Nichols, S., Gleadall-Siddall, D.O., Antony, R., Clark, A.L., Cleland, J.G.F. , Carroll, S. and Ingle, L. (2018) Estimated peak functional capacity: an accurate method for assessing change in peak oxygen consumption after cardiac rehabilitation? *Clinical Physiology and Functional Imaging*, 38(4), pp. 681-688.

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

Nichols, S., Gleadall-Siddall, D.O., Antony, R., Clark, A.L., Cleland, J.G.F. , Carroll, S. and Ingle, L. (2018) Estimated peak functional capacity: an accurate method for assessing change in peak oxygen consumption after cardiac rehabilitation? *Clinical Physiology and Functional Imaging*, 38(4), pp. 681-688. (doi:[10.1111/cpf.12468](https://doi.org/10.1111/cpf.12468))

This article may be used for non-commercial purposes in accordance with [Wiley Terms and Conditions for Self-Archiving](#).

<http://eprints.gla.ac.uk/147393/>

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 $\text{VO}_{2\text{peak}}$ changes after cardiac rehabilitation

***Nichols, S¹., Gleadall-Sidall, D.O²., Antony, R³., Clark, A.L³., Cleland, J.G.F⁴., Carroll S², Ingle, L²,**

Clinicaltrials.gov identifier: NCT01761448

*Address for correspondence

¹ Sport and Exercise Science

School of Biomedical Science

Catherine Cookson Building

Faculty of Medical Sciences

Newcastle University

Newcastle upon Tyne

NE2 4HH

Tel: 01482 466314

Fax: 01482 463855

Email: S.Nichols@hull.ac.uk

Sport, Health and Exercise Science

University of Hull

Cottingham Road

Hull

HU6 7RX

³Academic Cardiology

Castle Hill Hospital,

Castle Road,

Cottingham,

HU16 5JQ

⁴Imperial College London

Faculty of Medicine, National Heart and Lung Institute

London

SW3 6LY

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

Word Count 2427 exc. abstract

Abstract:

Objective: Maximal cardiopulmonary exercise testing (CPET) is the “gold standard” method of determining $\text{VO}_{2\text{peak}}$. When CPET is unavailable, $\text{VO}_{2\text{peak}}$ may be estimated from treadmill or cycle ergometer workloads and expressed as estimated metabolic equivalents (METs). Cardiac rehabilitation (CR) programmes use estimated $\text{VO}_{2\text{peak}}$ (METs) to report changes in cardiorespiratory fitness (CRF). However, the accuracy of determining changes in $\text{VO}_{2\text{peak}}$ 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 $29.6 \pm 3.8 \text{ kg}\cdot\text{m}^{-2}$) performed maximal CPET before and after an exercise based CR intervention. $\text{VO}_{2\text{peak}}$ 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 $\text{VO}_{2\text{peak}}$ and $\text{VO}_{2\text{peak}}$ estimated from METs was tested using Bland-Altman limits of agreement (LoA), and intraclass correlation coefficients.

Results: Directly determined $\text{VO}_{2\text{peak}}$ did not increase significantly following CR ($0.5 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (2.7%); $p=0.332$). In contrast, estimated $\text{VO}_{2\text{peak}}$ increased significantly (0.4 METs ; $1.4 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; 6.7%; $p=0.006$). The mean bias for estimated $\text{VO}_{2\text{peak}}$ versus directly-determined $\text{VO}_{2\text{peak}}$ was $0.7 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (LoA -4.7 to $5.9 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Aerobic efficiency, ($\Delta\text{VO}_2/\Delta\text{WR}$ slope) was significantly associated with estimated $\text{VO}_{2\text{peak}}$ 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

Clinicaltrial.gov identifier: NCT01761448

Introduction

Structured exercise training is a core component of most cardiac rehabilitation (CR) programmes ¹⁻⁴. The efficacy of exercise-based CR is predicated on appropriately personalised exercise training ⁵. 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] ⁶. 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} ^{7 8}. Estimates of VO_{2peak} are often expressed as estimated metabolic equivalents (METs). Although recently challenged ⁸ equations for estimating VO_{2peak} and METs are traditionally based on an assumed linear relationship between VO_2 and work rate ⁷. One MET (corresponding to resting metabolic rate) is assumed to equate to a VO_2 of $3.5 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ⁹. 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 ¹⁰. However, estimates of functional capacity may not accurately quantify VO_{2peak} , particularly during treadmill protocols ¹¹⁻¹³. 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 ^{14 15}. However, to our knowledge, the only relevant investigation in to 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. ¹⁶. We therefore aimed to investigate the accuracy of estimating changes in VO_{2peak} using the American College of Sports Medicine ⁷ 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 ^{17 18}. 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 ¹⁰. 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 ¹⁹ 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 ⁹. Estimated peak METs were calculated using the ACSM ⁷ 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 $6.12 \text{ kg} \cdot m \cdot min^{-1}$) and BM is

patient body mass. The term 'directly-determined' $\text{VO}_{2\text{peak}}$ and 'estimated $\text{VO}_{2\text{peak}}$ ' 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 η^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 ²⁰. Intraclass correlation coefficients (ICC) and Bland-Altman analysis were used to assess agreement between measurement methods ^{21 22}. 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 ²².

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 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 $ml \cdot kg^{-1} \cdot min^{-1}$; 95% CI: -0.6 to 1.8

ml·kg⁻¹·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·kg⁻¹·min⁻¹; 95% CI: -0.6 to 1.8 ml·kg⁻¹·min⁻¹ 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_{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/VCO₂ slope) also significantly improved following CR. The mean ΔVO₂/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 ΔVO₂/ΔWR 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 1B). 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 ($0.7 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; 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 survival²³ 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^{13 14} 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 ^{24 25}.

Given $\text{VO}_{2\text{peak}}$ 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 $\text{VO}_{2\text{peak}}$ change may in part, be attributed to test familiarisation and improved movement economy leading to a longer test duration ^{26 27}. 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 β -blockade all have the potential to influence the VO_2 /work rate relationship ²⁸⁻³². Indeed, approximately one fifth of the maximal CPET's conducted demonstrated poor aerobic efficiency ($\Delta\text{VO}_2/\Delta\text{WR}$ slope <8.4 mL/min/W). $\Delta\text{VO}_2/\Delta\text{WR}$ slope was negatively correlated with estimated $\text{VO}_{2\text{peak}}$ measurement error ($r=-0.496$, $p<0.001$) indicating that estimates of $\text{VO}_{2\text{peak}}$ over-predict directly determined $\text{VO}_{2\text{peak}}$ when patients are aerobically 'inefficient'. Inefficient cardiometabolic responses to exercise resulting in delayed oxygen kinetics, may prolong dependence on anaerobic metabolism ³⁰ 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 ⁶. With this in mind, it is doubtful that any practical CPET protocol is truly capable of predicting $\text{VO}_{2\text{peak}}$ based on workload alone. Accurately predicting $\text{VO}_{2\text{peak}}$ or $\text{VO}_{2\text{peak}}$ changes in CHD patients, as evidenced by our findings and others ^{13 14 16}, 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 ³³ However, poor agreement between estimated and directly determined changes in $\text{VO}_{2\text{peak}}$ 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.

Acknowledgements: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

The authors declare that there are no conflicts of interest

References

1. BACPR. Standards and Core Components for Cardiovascular Disease Prevention and Rehabilitation. 2012. <http://www.bacpr.com/resources/>.
2. Taylor RS, Unal B, Critchley JA, et al. 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(3):369-74. doi: 10.1097/01.hjr.0000199492.00967.11
3. Anderson L, Oldridge N, Thompson DR, et al. Exercise-Based Cardiac Rehabilitation for Coronary Heart DiseaseCochrane Systematic Review and Meta-Analysis. *Journal of the American College of Cardiology* 2016;67(1):1-12. doi: 10.1016/j.jacc.2015.10.044
4. Heran BS, Chen J, Ebrahim S, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2011;7
5. Uddin J, Zwisler A-D, Lewinter C, et al. 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 doi: 10.1177/2047487315604311
6. Mezzani A, Hamm LF, Jones AM, et al. 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(3):442-67. doi: 10.1177/2047487312460484
7. ACSM. ACSM's Guidelines for exercise testing and prescription. 9th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health 2013.
8. Buckley JP, Cardoso FMF, Birkett ST, et al. Oxygen Costs of the Incremental Shuttle Walk Test in Cardiac Rehabilitation Participants: An Historical and Contemporary Analysis. *Sports Med* 2016:1-10. doi: 10.1007/s40279-016-0521-1
9. Wasserman K, Hansen J, Sue D, et al. Principles of exercise testing and interpretation: Including pathophysiology and clinical applications. Fifth ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins 2011.
10. ACPICR. Standards for physical activity and exercise in the cardiovascular population. 3rd ed: Association of Chartered Physiotherapists in Cardiac Rehabilitation 2015.
11. Myers J, Buchanan N, Walsh D, et al. Comparison of the ramp versus standard exercise protocols. *Journal of the American College of Cardiology* 1991;17(6):1334-42. doi: 10.1016/S0735-1097(10)80144-5
12. Pinkstaff S, Peberdy MA, Kontos MC, et al. 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(4):254-60. doi: 10.1097/HCR.0b013e318211e3ed

13. Milani RV, Lavie CJ, Spiva H. Limitations of estimating metabolic equivalents in exercise assessment in patients with coronary artery disease. *The American journal of cardiology* 1995;75(14):940-42.
14. Froelicher V, Jensen D, Genter F, et al. A randomized trial of exercise training in patients with coronary heart disease. *JAMA* 1984;252(10):1291-97.
15. Kavanagh T, Mertens DJ, Hamm LF, et al. Prediction of Long-Term Prognosis in 12 169 Men Referred for Cardiac Rehabilitation. *Circulation* 2002;106(6):666-71. doi: 10.1161/01.cir.0000024413.15949.ed
16. Stuto A, Armario B, Cosentino E, et al. 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(suppl 1) doi: 10.1093/eurheartj/ehs309.P3382
17. Doherty P, Lewin R. The RAMIT trial, a pragmatic RCT of cardiac rehabilitation versus usual care: what does it tell us? *Heart* 2012;98(8):605-06. doi: 10.1136/heartjnl-2012-301728
18. Brodie D, Bethell H, Breen S. Cardiac rehabilitation in England: a detailed national survey. *European Journal of Cardiovascular Prevention & Rehabilitation* 2006;13(1):122-28. doi: 10.1097/01.hjr.0000192741.04103.d3
19. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986;60(6):2020-27.
20. Berg KE, Latin RW. Essentials of research methods in health, physical education, exercise science, and recreation: Lippincott Williams & Wilkins 2008.
21. Bland JM, Altman DG. Measuring agreement in method comparison studies. *Statistical Methods in Medical Research* 1999;8(2):135-60. doi: 10.1177/096228029900800204
22. Atkinson G, Nevill A. Statistical Methods For Assessing Measurement Error (Reliability) in Variables Relevant to Sports Medicine. *Sports Med* 1998;26(4):217-38. doi: 10.2165/00007256-199826040-00002
23. Vanhees L, Fagard R, Thijs L, et al. 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(14):1014-19.
24. Ghosh AK. Anaerobic Threshold: Its Concept and Role in Endurance Sport. *The Malaysian Journal of Medical Sciences : MJMS* 2004;11(1):24-36.
25. Sullivan M, Higginbotham M, Cobb F. Exercise training in patients with chronic heart failure delays ventilatory anaerobic threshold and improves submaximal exercise performance. *Circulation* 1989;79(2):324-29.
26. Fletcher GF, Balady GJ, Amsterdam EA, et al. Exercise standards for testing and training a statement for healthcare professionals from the American Heart Association. *Circulation* 2001;104(14):1694-740.
27. Russell SD, McNeer FR, Beere PA, et al. 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(1):107-14. doi: [http://dx.doi.org/10.1016/S0002-8703\(98\)70350-3](http://dx.doi.org/10.1016/S0002-8703(98)70350-3)

28. Brubaker PH, Kitzman DW. Chronotropic Incompetence: Causes, Consequences, and Management. *Circulation* 2011;123(9):1010-20. doi: 10.1161/circulationaha.110.940577
29. Poole DC, Hirai DM, Copp SW, et al. Muscle oxygen transport and utilization in heart failure: implications for exercise (in) tolerance. *American Journal of Physiology-Heart and Circulatory Physiology* 2012;302(5):H1050-H63.
30. Mezzani A, Agostoni P, Cohen-Solal A, et al. 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(3):249-67. doi: 10.1097/HJR.0b013e32832914c8
31. Hughson RL. Alterations in the oxygen deficit-oxygen debt relationships with beta-adrenergic receptor blockade in man. *The Journal of Physiology* 1984;349(1):375-87. doi: 10.1113/jphysiol.1984.sp015161
32. Belardinelli R, Lacalaprice F, Carle F, et al. Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing. *Eur Heart J* 2003;24(14):1304-13. doi: 10.1016/S0195-668X(03)00210-0 [published Online First: 2003/07/23]
33. Taylor C, Tsakirides C, Moxon J, et al. Submaximal fitness and mortality risk reduction in coronary heart disease: a retrospective cohort study of community-based exercise rehabilitation. *BMJ open* 2016;6(6):e011125.