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Chasland, LC, Green, DJ, Maiorana, AJ, Nosaka, K, Haynes, A, Dembo, L and Naylor, LH (2017) Eccentric Cycling: A Promising Modality for Patients with Chronic Heart Failure. *Medicine and Science in Sports and Exercise*, 49 (4). pp. 646-651. ISSN 1530-0315

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3 **Eccentric cycling: A promising modality for patients with chronic heart failure.**
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7 **Lauren C Chasland¹, Daniel J Green^{1,2,3}, Andrew J Maiorana^{4,5}, Kazunori Nosaka⁶,**
8 **Andrew Haynes¹, Lawrence Dembo⁷, Louise H Naylor^{1,5}**
9

10 ¹School of Sport Science, Exercise and Health,
11 The University of Western Australia, Perth, Western Australia
12

13 ²Research Institute for Sport and Exercise Science,
14 Liverpool John Moores University, Liverpool, United Kingdom
15

16 ³Principal Research Fellow, National Health and Medical Research Council, Australia
17

18 ⁴School of Physiotherapy and Exercise Science,
19 Curtin University, Perth, Western Australia
20

21 ⁵Allied Health Department,
22 Fiona Stanley Hospital, Perth, Western Australia.
23

24 ⁶Centre for Exercise and Sports Science Research, School of Medical and Health Sciences,
25 Edith Cowan University, Joondalup, Western Australia
26

27 ⁷Advanced Heart Failure and Cardiac Transplantation Unit
28 Fiona Stanley Hospital, Perth, Western Australia
29

30
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32
33
34
35
36 **Corresponding author:**

37 Winthrop Professor Daniel J Green
38 School of Sport Science, Exercise and Health M408
39 The University of Western Australia
40 35 Stirling Highway
41 Crawley, WA, 6009, Australia.
42 Telephone: +61 6488 2361
43 Fax: +61 6488 1039
44 Email: danny.green@uwa.edu.au
45

46 **Abstract**

47 **Introduction**

48 Chronic heart failure (CHF) is characterized by dyspnea and poor exercise tolerance, which
49 decreases aerobic capacity ($\dot{V}O_{2\text{peak}}$), a measure strongly correlated with quality of life and
50 mortality. In healthy populations, eccentric (ECC) cycling can be performed at a lower
51 oxygen demand for matched workload, compared to concentric (CON) cycling, but few
52 studies have previously investigated ECC cycling in CHF. We hypothesized that, when
53 matched for external workload (Watts), an ECC cycling bout would be performed at a lower
54 cardiorespiratory load ($\dot{V}O_2$) than CON in patients with CHF.

55 **Methods**

56 Eleven CHF patients (10 males) with impaired left ventricular systolic function (ejection
57 fraction $31\pm 12\%$) completed a CON $\dot{V}O_{2\text{peak}}$ test, with the subsequent ECC and CON
58 protocols set at 70% of individual maximal CON power (Watts). Oxygen consumption
59 ($\dot{V}O_2$), respiratory exchange ratio (RER), minute ventilation (\dot{V}_E), heart rate (HR) and rate
60 pressure product (RPP) were compared between conditions.

61 **Results**

62 ECC was performed at a lower $\dot{V}O_2$ (12.3 ± 1.3 vs. 14.1 ± 0.8 mL.kg⁻¹min⁻¹, P=0.01), RER
63 (0.92 ± 0.02 vs. 0.96 ± 0.01 , P=0.01) and \dot{V}_E (36.5 ± 4.4 vs. 40.2 ± 2.0 L/min, P=0.04) in
64 comparison to CON, despite both conditions being performed at matched workloads. Heart
65 rate (101 ± 5 vs. 96 ± 1 bpm; P=0.06) and RPP ($13,539\pm 788$ vs. $11,911\pm 227$ bpm.mmHg⁻¹,
66 P=0.15) were not significantly different between conditions.

67 **Conclusion**

68 When matched for external workload, ECC cycling can be performed with a lower oxygen
69 demand than CON in patients with CHF. Eccentric cycling is a promising modality for
70 cardiac rehabilitation in severely deconditioned patients with CHF.

71

72 **Keywords:** exercise, cardiac rehabilitation, oxygen uptake, exercise rehabilitation.

73

74 **Introduction**

75 Chronic heart failure (CHF) is a major global health burden (28). By 2030, the prevalence of
76 CHF is expected to increase a further 23% due to rising levels of obesity and diabetes,
77 alongside improved survival following myocardial infarction (19, 29). Hallmark symptoms of
78 CHF are dyspnea and fatigue on exertion (7), leading to impaired functional independence,
79 compromised quality of life and increased morbidity and mortality (32).

80

81 It is well established that peripheral abnormalities represent a locus of fatigue in CHF. The
82 sequelae of CHF involving sympathetic nervous system activation, increased inflammatory
83 cytokine release and excessive peripheral vasoconstriction (21), are associated with a
84 generalized skeletal muscle myopathy, which worsens as the disease progresses (3). First
85 conceptualized in 1996 by Coats et al. (8), the ‘muscle hypothesis’ proposes that the
86 activation of skeletal muscle metaboreceptors may underpin exertional dyspnea and fatigue,
87 and by way of a feedback loop, contribute to deteriorating left ventricular function. This
88 creates a vicious cycle whereby worsening exercise intolerance and subsequent
89 deconditioning induce further exacerbation of the condition.

90

91 However, such abnormalities in skeletal muscle function and blood flow are amenable to
92 exercise-mediated improvement (10, 18, 24, 25). Exercise training has shown to increase
93 aerobic capacity ($\dot{V}O_{2peak}$) in patients with CHF (13, 15, 31), a significant clinical finding
94 given that this measure is a strong prognostic indicator (9, 26). Exercise-based rehabilitation
95 programs are now an established component of CHF management worldwide, decreasing
96 hospitalizations, increasing health-related quality of life and possibly reducing long-term
97 mortality (31).

98 Conventionally, exercise training for patients with CHF has utilized concentric exercise such
99 as cycling, in which prime movers (e.g. knee extensors) shorten in pedalling. However, it can
100 be challenging to prescribe concentric cycling (CON) at an intensity sufficient to induce
101 peripheral adaptations, without causing dyspnea and fatigue in patients with more severe
102 CHF. An exercise modality that enables a greater localized stimulus to the muscle, without
103 increased cardiovascular demand, may provide an alternative pathway to attenuate skeletal
104 muscle abnormalities in CHF.

105

106 Eccentric cycling (ECC) possesses unique characteristics that differ from CON, making it a
107 potentially efficacious and clinically relevant alternative for CHF patients. In healthy young
108 males, at the same mechanical intensity (Watts), metabolic intensity ($\dot{V}O_2$) is significantly
109 lower when cycling eccentrically versus concentrically (36). The mechanisms underpinning
110 this phenomenon are not fully understood, but are likely the result of complex molecular
111 events resulting in less adenosine triphosphate (ATP) usage during ECC versus CON
112 exercise (20, 33).

113

114 As skeletal muscle has been identified as a key locus of exercise intolerance in patients with
115 CHF (34, 35), ECC may enable exercise to be performed at higher mechanical intensities
116 resulting in clinically important peripheral adaptations, without eliciting significant
117 symptoms. However, there is a paucity of literature comparing the acute effects of ECC and
118 CON cycling in patients with CHF, particularly studies in which the intensity of the sessions
119 is well matched. The aim of this study was to compare, in patients with CHF, the oxygen
120 demand associated with ECC and CON cycling performed at matched workloads. We
121 hypothesized that, when matched for power output (W), patients with CHF would be able to
122 perform an ECC cycling bout at a lower $\dot{V}O_2$ in comparison to CON.

123

124 **Methods**

125 Participants

126 Eleven participants with CHF NYHA class I to III with a reduced left ventricular systolic
127 function (ejection fraction <45%) who provided written informed consent were recruited
128 from Fiona Stanley Hospital. Ethics approval for the study was provided by the Royal Perth
129 Hospital Human Research Ethics Committee (HREC 14-160). Medical screening, performed
130 by a cardiologist, occurred before participants were accepted into the study. Participants were
131 excluded from the study if they met any of the following criteria: resting hypertension
132 (>165/95 mmHg), severe obstructive aortic valve stenosis, severe heart rhythm disorder
133 excluding safe participation in exercise, severe pulmonary hypertension (>70 mmHg), venous
134 thromboembolic history within the past three months, musculoskeletal comorbidity limiting
135 functional capacity beyond the CHF itself or inability to provide informed consent. As this
136 was a trial of patients undergoing routine medical therapy, heart failure medications did not
137 constitute exclusion. There were no changes in medication regimens or episodes of heart
138 failure decompensation during the course of the study.

139

140 Experimental design

141 Participants performed a medically supervised graded exercise test (GXT) on a conventional
142 electronically braked recumbent cycle ergometer (Corival, Lode BV, Groningen, The
143 Netherlands) with breath by breath $\dot{V}O_2$ and minute ventilation (\dot{V}_E) measured via indirect
144 calorimetry (Vyntus CPX, Jaeger, CareFusion, Germany) and respiratory exchange ratio
145 (RER) calculated automatically. Heart rate (HR) and rhythm were constantly monitored by
146 12-lead electrocardiogram (ECG). Stages were three minutes in duration and cycling was

147 maintained at a cadence of 60 revolutions per minute (rpm) with workload increased by 20 W
148 increments. Blood pressure was measured manually in the final minute of each stage and the
149 assessment was terminated when the participant reached volitional exhaustion.

150 Seven days after the GXT, participants performed an ECC cycling session. To familiarise the
151 participants with ECC cycling, each engaged in a short (three minute) familiarisation ECC
152 cycling bout consisting of 30 s without any load, followed by one minute at 30% of W_{\max}
153 (from GXT) and then one minute aiming for 70% W_{\max} and a further 30 s without any load.
154 When HR and $\dot{V}O_2$ had returned to baseline levels, participants performed a three minute
155 warm-up (30% of W_{\max}), followed by five minutes at a workload equivalent to 70% of
156 maximum CON workload (W) achieved during the GXT. Due to the oscillatory nature of
157 ECC cycling, the ECC session was always conducted first with workload averaged across
158 each 30 s period. This way, we were able to alter the workload during every 30 sec during the
159 CON session, to match the two conditions for power output (see Figure 1). Seven days later,
160 a CON session was performed, during which workload was matched to the ECC session. The
161 ECC and CON sessions were performed at the same time of day to help ensure medications
162 influenced the sessions equally.

163

164 In the current study, we matched the ECC and CON sessions based on workload, similar to
165 our previous work by Penailillo et al. (36). Because of the limited exercise capacity of the
166 participants in the present study, we minimized the exercise time to 5 min, but set the
167 intensity at 70% W_{\max} to compare between ECC and CON. Our pilot studies in healthy young
168 participants showed that when eccentric cycling duration is ~ less than 5 minutes, muscle
169 damage characterized by delayed onset muscle soreness and prolonged strength loss is
170 minimal. Based on this observation, we surmised that 5-min eccentric cycling would not
171 induce significant muscle soreness in our CHF cohort. The workload chosen in this study

172 equated to $\sim 75\%$ $\dot{V}O_{2\text{peak}}$, which is at the upper end of the range for continuous aerobic
173 exercise prescription for patients with CVD, as recommended by the ACSM (2).

174

175 Eccentric cycling (ECC) protocol

176 On arrival at the lab participants were attached to a 12-lead ECG and resting HR, rhythm and
177 BP recorded. Participants were given an explanation as to how to operate the ECC ergometer.
178 Eccentric cycling was performed on a recumbent ergometer (Eccentric Trainer, Metitur, Ltd,
179 Jyväskylä, Finland) with a 1.5 kW motor that powered the cranks in reverse. A target power
180 output line was calculated for each participant and displayed on a screen. Actual power
181 output was visually and numerically displayed on screen as a feedback mechanism for
182 participants. Cadence was set at 40 rpm to account for the difficulty in performing higher
183 cadence ECC cycle ergometer contractions.

184

185 A metabolic cart (Vyntus CPX, Jaeger, CareFusion, Germany) was used to measure oxygen
186 uptake and participants performed a three minute warm up, aiming for a power output
187 correlating to 30% W_{max} achieved during GXT. Following this, participants were instructed
188 to increase their wattage to 70% of W_{max} for a further five minutes. Heart rate, $\dot{V}O_2$ ($\text{ml}\cdot\text{kg}^{-1}\cdot$
189 min^{-1}), \dot{V}_E and RER were averaged across 10 s epochs with BP recorded at 1:30 and 4:30 of
190 the five minute protocol. This was followed by a three minute cool down during which
191 participants were instructed to keep their legs turning without applying any resistance.

192

193 Concentric (CON) cycling protocol

194 One week following the ECC session, participants completed a CON session using the
195 conventional recumbent cycle ergometer mentioned above, with resistance (W) adjusted

196 every 30 s to match workload attained during the ECC session. Participants were instructed to
197 cycle at 40 rpm. Identical measurements to those outlined in the ECC session were recorded.

198

199 Other measures

200 A visual analogue scale (VAS; 10-cm line, 0: no pain, 10: worst possible pain) was used to
201 assess exercise muscle soreness in the quadriceps muscles pre, immediately post, 1, 24, 48
202 and 72 hours after each exercise session as a marker of muscle damage. Blood lactate (BLa)
203 was measured before, immediately after and five minutes after each exercise by obtaining
204 blood samples from the fingertip using a Lactate Pro 2 (Arkay Inc., Japan).

205

206 Statistical analyses

207 An a-priori sample size calculation was calculated from Meyer. et al. (27), using an effect
208 size of 3.74, power of 0.8 and $p = 0.01$. This calculation indicated that a minimum sample
209 size of 8 was required. All results were analysed using SPSS (Version 20.0, IBM, USA) and
210 expressed as means \pm SD. As CON workload was manipulated every 30 s in order to closely
211 match it to the ECC workload of the previous session, average values for the final 10 s of
212 each 30 s epoch for $\dot{V}O_2$, HR, RER and \dot{V}_E were recorded. These values were averaged
213 across each minute of the exercise session to provide an overall average for the five minute
214 protocol. Statistical analyses for the above measures were conducted using these values.
215 Paired, two tailed t-tests were used to analyse the differences in outcome measures between
216 the two exercise protocols. For all analyses, statistical significance was set at $p \leq 0.05$.

217 **Results**

218 Participant characteristics

219 Participant characteristics are presented in Table 1. Five participants had ischemic
220 cardiomyopathy and six had non-ischemic cardiomyopathy as their primary diagnosis.
221 Medications remained unchanged throughout the course of the study. Each participant
222 completed all sessions without any adverse responses.

223

224 Comparison of ECC and CON sessions

225 Respiratory variables

226 Across the exercise period, $\dot{V}O_2$ was lower ($P=0.01$) in ECC ($12.3 \pm 1.3 \text{ ml.kg}^{-1}.\text{min}^{-1}$) than
227 CON ($14.1 \pm 0.8 \text{ ml.kg}^{-1}.\text{min}^{-1}$, Figure 2).

228

229 Respiratory exchange ratio (RER) was lower during ECC (0.92 ± 0.02) than CON ($0.96 \pm$
230 0.01 , $P=0.01$). Similarly, \dot{V}_E was also significantly lower during ECC (36.5 ± 4.4 vs. 40.2 ± 2.0
231 L/min , $P=0.04$). The average change in blood lactate (BLa) from pre to immediately post
232 exercise was similar between conditions (1.5 ± 3.7 vs. $2.7 \pm 3.8 \text{ mmol/L}$, $P=0.46$).

233

234 Hemodynamic variables

235 Heart rate (HR) was not statistically different during ECC ($101 \pm 5 \text{ bpm}$) and CON (96 ± 1
236 bpm , $P=0.06$). Similarly, there were no differences in mean arterial pressure (92 ± 1 vs. $89 \pm$
237 2 mmHg , $P=0.34$) or rate pressure product (RPP) ($13,539 \pm 788$ vs. $11,911 \pm 227$
238 bpm.mmHg^{-1} , $P=0.15$) between conditions.

239

240 Muscle soreness

241 No significant difference in muscle soreness existed between ECC and CON before and

242 immediately after exercise (0.82 ± 1.4 vs. 0.82 ± 1.3 cm). Muscle soreness was significantly
243 higher 24 hours (3.0 ± 3.1 vs. 0.5 ± 0.9 cm, $P=0.02$) and 48 hours after ECC exercise
244 compared to CON (2.1 ± 2.1 vs. 0.9 ± 0.7 cm, $P=0.01$), but this difference diminished 72
245 hours post-exercise (0.5 ± 2.0 vs. 0.0 ± 0.4 cm, $P=0.38$).

246

247

248 **Discussion**

249 The principal finding of this study is that, when matched for workload, $\dot{V}O_2$ was significantly
250 (~13%) lower during ECC compared to CON cycling in patients with CHF. This is
251 consistent with previous research in healthy populations reporting lower $\dot{V}O_2$ responses to
252 ECC than CON when matched for workload (1, 11, 36). ECC did not evoke significantly
253 higher cardiovascular demand, with similar HR, BP and RPP responses, to CON. The
254 corollary is that, for a given $\dot{V}O_2$, higher workloads can be attained during ECC. Exercise
255 that elicits a higher localized muscular stimulus, in the absence of increased cardiovascular
256 demand, is a clinically relevant finding for patients with CHF in whom skeletal muscle
257 maladaptations contribute significantly to exercise intolerance and impaired aerobic capacity
258 (14).

259

260 Some previous studies have compared ECC and CON in clinical populations (4, 5, 17, 27, 38,
261 40). These studies are broadly consistent with our data, in that they report higher power
262 outputs during ECC. Besson et al. (4) concluded that ECC was a safe alternative to CON in
263 CHF, inducing functional improvements in 6 min walk time following a seven week ECC
264 training program. Using the same protocol, the group conducted a follow up study concluding
265 that ECC induced similar improvements in maximal capacity and superior strength (triceps
266 surae) increases compared to CON (5). However, in both studies, workload (W) was

267 subjectively matched between conditions. Theodorou et al. (40) assessed the effect of ECC
268 exercise in participants with CHF via stair descending and ascending exercise. Eccentric and
269 isometric torque was reported to be greater in the ascending group, with concentric torque
270 similar between conditions. Although, the aforementioned studies used a between-subjects
271 design and individual differences may partially explain the results. The present study is
272 therefore the first, to our knowledge, to closely match intensity between conditions and use a
273 within-subjects design, allowing valid comparisons to be made between the acute responses
274 to ECC and CON cycling in individuals with CHF.

275

276 In addition to a lower $\dot{V}O_2$ response, we also observed significantly lower \dot{V}_E and RER
277 values during ECC. These results indicate that, when matched for workload, ECC can be
278 performed with a lower respiratory demand compared to CON. One of the mechanisms that
279 may be responsible for the lower oxygen demand involves actin-myosin cross-bridge cycling.
280 During ECC contractions some cross-bridges are forcibly detached, allowing ATP to be
281 stored, thereby lowering metabolic cost (33). Achieving a similar exercise workload with a
282 significantly lower oxygen demand is a clinically relevant and novel finding for CHF
283 patients, who commonly experience dyspnea, impaired skeletal muscle function and exercise
284 intolerance.

285

286 We reported a slightly increased HR during the ECC bout (~5 bpm, not statistically
287 significant). This is in contrast to two previous studies in healthy individuals, where a lower
288 hemodynamic burden (e.g. HR, BP) was reported during ECC compared to CON exercise
289 (11, 36). We speculate that our findings reflect the unfamiliar ECC cycling stimulus, which
290 our previous work shows can potentially exaggerate HR response, and that HR during ECC
291 cycling decreases with repeated exposures (36). Previous work by Penailillo et al. (36)

292 indicated that the HR response to an initial bout of ECC exercise is exaggerated, with
293 subsequent bouts of ECC at identical workloads eliciting a 12% lower HR response. The
294 mechanisms underlying this are currently not well understood, however the authors
295 speculated that this may be due to elevated metabolic stress or cycling efficiency experienced
296 during an initial ECC session. Meyer et al. (27) examined coronary artery disease patients
297 with preserved ventricular function and found HR during ECC was consistently higher than
298 during CON across a 20-min protocol following 5 and 8 weeks of a training program. In
299 contrast, significantly lower HRs during ECC were recorded by Besson et al. (4) in ECC
300 trained patients with CHF. In a similar population, who also underwent a training program,
301 Theodorou et al. (40) also reported lower HRs in the descending stair group following 6
302 weeks of training, although no statistical analysis was provided. However, the subjective
303 quantification of workload in these studies complicates interpretation of the results. In the
304 present study, HR responses during ECC were not significantly different compared to CON
305 at matched workloads. This may be related to the medication regimes of our participants,
306 which attenuate HR and BP responses to exercise. Additionally, the difference between ECC
307 and CON HR responses has been demonstrated to be intensity-dependent, with HR during
308 concentric exercise increasing more steeply with increasing workload (11). It is therefore
309 possible that the workload performed in this study was too light to reveal significant
310 differences in HR between the two conditions. Similarly, BP and RPP responses did not
311 significantly differ between the conditions. Given that RPP is an index of myocardial oxygen
312 demand (16), this finding has important implications and indicates that ECC exercise can be
313 performed with a similar hemodynamic response to CON exercise in patients with CHF.

314

315 Average levels of BLa were higher following CON, although this did not reach statistical
316 significance. These results are consistent with Perry et al. (37) and Dufour et al. (11) who

317 reported that ECC BLa did not accumulate in healthy populations until participants had
318 reached higher intensities (300 W) of cycling. Due to the low aerobic capacity in our
319 participants (in comparison to healthy populations), average power output did not exceed
320 90W during the exercise conditions. The average absolute (pre/post) change in BLa was
321 therefore small but, importantly, was not higher under the ECC condition.

322

323 Muscle soreness was significantly higher 24 and 48 hours after ECC compared to CON,
324 despite the fact that we matched cadence at 40 rpm for both conditions, as ECC is better
325 tolerated at slower speeds (6). These findings concur with those of Penailillo et al. (36) and
326 Elmer et al. (12) Although eccentric contractions demonstrate mechanical efficiency through
327 recruitment of fewer muscle fibers for a given level of tension (22, 39), increased muscle
328 soreness occurs due to connective tissue damage and inflammation (23). Only responses to a
329 single bout of ECC and CON were investigated in this study and we were therefore unable to
330 examine the repeated bout effect, whereby muscle soreness decreases significantly following
331 subsequent ECC bouts (30).

332

333 Several limitations of the present study are germane. Due to the highly specific nature of our
334 sample, our results cannot necessarily be extrapolated to all patients with cardiac-related
335 conditions. Also, although several females underwent the screening process, only one
336 satisfied the inclusion criteria. Thus, these results may not necessarily translate to females.
337 The order of the exercise sessions was unable to be randomized because we needed to
338 carefully assess ECC responses in order to match subsequent CON sessions. However, our
339 approach did allow us to match the conditions for power output, allowing valid comparisons
340 to be made.

341

342 The present study investigated the responses to ECC and CON. Currently, this form of
343 exercise requires relatively expensive ECC ergometers, which may be a barrier to its uptake
344 for many cardiac rehabilitation programs. However, cycling is only one form of ECC
345 exercise. Walking down hill, controlled lowering into a chair or lowering weights are all
346 functional eccentric based movements requiring little expense while taking advantage of the
347 unique properties of ECC contractions. Future studies should investigate if our promising
348 results related to ECC are also applicable to these more accessible exercise options.

349

350 In conclusion, this study has confirmed that, when matched for workload, ECC is performed
351 at a lower oxygen demand in comparison to CON in patients with CHF. Furthermore, this can
352 be attained with a similar hemodynamic demand. These findings suggest that greater external
353 workloads may be achieved eccentrically, for a given oxygen demand thereby creating a
354 foundation for further research. As functional capacity is severely restricted in patients with
355 CHF, ECC exercise has potential to enhance much needed peripheral adaptations and
356 functional capacity.

357

358

359 **Acknowledgements**

360 This work was supported by a Vanguard Grant (100576) from the National Heart Foundation
361 and Professor Green's research is supported by an NHMRC Principal Research Fellowship
362 (1090914). Lauren Chasland was supported by a REDiMED honours scholarship.

363 The authors would like to thank Dr. Aravinda Selvarajah and Dr. Yi Xian Chan for their
364 medical supervision of the graded exercise tests. The expert technical assistance of Tony
365 Roby, Chunbo Liu and Jude Ng is also gratefully acknowledged.

366

367 **Conflict of Interest**

368 The results of this study do not constitute endorsement by the American College of Sports
369 Medicine. The authors also wish to declare that the results of this study are presented clearly,
370 honestly, and without fabrication, falsification, or inappropriate data manipulation.

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Figure legend

Figure 1: Power outputs (W) during the 5 minute exercise protocol in the ECC and CON conditions.

Figure 2: Difference in power output (W), $\dot{V}O_2$ (ml.kg⁻¹.min⁻¹), RER (ml.kg⁻¹.min⁻¹), and \dot{V}_E (L/min) between ECC and CON. Data are expressed as a percent (%) of ECC, illustrating a significantly higher power output (W), with a lower $\dot{V}O_2$, RER and \dot{V}_E during the ECC condition compared to the CON session.

* P<0.01, # P<0.05

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