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

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

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Abstract

Background: This study investigated the effects of hypoxic exercise with and without tart cherry supplementation on post-exercise hypotension (PEH). **Method:** In a randomized order, 12 healthy young adults (9 men and 3 women) completed cycle exercise to exhaustion i) in normoxia without any supplementation (Norm), ii) in hypoxia (13% O_2) with placebo (Hypo), and iii) in hypoxia with tart cherry supplementation (Hypo+TC). Supplements were supplied for 5 days pre-trial (TC was 200 mg anthocyanin per day for 4 days and 100 mg on day 5). **Results:** Cycle exercise total energy expenditure was greater in Norm than Hypo and Hypo+TC (P<0.001) with no difference between Hypo and Hypo+TC (P=0.41). Mean arterial pressure (MAP) decreased during recovery in all trials (main effect of time, P<0.001), with no difference in PEH between the trials (P>0.05, change (Δ) in MAP from pre-exercise at 60 min recovery, mean difference, Norm Δ-4.4 mmHg, Hypo Δ-6.1 mmHg, and Hypo+TC Δ-5.2 mmHg). Cardiac baroreflex sensitivity decreased during recovery in all trials (P<0.001) and was lower in Hypo than Norm and Hypo+TC (main effect of trial, P=0.02). **Conclusion:** Post-exercise hypotension was not increased after exercise in hypoxia, with or without tart cherry supplementation, compared to exercise in normoxia.

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

Introduction

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

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

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

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

Methods

Participants

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

Study design

This study consisted of three trials **(Figure 1)**: (1) normobaric normoxic exercise without any supplementation (Norm); (2) normobaric hypoxic exercise (13% O_2) with a placebo (Hypo), and (3) normobaric hypoxic exercise (13% O_2) with TC supplementation (Hypo+TC). In a double-blinded and randomized manner, each participant ingested a placebo or TC capsule (Tart cherry 1200 mg containing 100 mg of anthocyanin, Nature's Life, Orem, UT, USA) twice per day for 4 days before the experimental trial, and once on the day of the experimental trial 2 h before beginning excise, which is consistent with studies reporting hemodynamic changes after single doses and 4–7 days of anthocyanin-rich supplementation (Matsumoto et al., 2005).

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

Experimental procedure

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

Measurements

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

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

Data Analysis

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

R interval (RMSSD). In the frequency domain, the extent of very low-frequency oscillations (0.0033-0.04 Hz), low-frequency oscillations (LF: 0.04–0.15 Hz), and high-frequency oscillations (HF: 0.15–0.4 Hz) was quantified using a fast Fourier transformation (Horiuchi and Thijssen, 2020). Total exercise energy expenditure (EE) was calculated using $\dot{V}O_2$ and $\dot{V}CO_2$ as follows: Total EE (J s^{-1}) = (3.869 × $\dot{V}O_2$) + (1.195 × $\dot{V}CO_2$) × 4.168 / 60 × 1000

where, the unit of $\dot{V}O_2$ and $\dot{V}CO_2$ were liter per minute (Horiuchi et al., 2017).

Statistics

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

Results

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

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

Cardiac BRS was reduced during recovery compared to pre-exercise (main effect of time, F=59.55, *P*<0.001, η^2=0.62). Moreover, a main effect of trial was detected (F=4.45, *P*=0.02, η^2=0.02), where overall cBRS was lower in Hypo than Norm (*P*=0.03) and Hypo+TC (*P*=0.06), with no difference between Norm and Hypo+TC (*P*=0.74, **Figure 3A**). No trial or time effects were detected for HR. An interaction was detected for HR due to higher resting HR on Hypo and Hypo+TC than Norm (F=2.29, *P*=0.01, η^2=0.01) (**Figure 3B**). There was no interaction or and trial effects in blood lactate (**Figure 3C**). For HRV metrics, no interactions or main effects of time were detected. However, regardless of the trial, cardiac parasympathetic activity indices (SDNN, RMSDD, log [HF]) were lower, and cardiac sympathetic activity index (log [LF/HF]) was higher during recovery compared with pre-exercise (**Table 1**). At 1 h post-exercise, changes in urinary 8-OHdG excretion from pre-exercise were 5.2±4.4 in Norm, 5.3±3.1 in Hypo, and 3.4±2.7 ng kg^{-1} h^{-1} in Hypo+TC, with a trend for a smaller increase in 8-OHdG excretion on Hypo+TC than Hypo (P=0.08).

Discussion

Our study showed that incremental leg cycling until exhaustion leads to reductions in MAP of 4–6 mmHg after exercise in untrained men, supporting the presence of PEH. These findings confirm the results of previous studies showing PEH after various exercise intensities, durations, and types (Jones et al., 2021; Marcal et al., 2021; Pimenta et al., 2019). In contrast to our hypothesis, PEH was not increased after exercise in hypoxia, with or without tart cherry supplementation, compared to exercise in normoxia. One possible explanation is the exercise was performed until exhaustion, which resulted in greater exercise energy expenditure and absolute work in Norm than Hypo or Hypo+TC. This is consistent with a recent study that revealed the magnitude of PEH was not different between normoxia and hypoxia when the absolute work of exercise was matched (Fornasiero et al., 2021). These findings have good ecological validity as those exercising in hypoxic conditions normally reduce workload due to increased perception of effort (Rossetti et al., 2017).

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

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

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

Conclusion

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

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Author Contributions: Conception of the study design (MH, SO); performing the experiments (MH); analyzing the data, and interpretation of the results (MH, SO); drafting of the first manuscript (MH); revising the manuscript (MH, SO); approval of the final manuscript (MH, SO).

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

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Figure legends

Figure 1. Experimental procedure. BP, blood pressure; cBRS, cardiac baroreflex sensitivity; HRV, heart rate variability; Suppl., supplementation; $\dot{V}O_2$, oxygen uptake; $\dot{V}CO_2$, carbon dioxide output

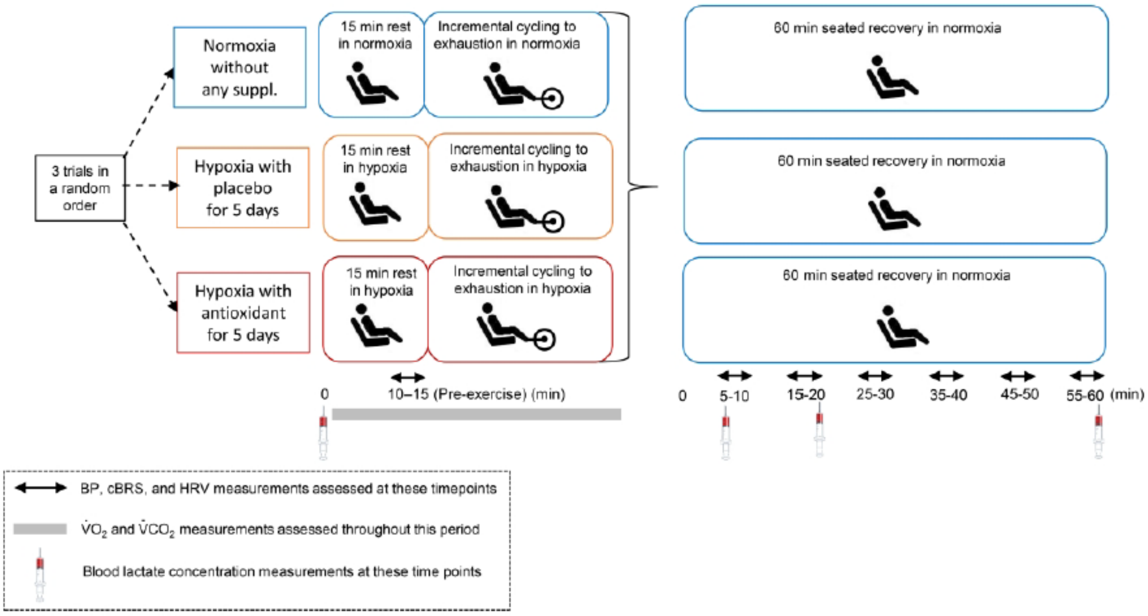

Figure 2. Mean arterial blood pressure (MAP; panel A), systolic blood pressure (SBP: panel B), and diastolic blood pressure (DBP; panel C) during a 1 h recovery period after exercising in normoxia (Norm; white circles), hypoxia with placebo (Hypo; black squares), and hypoxia with antioxidants (Hypo+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

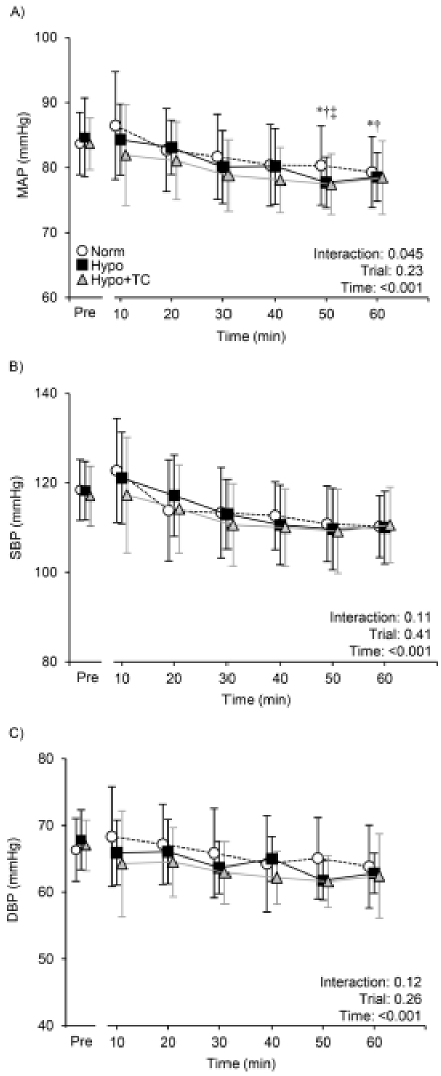

Figure 3. Cardiac baroreflex sensitivity (cBRS; panel A), heart rate (HR: panel B), and blood lactate (panel C) during a 1 h recovery period after exercising in Norm (white circles), Hypo (black squares), and Hypo+TC (gray triangles) trials. Values are mean ± SD. # and $ indicate differences compared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