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Short communication

Quantification of coronary artery disease using different modalities of cardiopulmonary exercise testing

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ABSTRACT

Background: This study examined the accuracy of cardiopulmonary exercise testing (CPET) on a treadmill (TM) and recumbent ergometry (RE) in the predicting coronary artery disease (CAD) severity and prognosis.
Methods: Forty Caucasian subjects, mean age 63.5 ± 7.6, with significant coronary artery lesions (≥50%) were included. Within two months of coronary angiography, TM and RE CPET were performed on two visits 2–4 days apart and subsequently followed up to 32 ± 10 months.
Results: Mean left ventricular ejection fraction was 56.7 ± 9.6%. TM CPET exhibited a higher occurrence of ST segment depression ≥ 1 mm (71.05% vs 28.95%, $p = 0.04$). Subjects with 1–2 stenotic coronary arteries (SCA) demonstrated a better CPET response compared to those with 3-SCA. ROC analysis revealed a high predictive value for the ventilation/carbon dioxide production (VE/VCO_2) slope obtained on TM (area 0.84, $p = 0.003$, Sn 88.9%, Sp 72%) in distinguishing between 1 and 2-SCA and 3-SCA. Among all CPET parameters, work efficiency ($\Delta VO_2/\Delta WR$) during RE predicted cumulative cardiac events ($p < 0.01$).
Conclusions: CPET parameters hold predictive value for CAD severity and prognosis. CPET on a TM appears to be more reliable in the quantification of CAD compared to RE.

1. Introduction

Improving diagnostic accuracy of standard exercise testing (SET) is important in clinical practice [1,2]. The addition of ventilatory gas exchange analysis to SET [i.e. cardiopulmonary exercise testing (CPET)] is yielding a greater sensitivity and specificity in detection of coronary artery disease (CAD) [3,4]. Diagnostic accuracy of CPET in CAD was previously demonstrated using upright cycle-ergometer, however using other stress modalities requires further investigations [3–5]. The aim of the present study was to assess the ability of selected CPET variables, obtained using treadmill (TM) and recumbent ergometer (RE) testing, to predict CAD severity and prognosis.

2. Methods

The study recruited 40 Caucasian patients with coronary arteries lesions (≥50%). All patients were clinically stable and did not exercise regularly. Exclusion criteria were chronic heart failure, unstable angina, recent acute coronary syndrome, uncontrolled hypertension and diabetes, anaemia and respiratory disease. Nitrates were stopped 24 h, calcium antagonists 48 h, and beta blockers 3 days before testing. The study was approved by the local Ethics Committee; all participants provided written informed consent.

Within two months of coronary angiography, patients performed two CPET (two-four days in between), one on a RE using a ramp increase in work rate (WR) and the other on a TM using the standard Bruce protocol [6]. Tests were symptom-limited (i.e. fatigue, dyspnea, angina), or were stopped when one of the following criteria was met: achieving respiratory exchange ratio (RER) ≥ 1.1; a hypertensive response to exercise (≥230/130 mm Hg); or ≥2 mm ST depression in at least two adjacent leads. Breath-by-breath data were collected using a Cardiovit CS200 device (Schiller, Baar, Switzerland). Oxygen consumption (VO_2), carbon-dioxide output (VCO_2), minute ventilation (VE), and the end-tidal partial pressure of CO_2 ($P_{ET}CO_2$) were determined at rest and peak exercise. PeakVO_2 and the peakRER was the average of last 15 s of CPET. VO_2 and $P_{ET}CO_2$ were also determined at ventilatory threshold (VAT–calculated with V-slope method). $\Delta VO_2/\Delta WR$ was determined during RE-CPET. The $\Delta VO_2/\Delta WR$slope was calculated as (peakVO_2-unloadedVO2)/T-0.75xS (T-time of incremental exercise, S-slope of WR increment in W/min) [5]. A $\Delta VO_2/\Delta WR$ inflection > 30° outside of the last 30 s of the test was defined as an ischemic response. O_2pulse flattening duration was calculated from the inflection point in $\Delta VO_2/\Delta WR$ to peak exercise and expressed in seconds [3,7].

All patients underwent standard echocardiography at rest [8], and coronary angiography using Judkins' technique [9]. Stenosis was considered significant if there was a ≥50% reduction in luminal diameter. The number of stenotic coronary arteries (SCA) was determined and also dichotomously categorized as 1-2-SCA or 3-SCA.

Patients were followed after the second CPET, for 32 ± 10 months, or until occurrence of an adverse event. The outcome measures were all-cause mortality or cardiovascular

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morbidity [i.e., acute coronary syndrome, hospitalization, percutaneous coronary intervention (PCI), or coronary artery bypass surgery (CABG)].

The differences between parameters were assessed by the Students's *t*-test. Logistic regression analysis was used to identify the best model of prediction. Hierarchical models were compared using Receiver Operating Characteristic (ROC) curve as measure of predictive ability. Two-by-two tables were built to estimate sensitivity, specificity, predictive values and 95% confidence intervals of CPET parameters versus coronary angiography. Kaplan-Meier survival curves examined the ability of CPET variable that gauged CAD severity to predict cumulative cardiac event occurrence rate. Statistical tests were considered significant when a two-tailed p-value was <0.05. The SPSS software package (SPSS version 17.0, SPSS Inc., Chicago, Illinois, USA) was used for all statistical analyses.

3. Results

The mean age of the study participants was 63.5 ± 7.6 years. There were no major cardiac events during CPET. Mean left ventricular ejection fraction was 56.7 ± 9.6%. Spirometry parameters demonstrated a normal response.

Parameters of CAD severity derived from coronary angiography are listed as follows: number of patients with 1-SCA 16, 2-SCA 14, 3-SCA 10.

TM-CPET had a higher occurrence of CPET termination due to ST segment depression ($p = 0.04$) [77.1% vs. 28.6%; 73.1% vs. 23.1% in patients with 1-2-SCA; 88.9% vs. 44.4% in patients with 3-SCA). There were no hypertensive responses to exercise. Chest pain, dyspnea or fatigue were present in 44.7% of subjects during TM-CPET and 35.1% during RE-CPET. The rest of subjects reached metabolic criteria for maximal exertion (i.e., peak RER ≥ 1.1).

Participants divided into groups according to the number of SCA, showed a number of significant differences in CPET responses during the TM testing only (Table 1).

ROC analysis was used to identify parameters distinguishing patients with 1-2-vessel-CAD compared to 3-vessel-CAD. The best predictive ability was shown for the VE/VCO_2slope obtained during TM-CPET (area under ROC curve 0.84, SE = 0.07, $p = 0.003$). The optimal threshold value for identifying patients with 3-vessel-CAD </≥32, produced a sensitivity and specificity of 88.9% and 72.0%, respectively (Fig. 1). The correlation coefficient between the VE/VCO_2slope and number of SCA was $r = 0.51$, $p = 0.002$.

During 32 ± 10 months of follow-up there were 0(0%) deaths, 6 (15%) myocardial infarctions, 8(20%) hospitalizations, 32(80%) revascularization procedures (CABG or PCI).

$\Delta VO_2/\Delta WR$ correlated with cumulative cardiovascular event occurrence ($r = -0.46$, $p = 0.01$) and was a significant predictor on univariate analysis (F = 7.57, p = 0.01).

VE/VCO_2slope obtained during TM-CPET, with cut of point of 32, showed tendency to distinguish patients with and without cardiovascular event occurrence during the follow-up period but did not reach statistical significance (Log Rank-Mantel Cox 2.77, $p = 0.09$).

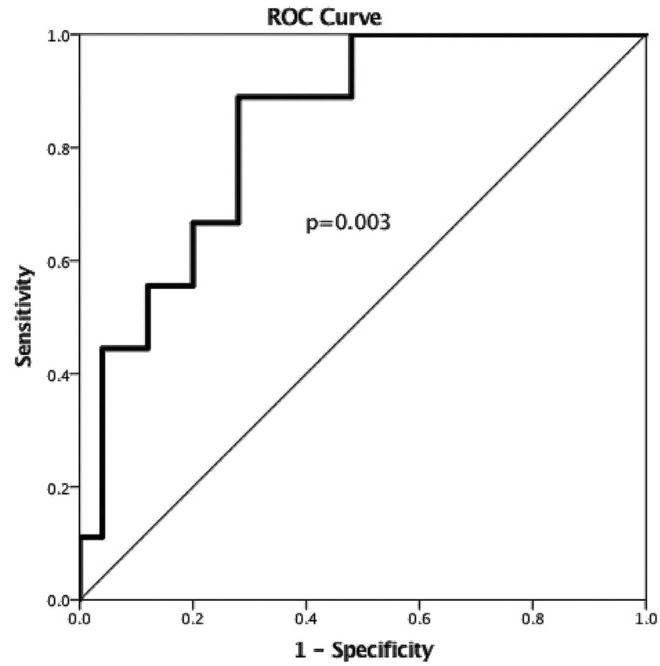

Fig. 1. ROC analysis for the VE/VCO_2 slope obtained during TM CPET in distinguishing between 1 and 2-vessel CAD vs. 3-vessel CAD (area under ROC curve 0.84, SE = 0.07, $p = 0.003$). The optimal threshold value for identifying patients with 3-vessel CAD </≥32, produced a Sn and Sp of 88.9% and 72.0%, respectively.

4. Discussion

The major findings of the present study suggest that ventilatory efficiency obtained during TM-CPET demonstrates high sensitivity and specificity to quantify severity of CAD, and that work efficiency obtained during RE-CPET is a strong predictor of prognosis in CAD.

The CPET has been proposed as an additional tool in detecting CAD, predicated on its ability to detect a decrease in stroke volume due to ischemia by O_2pulse and $\Delta VO_2/\Delta WR$slope measurements [3,10,11]. Present study findings support notion that VE/VCO_2slope is a sensitive marker of CAD [12]. Moreover, there is a clinical need for more precision in characterizing the functional consequences of myocardial ischemia in patients planned for invasive procedures [13]. Present study extricated the VE/VCO_2slope obtained during TM-CPET as a powerful marker able to differentiate between 3-vessel and 1-2-vessel-CAD, demonstrating an additional value in the quantification of CAD beyond SET and stress-echocardiography. The independence of VE/VCO_2slope on

Table 1
Differences in CPET parameters in patients with 1- and 2-vessel CAD compared to patients with 3-vessel CAD.

	RE			TM		
	1-2-SCA ($n = 30$)	3-SCA ($n = 10$)	p	1-2-SCA (n = 30)	3-SCA (n = 10)	p
Duration (min)	10.95 ± 1.96	10.00 ± 2.86	ns	7.58 ± 2.51	4.60 ± 1.96	0.003
HR peak (bpm)	118 ± 19	112 ± 17	ns	127 ± 20	123 ± 15	ns
Peak VO_2 ($ml \cdot min^{-1}$)	1416.00 ± 393.79	1.226.30 ± 369.13	ns	1753.30 ± 548.12	1405.60 ± 468.54	0.08
Peak VO_2 ($ml \cdot min^{-1} \cdot kg^{-1}$)	18.25 ± 4.18	15.26 ± 2.96	0.07	22.43 ± 7.04	17.00 ± 4.18	0.03
ΔVO_2/kg peak/rest ($ml \cdot min^{-1} \cdot kg^{-1}$)	13.45 ± 4.13	11.71 ± 2.66	ns	17.71 ± 5.06	12.92 ± 3.61	0.016
$P_{ET}CO_2$ VAT (mm Hg)	33.90 ± 4.06	33.34 ± 3.92	ns	33.20 ± 4.99	29.57 ± 2.71	0.046
VE/VCO_2 slope	29.50 ± 6.03	31.77 ± 4.74	ns	30.73 ± 5.27	37.31 ± 4.65	0.002
O_2 pulse peak (ml/beat)	12.04 ± 3.09	11.32 ± 3.53	ns	13.88 ± 3.94	11.41 ± 4.51	ns
O_2 pulse flattening (%)	64.3	50.0	ns			
O_2 pulse flattening time (s)	123.75 ± 98.04	101.25 ± 92.03	ns	–	–	–
$\Delta VO_2/\Delta WR$ ((ml/min)/watt)	7.99 ± 2.20	7.94 ± 2.59	ns	–	–	–

SCA - stenotic coronary arteries, O_2 pulse = Oxygen pulse; $P_{ET}CO_2$ VAT – End-tidal partial pressure of carbon-dioxide at ventilatory anaerobic threshold; RE = recumbent ergometer, TM = treadmill, VE = Ventilation; VO_2 = Oxygen consumption; VCO_2 = Carbon dioxide output; $\Delta VO_2/\Delta WR$ = Work efficiency, WR = work rate. Values are expressed as mean ± SD.

subjectivity of the interpreter and from effort [14], makes this finding even stronger, as many patients with CAD demonstrate symptoms or ST depression before reaching metabolic maximum. Thus, CPET appears to be useful in the quantification of CAD severity and burden of ischemia, which is important for subsequent revascularization strategies (i.e., PCI or CABG). Although it is more informative to perform CPET than a SET in CAD patients, the accessibility of CPET in certain settings does limit its broad application.

TM testing and upright cycle-ergometry constitute the most common modes of SET [7]. Previously recommended CPET measurements for detection of CAD require cycle-ergometer, which has limited broader CPET adoption in clinical practice [8]. Current study demonstrates that CPET responses indicate significant differences between 1-2-SCA and 3-SCA using TM-CPET only. It was also noticeable that ST segment changes were more pronounced during TM-CPET. The physiological basis of this finding may be attributable to a more extensive recruitment of muscle groups with a higher metabolic demands during TM compared to cycle-ergometry [15–17].

The present study revealed that $\Delta VO_2/\Delta WR$slope, which can be only obtained during cycle-ergometry, holds prognostic value in CAD. However, VE/VCO_2 slope value of 32, obtained during TM-CPET, demonstrated potential prognostic utility and may reach statistical significance in a larger study with more events, supporting the evidence of a significant prognostic utility in cardiac diseases [18].

4.1. Limitations

The major limitation of the present study is a small to moderate sample size, originating from hesitation of clinical care teams to perform two subsequent maximal CPETs in patients with extensive CAD without antianginal therapy. Unlike in clinical conditions, cardioprotective drugs, which significantly impact CPET results [19], were stopped before CPET to achieve better standardization of the study protocol, limiting the generalizability of the results. Since the VE/VCO_2slope may be confounded in the presence of other diseases, future studies in patients with CAD and comorbidities, individualized protocols and longer follow up period, are needed to refine the diagnostic/prognostic potential of the CPET in CAD management. Lastly, the applicability of CPET is confined by availability of resources needed, limiting its broader adoption.

5. Conclusion

The VE/VCO_2slope obtained using treadmill-CPET can be used to accurately differentiate between 3-vessel and 1-2-vessel-CAD. Compared to recumbent cycle-ergometer, the treadmill-CPET induces higher metabolic demand, enabling a more noticeable emergence of myocardial ischemia, making it a potentially better approach in the quantification of CAD.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.03.012.

Conflict of interests

The authors have nothing to disclose.

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