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

Romualdo Belardinelli [a,*], Francesca Lacalaprice [a], Luca Tiano [b], Andi Muçai [c], Gian Piero Perna [a]

[a] Cardiologia Riabilitativa e Preventiva, Azienda Ospedali Riuniti Lancisi-Umberto I-Salesi, Ancona, Italy
[b] Department of Biochemistry, Università Politecnica delle Marche, Ancona, Italy
[c] Catheterization and Angiography Laboratory, Azienda Ospedali Riuniti Lancisi-Umberto I-Salesi, Ancona, Italy

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

* Corresponding author at: Via Conca 71, 60020, Cardiologia Riabilitativa e Preventiva, Azienda Ospedali Riuniti Lancisi-Umberto I-Salesi, Ancona, Italy. Tel.: +39 071 5965344, +39 5965798 (hospital); fax: +39 071 5965042.
E-mail address: r.belardinelli@fastnet.it (R. Belardinelli).

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/l/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%).