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Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing

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KEYWORDS

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diagnostic accuracy

Background The objective of the study was to identify the parameter(s) of cardiopulmonary exercise testing (CPET) that can detect exercise-induced myocardial ischaemia (EIMI), and to determine its diagnostic accuracy for identifying patients with coronary artery disease (CAD).

Methods and results We prospectively studied 202 consecutive patients (173 men, 29 women, mean age 55.7±10.8 years) with documented CAD. All patients underwent an incremental exercise stress testing (ECG-St) with breath-by-breath gas exchange analysis, followed by a 2-day stress/rest gated SPECT myocardial scintigraphy (GSMS) as the gold standard for ischaemia detection. ROC analysis selected a two-variable model—O₂ pulse flattening duration, calculated from the onset of myocardial ischaemia to peak exercise, and $\Delta\text{VO}_2/\Delta\text{work}$ rate slope—to predict EIMI by CPET. GSMS identified 140 patients with reversible myocardial defects, with a Summed Difference Score (SDS) of 9.7±2.8, and excluded EIMI in 62 (SDS 1.3±1.6). ECG-St had low sensitivity (46%) and specificity (66%) to diagnose EIMI as compared with CPET (87% and 74%, respectively).

Conclusions The addition of gas exchange analysis improves the diagnostic accuracy of standard ECG stress testing in identifying EIMI. A two-variable model based on O₂ pulse flattening duration and $\Delta\text{VO}_2/\Delta\text{work}$ rate slope had the highest predictive ability to identify EIMI.

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Introduction

Cardiopulmonary exercise testing (CPET) is used in clinical cardiology to quantify the degree of cardiovascular dysfunction and to assess the prognosis of heart failure patients.¹ It is also employed to prescribe the intensity of exercise for patients

enrolled in cardiac rehabilitation programs, and to determine the pathophysiological causes of exercise limitation in patients with depressed functional capacity. Despite the increased spectrum of clinical applications, CPET is still less popular than the 'classical' ECG stress test for diagnosing coronary artery disease. The need to calibrate before each test, the insecurity of the examiner in interpreting the results of CPET studies and the cost of equipment may account for the decreased popularity of CPET. However, by coupling CPET studies with standard 12-lead ECG more detailed

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information about the haemodynamic response to exercise could be obtained than that provided by the standard ECG stress test, alone. Parameters from CPET, such as oxygen uptake (VO_2) at peak exercise, anaerobic threshold, O_2 pulse, $\Delta\text{VO}_2/\Delta\text{WR}$ and ventilatory equivalent at the anaerobic threshold or slope of ventilation versus CO_2 output (VE vs VCO_2), all might become abnormal in patients with cardiovascular disease. Thus, CPET might improve the diagnostic accuracy of an exercise stress test and help focus the patient's clinical disorder.

Stress-induced myocardial ischaemia is generally diagnosed on the basis of ST segment changes, angina, ventricular arrhythmias and/or systolic blood pressure drop with work rate increase. However, the identification of myocardial ischaemia by a standard 12-lead ECG is not possible in all cases. The sensitivity and specificity of exercise-induced ST segment depression is 66% and 84%, respectively, with a range of 40% for one-vessel disease and 90% for three-vessel disease.^{2,3} Gas exchange analysis may help to overcome the interpretative limitations of ECG stress testing, especially when conduction or ventricular repolarization abnormalities are present at rest. The rate of VO_2 increase as related to work rate has been proposed as an indicator of cardiovascular efficiency in patients without limiting factors in O_2 transport capacity, and flattening of oxygen uptake is commonly seen in heart failure patients or in patients receiving betablockers.¹

The analysis of gas exchange may be used to identify decreased stroke volume caused by myocardial ischaemia during exercise. Since regional myocardial ischaemia generally results in wall motion abnormalities, it is likely to be associated with haemodynamic changes, such as stroke volume and cardiac output depression during exercise. It is well known that in the cascade of events following myocardial ischaemia, angina pectoris and ECG ST segment changes are more delayed than regional myocardial dysfunction due to perfusion abnormalities.⁴ Thus, if myocardial ischaemia slows the rate of increase in cardiac output during a progressively increasing work rate exercise test, due to decreasing stroke volume, the rate of increase in oxygen uptake and possibly other related variables (O_2 pulse and $\Delta\text{VO}_2/\Delta\text{WR}$), measured by CPET, would become abnormal. These abnormalities should be evident before ECG ST segment depression and angina.

The objective of the present study were: (1) to select the parameter(s) of CPET that can predict the development of exercise-induced myocardial

Table 1 Clinical characteristics

Male/female (n)	202, 173/29
Age (years)	55.7±11
Ejection fraction (%)	53.5±11
Peak VO_2 (ml/kg/min)	21.3±4
Coronary lesion score ^a	1.8±0.7
Coronary vessels, n (1/2/3)	80/81/41
Previous acute myocardial infarction, n (%)	80 (39.6)
Previous PTCA, n (%)	98 (48.5)

^aThe number of major coronary arteries with at least one significant ($\pm 75\%$) stenosis, expressed as mean±SD.

ischaemia in patients with known coronary artery disease; and (2) to determine if the analysis of gas exchange during an increasing work rate exercise test will improve the diagnostic accuracy of the standard ECG stress test for identifying myocardial ischaemia in patients with coronary artery disease.

Methods

We prospectively studied 202 patients (173 men, 29 women, mean age 55.7±10.8 years) with coronary artery disease (Table 1). A group of 196 healthy subjects (172 men, 24 women, mean age 57.2±12) served as control for CPET data. All patients had a coronary angiography within 3 months of the exercise test. They did not exercise regularly, and were not involved in exercise training programmes in the last 2 months. Inclusion criteria were: documented coronary artery disease and clinical stability evidenced by no recent hospitalization for angina or need to modify medications during the last 3 months. Exclusion criteria were: chronic heart failure, unstable angina, recent acute coronary syndrome, uncontrolled hypertension or diabetes, anaemia, respiratory disease and inability to exercise. Antianginal medications were stopped before each test: nitrates for 24 h, calcium-antagonists for 48 h, beta-blockers for 5 days. Tea, coffee, cola-drinks, chocolate and smoking were not allowed for 24 h before the evaluation.

Protocol

The protocol was approved by the local Ethical Committee. All patients signed an informed consent. They underwent a cardiopulmonary exercise testing and a myocardial scintigraphy on the same day. All tests were performed in the morning in the fasting state.

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. After calibration of the volumes and gas exchange analysers, patients breathed through a Rudolph mask connected to a two-way respiratory valve. Expired gases and volumes were analysed, breath-by-breath, with a metabolic cart (Sensormedics 2900 Z, Yorba Linda, CA). Heart rate and blood pressure were measured every minute during increasing work rate exercise and recovery. A 12-lead ECG was recorded every minute. The exercise test was stopped when one or more of the following criteria were present: predicted heart rate, fatigue, dyspnoea, excessive systemic blood pressure increase ($\geq 230/130$ mmHg), ≥ 2 mm ST depression in at least two adjacent leads and/or angina. The ischaemic threshold was considered the onset of a 1 mm ST segment depression in at least two adjacent leads as work rate was increased, and was expressed as heart rate or rate-pressure product (RPP). The anaerobic threshold was measured by the V-slope method.⁵ Peak oxygen uptake was the average oxygen uptake during the last 15 s of exercise. $\Delta\text{VO}_2/\Delta\text{WR}$ slope was automatically calculated as: $\text{peak VO}_2 - \text{unloaded VO}_2 / T - 0.75 \times S$, where peak VO_2 is VO_2 at peak exercise, T is the time of incremental exercise, S is the slope of work rate increment in watts per minute.⁶ In healthy subjects, $\Delta\text{VO}_2/\Delta\text{WR}$ 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.^{1,10} We considered $\Delta\text{VO}_2/\Delta\text{WR}$ slope as abnormal when an inflection was evident in VO_2 as a function of work rate during the exercise test, with the evidence of a normal slope (a-a' in Fig. 1) from start to the inflection point, and a flattened slope (b-b' in Fig. 1), from the inflection point to peak exercise. The evidence of an inflection in VO_2 during the last 30 s of exercise was not considered as abnormal, because it can be the result of a plateau in VO_2 frequently occurring in normal subjects. For both slopes, the best fit was determined by least squares regression analysis. O_2 pulse was calculated as $\text{VO}_2/\text{heart rate}$. On the basis of ROC analysis, O_2 pulse flattening duration was calculated from the inflection point occurring in VO_2 as related to work rate to peak exercise, and expressed as seconds (Fig. 2). Abnormal $\Delta\text{VO}_2/\Delta\text{WR}$ slope and O_2 pulse flattening duration were defined as a value falling outside the established 95% CI for a normal database from our laboratory. Tests were interpreted by two 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, intraobserver and

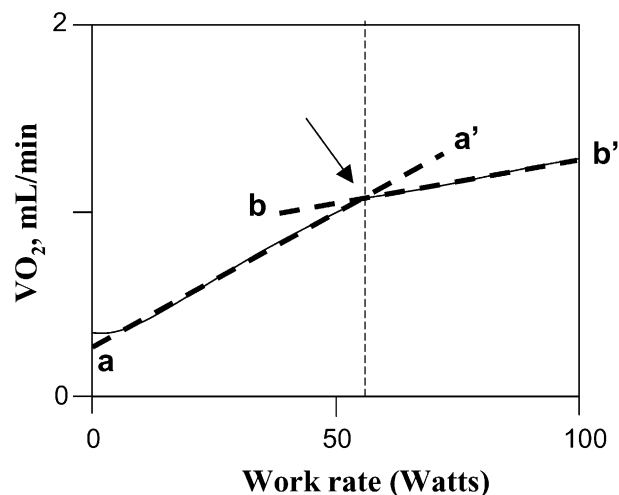


Fig. 1 The method of calculation of the inflection point on the $\Delta\text{VO}_2/\Delta\text{WR}$ graph. Oxygen uptake (VO_2) as a function of work rate (W) during a progressively increasing work rate test. In patients with coronary artery disease who have a reversible defect on myocardial scintigraphy, $\Delta\text{VO}_2/\Delta\text{WR}$ slope is not linear from start to peak exercise, but it is possible to select a point (arrow), above which the rate of increase in VO_2 as related to work rate becomes delayed. The transition from a normal increase in VO_2 as related to work rate (a-a' slope) to a slow increase in VO_2 (b-b' slope) has been considered the onset of myocardial ischaemia. For details, see text.

interobserver variability was assessed in 50 patients with documented coronary artery disease (40 men, 10 women, mean age 55 ± 10) and 50 healthy subjects matched for age, sex, height and weight. Intraobserver variability was $3.5 \pm 6\%$ and interobserver variability was $4.8 \pm 5\%$.

Myocardial scintigraphy

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 h later (2-day stress/rest protocol).⁷ A gated-SPECT acquisition results in a standard SPECT data set from which perfusion is assessed, and a larger gated SPECT data set, from which function is evaluated. After acquisition of 16 projection images at each projection angle, raw data were reviewed by the endless-loop cinematic display of the rotating projection images. Images were then reoriented relative to the axis of orientation of the heart in the chest, appropriately aligned and displayed simultaneously in interleaved fashion. A three-dimensional algorithm was used for perfusion quantitation, providing

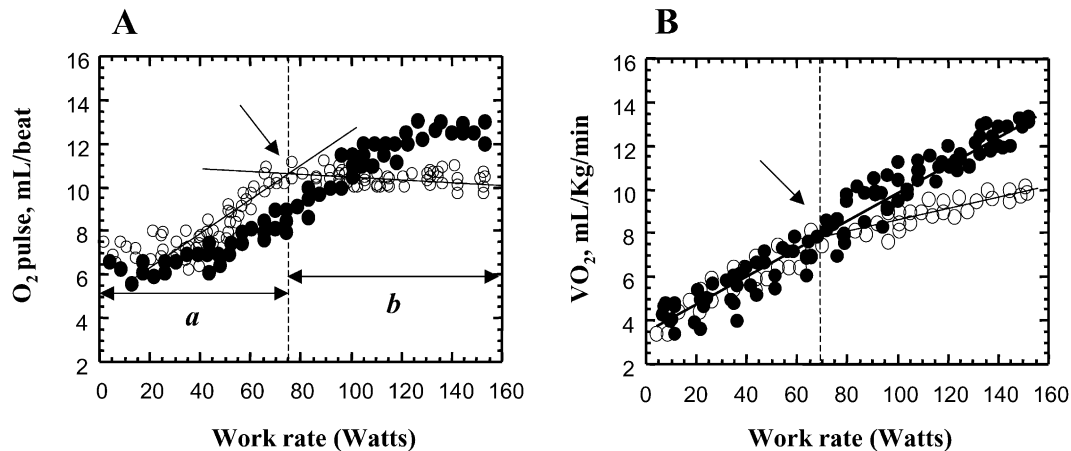


Fig. 2 An example of O_2 pulse (a) and $\Delta VO_2/\Delta$ work rate (b) slope in two representative patients. One had a negative ECG stress testing and a negative scan (closed circles). The other developed myocardial ischaemia during exercise, and also had a reversible myocardial defect on scintigraphy (SDS 14, SSS 15) (open circles). The dotted line indicates the onset of flattening in both O_2 pulse and VO_2 as related to work rate increase, evident only in the patient with a positive scan. Note the absence of flattening in both O_2 pulse and VO_2 as related to work rate in the patient who had no ST segment changes during exercise and a negative scan. In (b), the slope above the inflection point is flattened as compared with the slope from start to the inflection point (3.5 ml/min/W vs 9.1 ml/min/W). For details, see text. (a) Time to O_2 pulse flattening; (b) O_2 pulse flattening duration.

accurate registration of end-diastolic and end-systolic frames, with improved assessment of regional function.⁸

A semiquantitative 20-segment scoring system was used, with each segment scored according to a 5-point scheme as follows: 0=normal; 1=slight reduction of uptake; 2=moderate reduction; 3=severe reduction; 4=absent uptake. 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). Quantitative measurements of left ventricular volumes from gated perfusion SPECT images were obtained, from which ejection fraction was automatically calculated. Segmental wall thickening analysis was performed using a five-slice display with three representative short-axis slices, one vertical and one horizontal long axis mid-ventricular tomograms. Images were displayed using a cine format, alternating with the contour on-contour off mode, in order to improve accuracy of wall motion interpretation. For wall thickening quantification, a ten-step colour scale was used with a 4-point scoring system from 0 (normal) to 3 (absent thickening).⁷ The severity of myocardial ischaemia was defined on the basis of summed difference score: <3, no reversibility; 3–7, mild ischaemia; 7–12, moderate ischaemia; >12, severe ischaemia.⁹ We also considered the summed stress score, grading myocardial ischaemia as mild (between 4 and 8), moderate (9–13) and severe (>13). Images were interpreted by two skilled evaluators

blinded to each other's interpretation and clinical picture. A consensus decision was obtained in all cases.

Statistical analysis

Statistical analysis was performed using SAS statistical software (SAS Institute v.8.2, Inc, Cary, NC). Unpaired Student's *t*-tests 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. One way ANOVA was used to compare clinical, haemodynamic and metabolic variables among groups of patients stratified according to SSS score. 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 as gold standard for both. Logistic regression analysis was performed to identify the best model to predict probability of myocardial ischaemia on nuclear studies. Hierarchical models were defined considering statistical significance and clinical relevance of independent variables, taking into consideration principal effects and second level interactions in each model. They were compared using likelihood ratio test as measure of goodness of fit and area under Receiver Operating Characteristics (ROC) curve, as measure of predictive ability. A level of $p < 0.05$ was considered indicative of statistical significance. Data are mean \pm SD.

Table 2 ECG stress test, cardiopulmonary exercise testing and gated-SPECT parameters of left ventricular function in patients with absence or presence of myocardial ischaemia on myocardial ECG stress test

	No ischaemia (n=62)	Ischaemia (n=140)	All (n=202)	p ^a
ECG stress				
Heart rate, rest (beats/min)	78±10	73±12	76±12	0.005
Heart rate, IT ^b (beats/min)	125±10	120±9	122±9	0.001
Heart rate, peak (beats/min)	155±10	149±7	152±8	0.001
Systolic blood pressure, rest (mmHg)	135±15	138±16	136±15	0.21
Systolic blood pressure, IT (mmHg)	150±15	140±10	145±10	0.001
Systolic blood pressure, peak (mmHg)	192±25	180±19	185±22	0.001
Diastolic blood pressure, rest (mmHg)	84±12	85±11	85±12	0.56
Diastolic blood pressure, IT (mmHg)	94±12	90±11	92±11	0.02
Diastolic blood pressure, peak (mmHg)	97±13	102±11	98±12	0.005
Rate-pressure product, IT (mmHg)	18 750±1780	16 800±1840	18 300±1810	0.001
CPET				
Oxygen uptake, rest (ml/min)	391±161	435±177	422±168	0.09
Oxygen uptake, IT (ml/min)	1123±241	932±191	982±218	0.001
Oxygen uptake, AT (ml/kg/min)	11.5±2.5	11.0±2.6	11.3±2.5	0.20
Oxygen uptake, peak (ml/min)	1685±290	1632±256	1650±285	0.19
Oxygen uptake, peak (ml/kg/min)	21.7±5.2	21.1±3.4	21.3±4	0.33
VCO ₂ ^c , peak (ml/min)	1895±288	1845±251	1862±266	0.21
Ventilation, peak (l/min)	62±15	52±10	56±12	0.001
Respiratory exchange ratio	1.15±0.8	1.12±0.5	1.13±0.6	0.74
O ₂ pulse, rest (ml/kg/min)	5.2±1.8	5.7±1.6	5.5±1.6	0.06
O ₂ pulse, IT (ml/kg/min)	10.7±2.3	7.1±2.0	8.6±2.1	0.001
O ₂ pulse, peak (ml/kg/min)	14.6±4.2	13.1±3.3	13.5±3.7	0.007
ΔVO ₂ /ΔWR (ml/min/W)	8.7±1.0	8.1±0.8	8.3±0.9	0.001
Workload, peak (W)	175±45	153±38	163±41	0.001
Gated-SPECT				
Summed Stress Score (SSS)	2.5±1.2	12.6±4.5	9.7±4.9	0.001
Summed Difference Score (SDS)	1.3±1.6	9.7±2.8	5.4±2.2	0.001
End-diastolic volume, peak (ml)	115±32	142±44	129±36	0.001
End-systolic volume, peak (ml)	42±21	69±21	54±24	0.001
Ejection fraction, rest (%)	52.9±11	53.8±11	53.5±11	0.63
Ejection fraction, peak (%)	61±22	41±26	55±23	0.001
Systolic wall thickening score index	0.13±0.4	1.06±0.5	0.77±0.65	0.001

^ap values by unpaired *t*-test. Results from healthy subjects: Peak VO₂=26.4±6.9 ml/kg/min; anaerobic threshold=14.5±3.7 ml/kg/min; ventilation=68.3±18 l/min; heart rate, peak=157±16 beats/min; systolic blood pressure, peak=184±30 mmHg; ΔVO₂/ΔWR=9.5±1.2 ml/min/W.

^bIT: ischaemic threshold.

^cVCO₂: carbon dioxide production.

Results

All patients completed the protocol. Electrocardiographic, CPET and gated-SPECT parameters of left ventricular function are shown in Table 2. On the basis of the SDS, 62 patients had no perfusion defects (31%), and 140 had at least one perfusion defect (59%). Of patients with a positive scan, 29 patients had a mild ischaemia (SSS=5.6±1.5, SDS=4.1±3.5), 52 patients had a moderate ischaemia (SSS=10.7±1.3, SDS=8.9±2.8), and 59 severe myocardial ischaemia (SSS=17.4±2.9, SDS=14.8±2.7). The number of diseased coronary arteries was not different between patients with mild and moderate myocardial ischaemia (1.5±0.6

and 1.6±0.6, respectively), while it was higher in patients with severe ischaemia (2.5±0.6, *p*<0.0001).

ECG stress testing

An ischaemic threshold was identified in 85 patients (heart rate=122±9 beats/min; rate pressure product=18 300±1800 mmHg/beats/min), with a test duration of 445±76 s (range 270–620 s). Standard ECG stress testing had low sensitivity (46%) and specificity (66%), with a positive predictive value of 76% and a negative predictive value of 35% to diagnose myocardial ischaemia. According to positivity criteria, ECG stress testing diagnosed

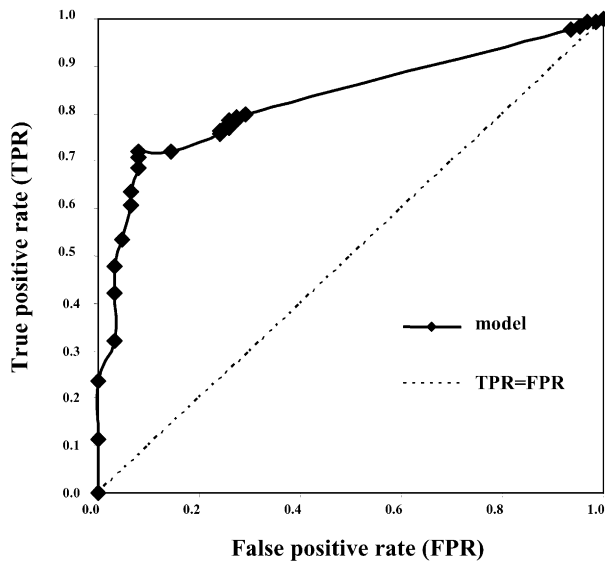


Fig. 3 ROC curve for the best predictive model. The diagonal line indicates a predictive ability of the variables no better than chance (TPR=FPR: true positive rate equal to false positive rate). Area under the curve=0.834.

myocardial ischaemia in 64 out of 140 patients with a positive myocardial scintigraphy, and excluded myocardial ischaemia in 41 out of 62 patients without reversible myocardial defects on scintigraphy.

Cardiopulmonary exercise testing

Initially, we considered the following parameters for detecting myocardial ischaemia: peak ventilation and peak VO_2 , anaerobic threshold, end tidal PO_2 and PCO_2 , ventilatory equivalents at the anaerobic threshold and at peak exercise, respiratory exchange ratio at peak, physiological dead space/tidal volume ratio (VD/VT), rest and peak O_2 pulse, and $\Delta\text{VO}_2/\Delta\text{WR}$ slope. According to logistic regression analysis, the independent predictors of a positive myocardial scintigraphy were O_2 pulse flattening duration (β coefficient 0.020, $p < 0.001$) and $\Delta\text{VO}_2/\Delta\text{WR}$ b-b' slope ($\beta - 0.54$, $p = 0.0001$), with a cutoff value of 3.9 ml/min/W. A negative CPET test was considered when neither O_2 pulse flattening during work rate increase, nor $\Delta\text{VO}_2/\Delta\text{WR}$ b-b' slope were present at the same time. The area under ROC curve was 0.83, showing a good predictive ability (Fig. 3). A level of predictive probability of myocardial ischaemia equal or greater than 0.44 identified the point of ROC curve with the greatest sensitivity and specificity. Patients with a positive scan had a lower heart rate, systolic blood pressure and O_2 pulse at the ischaemic threshold and at peak exercise, while peak VO_2 and CO_2 output were not

significantly different from patients with a negative scan (Table 2). However, peak VO_2 and peak O_2 pulse were lower the more severe the myocardial ischaemia (Table 3). There were no gender-related differences in clinical, angiographic and scintigraphic parameters, except for resting ejection fraction, that was lower in women (48.5 ± 14.2 vs 54 ± 13 , $p = 0.009$). Patients with a positive scan also had qualitative abnormalities in O_2 pulse and $\Delta\text{VO}_2/\Delta\text{WR}$. An example of these abnormalities in two representative patients are reported in Fig. 2. The reduced increase in $\Delta\text{VO}_2/\Delta\text{WR}$ and the flattening in O_2 pulse occurred simultaneously, indicating the same phenomenon. If we consider O_2 pulse flattening duration and $\Delta\text{VO}_2/\Delta\text{WR}$ b-b' together, CPET identified 122 out of 140 patients with a positive scan, and ruled out myocardial ischaemia in 46 out of 62 patients with a negative scan. As compared with standard ECG stress testing, CPET had higher sensitivity (87%), specificity (74%), and also positive and negative predictive values (positive predictive value: 88%; negative predictive value: 72%). As related to the presence of one, two or three vessel disease, CPET has a sensitivity of 50%, 72% and 80%, respectively, and a specificity of 54%, 58% and 62%. The absence of CPET abnormalities helped to exclude myocardial ischaemia and improved the specificity by 32% (from 66 to 87%). In the 76 patients with a negative ECG stress testing who had a positive scan (false negatives), O_2 pulse flattening and $\Delta\text{VO}_2/\Delta\text{WR}$ b-b' < 3.9 ml/min/W were present in 58 patients. If we consider both abnormalities together, the sensitivity of ECG stress testing would be substantially improved by 89%. Of 29 women, 15 had a positive scan (51.7%) and 14 a negative scan (48.3%). CPET identified 12 out of 15 positive studies (sensitivity 80%), and excluded positivity in nine out of 14 (specificity 64%).

Of the 85 patients with a positive ECG stress test, 21 had no reversible myocardial defects (false positives). In all of these patients, ECG abnormalities were present at rest (previous acute myocardial infarction or conduction abnormalities). In 19 out of 21 patients there were no abnormalities in O_2 pulse as well as $\Delta\text{VO}_2/\Delta\text{WR}$. However, if we consider O_2 pulse flattening duration alone as a marker of ischaemia, both sensitivity and specificity were lower and similar to those of ECG stress testing (51% and 60%, respectively). As shown in Table 3, O_2 pulse flattening duration, O_2 pulse at peak exercise, peak VO_2 and $\Delta\text{VO}_2/\Delta\text{WR}$ b-b' were progressively reduced as the number of diseased coronary vessels and the severity of left ventricular dysfunction increased. No differences were observed in

Table 3 Clinical, haemodynamic and metabolic variables in patients with a positive myocardial scintigraphy according to the summed difference score

	Summed Stress Score (SSS)			<i>p</i> ^a
	3–7 <i>n</i> =20	7–12 <i>n</i> =52	>12 <i>n</i> =59	
Summed Stress Score (SSS)	5.6±1.5	10.7±1.3	17.4±2.9	0.0001
Summed Difference Score (SDS)	4.1±3.5	8.9±2.8	14.8±2.7	0.001
Coronary vessel score, mean±SD	1.5±0.6	1.6±0.6	2.5±0.6	0.007
Systolic wall thickening score index	1.4±0.9	1.72±0.8	2.04±0.9	0.0001
Resting ejection fraction (%)	53.5±11	55.8±10.4	50.5±12.3	0.04
O ₂ pulse flattening duration (s)	119±42	99.8±24	91.7±16.5	0.0018
Time to O ₂ pulse flattening (s)	365±55	368±67	317±61	0.0002
Peak O ₂ pulse (ml/beat)	15.5±3.9	13.4±3.6	12.0±2.4	0.0001
Peak VO ₂ (ml/kg/min)	22.1±4.5	21.1±4.1	20.4±2.8	0.04
ΔVO ₂ /ΔWR, a-a' slope (ml/min/W)	9.0±1.0	8.7±0.8	8.8±0.7	0.29
ΔVO ₂ /ΔWR, b-b' slope (ml/min/W)	8.2±2.4	5.1±2.3	3.5±2.0	0.0001

^a*p* values by one-way ANOVA.

ΔVO₂/ΔWR a-a' and ventilation. Of the 59 patients with SDS >12, CPET was positive in 54, while in the 81 patients with SDS <12 the sensitivity of CPET was lower (60%). Either O₂ pulse flattening duration or ΔVO₂/ΔWR b-b' slope were correlated with systolic wall thickening score index at peak exercise, which reflects the degree of contractile dysfunction (*r*=−0.68 and −0.72, respectively; *p*<0.001 for both).

Discussion

The results of the present study indicate that O₂ pulse flattening duration and ΔVO₂/ΔWR b-b' slope were the two strongest independent predictors of exercise-induced myocardial ischaemia. They also demonstrate that cardiopulmonary exercise testing is more accurate than standard ECG stress testing in identifying patients with coronary artery disease and exercise-induced myocardial ischaemia, and for excluding patients who do not develop myocardial ischaemia during exercise. When gas exchange analysis was added to ECG stress testing, sensitivity improved by 89%, from 46% to 87%, and specificity improved from 66% to 74%. Specificity was lower in women (64%). A plausible explanation may be that the group of women had lower resting ejection fraction, suggesting a greater amount of dysfunctional myocardium, that may have determined a flatter VO₂ kinetics and an early O₂ pulse flattening (Table 4).

In patients with resting ECG abnormalities, such as those who had had a previous myocardial infarction or have conduction abnormalities, or in whom the interpretation of ECG changes during exercise is difficult, gas exchange analysis may help

Table 4 Differences between women and men

	Women (<i>n</i> =29)	Men (<i>n</i> =173)	<i>p</i>
Peak O ₂ , pulse (ml/beat)	13.8±4.3	13.5±3.6	0.67
Peak VO ₂ (ml/kg/min)	21.4±4.4	21.3±3.9	0.87
Peak workload (W)	166±7	162±39	0.66
Exercise duration (s)	280±222	311±215	0.48
Time to O ₂ P flattening (s)	212±179	240±169	0.41
O ₂ pulse flattening duration (s)	60.5±49	68.5±50.1	0.43
ΔVO ₂ /ΔW (ml/min/W)	6.09±2.8	5.8±2.7	0.59
ΔVO ₂ /ΔW (ml/min/W)	4.17±1.6	4.26±1.4	0.81
Vessel (<i>n</i>)	1.89±0.78	1.79±0.75	0.49
Age (years)	55.2±10.6	55.8±10.9	0.78
SWTI	0.81±0.73	0.77±0.76	0.70
SSS	11.6±5.2	10.9±4.8	0.46
Resting ejection fraction (%)	48.5±14.2	54±10.3	0.009
Peak ejection fraction (%)	44.5±11	49.4±10	0.017

the clinician exclude acute myocardial ischaemia. Of the 21 patients with resting conduction or ventricular repolarization abnormalities who had a false positive ECG stress test, 19 had normal increase in O₂ pulse as well as ΔVO₂/ΔWR slope. Thus, in the presence of ST depression, the absence of CPET abnormalities can exclude exercise-induced myocardial ischaemia in 74% of patients. However, gas exchange analysis may identify patients with myocardial ischaemia without ECG abnormalities or with borderline changes during stress testing. These preliminary observations need to be confirmed in a larger population.

Exercise-induced myocardial ischaemia, left ventricular function and VO₂ kinetics

How can we explain the improved diagnostic accuracy of CPET in patients with coronary artery

disease? The results of the study by Zafrir et al., where a significant inverse correlation was found between the severity of myocardial ischaemia on nuclear imaging and $\Delta\text{VO}_2/\Delta\text{WR}$ slope ($r=-0.33$, $p=0.016$),¹³ suggest, as a possible explanation, a strict link between VO_2 kinetics and left ventricular function during ischaemia. Previous studies have shown that patients with depressed left ventricular systolic function have a delayed VO_2 kinetics, and also a flatter $\Delta\text{VO}_2/\Delta\text{WR}$ slope than normal subjects.^{6,11,12} A depressed $\Delta\text{VO}_2/\Delta\text{WR}$ slope, associated with a low O_2 pulse response to work rate increase, was recently described in a group of men with documented coronary artery disease and ST depression on ECG stress testing.¹⁴ Both abnormalities were inversely related to the severity of underlying coronary artery disease, being more depressed the greater the number of diseased vessels. In contrast to heart failure patients, in which $\Delta\text{VO}_2/\Delta\text{WR}$ slope may begin to flatten from the beginning to peak exercise, and the degree of flattening is related to the level of functional impairment, we found that $\Delta\text{VO}_2/\Delta\text{WR}$ slope is normal from the start of exercise to a point corresponding to the onset of myocardial ischaemia. Then as work rate increases further, an inflection point is evident in the majority of patients with detectable myocardial ischaemia, above which the rate of increase in VO_2 as related to work rate is flatter until peak exercise. As a matter of fact, $\Delta\text{VO}_2/\Delta\text{WR}$ slope was 9.4 ± 0.5 ml/min/W from start of exercise to the inflection point, not dissimilar from $\Delta\text{VO}_2/\Delta\text{WR}$ slope in healthy controls (9.5 ± 1.2 ml/min/W). However, $\Delta\text{VO}_2/\Delta\text{WR}$ b-b' slope was significantly flatter the greater the severity of myocardial ischaemia (Table 3), and a cutoff value of 3.9 ml/min/W was selected by hierarchical model as the strongest independent predictor of myocardial ischaemia.

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.⁴ 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 ($\Delta\text{VO}_2/\Delta\text{WR}$). VO_2 increase relative to work rate increase will abruptly decrease above the ischaemic point.¹

There is evidence that abnormalities of left ventricular function during exercise almost invariably precede ST segment depression and angina in patients with stable coronary artery disease. Thus, VO_2 kinetics may be delayed, reflecting exercise-induced myocardial dysfunction, and CPET abnormalities may be evident earlier than ECG changes and clinical signs. In the present study, of 57 patients who developed ST depression during exercise and who also had a positive scan, VO_2 flattening was present in 52 and started much earlier than ST downsloping (265 ± 53 vs 476 ± 31 , $p<0.001$) (Fig. 4). In the study by Upton et al.,¹⁵ either stroke volume or cardiac output stopped 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. 4).¹ This hypothesis is suggested by the correlation of both O_2 pulse flattening duration and $\Delta\text{VO}_2/\Delta\text{WR}$ with the degree of contractile dysfunction expressed by systolic wall thickening score index at peak exercise.

Limitations

CPET limitations are related to the generalizability of results in those patients who develop myocardial ischaemia during exercise who have O_2 transport capacity limitations, in whom $\Delta\text{VO}_2/\Delta\text{WR}$ slope is generally flat and the interpretation of results difficult. For this reason, we excluded patients with chronic heart failure, anaemia and respiratory disease. Treadmill exercise protocols with step increase in work rate do not allow measures of $\Delta\text{VO}_2/\Delta\text{WR}$, since the work rate is not accurately quantified and is not increased linearly. Rarely,

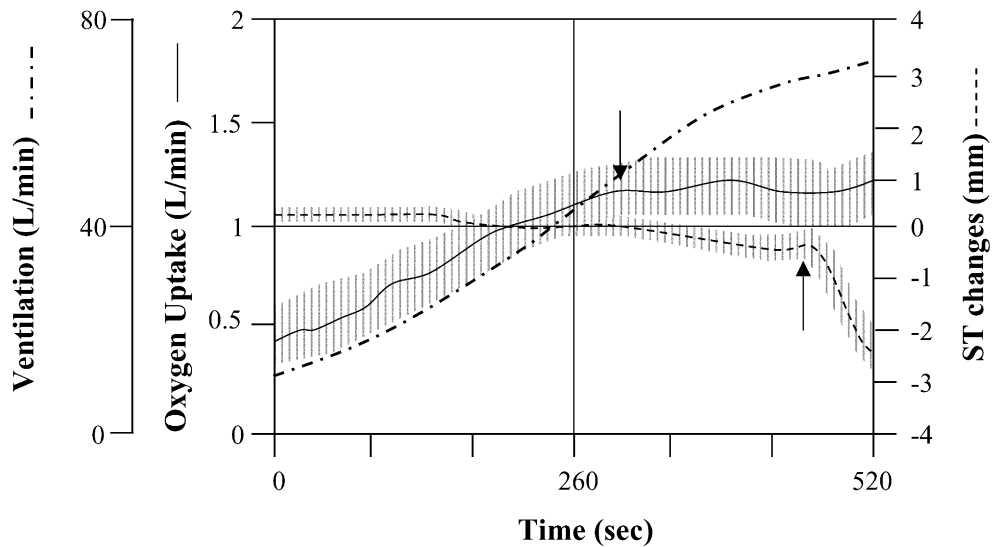


Fig. 4 Temporal changes in ST segment depression (dotted line) and oxygen uptake (filled line) in 52 patients with a positive ECG stress test and a reversible myocardial defect on myocardial scintigraphy. A flattening in oxygen uptake was evident much earlier (265 ± 33 s) than ST depression. Note that ventilation continues to rise with work rate increase independently from oxygen uptake. For details, see text

patients breathe erratically through the mouth-piece, and measures of ventilation and gas exchange are difficult to analyse. Repeating the test after calming the patient allows investigator to obtain the important gas exchange parameters. In some especially young patients, with a low ischaemic threshold, O_2 pulse flattens early, approximately at the same level expected in normal sedentary subjects, corresponding to 40% of peak workload. This behaviour may suggest false positive interpretations. However, the analysis of $\Delta VO_2/\Delta W$ slope may help to exclude false positivities.

Conclusions

Gas exchange analysis is an inexpensive tool for testing cardiac function that improves the diagnostic accuracy of standard ECG stress test for detecting myocardial ischaemia. Left ventricular dysfunction is caused by myocardial ischaemia and delays VO_2 kinetics. Both abnormalities precede ST segment depression and angina, which are generally the last events of the ischaemic cascade. The analysis of O_2 pulse and $\Delta VO_2/\Delta W$ slope has been shown to have the best predictive ability for identifying myocardial ischaemia induced by exercise. Gas exchange analysis can be also useful when the ECG is uninterpretable for myocardial ischaemia. The results of this study must be confirmed in larger clinical trials in order to make CPET a routinely

used tool in conjunction with the ECG, in the diagnostic evaluation of patients with coronary artery disease.

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References

1. Wasserman K, Hansen JE, Sue DY et al. Principles of Exercise Testing and Interpretation, 3rd edn, 1996. Lea & Febiger: Philadelphia.
2. Iskandrian AS, Heo J, Lemlek J et al. Identification of high-risk patients with left main and three-vessel coronary artery disease using stepwise discriminant analysis of clinical, exercise, and tomographic thallium data. *Am Heart J* 1983;125:221-5.
3. Gianrossi R, Detrano R, Mulvihill D et al. Exercise-induced ST depression in the diagnosis of coronary artery disease: a meta-analysis. *Circulation* 1989;80:87-98.
4. Jengo JA, Oren V, Conant R et al. Effects of maximal exercise stress on left ventricular function in patients with coronary artery disease using first pass radionuclide angiocardiology. *Circulation* 1979;59:60-5.
5. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986;60:2020-7.
6. Hansen JE, Casaburi R, Cooper DM et al. Oxygen uptake as related to work rate increment during cycle ergometer exercise. *Eur J Appl Physiol* 1988;57:140-5.
7. Bateman TM, Berman DS, Heller GV et al. American Society of Nuclear Cardiology position statement on electrocardiographic gating of myocardial perfusion SPECT scintigrams. *J Nucl Cardiol* 1999;6:470-1.

8. Germano G, Kavanagh PB, Waetcher P et al. A new algorithm for the quantitation of myocardial perfusion SPECT I: technical principles and reproducibility. *J Nucl Med* 2000; **41**:712–9.
9. Sharir T, Germano G, Kang X et al. Prediction of myocardial infarction versus cardiac death by gated myocardial perfusion SPECT: Risk stratification by the amount of stress-induced ischemia and poststress ejection fraction. *J Nucl Med* 2001; **42**:831–7.
10. Hollenberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. *J Am Coll Cardiol* 2000; **36**:193–8.
11. Sietsema KE, Daly JA, Wasserman K. Early dynamics of O₂ uptake and heart rate as affected by exercise work rate. *J Appl Physiol* 1989; **67**:2535–41.
12. Stringer WW, Hansen JE, Wasserman K. Cardiac output estimated noninvasively from oxygen uptake during exercise. *J Appl Physiol* 1997; **82**:908–12.
13. Zafir N, Fink G, Klainmann A et al. Relation between aerobic capacity and extent of myocardial ischemia in patients with normal cardiac function. *Am Heart J* 1999; **138**:1088–92.
14. Itoh H, Tajima A, Koike A et al. Oxygen uptake abnormalities during exercise in coronary artery disease. In: Wasserman K, editor. *Cardiopulmonary Exercise Testing and Cardiovascular Health*. Armonk, NY: Futura Publishing Co; 2002, p. 165–72.
15. Upton MT, Rerych SK, Newman GE et al. Detecting abnormalities in left ventricular function during exercise before angina and ST segment depression. *Circulation* 1980; **62**:341–9.