrate that CPET is more accurate than standard ECG stress testing in identifying or excluding O-CAD in patients referred for chest pain. As compared with ECG stress testing, sensitivity, specificity, PPV and NPV were all improved. Patients with a peak VO_2 > 91% of predicted VO_2 max and absence of VO_2-related signs of myocardial ischemia had no evidence of IHD in 100% of cases. Moreover, CPET result predicts clinical outcome. Patients with a positive CPET have a worse outcome over a 48 ± 7 month follow-up (RR 0.59, $P < 0.001$).

Table 2
Parameters from cardiopulmonary exercise stress tests with and without inducible myocardial ischemia.

	Negative $n = 71$	Positive $n = 73$	P
Heart rate, rest (b/min)	73 ± 14	69 ± 12	0.81
Heart rate, peak (b/min)	144 ± 11	149 ± 9	074
Systolic blood pressure, peak (mm Hg)	187 ± 32	188 ± 29	0.82
$V0_2$, peak (ml/kg/min)	18.4 ± 6	17.4 ± 4	0.13
$V0_2$ AT (ml/kg/min)	11.0 ± 5	10.8 ± 4.5	0.66
Ventilation, peak (l/min)	60.7 ± 20	58 ± 18	0.27
Respiratory exchange ratio, peak	1.21 ± 0.8	1.19 ± 0.8	0.58
Double product, peak (b/min/mm Hg)	25,247 ± 7000	26,158 ± 5607	0.23
Workload, peak (Watts)	139 ± 53	136 ± 40	0.59
$VE/VO_{2\ AT}$	30.5 ± 5.4	30.0 ± 3.3	0.47
$VE/VCO_{2\ AT}$	28.6 ± 5.4	28.1 ± 3.5	0.41
$\Delta VO_2/\Delta W$ slope (ml/min/W)	8.4 ± 1.6	7.8 ± 1.8	0.04
Heart rate/$V0_2$ slope (b/min/ml)	3.8 ± 1.7	4.5 ± 1.7	0.0001
$YE/VC0_2$ slope	31.4 ± 15	33.4 ± 16	0.17

Table 3
Gender-related differences in subjects with a positive and a negative CPET who underwent coronary angiography and mycoardial nuclear SPECT imaging.

Positive CPET	Men		Women		All	
	($n = 58$)		($n = 15$)		($n = 73$)	
	CAD	No CAD	CAD	No CAD	CAD	No CAD
Coronary angiography, *n*	55	3	9	6	64	9
Nuclear imaging, *n*	46	12	13	2	59	14
ECG stress testing, *n*	30	28	10	5	40	33
Negative CPET	Men		Women		All	
	($n = 57$)		($n = 14$)		($n = 71$)	
	CAD	no CAD	CAD	no CAD	**CAD**	no CAD
Coronary angiography, *n*	2	55	1	13	3	68
Nuclear imaging, *n*	1	56	1	13	2	69
ECG stress testing, *n*	7	50	6	8	13	54

CAD = coronary artery disease

5.1. The role of CPET in patients with chest pain

CPET is a safe and inexpensive tool providing a unique opportunity to monitor ventilation and gas exchange noninvasively and operator independently. Moreover, modern technology reduced the time required for the execution of a CPET very close to that of a traditional ECG stress test. In a study from our laboratory in 191 consecutive subjects there was a difference of 63 s between the two tests (data on file).

How can we explain the improved diagnostic accuracy of CPET in patients with chest pain and suspected coronary artery disease? Coronary artery disease is functionally important when the extractable O_2 flow to the myocardium is exceeded by the O_2 demand. An area of the myocardium in which the O_2 demand for ATP regeneration exceeds the extractable O_2 flow, that area of the myocardium must stop contracting. But when an exercise level is reached for which the diastolic time is reduced by increase in heart rate to the level where O_2 filling of the coronaries is shortened, and simultaneously cardiac work is increased, the extractable O_2 flow may fall below the O_2 demand in the region of the myocardium served by stenotic vessels. Thus this region of the myocardium will not be able to contract during exercise and it will be functioning dyskinetically [12]. Consequently, stroke volume will decrease and heart rate will increase relative to VO_2 increase. At this work rate, O_2 pulse will become flat or even decrease. This will likely result in the failure for O_2 flow to the exercising muscle to increase in pace with the skeletal muscle work rate, thereby causing a decrease in the rate of increase in VO_2 relative to work rate ($\Delta VO_2/\Delta WR$). Oxygen uptake increase relative to work rate increase will abruptly decrease above the ischemic point. Thus, myocardial ischemia determines abnormal contractility causing LV function depression. It should be considered that VO_2 flattening is strictly dependent on heart rate increase during exercise. When mechanical dysfunction sets in from inducible ischemia, heart rate immediately steepens at the same point in time that stroke volume flattens. The amount of VO_2 flattening thus will depend on how effective the heart rate compensation mechanism is by the autonomous nervous system. This date set confirms that the patients with the highest ischemic burdens had the most pronounced flattening of VO_2.

In the study of Upton et al. [13] a clear correlation was demonstrated between myocardial ischemia and LV function in patients with O-CAD. In fact, as compared with normal subjects, patients with reversible myocardial defects on nuclear planar imaging had a reduction in wall motion score index which was associated with depressed ejection fraction. In another study, [14] a significant inverse correlation was found between the severity of myocardial ischemia on nuclear imaging and $\Delta VO_2/\Delta WR$ slope ($r = -0.33$, $P = 0.016$), suggesting a strict link between VO_2 kinetics and left ventricular function during ischemia. This link has been confirmed in 2 recent studies. In both, patients with inducible ischemia had a delayed VO_2 kinetics, reflected in abnormalities in $\Delta VO_2/\Delta WR$ slope and O_2 pulse which were not evident in normal subjects [15,16]. A depressed $\Delta VO_2/\Delta WR$ slope, associated with a low O_2 pulse response to work rate increase, was also described by our group in patients with documented coronary artery disease and ST depression on ECG stress testing [8]. Both abnormalities were inversely related to the severity of myocardial ischemia assessed by SPECT imaging. In contrast to heart failure patients, in which $\Delta VO_2/\Delta WR$ slope may begin to flatten from the beginning of work rate increase, and the degree of flattening is related to the level of cardiovascular impairment, $\Delta VO_2/\Delta WR$ slope was normal from start of work rate increase to a point corresponding to the onset of myocardial ischemia. Then, as work rate increased further, an inflection point was evident in the majority of patients with detectable myocardial ischemia, above which the rate of increase in VO_2 as related to work rate was flatter until peak exercise ("double slope" sign). As a matter of fact, $\Delta VO_2/\Delta WR$ slope was 9.4 ± 0.5 ml/min/W from start of exercise to the inflection point, not dissimilar from $\Delta VO_2/\Delta WR$ slope in healthy controls (9.5 ± 1.2 ml/min/W). However, $\Delta VO_2/\Delta WR$ slope 2 was significantly flatter the greater the severity of myocardial ischemia, and a cut-off value of 3.9 ml/min/W was selected by hierarchical model as the strongest independent predictor of myocardial ischemia. The "double slope" sign should be accompanied by O_2 pulse flattening

Table 4
Cardiac events during the follow-up.

	All pts	CPET pos	CPET neg	Absolute	RJR	*P*
	($n = 1265$)(%)	($n = 73$)(%)	($n = 1192$) (%)	Difference (%)	(95% CI)	
Cardiac death	0	0	0	0	–	–
ACS + PCI	8 (0.6)	4 (5.5)	4 (0.3)	5.2	1.10 (0.69–1.61)	0.45
CABG	28 (2.7)	26 (36)	2 (0.16)	35.8	0.61 (0.35–0.92)	0.002
PCI + CABG	4 (0.3)	2 (2.7)	2 (0.16)	2.5	1.0 (0.88–1.25)	0.76
Total events	42 (3.3)	32 (43.8)	8 (0.67)	43.1	0.59 (0.33–0.91)	0.001

POS = evidence of at least one significant coronary artery stenosis on coronary angiography or perfusion defect on nuclear imaging; NBG = absence of coronary artery stenosis or perfusion defect. RR = relative risk.

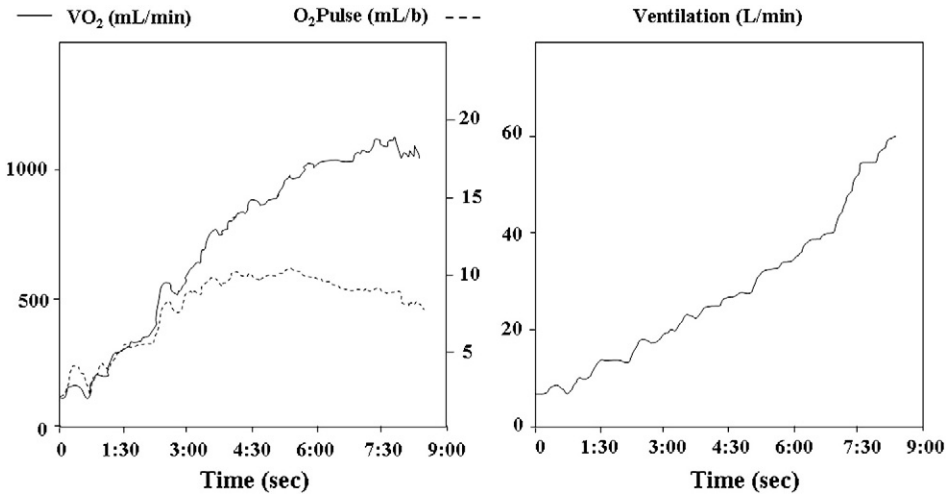

Fig. 2. An example of VO_2, O_2 pulse and ventilation responses during an incremental protocol on a cycle ergometer (20 W/min,ramp) in a 70 year old man referred for chest discomfort. Both VO_2 and O_2 pulse flatten, while ventilation continues to rise without any evident point of inflection. For explanation, see text.

which must have the same duration as slope 2. The predictive ability of the model was good (C-statistics 0.84). Similar results were observed in the present study. True positives had a normal slope 1 (9.6 ± 0.4 ml/min/W) and a depressed slope 2 (2.7 ± 1.1 ml/min/W). O_2 pulse flattening and $\Delta VO_2/\Delta WR$ slope 2 had similar duration (255 ± 48 s).

There is evidence that abnormalities of left ventricular function during exercise almost invariably come before ST segment depression and angina in patients with stable coronary artery disease [12]. Thus, VO_2 kinetics is delayed, reflecting exercise-induced myocardial dysfunction, and CPET abnormalities may be evident earlier than ECG changes and clinical signs [17]. In the present study, of 40 patients who developed ST depression during exercise and also had a positive scan, VO_2 flattening started much earlier than ST downsloping (255 ± 48 vs 490 ± 41 sec, $P < 0.001$). In the study by Upton et al., [13] either stroke volume or cardiac output ceased to increase during cycle-ergometer exercise before the onset of ST segment depression. No patient had angina before the onset of ST depression. Regional wall motion score index was decreased at peak exercise as compared to the beginning (from 5.7 ± 0.7 at rest to 3 ± 1.2), and contractility abnormalities were accompanied by a decrease in ejection fraction and by an increase in end-systolic volume during work rate increase. However, gas exchange analysis was not performed. Oxygen uptake changes in response to incremental exercise are primarily a cardiac function, depending on change in cardiac contractility and pulmonary blood flow, and are substantially independent of change in ventilation (Fig. 2). This hypothesis is suggested by the correlation of both O_2 pulse flattening duration and $\Delta VO_2/\Delta WR$ with the degree of contractile dysfunction expressed by SWTI at peak exercise ($P < 0.0001$).

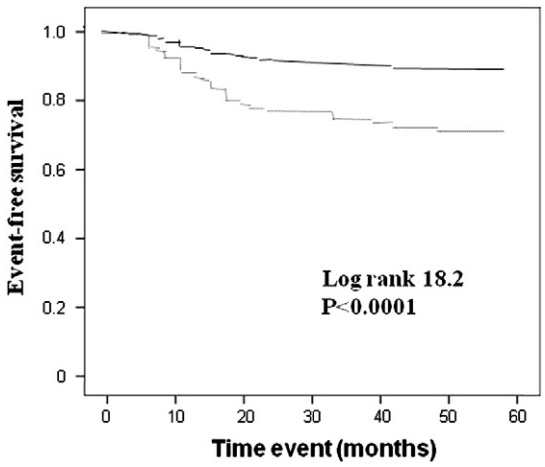

Fig. 3. Kaplan–Meier plot depicting temporal distribution of cumulative events in subjects with chest pain and a negative CPET (bold line) vs subjects with chest pain and a positive CPET (dotted line).

5.2. Women

There is evidence that women are less likely than age-matched men to have flow limiting CAD; triple vessel disease or left main CAD are more common in men [18]. The high prevalence of non-obstructive CAD and single vessel disease results in an observed decreased diagnostic accuracy of traditional ECG stress testing. In the present investigation, of 15 women with a positive CPET, 9 had evidence of O-CAD by angiography and 13 had a perfusion defect on nuclear imaging. All these women had an intermediate pre-test probability of O-CAD. In 10 women with a positive CPET there was ST depression, while ECG was not diagnostic in 5 of them. In a metaanalysis of 19 ECG stress testing studies on 3721 women, sensitivity and specificity were 61% and 70%, while they were 72% and 77% in 1977 men [19]. In a group of 976 symptomatic women referred for ECG stress testing and coronary angiography significant coronary stenosis was present in 19%, 35% and 89% of pre-test low-moderate and high risk women [20]. In our population a significant coronary artery stenosis was detected in 60% of women, while a perfusion defect was evident in 87% of women with a positive CPET. This discrepancy between myocardial ischemia and the number and severity of coronary artery stenoses has been demonstrated in the past [21]. The results of the present trial are in agreement with the WOMEN trial in preferring a non-invasive cost-effective exercise testing in predicting clinical outcome in women with suspected CAD [22].

5.3. Predictive value of CPET

The predictive value of CPET as well as ECG stress testing for diagnosing O-CAD depends on pre-test probability. In the present study, subjects with low pre-test probability had a significant lower cardiac events rate during the follow up as compared with those with intermediate and high probability of O-CAD. Both sensitivity and positive predictive value were higher with CPET than ECG stress test (27% (44% vs 31%) and 43% (76% vs 43%), respectively, $P < 0.001$ for both). Specificity and negative predictive value were not significantly different (99% vs

98%, 97% vs 97%, respectively, *P* NS). However, as compared with ECG stress test, positive predictive value was 43% higher with CPET in subjects with low pre-test probability of O-CAD (35% vs 20%, $P < 0.01$), 30% higher in the group with intermediate probability (60% vs 42%, $P < 0.01$), and 36% higher in the high probability group (84% vs 54%, $P < 0.005$). Similar improvements were observed in negative predictive values in the 3 pre-test probability subgroups (16%, 20% and 43%, respectively). We observed this trend already described in the past in other studies with ECG stress test, with NPV increasing with lower pre-test probability of disease and PPV decreasing. However, we demonstrated that CPET analysis improves the prognostic accuracy of ECG stress test in patients with suspected O-CAD.

5.4. Limitations

Routine interpretation of CPET is the presence of abnormalities in O_2 transport capacity which are generally associated with a depressed $\Delta VO_2/\Delta WR$ slope, can make the interpretation of results sometimes problematic. For this reason, we excluded patients with severe chronic heart failure, anemia and respiratory disease. Treadmill exercise protocols with step increase in work rate do not allow measures of $\Delta VO_2/\Delta WR$, since the work rate is not expressed in Watts and is not increased linearly. Rarely, patients breath eratically through the mouthpiece, and measures of ventilation and gas exchange are difficult to analyze. For this reason, we chose a Rudolph mask which guarantees a perfect adherence to the patient's face, eliminating the risk of artefacts in gas exchange analysis. Sometimes, test repetition after calming the patient allows clinician to obtain good quality gas exchange recordings. In some young patients, O_2 pulse flattens early, approximately at the same level expected in normal sedentary subjects, corresponding to 40–50% of peak workload. This behavior may suggest false positive interpretations. However, the combined analysis of $\Delta VO_2/\Delta WR$ slope may help to exclude false positive tests. Moreover, we did not compare CPET with stress echocardiography, which is a popular test in patients with suspected CAD. Nuclear imaging is not a gold standard for microcoronary artery disease and, when abnormal, is likely detecting a reversible ischemic bed with a mechanism which likely includes microvascular dysfunction. We are aware that an abnormal scan with normal coronary arteries is likely detecting micro-CAD, and that a normal nuclear scan does not rule out micro-CAD. However, nuclear imaging is widely accepted as the most popular diagnostic tool in CAD, and we used it to compare CPET results in a group of negative and positive tests [23]. Furthermore, most events (32 out of 42 = 76%) were represented by CABG, which is an expected occurrence in patients with a positive angiography.

6. Conclusions

The results of the present study provides valuable insight that CPET could fit the role to identify patients appropriate for further evaluation with other more expensive, toxic and invasive modalities. A recent paper reported that the percentage of abnormal SPECT studies has dropped dramatically from ~40% to ~5% in the last 20 years and stressed the need for another modality to be used before nuclear [24]. As compared with ECG stress testing, sensitivity, specificity, PPV and NPV were all improved. Patients with a peak $VO_2 > 91\%$ of predicted VO_2 max and absence of VO_2-related signs of myocardial ischemia had no evidence of O-CAD in 100% of cases. Gas exchange analysis is particularly helpful when ECG is not interpretable for myocardial ischemia. Moreover, CPET result predicts clinical outcome. The results of this study must be confirmed in larger clinical trials in order to consider CPET in clinical practice to detect or exclude inducible myocardial ischemia not only in patients with a documented CAD, but also in subjects with chest pain of unknown origin.

Conflict of interest disclosures

None.

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