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

Introduction

Improving the diagnostic accuracy of the standard exercise testing is highly advantageous, particularly in specific patient populations.[1,2] It was proposed that the addition of ventilatory gas exchange analysis to the standard exercise test [i.e. cardiopulmonary exercise testing (CPET)] may improve diagnostic resolution in a cost-effective manner.[3,4] The superiority of CPET to standard exercise testing in the detection of coronary artery disease (CAD) was demonstrated by Belardinelli et al., yielding a greater sensitivity and specificity, predicated on its ability to detect a real time decrease in stroke volume due to ischemia.[3,4] However, the proposed model of ischemia detection through CPET requires testing on upright bicycle [3,4,5], without consideration of other exercise modes.

The aim of this study was to assess the ability of select CPET variables, obtained during both treadmill (TM) and recumbent ergometer (RE) testing, to predict CAD severity and prognosis.

Methods:

We prospectively studied 40 Caucasian subjects with significant coronary arteries lesions (≥50%) documented by coronary angiography performed within two months of CPET. All subjects were clinically stable and did not exercise regularly. Exclusion criteria were chronic heart failure, unstable angina, recent acute coronary syndrome, uncontrolled hypertension and diabetes, anemia and respiratory disease. Nitrates were stopped for 24h, calcium antagonists for 48h, and beta blockers for 3 days before testing. The study was approved by the local Ethics Committee and all participants provided written informed consent.

Patients performed two CPET (two-four days in between), in the morning in a fasting state, 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., exercise limiting fatigue, dyspnea or 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 mmHg); or ≥2 mm ST depression in at least two adjacent leads. Breath by breath data was collected during CPET 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 CO2 ($P_{ET}CO_2$) were determined at rest and peak exercise. PeakVO_2 and the peakRER was the average of last 15s of CPET. VO_2 and $P_{ET}CO_2$ were determined at ventilatory threshold (VAT) as well. VAT was measured by the 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 (WR-work rate, T-time of incremental exercise, S-slope of work rate increment in W/min).[5] A $\Delta VO_2/\Delta WR$ inflection >30º outside of the last 30s of the test was defined as an ischemic response. Also, the double slope sign in the O_2pulse curve during RE-CPET was considered indicative of ischemia. 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]

Vivid 9 ultrasound device (BTO6, 1.5–3.6 MHz; GE Healthcare Technologies, Waukesha, WI, USA) was used to perform standard echocardiography at rest according to recommended criteria.[8]

Judkins' technique was used to perform coronary angiography.[9] Stenosis was considered hemodynamically 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 tracked 32±10 months. Follow-up started the day after the second CPET. Follow-up ended with an adverse event or at 32 months if a subject remained event-free. Measures of outcome were prospectively defined as all-cause mortality or cardiovascular 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 performed to identify the best model to predict probability of CAD on coronary angiography and CPET 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 area under the Receiver Operating Characteristic (ROC) curve, as measure of predictive ability. Two-by-two tables were built to estimate sensitivity (Sn), specificity (Sp), predictive values and 95% confidence intervals of CPET parameters, using coronary angiography as the gold standard. Kaplan-Meier survival curves were then plotted to examine 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.

Results:

Of 40 subjects enrolled, mean age 63.5±7.6, there were no major cardiac events, deaths or undue cardiac stress during testing. 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.

During TM-CPET, 77.1% patients stopped the test due to ST depression (73.1% in patients with 1 and 2-SCA, and 88.9% with 3-SCA), whereas during RE-CPET 28.6% exhibited ST depression (23.1% in patients with 1 and 2-SCA, and 44.4% with 3-SCA); TM-CPET exhibited a higher occurrence of ST segment depression ≥1mm (p=0.04). There were no hypertensive reactions in any group. Chest pain, dyspnea or fatigue were present in 35.14% of patients tested on RE, and 44.74% patients tested TM. The rest of patients reached metabolic criteria for the test maximality (RER≥1.1).

Subjects divided into groups according to the number of SCA, showed a number of significant differences in CPET responses during the TM testing only, as listed in **Table 1.**

In order to find parameters to distinguish between those with 1 and 2-vessel-CAD compared to 3-vessel-CAD, ROC analysis was used. The best predictive ability was shown for the VE/VCO_2 slope 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 Sn and Sp of 88.9% and 72.0%, respectively, as shown at **Figure 1.** The coefficient of correlation of VE/VCO_2 slope 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).

ΔVO2/ΔWR obtained during RE-CPET significantly correlated with cumulative cardiovascular event occurrence (r= -0.46, p=0.01). On the univariate analysis it was shown as the predictor (F=7.57, p=0.01).

VE/VCO_2 slope obtained during TM-CPET, with cut of point of 32, showed tendency to distinguish patients with and without cardiovascular event occurrence during the 32±10 month follow-up period but did not reach statistical significance (Log Rank-Mantel Cox 2.77, p=0.09)**.**

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, by O_2 pulse and $\Delta VO_2/\Delta WR$ slope measurements, which reflect stroke volume decrease during ischemia.[3,10,11] Taking into consideration the ability of CPET to detect metabolic changes, exploring its value in another point of ischemic cascade, may add a new strength in the detection of CAD. Accordingly, the results of the present study demonstrate the diagnostic value of the ventilatory efficiency in the detection of CAD, which is supported by recent studies.[12] Moreover, the fact that angiographically quantified CAD and subsequent PCI does not necessarily lead to improved outcomes warrants the need for more precision in characterizing the functional consequences of myocardial ischemia in patients planned for invasive procedures.[13] It is reasonable to postulate that CPET gives an additional value in the quantification of CAD in relation to the standard exercise test and stress-echocardiography, as it is expressed in numbers and less dependent on subjectivity of the interpreter. Current study extricated the VE/VCO_2 slope obtained during TM-CPET as a power marker able to differentiate between 3-vessel and 1-2-vessel-CAD. The independency of VE/VCO_2 slope from effort [14], makes this finding even stronger, as many patients with extensive CAD exhibit intensive chest pain, fatigue, or significant ST segment depression before reaching RER $\geq$1.1, after which further testing may increase the risk for acute myocardial infarction.Thus, CPET appears to be more informative than standard ECG and useful in the quantification of CAD severity and burden of ischemia, which is important for subsequent revascularization strategy, PCI or CABG. Although it would always be more

informative to perform CPET than standard ECG in CAD patients, the accessibility of CPET limits it's usage. Indeed, it requires equipment and well trained professionals which is not common worldwide.

By far, TM testing and upright cycle-ergometry constitute the most common modes of exercise test both in clinical practice and the research setting.[7] The fact that previously suggested analysis of the O_2pulse and $\Delta VO_2/\Delta WR$ slope requires cycle-ergometer testing [8] has limited broader applicability and adoption of CPET. Current study demonstrates that CPET responses indicate significant differences between 1-2-SCA and 3-SCA only during TM-CPET. It was noticeable that patients tested on the TM exhibited more pronounced ST segment changes. The physiological basis of this finding may be attributable to a more extensive recruitment of muscle groups with a higher aerobic demands during TM exercise compared to cycle-ergometry.[15,16,17] It seems that, in comparison to RE, TM exercise results in a higher overall metabolic requirements, including the heart's need to deliver more oxygen, enabling a more noticeable emergence of ischemia, detected by an increase in the VE/VCO_2 slope.

The present study revealed that $\Delta VO_2/\Delta WR$ slope, which can be only obtained during RE, holds predictive value for CAD prognosis. Kaplan–Meyer analysis failed to determine a statistically significant predictor of cumulative cardiac events, however the VE/VCO_2 slope value of 32, obtained during TM-CPET, demonstrated potential prognostic utility and may reach statistical significance in a larger cohort with more events, adding a value to already shown prognostic significance of the VE/VCO_2 slope in other cardiac diseases.[18]

In the present study, unlike in clinical practice, certain cardioprotective drugs were stopped before CPET to achieve better standardisation of the study protocol, which, to some extent, limits the applicability of the results. Medications significantly impact

cardiopulmonary variables [19], as such, diagnostic and prognostic value of CPET in CAD patients needs to be reassessed in trials without removal of cardioprotective therapy.

Limitations

The limitation of this study is small number of patients, which is due to large proportion of patients with extensive CAD performing CPET in duplicate, without antianginal therapy. The results of this study have to be evaluated in larger clinical trials, with longer follow up period, in order to evaluate diagnostic/prognostic potential of CPET in patients with CAD. Since VE/VCO_2 slope may be confounded in the presence of other diseases, larger cohort of patients is appreciated to refine the diagnostic/prognostic potential of CPET in patients with CAD and comorbidities. Moreover, trials without removal of cardioprotective therapy, and individualised CPET protocols, are highly warranted. Finally, the applicability of CPET is confined by it's availability and may be one of the limitations to accomplish a routine use of CPET in CAD management.

Conclusion

The VE/VCO_2 slope obtained during TM-CPET can be used to accurately differentiate between 3-vessel and 1-2-vessel-CAD which is important for planning invasive therapeutic strategies. Compared to RE, it seems that TM testing exceeds higher overall metabolic requirements, enabling a more noticeable emergence of myocardial ischemia, making it a potentially better approach in the quantification of CAD.

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Figure legends:

Figure 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.

Figure 1S. Kaplan-Meier analysis of VE/VCO_2 slope obtained on TM in distinguishing between patients with and without cardiovascular event occurrence during 32±10 month follow-up period (Log Rank-Mantel Cox 2.77, p=0.09)