

**Estimated peak functional capacity: an accurate method for assessing change in peak oxygen consumption after cardiac rehabilitation?**

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**Full Title: Are estimates of peak functional capacity an accurate method for estimating change in peak oxygen consumption after cardiac rehabilitation?**

**Short Title: Estimated functional capacity: A poor surrogate of  $VO_{2peak}$  changes after cardiac rehabilitation**

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These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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**Abstract:**

**Objective:** Maximal cardiopulmonary exercise testing (CPET) is the “gold standard” method of determining  $VO_{2peak}$ . When CPET is unavailable,  $VO_{2peak}$  may be estimated from treadmill or cycle ergometer workloads and expressed as estimated metabolic equivalents (METs). Cardiac rehabilitation (CR) programmes use estimated  $VO_{2peak}$  (METs) to report changes in cardiorespiratory fitness (CRF). However, the accuracy of determining changes in  $VO_{2peak}$  based on estimated functional capacity is not known.

**Methods:** 27 patients with coronary heart disease (88.9% male; age  $59.5 \pm 10.0$  years, body mass index  $29.6 \pm 3.8$   $kg \cdot m^{-2}$ ) performed maximal CPET before and after an exercise based CR intervention.  $VO_{2peak}$  was directly determined using ventilatory gas exchange data and was also estimated using the American College of Sports Medicine (ACSM) leg cycling equation for METs. Agreement between changes in directly determined  $VO_{2peak}$  and  $VO_{2peak}$  estimated from METs was tested using Bland-Altman limits of agreement (LoA), and intraclass correlation coefficients.

**Results:** Directly determined  $VO_{2peak}$  did not increase significantly following CR ( $0.5$   $ml \cdot kg^{-1} \cdot min^{-1}$  (2.7%);  $p=0.332$ ). In contrast, estimated  $VO_{2peak}$  increased significantly ( $0.4$  METs;  $1.4$   $ml \cdot kg^{-1} \cdot min^{-1}$ ; 6.7%;  $p=0.006$ ). The mean bias for estimated  $VO_{2peak}$  versus directly-determined  $VO_{2peak}$  was  $0.7$   $ml \cdot kg^{-1} \cdot min^{-1}$  (LoA  $-4.7$  to  $5.9$   $ml \cdot kg^{-1} \cdot min^{-1}$ ). Aerobic efficiency, ( $\Delta VO_2 / \Delta WR$  slope) was significantly associated with estimated  $VO_{2peak}$  measurement error.

**Conclusion:** Changes in estimated  $VO_{2peak}$  determined using the ACSM equation for leg cycling are not accurate surrogates for directly determined changes in  $VO_{2peak}$ . Reporting mean CRF changes using estimated METs may over-estimate the efficacy of CR and lead to a different interpretation of study findings compared to directly determined  $VO_{2peak}$ .

Key Words: CHD, Coronary Heart Disease, Cardiac Rehab, Cardiovascular Rehab, Exercise Testing, Cardiopulmonary Exercise Testing, Metabolic Equivalents, METs

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## Introduction

Structured exercise training is a core component of most cardiac rehabilitation (CR) programmes<sup>1-4</sup>. The efficacy of exercise-based CR is predicated on appropriately personalised exercise training<sup>5</sup>. Exercise prescriptions should be based on an individualised assessment that includes an initial exercise test. Maximal cardiopulmonary exercise testing (CPET) is the “gold standard” method for determining cardiorespiratory fitness [CRF]<sup>6</sup>. Information obtained during CPET provides some of the most accurate data on which to base an exercise prescription and to determine changes in CRF following the completion of a CR programme.

Where CPET is not available, workloads achieved during an incremental exercise test may be used to estimate  $VO_{2peak}$ <sup>7,8</sup>. Estimates of  $VO_{2peak}$  are often expressed as estimated metabolic equivalents (METs). Although recently challenged<sup>8</sup> equations for estimating  $VO_{2peak}$  and METs are traditionally based on an assumed linear relationship between  $VO_2$  and work rate<sup>7</sup>. One MET (corresponding to resting metabolic rate) is assumed to equate to a  $VO_2$  of  $3.5 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ <sup>9</sup>. Increases in estimated functional capacity during an exercise test are commonly expressed in multiples of resting metabolic rate. Peak estimated METs achieved during maximal exercise testing are used to risk-stratify patients, prescribe individual exercise intensities for exercise training, and to determine changes in CRF following exercise interventions<sup>10</sup>. However, estimates of functional capacity may not accurately quantify  $VO_{2peak}$ , particularly during treadmill protocols<sup>11-13</sup>. Whilst the limitations of estimating  $VO_{2peak}$

from a single exercise test are known, the accuracy of estimated changes in  $VO_{2peak}$  following an exercise training intervention is unclear.

Large discrepancies between estimated, and directly determined  $VO_{2peak}$  have previously been reported<sup>14 15</sup>. However, to our knowledge, the only relevant investigation into the suitability of estimating  $VO_{2peak}$  change from peak METs found no correlation ( $r=0.24$ ;  $p=0.100$ ) in 50 patients with coronary heart disease (CHD) undertaking maximal treadmill testing (Milani et al. 1995). Stuto, et al. (2013) also present data showing that the increase in directly determined  $VO_{2peak}$  following CR (14.7%) was not accurately reflected by a much lower improvement in functional capacity (3.85%) following CR. Thus, in this elderly cohort of patients attending CR, change in estimated peak METs do not appear to reflect improvement in directly determined  $VO_{2peak}$ . However this was not specifically addressed by Stuto, et al.<sup>16</sup>. We therefore aimed to investigate the accuracy of estimating changes in  $VO_{2peak}$  using the American College of Sports Medicine<sup>7</sup> leg cycling equation in patients with CHD.

## **Methods**

### **Study design**

Ethical approval was provided by the Yorkshire and the Humber NHS Research Ethics Committee (12/YH/0072). All patients provided written informed consent. All patients had agreed to participate in routine CR as delivered by their local National Health Service provider, and were a minimum of 28 days' post cardiac event at the time of

baseline assessment (Visit 1). Patients were included if they had completed maximal CPET before (visit 1) and following the completion of their CR exercise programme (visit 2). Clinical information collected included cardiac diagnosis, past medical history, medications, smoking status, resting heart rate, blood pressure, waist circumference measurement, and body mass index (BMI). Ejection Fraction (EF) was determined from a resting echocardiogram. Patients with New York Heart Failure Classification (NYHA) IV, a left ventricular ejection fraction <30%, or a pacemaker/implantable cardioverter defibrillator, were excluded.

#### Cardiac Rehabilitation Programme

Patients were recruited from four different CR centres in Yorkshire and Northern Lincolnshire (UK) between January and March 2013. CR provision remains inequitable across the UK<sup>17,18</sup>. The diversity of practice was reflected by the characteristics of the CR programmes included in this study. All CR programmes used interval circuit training with alternating cardiovascular and active recovery exercises. Exercise was prescribed at 40-70% of estimated heart rate reserve [HRR] using formulae recommended by the Association of Chartered Physiotherapist in Cardiac Rehabilitation<sup>10</sup>. The programme length varied from 4-24 sessions conducted over a 4-12 week period. The median number of exercise sessions during follow up was 15 (range: 0 to 62).

#### Cardiopulmonary Exercise Testing

At baseline and after completion of training, patients undertook symptom-limited maximal CPET following a 25W, two-minute stage, incremental electronically-braked

cycle ergometer protocol (GE Healthcare e-Bike, Chalfont St Giles, United Kingdom). Patients started pedalling at 25W without a prior unloaded cycling phase. Breath-by-breath metabolic gas measurements were collected via an Innocor (Innovision, Glamsbjerg, Denmark) metabolic cart. Calibration was performed prior to each exercise test according to the manufacturer's instructions. ECG and heart rate (HR) were continuously recorded using a GE Case System (GE Healthcare, Chalfont St Giles, United Kingdom) BP was monitored at two minute intervals using a Tango automated sphygmomanometer (SunTech Medical, Eynsham, United Kingdom).

Exercise was terminated if a patient experienced chest pain or achieved any of the test termination criteria outlined by the American Thoracic Society (2003). Data were exported as breath-by-breath values and post-processed to generate 15 second averages using Microsoft Excel (Microsoft, Redmond WA, USE).  $VO_{2peak}$  and peak respiratory exchange ratio (RER) were both averaged over the final 30 seconds of CPET.  $VO_{2peak}$  was standardised to body mass and reported as ( $ml \cdot kg^{-1} \cdot min^{-1}$ ). The ventilatory anaerobic threshold (VAT) was determined using the V-slope method<sup>19</sup> and also reported standardised to body mass. The slope of  $VO_2$  as a function of work rate ( $\Delta VO_2 / \Delta WR$  slope), a measure of aerobic efficiency, was determined using linear regression from data obtained throughout the CPET.  $\Delta VO_2 / \Delta WR$  slope values  $< 8.4$   $ml / min^{-1} / W$  were considered abnormal<sup>9</sup>. Estimated peak METs were calculated using the ACSM<sup>7</sup> leg cycling equation:

$$VO_2 = (1.8 \times kg \cdot m \cdot min^{-1}) / BM + (7.0)$$

Where  $kg \cdot m$  is Kilogram metres (and where 1W is equal to  $6.12 \text{ kg} \cdot \text{m} \cdot \text{min}^{-1}$ ) and BM is

patient body mass. The term 'directly-determined'  $VO_{2peak}$  and 'estimated  $VO_{2peak}$ ' are used to distinguish between the two variables.

Patients were asked to rate their perceived exertion (RPE) at the end of every two-minute stage during and at peak exercise using the 6-20 Borg score (Borg, 1982). Instructions for the use of the Borg score were given to patients prior to CPET using a standardised list of terms.

### Statistical Analysis

Statistical analysis was performed using SPSS version 22 (IBM, New York, USA). Data were visually assessed for normality and heteroscedasticity. Categorical data are reported as percentages. Continuous normally distributed variables are displayed as mean with 95% confidence intervals (95% CI) or standard deviation ( $\pm$ ) where specified. Statistically significant differences ( $p < 0.05$ ) were calculated using repeated measures analysis of variance (ANOVA) and repeated measures analysis of covariance (ANCOVA). Partial  $\eta^2$  ( $\eta_p^2$ ) effect sizes were also calculated with 0.01, 0.06 and 0.14 representing small, medium, and large effect sizes respectively (Richardson, 2011). Pearson correlations were used to assess the strength of the relationship between variables. An  $r$  value of  $<0.25$ , 0.26 to 0.50, 0.51 to 0.75, and,  $>0.75$  were considered weak, moderate, fair and strong associations, respectively <sup>20</sup>. Intraclass correlation coefficients (ICC) and Bland-Altman analysis were used to assess agreement between measurement methods <sup>21 22</sup>. The maximum acceptable difference between assessment methods was set at  $3.5 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  (1 MET). A 1 MET increase in

functional capacity has been shown to carry significant survival benefits (12%) (Myers et al, 2002). A measurement error greater than 1 MET would not only suggest that estimates of  $VO_{2peak}$  do not reliably interpret patient risk, but also that they are poor markers for monitoring CRF change. A consensus on ICC strength has not been reached, but we defined moderate agreement as an ICC of 0.6–0.75, good agreement between 0.75 and 0.9 and excellent  $>0.9$  <sup>22</sup>.

## Results

### Patient Characteristics

Patient characteristics and medications at baseline are reported in Table 1.  $n=44$  patients conducted a baseline maximal CPET.  $n=17$  were lost to follow-up.  $n=27$  were included for analysis. (88.9% male; age  $59.5 \pm 10.0$  years, body mass index [BMI]  $29.6 \pm 3.8 \text{ kg}\cdot\text{m}^{-2}$ ). The median number of exercise sessions conducted at follow up was 15 (range: 0 to 62). Five patients failed to attend at least one exercise session.

### Cardiorespiratory Fitness Change

Table 2 shows changes in key CPET variables. Despite a significant increase in exercise test duration and peak power output [watts], there was no significant change in directly-determined  $VO_{2peak}$  (mean change: 2.7%;  $0.5 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ; 95% CI: -0.6 to 1.8

ml·kg<sup>-1</sup>·min<sup>-1</sup>). There were no significant changes in peak HR or RPE (indicators of patient effort) between CPETs. Peak RER, however, was significantly higher at visit 2 compared to visit 1. Change in directly determined VO<sub>2peak</sub> remained non-significant when RER change was considered as a covariate (mean change 0.6 ml·kg<sup>-1</sup>·min<sup>-1</sup>; 95% CI: -0.6 to 1.8 ml·kg<sup>-1</sup>·min<sup>-1</sup> p=0.324).

Consistent with the increased workload, there was a significant increase in estimated peak METs (mean change: 6.7%; 0.4 METs; 95% CI: 0.1 to 0.6 METs). This corresponded to an estimated VO<sub>2peak</sub> change of 1.4 ml·kg<sup>-1</sup>·min<sup>-1</sup>. The VAT (mean change: 9.9%; 1.4 ml·kg<sup>-1</sup>·min<sup>-1</sup>; 95% CI: 0.5 to 2.3 ml·kg<sup>-1</sup>·min<sup>-1</sup>), and ventilatory efficiency slope (VE/VCO<sub>2</sub> slope) also significantly improved following CR. The mean ΔVO<sub>2</sub>/ΔWR slope was within normal limits at both visits and did not change significantly between visits. However, 19% (n=10) of all exercise tests had a ΔVO<sub>2</sub>/ΔWR slope below the lower limit of normal (<8.4 mL/min/W).

#### Agreement between Directly-Determined VO<sub>2peak</sub> and Estimated VO<sub>2peak</sub>

Correlations and measures of agreement for CPET variables are presented in Table 3. There was a significant association between directly determined VO<sub>2peak</sub> and estimated VO<sub>2peak</sub> on both pre and post- cardiac rehabilitation visits (Figure 1A and 1B). The mean bias and limits of agreement for estimated VO<sub>2peak</sub> on both tests are also presented in Table 3. The association between changes in directly-determined VO<sub>2peak</sub> and estimated VO<sub>2peak</sub> was substantially reduced (Figure 1C, r=0.527, p=0.05).

The ICC between the two measurements was not non-significant (ICC 0.358; 95% CI - 0.442 to 0.711;  $p=0.138$ ). Bland-Altman Analysis (Figure 2) showed the mean bias for changes in  $VO_{2peak}$  was less than the maximal acceptable difference ( $0.7 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ; 95% CI  $-0.4$  to  $1.8 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ;  $p=0.178$ ;  $\eta_p^2 = 0.069$ ). However, the limits of agreement (LoA) were far wider ( $-4.7$  to  $5.9 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ; lower LoA 95% CI:  $-5.1$  to  $-4.3$ ; upper LoA 95% CI:  $5.5$  to  $6.3 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ).  $VO_{2peak}$  measurement error was greater than the maximal acceptable difference in 33%. There was a significant, moderate negative correlation between  $VO_{2peak}$  measurement error (estimated  $VO_{2peak}$  minus directly determined  $VO_{2peak}$ ) and  $\Delta VO_2/\Delta WR$  slope (Figure 3,  $r=-0.496$ ,  $p<0.001$ ).

## Discussion

We found that estimated METS derived from the ACSM leg cycling equation are significantly and consistently associated with directly-determined oxygen consumption in a representative cohort of patients attending CR. However, the LoA from our Bland-Altman analysis suggest that estimated functional capacity change does not accurately reflect directly determined  $VO_{2peak}$  changes following a CR exercise training intervention. This is supported by our failure to find a significant ICC between the two measurements.

Increasing  $VO_{2peak}$  through structured exercise training improves survival<sup>23</sup> in patients with CHD and, consequently, improving  $VO_{2peak}$  remains a key objective for CR practitioners. Practitioners need to have confidence in the efficacy of the outcome measures they report. Given that CR programme outcome data are often expressed in

estimated METs, there is a requirement to examine the suitability of estimated functional capacity to accurately determine changes in  $VO_{2peak}$ .

Significant mean improvements in peak exercise time, power output and associated improvements in estimated METs following cardiac rehabilitation were not accompanied by improved mean peak oxygen consumption in the present study. These findings question the appropriateness of using estimated  $VO_{2peak}$  (METs) as a surrogate indicator of improvements in  $VO_{2peak}$ . Reporting estimated METs alone may lead to inaccurate interpretations of the efficacy of exercise interventions within rehabilitation settings.

Estimating mean changes in  $VO_{2peak}$  (through widely applied MET equations) over predicted actual  $VO_{2peak}$  by more than two-fold in this patient group. These findings are consistent with previously published data<sup>13 14</sup> which indicate poor agreement between estimates of  $VO_{2peak}$  change and directly determined  $VO_{2peak}$  change. However, our findings contradict those of Stuto and colleagues (2013) who demonstrate a lower relative improvement in functional capacity (3.85%) compared to directly determined  $VO_{2peak}$  (14.7%). The limited information provided within this study abstract limits comparison of study findings. However, these findings may have important implications when interpreting the CRF benefits of CR.

Improvements in other aspects of cardiorespiratory fitness were observed following exercise training in this cohort. VAT significantly increased following exercise-based CR. Improvements in VAT are associated with increased endurance capacity, less

blood lactate accumulation and associated acid-base metabolic perturbations<sup>24 25</sup>. Given  $VO_{2peak}$  remained unchanged, changes in the VAT are likely to have contributed to improved exercise capacity and estimated MET changes.

The failure of estimated MET change to accurately predict directly determined  $VO_{2peak}$  change may in part, be attributed to test familiarisation and improved movement economy leading to a longer test duration<sup>26 27</sup>. However, the use of a cycle ergometer as opposed to a treadmill may partially mitigate these factors. It is possible that the use of our step protocol (2 minute stages, 25W Increments) may have led to a weaker association between  $VO_2$  and work rate. Two minutes may have been inadequate time to attain  $VO_2$  steady-state. Less predictable  $VO_2$ /work rate relationships have been observed in patients with cardiovascular disease. Poor oxygen uptake kinetics resulting from poor muscle oxygen extraction, myocardial dysfunction, chronotropic incompetence and  $\beta$ -blockade all have the potential to influence the  $VO_2$ /work rate relationship<sup>28-32</sup>. Indeed, approximately one fifth of the maximal CPET's conducted demonstrated poor aerobic efficiency ( $\Delta VO_2/\Delta WR$  slope  $<8.4$  mL/min/W).  $\Delta VO_2/\Delta WR$  slope was negatively correlated with estimated  $VO_{2peak}$  measurement error ( $r=-0.496$ ,  $p<0.001$ ) indicating that estimates of  $VO_{2peak}$  over-predict directly determined  $VO_{2peak}$  when patients are aerobically 'inefficient'. Inefficient cardiometabolic responses to exercise resulting in delayed oxygen kinetics, may prolong dependence on anaerobic metabolism<sup>30</sup> during sequential work rate transitions. In such instances, the assumptions of linearity between work rate and  $VO_2$  would not apply and work rate would therefore not be indicative of  $VO_2$ . This issue is particularly pertinent above the VAT where  $VO_2$  steady-state attainment can take up to 15 minutes due to the

presence of a  $VO_2$  slow component. Steady state attainment above critical power i.e. near peak exercise, is not achieved<sup>6</sup>. With this in mind, it is doubtful that any practical CPET protocol is truly capable of predicting  $VO_{2peak}$  based on workload alone. Accurately predicting  $VO_{2peak}$  or  $VO_{2peak}$  changes in CHD patients, as evidenced by our findings and others<sup>13 14 16</sup>, poses significant challenges, particularly at an individual patient level.

Assessing functional capacity (by estimating METs) remains useful in the broad classification of baseline cardiorespiratory fitness and prognostic risk classification among participants attending for cardiac rehabilitation<sup>33</sup> However, poor agreement between estimated and directly determined changes in  $VO_{2peak}$  questions the validity of this “widely used metric” in reporting CRF changes within CR settings. Our data require further validation in larger samples of cardiac rehabilitation patients. Practitioners should explore opportunities to integrate scientifically robust exercise testing techniques, such as CPET, in evaluating clinically meaningful improvements in CRF outcomes from exercise rehabilitation.

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The authors declare that there are no conflicts of interest

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