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

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Full Title: Estimated peak functional capacity; an accurate method for assessing 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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Abstract:

Objective: 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 ± 10.0 years, body mass index 29.6 ± 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. Agreement between changes in directly determined VO_{2peak} and estimated VO_{2peak} was evaluated using Bland-Altman limits of agreement (LoA), and intraclass correlation coefficients.

Results: Directly-determined VO_{2peak} did not increase following CR (0.5 $ml \cdot kg^{-1} \cdot min^{-1}$ (2.7%); p=0.332). 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: Change in estimated VO_{2peak} derived from the ACSM leg cycling equation is not an accurate surrogate for directly-determined changes in VO_{2peak}. Our findings show poor agreement between estimates of VO_{2peak} and directly-determined VO_{2peak}. Applying estimates of VO_{2peak} to determine CRF change may over-estimate the efficacy of CR and lead to a different interpretation of study findings.

Key Words: Coronary Heart Disease, Cardiac Rehabilitation, Exercise Testing, Cardiopulmonary Exercise Testing, Metabolic Equivalents, METs, Estimated VO_{2peak}, VO_{2peak}

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Introduction

Structured exercise training is a core component of most cardiac rehabilitation (CR) programmes (Anderson*, et al.* 2016; BACPR 2012; Heran*, et al.* 2011; Taylor*, et al.* 2006). The efficacy of exercise-based CR is predicated on appropriately personalised exercise training (Uddin*, et al.* 2015). 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] (Mezzani*, et al.* 2013). 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 (on treadmill or cycle ergometry) may be used to estimate VO_{2peak} (ACSM 2013; Buckley*, et al.* 2016). Estimates of VO_{2peak} are commonly expressed as estimated metabolic equivalents (METs). Although recently challenged (Buckley, et al. 2016) equations for estimating VO_{2peak} and METs are traditionally based on an assumed linear relationship between VO_2 and work rate (ACSM 2013). Despite contradictory evidence, (Byrne*, et al.* 2005) one MET (corresponding to resting metabolic rate) is widely accepted to equate to a VO_2 of 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$ (Wasserman*, et al.* 2011). Changes in estimated functional capacity during an exercise test are commonly expressed in multiples of resting metabolic rate. This metric allows comparisons of participant results from exercise testing undertaken using estimated versus direct determinated VO_{2peak}. 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 (ACPICR 2015). However, estimates of functional capacity may not accurately quantify VO_{2peak}, particularly during treadmill protocols (Milani*, et al.* 1995; Myers*, et al.* 1991; Pinkstaff*, et al.* 2011). 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 (Froelicher*, et al.* 1984; Kavanagh*, et al.* 2002). However, to our knowledge, the only relevant investigation examining the suitability of estimating VO_{2peak} change from peak METs found no significant correlation (r=0.24) 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} (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 did not appear to reflect improvement in directly determined VO_{2peak}. However, this was not specifically addressed by Stuto*, et al.* (2013). We therefore aimed to investigate the accuracy of estimating changes in VO_{2peak} using the American College of Sports Medicine (ACSM 2013) 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 (Brodie*, et al.* 2006; Doherty & Lewin 2012). 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 (ACPICR 2015). 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 a CPET to volitional exhaustion or limiting symptoms 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 (Beaver, *et al.* 1986) 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 (Wasserman, et al. 2011). Estimated peak METs were calculated using the ACSM (2013) leg cycling equation:

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

Where kg·m is Kilogram metres (and where 1W is equal to 6.12 kg·m·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 (±) 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 (η_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 (Berg & Latin 2008). Intraclass correlation coefficients (ICC) and Bland-Altman analysis were used to assess agreement between measurement methods (Atkinson & Nevill 1998; Bland & Altman 1999). The maximum acceptable difference between assessment methods was set at 3.5 ml·kg^{-1}·min^{-1} (1 MET). A recent sampling of studies expressing exercise capacity in terms of survival benefit, showed that a 1 MET increase in CRF (including estimated functional capacity or directly-determined VO_2) carried significant survival benefits in both healthy adults and patients with CHD [ranging from 8-35%] (Ross, *et al.* 2016). Further, the AHA scientific statement on importance of assessing CRF in clinical practice refers to a 1 MET improvement as a clinically significant improvement in CRF (Ross, *et al.* 2016). 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 (Atkinson & Nevill 1998).

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 ± 10.0 years, body mass index [BMI] 29.6 ± 3.8 $kg \cdot m^{-2}$). 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 Changes

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 $ml \cdot kg^{-1} \cdot min^{-1}$; 95% CI: -0.6 to 1.8 $ml \cdot kg^{-1} \cdot min^{-1}$). 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_{2peak} remained non-significant when RER change was considered as a covariate (mean change 0.6 $ml \cdot kg^{-1} \cdot min^{-1}$; 95% CI: -0.6 to 1.8 $ml \cdot kg^{-1} \cdot min^{-1}$ p=0.324).

Consistent with the increased workload, there was a significant increase in estimated functional capacity or peak METs (mean change: 6.7%; 0.4 METs; 95% CI: 0.1 to 0.6 METs). This corresponded to an estimated VO_{2peak} change of 1.4 ml·kg^{-1}·min^{-1}. The VAT (mean change: 9.9%; 1.4 ml·kg^{-1}·min^{-1}; 95% CI: 0.5 to 2.3 ml·kg^{-1}·min^{-1}), and ventilatory efficiency slope (VE/VCO_2 slope) also significantly improved following CR. The mean $\Delta VO_2/\Delta WR$ 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 $\Delta VO_2/\Delta WR$ slope below the lower limit of normal (<8.4 mL/min/W).

Agreement between Directly-Determined VO_{2peak} and Estimated VO_{2peak}

Correlations and measures of agreement for CPET variables are presented in Table 3. There was a significant association between directly determined VO_{2peak} and estimated VO_{2peak} on both pre and post- cardiac rehabilitation visits (Figure 1A and 1 B). The mean bias and limits of agreement for estimated VO_{2peak} on both tests are also presented in Table 3. The association between changes in directly-determined VO_{2peak} and estimated VO_{2peak} 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 ml·kg^{-1}·min^{-1}; 95% CI -0.4 to 1.8 ml·kg^{-1}·min^{-1}; p=0.178; η_p^2= 0.069). However, the limits of agreement (LoA) were considerably wider (-4.7 to 5.9 ml·kg^{-1}·min^{-1}; lower LoA 95% CI: -5.1 to -4.3; upper LoA

95% CI: 5.5 to 6.3 $ml \cdot kg^{-1} \cdot min^{-1}$). VO_{2peak} measurement error was higher than the maximal clinically acceptable difference in 33% of participants. There was a significant, moderate negative correlation between VO_{2peak} measurement error (estimated VO_{2peak} minus directly determined VO_{2peak}) and the $\Delta VO_2/\Delta WR$ slope at visit 1 and 2 (Figure 3, $r=-0.496$, $p<0.001$).

Discussion

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 changes in estimated functional capacity do 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 (Vanhees, *et al.* 1995) 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 from functional capacity testing are often expressed in estimated METs, there is a requirement to examine the suitability of estimated functional capacity to accurately reflect 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 (Froelicher, et al. 1984; Milani, et al. 1995) 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 described 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 the study findings. However, these findings may have important implications when interpreting the CRF benefits of CR.

Improvements in other CPET components of cardiorespiratory fitness were observed following exercise training in this cohort. The 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 (Ghosh 2004; Sullivan*, et al.* 1989). 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 (Fletcher*, et al.* 2001; Russell*, et al.* 1998). However, the use of a cycle ergometer as opposed to a treadmill may partially mitigate these influences. 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, especially in patients with CHD. 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 β-blockade all have the potential to influence the VO_2/work rate relationship (Belardinelli*, et al.* 2003; Brubaker & Kitzman 2011; Hughson 1984; Mezzani*, et al.* 2009; Poole*, et al.* 2012). 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 also prolong dependence on anaerobic metabolism (Mezzani, et al. 2009) 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 of the VO_2-work rate relationship 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 (Mezzani, et al. 2013). With this in mind, it is doubtful that any practical CPET protocol is truly capable of predicting VO_2 based on workload alone. Accurately estimating VO_{2peak} , moreover VO_{2peak} changes in CHD patients, as evidenced by our findings and others (Froelicher, et al. 1984; Milani, et al. 1995; Stuto, et al. 2013), 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 (Taylor*, et al.* 2016). However, poor agreement between estimated and directly-determined changes in VO_{2peak} questions the validity of this “widely used metric” when 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 demonstrating clinically meaningful improvements in CRF outcomes from exercise rehabilitation.

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References

ACPICR. *Standards for physical activity and exercise in the cardiovascular population* (2015). Association of Chartered Physiotherapists in Cardiac Rehabilitation

ACSM. *ACSM's Guidelines for exercise testing and prescription* (2013). Wolters Kluwer/Lippincott Williams & Wilkins Health, Philadelphia.

Anderson L, Oldridge N, Thompson DR, Zwisler A-D, Rees K, Martin N and Taylor RS. Exercise-Based Cardiac Rehabilitation for Coronary Heart DiseaseCochrane Systematic Review and Meta-Analysis. *Journal of the American College of Cardiology* (2016); **67**: 1-12.

Atkinson G and Nevill A. Statistical Methods For Assessing Measurement Error (Reliability) in Variables Relevant to Sports Medicine. *Sports Med* (1998); **26**: 217-238.

BACPR. *Standards and Core Components for Cardiovascular Disease Prevention and Rehabilitation* (2012). Available at http://www.bacpr.com/resources/.

Beaver WL, Wasserman K and Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* (1986); **60**: 2020-2027.

Belardinelli R, Lacalaprice F, Carle F, Minnucci A, Cianci G, Perna G and D'Eusanio G. Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing. *Eur Heart J* (2003); **24**: 1304-1313.

Berg KE and Latin RW. *Essentials of research methods in health, physical education, exercise science, and recreation* (2008). Lippincott Williams & Wilkins.

Bland JM and Altman DG. Measuring agreement in method comparison studies. *Statistical Methods in Medical Research* (1999); **8**: 135-160.

Brodie D, Bethell H and Breen S. Cardiac rehabilitation in England: a detailed national survey. *European Journal of Cardiovascular Prevention & Rehabilitation* (2006); **13**: 122-128.

Brubaker PH and Kitzman DW. Chronotropic Incompetence: Causes, Consequences, and Management. *Circulation* (2011); **123**: 1010-1020.

Buckley JP, Cardoso FMF, Birkett ST and Sandercock GRH. Oxygen Costs of the Incremental Shuttle Walk Test in Cardiac Rehabilitation Participants: An Historical and Contemporary Analysis. *Sports Med* (2016): 1-10.

Byrne NM, Hills AP, Hunter GR, Weinsier RL and Schutz Y. Metabolic equivalent: one size does not fit all. *Journal of Applied physiology* (2005); **99**: 1112-1119.

Doherty P and Lewin R. The RAMIT trial, a pragmatic RCT of cardiac rehabilitation versus usual care: what does it tell us? *Heart* (2012); **98**: 605-606.

Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, Froelicher VF, Leon AS, Piña IL and Rodney R. Exercise standards for testing and training a statement for healthcare professionals from the American Heart Association. *Circulation* (2001); **104**: 1694-1740.

Froelicher V, Jensen D, Genter F, Sullivan M, McKirnan MD, Witztum K, Scharf J, Strong ML and Ashburn W. A randomized trial of exercise training in patients with coronary heart disease. *JAMA* (1984); **252**: 1291-1297.

Ghosh AK. Anaerobic Threshold: Its Concept and Role in Endurance Sport. *The Malaysian Journal of Medical Sciences : MJMS* (2004); **11**: 24-36.

Heran BS, Chen J, Ebrahim S, Moxham T, Oldridge N, Rees K, Thompson DR and Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* (2011); **7**.

Hughson RL. Alterations in the oxygen deficit-oxygen debt relationships with beta-adrenergic receptor blockade in man. *The Journal of Physiology* (1984); **349**: 375-387.

Kavanagh T, Mertens DJ, Hamm LF, Beyene J, Kennedy J, Corey P and Shephard RJ. Prediction of Long-Term Prognosis in 12 169 Men Referred for Cardiac Rehabilitation. *Circulation* (2002); **106**: 666-671.

Mezzani A, Agostoni P, Cohen-Solal A, Corrà U, Jegier A, Kouidi E, Mazic S, Meurin P, Piepoli M, Simon A, Laethem CV and Vanhees L. Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report from the Exercise Physiology Section of the European Association for Cardiovascular Prevention and Rehabilitation. *European Journal of Cardiovascular Prevention & Rehabilitation* (2009); **16**: 249-267.

Mezzani A, Hamm LF, Jones AM, McBride PE, Moholdt T, Stone JA, Urhausen A and Williams MA. Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation and the Canadian Association of Cardiac Rehabilitation. *European Journal of Preventive Cardiology* (2013); **20**: 442-467.

Milani RV, Lavie CJ and Spiva H. Limitations of estimating metabolic equivalents in exercise assessment in patients with coronary artery disease. *The American journal of cardiology* (1995); **75**: 940-942.

Myers J, Buchanan N, Walsh D, Kraemer M, McAuley P, Hamilton-Wessler M and Froelicher VF. Comparison of the ramp versus standard exercise protocols. *Journal of the American College of Cardiology* (1991); **17**: 1334-1342.

Pinkstaff S, Peberdy MA, Kontos MC, Fabiato A, Finucane S and Arena R. Overestimation of Aerobic Capacity With the Bruce Treadmill Protocol in Patients Being Assessed for Suspected Myocardial Ischemia. *Journal of Cardiopulmonary Rehabilitation and Prevention* (2011); **31**: 254-260.

Poole DC, Hirai DM, Copp SW and Musch TI. Muscle oxygen transport and utilization in heart failure: implications for exercise (in) tolerance. *American Journal of Physiology-Heart and Circulatory Physiology* (2012); **302**: H1050-H1063.

Ross R, Blair SN, Arena R, Church TS, Després J-P, Franklin BA, Haskell WL, Kaminsky LA, Levine BD and Lavie CJ. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association. *Circulation* (2016): CIR. 0000000000000461.

Russell SD, McNeer FR, Beere PA, Logan LJ and Higginbotham MB. Improvement in the mechanical efficiency of walking: An explanation for the “placebo effect” seen during repeated exercise testing of patients with heart failure. *Am Heart J* (1998); **135**: 107-114.

Stuto A, Armaro B, Cosentino E, Ambu A, Bottaro G, Lo Giudice A, Canonico G, Vitale L, Carpenzano G and Basile G. Cardiopulmonary exercise stress testing vs standard exercise stress testing to estimate the actual changes in functional capacity after cardiac rehabilitation in older patients. *European Heart Journal* (2013); **34**.

Sullivan M, Higginbotham M and Cobb F. Exercise training in patients with chronic heart failure delays ventilatory anaerobic threshold and improves submaximal exercise performance. *Circulation* (1989); **79**: 324-329.

Taylor C, Tsakirides C, Moxon J, Moxon JW, Dudfield M, Witte KK, Ingle L and Carroll S. Submaximal fitness and mortality risk reduction in coronary heart disease: a retrospective cohort study of community-based exercise rehabilitation. *BMJ open* (2016); **6**: e011125.

Taylor RS, Unal B, Critchley JA and Capewell S. Mortality reductions in patients receiving exercise-based cardiac rehabilitation: how much can be attributed to cardiovascular risk factor improvements? *European Journal of Cardiovascular Prevention & Rehabilitation* (2006); **13**: 369-374.

Uddin J, Zwisler A-D, Lewinter C, Moniruzzaman M, Lund K, Tang LH and Taylor RS. Predictors of exercise capacity following exercise-based rehabilitation in patients with coronary heart disease and heart failure: A meta-regression analysis. *European Journal of Preventive Cardiology* (2015).

Vanhees L, Fagard R, Thijs L and Amery A. Prognostic value of training-induced change in peak exercise capacity in patients with myocardial infarcts and patients with coronary bypass surgery. *The American journal of cardiology* (1995); **76**: 1014-1019.

Wasserman K, Hansen J, Sue D, Stringer W, Sietsema K, Sun X-G and Whipp B. *Principles of exercise testing and interpretation: Including pathophysiology and clinical applications* (2011). Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia.

Table 1 – Patient Characteristics and Medication

Variable	All Patients
Participants	*n*=27
Sex (% male)	*n*=24 (88.9)
Age (Years)	59.5 ± 10.0
BMI (kg·m^{-2})	29.6 ± 3.8
Waist Circumference (cm)	106.1 ± 10.0
LVEF (%)	58.9 ± 9.2
SBP (mmHg)	140 ± 19
DBP (mmHg)	83 ± 10
HR (bpm)	60 ± 7
MI (%)	*n*=16 (59.3)
PCI (%)	*n*=10 (37.0)
CABG (%)	*n*=1 (3.7)
PMH MI (%)	*n*=12 (44.4)
PMH CABG (%)	*n*=3 (11.1)
Type 2 Diabetes (%)	*n*=5 (18.5)
Asthma (%)	*n*=1 (3.7)
COPD (%)	*n*=2 (7.4)
Atrial Fibrillation (%)	*n*=3 (11.1)
Smoking (%)	*n*=4 (14.8)
Aspirin (%)	*n*=26 (96.2)
Ticagrelor (%)	*n*=10 (37.0)
Clopidogrel (%)	*n*=15 (55.6)
Beta-Blocker (%)	*n*=22 (81.5)
ACE-Inhibitor (%)	*n*=16 (59.3)
Statin (%)	*n*=26 (96.2)

BMI = Body Mass Index; EF = Ejection Fraction; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HR = Resting HR; MI = Myocardial Infarction; PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery Bypass Graft; PMH = Past Medical History; COPD = Chronic Obstructive Pulmonary Disease; ACE = Angiotensin Converting Enzyme

Table 2 - Cardiorespiratory Fitness Changes

	Visit 1 (±SD)	Visit 2 (±SD)	Mean Change (95% CI)	*P*-Value	η_p^2
VO_{2peak} (ml·kg^{-1}·min^{-1})	21.9 ± 7.6	22.5 ± 7.2	0.5 (-0.6 to 1.8)	0.332	0.036
Estimated VO_{2peak} (ml·kg^{-1}·min^{-1})	20.9 ± 6.4	22.2 ± 6.7	1.3 (0.4 to 2.2)	0.006*	0.254ǂ
Estimated peak METs	6.0 ± 1.8	6.4 ± 1.9	0.4 (0.1 to 0.6)	0.006*	0.254ǂ
Exercise Test Duration (Sec)	585.4 ± 228.1	651.8 ± 250.0	66.4 (9.9 to 122.9)	0.023*	0.184ǂ
Peak Watts	111.1 ± 49.2	118.5 ± 48.8	7.4 (1.4 to 13.4)	0.018*	0.198ǂ
VO_2 at VAT (ml·kg^{-1}·min^{-1})	14.1 ± 4.5	15.5 ± 5.3	1.4 (0.5 to 2.3)	0.005*	0.276ǂ
$\Delta VO_2/\Delta WR$ slope	10.2 ± 2.0	10.2 ± 2.1	0.1 (-0.7 to 0.9)	0.829	0.002
VE/VCO_2 slope	32.1 ± 6.9	28.9 ± 5.8	-3.2 (-5.0 to -1.3)	0.002*	0.321ǂ
Peak RER	1.02 ± 0.09	1.06 ± 0.7	0.04 (0.2 to 0.07)	0.002*	0.330ǂ
Peak HR (bpm)	130 ± 25	129 ± 24	-1 (-6 to 4)	0.714	0.005
Peak Borg Score	17.7 ± 2.1	16.9 ± 2.6	-0.8 (-2.1 to 0.4)	0.192	0.064
Peak SBP (mmHg)	182 ± 26	185 ± 22	3 (-6 to 12)	0.485	0.019
Peak DBP (mmHg)	90 ± 14	97 ± 14	6 (0 to 12)	0.037*	0.157

VO_{2peak} = Peak Oxygen Uptake; VAT = Ventilatory Anaerobic Threshold; VE/VCO_2 = Ventilatory Efficiency with Respect to CO_2 Elimination; $\Delta VO_2/\Delta WR$ slope = Change in Oxygen Uptake Vs. Change in Work Rate slope; RER = Respiratory Exchange Ratio; HR = Heart Rate; BPM = Beats per Minute; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; sec=seconds; METs = Metabolic Equivalents

*= statistically significant; ǂ = Large Effect Size

Table 3 – Measures of Agreement between Measured and Estimated VO_{2peak}

	Correlation (r)	Mean Bias ($ml \cdot kg^{-1} \cdot min^{-1}$)	LoA ($ml \cdot kg^{-1} \cdot min^{-1}$)	ICC (95% CI)
VO_{2peak} Vs. Estimated VO_{2peak} at Visit 1	0.958*	-1 .0*	-5.6 to 3.6	0.967 (0.921 to 0.986)*
VO_{2peak} Vs. Estimated VO_{2peak} at Visit 2	0.945*	0.3	-4.8 to 4.3	0.971 (0.936 to 0.987)*
Change in Estimated VO_{2peak} Vs. Measured VO_{2peak}	0.527*	0.7	-4.6 to 5.9	0.358 (-0.442 to 0.711)

r = Correlation Coefficient; LoA = Limits of Agreement; ICC = Intraclass Correlation; VO_{2peak} = Peak Oxygen Uptake

*= Statistically Significant

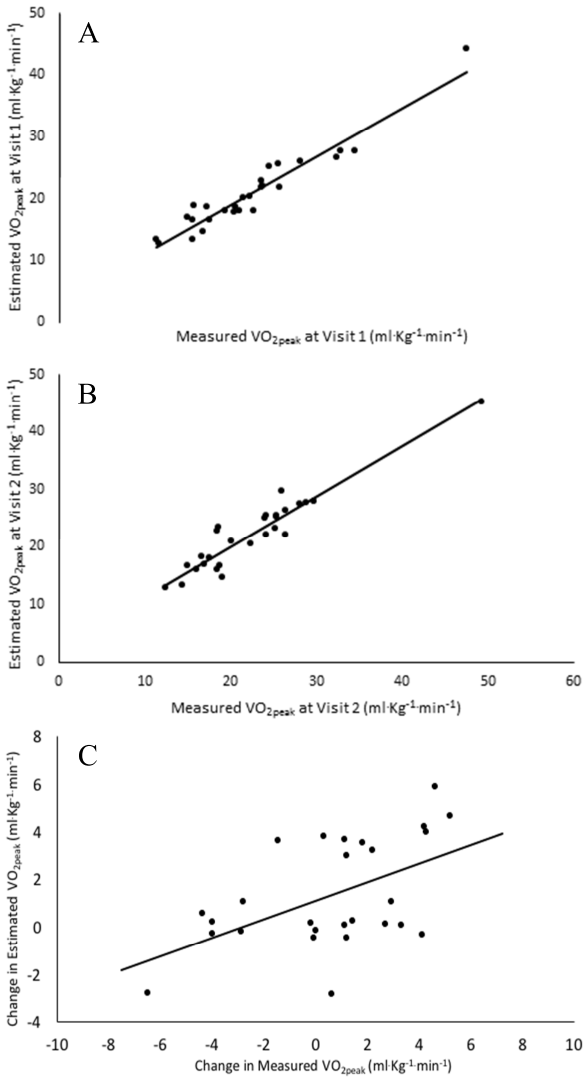

Figure 1 – Correlations showing the relationship between directly determined VO_{2peak} and estimated VO_{2peak} for visit 1 (panel A; r = 0.958, p<0.001) and visit 2 (panel B; r=0.945, p<0.001) Panel C shows correlation between directly determined VO_{2peak} change and estimated VO_{2peak} change between visit 1 and 2 (r=0.527, p<0.05).

VO_{2peak} = peak oxygen uptake

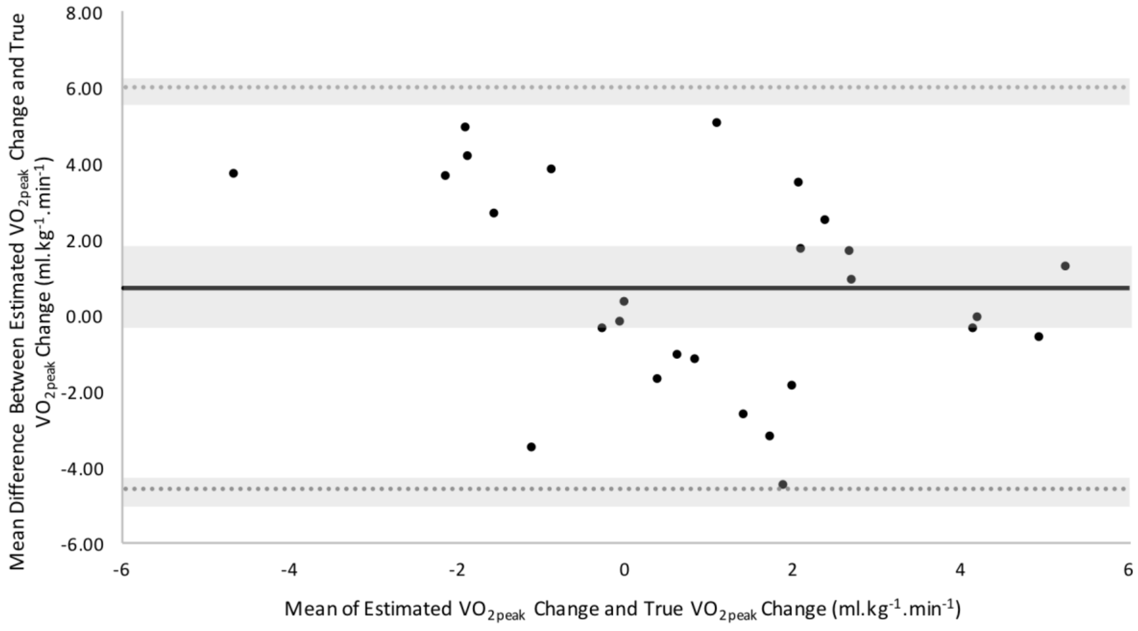

Figure 3 – Bland-Altman plot showing mean bias (0.7 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$), LoA (-4.6.3 to 5.9 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$) with 95% CI (grey shaded area).

VO_{2peak} = peak oxygen uptake

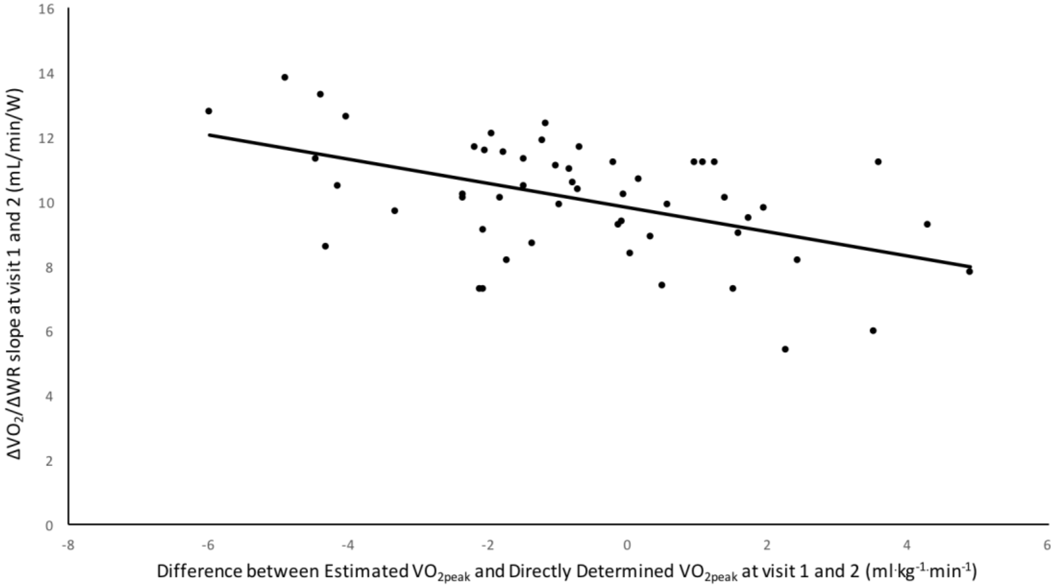

Figure 4 – Correlation showing a significant, moderate negative correlation between $\Delta VO_2/\Delta WR$ slope and estimated VO2peak measurement error