1 **Does exercise training prescription based on estimated heart rate training zones exceed**

2 **the ventilatory anaerobic threshold in patients with coronary heart disease undergoing**

3 **usual-care cardiovascular rehabilitation?: A United Kingdom perspective.**

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1   Abstract

2   **Background:** In the United Kingdom (UK), exercise intensity is prescribed from a fixed

3   percentage range (% heart rate reserve; %HRR) in cardiac rehabilitation (CR) programmes.

4   We aimed to determine the accuracy of this approach by comparing it with an objective,

5   threshold-based approach incorporating the accurate determination of ventilatory

6   anaerobic threshold (VAT). We also aimed to investigate the role of baseline

7   cardiorespiratory fitness status, and exercise testing mode dependency (cycle v treadmill

8   ergometer) on these relationships.

9   **Design/Methods:** A maximal cardiopulmonary exercise test was conducted on a cycle

10   ergometer or a treadmill before and following usual-care circuit training from two separate

11   CR programmes from a single region in the UK. The heart rate corresponding to VAT was

12   compared to current heart rate-based exercise prescription guidelines.

13   **Results:** We included 112 referred patients (61 years [59-63]; body mass index 29 $kg·m^{-2}$

14   [29-30]; 88% male). There was a significant but relatively weak correlation *(r=0.32; P=0.001)*

15   between measured and predicted %HRR, and values were significantly different from each

16   other (*P*=0.005). Within this cohort, we found that 55% of patients had their VAT identified

17   outside of the 40-70% predicted HRR exercise training zone. In the majority of participants

18   (45%), the VAT occurred at an exercise intensity <40% HRR). Moreover, 57% of patients with

19   low levels of cardiorespiratory achieved VAT at <40% HRR. Whereas, 30% of patients with

20   higher fitness achieved their VAT at >70% HRR. VAT was significantly higher on the treadmill

21   than the cycle ergometer *(P<0.001)*.

22   **Conclusion:** In the UK, current guidelines for prescribing exercise intensity are based on a

23   fixed percentage range. Our findings indicate that this approach may be inaccurate in a large

24   proportion of patients undertaking CR.

25   **Word Count:** 274 words

26   **Key words**: cardiac rehabilitation, exercise prescription, cardiorespiratory fitness,

27   ventilatory anaerobic threshold.

28

1   Introduction

2   Cardiovascular rehabilitation (CR) is a multi-disciplinary secondary prevention programme

3   that has been shown to contribute to reduced hospital admissions, and improvements in

4   patient quality of life, following a cardiac event.(1-4) Historically, a 1% improvement in peak

5   oxygen uptake (VO_{2peak}) resulting from exercise-based CR, was thought to confer a 2%

6   reduction in premature mortality.(5) Similarly, every 3.5 $ml^{.}kg^{-1.}min^{-1}$ increment in VO_{2peak}

7   has been associated with a 12-13% survival benefit (6, 7) in men referred for exercise

8   testing. Therefore, it is essential that the prescribed dose of exercise is sufficient to

9   stimulate improvements in VO_{2peak} following CR. Recent systematic reviews and meta-

10   analyses have shown that increased exercise intensity is an important factor in achieving

11   superior outcomes in patients with cardiovascular disease.(8, 9)

12   The prescribed dose of exercise can be influenced by manipulating exercise frequency,

13   duration, type/mode, and/or intensity [exercise dose].(10) In the United Kingdom (UK),

14   current long-term exercise training guidelines for patients undertaking CR, recommend

15   exercise training intensities between 40-70% heart rate reserve (HRR), oxygen uptake

16   reserve (VO_2R), or a Borg rating of perceived exertion (RPE) between 11-14.(11, 12) Both

17   continuous and interval training at an objective physiological threshold has been shown to have a

18   beneficial impact by improving VO_2peak.(13) Training at or above the ventilatory anaerobic

19   threshold (VAT), often referred to as the first ventilatory threshold (VT1), indicates the

20   point above which, further increments in work rate are increasingly supplemented through

21   anaerobic metabolism.(14-17) Despite being associated with mild metabolic

22   perturbations,(16, 17) regular exercise bouts conducted at work rates equivalent to VAT are

23   well tolerated,(18) and induce physiological adaptation leading to improved

24   cardiorespiratory fitness (CRF) and other cardiovascular risk factors.(19, 20) However, whilst

1 work rates corresponding to VAT may represent a minimum intensity needed to improve

2 CRF, metabolic gas equipment and calibrated ergometers are often not available in a CR

3 setting in the UK. Prescribing exercise as a percentage of measured HRR, or most typically

4 estimated HRR, is often a more practical and realistic alternative in UK cardiac rehabilitation

5 settings.(10)

6 The 40% HRR threshold is cited as the lowest effective exercise intensity for improving CRF

7 in patients undertaking CR.(10, 12) The individual VAT is widely accepted to occur between

8 45-65% HRR in healthy and cardiac patients,(8) with lower values reported in patients with a

9 chronic cardiovascular disease.(10) However, the distribution of VAT values, and its relation

10 to exercise capacity, is unclear in patients undertaking CR. How commonly VAT occurs

11 within discrete exercise intensity ranges is also under-reported in patients with coronary

12 artery disease. Tan *et al* (21) showed that the mean VAT was equal to 82% of maximal heart

13 rate (HR), in 19 cardiac patients referred for a cardiopulmonary exercise test (CPET) prior to

14 CR, (21). However, the mode of exercise testing may also influence when an individual's VAT

15 occurs.

16 In the UK, the mode of exercise testing varies between CR programmes. This means that a

17 patient's exercise prescription could be based on a number of different submaximal exercise

18 tests, including the 6-min walk test, incremental shuttle walk test, step test, or cycle

19 ergometry. The differing metabolic responses to cycling compared with walking may affect a

20 patient's peak oxygen uptake ($\dot{V}O_{2peak}$), and the occurrence of VAT. This, in turn, may

21 significantly affect the accuracy of exercise intensity prescription. These issues have not

22 been addressed sufficiently within UK guidelines for exercise prescription in CR

23 programmes. This information may help practitioners to optimise a patient's initial exercise

1   prescription and maximise the improvements associated with exercise training

2   programmes. This is especially important when the frequency and duration of CR sessions

3   are finite. We aimed to determine the accuracy of the standard UK approach for prescribing

4   exercise in patients undertaking CR by comparing it with objective measures of exercise

5   prescription, namely $\dot{V}O_{2peak}$ and VAT. Secondary aims were to determine how exercise

6   modality (exercise testing with cycle versus treadmill ergometer), and baseline levels of CRF

7   affected the concordance of VAT and HRR measures.

8

9   Methods

10   Data was collated from the baseline assessment of two separate cohorts who undertook a

11   maximal effort CPET to volitional exhaustion prior to commencing a CR programme. The

12   methods for these studies have previously been reported.[22, 23] Ethical approval was

13   provided by the Yorkshire and Humber – Sheffield National (12/YH/0072) and Humber

14   Bridge NHS (12/YH/0278) Research Ethics Committees. Briefly, patients were recruited

15   following a referral to CR for angina, myocardial infarction (MI), coronary artery bypass graft

16   (CABG), or percutaneous coronary intervention (PCI). Patients attended a baseline study

17   assessment, where written informed consent was obtained. CPET was conducted on a cycle

18   ergometer following a 25W incremental protocol, or on a treadmill following the modified

19   Bruce protocol,[24] adopting previously outlined test termination and maximal effort

20   criteria.[15, 25] Breath-by-breath metabolic gas exchange data were collected using an

21   Innocor (Innovision, Glamsbjerg, Denmark) or Oxycon-Pro metabolic cart (Jaeger,

22   Hoechburg, Germany), respectively, which were calibrated according to manufacturers'

23   instructions and current recommendations.[26] Peak values were averaged over the final 30

seconds of the CPET. VO_{2peak} was reported in absolute values ($L \cdot min^{-1}$) and standardised to each patient's body mass ($ml \cdot kg^{-1} \cdot min^{-1}$). Individualised VAT was independently determined by two investigators (using the average of the middle five of every seven breaths plotted in the V-slope method, and verified using the ventilatory equivalents.[14, 27] Where investigators reported different VAT values, a third reviewer was consulted and the threshold value agreed by consensus. The VAT was reported in $L \cdot min^{-1}$ and $ml \cdot kg^{-1} \cdot min^{-1}$ and expressed as a percentage of directly-determined and predicted VO_{2peak}.[28] The HR at VAT was then established and reported as a ratio of HRmax and HRR determined from CPET, and as a ratio of predicted HRmax and HRR with relevant adjustment for the effects of beta-blockade on maximal heart rates as follows [10]):

$$((205.8 - (0.685 \times age)) - \text{resting heart rate (-30 beats per min if taking beta-blockers)}$$

To characterise where a patients VAT occurred in relation to established training zones, the VAT values were categorically assigned to exercise intensity groups of <40%, 40-49%, 50-59%, 60-69%, 70%, and >70% of measured, and predicted HRR. Adjustment for β-blockades were made where appropriate,[12]. We assessed how many patients had a VAT that occurred within the exercise training intensity ranges recommended by UK CR guidelines, namely 40-70% HRR, or an RPE between 11-14.[11, 12] Patients were sub-categorised according to individual CRF levels as low (<5 METs for women, <6 METs for men), moderate (5<7 METs for women, 6<8 METs for men), and high CRF (≥7 METs for women, ≥ 8 METs for men), based on exercise capacity (MET) thresholds derived from the international literature and previously applied to cardiac patients in the UK.[29] These sub-groups were then

1 categorised based on the HRR zone that the individualised VAT occurred within. We also

2 conducted sub-analyses on patients who undertook their CPET either on a treadmill or cycle

3 ergometer.

4

5 ### Data analysis

6 Statistical analysis was conducted using SPSS version 24 (IBM, NY, USA). When data was not

7 normally distributed, normalisation of the distribution was attempted using log_{10}

8 transformation. Logarithmically transformed data was analysed in its transformed state and

9 reported as an arithmetic mean to allow for meaningful interpretation. Normally distributed

10 and transformed data were analysed using a univariate general linear model with

11 significance set at arbitrary level *(P<0.05)*, and is presented as mean (95% confidence

12 intervals), and partial-eta squared (η_p^2) effect sizes, with 0.01, 0.06, and 0.14 denoting

13 small, moderate, and large effects, respectively (30). For non-normally distributed data, a

14 Mann-Whitney U test was conducted with median and range reported. Categorical data was

15 analysed using a Chi-squared test of independence and reported as percentage and

16 frequency. When ≥1 cell had an expected value <5, the Fisher's exact test was used.

17

18 ### Results

19 ### Patient Characteristics

20 One-hundred and twelve (*n*=112) cardiac patients were included for analysis (61.3 years

21 [59.4-63.1]; 29.3 kg·m^{-2} [28.5-30.1]; 88% male). Forty-two patients (*n*=42; 37.5%) undertook

22 their CPET on a cycle ergometer. Patients on a cycle ergometer achieved 79.1% of their

23 predicted HRmax [74.6-83.6%], an RPE of 18 [17-18], and a peak respiratory exchange ratio

1 (RER) of 1.02 [1.00-1.05]. Seventy (*n*=70*)* patients undertook CPET on a treadmill. Patients

2 conducting CPET on a treadmill achieved 82.3% [79.7-84.9%] of predicted HRmax), an RPE of

3 17.8 [17.3-18.3], and a peak RER of 1.09 [1.06-1.11]). 77% and 86% of the patients

4 undergoing cycle and treadmill testing, respectively, were prescribed beta-blockers. The

5 majority of patients had a diagnosis of myocardial infarction (MI) with primary (32.5%) or

6 elective (28.9%) PCI. There was a greater prevalence of active smokers *(P=0.017)* in those

7 that conducted a CPET on a cycle ergometer. There were significant between-group

8 differences for age (*P*=0.012; η_p^2=0.054), and resting HR (mean difference 5.8bpm (95% CI

9 1.0-10.5bpm) *P*=0.032; Table 1) between the test modality groups. 42 out of 112 patients,

10 were classified within the lower cardiorespiratory fitness group, 50 in the moderate-fit

11 group, and 20 in the high-fit group (Table 2).

12

13

14 VAT, HRR zones, and CRF categories

15 Measured HRR (72 ± 15 bpm) derived from maximal CPET demonstrated only a modest

16 correlation with predicted HRR (77.99 ± 20.42bpm) (using current UK CR guidelines (*r*=0.32;

17 *P*=0.001). However, the directly determined and predicted HRR/peak HR variables were

18 significantly different from each other (mean difference = 6.74bpm (95% CI 2.99-10.49bpm)

19 *P*=0.001). The VAT occurred within 40-70% of directly determined HRR range in 61.6% of

20 patients. In the remaining 38.4% of patients, 33.9% achieved their VAT at <40% HRR, and in

21 4.5% of patients, their VAT did not occur until >70% HRR. For predicted HRR, VAT occurred

22 within 40-70% HRR in 44.6% of patients. Of the remaining 55.4% of patients, 45.4% achieved

23 VAT at <40% HRR, and 9.8% at >70% HRR (Table 2).

1 The VAT occurred between 40-70% of predicted HRR in 21.4% of patients undertaking

2 cycling exercise. The majority (76.2%) of patients exceeded the VAT at <40% HRR. For

3 patients undertaking CPET on a treadmill, 58.5% of patients had a VAT that occurred

4 between 40-70% of predicted HRR, and 27.1% had a VAT that occurred at <40% HRR.

5 Interestingly, the VAT occurred between 40-70% of predicted HRR in 35.8% of patients that

6 were categorised as having a low CRF. 57.1% of patients exceeded their VAT at <40% of

7 their HRR. For higher-fit patients, VAT occurred between 40-70% of predicted HRR in 50% of

8 patients, at <40% HRR in 20%, and >70% HRR for the remaining 30% of patients (Table 2).

9 Figure 1 shows the inter-quartile range for VAT as a percentage of predicted HRR, based on

10 CRF category, and exercise testing modality. The VAT occurred at a higher percentage of

11 VO_{2peak} in patients with a higher CRF. This observation was also evident when CPET was

12 conducted on a treadmill for all CRF categories, but most apparently in the moderate and

13 high-fit groups.

14

15 Directly measured compared with predicted cardiorespiratory fitness variables

16 Mean VO_{2peak} was not significantly different between exercise modality groups in absolute

17 units ($P=0.644$; $\eta_p^2=0.002$), or relative to body mass ($P=0.359$; $\eta_p^2=0.008$) (Table 3).

18 However, absolute ($P=0.027$) and relative ($P=0.001$) VAT was significantly different across

19 the different CRF groups. VAT occurred at a higher percentage of predicted ($P=0.003$;

20 $\eta_p^2=0.08$) and measured VO_{2peak} ($P<0.001$; $\eta_p^2=0.151$), and HRR ($P<0.001$; $\eta_p^2=0.132$) in

21 patients exercising on the treadmill. Measured HRR ($P=0.012$; $\eta_p^2=0.056$), and HR at VAT

22 ($P=0.016$; $\eta_p^2=0.052$) were significantly higher in the treadmill group. There was a significant

1   between-group difference for predicted HRmax adjusted for β-blockade (*P*=0.003; Table 4).

2   However, there was no difference in predicted HRR (*P*=0.863 η_p^2=<0.001) or VO$_{2peak}$

3   between groups (*P*=0.815, η_p^2<0.001). Figures 2a and 2b highlight individual case studies

4   which demonstrate how the predicted HRR method can either over- or under- estimate

5   individualised exercise prescription versus directly determined HRR and VAT.

6

7   Discussion

8   This study aimed to determine the accuracy of the standard UK approach for prescribing

9   exercise in patients undertaking CR. This method of determining target heart rates for

10   exercise training in cardiac patients relies largely on predictive methods for determining

11   maximal HR (including patients taking beta-blockade). We sought to compare it with a more

12   objective measure of exercise prescription, namely the VAT derived from respiratory gas

13   exchange during a maximal CPET. Our findings indicate that current UK CR exercise

14   prescription guidelines appear susceptible to substantial inaccuracy with more than half of

15   our cohort achieving a VAT outside the recommended target range of 40-70% HRR. We

16   found that 45% of patients had VAT identified at <40% HRR, and in 9% of patients, VAT was

17   identified at >70% HRR, suggesting that the required exercise intensity spectrum is wider

18   than the recommended 40-70 HRR%.

19   When considering baseline cardiorespiratory fitness, the proportion of patients whose VAT

20   occurred outside the guidelines increased. 57% of low-fit patients achieving VAT at <40%

21   HRR, and 30% of high-fit patients achieving VAT at >70% HRR, confirming that VAT occurs

22   later with increasing CRF in cardiac patients.(31) For those who achieved VAT at <40% HRR,

their exercise prescription may overly exceed VAT and prove too challenging, whilst for those that achieve VAT >70%HRR, their prescription is unlikely to induce a training stimulus and prove too easy. We speculate that this may contribute to the 23% attrition rate recently reported in UK CR,(32) as some patients overly exceed their training stimulus (i.e. low fit patients), which may be uncomfortable, whilst some do not reach it, thus providing minimal benefit (i.e. high fit patients), both of which may cause patients to discontinue CR.

Therefore, a *one size fits all* approach, relying on predictive methods for maximal HR and estimated HRR to prescribe exercise appears ineffective. Exercise prescription within cardiac rehabilitation settings needs to be more accurate, patient specific and fine-tuned, ideally based on ventilatory markers, actual HRR and baseline fitness category determined via CPET.(33) One option could be to shift from 'range-based' to 'threshold-based' CR exercise prescription, with moderate-high intensity exercise, corresponding to work rates between VAT and critical power, being recommended.(17) Based on the current data, CPET would aid prescription to ensure that *all* patients achieved VAT during CR, whilst also ensuring it is not overly exceeded. This is important given that certain cardiac patients, namely those who may be more deconditioned, often perform activities of daily living at levels of VO_2 that exceed VAT.(34) Therefore, exercising in steady-state conditions above VAT is vital for these patients, but may not be possible if it is exceeded. In the late 1970s, limitations in the relative percent method (i.e %HRR) for prescribing exercise intensity were identified, with a study by Katch *et al* showing this method failed to consider individual metabolic differences,(35) yet it is still a recommended approach today.(8,10) More recent investigations have proposed a more individualised exercise prescription based on ventilatory thresholds to personalise individualised training load based on metabolic responses.(36, 37) Recently, Weatherwax *et al* reported that in sedentary adults, 12 weeks

1 of aerobic exercise training based on an individualised exercise prescription using VAT had a

2 greater effect on the incidence of training response compared to a standardised approach

3 using HRR. While the exact mechanisms are still not entirely understood, it is believed that

4 exercise intensity prescribed with the use of ventilatory thresholds takes into consideration

5 individual metabolic characteristics which are overlooked when using relative percent

6 methods.(38)

7

8 The current data also indicate that VAT is mode-dependant for the overall cohort and across

9 all three CRF categories. Similar to previous suggestions,(17) VAT occurred at around 50%

10 HRR on the treadmill but is 12-15% lower on the cycle. A similar relation has also been

11 observed in patients with chronic heart failure.(39) This mode dependency is also evident in

12 terms of predicted HRR zones, which are adopted in most UK CR centres, with >75% of

13 patients on a cycle ergometer achieving VAT at <40% HRR, compared with just 27% of

14 patients exercising on a treadmill. Previous research has identified a VAT mode dependency

15 in cardiac patients based on VO_2.(40) The current results differ somewhat as they show a

16 mode dependency for patients who are yet to begin as opposed to those who have finished

17 CR. Furthermore, in the current study this mode dependency is expressed using HRR, which

18 is adopted in most CR centres, rather than VO_2.

19 UK CR is provided by the state-funded National Health Service, unlike CR operating in other

20 international and EU countries,(15) the integration of CPET equipment is not currently

21 incorporated into most UK centres and may prove to be prohibitive.(41) Another possible

22 solution could be to increase the upper intensity limit of exercise prescription in line with

23 international guidelines at 80% HRR, especially for patients in a higher fit category.(10, 42)

Of the 10 patients whose VAT occurred at >70% HRR, 6 achieved VAT at <80% HRR. This suggests that increasing the upper range of exercise prescription guidelines could be helpful to a small cohort of patients, and provide greater scope for training progression in those that could tolerate it; aligning UK guidelines closer to those seen internationally.(43) This does not however, address the issue for those who achieved VAT at <40%. A further alternative to personalise exercise prescription across the whole spectrum would be to identify the HR range corresponding to an RPE of 11-13, given that VAT has been shown to occur around this point (44, 45). Submaximal testing is routinely performed in UK CR and identification and utilisation of the HR between these points during testing could ensure more patients are exercising at or around the VAT. One caveat to such an option is that RPE is a subjective tool, meaning that appropriate anchoring of key values would be required for each patient, and this would need to be applied consistently within and between each CR centre in the UK.

To be able to confidently prescribe an individualised exercise programme in a safe and effective manner can be challenging in a cardiac population. The healthcare professional must be able to account for medication usage, presence of non-CV co-morbidities, and for example, adverse events during exercise testing. Hansen and colleagues [46] showed significant inter-clinician variance in prescribing exercise for patients with different CVDs, highlighting the challenges posed. Further training and education is key, however, digital resources are available to assist practitioner decision-making processes. For example, the European Association of Preventive Cardiology recently developed the Exercise Prescription in Everyday Practice and Rehabilitative Training (EXPERT) tool.[47] The EXPERT tool is an interactive, digital training and decision support system that assists healthcare professionals in prescribing clinically effective and medically safe exercise training programmes for CVD

patients. The adoption of tools such as EXPERT should be more widely encouraged and facilitated to support decision making processes around exercise prescription in cardiac populations. The impact of their utility within clinical practice could then be audited to determine changes in efficacy.

Limitations

The key limitation is that the two groups are made up of separate patients who varied on some baseline characteristics. Ideally, all patients would have completed a CPET using both modalities to reduce any individual effect.

Conclusion

To our knowledge, this is the first study of its kind to explore VAT in terms of prescribed HRR zones for cardiac patients to identify the accuracy of current UK CR exercise prescription guidelines. For a large proportion of patients, the guidelines are inaccurate with many patients achieving VAT at <40% HRR, meaning their exercise prescription may be overly challenging. Conversely, 30% of high-fit patients achieved VAT at >70% HRR, meaning their prescription may be too conservative to provide a stimulus. This under/over-prescription may lead patients to unnecessarily discontinue their CR (see Figures 2a and 2b). Therefore, for UK CR, a *one size fits all* approach is ineffective and a shift from predictive equations and submaximal exercise tests to gold-standard CPET on entry to CR would be required to improve exercise prescription. However, this may not be viable for a number of reasons, meaning that adoption of less conservative guidelines could provide a solution to ensuring that a larger proportion of patients achieve a training stimulus. Furthermore, although

1   VO_{2peak} did not demonstrate a mode dependency, VAT did. This suggests that it may be

2   necessary to conduct a CPET using both modalities, or tailor exercise prescription based on

3   the modality used. Future research could confirm this mode dependency for HRR at VAT in

4   cardiac patients by testing the same group of patients twice, once during each modality.

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Table 1

Table 1. Clinical characteristics of patients grouped by exercise modality

Mean (95% CI) † = median and ranges

Variable	Pooled (cycle and treadmill data)	Cycle	Treadmill	P-value	Partial eta-squared
Sex (male/female)	100/14 (87.70% male)	40/4 (90.0% male)	60/10 (85.7% male)	0.411	
Age (years)	61.25 (95% CI; 59.35 to 63.14)	63.13 (95% CI; 60.75 to 65.51)	58.25 (95% CI; 55.21 to 61.29)	**0.012***	0.054
BMI (kg/m^2)T	29.30 (95% CI; 28.54 to 30.07)	30.1 (95% CI; 28.8 to 31.44)	28.80 (95%CI; 29.74 to 27.90)	0.101	0.024
Resting SBP (mmHg)**Tr**	131.55(95% CI; 127.94 to 135.27)	139.57 (95%CI 134.39 to 144.95)	126.74(95% CI; 122.18 to 131.46)	**0.001****	0.099
Resting DBP (mmHg)†	83 (60 to 149)	85.50 (62 to 104)	82 (60 to 149)	0.09	
LVEF (%)	55.77 (95% CI; 54.34 to 57.20)	57.05 (95%CI; 54.35 to 59.75)	54.99 (95%CI; 53.35 to 56.62)	0.167	0.017

Resting HR (bpm)†	60 (42 to 95)	64 (44 to 95)	56 (42 to 91)	**0.008****
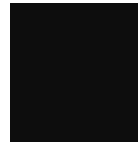
BMI, Body mass index. kg·m^{-2}, kilogram per metre squared. SBP, systolic blood pressure. mmHg, millimetres of mercury. DBP, diastolic blood pressure. LVEF, left ventricular ejection fraction. HR, Heart Rate. Bpm, beats per minute.

*$P<0.05$, **$P<0.01$, ***$P<0.001$. †, Variables are reported as median (minimum and maximum) values and analysed using a non-parametric test.

Tr, transformed using $\log_{10}$ transformation and reported as arithmetic mean for meaningful interpretation.

Table 2 - Revised

Table 2. The occurrence of VAT in relation to predicted HRR training zones, stratified by exercise modality and baseline CRF levels

Predicted HRR threshold	Number of patients (%)		
	Pooled cycle and treadmill	Cycle	Treadmill
<40% predicted HRR	51 (45.4%)	32 (76.2%)	19 (27.1%)
40-49% predicted HRR	24 (21.4%)	5 (11.9%)	19(27.1%)
50-59% predicted HRR	15 (13.4%)	4 (9.5%)	11 (15.7%)
60-69% predicted HRR	11 (9.8%)	0	11(15.7%)
>70% predicted HRR	11 (9.8%)	1 (2.4%)	10(14.3%)
Total within 40-70% HRR	**44.6%**	**21.4%**	**58.5%**

	Baseline CRF category		
	Low Fit	Mod Fit	High Fit
<40% predicted HRR	24 (57.1%)	23 (46%)	4 (20%)
40-49% predicted HRR	11 (26.2%)	11 (22%)	2 (10%)
50-59% predicted HRR	2 (4.8%)	8 (16%)	5 (25%)
60-69% predicted HRR	2(4.8%)	6 (12%)	3 (15%)
>70% predicted HRR	3 (7.1%)	2(4%)	6 (30%)
Total within 40-70% HRR	**35.8%**	**50%**	**50%**

Predicted heart rate reserve using current guidelines, accounting for beta-blockade. Baseline fitness category based on Taylor et al. (2016); low fit <5 METs for women and <6 METs for men, mod fit = 5<7 METs for women and 6<8 METs for men, high fit ≥7 METs for women, and ≥8 METs for men. VAT, ventilatory anaerobic threshold. HRR, heart rate reserve. MET, metabolic equivalent where 1 MET = $3.5 ml·kg^{-1}·min^{-1}$.

Table 3

Table 3. Cardiorespiratory data based on maximal CPET in patients using cycle and treadmill exercise modalities

	Pooled	Cycle	Treadmill	P-value	Partial eta-squared
VO_{2peak} (L·min^{-1})	2.00 (95% CI; 1.88 to 2.11)	2.03 (95% CI; 1.82 to 2.25)	1.98 (95% CI; 1.83 to 2.12)	0.644	**0.002**
VO_{2peak} (ml·kg^{-1}·min^{-1}) **Tr**	22.12 (95% CI; 19.8 to 24.7)	21.43 (95% CI; 18.0 to 25.5)	22.55 (95%CI; 19.7 to 25.8)	0.359	**0.008**
HRmax (bpm)†	137 (88 to 181)	131 (88 to 181)	139 (88 to 169)	0.32	
HRR (bpm)	71.5 (95% CI; 67.7 to 75.4)	65.1 (95% CI; 58.9 to 71.3)	75.43 (95% CI; 70.69 to 80.17)	**0.009***	0.061
VAT (ml·kg^{-1}·min^{-1}) †	13.1 (8.2 to 29.7)	13.3 (8.2 to 26.0)	16.6 (8.6 to 30.0)	**0.001***	
VAT (L·min^{-1}) †	1.3 (0.7 to 2.5)	1.15 (0.7 to 2.0)	1.35 (0.7 to 2.5)	**0.027***	
HR at VAT (bpm)	94 (95% CI; 91 to 97)	90 (95% CI; 85 to 94)	97 (95%CI; 93 to 101)	**0.016***	**0.05**
VAT (% of VO_{2peak})	67.5 (95%CI; 65 to 70)	61.3 (95%CI; 58 to 65)	71.1 (95%CI; 68 to 74)	**<0.001***	0.151
VAT (% of predicted VO_{2peak}) **Tr**	56.8 (95%CI; 52 to 63)	51.8 (95%CI; 45 to 60)	60.1 (95%CI; 53 to 68)	**0.003****	0.08

|					
VAT (% of HRR)	45.90 (95%CI; 43 to 49)	39.45 (95%CI; 35.6 to 43.3)	49.77 (95%CI; 46.5 to 53.0)	**<0.001*****	0.129
VAT (% of HRmax)	71.58 (95%CI; 70.1 to 73.1)	69.81 (95%CI; 66.9 to 72.7)	72.64 (95%CI; 70.9 to 74.4)	0.072	**0.029**

CPET, cardiopulmonary exercise test. VO_{2Peak}, Peak oxygen consumption. HRmax, maximum heart rate. Bpm, beats per minute. HRR, heart rate reserve. VAT = ventilatory anaerobic threshold. HR, heart rate. *$P<0.05$, **$P<0.01$, ***$P<0.001$. †,Variables are reported as median (minimum and maximum) values analysed using a non-parametric test. **Tr**, transformed using $\log_{10}$ transformation and reported as arithmetic mean for meaningful interpretation.

Table 4

Table 4. Relation between predicted and measured variables stratified by mode of exercise

	Pooled	Cycle	Treadmill	P-value	Partial eta-squared
Predicted HRmax (adjusted for β-blockade; bpm) †	136 (118 to 174)	138 (126 to 174)	134 (118 to 167)	**0.009****	
VAT (% of predicted HRmax adjusted for β-blockade)	67.97 (65.86 to 70.07)	62.74 (59.68 to 65.80)	71.10 (68.50 to 73.71)	**<0.001****	0.131
Predicted HRR (adjusted for β-blockade; bpm)	77.85 (95%CI; 75.04 to 80.66)	77.93 (95% CI; 73.19 to 82.68)	77.8 (95%CI; 74.24 to 81.36)	0.965	**<0.001**
VAT (% of Predicted HRR adjusted for β-blockade)†	40.35 (9.57 to 87.93)	30.49 (9.57 to 69.23)	47.06 (12 to 87.93)	<0.001***	
Predicted VO$_{2Peak}$ (ml·min^{-1})	2272.14 (95% CI; 2184.11 to 2360.17)	2258.79 (95% CI; 2114.05 to 2403.53)	2280.35 (95%CI; 2166.68 to 2394.01)	0.815	<0.001
VO$_{2Peak}$ (% of Predicted VO$_{2Peak}$)	87.85 (95%CI; 84.11 to 91.58)	89.99 (95%CI; 82.64 to 97.35)	86.56 (95% CI; 82.40 to 90.72)	0.380	0.007

HRmax, maximal heart rate. Bpm, beats per minute. VAT, ventilatory anaerobic threshold. HRR, heart rate reserve. VO$_{2Peak}$, Peak oxygen consumption

*$P<0.05$, **$P<0.01$, ***$P<0.001$. †, Variables are reported as median (minimum and maximum) values and analysed using a non-parametric test.
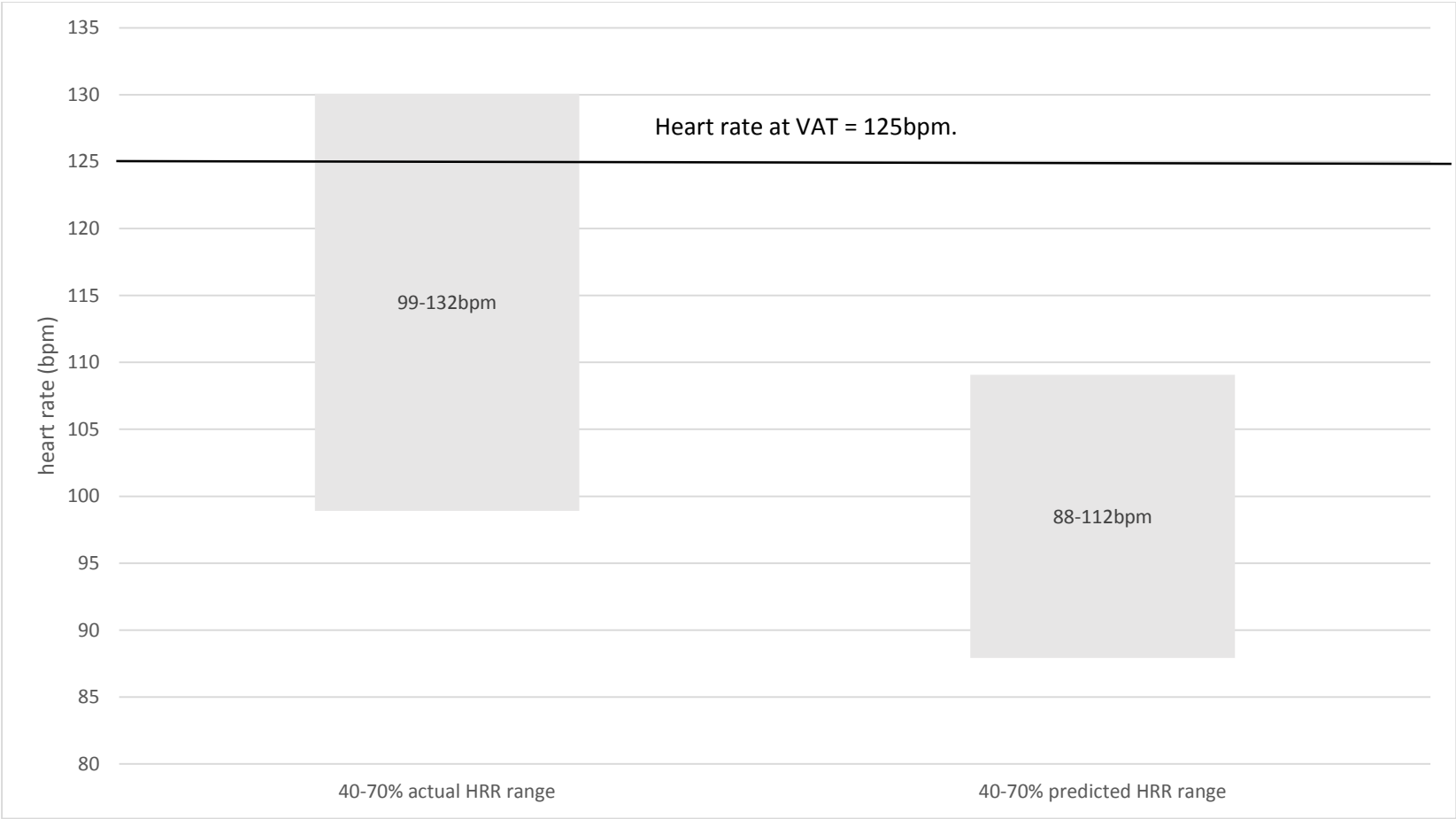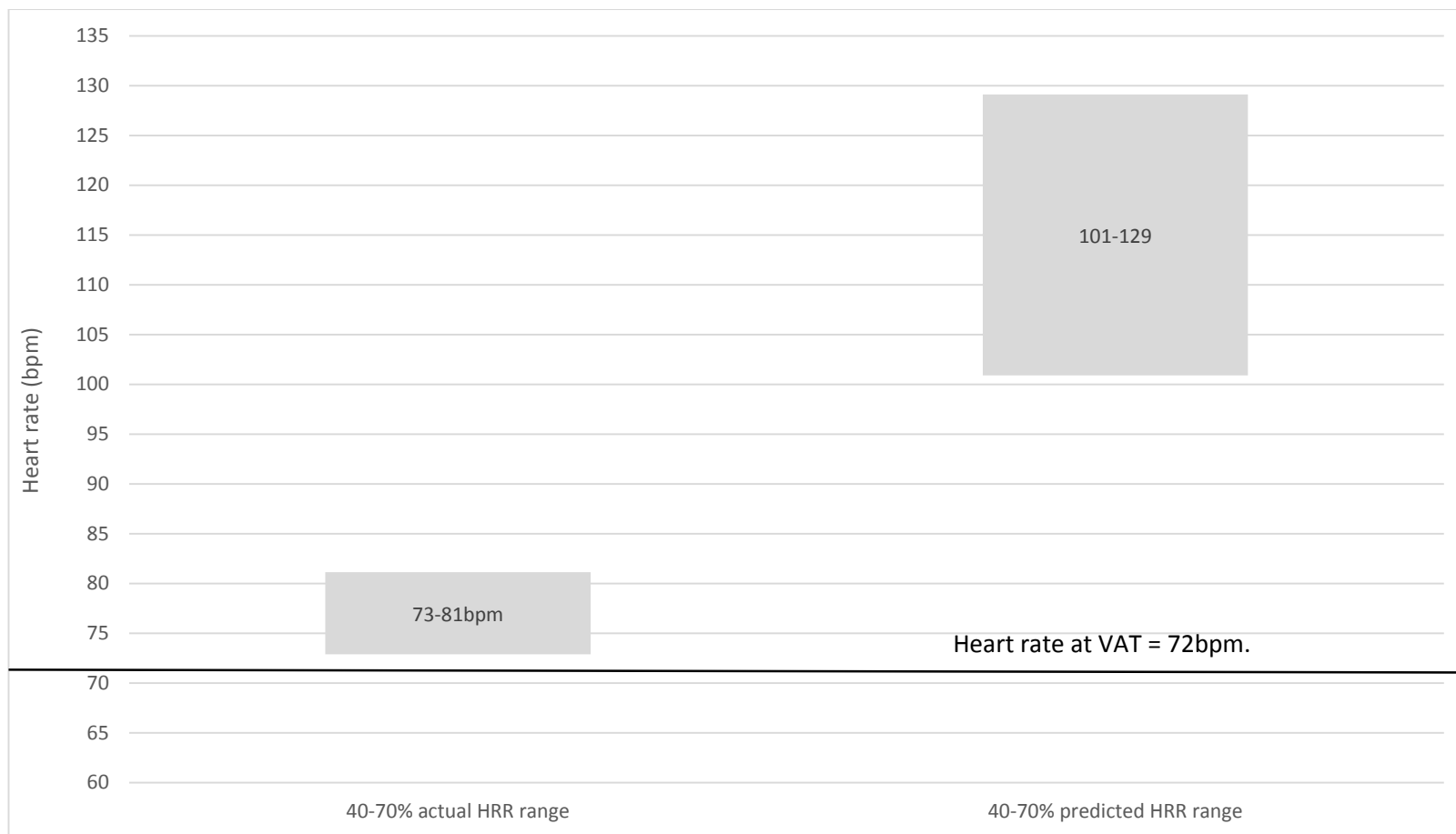
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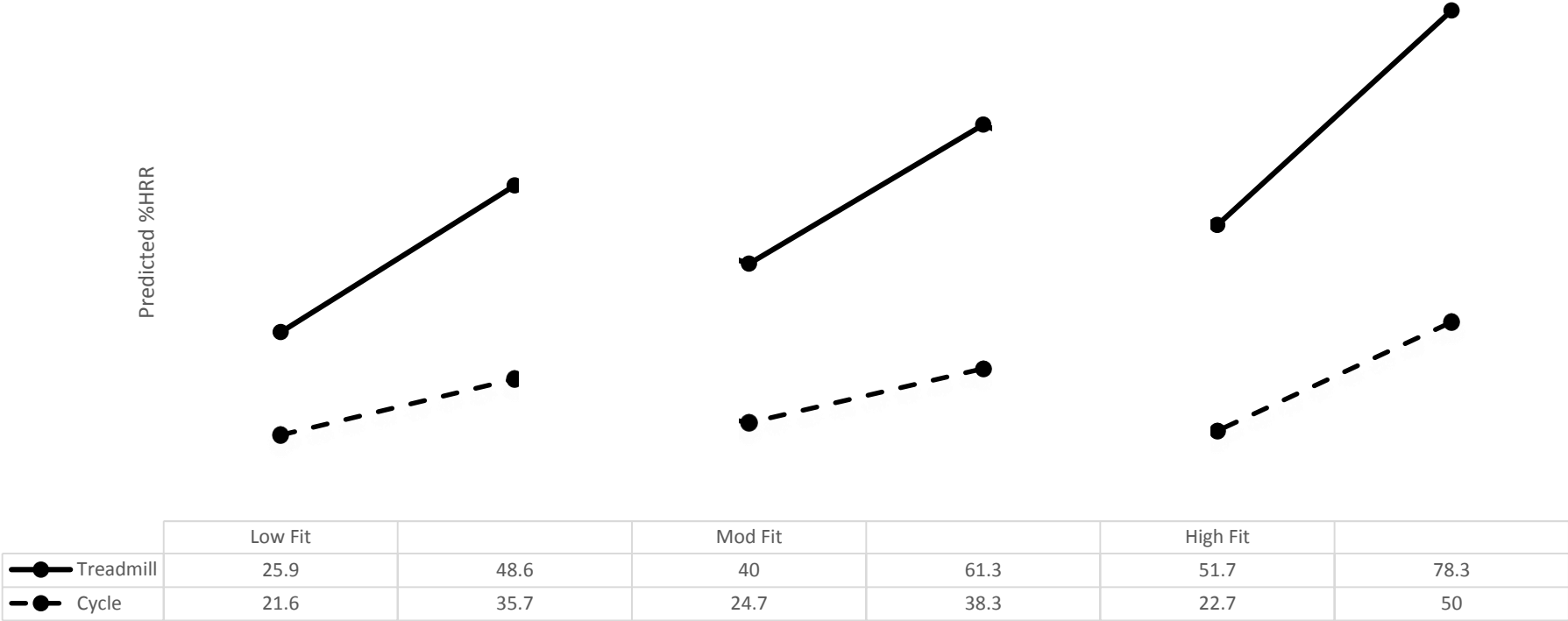
Figure 1. Inter-quartile range of VAT identification based on predicted HRR (% range) in cardiac patients separated by exercise modality and CRF category

	Low Fit		Mod Fit		High Fit	
Treadmill	25.9	48.6	40	61.3	51.7	78.3
Cycle	21.6	35.7	24.7	38.3	22.7	50

Predicted HRR using current guidelines, accounting for beta-blockade. Baseline CRF category based on Taylor et al. (2016); low fit <5 METs for women, and <6 METs for men, mod fit 5<7METs for women, and 6<8 METs for men, high fit ≥7 METs for women, and ≥8 METs for men. VAT, ventilatory anaerobic threshold. HRR, heart rate reserve. MET, metabolic equivalent where 1 MET = 3.5ml·kg^{-1}·min^{-1}.

Figure 2a. A case study highlighting how the 40-70% HRR prediction equation may under-estimate individualised exercise prescription. A 58 year-old male taking beta-blockers with a BMI of 24.8, VO_2peak of 35.28 $ml·kg^{-1}·min^{-1}$ in the high fitness category. CPET was conducted on a treadmill. Solid line corresponds to heart rate at ventilatory anaerobic threshold, which is 125bpm.

Figure 2b. A case study highlighting how the 40-70% HRR prediction equation may over-estimate individualised exercise prescription. A 71 year-old male not taking beta-blockers with a BMI of 25.8, VO2peak of 13.82 ml·kg^{-1}·min^{-1} in the low fitness category. CPET was conducted on a cycle. Solid line corresponds to heart rate at ventilatory anaerobic threshold, which is 72bpm.

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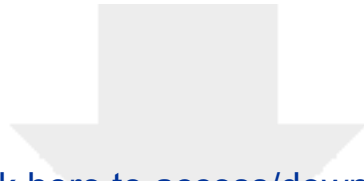
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