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Including Cardiopulmonary Measurements Improves Diagnostic Accuracy of CAD During Exercise Testing

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Abstract

INBAR, O., FACSM, E., BAR-RATZON, T., DLIN, R. and KLAINMAN.E. Including Cardiopulmonary Measurements Improves Diagnostic Accuracy of CAD During Exercise Testing. Adv. Exerc. Sports Physiol., Vol.11, No.1 pp.1-8, 2005. ***Background and objectives***: Exercise electrocardiography (ECG stress test) has relatively poor specificity and predictive accuracy for identifying coronary artery disease (CAD). Adding specific and relevant cardiopulmonary-related variables is proposed to accurately distinguish patients with CAD from those without disease. The aim of the present study was to objectively assess the diagnostic accuracy of CAD using variables measured during cardiopulmonary exercise test (CPET). ***Material and Methods***: Thirty-five apparently healthy subjects underwent exercise stress test, cardiopulmonary exercise test, and cineangiography, for suspected CAD. ***Results***: Analysis of the cineangiography showed that 10 subjects (out of the 35 subjects) had significant CAD. Standard exercise electrocardiographic criteria identified significant CAD with sensitivity of 90%, but with specificity and predictive accuracy of only 48% and 60%, respectively. Adding specific cardiopulmonary variables (ventilatory anaerobic threshold, O_2pulse at peak exercise, and O_2pulse trending phenomenon) identified CAD with a sensitivity of 80%, and specificity of 92%. The overall predictive accuracy of the exercise test, when adding those cardiopulmonary variables to the standard stress ECG, was 88.6%, compared with 60% for the standard ST-depression combined with clinical (symptom) criteria. Adding new sample of subjects (N=7) who were tested and evaluated under similar testing and evaluation conditions but different settings, location, and experts, support our original findings concerning the CPET's predictive accuracy of the proposed diagnostic equation. ***Conclusions***: Albeit the small sample, it seems that using **cardiopulmonary** exercise testing can significantly improve the diagnostic accuracy of the commonly used exercise stress test.

Keywords: exercise stress testing, specificity, sensitivity, cardiopulmonary exercise testing

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Introduction

Exercise testing has been established as a diagnostic and management tool in cardiac disorders, especially in coronary artery disease (7, 9). The major emphasis placed on interpretation of the exercise electrocardiogram (ECG) has, however, tended to de-emphasize the value and significance of other obtainable exercise variables such as cardiovascular, metabolic, ventilatory, and gas-exchange indices (27, 28, 33).

The clinical exercise test, also called an exercise stress test, helps physicians to evaluate how well an individual's heart behaves during physical exertion. During the test, heart rate, blood pressure, electrocardiogram (ECG) and patient's symptoms are recorded while the patient exercises (usually on a treadmill or cycle ergometer).

Exercise stressing of coronary perfusion, left and right ventricular performance, systemic and pulmonary arterial pressures, electrical abnormalities of the heart, and metabolic or gas exchange deficiencies, provide information critical for making diagnostic and/or therapeutic decisions. Exercise stress test results can recognize if there is inadequate blood supply through the coronary arteries. A diagnosis of coronary heart disease is made by using results of the exercise test, along with other clinical information, such as familial and personal history of ischemic heart disease (IHD), symptoms, and risk factors. With the clinical application of the conventional exercise stress tests, the degrees of sensitivity and specificity, based upon electrocardiographic analysis, have been shown to be less than optimal, with a relatively high percent of false positive and false negative test results with coronary angiography serving as the criterion method (8, 13, 18, 22).

Although coronary angiography is still considered the criterion method ("gold standard") of diagnosing CAD (5, 31), the procedure is invasive and involves related risks. The above therefore, highlighted the need for accurate noninvasive diagnostic method of significant CAD.

The assessment of cardiopulmonary function during exercise has become an increasingly accepted concept in

cardiopulmonary evaluation in the past 10 years (3, 11, 17, 24, 25, 27, 29). The recent clinical availability of the breath-by-breath systems to study metabolic, cardiovascular, respiratory, and gas-exchange responses during exercise, now enables the cardiologist to evaluate the functional status of both pulmonary and cardiovascular systems and to assess various additional aspects of cardiac function during exercise (19, 25, 27, 30, 31).

The cardiopulmonary exercise test (CPET) may therefore provide a more sensitive diagnostic tool in detecting cardiovascular as well as pulmonary disorders, than the traditional stress test that provides information only on the blood pressure, symptoms and ECG changes.

The aim of the present study was to investigate the contribution of cardiopulmonary responses obtained during incremental exercise challenge to the identification of significant coronary artery disease (CAD). This was attempted by comparing the diagnostic accuracy of selected cardiopulmonary-related responses with those of standard ECG stress test criteria, in identifying significant CAD among apparently healthy and coronary risk carrier subjects.

Methods

Subjects

The original sample consisted of 130 seemingly healthy subjects between the age of 35 to 70 years, some with several cardiac risk factors (hypercholestrolemia, overweight, smoking, family history) and/or complaints of chest pain, that were referred by their physician to perform an exercise stress test. Of this sample, and based on their symptoms, clinical signs, and exercise ECG findings, approximately sixty subjects were referred for further cardiac evaluation, including coronary angiography, by the attending cardiologist.

Only subjects who completed the coronary angiography without intervening treatment (percutaneous transluminal coronary angioplasty - PTCA) were referred by their attending cardiologist to perform a cardiopulmonary exercise test (CPET). At the end of the subjects` selection process thirty-five subjects completed all three tests [stress ECG (screening), coronary angiography, and the CPET], and formed the final study sample.

Subjects were fully informed of the procedures, risks, and discomforts involved in performing the CPET and gave their signed informed consent for participation. The investigation conformed to the principles outlined in the Declaration of Helsinki (Cardiovascular Research 1997; 35:2-3), and the institution's Helsinki committee for human experimentation approved the study.

Exercise stress test

A 12-lead ECG and heart rate (HR) were monitored on a three-channel recorder (Cardiofax, Japan) prior to and throughout the test with recordings at the end of each minute of exercise and during a five-minute recovery period. All exercise stress tests were performed on a treadmill (Quinton, 65, WA, USA) using modified Balke protocol (4). Blood pressure was measured by means of auscultation, using mercury sphygmomanometer, at rest and every 2-min during exercise and during the recovery period. A test was terminated upon relevant clinical symptoms or signs (outlined by the AHA), or when reaching at least 95% of the individually assigned age-related maximal HR (220-age). Exercise tests were evaluated using standard electrocardiographic criteria (see bellow).

Two cardiologists, experts in exercise stress testing, made independent electrocardiographic, and symptomatic interpretations of the stress test and referred the subjects for further evaluation when indicated.

An ischemic ST deviation was defined as ST depression, measured 0.08 seconds from the J point, of 0.5 mV or more of a horizontal or down-sloping shape or at least 1.0 mv of an upsloping shape, followed by horizontal and/or down sloping pattern during recovery (25).

Cardiopulmonary exercise test (CPET)

The CPET was also carried out on a treadmill (Quinton 65, USA), using the same exercise protocol (modified Balke protocol), in which the speed (4-6 km/h) remains constant while the slope is elevated by 2% each minute until volitional exhaustion or until the appearance of effort limiting clinical signs (see below). A 12-lead ECG was monitored on a three-channel recorder prior to and throughout the test with recordings at the end of each minute of exercise and during the recovery period (identical equipment and procedures as during the screening stress ECG test). Blood pressure was also measured as above.

Expired O_2 and CO_2 gases and the rate of airflow were measured breath-by-breath at rest and throughout the exercise period using the SensorMedics (V_{MAX} 29, Anaheim, CA) automated metabolic and respiratory diagnostic system. The system was calibrated before each test using standard reference gases with known concentrations. The measured or calculated cardiopulmonary variables included: Oxygen uptake ($\dot{V}O_2$), carbon dioxide output (VCO_2), heart-rate (HR), blood pressure (BP), peak and the trending phenomenon of oxygen pulse (O_2pulse), ventilatory anaerobic threshold (VAT), minute ventilation (V_E), tidal volume (Vt), breathing frequency (Bf), ventilatory equivalent for oxygen ($V_E/\dot{V}O_2$), and carbon dioxide (V_E/VCO_2), physiological dead space (Vd/Vt), end-tidal PO_2 (P_{ETO2}), and end-tidal PCO_2 (P_{ETCO2}).

Each of the CPETs was continued to maximal volitional effort [verified by age-predicted maximal HR, RQ $\geq$ 1.15, and/or falling P_{ETCO2} (by 3-4 mmHg)], unless there were overt limiting symptoms, such as abnormalities of rhythm, blood pressure abnormalities, or marked ST dis-

placement (>3mm).

The VAT was determined visually by two experienced reviewers and expressed as $\dot{V}O_2$ (ml/min) or as $\dot{V}O_2$/kg using previously established criteria (6). 1) The onset of a non-linear rise in VCO_2 when plotted against $\dot{V}O_2$ on equal axes; 2) The onset of a systematic increase in the ventilatory equivalent for O_2 ($V_E/\dot{V}O_2$) without a systematic increase in the ventilatory equivalent for CO_2 (V_E/VCO_2).

O_2pulse trending phenomena (response dynamics) were classified (visually) into three types: up sloping (normal response), flat, or down sloping (15, 27). Each response pattern was assigned categorical value of 1, 2, or 3, respectively.

Cineangiography

Left ventricellography and selective coronary arteriography were performed. Single-plane left ventriculography was accomplished in the 30^0 right anterior oblique positions. All angiographic images were recorded on 35-mm film at 10 frames/sec and reviewed on a Tagarno projector. Two experienced cardiologists independently assessed each angiogram by coding the degree and location of coronary artery lesions. Total coronary occlusion was defined (10), as the absence of forward flow of contrast material in the involved artery. Lesions of less than 70% were considered non significant. Each subject was classified as having none, one, two, or three-vessel coronary artery disease. Obstructions of diagonal and marginal branches were considered lesions of the left anterior descending and circumflex coronary arteries, respectively. Collateral circulation was judged as well developed when the diameter of the retrograde receiving vessel measured more than 1 mm and the vessel of origin showing nonobstructive lesions. All angiographic studies were carried out at the Sheba Medical Center in Tel-Hashomer, or at the Heart Institute of the Ramat Marpe Hospital in Ramat-Gan.

All subjects were free of medications other than antiplatelet aggregates (Aspirin) and were instructed to refrain from medications prior (24 hours) to the performance of each of the exercise studies. The period elapsed between the performance of the first (stress ECG) and the last test (CPET), was typically 5-6 weeks.

Definitions of test performance

The sensitivity of a criterion for recognition of significant CAD was defined as the percentage of patients with significant CAD, as demonstrated by cineangiography, who had a positive test result (during the exercise stress test or CPET). The specificity of a criterion was defined as the percentage of patients without significant CAD, as demonstrated by cineangiography, who had a negative test result during the exercise stress test or CPET. Overall test accuracy was defined as the percentage of patients correctly diagnosed either having or not having significant CAD; this was the proportion of combined true-positive and true-negative test results based on each test's criteria.

Data analysis

Electrocardiographic and CPET variables were compared in terms of test sensitivity, specificity, and overall test accuracy. To test the hypothesis that electrocardiographic or CPET criteria and those of the cineangiography, are independent, Chi-Square analysis was carried out.

Multivariate linear discriminant function analysis was used to identify those variables that could best identify CAD. In our study, groups were formed by the classification of having (or not) coronary artery disease (dependent variable). The discriminating (independent) variables consisted of ECG (ischemic or none-ischemic) and CPET scoring (O_2 pulse slope) (transferred to dummy variables) and/or actual (numerical) values at sub-maximal and maximal exercise. The independent variables were selected in a stepwise manner for entry into the analysis on the basis of their discriminating power, and the weighted coefficients were calculated with established statistical methods. To compare group mean values (normal vs. CAD) the Student t test for unpaired samples was used. The SPSS 11.0 statistical package was used for all statistical procedures.

Results

Distribution of disease and subgroup characteristics

The group comprised of 33 men and 2 women whose mean age was 53.5 years (range 35 to 70). The outcome of the cardiac angiography established that nine patients (26%) had a narrowing of 50 to 70 percent in a single vessel, five subjects (20%) had a narrowing greater than 70 percent in a single vessel, and five (20%) subjects showed significant narrowing in two vessels, other than proximal left arterial descending (LAD) (Table 1). In our sample, none showed three vessels disease or significant narrowing of the Left Main artery. Based on this study's angiographic criteria (lesion>70% in at least one vessel), 10 subjects proved having significant CAD while 25 showed no significant narrowing in their coronary arteries.

Based on the angiographic results the sample was di-

Table 1 Subject's distribution by severity and location of coronary artery lesions (cineangiograpgy)*

Obstruction >70%	# of cases (%)	Location of obstruction (>70%)	# of cases (%)
1 vessel	5 (14.3)	Proximal	3 (8.6%)
2 vessels	5 (14.3)	Medial	5 (14.3%)
3 vessels	none	Distal	2 (5.7)

* Remaining subjects (N=25) showed obstruction<70% in their coronary arteries.

vided into those subjects with significant CAD and those without such abnormality. The physical and some resting pulmonary characteristics of the 10 subjects with, and the 25 subjects without significant CAD are presented in Table 2. Patients with CAD were older, but were similar to those without any meaningful coronary narrowing, in all other characteristics.

Standard electrocardiographic criteria

Subject's distribution by type, magnitude, and duration of ST segment changes during exercise and recovery is presented in table 3. Fourteen subjects (40%) showed no ECG changes during exercise and/or recovery. Fifteen subjects (43%) demonstrated ST segment depression between 1 and 2 mm, while 3 (9%) displayed ST depression greater than 2 mm. Horizontal, upsloping or downsloping ST segment changes were evident in eleven (31%), eight (23%), and two (6%) subjects, respectively. ST segment changes during recovery were found in 15 (43.5%) of the subjects' sample.

The ability of the electrocardiographic findings to correctly distinguish patients with significant CAD from a similarly symptomatic group with no CAD (using discriminant analysis) is shown in Table 4. Standard assessment of the exercise electrocardiograms (type, depth, and duration of ST depression) revealed that out of the 35 subjects, 22 (63%) showed positive test, while 13 subjects (37%) had negative test.

Out of the 22 positive exercise stress tests (stress ECG) only nine subjects (41%) were classified as CAD patients by the angiography (true positive - TP). Thus, 13 of the 22 subjects (59%) demonstrated false positive tests (FP). Out of the 13 subjects with negative stress ergometry, 12 (92%) indeed demonstrated negative angiography (true negative - TN), while only one (8%) showed significant narrowing on angiography (false negative - FN).

Based on the above findings it was implied that standard electrocardiographic criteria of CAD has a sensitivity [TP/(TP+FN)] of 90%, specificity [(TN/(TN+FP)] of 48%, and an overall predictive accuracy of 60% (21 correct identification out of the 35 cases).

Adding cardiopulmonary variables

Values at maximal effort of the 10 subjects with and the 25 subjects without CAD are presented in table 5. Excluding VAT and O_2pulse slope (both not just at maximal effort), it appears that no single cardiopulmonary response at maximal effort could successfully divide the subject sample into its two sub groups.

The numerical values of the various cardiopulmonary parameters were entered into the discriminant analysis. Additionally, the O_2pulse slope during the exercise test was characterized as down sloping, flat, or up sloping (as a function of exercise intensity) and was entered into the discriminant analysis (as 3, 2 or 1, respectively).

The following is the diagnostic equation modelled by the discriminant analysis, quantifying the relationship between the angiographic test results and the various CPET variables:

$$CAD_{pred} = [-0.540\ (only\ if\ ST\ depression \geq 2mm)] - (1.046 * VAT) + (1.162 * Peak\ O_2 pulse) - [0.757\ (only\ if\ O_2 pulse\ slope\ is\ if\ down\ sloping)]$$

If the outcome of solving the equation is <0, the chances are that the patient has significant coronary occlusion. If the outcome is >0, the chances are that there is no

Table 2 Physical and pulmonary characteristics - Comparison between the CAD and the normal groups

Variable	Normal	CAD	p value*
Age (yr)	50.8±9.5	60.4±11.2	0.01
Weight (kg)	82.3±17.9	77.7±10.5	0.46
Height (cm)	172±6.3	168±5.1	0.07
FVC (%pred.)	91±8.2	85±7.3	0.08
FEV_1 (%pred.)	87±10.2	83±10.9	0.09
$PEF_{25\%-75\%}$ (%pred.)	75±11.2	69±13.5	0.10

* - Bold numbers denote significant difference between groups ($p<0.05$)

FVC=Force vital capacity; FEV1=Force expiratory volume in one second; %pred.=Percent of predicted value [based on Quanjer et al. 1993 (23)].

Table 3 Subject's distribution by type, magnitude, and duration of ST segment depression during exercise and recovery

Type of depression		Magnitude of ST depression (mm)		Duration of ST depression during recovery (min)	
	# cases (%)		# cases (%)		# cases (%)
None	14 (40%)	-		-	
Upsloping	8 (23%)	0-1	3 (8.5%)	0-1	6 (17%)
Horizontal	11 (31%)	1-2	15 (43%)	1-5	10 (29%)
Downsloping	2 (6%)	>2	3 (8.5%)	>5	5 (14%)

Table 4 Cross-classification of CAD diagnosed by angiography or elctrocardiography

			ECG	
			Normal	CAD
Angiogram	Normal	count	12	13
		%within "true"	48%	52%
	CAD	count	1	9
		%within "true"	10%	90%

Table 5 Values at peak exercise¥- comparison between normal and CAD patients

Variable	Normal	CAD	p value*
VO_2 (ml/kg/min)	22.7±6.2	22.6±5.2	0.70
HR (beat/min)	149±19	141±25	0.20
O_2pulse, (ml/kg/min*100)	15.5±3.4	16.3±4.2	0.60
SBP (mmHg)	183±25	183±13	0.90
DBP (mmHg)	90±10	88±11	0.45
RER	1.15±0.08	1.17±0.09	0.28
V_E (liter/min)	62.9±16.8	61.1±16.2	0.61
Vt (liter)	1.94±0.16	1.89±0.18	0.38
Bf (breaths/min)	32±6	31±7	0.80
P_{ETO2} (mmHg)	115.2±4.9	116.4±7.1	0.13
P_{ETCO2} (mmHg)	37.6±3.6	34.5±4.9	0.30
¥VAT (ml/kg/min)	15.6±4.0	12.5±3.2	0.03
¥O_2pulse_{slope} (category)	2.7±0.5	2.0±0.4	0.04

*- Bold numbers denote significant difference between groups ($p<0.05$).

a. VO_2=Oxygen uptake; HR=Heart rate; O_{2pulse}=Oxygen pulse; SBP=asuSystolic blood pressure; DBP=Diastolic blood pressure; RER=Respiratory exchange ratio; VE=Minute ventilation; Vt=Tidal volume; Bf=Breathing frequency; P_{ETO2}=End tidal O_2; P_{ETCO2}=End tidal CO_2; VAT=Ventilatory anaerobic threshold; O_2pulse_{slope}=Slope of oxygen pulse as a function of exercise intensity (in categories 1, 2, 3) (see description in methods).¥ - Variables determined at sub-maximal exercise.

coronary occlusion [*Wilk's Lambda=0.442; $F_{(4, 30)}=9.45$, $p<0.001$*].

The ability of the CPET variables to identify significant CAD, using the above diagnostic equation, is shown in Table 6. It was revealed that out of the 25 subjects with negative angiographic findings, 23 (92%) also showed negative CPET (true negative-TN), while out of the 10 subjects classified as having CAD by the angiography, eight subjects (80%) were also classified as having positive CPET (true positive-TP). Likewise, out of the 25 subjects showing negative CPET, only two (8%) proved having significant CAD (false negative-FN). Of the 10 subjects corroborating positive CPET, two (20%) were found free of any significant coronary narrowing (false positive-FP). Based on the above it was indicated that cardiopulmonary variables bear sensitivity of 80%, specificity of 92%, and an overall test accuracy and predictive power of 88.6%, in identifying significant CAD (31 correct identifications out of the 35 cases).

Table 6 Cross-classification of CAD diagnosed by angiography or CPET

			CPET	
			Normal	CAD
Angiogram	Normal	count	23	2
		%within "true"	92%	8%
	CAD	count	2	8
		%within"true"	8%	80%

Subsequent to the completion of the data analysis of the original sample and in attempt to consider whether the model derived from the analysis of the original data set is transportable to similar subjects in other locations, an independent sample of seven subjects was studied (2). The sample consisted of consecutive subjects who underwent referral, selection, and testing procedures identical to those of the original sample. All testing and interpretations were done at the Links Clinic in Edmonton, Canada, by expert cardiologists and physiologists, independently. Table 7 presents the relevant angiographic and physiologic findings of the added sample. Of the seven subjects, three were found (by the coronary angiography) to suffer from significant CAD, while the other four proved free of such pathology.

As shown in table 8, "solving" for the proposed diagnostic equation, six out of the seven subjects (86%) were correctly identified. It should be noted that in this new sample, like in the original one, the ECG sensitivity was extremely high (100%), while its specificity was very low (50%) (See table 7). Furthermore, the ECG correctly identified five out of the seven subjects (71%) compared with the 86% over all accuracy of the CPET.

Discussion

Our data demonstrated an improved diagnostic ability for CAD by the addition of cardiopulmonary variables measured during an incremental exercise task. The high sensitivity (80%), specificity (92%), and overall accuracy (88.6%) of the CPET are in obvious advantage compared with the respective performance criteria of the standard exercise electrocardiography, for the detection of CAD (see table 4). The observed high diagnostic power of the CPET is comparable only to invasive tests such as cineangiography (26) or to standard stress testing done on populations with very high risk for CAD (16).

These findings support the notion and data put for-

ward by Weber and Janiki (30), Wassermann et al (28), and others (1, 21), concerning the ability of specific cardiopulmonary responses during an incremental exercise, singly or jointly, to accurately assess the presence or absence of heart diseases in general and CAD in particular.

Standard electrocardiograph criteria

The well-documented limitations of the standard exercise electrocardiograph are highlighted by our findings. Horizontal or downsloping ST-segment depression identified significant CAD with high sensitivity (90%), very low specificity (48%), and with an overall test accuracy of only 60%. It should be pointed out that the relatively high sensitivity stems mostly from the large number of false positive tests (13 out of 25＝52%) rather than from true test sensitivity.

Therefore, and in close agreement with abundant previous reports (13, 18, 24), this standard electrocardiographic criterion is of limited accuracy in populations similar to the one in the present study.

Rationale for adding cardiovascular responses during exercise

The onset of the development of lactic acidosis during exercise depends on the work rate at which the muscle capillary critical PO_2 is reached. The increase in lactate is essential to continue exercise beyond the anaerobic threshold (AT) because the H^+ that accompanies the lactate increase facilitates oxyhemoglobin dissociation without decreasing capillary PO_2. The difference between a normal subject and a patient with heart disease is that critical PO_2 is reached at a lower than normal $\dot{V}O_2$. Thus heart disease affects the $\dot{V}O_2$ and the VCO_2 kinetics, reflection of a reduced AT (27, 30).

The relationship between heart rate and oxygen uptake (O_2pulse) yields information on the cardiac stroke volume and oxygen content difference between arterial and mixed venous blood. As the work rate is increased, the O_2pulse continuously rises in a fashion similar to that of the stroke volume (12, 27). The rise in the O_2pulse is due, to both the increases in stroke volume and in the arterial-mixed venous O_2 difference. If, however, the stroke volume is reduced, the arterial-mixed venous oxygen difference and, therefore, the O_2pulse, reach maximal values at a relatively low work rate, and the O_2 pulse approaches an early asymptote and in severe cases even a down-sloping pattern (12, 14, 15, 27). Thus, the O_2pulse during and at maximal exercise reflects the sub-maximal and maximal stroke volume, respectively.

These observations suggest that such specific responses, when obtained during exercise, individually but more so when combined, should reflect more severe myocardial oxygen supply-demand imbalance than standard analysis of exercise ST depression.

The advantage of adding specific cardiopulmonary responses (mainly, VAT, peak and slope of O_2pulse), in terms of test accuracy, was found in the present investigation, in a sample with CAD prevalence range of 25-30%, which is the prevalence range most commonly found in populations undergoing evaluations for suspected CAD (8, 18). Thus, incorporation of such variables into exercise testing criteria for recognition of significant CAD should improve true-positive diagnoses without markedly increasing false-positive diagnoses in patients with CAD.

The employment of CPET, therefore, can make exercise testing a more accurate predictor of presence of CAD, as well as valuable adjunct in determining the therapeutic effectiveness of drugs and procedures.

Limitations of study design

Findings favourable to the cardiopulmonary response analysis emerge despite intrinsic study design bias against the method. Because our study was semi-retrospective and none-randomized, there were fewer than optimal observations. Nevertheless, and even with these limitations, the improved accuracy of the exercise test is impressive.

An additional limitation bearing on general applicability of the CPET method involves patient selection in our study. Although consecutive volunteers who met entry criteria form the basis of this report, we cannot assume that the group studied is representative, because all included subjects, by definition, underwent coronary angiography. Catheterization in this group might have been based on potentially predictive symptoms, and in some cases may have been prompted by the electrocardiographic findings at exercise stress testing. Although in no case were the CPET findings a pre-test consideration, prospective validation is required to exclude possible bias introduced by otherwise unrecognized electrocardiographic changes. Assessment of the performance (prediction accuracy) of the diagnostic model using a new data set (tables 7 and 8) however, strengthen those of the original group and extend its validity and applicability to data collected and interpreted outside of the initial setting. We should, nonetheless, emphasize that more studies using larger and more diverse subject samples are needed before employment of this promising approach is warranted.

Angiographic findings were used in this study as a decisive evidence for presence or absence of CAD. There are several reports pointing to the limitations of this method in identifying ischemic syndrome (14, 15, 16). Furthermore, while ischemia is a functional syndrome and is caused by an unmatched cardiac O_2 demand, angiography bears information associated predominantly with the anatomy of the coronary bed. This is why it is not uncommon to see individuals suffering significant occlusion in their major coronaries, but without significant degree of angina (16). Since CPET variables are function-related, the small but mean-

Table 7 Pertinent angiographic, cardiopulmonary, and ECG data in new sample

Subject	ST segment Depression (mm)	O_2 pulse slope (response)	O_2 pulse peak (ml/b/kg/min)	VAT (ml/kg/min)	Angiography
1	<2 mm	up-sloping	27	27	<70 %
2	<2 mm	down-sloping	15	22	<70 %
3	≥2mm	down-sloping	18	19	1 vessel (100%)
4	≥2mm	up-sloping	23	26	<70 %
5	≥2mm	up-sloping	23	20	<70 %
6	≥2mm	up-sloping	14	14	2 vessels
7	≥2mm	flat	19	23	1 vessel (95%)

Table 8 Cross-classification of CAD diagnosed by angiography or CPET in the added sample (using the proposed diagnostic equation)

			CPET	
			Normal	CAD
Angiogram	Normal	count	3	1
		%within "true"	75%	25%
	CAD	count	0	3
		%within"true"	0%	100%

ingful discrepancy between the CPET and angiography "scoring" (89 Vs 100 %), could be ascribed, at least in part, to the known breach between those two entities (function and structure). Finally, the relatively small size of our final cohort limits the applicability and generality of its findings. Further effort should, therefore, be attempted to validate the study's diagnostic equation.

Implications

The ability of the selected CPET variables to identify the existence of significant CAD has several important implications. First, noninvasive identification of significant CAD in otherwise apparently healthy individuals may be possible with a high degree of sensitivity and specificity. Second, the CPET may provide the ability to evaluate progression of CAD in an individual patient by following serial CPETs. Third, patients may be followed up after coronary artery bypass surgery or coronary angioplasty for occult graft closure or reclusion by comparing immediate post-procedure CPET results with subsequent tests (14, 32).

The number of possible uses for the CPET highlights the importance of further prospective validation of the technique.

Conclusions

Two variables measured during cardiopulmonary stress test- anaerobic threshold, and O_2pulse (peak and trending) - appear to strengthen significantly (by 47%), the diagnostic accuracy of the exercise stress test in its traditional form (stress ECG+blood pressure and symptoms). If indeed so, the addition of such variables during the exercise test will improve the exercise test's diagnostic power and consequently reduce, at least in some patients, the need for more costly clinical procedures such as semi-invasive radio nuclear scintigraphy, echocardiography, and/or the invasive coronary angiography. The relatively small number of subjects tested, may be perceived as an enormous weakness in such a study. However, the extremely high reliability coefficients and narrow confidence intervals in most variables and the similarity of responses in the added sample indicate that subject number was not a major issue. Yet, we believe that further research in this area is needed, and that presentation of these findings should encourage others to peruse this promising line of research.

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