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1 **Post-exercise hypotension after exercising in hypoxia with and without tart cherry**
2 **supplementation**

3

4 *Short running title: Hypoxia and tart cherry effects on post-exercise hypotension*

5

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18

19

20 **Abstract**

21 **Background:** This study investigated the effects of hypoxic exercise with and without tart
22 cherry supplementation on post-exercise hypotension (PEH). **Method:** In a randomized order,
23 12 healthy young adults (9 men and 3 women) completed cycle exercise to exhaustion i) in
24 normoxia without any supplementation (Norm), ii) in hypoxia (13% O₂) with placebo (Hypo),
25 and iii) in hypoxia with tart cherry supplementation (Hypo+TC). Supplements were supplied
26 for 5 days pre-trial (TC was 200 mg anthocyanin per day for 4 days and 100 mg on day 5).
27 **Results:** Cycle exercise total energy expenditure was greater in Norm than Hypo and Hypo+TC
28 ($P<0.001$) with no difference between Hypo and Hypo+TC ($P=0.41$). Mean arterial pressure
29 (MAP) decreased during recovery in all trials (main effect of time, $P<0.001$), with no difference
30 in PEH between the trials ($P>0.05$, change (Δ) in MAP from pre-exercise at 60 min recovery,
31 mean difference, Norm Δ -4.4 mmHg, Hypo Δ -6.1 mmHg, and Hypo+TC Δ -5.2 mmHg).
32 Cardiac baroreflex sensitivity decreased during recovery in all trials ($P<0.001$) and was lower
33 in Hypo than Norm and Hypo+TC (main effect of trial, $P=0.02$). **Conclusion:** Post-exercise
34 hypotension was not increased after exercise in hypoxia, with or without tart cherry
35 supplementation, compared to exercise in normoxia.

36

37 **Keywords:** *baroreflex sensitivity, hypoxic vasodilation, mean arterial pressure, polyphenol*

38

39 **Introduction**

40 Arterial blood pressure (BP) is reduced for up to 24 h following a single session of physical
41 exercise; a phenomenon called “Post Exercise Hypotension (PEH)” (Halliwill et al., 2014). It
42 is clinically important to investigate factors that enhance PEH as the magnitude of PEH after
43 acute exercise relates to the beneficial BP-lowering effects of exercise training (Kleinnibbelink
44 et al., 2020). While various factors such as exercise mode, intensity, and duration, and
45 environmental temperature may influence PEH, few studies have investigated the effect of
46 hypoxia on PEH (Halliwill et al., 2014; Horiuchi and Oliver, 2023). PEH follows a decrease in
47 peripheral vascular resistance (Brito et al., 2014), and as hypoxia enhances vasodilation (Joyner
48 and Casey, 2014), greater PEH may be anticipated after exercising in hypoxia than normoxia,
49 which has been confirmed in some (Horiuchi et al., 2016a; 2018; Saito et al., 2019), but not all
50 previous studies (Fornasiero et al., 2021; Horiuchi et al., 2022; Kleinnibbelink et al., 2020). BP
51 may not be reduced after exercise in hypoxia due to an attenuation of baroreflex sensitivity
52 (BRS) and a shift in cardiac autonomic function to sympathetic activity (Bourdillon et al., 2023;
53 Halliwill et al., 2014).

54 Tart cherries, and other dark-coloured berries, are rich in antioxidants and polyphenols
55 including anthocyanins (Keane et al., 2016). In normoxic conditions, anthocyanin-rich
56 supplements have been shown to increase peripheral artery diameter and blood flow (Barnes et
57 al., 2020; Cook et al., 2023; Matsumoto et al., 2005), and reduce peripheral vascular resistance

58 (Barnes, 2020), which precedes PEH (Halliwill et al., 2014). Moreover, a recent study in
59 normoxia reported a larger decrease in post-exercise systolic blood pressure, but not diastolic
60 or mean arterial pressure (MAP), following 7 days of an anthocyanin-rich supplement
61 compared to a placebo (Shan and Cook, 2023). These vascular effects may be mediated by
62 polyphenols and circulating metabolites' improving nitric oxide bioavailability (Bell and
63 Gochenaur, 2006; Xu et al., 2004) and reducing oxidative stress, which is elevated post-exercise
64 and in hypoxic environments. PEH may also be expected to be greater after hypoxic exercise
65 and anthocyanin-rich supplementation compared to normoxic or hypoxic exercise alone, as
66 antioxidant supplementation has previously been shown to restore the imbalance of cardiac
67 autonomic nervous activity, as assessed by heart rate variability (HRV) in humans (Weggen et
68 al., 2021), and improve BRS in rats (Alves et al., 2015; Garcia et al., 2017).

69 Accordingly, this study investigated the effects of tart cherry (TC) supplementation on
70 PEH after exercising in hypoxia. We hypothesized that the magnitude of PEH would be greater
71 in hypoxia compared to normoxia, and PEH would be further accentuated with TC
72 supplementation.

73

74 **Methods**

75 *Participants*

76 The present report presents additional recovery and normoxia data from previously published

77 investigations that examined tart cherry supplementation effects on hypoxic exercise
78 performance (Horiuchi et al., 2023). This study was approved by the Ethical Committee of
79 Mount Fuji Research Institute in Japan and was performed following Declaration of Helsinki
80 guidelines (No. 202001). Of the 13 participants in the previous study, 12 (9 men and 3 women)
81 performed an additional normoxic exercise and recovery experimental trial. The participants'
82 age, height, and body mass were 21 ± 1 years, 169 ± 7 cm, and 62.1 ± 8.9 kg, respectively
83 (values are mean \pm standard deviation [SD]). All participants were non-smokers, had no history
84 of cardiovascular disease, and had not been exposed to an altitude higher than 1,500 m in the 6
85 months before the study.

86

87 *Study design*

88 This study consisted of three trials (**Figure 1**): (1) normobaric normoxic exercise without any
89 supplementation (Norm); (2) normobaric hypoxic exercise (13% O₂) with a placebo (Hypo),
90 and (3) normobaric hypoxic exercise (13% O₂) with TC supplementation (Hypo+TC). In a
91 double-blinded and randomized manner, each participant ingested a placebo or TC capsule (Tart
92 cherry 1200 mg containing 100 mg of anthocyanin, Nature's Life, Orem, UT, USA) twice per
93 day for 4 days before the experimental trial, and once on the day of the experimental trial 2 h
94 before beginning exercise, which is consistent with studies reporting hemodynamic changes after
95 single doses and 4–7 days of anthocyanin-rich supplementation (Matsumoto et al., 2005).

96 Participants were provided a list of antioxidant-rich foods and instructed to avoid these while
97 in the study.

98

99 *Experimental procedure*

100 The exercise was performed on a cycle ergometer (COMBI232-C, COMBI, Japan) in an
101 environmental chamber (24 C°, 50% relative humidity, TBR-4, 5SA2GX, Tabai Espec Co. Ltd.,
102 Tokyo, Japan). After a 15-minute semi-recumbent rest, participants performed incremental leg
103 cycling exercise to exhaustion, consisting of three 4 min incremental stages (40-80-120 Watts
104 [W] for men, and 30-60-90 W for women, with each stage lasting 3 min), followed by an
105 increase in workload of 20 W (men) or 10 W (women) per min until exhaustion. The pedal
106 cadence was set at 60 rpm using a metronome. After exhaustion, the participants sat semi-
107 recumbent for 60 minutes in normoxia in all trials.

108

109 *Measurements*

110 At rest and during exercise, pulmonary oxygen uptake ($\dot{V}O_2$) and carbon dioxide output ($\dot{V}CO_2$)
111 were measured by a metabolic cart (AE-310S, Minato Medical Science, Osaka, Japan) and beat-
112 by-beat BP was measured using finger photoplethysmography at the middle or index finger
113 (MUB-101; Medisens Inc., Tokyo, Japan) as the time-averaged from the beat-by-beat pressure
114 wave (Horiuchi et al., 2016b). Beat-by-beat BP data were stored with a sampling frequency of

115 200 Hz by a field data recorder (es8; TEAC, Tokyo, Japan), and transferred to a laptop computer
116 for further analysis. Based on a previous study (Horiuchi and Thijssen, 2020), heart rate (HR)
117 was measured using a portable HR monitor (Check-My-Heart, TRYTECH Co., Ltd., Tokyo,
118 Japan), and HRV was calculated by accompanying HRV analysis software. Participants were
119 instructed to breathe normally throughout testing. Fingertip blood samples (0.3 μ L) were taken
120 to measure blood lactate concentration (Lactate Pro 2LT-1730; Arkray, Tokyo, Japan) pre-
121 exercise, 5, 20, and 60 min of recovery. Total urine samples were collected pre-exercise and 1
122 h post-exercise and analyzed for urinary 8-hydro-2' deoxyguanosine (8-OHdG), an index of
123 oxidative DNA damage, as described previously (Horiuchi et al., 2023).

124

125 *Data Analysis*

126 To calculate spontaneous cardiac BRS (cBRS), the beat-to-beat systolic BP (SBP) time series
127 and RR interval were analyzed for more than 3 consecutive beats, with increasing or falling
128 direction from a 5-min steady-state data segment at rest and during recovery (Carrington and
129 White, 2001; Horiuchi and Oliver, 2023; Ogoh et al., 2005). Linear regression was applied to
130 each baroreflex sequence, with only sequences with an $R^2 > 0.85$ accepted (Horiuchi and Oliver,
131 2023; Iellamo et al., 1994). The overall average slope of the SBP–RR interval was calculated
132 as spontaneous cBRS. Time domain HRV was calculated by the standard deviation of the
133 normal-to-normal intervals (SDNN) and the root-mean-square of successive differences in R-

134 R interval (RMSSD). In the frequency domain, the extent of very low-frequency oscillations
135 (0.0033-0.04 Hz), low-frequency oscillations (LF: 0.04–0.15 Hz), and high-frequency
136 oscillations (HF: 0.15–0.4 Hz) was quantified using a fast Fourier transformation (Horiuchi and
137 Thijssen, 2020). Total exercise energy expenditure (EE) was calculated using $\dot{V}O_2$ and $\dot{V}CO_2$
138 as follows: Total EE ($J s^{-1}$) = $(3.869 \times \dot{V}O_2) + (1.195 \times \dot{V}CO_2) \times 4.168 / 60 \times 1000$
139 where, the unit of $\dot{V}O_2$ and $\dot{V}CO_2$ were liter per minute (Horiuchi et al., 2017).

140

141 *Statistics*

142 Data are presented mean \pm SD. Statistical analyses were performed using commercial software
143 (Jamovi, 3.2.3). One-way repeated measures analysis of variance (ANOVA) compared the total
144 EE across the three trials, and changes in urinary 8OHdG excretion. A two-way (time \times trials)
145 repeated ANOVA compared time course changes in all physiological variables (BPs, HR, HRV,
146 and blood lactate). For further comparisons, Tukey's post hoc test was used. Effect size was
147 calculated as η^2 , defined as small ($\eta^2 = 0.01$), medium ($\eta^2 = 0.06$), and large ($\eta^2 = 0.14$) (Lakens,
148 2013). Statistical significance was set at $P < 0.05$. The normality of the data was examined
149 using the Bartlett and Levene test. If equal variance failed, logarithmic transformation data were
150 used for further analysis (HF and LF/HF).

151

152 **Results**

153 Cycle exercise total EE was detected to be different between the trials ($F=34.5$, $P<0.001$,
154 $\eta^2=0.21$), where total exercise EE in Norm (846 ± 189 J s^{-1}) was greater than Hypo (672 ± 125 J
155 s^{-1}) and Hypo+TC (692 ± 153 J s^{-1}) ($P<0.001$, respectively), with no differences detected
156 between Hypo and Hypo+TC ($P=0.41$).

157
158 During the 60 min recovery, an interaction effect was found for MAP ($F=1.86$, $P=0.045$,
159 $\eta^2=0.013$), but not for SBP and DBP (**Figure 2**). Mean arterial pressure decreased in all trials
160 (main effect of time, $F=14.51$, $P<0.001$, $\eta^2=0.15$), with no difference detected in PEH between
161 trials ($P>0.05$, change (Δ) in MAP from pre-exercise at 60 min recovery, mean difference [95%
162 confidence interval], Norm $\Delta-4.4$ [-6.0, -2.8] mmHg, Hypo $\Delta-6.0$ [-8.5, -3.7] mmHg, and
163 Hypo+TC $\Delta-5.2$ [-8.8, -1.6] mmHg, **Figure 2A**).

164
165 Cardiac BRS was reduced during recovery compared to pre-exercise (main effect of time,
166 $F=59.55$, $P<0.001$, $\eta^2=0.62$). Moreover, a main effect of trial was detected ($F=4.45$, $P=0.02$,
167 $\eta^2=0.02$), where overall cBRS was lower in Hypo than Norm ($P=0.03$) and Hypo+TC ($P=0.06$),
168 with no difference between Norm and Hypo+TC ($P=0.74$, **Figure 3A**). No trial or time effects
169 were detected for HR. An interaction was detected for HR due to higher resting HR on Hypo
170 and Hypo+TC than Norm ($F=2.29$, $P=0.01$, $\eta^2=0.01$) (**Figure 3B**). There was no interaction or
171 and trial effects in blood lactate (**Figure 3C**). For HRV metrics, no interactions or main effects

172 of time were detected. However, regardless of the trial, cardiac parasympathetic activity indices
173 (SDNN, RMSDD, log [HF]) were lower, and cardiac sympathetic activity index (log [LF/HF])
174 was higher during recovery compared with pre-exercise (**Table 1**). At 1 h post-exercise, changes
175 in urinary 8-OHdG excretion from pre-exercise were 5.2 ± 4.4 in Norm, 5.3 ± 3.1 in Hypo, and
176 3.4 ± 2.7 ng kg⁻¹ h⁻¹ in Hypo+TC, with a trend for a smaller increase in 8-OHdG excretion on
177 Hypo+TC than Hypo ($P=0.08$).

178

179 **Discussion**

180 Our study showed that incremental leg cycling until exhaustion leads to reductions in
181 MAP of 4–6 mmHg after exercise in untrained men, supporting the presence of PEH. These
182 findings confirm the results of previous studies showing PEH after various exercise intensities,
183 durations, and types (Jones et al., 2021; Marcal et al., 2021; Pimenta et al., 2019). In contrast
184 to our hypothesis, PEH was not increased after exercise in hypoxia, with or without tart cherry
185 supplementation, compared to exercise in normoxia. One possible explanation is the exercise
186 was performed until exhaustion, which resulted in greater exercise energy expenditure and
187 absolute work in Norm than Hypo or Hypo+TC. This is consistent with a recent study that
188 revealed the magnitude of PEH was not different between normoxia and hypoxia when the
189 absolute work of exercise was matched (Fornasiero et al., 2021). These findings have good
190 ecological validity as those exercising in hypoxic conditions normally reduce workload due to

191 increased perception of effort (Rossetti et al., 2017).

192 Tart cherry supplementation before exercise in hypoxia did not further accentuate PEH
193 compared to exercise in hypoxia alone. These unique findings build upon the limited research
194 in normoxia to examine the effect of anthocyanin-rich supplementation on PEH (Shan and Cook,
195 2023). Consistent with this previous study we reported no difference in MAP or DBP post-
196 exercise after placebo and anthocyanin-rich supplementation. In contrast, we did not observe a
197 larger decrease in post-exercise SBP, which may be explained by the different types (tart cherry
198 vs New Zealand blackcurrant) and dose of anthocyanin-rich supplementation (7 vs 4 days, and
199 210 vs 100 mg anthocyanin on the final day).

200 In the present study, HRV indices during recovery indicated a shift in cardiac
201 autonomic balance compared to pre-exercise, i.e., increased cardiac sympathetic activity and
202 decreased cardiac parasympathetic activity; however, these indices were not influenced by
203 hypoxia or tart cherry supplementation. cBRS was lowest during recovery after exercise in
204 Hypo, which is consistent with previous research indicating hypoxia lowers cBRS (Bourdillon
205 et al., 2023). cBRS was similar during recovery in Hypo+TC to Norm, suggesting tart cherry
206 supplementation restored cBRS, lowered by exercise in hypoxia. One possible explanation is
207 oxidative stress tended to be lower after hypoxic exercise with tart cherry supplementation
208 compared to a placebo. This explanation is supported by animal research reporting
209 improvements in baroreflex sensitivity after antioxidant supplementation (Alves et al., 2015;

210 Garcia et al., 2017). Improvements in oxidative stress and cBRS sensitivity with tart cherry
211 supplementation at the same time as similar magnitude of PEH in all trials suggests a limited
212 regulatory role of oral antioxidants and cBRS in PEH. Previous research has also shown the
213 intravenous infusion of antioxidants did not influence PEH (Romero et al., 2015). Therefore,
214 non-antioxidant mechanisms, like increased NO bioavailability, may explain the greater
215 reductions in post-exercise BP observed after consuming anthocyanin-rich supplements (Shan
216 and Cook, 2023).

217

218 **Conclusion**

219 Post-exercise hypotension was not increased after exercise in hypoxia, with or without
220 tart cherry supplementation, compared to exercise in normoxia.

221

222

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230

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233

234 **Disclosure statement:** The authors declare no conflict of interest related with this study.

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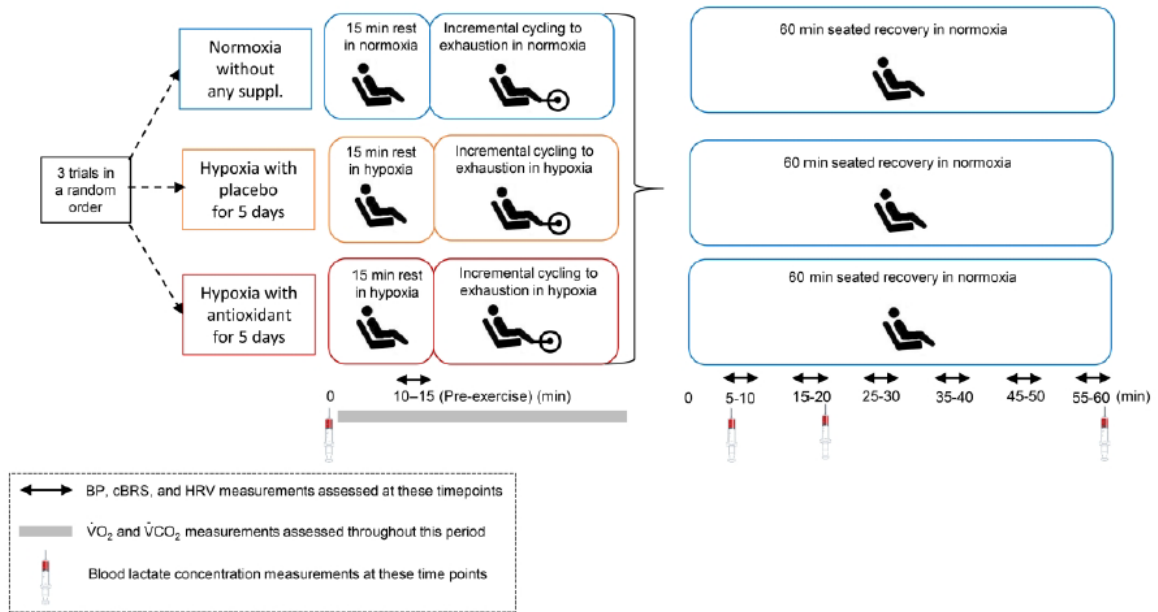
386

387 **Figure legends**

388 **Figure 1. Experimental procedure.** BP, blood pressure; cBRS, cardiac baroreflex sensitivity;

389 HRV, heart rate variability; Suppl., supplementation; $\dot{V}O_2$, oxygen uptake; $\dot{V}CO_2$, carbon

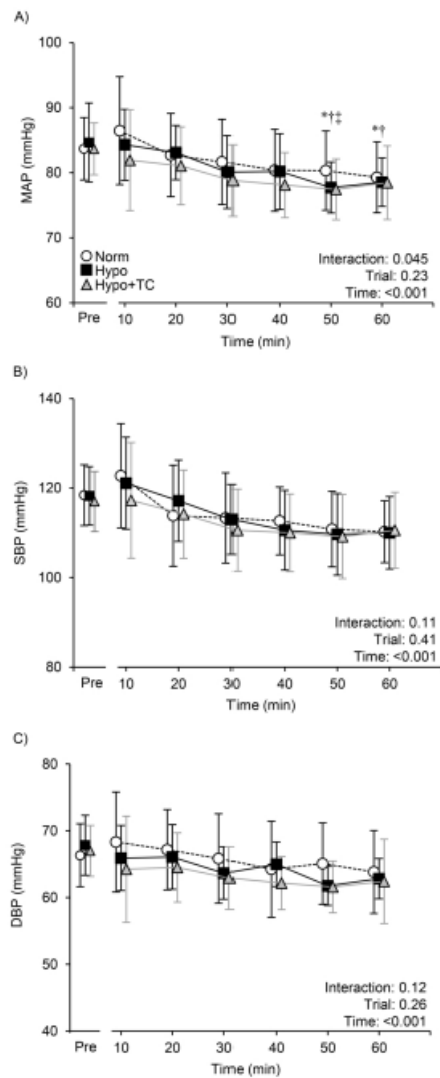
390 dioxide output



391

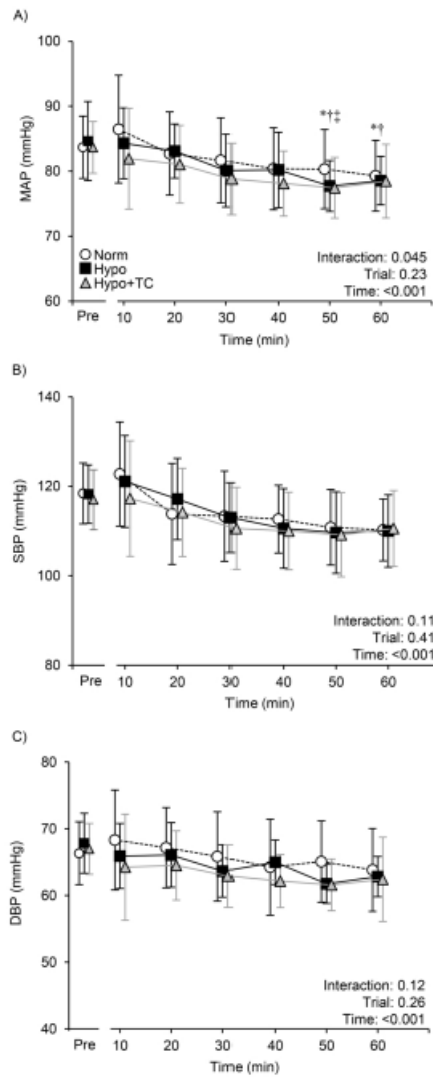
392

393 **Figure 2.** Mean arterial blood pressure (MAP; panel A), systolic blood pressure (SBP; panel
 394 B), and diastolic blood pressure (DBP; panel C) during a 1 h recovery period after exercising
 395 in normoxia (Norm; white circles), hypoxia with placebo (Hypo; black squares), and hypoxia
 396 with antioxidants (Hypo+ TC; gray triangles) trials. Values are mean \pm standard deviation (SD).
 397 *†‡ indicates a difference compared with the pre-exercise value in Norm, Hypo, and Hypo+
 398 TC trials, respectively.



399
 400

401 **Figure 3.** Cardiac baroreflex sensitivity (cBRS; panel A), heart rate (HR: panel B), and blood
 402 lactate (panel C) during a 1 h recovery period after exercising in Norm (white circles), Hypo
 403 (black squares), and Hypo+TC (gray triangles) trials. Values are mean \pm SD. # and \$ indicate
 404 differences compared with Norm trial.



405