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Peer-reviewed author version

MILANI, Juliana; MILANI, Mauricio; VILACA CAVALLARI MACHADO, Felipe; Wilhelm, Matthias; Marcin, Thimo; D'Ascenzi, Flavio; Cavigli, Luna; KEYTSMAN, Charly; FALTER, Maarten; Braga, Fabrício; Donelli Da Silveira, Anderson; Graziella Franca, Bernardelli Cipriano; Cornelissen, Veronique; VERBOVEN, Kenneth; Gerson, Cipriano Junior & HANSEN, Dominique (2024) Setting the Exercise Intensity in Cardiovascular Rehabilitation for Patients with Cardiometabolic Disease: Is it different between males and females?. In: European Journal of Preventive Cardiology, 00 , p. 1 -3.

DOI: 10.1093/eurjpc/zwae367
Handle: http://hdl.handle.net/1942/44868

TITLE PAGE
Research Letter

Setting the Exercise Intensity in Cardiovascular Rehabilitation for Patients with Cardiometabolic Disease: Is it different between males and females?

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RUNNING HEAD: Exercise Intensity: Sex Considerations

INFORMATION ABOUT PREVIOUS PRESENTATIONS: None of the contents of this paper have previously been published or presented.

DISCLAIMERS: The authors declare no conflicts of interest

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WORD COUNT (excluding references): 994

Tables: 01

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Contemporary cardiovascular research increasingly considers sex as a biological variable in exercise prescription to better comprehend physiological differences and develop tailored plans, optimizing cardiovascular health and outcomes for both men and women[1,2]. This is important as exercise prescription should not follow 'one-size-fits-all' methodology, and emerging evidence of sex-related differences in exercise responses—due to anatomical and physiological characteristics—may affect oxygen transport, utilization, and fatigue resistance in both acute and chronic exercise[3].

In cardiovascular rehabilitation and for healthy individuals, ventilatory thresholds (VTs) obtained by cardiopulmonary exercise test (CPET) are preferred for exercise intensity prescription over peak effort percentages like heart rate (%HR_{peak}) or oxygen uptake (%VO_{2peak})[4,5]. However, when CPET is unavailable, guidelines recommend using peak effort indices (e.g., %HR_{peak}, or percentage of peak cycle-ergometer load (%W_{peak}))[4,6].

Nevertheless, recent observations indicate that, at least in healthy individuals, the lactate threshold occurs at a higher %VO_{2peak} and %HR_{peak} in women compared to men[5]. This underscores the limitations of current exercise prescription methods based on these metrics, potentially failing to regulate the metabolic stimulus needed for equivalent training adaptations. Thomas et al.[7] found that fixed VO_{2peak} percentages (60%-90%) improved exercise capacity similarly across sexes. However, the commonly-observed lower baseline VO_{2peak} in females raises concerns about exercise stimulus equivalence.

Hence, uncertainties remain as to whether males and females experience similar levels of metabolic stimulus based on the domain schema, particularly in patients with cardiometabolic diseases (CMD)[1,3].

Therefore, this study aims to compare physiological responses (%VO_{2peak}, %HR_{peak}, percentage of heart rate reserve (%HRR), or %W_{peak} at the first and second VTs (VT_1 and VT_2) between females and males with CMD. We hypothesize that these differences exist, may influence exercise prescription recommendations, and require sex-specific ranges to properly control the metabolic stimulus.

We analyzed 3,269 CPETs from twelve centers across nine countries (nine in Europe and three in South America) for VTs and their correlation with %VO_{2peak}, %HR_{peak}, %HRR, and %W_{peak}. Our retrospective study used data from prior prospective studies, approved by all relevant ethics committees (See supplementary material).

The inclusion criteria comprised individuals aged ≥20 years with a peak respiratory exchange ratio above 1.00 and without pulmonary, neurological, or severe orthopedic disorders. Exclusion criteria included pacemakers or implantable cardioverter devices without sinus rhythm during exercise and unidentified VTs. Patients underwent symptom-limited CPETs on cycle-ergometer or treadmill with individualized ramp protocols, including breath-by-breath gas analysis and electrocardiographic monitoring. Each laboratory followed international standards for device calibration, exercise protocols, and analysis[4,8].

Data were expressed as median and interquartile range (IQR) or absolute and relative frequency. Sex comparisons utilized Mann-Whitney U tests or Chi-square tests. We used multivariable linear regression with a stepwise forward algorithm to evaluate the independent effect of sex on %VO_{2peak}, %HR_{peak}, %HRR, and W_{peak} at VTs, ensuring assumptions were met. Predictors were selected based on background knowledge of their effects on exercise response. Thus, five independent variables were considered: sex, ergometer, age, body mass index, and beta-blocker use. First, sex was tested in a univariate model (Model 1), followed by adding ergometer (Model 2) and by multivariate analysis (Model 3). Only significant predictors remained in Model 3. If sex was not significant in Model 1, further models were not used. Analyses were performed using IBM-SPSS ($p<0.05$).

The sample comprised 701 women and 2,568 men (median ages: 63 years (IQR: 52-70) and 64 years (IQR: 54-71), respectively). Coronary artery disease prevalence was 76.6% in males and 60.5% in females, while heart failure prevalence was 19.5% and 31.0%, respectively (Supplementary Table S1).

On cycle-ergometer, females exhibited higher $\%VO_{2peak}$ at VT_1 (62.8% vs. 58.4%) and at VT_2 (86.9% vs. 84.2%), as well as higher $\%HR_{peak}$ at VT_1 (76.0% vs. 73.4%) and at VT_2 (90.3% vs. 89.1%), compared to males ($p<0.001$). Additionally, females showed higher %HRR at VT_1 (41.9% vs. 40.0%, $p=0.033$) and at VT_2 (77.2% vs. 75.3%, $p=0.002$). However, $\%W_{peak}$ was not different (Table 1). On treadmill, slightly different results were observed: females showed only VT_1 at a higher $\%VO_{2peak}$ (65.2% vs. 59.3%, $p<0.001$). Additionally, females had VTs at a higher $\%HR_{peak}$ than males (VT_1: 74.0% vs. 70.2%, $p<0.001$; VT_2: 91.7% vs. 90.8%, $p=0.005$), but no significant differences in %HRR (Table 1 and Supplementary Figures S1-S4). Although significant sex differences were found in VTs on both ergometers, they remained below 5%, questioning their clinical relevance for distinct prescription recommendations.

The multivariable linear regression indicated that the models were weak, explaining less than 7% of the variation for HR-based measures and less than 15% for $\%VO_{2peak}$ (Supplementary Table S2). Most predictors had influences below 5%. Sex emerged as a significant predictor in $\%VO_{2peak}$ and $\%HR_{peak}$, although with a low magnitude effect. Notably, sex had no significant influence on $\%W_{peak}$ for both VTs, nor on %HRR at VT_1. At VT_2, the ergometer influenced $\%VO_{2peak}$ and %HRR by 5% to 6%, yet again raising doubts about its clinical relevance despite statistical significance.

The results align with our recent findings on equations predicting HR at VTs using multiple regression analyses with exercise-derived predictors, in which sex was not included as a significant independent variable in the final models[6,9].

Importantly, current evidence shows that no fixed percentage of peak effort consistently defines domain-specific distribution during constant-work exercise, affecting exercise results and aerobic prescription frameworks[4-6]. Alternatively, prescriptions based on %HRR are more accurate than peak effort percentages[9]. Our study indicated that sex had minimal effect on %HRR at VT_2 and none at VT_1.

One limitation of this study was the lack of data on sex-specific risk factors, often undocumented but recognized as early indicators of cardiovascular risk, such as adverse pregnancy outcomes, lack of breastfeeding, early menopause, polycystic ovary syndrome, and infertility[10]. More research is required to better understand these unique sex-specific disease mechanisms.

In conclusion, while significant sex differences in $\%VO_{2peak}$ and $\%HR_{peak}$ were found, their clinical relevance appears limited. This suggests that current exercise prescription methods may not require substantial adjustments based solely on sex for patients with CMD. Further studies are necessary to validate these results and explore more personalized exercise strategies.

ACKNOWLEDGMENTS

We express our sincere appreciation to the laboratory staff across all participating centers, as well as to the physicians and other healthcare professionals who were involved in CPET evaluations.

FUNDING

Financial support by the Special Research Fund (BOF) from Hasselt University/Belgium, BOF23DOCBL10 (JGPOM) and BOF23KV10 (MM)) and from Flanders Research Foundation FWO, 1SE1222N (MF). This study was also supported by public research grants and scholarships from Brazilian fostering agencies: *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* [CAPES (Coordination for the Advancement of Higher Education Personnel)], *Conselho Nacional de Desenvolvimento Científico e Tecnológico* [CNPq (National Council of Scientific and Technological Development)] and Fundação de Apoio a Pesquisa do Distrito Federal [FAPDF (The State Funding Agency of Distrito Federal)].

CONFLICTS OF INTEREST

No potential conflict of interest is reported by the authors.

AUTHORS' CONTRIBUTIONS

JGPOM: conception and design, analysis and interpretation of the results, drafted the article; MM: analysis and interpretation of the results, revised it critically; FVCM, GFBC, KV: interpretation of the results, revised it critically; MW, TM, FDA, LC, CK, MF, FB, ADS, VC: acquisition of data, revised it critically; GCJ: conception and design, analysis and interpretation of the results, revised it critically, supervision; DH: conception and design, analysis and interpretation of data, revised it critically, supervision. All authors provided their final endorsement and committed to being responsible for all facets of the work, ensuring its integrity and accuracy.

DATA AVAILABILITY STATEMENT

Data cannot be publicly shared due to legislative restrictions in certain participating countries. However, researchers who meet the criteria for accessing confidential data may request it upon reasonable inquiry.

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Table 1. Cardiopulmonary Exercise Test Variables by Sexes and Ergometers.

	Cycle-ergometer			Treadmill		
CPET variables	Female (n = 351)	Male (n =1,410)	p-value	Female (n = 350)	Male (n =1,158)	p-value
VO_{2peak}, $L.min^{-1}$	1.16 (0.96, 1.39)	1.67 (1.32, 2.07)	< 0.001	1.11 (0.91, 1.36)	1.85 (1.41, 2.31)	< 0.001
VO_{2peak}, $mL.kg^{-1}.min^{-1}$	16.4 (14.1, 19.9)	20.1 (16.4, 25.0)	< 0.001	16.9 (14.3, 20.1)	22.1 (17.7, 28.0)	< 0.001
RER_{peak}	1.12 (1.09, 1.20)	1.13 (1.10, 1.20)	0.138	1.16 (1.11, 1.23)	1.18 (1.11, 1.25)	0.009
HR_{peak}, bpm	124 (109, 146)	128 (111, 146)	0.100	136 (117, 152)	142 (123, 160)	< 0.001
HR_{peak}, % predicted*	76.8 (68.1, 88.8)	79.5 (69.8, 89.5)	0.07	80.6 (70.7, 88.9)	85.0 (75.0, 94.3)	< 0.001
HR_{rest}, bpm	69 (62, 80)	68 (60, 76)	0.002	71 (63, 82)	68 (61, 76)	< 0.001
HRR, bpm	55 (41, 73)	60 (44, 76)	0.002	62 (46, 78)	72 (54, 90)	< 0.001
Peak load (W_{peak})	90 (72, 114)	137 (107, 176)	< 0.001	--	--	--
Peak speed (km/h)	--	--	--	5.9 (5.2, 6.7)	7.1 (6.0, 8.8)	< 0.001
Peak inclination (%)	--	--	--	6.5 (5.0, 8.0)	5.0 (3.5, 7.0)	< 0.001
VO_2 at VT_1, $mL.kg^{-1}.min^{-1}$	10.3 (8.7, 12.2)	11.6 (9.8, 13.9)	< 0.001	10.9 (9.5, 12.6)	12.9 (11.1, 15.3)	< 0.001
VO_2 at VT_1, $\%VO_{2peak}$	62.8 (55.0, 68.9)	58.4 (51.3, 65.7)	< 0.001	65.2 (59.3, 71.7)	59.3 (52.6, 66.5)	< 0.001
HR at VT_1, bpm	92 (83, 105)	92 (83, 103)	0.297	96 (89, 106)	98 (88, 109)	0.656
HR at VT_1, $\%HR_{peak}$	76.0 (68.8, 81.7)	73.4 (66.4, 79.5)	< 0.001	74.0 (66.7, 79.8)	70.2 (64.8, 76.8)	< 0.001
HR at VT_1, %HRR	41.9 (33.3, 52.5)	40.0 (31.3, 50.6)	0.033	41.3 (32.9, 49.4)	40.3 (33.3, 48.5)	0.467
Load at VT_1, W	39 (29, 51)	60 (47, 81)	< 0.001	--	--	--
Load at VT_1, $\%W_{peak}$	44.1 (36.0, 53.3)	45.3 (37.8, 53.7)	0.166	--	--	--
Speed at VT_1 (km/h)	--	--	--	3.9 (3.2, 4.6)	4.9 (4.0, 5.7)	< 0.001

Inclination at VT_1 (%)	--	--	--	2.5 (2.0, 3.0)	2.0 (1.5, 3.0)	< 0.001
VO_2 at VT_2, $mL.kg^{-1}.min^{-1}$	14.4 (12.2, 17.2)	16.6 (13.7, 20.6)	< 0.001	15.3 (13.0, 17.9)	19.8 (15.8, 25.2)	< 0.001
VO_2 at VT_2, $\%VO_{2peak}$	86.9 (81.8, 90.8)	84.2 (78.9, 89.4)	< 0.001	90.9 (86.7, 95.2)	90.6 (85.8, 94.8)	0.205
HR at VT_2, bpm	110 (98, 127)	112 (100, 126)	0.905	122 (107, 136)	127 (110, 144)	< 0.001
HR at VT_2, $\%HR_{peak}$	90.3 (86.6, 94.5)	89.1 (84.5, 93.0)	< 0.001	91.7 (87.3, 95.6)	90.8 (86.8, 94.0)	0.005
HR at VT_2, %HRR	77.2 (69.0, 85.6)	75.3 (66.2, 83.6)	0.002	81.5 (72.7, 88.9)	80.6 (73.3, 87.9)	0.514
Load at VT_2, W	71 (57, 90)	107 (84, 138)	< 0.001	--	--	--
Load at VT_2, $\%W_{peak}$	80.0 (73.3, 85.9)	78.7 (72.8, 84.6)	0.095	--	--	--
Speed at VT_2 (km/h)	--	--	--	5.4 (4.6, 6.1)	6.4 (5.4, 7.7)	< 0.001
Inclination at VT_2 (%)	--	--	--	5.5 (4.0, 6.5)	4.0 (3.0, 5.5)	< 0.001

Data expressed as median and interquartile range.

Statistics: Mann-Whitney U test

*Reference: Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. *J Am Coll Cardiol* 2001;**37**:153-156. doi: 10.1016/s0735-1097(00)01054-8

HR, heart rate; HRR, heart rate reserve; HR_{rest}, rest heart rate; HR_{peak}, peak heart rate; RER_{peak}, peak respiratory exchange ratio; VO_2, oxygen uptake; VO_{2peak}, peak oxygen uptake; VT_1, first ventilatory threshold; VT_2, second ventilatory threshold; $\%HR_{peak}$, percentage of peak heart rate; %HRR, percentage of heart rate reserve; $\%VO_{2peak}$, percentage of peak oxygen uptake.