Impact of Exercise Training Response on Quality of Life and Cardiovascular Risk Factor Profiles in People with Coronary Artery Disease: Insights from the HIIT or MISS UK trial

Abstract:

Objective: To compare the characteristics of "responders" and "non-responders" to 8-weeks of exercise training to determine differences in key cardiovascular disease outcomes in people with coronary artery disease (CAD).

Design: Secondary analysis of data from the HIIT or MISS UK trial.

Setting: Six outpatient National Health Service cardiac rehabilitation centers in the UK. In people with CAD attending cardiac rehabilitation, the HIIT or MISS UK trial reported that short-term, low-volume, high intensity interval training (HIIT) was more effective than moderate intensity steady state (MISS) exercise training for improving peak oxygen uptake (VO_2peak).

Participants: 382 participants with CAD (mean age: 58.8 ± 9.6 years; mean BMI: 29.0 ± 4.3 $kg \cdot m^{-2}$).

Main Outcome Measures: We identified "responders" and "non-responders" based on a meaningful change in peak oxygen uptake, using two established methods. Key clinical, quality of life, and cardiopulmonary exercise test (CPET)-derived outcomes were compared between groups.

Results: Responders were more likely to be younger (P<0.05), and demonstrate greater improvement in CPET-related outcomes e.g. oxygen uptake efficiency slope (OUES), ventilatory efficiency (VE/VCO_2 slope), and peak power output (all comparisons, P<0.001). Responders were more likely to observe improvements in quality of life (EQ-5D-5L; mean Δ 13.6 v mean Δ 9.4; P=0.045), and HDL-cholesterol (mean Δ 0.09 $mmol.L^{-1}$ v mean Δ 0.04 $mmol.L^{-1}$; P=0.004), compared to non-responders.

Conclusions: In people with CAD attending cardiac rehabilitation, "responders" to exercise training were more likely to be younger, and demonstrate greater improvements in health-related QoL and HDL-cholesterol.

Keywords: training volume; Intensity; heart disease; HIIT; exercise dose; exercise prescription

Abbreviations:

CAD - coronary artery disease
HIIT - high intensity interval training
MISS - moderate intensity steady state
CPET - cardiopulmonary exercise test
VO_2peak - peak oxygen uptake
OUES - oxygen uptake efficiency slope
VE/VCO_2 slope - slope of the relation between minute ventilation and carbon dioxide production
BMI - body mass index
HDL-c - high density lipoprotein- cholesterol
CR - cardiac rehabilitation
SSPCR - Section on Secondary Prevention and Cardiac Rehabilitation
EAPC - European Association of Prevention Cardiology
UK - United Kingdom
QoL - quality of life
VE - ventilation
CONSORT - Consolidated Standards of Reporting Trials
MI - myocardial infarction
CABG - coronary artery bypass graft
PCI - percutaneous coronary intervention
hs-CRP - high sensitivity C-reactive protein
eGFR - estimated glomerular filtration rate
PPO - peak power output
SD - standard deviation
MCID - minimal clinically important difference
VAS - visual analogue scale

Highlights:

- “Responders” to exercise training are more likely to be younger;
- “Responders” to exercise training are more likely to demonstrate improvements in cardiopulmonary exercise test-derived outcomes, health-related QoL, and HDL-cholesterol.

Introduction

In people with coronary artery disease (CAD), a core component of the rehabilitation process is exercise training which should be prescribed according to the FITT principles (frequency, intensity, time, and type of training), including both aerobic and resistance training components [1]. General recommendations for aerobic training propose a training frequency of at least 3 days per week, (preferably 6–7 days), with progression from interval to continuous training considered best practice [2]. Our landmark trial, HIIT or MISS UK, showed that eight weeks of high intensity interval training (HIIT) exercise was more effective than moderate intensity (MISS) exercise training for improving cardiorespiratory fitness in 382 people with CAD attending cardiac rehabilitation (CR), although the aerobic training component was provided at a lower frequency (2 times per week) than this recommendation [3]. Additionally, HIIT training was safe, well tolerated and cost-effective [4].

Improved maximal aerobic fitness (typically measured by VO_2peak) following exercise training has firmly established survival benefits independent of other important risk factors in epidemiological studies [5-8]. Small increments in VO_2peak result in a significantly lower risk of mortality [9]. Indeed, at the population level an increase of 1.0 $ml \cdot kg^{-1} \cdot min^{-1}$ in VO_2peak is associated with a 15% reduction in all-cause and cardiovascular mortality in people with CAD [8]. However, clinical trials have consistently reported large inter-individual differences in training responses following CR (measured by Δ VO_2peak) [10,11]. A minimum of 20% of participants do not appear to respond to a traditional exercise training stimulus despite adequate compliance [5-7].

Although responders and non-responders to exercise training may have different phenotypes and genotypes, leading to significant variability in response, the selection of the most appropriate training modality/intensity/volume may also play a central role. A recent ‘call to action’ from the Section on Secondary Prevention and Cardiac Rehabilitation (SSPCR) of the European Association of Prevention Cardiology (EAPC) [12] concluded that the proportion of indi-

viduals who respond to training intensity (higher v moderate intensity) is not significantly different, rather, it is the total training volume that increases the likelihood of responding sufficiently to the stimulus. In the United Kingdom (UK), this conclusion is particularly challenging as CR interventions are sub-optimal in terms of delivering an appropriate training volume [13,14]. Indeed, they deliver one-third of the exercise dose, and produce less than half the magnitude of fitness gains reported in other countries [13].

Peak oxygen uptake is typically evaluated when conducting a cardiopulmonary exercise (CPET). However, CPET has a broader utility including screening and assessment, and providing diagnostic and prognostic information in patients with CAD. In CAD, exercise intolerance is a cardinal feature, and routinely measured CPET variables can provide important patient-specific prognostic information. For example, the VE/VCO_2 slope, which reflects ventilatory efficiency by identifying the minute ventilation required to eliminate carbon dioxide, is commonly used for risk stratification, with a value >35 indicative of listing for heart transplantation [15]. Likewise, the oxygen uptake efficiency slope (OUES) - the slope of the relation between oxygen uptake (VO_2) and logarithmically transformed minute ventilation (log VE), may have prognostic value. For example, patients in end-stage heart failure with an OUES >1.6 had a higher 2-year survival rate than those with an OUES <1.6 [16]. These CPET-related prognostic variables can be improved through effective exercise training [1].

The focus on training response and its impact on health-related quality of life (QoL) and cardiovascular risk factor profiles has received very little attention. In people with CAD, systematic reviews and meta-analyses have shown no difference in QoL outcomes between high- and moderate-intensity training [17]. Modifying cardiovascular risk factor profiles is a key consideration for exercise training interventions but is often overlooked [18]. Whilst there is strong evidence that cardiovascular risk factor profiles can be improved through exercise training, the impact of response and non-response to training has received little attention in this context.

We conducted a secondary analysis of data from the HIIT or MISS UK trial in the context of the EAPC “call to action’ to investigate the importance of exercise intensity in determining

responders and non-responders to exercise training. Further, we aimed to identify whether responders were more likely to demonstrate improvements in key CPET-derived variables, and to evaluate differences in QoL, cardiovascular risk factor profiles, and demographic characteristics compared to non-responders.

Methods

This was a secondary analysis of a pragmatic, parallel group, assessor-blind randomised controlled trial (HIIT or MISS UK) testing the effectiveness of a low-volume HIIT protocol compared to MISS training in six UK National Health Service (NHS) cardiac rehabilitation programmes in the UK. The trial protocol was approved by the NHS Health Research Authority, East Midlands - Leicester South Research Ethics Committee (16/EM/0079), and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guideline [19].

Participants and procedures

The full trial protocol and intervention have been published elsewhere [20]. In brief, patients referred for CR with a diagnosis of myocardial infarction (MI), coronary artery bypass graft (CABG) surgery, angiographically documented CAD, and/or elective percutaneous coronary intervention (PCI) were eligible. Clinically stable participants aged 18 – 80 years, with left ventricular ejection fraction >35% were recruited. Exercise sessions were conducted in accordance with the Association for Chartered Physiotherapists in Cardiac Rehabilitation guidelines [21].

Frequency, time and type of training were similar for HIIT and MISS (2 sessions per week for 8 weeks; 20-40 min of training per session for HIIT and MISS; Type: aerobic). Training intensity differed between HIIT and MISS (MISS, 40-70% heart rate reserve (%HRR); HIIT, 10 x 1

min intervals at 85-90% peak power output (PPO) or >85% HR_{max} interspersed with 10 x 1 min intervals at 20-25% PPO; 20 min total per session).

Cardiopulmonary exercise test (CPET)

Cardiopulmonary exercise testing (CPET) was conducted prior to and following the exercise intervention using a standard bicycle ramp protocol in accordance with American Thoracic Society guideline [22]. Participants were encouraged to maintain a cadence of 70 rpm until symptom-limited volitional fatigue prevented continuation. Criteria for the assessment of a good participant effort was a peak respiratory exchange ratio (RER) >1.10, peak HR ≥85% predicted and RPE ≥18. Key CPET-related variables of interest were peak oxygen uptake (VO_2 peak), heart rate recovery, oxygen uptake efficiency slope (OUES), VE/VCO_2 slope, rate pressure product, and peak power output.

Quality of life and cardiovascular risk factor profiles

We measured health-related QoL using the five-item EuroQoL EQ-5D-5L inventory [23], which produces a health utility score (1= equivalent to full health; 0=dead), and a self-rated health score via a visual analogue scale (VAS; 100=best health; 0=worst health). To evaluate cardiovascular disease risk factors we conducted a biochemical analysis on whole blood samples which were obtained via standard venipuncture techniques, allowed to clot, and then centrifuged at 4000 rpm for 10 minutes prior to serum being aliquoted and stored frozen at -80°C. Samples were analysed for creatinine, high sensitivity C-reactive protein (hs-CRP), estimated glomerular filtration rate (eGFR), and full lipid profile at baseline and 8-weeks later (following the exercise training programme). Other established cardiovascular disease risk factors including blood pressure and body mass index were investigated.

Outcome measures

To identify those responding or not responding to exercise training, outcomes were assessed at baseline and 8 weeks. The primary outcome was the change in peak oxygen uptake between baseline and eight weeks.

In the HIIT or MISS UK trial, we showed that people undertaking HIIT were more likely to achieve a clinically meaningful peak VO_2 response to the training stimulus than those undertaking MISS (55% v 34%) [3]. This was calculated using absolute probability thresholds [24,25] to account for measurement error and random within subject variation. Individuals who exceeded the 75% probability that their change in VO_2peak was greater than a minimal clinically important difference (MCID) of 1.0 $ml \cdot kg^{-1} \cdot min^{-1}$ after adjusting for measurement error, were classified as responders. For comparative purposes, we also followed the EAPC guidance for identifying 'non-response' in a CAD population by identifying a decrease in VO_2peak, or an increase within the typical error of measurement of approximately 6% [11,12,26]. As the latter represents a more pragmatic threshold which can be simply applied by a healthcare professional working in clinical practice, a threshold measure of >6% improvement in VO_2peak was used to define a responder for the evaluation performed in the current study.

Statistical analysis

Continuous data were summarised with mean and standard deviation (SD), and categorical data were summarised with frequency count and percentage. Data distribution was interrogated and found to be normal. For each variable analysed, we report the number of available observations. A between-group comparison between responders and non-responders, identifying the change in outcome variables between baseline and 8 weeks was conducted using an independent samples t-test. Differences in clinical and demographic variables for responders to exercise training were evaluated using Chi-square tests. An alpha level of $P<0.05$ was

used to denote statistical significance. SPSS version 27 (IBM, NY, USA) was used to analyse the data.

Results

Our analysis showed that 382 participants (mean age: 58.8 ± 9.6 years; mean BMI: 29.0 ± 4.3 $kg \cdot m^{-2}$; 93% male) were randomised in the primary trial to HIIT (n=187) or MISS (n=195) training, with 136 and 154 participants, respectively, completing the 8-week intervention. VO_{2peak} was found to have improved to a greater extent with HIIT than with MISS after adjusting for age, sex and study site Using the EAPC-reported threshold, the proportion of responders was 60% in the HIIT group and 39% in the MISS group (Figure 1).

Combining both HIIT and MISS interventions, using the EAPC-reported threshold, 48% of people who completed the eight-week intervention were classified as responders. Demographic and clinical characteristics of those responding vs not responding to the training stimulus are compared in Table 1. Age was a key determinant of exercise training response. 58% of individuals aged up to 50 years responded to exercise training, whereas only 40% of participants aged over 70 years responded (*P*=0.04). In Table 2, we report differences in key CPET parameters for responders and non-responders. We found a significant difference between responders and non-responders in relation to Δ peak METs, Δ VE/VCO_2 slope, $\Delta VO_2/\Delta WR$, Δ OUES, Δ HRR at 1 min, Δ RPPmax, Δ VEpeak, Δ SBPpeak Δ SV, Δ total exercise time, Δ peak power output.

Table 3 shows differences in health-related QoL and cardiovascular risk factor profiles in responders and non-responders. A significant difference (*P*=0.045) was evident between responders (baseline: 71.2 ± 19.0; 8 weeks: 84.8 ± 11.0) and non-responders (baseline: 73.3 ± 17.7; 8 weeks: 82.7 ± 11.7) in the change in EQ-5D-5L (VAS). When responders to HIIT and MISS training sub-groups were analysed independently, both modes of training maintained significant improvements in EQ-5D-5L (VAS) (both observations; *P*<0.05).

We noted a significant difference (*P*=0.004) between responders (baseline: 1.00 ± 0.21 mmol.L^{-1}; 8 weeks: 1.09 ± 0.24 mmol.L^{-1}) and non-responders (baseline: 1.03 ± 0.25 mmol.L^{-1}; 8 weeks: 1.07 ± 0.27 mmol.L^{-1}) in the change in HDL-c. However, following sub-group analysis, this relationship strengthened in the responders to HIIT training only (non-responders: Δ change 0.02 mmol.L^{-1}; responders: Δ change 0.10 mmol.L$^{-1;}$ *P*=0.001), and was lost in the responders to MISS training only sub-group (*P*=0.267). No other differences across QoL measures and cardiovascular risk factors were noted between responders and non-responders (Table 3).

Discussion

In people with CAD attending cardiac rehabilitation, "responders" to exercise training were more likely to be younger, and demonstrate greater improvement in a range of cardiovascular disease risk markers, compared to non-responders. Our analysis showed that the HIIT group had 21% more responders than the MISS group using the 6% threshold (60% HIIT v 39% MISS; *P*=0.001), which is an identical finding to our original trial using absolute probability thresholds (55% HIIT v 34% MISS) [3]. A systematic review and meta-analysis of 31 exercise training trials in people with heart failure reported that for each 10% increase in applied exercise intensity (%HRpeak) across trials [27], VO_2peak increased by a mean of 1.0 mL·kg^{-1}·min^{-1} [27], which is in agreement with our analysis from a large CAD population. Furthermore, meta-regression and meta-analysis based on 55 trials identified exercise intensity as the most important predictor of increased exercise capacity following CR [28].

Numerous factors have been identified which are likely to affect the individual response to exercise training, including genetic and epigenetic factors, environment, pharmacology, nutrition and sex [12]. Perhaps the most important determinant is genetic factors which may explain up to 50% of the individual response in VO_2peak, as reported in 473 health sedentary, individuals in the HERITAGE Family Study after 5 months of moderate intensity exercise training [29]. It is unclear whether HERITAGE outcomes can be extrapolated to individuals with CAD. The dose of exercise training required to reduce the risk of non-response has been

previously examined in healthy populations as well as obese and post-menopausal females, with similar trends evident. In obese adults exposed to three doses of exercise training delivered over a 6-month period [30], non-response was observed in 39%, 18% and 0% of individuals randomised to either (i) low-duration (180–300 kcal per session), low-intensity (50% VO_2peak) training regimen; (ii) high-duration (360–600 kcal per session), low-intensity (50% VO_2peak) training or; iii) high-duration (360–600 kcal per session), high-intensity (75% VO_2peak) training, respectively. Likewise, a similar decline in the prevalence of non-response was demonstrated in postmenopausal women allocated to four to five exercise sessions per week requiring 4, 8 or 12 kcal kg^{-1} over a 6-month intervention [31].

Two systematic reviews concluded that the total energy expenditure of the overall programme is the strongest predictor of improvements in exercise capacity in people with HF [32,33]. A meta-analysis by Hashbullah and colleagues [32] indicated that high intensity exercise achieving at least 460 kcal weekly energy expenditure may provide the greatest stimulus for changes in cardiorespiratory fitness. A meta-analysis and meta-regression by Vromen and colleagues [33] also highlighted the importance of total energy expenditure for improving exercise capacity followed by session frequency, session duration and session intensity. Thus, effective training programmes require high total energy expenditure as a main goal. The authors [31] proposed that primarily increasing training frequency and session duration are more likely to yield the largest improvement in exercise capacity.

The recent ‘call to action’ from the SSPCR of the EAPC [12] highlighted that the evidence regarding the additional benefits of higher intensity exercise training is still conflicted. They proposed that total energy expenditure may be more relevant for improvements in exercise capacity than exercise intensity. However, in the UK for example, CR programmes provide approximately one-third of the exercise volume, and produce less than half the magnitude of cardiorespiratory fitness gains reported in other countries [13]. These under-dosed and low volume CR programmes, typically two training sessions per week for 6-8 weeks (12-16 sessions in total), are commonplace in UK CR provision and mean that total energy expenditure

is lower compared to programmes in other countries. Therefore, in these circumstances our findings indicate that exercise intensity may be the key discriminator that determines whether cardiorespiratory fitness increases in typically low volume programme settings.

Our findings indicate that positive responders to training, based on change in peak VO_2, are more likely to observe improvements in health-related QoL (EQ-5D-5L VAS) than non-responders (in all responders, and following sub-group analysis [responders to HIIT only, or MISS only training]). To our knowledge, this has not been reported previously, however, there are conflicting findings from other studies which have compared different intensities of exercise training on health-related QoL in people with CAD. Trials have consistently used different tools for assessing health-related QoL, for example, using the SF-12, investigators observed significantly improved physical and mental domains in HIIT compared to MISS groups [34]. However, another trial, using the MacNew questionnaire showed improvements in both HIIT and MISS groups [35], whereas others, using both the SF-36 and MacNew questionnaires showed no differences in health-related QoL between HIIT or MISS groups [36].

Our analysis highlighted that positive responders to training were more likely to observe increases in HDL-c compared to non-responders, and this relationship was mediated, following sub-group analysis, by HIIT training. This is an important observation, as larger size and density of HDL-c is associated with improved health and performance [37]. Few studies have examined the impact of exercise training on changes in HDL-c structure and function in people with CAD, although the condition is strongly associated with dysfunctional HDL-c [38]. The application of exercise training is thought to be effective for reducing the risk of CAD by reinforcing the anti-inflammatory function of HDL-c [39]. Our findings highlight that exercise intensity is a key discriminator for driving improvements in individual HDL-c profiles.

Study Limitations

Limitations included the loss to follow-up of 31 participants due to the COVID-19 pandemic and subsequent lock-down restrictions. Secondly, our trial population was predominantly white male, reducing the confidence that we can generalise our findings to different demographic groups.

Conclusions

In people with CAD, those responding to an 8-week exercise training programme are more likely to be younger, and achieve greater improvements in key prognostic cardiopulmonary exercise testing variables, health-related QoL, and HDL-c, compared to non-responders.

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Figure Legends

Figure 1. Individual percentage changes in peak oxygen uptake and the impact of 8 weeks of low-volume HIIT (right panel) or MISS (left panel) training in people with CAD. Responders and non-responders to training stimulus identified.