TITLE PAGE:

Oxygen consumption and carbon – dioxide recovery kinetics in the prediction of coronary artery disease severity and outcome

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RUNNING HEAD: Gas exchange in recovery and coronary artery disease

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Abstract

Background: Revascularization appears to be beneficial only in patients with high levels of ischemia. This study examined the utility of gas analysis during the recovery phase of cardiopulmonary exercise testing (CPET) in predicting coronary artery disease (CAD) severity and prognosis.

Methods: 40 Caucasian patients (21.2% females), mean age 63.5±7.6 with significant coronary artery lesions (≥50%) were studied. Within two months of coronary angiography, CPET on a treadmill (TM) and recumbent ergometer (RE) were performed on two visits 2-4 days apart; subjects were subsequently followed 32±10 months. Myocardial wall motion was recorded by echocardiography at rest and peak exercise. Ischemia was quantified by the wall motion score index (WMSI).

Results: Mean ejection fraction was 56.7±9.6%. Patients with 1-2 stenotic coronary arteries (SCA) showed a poorer CPET response during the recovery phase than patients with 3-SCA. ROC analysis revealed the change of carbon-dioxide output (ΔVCO_2) recovery/peak (area under ROC curve 0.77, p=0.02, Sn=87.5%, Sp=70.4%) and oxygen uptake (ΔVO_2) recovery/peak during TM CPET (area under ROC curve 0.76, p=0.03, Sn 75.0%, Sp 77.8%) were significantin distinguishing between 1-2-SCA and 3-SCA.The same variables predicted ΔWMSI peak/rest on univariate analysis ($p<0.05$). Multivariate Cox analysis revealed a high predictive value of ΔVO_2 recovery/peak obtained during TM CPET for composite endpoint of cumulative cardiac events (HR=1.27, CI=1.07-1.51, p=0.008).

Conclusions: The current study suggests CPET parameters in recovery hold predictive value for CAD severity and prognosis. TM testing seems to be a better approach in the assessment of CAD severity and prognosis.

Key words: cardiopulmonary exercise test, coronary artery disease, carbon – dioxide, oxygen uptake, recovery

Abbreviations

ACE - angiotensin converting enzyme

BMI - body mass index

BW - body weight,

CABG - coronary artery bypass graft

CAD - coronary artery disease

CPET - cardiopulmonary exercise test

EF - left ventricular ejection fraction,

HR - heart rate

MI - myocardial infarction

SCA –number of stenotic coronary arteries

PETCO2 - end-tidal pressure of CO2

PCI - percutaneous coronary intervention

RE – recumbent ergometer

RER - respiratory exchange ratio

SE - stress echocardiography

VCO2 - carbon–dioxide output

VE - ventilation

VO2 - oxygen consumption

WMSI - wall motion score index

WR - work rate

1. Introduction:

Coronary artery disease (CAD) continues to result in high morbidity and mortality, despite considerable improvements in identification and treatment, resulting in 19% of all-cause deaths in men and 20% in women. More than 870,000 men and women die as a

consequence of CAD annually, making it the most common single cause of death. [1] Detection of CAD during standard exercise testing, otherwise known as a *stress test*, is commonly based on analysis of ST segment depression, which is powerful prognostic marker, along with the duration of exercise and exercise capacity. [2, 3 ,4] In order to improve diagnostic resolution, the recovery phase of stress testing has received an increasing amount of attention in recent years. [2] Accordingly, markers such as the rapidity of recovery of ST segment changes and systolic blood pressure changes have demonstrated diagnostic and prognostic value. [3] Moreover, the abnormality of the change in heart rate (HR) in recovery phase, has consistently demonstrated prognostic value in patients with known CAD. [2, 3, 4,5,6] However, a meta-analysis of 147 studies found stress testing has a pooled sensitivity (Sn) of 68% and specificity (Sp) of 77% for detection of CAD. [7]

Improving the diagnostic accuracy of the standard exercise testing is still highly advantageous, particularly in specific patient populations, such as women, those undergoing a revascularization procedure, as well as in the presence of confounders such as resting ST-depression, digoxin usage, left bundle branch block and left ventricular hypertrophy with repolarization changes. [2, 3] Another important issue in the diagnosis of CAD is the lack of objective tools for its quantification, important for interventional decision making [e.g., percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG)] [2, 3, 8], as there is increasing evidence in the literature suggesting that revascularization may only be beneficial in patients with high levels of ischemia.[9]Therefore, the number of noninvasive echocardiographic and radionuclide imaging studies performed to identify ischemic heart disease has grown considerably, with the added risk of radiation exposure and greater costs. [3] Concomitantly, it has been proposed that the addition of ventilatory gas exchange analysis to the standard exercise test [i.e. cardiopulmonary exercise testing (CPET)] may improve diagnostic performance. [10] The superiority of CPET to standard exercise testing in the

detection of CAD was demonstrated by Belardinelli et al, yielding a greater Sn and Sp, attributable to its potential to detect real-time decreases in stroke volume with the onset of ischemia, by the oxygen (O_2) pulse and work efficiency [i.e., change in oxygen uptake to change in work rate ($\Delta VO_2/\Delta WR$)] measurements. [10] A recent study has also shown the diagnostic value of the minute ventilation/carbon dioxide production (VE/VCO_2) slope in the detection of CAD. [11] As CPET allows for a comprehensive evaluation of metabolic changes and overall physiologic impairment, objectively expressed in numbers, and in a cost effective manner, it may hold additional value in CAD quantification and prognosis. [12] As such, we hypothesized that gas exchange in the recovery phase may bring more information than ECG alone, based on the fact that recovery period carries a higher metabolic and ventilatory demand, characterized by recovery of energy stores and repayment of the O_2 deficit. In ischemic patients, this process may be altered affecting kinetics of VO_2 and VCO_2 after exercise. Moreover, the proposed model of ischemia detection through CPET requires testing on an upright bicycle [10], without consideration of other exercise modes.

Thus, the aim of the current study was to assess the ability of select CPET variables during the recovery phase, obtained during both treadmill (TM) and recumbent ergometer (RE) testing, to predict CAD severity, as a primary study objective, and CAD prognosis, as a secondary study objective.

2. Materials and Methods:

2.1. Patients

We prospectively studied 40 Caucasian patients (21.2% females), with significant coronary artery lesions (≥50%) documented by coronary angiography performed within two months of CPET and SE. We collected clinical data from patients during a preliminary visit including age, height, weight, body mass index, other cardiovascular risk factors, previous myocardial infarction (MI) and revascularization (PCI or CABG), which are listed in **Table 1.**

All subjects were clinically stable and did not exercise regularly. Exclusion criteria were chronic heart failure, unstable angina, recent acute coronary syndrome, uncontrolled hypertension, diabetes, anemia, respiratory disease and the inability to exercise. Nitrates were stopped for 24 h, calcium antagonists for 48h, and beta blockers for 3 days before testing. Tea, coffee, cola-drinks, chocolate and smoking were not allowed for 24h before evaluation. The participants underwent the study after providing written informed consent, approved by the Local Ethical Committee.

2.2 Protocol

In order to satisfy the primary study objective, we compared CPET responses in recovery on a TM and RE combined, with stress echocardiography (SE) and coronary angiography as the gold standard for diagnosis of CAD. In order to satisfy the secondary study objective, subjects were followed for 32 ± 10 months to document the occurrence of cardiovascular events.

2.3 Cardiopulmonary exercise testing

CPET was performed in the morning in a fasting state. Patients performed two tests in a random order (two-four days apart), one on a RE using a ramp increase in WR (15 Watts/minute) and the other on a TM using the standard Bruce protocol.[13] The WR during TM testing was automatically calculated according to the formula of manufacturer (HP cosmos sports & medical gmbh, Nussdorf – Traunstein, Germany), as follows: $WR = [mv \cdot (2.11 + 0.25g) - 2.2m - 151] / 10.5$, where WR (W) = load, m (kg) = body mass, v (km/h) = speed and g (%) = inclination.Of 40 patients, 2 did not perform the test on TM and 3 did not perform test on RE, all declining to be tested twice. Tests were symptom-limited (i.e., exercise limiting fatigue, dyspnea or angina), or were stopped when one of the following criteria was met: 1) achieving respiratory exchange ratio (RER) ≥1.1; 2) 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 CS 200 device (Schiller, Baar, Switzerland). Before each test, the equipment was calibrated according to the manufacturer's specifications using reference gases. Ambient conditions were accounted for as well. Oxygen uptake (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, peak exercise and after 3 minutes of recovery. Peak VO_2 and the peak RER was the average of the last 15 s of CPET. The changes recovery/peak for tested variables were calculated as the difference between values after three minutes of recovery and peak values. Tests were interpreted by experienced evaluators who were blinded to subject names, other study results, clinical history and physical findings.

2.4 Echocardiography

Standard M – mode and two – dimensional echocardiography was performed at rest and during maximal effort on a Vivid 9 ultrasound device (BTO6, 1.5–3.6 MHz; GE Healthcare Technologies, Waukesha, WI, USA). Echocardiograms were obtained by two experienced readers according to recommended criteria [14] and met standard criteria for technical quality. B – mode echocardiography was performed to assess ejection fraction (EF). Wall motion was recorded at the beginning of the TM CPET and at maximal effort, reported using conventional 16-segment model. [15] Contractility of the individual segments was scored as follows: 1) normal or hypercontractile; 2) hypokinesia; 3) akinesia; and 4) dyskinesia. An ischemic response was defined as worsening of left ventricular wall motion during exercise testing in comparison to the resting condition. Ischemia was quantified by the wall motion score index (WMSI), which was calculated by dividing the sum of the score of each segment between the number of visualized segments. [15]

2.5 Coronary angiography

Coronary angiography was performed by the Judkins' technique. [16] 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.

2.6 Follow-up

Follow-up started the day after the final 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, PCI or CABG).

2.7. Statistical analysis

The results are expressed by classic descriptive parameters - mean and standard deviation for parametric variables and median for variables that were not normally distributed. In order to apply parametric statistics, analysis of distribution was performed by the Kolmogorov - Smirnov test. The differences between the groups stratified according to presence of 1-2-SCA and 3-SCA were tested by Student’s t test for independent samples. The Mann-Whitney test was used for nonparametric variables. Correlations between variables were performed by Pearson`s correlation test and the Spearman`s rank correlation test. Logistic regression analysis was performed to identify the best model to predict probability of CAD on coronary angiography and SE 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 Sn, 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. Univariate and multivariate Cox regression analysis was also used to assess the prognostic value of key CPET measures. Statistical tests were considered significant when a p-value was <0.05. The SPSS software package (SPSS version 17.0, SPSS Inc., Armonk, New York, USA) was used for listed statistical analyses. Furthermore, in order to assess sensitivity to censored subjects, Harrell's C was also calculated, as a measure of goodness of fit for binary outcomes in a survival analysis regression model, being equivalent to the area under the ROC curve. For this analysis STATA 14 (STATA, College Station, TX) program was used.

3. Results

Of 40 subjects enrolled (mean age 63.5 ± 7.6) 25 had minor arrhythmias during testing (i.e. supraventricular and ventricular premature ectopic beats); there were no major cardiac events, deaths or undue cardiac stress during testing, the latter of which was documented by normal troponin and myoglobin after each test. Chest pain or dyspnea was present in 13/37 (35.14%) patients tested on RE, and in 17/38 (44.74%) patients tested on TM. ST segment depression ≥1mm was recorded in 71.05% subjects tested on a TM, while on the RE in 27.02%; which was significantly more frequent (p=0.04). Clinical and echocardiographic data are shown in **Table 1.** Spirometry parameters demonstrated a normal response.

Parameters of CAD severity derived from coronary angiography and SE are listed as follows: 1) number of patients with 1-SCA 16, 2-SCA 14 and 3-SCA 10; 2) WMSI rest 1.14±0.17; 3) WMSI peak1.38 ± 0.26; and 4) ΔWMSI peak/rest 0.24±0.17.

When subjects were divided into groups according to the number of SCA, there were a number of significant differences in CPET responses during the TM testing only, except for ΔHR recovery/peak which differed during RE testing, as listed in **Table 2.** and **Figure 1a.**

In order to find parameters to distinguish between those with 1 and 2-vessel CAD compared to 3-vessel CAD, ROC analysis was used. Among measured CPET parameters the

best predictive ability was shown for the ΔVCO_2 recovery/peak obtained during TM CPET (area under ROC curve 0.77, SE=0.09, p=0.02)**.** The optimal threshold value for identifying patients with 3-vessel CAD≥ -0.76 l/min, produced a Sn and Sp of 87.5% and 70.4%, respectively, as shown at **Figure 1b.** Predictive value was also shown for ΔVO_2 recovery/peak obtained during TM CPET (area under ROC curve 0.76, SE=0.10, p=0.03), with an optimal threshold value for identifying patients with 3-vessel CAD≥ -12.51 ml●kg^{-1}●min^{-1} (Sn 75.0%, Sp 77.8%). On ROC analysis ΔHR recovery/peak obtained during RE CPETandΔVE recovery/peak obtained during TM CPET did not reach statistical significance in predicting CAD severity (area under ROC curve 0.72, 0.73; SE=0.06, 0.10; p=0.06, 0.054 respectively).

Binary logistic regression also demonstrates that significant discriminators between 1,2-vessel and 3-vessel CAD were: 1) ΔVCO_2 recovery/peak obtained during TM CPET (OR=6.80, CI=0.98-46.98, p=0.04); and 2) ΔVO_2 recovery/peak (OR=1.26, CI=1.00-1.59, p=0.04). ΔHR recovery/peak obtained during RE CPET (OR=1.09, CI=1.00-1.19, p=0.06) and ΔVE recovery/peak obtained during TM CPET (OR=1.05, CI=0.99-1.11, p>0.05) did not reach statistical significance.

On binary logistic regression, ST segment depression registered during TM and RE CPET did not show significance in distinguishing between 1 and 2-vessel CAD compared to 3-vessel CAD (B=0.40, 0.98; SE=0.91, 1.25; p=0.28, 0.75, respectively).

On univariate analysis, the predictors of ΔWMSI peak/rest were ΔVCO_2 recovery/peak (R=0.4, F=6.44, p=0.016), ΔVE recovery/peak (R=0.4, F=6.16, p=0.018) and ΔVO_2 recovery/peak (R=0.34, F=4.36, p=0.045), obtained during TM CPET, as listed in **Table 3.**

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

On univariate Cox regression analysis, ΔHR recovery/peak obtained during RE and TM CPET did not show statistical significance in the prediction of cardiovascular event occurrence (HR=1.03, 1.01; CI=0.99-1.07, 0.98-1.03; p>0.05, respectively). The same was shown for ST segment depression registered during TM and RE CPET (HR=1.24, 0.89; CI=0.49-3.19, 0.36-2.21; p>0.05, respectively), as well as for ΔVO_2 recovery/peak during RE CPET (HR=1.07, CI=0.94-1.23, p>0.05), whereas ΔVO_2 recovery/peak during TM CPET tended to be a significant predictor of cardiac event occurence (HR=1.08, CI=0.98-1.19, p=0.08). Multivariate model including all these variables extricated ΔVO_2 recovery/peak during TM CPET as significant predictor of cardiac event occurence (HR=1.27, CI=1.07-1.51, p=0.008).

Among measured CPET parameters, ROC analysis revealed a high predictive value of ΔVO_2 recovery/peak obtained during TM CPET for composite endpoint of cumulative cardiac events (area under ROC curve 0.86, SE=0.08, p=0.013). The optimal threshold value for identifying patients who will exhibit cardiac event $\geq$ -12.71 $ml \bullet kg^{-1} \bullet min^{-1}$ produced a Sn and Sp of 91.3% and 80.0%, respectively, as shown at **Figure 2a.**

As ROC analysis did not take into account sensitivity to censored subjects, in order to achieve this goal, equivalent Harrell's C analysis was performed, showing the value of 0.77 for applied multivariate Cox regression model.

On Kaplan-Meier analysis ΔVO_2 recovery/peak as percentage of peak VO_2obtained during TM CPET, with cut of point of -67.27%, 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 3.14, p=0.07), as shown in **Figure 2b.**

Patients with prolongedΔVO_2 recovery/peak obtained on a TM showed more frequent cardiovascular event occurrence, as shown at **Figure 2c**.

4. Disscussion

The current study revealed that patients with more severe CAD exhibited a prolonged decrease in VO_2 and VCO_2 after three minutes of TM CPET, as well as HR after three minutes of RE. A high predictive value of ΔVCO_2 recovery/peak and ΔVO_2 recovery/peak for CAD disease severity, as well as for the amount of ischemia during effort, was shown. Moreover, the ability of ΔVO_2 recovery/peak obtained on TM to predict the composite morbidity and mortality endpoint was demonstrated. Thus, the superiority of gas analysis during recovery upon ST segment and HR recovery changes, which have proven diagnostic and prognostic value for CAD [3, 5], was shown.

Pathophysiological basis of diagnostic and prognostic performance of expired gas analysis during recovery in CAD

The recovery period after exercise is characterized by the decline in cardiopulmonary parameters such as HR, VO_2 and VCO_2, which is likely the manifestation of vagal reactivation. [2, 13, 17] It has been found that kinetics of these variables in recovery phase is also related to the recovery of energy stores in active muscles.[18, 19] There is direct link between blood lactate concentration built up during vigorous exercise and the amount of extra oxygen required to oxidize it, known as O_2 debt, which will be repaid during recovery period. [20] Thus, gas exchange after exercise is a represent of cellular respiration coupled by cardiovascular and ventilatory mechanisms.[20] As previous studies demonstrated that heart rate declines more slowly in CAD patients in comparison to healthy population with strong prognostic power [2, 3, 4, 5, 6], we hypothesized that repayment of the O_2 debt is

prolonged in these patients in parallel with the delayed recovery of energy stores in peripheral muscles and that the kinetics of recovery of VO_2 and VCO_2 after exercise is a specific marker of the circulatory response during exercise. Moreover, HR early after exercise, at the first minute of recovery, was shown to have a robust prognostic value. [2, 3, 4, 5, 6]. Knowing that recovery of energy stores and repayment of the O_2 deficit is most intensive during the first 30 s after exercise and that complete recovery of energy stores and acid-base status, as well as O_2 uptake, may last several minutes and continues even 24h after high intensity exercise, to achieve pre-exercise levels [17, 18, 20], we have arbitarily chosen the 3 min recovery period for our analysis. Indeed, in this study patients with more severe CAD exhibited a delayed decrease of VO_2 and VCO_2in recovery phase. Previous studies reported prolonged kinetics of VO_2 or VCO_2 during recovery from maximal exercise in heart failure patients, which was explained by impairment of the circulatory response to exercise and delayed recovery of cardiac output after exercise, as well as slower kinetics of muscle energy store recovery. [21, 22] However, to our knowledge, only one study assessed this phenomenon in a small CAD cohort, failing to show any significant alterations in VO_2 recovery kinetics in comparison to an apparently healthy cohort. [22]

It is known that ischemia is characterized by a drop in tissue oxygen levels, and rapid conversion from aerobic to anaerobic metabolism, global lactate production and consequent acidosis. [23] Lactic acid may thus be retained in muscle, decomposing bicarbonate and raising CO_2 blood levels, keeping ventilation high which is multifaceted with both central and peripheral chemoreceptors and skeletal muscle metaboreceptors. [24] The oxidative energy obtained from pyruvate-to-lactate mechanism may account for majority of the total O_2 deficit in the ischemic condition, and must be repaid during the recovery period of exercise as O_2debt, which acts as a major factor of influence on the ventilatory response after exercise. [20]As the degree of ischemia dictates both lactate levels and glucose utilization [23, 25], it is

reasonable to hypothesize that the severity of CAD is closely related to ventilatory response in recovery period. This may be an explanation for the lower CO_2 decrease in recovery after exercise in patients with 3-SCA in comparison to 1-2-SCA, as found in this study, and high predictive value of ΔVCO_2 recovery/peak for CAD disease severity, as well as for the amount of ischemia during effort. Additional mechanism explaining this finding may be the maintenance of decreased stroke volume due to impaired contractility, and consequently cardiac output, during recovery period as well, in accordance with severity of CAD [26], causing metabolic changes raising CO_2 in the blood [23, 25], and decrease of the blood flow that limits CO_2 return to the lung leading to prolongation of CO2 elimination. Besides, generalized vasoconstriction mediated by stimulation of skeletal muscle metaboreceptors, central and peripheral chemoreceptors by metabolic changes, and baroreceptors by a decreased cardiac output, which is followed by further decrease of stroke volume [23, 24], leads to an abnormal ventilatory response. Moreover, the impact of impaired release of endothelial vasodilators (e.g., NO, prostacyclins), due to endothelial dysfunction, and the constrictor effect of catecholamines on systemic and pulmonary arterial smooth muscle during stress and exercise in ischemic patients, as contributing factors cannot be ignored. [27]

It is well known that recovery kinetics of HR are affected by physical conditioning, body position, type of exercise, hypoxia, metabolic disorders, vascular volume or peripheral resistance, ventricular dysfunction, blood volume, sinus node function and medications.[2, 28] As VO_2, according to the Fick equation, is the instantaneous product of cardiac output, ie, HR multiplied by stroke volume, and arteriovenous difference for oxygen, it is not surprising that the recovery kinetics of VO_2, which appear to be related to O_2 debt after exercise [20], and therefore used as an index of oxidative capacity [29] are affected by the same factors. Accordingly, it was shown that VO_2 recovery kinetics may be changed by training [30], presence of chronic obstructive pulmonary disease [31] and heart failure [22]. Furthermore, it

has been demostrated that in patients with mild left ventricular dysfunction there is an overshoot of the arteriovenous difference for oxygen after exercise, descending beyond resting values after three minutes of recovery, because of the redistribution of blood flow to non exercising areas secondary to metabolic acidosis–induced or sympathetic-induced vasoconstriction. [32] This finding suggests that blood flow during recovery in these patients is excessive for the oxygen demand of the whole body, leading to a prolonged recovery kinetics of VO_2. Moreover, the decrease in blood velocity that causes an increased transit time between peripheral muscles and the mouth, venous return and thus cardiac output, greatly affect VO_2 kinetics after exercise. [21] Considering these findings, it is not surprising that VO_2 in recovery was shown to be prognostic marker of death, heart transplantation, and mechanical heart implantation in severe heart failure, even stronger than peak VO_2. [33] In the same direction, as decrease of stroke volume and generalized vasoconstriction characterize ischemic condition, it is reasonable to preclude that VO_2 recovery kinetics may also have power in predicting of CAD severity and prognosis, and even more so than HR, as it represents not only cardiac output changes during recovery after exercise, but also complex peripheral metabolic processes of the whole body. [20, 18, 21, 34] This study revealed the predictive value of ΔVO_2 recovery/peak for CAD disease severity, as well as for the amount of ischemia during effort. Kaplan – Meyer analysis failed to determine a statistically significant predictor of cumulative cardiac events, however Cox regression extricated ΔVO_2 recovery/peak obtained during TM CPET as parameter of potential utility.

Responses in TM CPET and RE CPET during recovery in CAD

Interesting point of this study was that CPET responses in recovery indicated significant differences between 1-2-SCA and 3-SCA only during TM CPET, except for HR response, probably because of more mechanical stability in detection of HR during RE. On the other hand, according to previous studies it is exclusively recommended to use bicycle

CPET in diagnosing CAD. [10, 12] There have been a number studies comparing the physiological responses in TM CPET and RE CPET, including gas exchange performance, showing different results [35, 36, 37], however the kinetics of $\dot{V}O_2$ and VCO_2 during recovery for different exercise modes is largely unexplored. [38] Controversy persists whether an impaired oxidative capacity versus deficiency of oxygen delivery leads to the onset of lactic acid production, hence it is possible that both processes, the pattern of muscle fiber recruitment and an imbalance between oxygen supply and oxidative metabolism, contribute to the increase in lactic acid with an increase of the exercise intensity, the level of which appears to be a powerful discriminator of diseased and non-diseased coronary status. [39] During TM testing extensive use of oxidative metabolic pathways from different muscle groups leads to a higher desaturation level [37, 40], which seems to be an important advantage in causing myocardial ischemia during TE testing, by exposing the heart to the condition of higher demands in hypoxic environment. On the contrary, during cycling protocols, there is dominant usage of anaerobic pathways [40], therefore high lactate levels do not necessarily represent global ischemia and deficiency of oxygen delivery attributable to impaired cardiac function. It seems that, in comparison to RE, TM testing results in higher overall metabolic requirements, including the heart's need to deliver more oxygen, enabling a more noticeable emergence of ischemia. Thus, CPET on a TM seems to be more reliable in the assessment of CAD severity and prognosis in comparison to RE.

Considering the fact that angiographically quantified CAD and subsequent revascularization does not necessarily lead to improved outcomes [9], there is indisputable need for improvement of noninvasive diagnostic procedures in terms of more precision in characterizing the functional consequences of myocardial ischemia. The potential diagnostic utility of CPET as an objective, quantitative, safe and effective method is promising. The analysis of gas exchange parameters three minutes after termination of CPET on a TM, ΔVO_2

recovery/peak and ΔVCO_2 recovery/peak, may change the perspective of CAD management in terms of prognosis.

4. Limitations: The VO_2 and VCO_2 are CPET parameters easily obtained and interpreted, however the recovery kinetics of these variables is affected by training status [30], and altered in some pathological conditions including heart failure and ventilatory diseases.[30, 31, 22] As such, the Sp of these measurements in quantification and prognosis of CAD may be confounded in the presence of other diseases. Hence, further research in a larger cohort of patients with CAD is warranted to refine the diagnostic and prognostic potential of recovery CPET parameters. Namely, due to a short follow up in the present study, the composite end-point was based only on the number of hospitalizations, MI occurrence and revascularization procedures, which significantly linked CAD severity assessment and prognosis, as revascularization, is based on clinical decision making, especially the burden of ischemia. The results of this study have to be evaluated in larger clinical trials, with longer follow up period, in order to accomplish a routine use of CPET recovery kinetics in CAD management. Moreover, the analysis of recovery kinetics in CAD patients would likely be more informative if standard methods to assess recovery kinetics were used, such as constant work load protocols. [20] However, the aim of the present study was to find the most practical way to strengthen recovery data derived from commonly used protocols in clinical practice, including the Bruce protocol, as we hypothesized that adding gas analysis to these standard procedures during recovery would be more informative and sharpen prognostic resolution with very little additional practical efforts. Additional work should be carried out to make this method accepted by physicians and incorporated in daily clinical practice.

5. Conclusion:

CPET parameters in recovery hold predictive value for CAD severity and prognosis, which is likely attributable to their power to detect hemodynamic, but also metabolic

derangements. ΔVCO_2 recovery/peak and ΔVO_2 recovery/peak obtained after three minutes of TM testing, as objective parameters, demonstrated predictive value in distinguishing between 3-vessel and 1-2-vessel CAD, and for the amount of ischemia, which is important for planning invasive therapeutic strategies. ΔVO_2 recovery/peak obtained after three minutes of TM CPET was shown as potential prognostic parameter. In comparison 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 and prognosis of CAD.

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