Original Research

Change in the cardiopulmonary exercise testing response in patients with coronary artery disease who do not choose to participate in cardiac rehabilitation

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Abstract:
Background: The purpose of the present study is to track changes in the cardiopulmonary exercise testing (CPET) response in a coronary artery disease (CAD) cohort who underwent a revascularisation intervention or optimisation of medical management.
Materials and Methods: A retrospective, observational study of 138 patients with CAD (20% female, mean age 65±9 years) who underwent percutaneous intervention (PCI), coronary artery bypass graph (CABG), or medical management.. CPET was completed after treatment for CAD and during a follow-up visit, with a mean study length of 13±5 months. Peak oxygen consumption (VO2), VO2 at the ventilatory threshold (VT), peak O2 pulse, the minute ventilation/carbon dioxide production (VE/VCO2) slope, the oxygen uptake efficiency slope (OUES) and the VO2 /WR slope were determined at baseline and during the follow-up CPET.
Results: A significant reduction ($p<0.001$) in: 1) peak VO_2 (19.2±4.3 vs. 18.2±4.3 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$) and 2) VO_2 at VT (11.9±2.4 vs. 11.4±2.4 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$) was observed. There were no significant changes ($p \geq 0.25$) in the following variables between CPETs: 1) peak O_2 pulse (12.4±3.2 vs. 12.3±3.2 ml/beat); 2) VE/VCO_2 slope (27.9±4.8 vs. 28.1±4.4); 3)OUES (1.9±0.5 vs. 1.9±0.50); and 4) VO_2/WR slope (9.0±0.98 vs. 8.9±1.2 $ml \cdot min^{-1} \cdot Watt^{-1}$).
Conclusion: The current study indicates that several key CPET markers of physiologic integrity remain stable in patients with CAD. Functional capacity and sub-maximal aerobic exercise tolerance parameters indicated signs of decline at follow-up.

Introduction

Cardiac rehabilitation (CR) is considered a gold standard of care for those diagnosed with coronary artery disease (CAD) and has received a Class 1 Recommendation from the European Society of Cardiology and American College of Cardiology [1-2]. The goals of CR are to improve cardiovascular work efficiency, increase exercise tolerance to reduce physical decline, and maintain physical capacity [3-7]. These goals can be met through a combination of cardiovascular training, weight training, and regular adherence to dietary and caloric planning. These goals were supported by a Cochrane systematic review in 2016 by Anderson et al [7], where CR was shown to reduce cardiovascular mortality, the risk of hospital admissions, and provide improvements in quality of life. This review included 63 studies with 14,486 participants in total, and a median follow-up of 12 months and a minimum of six months follow-up. Following myocardial infarction or revascularization, comparisons were made between patients who participated in CR and those who did not. Despite the strong evidence in support of CR, up to 70% of eligible patients did not participate in CR [8]. In another study by Fried et al [9], many older patients with multiple co-morbidities had reported their struggle with understanding the relationship between their diseases and treatment, which may lead to poor uptake and attendance in CR.

Functional exercise capacity (FC) is defined using a calculated peak oxygen consumption (VO_2) determined by age, weight, and gender. VO_2 is measured by multiplying the cardiac output with the arteriovenous oxygen difference. In other words, FC is the maximal capacity of the body to transport oxygen during exercise. There are multiple methods to determine FC. Cardiologists have primarily relied on treadmill stress testing, but more recently, the utilization of CPET has shown an advantage in allowing for a more comprehensive panel of cardiorespiratory fitness markers, which are further discussed in the methods section of this article. FC changes following CR are well documented [10-15]. However, in patients who do not participate in CR, changes in cardiac biomarkers obtained from CPET remain unclear.

Aim

To document the changes in FC in patients who do not participate in post-intervention CR.

Hypothesis

A decrease in functional capacity is correlated with not participating in CR and a sedentary lifestyle. Furthermore, patients who participate in CR following revascularisation have an improved FC.

Materials and Methods:

Study design

This study is a retrospective, observational study. The study was considered completed when participants had finished both aspects of the study.

Participant selection and recruitment

This study included patients who were diagnosed with CAD via an angiogram. These patients underwent revascularisation or optimisation of medical management, such as percutaneous coronary intervention (PCI), coronary artery bypass (CABG), or medication modification. All patients were recruited from a single community cardiology practice in Whitby, Ontario Canada between January 2014 and June 2017. It is standard practice in this clinic to refer all patients to cardiac rehabilitation and this is provided free of charge to the patient. All participants were clinically stable. During consultation with the physician, eligible patients revealed that they exercised no more than once per week, and did not want to participate in CR, even when medically advised to do so. Patients were excluded if they were clinically unstable, exercised regularly, had any interest in CR, or refused to repeat CPET after a year for reassessment of their status. Clinically unstable patients included those with chronic heart failure, respiratory disease, anaemia, uncontrolled hypertension, and inability to exercise due to lower extremity or joint issues. All participants signed two written informed consent forms, one for the procedure and another for their data and outcomes to be used for research purposes only. These consent forms were approved by the Canadian Association of Research Ethics Board.

Outcome and measures

Diagnostic and prognostic markers derived from CPET were used to measure the improvement of cardiac efficiency post-intervention and after one year. CPET was completed as part of routine management and the patients consented to have their data recorded for retrospective study purposes. Routine management included a post-intervention assessment of patients to assess functional capacity. The CPET cardiorespiratory fitness markers used in this study were VO_2, VO_2 at ventilatory threshold (VT), peak O_2 pulse, the minute ventilation/carbon dioxide production (VE/VCO_2) slope, the oxygen uptake efficiency slope (OUES) and the VO_2/WR slope. As previously described [10-15], VT is calculated using the slope of VO_2/VCO_2 and represents the point at which CO_2 production becomes greater than the increase in VO_2, thus causing the slope to steadily decrease. The VE/VCO2 slope is the minute carbon dioxide production. The OUES is the relationship between ventilation and oxygen uptake. The VO_2/WR slope is the relationship between oxygen uptake and work rate.

CPET Procedure

CPET was performed 4-6 weeks post-intervention and follow-up was scheduled for 12 months after this first session. CPET was performed on an electromagnetically-braked cycle ergometer using a customized linear-ramp protocol designed to elicit fatigue within 8-12 minutes of exercise. CPET was completed as per guidelines [16]. Medications were not withheld prior to testing. CPET was used with three minutes of unloaded cycling that progressively increased 10-

15 watt/min until optimal test duration was completed. There was no change in ramp intensity. Completion of the test was patient-dependent; requiring maximum exertion (ME), as defined by the respiration exchange ratio (RER). CPET sessions were completed by one of two qualified exercise physiologists and a medical student under physician supervision. Patient history and exercise status were not provided to the conductors of the test prior to patient investigation. Technicians who were operating the test session were blinded to the recruitment for the study. Standard 12-lead electrocardiograms (ECG) were obtained at rest and throughout the procedure. Reasons for stopping a session were based on symptoms, designated criteria, or completion of the timed test. Symptoms included pre-syncope, exercise fatigue, dyspnoea, or stable angina. The designated criteria included achieving a respiratory exchange ratio ≥ 1.1, blood pressure $\geq$230/130 mmHg or drop in systolic pressure $\geq$20 mmHg. Stress ECGs were analyzed for ST changes at peak exercise. A normal response was defined as a lack of significant ST-segment changes. A positive response was defined as ST-segment depression of 1 mm or greater (upsloping or flat) in two or more leads. Studies were considered indeterminate if they had significant artifact or other abnormalities such as left bundle branch block or ST-segment change <1 mm [17]. Spirometry and CPET machines are owned, operated and maintained by MET-TEST (USA), using the Metabolic Cart made by Cosmed (Italy). The equipment was calibrated to the manufacturer's specifications prior to each test.

Analysis

VO_2 and VCO_2 were measured at every breath and the averages over 10 seconds and 30 seconds were displayed on the device monitor, numerically and graphically respectively. Peak VO_2 was expressed as the highest averaged interval during the final 20 seconds of testing. VE and VCO_2 values were acquired from the beginning of exercise to the time of peak exertion. These values were placed into the spreadsheet software Microsoft Excel (Microsoft Corp., Bellevue, WA) to calculate the slope of VE/VCO_2.

Statistical testing

All data is presented as the mean ± standard error (SE) and was analysed by a one-way ANOVA and Bonferroni post-hoc testing. A confidence interval of 95% was used and p-values <0.05 were considered statistically significant.

Results

Participant Characteristics

Every patient of the clinic who underwent CPET as routine investigation, was approached to take part in research. In total, 250 patients were eligible for this study, with 138 consenting for post-corrective intervention and follow-up appointment. The mean age of patients was 65±9 years and a total of 20% were female. All participants had CAD and received some sort of cardiac intervention – 53 participants underwent PCI, 68 participants underwent CABG, and 17 received pharmacological intervention. Data containing co-morbidities to cardiac disease, such as hypertension, diabetes, dyslipidaemia were not stored. In terms of patient management, the only data recorded was whether the patient exercised regularly or not and was used for exclusion criteria.

Outcome data
Data from the one-year follow-up was variable as repeat testing was dependent on the patient returning to clinic and re-consenting for their testing data being used for research purposes. Patients returned on average 13 months after corrective intervention (± 5 months).

There was a significant decline in peak VO_2 and VO_2 at VT, which demonstrates a decline in FC and sub-maximal aerobic exercise over time (see Table 1). Peak VO_2 declined from 19.2±4.3 to 18.2±4.3 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$ and VO_2 at VT declined from 11.9±2.4 to 11.4±2.4 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$. Both were significantly reduced, with a $p<0.001$. However, there was no significant difference in peak O2 pulse, VE/VCO_2 slope, OUES, and VO2 /WR slope ($p>0.05$).

Discussion

Cardiac rehabilitation
The importance of CR is well-documented and well-understood. Patients who have undergone CR have shown significant improvements in CPET markers [15]. Hence, CR is recommended by multiple national and international agencies [1-2]. This study demonstrates that most of the traditional CPET markers (peak oxygen consumption, VO_2 at ventilatory threshold, peak O_2 pulse, the minute ventilation/carbon dioxide production slope, the oxygen uptake efficiency slope and VO_2/WR slope) did not improve in patients with CAD who did not participate in CR. Previous studies have not singularly examined patients who do not participate in CR. These findings are expected as intervention for patients with CAD do not provide symptomatic benefit to the extent that one would assume when using the intervention alone. There is evidence thay medical and therapeutic lifestyle changes and appropriate cardiac rehabilitation are more beneficial [18]. Furthermore, the FC and sub-maximal aerobic exercise tolerance markers showed significant decline on follow-up testing. Possible explanations for this decline may include a sedentary lifestyle and lack of compliance with medical advice and management [19]. These findings all support the necessity of cardiac rehabilitation to include education on maintaining a therapeutic lifestyle in patients post-intervention CAD patients. Further research would be necessary to determine the impact of a lack of cardiac rehabilitation on the occurrence of cardiac events. The wealth of data provided by the CPET in cardiac stress testing provides an interesting new modality for future research and overall patient care.

Limitations
A limitation of the study is that data on patient demographics, such as co-morbidities to cardiac disease and history of previous cardiac disease was not stored. Other data that should have been stored included smoking status, family history of cardiac disease, and medications, but these

details were unavailable. This study also contains a measurement bias, in which the variation of follow-up had a difference of 10 months. This was dependent on each patient scheduling and then attending their follow-up appointment. Including an additional longitudinal measure, such as five-year follow-up would further strengthen the findings.

Conclusion

It can be inferred that an absence of appropriate cardiac rehabilitation can increase the risk of deterioration in FC. This is supported by the decrease or lack of significant change in CPET parameters, such as peak VO_2 and VO_2 at VT, when assessing patients post-intervention. This data suggests that PCI or CABG alone may not translate to an improvement in cardiac function. However, participation in appropriate CR has been shown to measurably improve FC and exercise tolerance [1-7]. These studies serve as evidence that a therapeutic lifestyle with aerobic physical activity needs to be re-emphasised to patients alongside aggressive risk factor control measures, such as blood pressure and lipid management. These changes further support the importance of CR referral and maintaining patient compliance to regularly scheduled rehabilitation sessions. CPET is a valuable addition to the armamentarium in combating mortality and morbidities of patients with CAD.

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Table 1. Changes in functional exercise capacity over time post-intervention

	Post-Intervention n=138	1 Year Follow-Up n=138	p-value
Peak O_2	19.2±4.3 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$	18.2±4.3 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$	$p<0.001$
VO_2 at VT	11.9±2.4 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$	11.4±2.4 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$	$p<0.001$
Peak O_2 Pulse	12.4±3.2 ml/beat	12.3±3.2 ml/beat	$p>0.05$
VE/VC O_2 Slope	27.9±4.8	28.1±4.4	$p>0.05$
VO_2/WR Slope	9.0±0.98 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$	8.9±1.2 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$	$p>0.05$
OUES	1.9±0.5	1.9±0.5	$p>0.05$