nutraceuticals

MDPI

Article

Yohimbine Ingestion Mitigates Morning-Associated Decrements in High-Intensity Exercise Performance

Christopher G. Ballmann [1,2,3,*,†], Rebecca R. Rogers [2,†], Megan E. Barnes [4], Camryn R. Cowan [4], Carson C. Elwell [4], Kailey A. Luiken [4], Grace Y. Lehman [4], Julia C. Kaylor [4], Ella G. Simpson [4], Spencer B. Westbrooks [4], Maria J. Miller [4], Courteney L. Benjamin [4] and Tyler D. Williams [4]

1 Department of Human Studies, University of Alabama at Birmingham, Birmingham, AL 35294, USA
2 Center for Engagement in Disability Health and Rehabilitation Sciences (CEDHARS), University of Alabama at Birmingham, Birmingham, AL 35209, USA; rrrogers@uab.edu
3 University Center for Exercise Medicine (UCEM), University of Alabama at Birmingham, Birmingham, AL 35209, USA
4 Department of Kinesiology, Samford University, Birmingham, AL 35229, USA
* Correspondence: cgb0002@uab.edu
† These authors contributed equally to this work.

Abstract: Exercise performance tends to suffer during the morning compared to the evening, which may decrease potential training adaptations. Currently, it is unclear how nutritional interventions may affect this phenomenon and whether supplementation may allow for the attainment of optimal performance regardless of the time of day. The purpose of this study was to investigate the effects of acute yohimbine ingestion on morning-associated decrements in performance and psychophysiological responses to exercise. Physically active females (n = 16) were recruited to participate in three total visits, each with a different treatment: (1) placebo-morning (PL-AM), (2) yohimbine-morning (YHM-AM; oral 2.5 mg), and (3) placebo-afternoon (PM). The morning and afternoon visits occurred between 7:00–8:00 h and 16:00–17:00 h, respectively. The experimental treatments in the morning were ingested 20 min prior to capillary blood collection, which was completed pre- and post-exercise. Following a warm-up, participants completed a 2000 m time trial on a rowing ergometer. Power output, heart rate (HR), and rating of perceived exertion (RPE) were recorded every minute. Time to competition (TTC) and subjective energy, focus, and alertness were documented post-exercise. Pre- and post-exercise blood lactate (La) and plasma hypoxanthine (HX) levels were also assessed. The trials were separated by a 48 h washout period. The results showed that power output ($p = 0.010$) was lower and TTC ($p = 0.003$) was significantly slower with PL-AM compared to PM. Furthermore, YHM-AM resulted in higher power output ($p = 0.035$) and faster TTC ($p = 0.007$) compared to PL-AM, with no differences compared to PM ($p > 0.05$). Post-exercise La was significantly lower with YHM-AM compared to PL-AM ($p = 0.046$) and PM ($p = 0.001$). Pre-exercise plasma HX, as measured via conversion to xanthine, was significantly higher with PM ($p = 0.039$), while the levels trended higher with YHM-AM ($p = 0.060$) compared to PL-AM. Subjective energy was higher with YHM-AM ($p = 0.045$) and PM ($p = 0.009$) compared to PL-AM, while alertness was only higher for YHM-AM compared to PL-AM ($p = 0.045$). No statistical differences between the treatments were found for RPE or HR ($p > 0.05$). These findings indicate that YHM ingestion attenuates performance decrements in the morning. Improvements in performance may be underpinned by improved feelings of energy and alterations in metabolism. Practically, YHM may represent an effective ergogenic aid to combat a lack of energy and low performance during the morning.

Keywords: yohimbine hydrochloride; endurance; power; energy; fatigue

Citation: Ballmann, C.G.; Rogers, R.R.; Barnes, M.E.; Cowan, C.R.; Elwell, C.C.; Luiken, K.A.; Lehman, G.Y.; Kaylor, J.C.; Simpson, E.G.; Westbrooks, S.B.; et al. Yohimbine Ingestion Mitigates Morning-Associated Decrements in High-Intensity Exercise Performance. *Nutraceuticals* **2024**, *4*, 23–34. https://doi.org/10.3390/nutraceuticals4010002

Academic Editor: Ronan Lordan

Received: 8 October 2023
Revised: 14 December 2023
Accepted: 18 December 2023
Published: 2 January 2024

1. Introduction

Light–dark cycles alter nearly all physiological processes, which often operate in a circadian- or time-of-day-dependent manner. While controlled at the cellular level, circa-

dian fluctuations in cell activity ultimately influence whole organ function [1]. Regarding skeletal muscle specifically, changes in muscle blood flow [2], temperature [3], and force generation [4] have been shown to be dependent on the time of day and are limiting factors for exercise performance [5,6]. A myriad of evidence exists showing that this translates to whole human physiology and performance, whereby physical performance and exercise capacity tend to suffer during the morning (AM) times versus afternoon (PM) [7,8]. From a practical perspective, habitual training at peak or near-peak performance is critical for maximizing adaptations. Athletes and recreational exercisers may be confined to early or irregular hours for training, leaving the need for ways to ensure similar performance and training ability regardless of the time of day. However, feasible interventions to combat decreases in performance during morning times have yet to be fully elucidated, especially in the context of dietary supplementation.

Yohimbine (YHM) is an α2-adrenergic receptor antagonist, which is most commonly derived from the bark of the *Corynanthe johimbe* tree [9]. In African folk medicine, YHM was used in efforts to combat fatigue, increase alertness, and enhance sexual drive [10]. YHM ingestion is well documented to result in increases in sympathetic nervous system stimulation, manifesting as systemic increases in circulating epinephrine and norepinephrine [11,12]. Noted consequences of sympathetic activation have been shown to include increased alertness [13], muscular force [14], and muscle/cerebral hyperemia [15], which may have implications on exercise performance. When administered acutely before exercise, YHM has been shown to improve muscular power while concomitantly lowering blood lactate and perceptual fatigue in females [16]. This is thought to be in part due to increased catecholamine release, possibly leading to adaptative hemodynamic changes. Furthermore, acute YHM ingestion before repeated bench press exercise has been shown to increase repetition volume as well as improve subjective feelings of energy and alertness [13]. Improvements in aerobic capacity during cycling have also been reported with acute YHM ingestion in trained males [17]. Altogether, YHM has been shown to possess ergogenic potential when taken acutely prior to various modes of exercise. However, no studies on YHM and exercise have manipulated the time of day, leaving the possible effects of YHM on diurnal variations in exercise performance unknown.

Since exercise performance tends to suffer during AM times and YHM has been repeatedly shown to improve exercise performance as a purported stimulant [13,16,17], it is plausible that YHM may be able to mitigate AM decrements in performance. However, virtually no studies have directly investigated how YHM may influence diurnal changes in whole body physiology, especially in the context of exercise. Other α2-adrenergic receptor antagonists have been shown to increase norepinephrine release, resulting in altered circadian rhythms of melatonin and cortisol and suggesting possible changes to exercise stress responses [18]. Sympathetic activity, which YHM exacerbates, has been reported to be markedly lower in the morning, which may present as lower metabolic activity and cardiovascular autonomic modulation [19]. Psychological arousal and feelings of energy have been shown to suffer at morning times, while YHM has been shown to improve these indices in resistance-trained males [13]. Furthermore, other neural stimulants (i.e., caffeine and ephedrine) have also been reported to abolish diurnal fluctuations in maximal sprint and bench press exercise performance [20,21]. However, no studies to date have identified if dietary YHM may provide benefits toward preventing decreases in exercise performance during morning times. Therefore, the purpose of this study was to investigate if acute YHM supplementation can prevent morning losses in rowing performance and determine how psychophysiological responses may be altered. We hypothesized that YHM ingestion would attenuate decreases in power and time to completion during the morning compared to PL. We also hypothesized that heart rate, alertness, feelings of energy, and indirect biomarkers of muscle metabolism would be increased compared to PL.

2. Materials and Methods

2.1. Study Design

Physically active females were recruited to participate. In a double-blinded, crossover, and counterbalanced approach, participants completed three total visits, each with a different randomized treatment: (1) placebo-morning (PL-AM), (2) yohimbine-morning (YHM-AM), and (3) placebo-afternoon (PM) [8]. The morning and afternoon visits occurred between 7:00 and 8:00 h and 16:00–17:00 h, respectively, and were separated by a minimum of 48 h [8,13]. During each visit, the participants consumed their corresponding treatments and then completed a 2000 m rowing time trial. Time to completion (TTC), relative power output, HR, and RPE were taken every minute during the exercise and averaged for analysis. Blood lactate (La) and hypoxanthine (HPX) were measured prior to exercise (Pre) and immediately after exercise (Post). The visits were identical except for time of day and treatment. Before data collection, verbal and written informed consent was obtained from each participant, and all experimental procedures were performed in accordance with the Declaration of Helsinki and approved by the Samford University Institutional Review Board (EXPD-HP-21-SUM-1; July 2021).

2.2. Participants

To determine sample size, an a priori power analysis was conducted using G*power statistical software (G*power V 3.1.9.4). A previous investigation from our lab measuring resistance exercise volume showed a greater number of repetitions performed with YHM versus PL supplementation, with a calculated effect size of d = 0.82 [16]. To calculate an adequate sample size, the following factors were utilized: test = *t*-test (matched pairs), d = 0.82, $\alpha = 0.05$, and $1 - \beta = 0.8$. This calculated to a minimum sample size range of n = 14 for adequate power. Physically active females (n = 16; age= 20.8 $\pm$ 1.2 years; height = 162.5 $\pm$ 7.9 cm; body mass = 71.6 $\pm$ 4.6 kg) volunteered to participate. To be considered physically active, participants had to self-report accruing at least 150 min/wk of moderate-intensity exercise. Participants were excluded if they had a lower body injury within 6 months prior to participation, had a chronic disease limiting exercise (cardiovascular, metabolic, or renal), and were currently supplementing with YHM or any of its forms (i.e., rauwolscine) [13,16]. To ensure suitability and safety of exercise testing, a physical activity readiness questionnaire (PARQ) was filled out and signed by each participant [22]. Participants were instructed to refrain from consuming caffeine, nicotine, and other stimulants (e.g., pre-workout). They were also asked to abstain from alcohol 12 h before and engaging in vigorous exercise 24 h before each visit. Participants were also asked to maintain similar sleep and dietary habits to the best of their ability. Participants were unaware of any experimental hypotheses.

2.3. Supplementation

Supplementation for all treatments was followed in an identical manner to previous work from our group [13,16]. For each visit, participants consumed either a PL (gluten-free cornstarch) or Yohimbine Hydrochloride (YHM; 2.5 mg; Primaforce, Burlington, NC, USA) treatment 20 min prior to the first blood sample. The treatments were orally ingested and delivered in indistinguishable gelatin capsules (size 0; transparent), with the color and shape of capsules being identical between treatments. Furthermore, the treatments were distributed in a double-blinded manner whereby an independent researcher organized non-identifiable opaque bags containing each treatment. No participants reported any side effects from supplementation throughout the investigation. Participants ingested the same PL treatment during PL-AM and PM trials in efforts to minimize participant bias. Participants were unaware of any experimental hypotheses.

2.4. Metabolic Biomarkers (Blood Lactate and Plasma Hypoxanthine)

Capillary blood samples were collected in accordance with previous methods from investigations in our lab [16,23]. Briefly, ~500 µL of capillary blood was collected from the

fourth finger via finger prick using a 17-gauge 2.0 mm depth disposable blade lancet. The first drops of blood were used to quantify blood La using a portable lactate meter (Lactate Plus Meter, Nova Biomedical, Waltham, MA, USA). To obtain the remaining blood volume, a gentle massaging technique was used as whole blood was collected through capillary action into lithium heparin-coated microvette® tubes (SARSTEDT, Newton, NC, USA). To obtain plasma, whole blood was immediately centrifuged at 10,000 rpm for 10 min, and plasma was decanted and subsequently stored at −80 °C until biochemical analysis was performed at the conclusion of data collection. Hypoxanthine levels were determined using a commercially available colorimetric assay through enzymatic conversion of hypoxanthine ® xanthine (Raybiotech, Peachtree Corners, GA, USA) [24]. All samples were analyzed in duplicate and according to the manufacturer's instructions.

2.5. Procedures

Upon arrival, height and weight were recorded, and participants consumed their corresponding treatment 20 min prior to the first blood collection. Participants were outfitted with a chest-strap HR monitor (Polar Electro, Lake Success, NY, USA) and HR was monitored throughout the testing. Participants then completed a 2000 m rowing time trial as previously described by Karow et al. and others [25,26]. Briefly, 20 min following supplement ingestion, participants completed a 5 min warm-up on a stationary rowing ergometer (Concept2, Morrisville, VT, USA), which was timed once they achieved 50% of their age-predicted HRmax. After the warm-up, participants were directed to row 2000 m as fast as possible while the researchers provided verbal encouragement. HR, RPE (1–10 scale), and power output were documented each minute and then averaged for analysis. Blood collection procedures were repeated as previously described at the end of the exercise. Time to completion and subjective feelings of energy, focus, and alertness were documented at the end of the exercise. A 5-point Likert-scale questionnaire (1 = very low; 2 = low; 3 = average; 4 = high; 5 = very high) was used to assess energy, focus, and alertness levels as described by Hoffman et al. and others [13,27].

2.6. Data Analysis

All data were analyzed using Jamovi statistical software (Version 0.9; Sydney, Australia). A Shapiro–Wilk test was used to confirm data normality. A 1 × 3 [Trial × Treatment] repeated measures ANOVA was used for the analysis of power output, TTC, HR, RPE, and subjective energy, focus, and alertness ratings. For the analysis of metabolic biomarkers, a 2 × 3 [Timepoint × Treatment] repeated measures ANOVA was used with a Bonferroni–Holm post hoc test. For significant main effects, post hoc analysis of individual means was performed as previously recommended by Wei et al. [28]. Estimates of effect size for the main effects were calculated using eta squared (η^2) and interpreted as follows: 0.01—small; 0.06—medium; and ≥0.14—large [29,30]. For individual mean comparisons, Cohen's d effect sizes (d) were calculated between conditions and interpreted as follows: 0.2—small; 0.5—moderate; and 0.8—large [29,30]. Significance was set at $p \leq 0.05$ a priori. All data are presented as mean ± standard deviation (SD).

3. Results

3.1. Power Output and Time to Completion (TTC)

Average power output over the time trial and TTC are presented in Figure 1. For power output (watts; Figure 1a), there was a main effect for treatment ($p = 0.006$; $\eta^2 = 0.079$). Post hoc analysis revealed that power output was higher during PM ($p = 0.010$; d = 0.638) and YHM-AM ($p = 0.035$; d = 0.730) compared to PL-AM. However, no differences were observed between PM and YHM-AM ($p = 0.495$; d = 0.074). For TTC (minutes; Figure 1b), there was a main effect for treatment ($p < 0.001$; $\eta^2 = 0.072$), whereby TTC was faster during PM ($p = 0.031$; d = 0.610) and YHM-AM ($p = 0.031$; d = 0.477) compared to PL-AM. No differences were noted when comparing TTC of PM and YHM-AM ($p = 0.031$; d = 0.142).

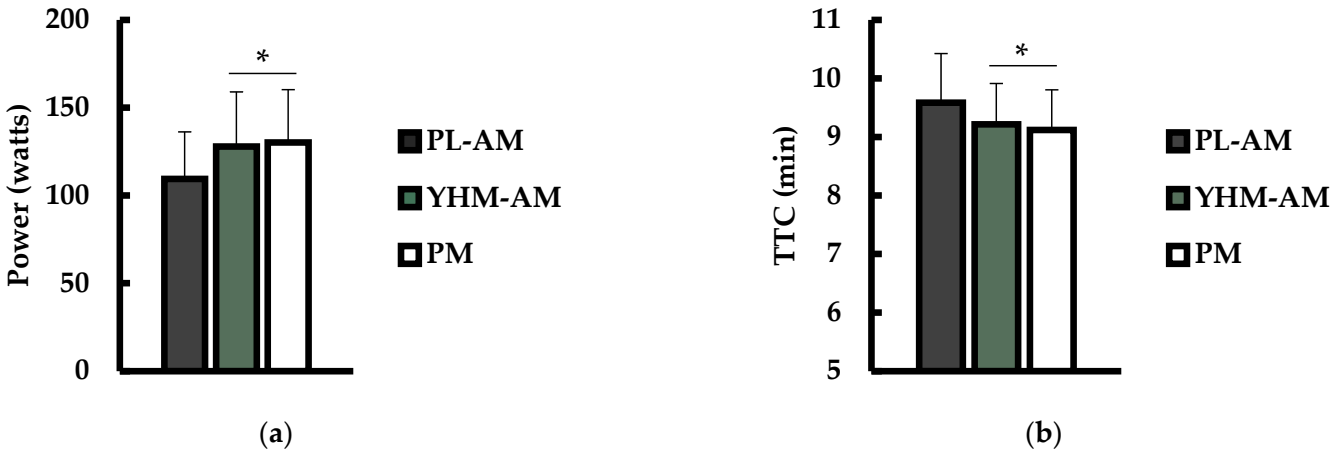


Figure 1. Changes in (**a**) average power output (watts) and (**b**) time to completion (TTC; minutes) between placebo-morning (PL-AM; black), yohimbine-morning (YHM-AM; green), and placebo-afternoon (PM; white). Data are presented mean ± SD. * indicates significantly different from PL-AM ($p < 0.05$).

3.2. Heart Rate (HR), Rate of Perceived Exertion (RPE), and Subjective Ratings of Energy, Focus, and Alertness

For average HR (bpm; Figure 2a), there were no differences between treatments ($p = 0.270$; $\eta^2 = 0.015$). Furthermore, there were no differences in average RPE (1–10 scale; Figure 2b) between treatments ($p = 0.089$; $\eta^2 = 0.048$). An analysis of subjective measures (arbitrary units; Figure 2c) revealed significant main effects of treatment for energy ($p = 0.008$; $\eta^2 = 0.160$) and alertness ($p = 0.032$; $\eta^2 = 0.170$) but not for focus ($p = 0.960$; $\eta^2 = 0.001$). Specifically, subjective energy was significantly higher during PM ($p = 0.009$; d = 0.910) and YHM-AM ($p = 0.045$; d = 0.791) treatments compared to PL-AM. Subjective alertness was higher with YHM-AM compared to PL-AM ($p = 0.045$; d = 0.477). No differences in alertness were noted between PL-AM ($p = 0.999$; d = 0.001) and YHM-AM ($p = 0.092$; d = 0.375).

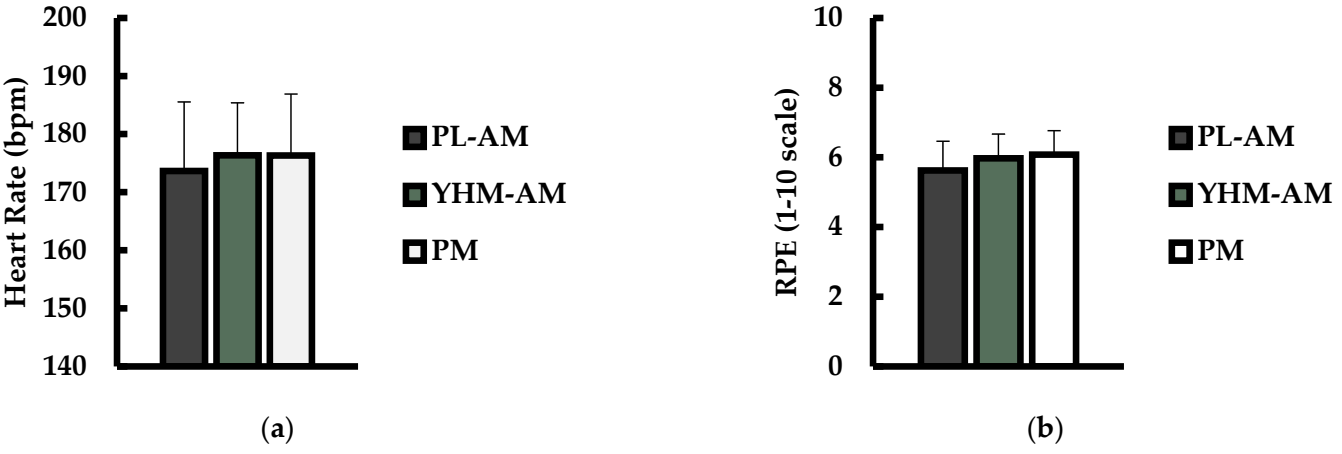
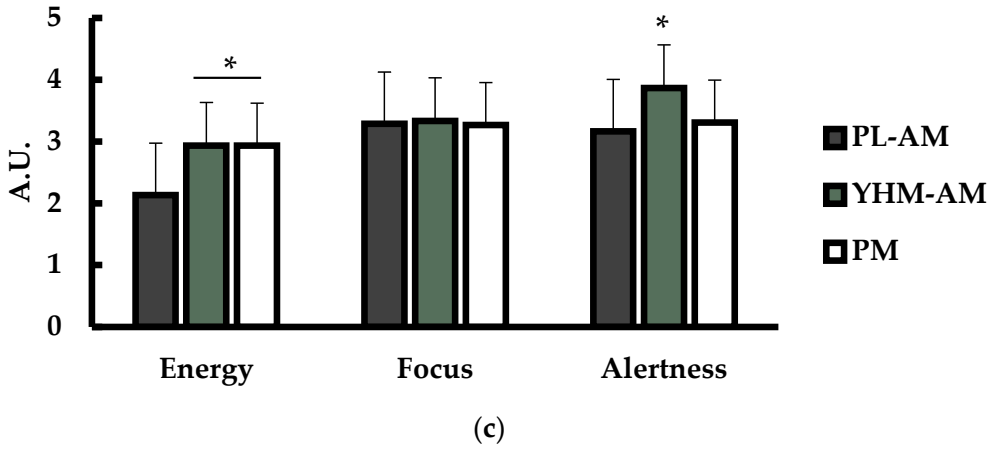


Figure 2. *Cont.*

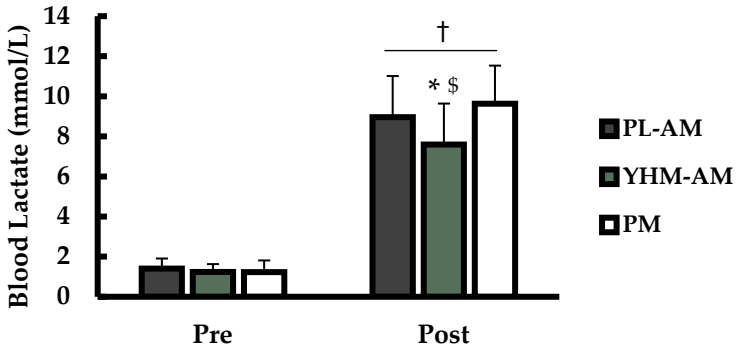


(**c**)

Figure 2. Changes in (**a**) average heart rate (HR; bpm), (**b**) rate of perceived exertion (RPE; 1–10 scale), and (**c**) subjective ratings of energy, focus, and alertness between placebo-morning (PL-AM; black), yohimbine-morning (YHM-AM; green), and placebo-afternoon (PM; white). Data are presented mean ± SD. * indicates significantly different from PL-AM ($p < 0.05$).

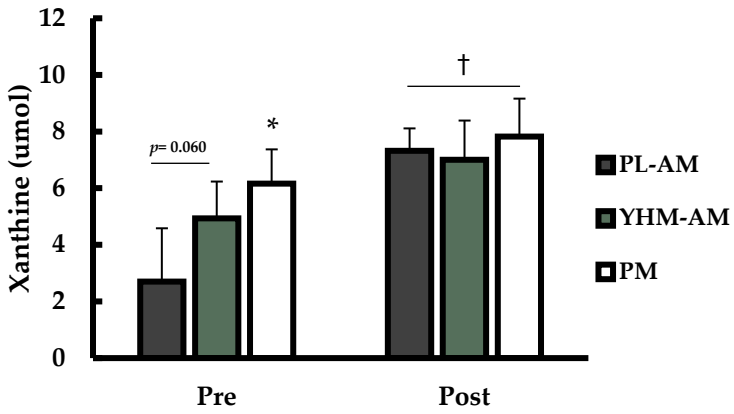
3.3. Blood Lactate (La) and Plasma Hypoxanthine (HX)

Pre- and post-exercise La (mmol/L) results are shown in Figure 3a. The analysis revealed main effects for time point ($p < 0.001$; $\eta^2 = 0.856$) and treatment ($p = 0.002$; $\eta^2 = 0.018$). There was also an interaction for time point x treatment ($p = 0.008$; $\eta^2 = 0.008$). Post-exercise La concentrations were significantly higher than pre-exercise concentrations regardless of treatment ($p < 0.001$; d = 5.382). Furthermore, post-exercise La was significantly lower during YHM-AM compared to PL-AM ($p = 0.036$; d = 0.667) and PM ($p < 0.001$; d = 1.033). Pre- and post-exercise hypoxanthine (mmol/L) results are shown in Figure 3b and are reflected in the conversion of hypoxanthine to xanthine. There were main effects for time point ($p < 0.001$; $\eta^2 = 0.421$) and treatment ($p = 0.003$; $\eta^2 = 0.143$). An interaction for time point x treatment ($p = 0.005$; $\eta^2 = 0.093$) also existed. Hypoxanthine levels were significantly higher post-exercise compared to pre-exercise ($p < 0.001$; d = 4.562). For treatment, pre-exercise hypoxanthine levels were significantly higher during PM compared to PL-AM ($p = 0.039$; d = 3.75), while the levels trended higher with YHM-AM compared to PL-AM ($p = 0.060$; d = 0.645).



(**a**)

Figure 3. *Cont.*



(**b**)

Figure 3. Changes in (**a**) blood lactate (La; mmol/L) and (**b**) plasma hypoxanthine (umol) concentrations before (Pre) and after exercise (Post) between placebo-morning (PL-AM; grey), yohimbine-morning (YHM-AM; green), and placebo-afternoon (PM; white). Data are presented as mean ± SD. * indicates significantly different from PL-AM ($p < 0.05$). $ indicates significantly different from PM ($p < 0.05$). † indicates significantly different from Pre ($p < 0.05$). Note: Hypoxanthine was detected via enzymatic conversion to xanthine for quantification purposes.

4. Discussion

Diurnal patterns in physical performance have been widely described, with AM times typically resulting in poorer performance outcomes [7,8,21]. Given this, training in the AM may present challenges for athletes and recreational exercisers as training performance will dictate enhanced physiological adaptations and sports performance. YHM is a potent sympathomimetic that has been incompletely characterized in the context of exercise despite a high prevalence in nutritional supplements. Previous work from our group has shown that acute YHM ingestion improves sprint and bench press performance [13,16]. However, it is unknown if YHM may be able to combat AM-associated declines in physical performance. Thus, this study sought to elucidate if acute YHM supplementation could abolish decreases in rowing performance during AM times and further characterize subjective and objective markers of energy and fatigue. The main findings revealed that acute YHM supplementation in the AM resulted in greater power output and faster TTC during a rowing time trial compared to PL-AM, which was similar to performance in the PM. While no changes in HR or RPE were noted between treatments, subjective ratings of energy and alertness were enhanced with YHM-AM. Post-exercise La was significantly lower with YHM-AM compared to PL-AM and PM, while pre-exercise hypoxanthine levels trended higher with YHM-AM compared to PL-AM. Although physiological determinants of performance enhancement were not assessed comprehensively, these findings may have important implications regarding using YHM to combat decreases in performance associated with morning times.

Both power output and TTC were worse during PL-AM compared to PM, which further reinforces the notion of diurnal changes in exercise performance [31]. Indeed, lower performance in the AM has been widely described in various modes of exercise, including resistance, sprint, and endurance-based exercise [7,8,32]. The physiological underpinnings of performance decrements during the AM are multi-faceted and have yet to be fully explicated, but may be linked to lower core/muscle temperatures and alterations in autonomic nervous system activity [33,34]. Presently, acute YHM ingestion during the AM attenuated diurnal losses in performance and restored them to similar values as during the PM. This supports previous findings of improved power capabilities with acute YHM ingestion. For example, Barnes et al. showed enhanced power output and lower fatigue (power output loss) during repeated sprint exercise in physically active females [16]. Interestingly, catecholamine levels were also shown to be elevated prior to sprinting, suggesting

increased sympathetic neural activation. While not directly confirmed, performance enhancement with YHM in the AM may be rooted in similar mechanisms such as increases in catecholamines. Although some debate exists, autonomic output has been shown to be altered in the AM upon waking, whereby sympathetic activity progressively increases in intensity hours thereafter [35]. This phenomenon is largely influenced by regulatory mechanisms through α-adrenergic receptors, which YHM potently antagonizes [36]. The initiation of these responses triggers increases in cardiac function, muscle contractility, and alteration in distribution of blood flow, which may ultimately control exercise performance. For example, Roatta et al. showed that increases in sympathetic activity alter motor neuron firing rates and accelerate the relaxation rates of muscle fibers [37]. Since YHM possesses sympathomimetic properties capable of elevating sympathetic output to muscle [38], the improvements with acute YHM ingestion may manifest in a more rapid induction of sympathetic activity in the AM, thereby leading to altered inotropic effects whereby muscle contractile force is increased while relaxation is hastened, allowing for more frequent contractions. However, it should be noted that sympathetic activation was not directly measured in the current investigation, leaving the precise mechanisms of continuation of sympathetic activation unknown. Future research is needed to understand possible ways of how YHM influences sympathetic output throughout the day.

Psychologically, heightened feelings of energy and alertness were also noted with YHM ingestion during the AM, which suggests heightened psychological arousal. This reinforces previous findings showing increased energy and lower fatigue with acute YHM ingestion in resistance-trained males [13]. Of particular importance, these subjective changes occur concomitantly with increases in repetition volume and muscular endurance [13]. Other studies have suggested that YHM ingestion increases neural signaling in the pre-frontal cortex, which could lead to greater anticipatory drive [39]. Taken together, YHM might have increased neural drive, leading to greater arousal and, thereby, increasing power output and endurance performance. Given that arousal is under circadian control and tends to be lowest during AM times [40], the addition of YHM ingestion might have improved performance through the abrogation of AM-associated declines.

Irrespective of treatment and time of day, HR and RPE remained largely unaltered during exercise. The lack of changes in HR is in opposition to previous work showing that average HR was elevated during exercise when performing repeated sprints following YHM ingestion [16]. Physiologically, previous work showing increased plasma catecholamines and NE spillover following YHM administration supports the notion of YHM-induced increases in exercise HR [12,16]. While the lack of changes in HR observed in the current study remains unclear, the disparities in findings may be due to differences in the alteration of cardiac function during exercise. Previous evidence has suggested that stroke volume during physical activity is under circadian control, whereby stroke volume progressively increases throughout the day and peaks during evening times [41]. Given that stroke volume may be a limiting factor to systemic oxygen delivery during exercise [42,43], greater stroke volume in the evening might have allowed for better rowing performance and might have blunted exercise-induced escalations in HR during PM compared to AM. YHM has been shown to possess inotropic properties, which are likely mediated through catecholamine release and NE spill over at sympathetic junctions [38]. Increases in circulating epinephrine, as previously shown with acute YHM ingestion [16], have been implicated in the amplification in stroke volume during exercise through inotropic mechanisms [44]. While purely speculative, increases in stroke volume could explain the lack of changes in HR since higher stroke volumes have been shown to decrease chronotropic responses to exercise [43]. However, it should be cautioned that the role of YHM in cardiac function has not been well studied in humans and investigations with more comprehensive measurements of cardiac function are warranted. Furthermore, the lack of changes in RPE may be related to this since RPE closely follows the trends of cardiac variables [45]. However, the lack of changes in RPE with increases in performance, as observed in the current study,

may be viewed favorably as it suggests that participants were able to exercise at higher work rates with YHM in the AM despite not perceiving additional exertion.

In attempts to characterize underlying metabolic changes, La and HX were measured pre- and post-exercise as indirect humoral markers of metabolic activity. As expected, La increased from pre- to post-exercise. However, La did not appear to be dependent on AM or PM times. Intriguingly, the addition of YHM in the AM resulted in lower post-exercise La levels. This agrees with previous findings showing lower post-exercise La following YHM ingestion with repeated sprints in trained females [16]. While not confirmed in the current study, YHM has been well described to alter hemodynamics through enhanced catecholamine responses. Release of epinephrine has been shown to shunt blood flow away from visceral areas to active skeletal muscle. This may, in turn, explain the lower post-exercise La levels in that enhanced oxygen delivery may blunt La formation and increased circulation may aid in La clearance. Ultimately, this may lead to decreases in fatigue and may aid in explaining the superior performance in the AM when supplemented with YHM compared to PL. HX, an indirect humoral marker of ATP breakdown, was also increased pre- to post-exercise irrespective of treatment or time, supporting the expectation of elevated metabolic rate and energy breakdown with exercise. However, pre-exercise HX was significantly higher during PM versus PL-AM, while YHM ingestion only resulted in trends showing higher levels of HX pre-exercise. We interpret this to indicate that energy breakdown is likely higher during PM compared to AM, while YHM might have partially abolished these differences. Differences in AM and PM HX levels may manifest in differences in thermal states as body temperature steadily increases throughout the day, resulting in increased metabolic rate. YHM has been reported to abrogate hypothermia and might have resulted in increased body temperatures in the current study during the AM times, which could have accelerated energy breakdown and metabolism. However, it is unclear how this relates to performance and if increases in basal HX result in adaptive or maladaptive responses. Further mechanistic physiological evidence is a dire need in this area and may aid in our understating of how α-adrenergic receptors mediate diurnal changes during exercise performance.

While the current study provides novel information on how YHM mitigates diurnal changes in exercise performance, there were several limitations. Although deemed adequate for an a priori power analysis, samples from larger and more diverse populations will be needed beyond the homogenous one used in the current study to make widespread recommendations on YHM supplementation. Furthermore, accounting for factors such as maximal oxygen consumption, body composition, and habitual nutrition will need further study. Neither participant chronotype (i.e., morning or afternoon "person") nor preference for time of day to exercise were controlled for in the current study. Thus, we cannot rule out the possibility that the participants may have been habituated to exercising at different times of day than the times used for data collection. The menstrual cycle phase of the participants was not strictly controlled for, which might have influenced the results. But, it is worth noting that our basis for excluding this control is due to previous evidence showing that acute high-intensity exercise performance, such as that of the current investigation, remains largely unchanged regardless of menstrual cycle phase [46–49]. Furthermore, females are extremely understudied in exercise research, and the current results add to the body of exercise literature utilizing females [46,50]. More research studies on YHM supplementation with females are still required to form firm conclusions on efficacy. In conclusion, acute YHM ingestion mitigates endurance exercise performance loss during AM times and effectively restores performance to the level during PM. From a practical standpoint, loss in training volume and intensity, as seen during AM times, may lead to poorer training adaptation over time. Thus, YHM may be an effective way to improve exercise performance during AM times and may optimize training to improve adaptations over time. Study on chronic supplementation is a dire need and may provide knowledge on how to integrate supplementation most effectively into training and sports.

Author Contributions: Conceptualization, C.G.B., R.R.R., C.L.B. and T.D.W.; data curation, C.G.B., M.E.B., C.R.C., C.C.E., K.A.L. and G.Y.L.; formal analysis, C.G.B. and R.R.R.; investigation, C.G.B., R.R.R., M.E.B., C.R.C., K.A.L., G.Y.L., J.C.K., E.G.S., C.C.E., S.B.W., M.J.M., C.L.B. and T.D.W.; methodology, C.G.B., R.R.R., M.E.B., C.R.C., K.A.L., G.Y.L., J.C.K., E.G.S., C.C.E., S.B.W., M.J.M., C.L.B. and T.D.W.; supervision, C.G.B. and R.R.R.; writing—original draft preparation, C.G.B.; writing—review and editing, C.G.B., R.R.R., C.L.B. and T.D.W. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: All experimental procedures were conducted in accordance with the Declaration of Helsinki and approved by the Samford University Institutional Review Board (EXPD-HP-21-SUM-1; July 2021).

Informed Consent Statement: Prior to any data collection, verbal and written informed consent was obtained from each participant.

Data Availability Statement: Data are contained and available within this manuscript.

Acknowledgments: We would like to thank Ellah Ball for her support with data collection.

Conflicts of Interest: The authors declare no conflict of interest. All research was conducted entirely independently.

References

1. McGinnis, G.R.; Young, M.E. Circadian regulation of metabolic homeostasis: Causes and consequences. *Nat. Sci. Sleep.* **2016**, *8*, 163–180. [PubMed]
2. Kaneko, M.; Zechman, F.W.; Smith, R.E. Circadian variation in human peripheral blood flow levels and exercise responses. *J. Appl. Physiol.* **1968**, *25*, 109–114. [CrossRef]
3. Racinais, S.; Blonc, S.; Hue, O. Effects of active warm-up and diurnal increase in temperature on muscular power. *Med. Sci. Sports Exerc.* **2005**, *37*, 2134–2139. [CrossRef] [PubMed]
4. Martin, A.; Carpentier, A.; Guissard, N.; Van Hoecke, J.; Duchateau, J. Effect of time of day on force variation in a human muscle. *Muscle Nerve* **1999**, *22*, 1380–1387. [CrossRef]
5. Ayala, V.; Martínez-Bebia, M.; Latorre, J.A.; Gimenez-Blasi, N.; Jimenez-Casquet, M.J.; Conde-Pipo, J.; Bach-Faig, A.; Mariscal-Arcas, M. Influence of circadian rhythms on sports performance. *Chronobiol. Int.* **2021**, *38*, 1522–1536. [CrossRef] [PubMed]
6. Nobari, H.; Azarian, S.; Saedmocheshi, S.; Valdés-Badilla, P.; Calvo, T.G. Narrative review: The role of circadian rhythm on sports performance, hormonal regulation, immune system function, and injury prevention in athletes. *Heliyon* **2023**, *9*, e19636. [CrossRef] [PubMed]
7. Blazer, H.J.; Jordan, C.L.; Pederson, J.A.; Rogers, R.R.; Williams, T.D.; Marshall, M.R.; Ballmann, C.G. Effects of time-of-day training preference on resistance-exercise performance. *Res. Q. Exerc. Sport.* **2021**, *92*, 492–499. [CrossRef]
8. Dumar, A.M.; Huntington, A.F.; Rogers, R.R.; Kopec, T.J.; Williams, T.D.; Ballmann, C.G. Acute beetroot juice supplementation attenuates morning-associated decrements in supramaximal exercise performance in trained sprinters. *Int. J. Environ. Res. Public Health* **2021**, *18*, 412. [CrossRef]
9. Shannon, M.; Neuman, M.I. Yohimbine. *Pediatr. Emerg. Care* **2000**, *16*, 49–50. [CrossRef]
10. Small, J. Yohimbe bark: Its history and identification in commerce. *Pharma J.* **1922**, *108*, 264–311.
11. Swann, A.C.; Birnbaum, D.; Jagar, A.A.; Dougherty, D.M.; Moeller, F.G. Acute yohimbine increases laboratory-measured impulsivity in normal subjects. *Biol. Psychiatry* **2005**, *57*, 1209–1211. [CrossRef]
12. Grossman, E.; Rea, R.F.; Hoffman, A.; Goldstein, D.S. Yohimbine increases sympathetic nerve activity and norepinephrine spillover in normal volunteers. *Am. J. Physiol.-Regul. Integr. Comp. Physiol.* **1991**, *260*, R142–R147. [CrossRef]
13. Williams, T.D.; Boag, L.E.; Helton, C.L.; Middleton, M.L.; Rogers, R.R.; Sternenberg, L.H.; Ballmann, C.G. Effects of Acute Yohimbine Hydrochloride Ingestion on Bench Press Performance in Resistance-Trained Males. *Muscles* **2022**, *1*, 82–91. [CrossRef]
14. Roatta, S.; Farina, D. Sympathetic actions on the skeletal muscle. *Exerc. Sport. Sci. Rev.* **2010**, *38*, 31–35. [CrossRef]
15. Cameron, O.G.; Zubieta, J.K.; Grunhaus, L.; Minoshima, S. Effects of yohimbine on cerebral blood flow, symptoms, and physiological functions in humans. *Psychosom. Med.* **2000**, *62*, 549–559. [CrossRef]
16. Barnes, M.E.; Cowan, C.R.; Boag, L.E.; Hill, J.G.; Jones, M.L.; Nixon, K.M.; Parker, M.G.; Parker, S.K.; Raymond, M.V.; Sternenberg, L.H.; et al. Effects of Acute Yohimbine Hydrochloride Supplementation on Repeated Supramaximal Sprint Performance. *Int. J. Environ. Res. Public Health* **2022**, *19*, 1316. [CrossRef]
17. Al-Kuraishy, H.M.; AN Abood, H.; Al-Gareeb, I.A. Ergogenic Effects of Yohimbine: Standardized Cycling Clinical Study. *Kerbala J. Med.* **2014**, *7*, 1850–1855.
18. Laakso, M.-L.; Mustanoja, S.M.; Hätönen, T.; Alila-Johansson, A. Alpha2-adrenoceptor agonist medetomidine affects the melatonin rhythm in rats. *Neurosci. Lett.* **1997**, *238*, 61–64. [CrossRef]
19. Thosar, S.S.; Shea, S.A. Circadian control of human cardiovascular function. *Curr. Opin. Pharmacol.* **2021**, *57*, 89–97. [CrossRef]

20. Souissi, M.; Abedelmalek, S.; Chtourou, H.; Boussita, A.; Hakim, A.; Sahnoun, Z. Effects of time-of-day and caffeine ingestion on mood states, simple reaction time, and short-term maximal performance in elite judoists. *Biol. Rhythm. Res.* **2013**, *44*, 897–907. [CrossRef]
21. Mora-Rodríguez, R.; Pallarés, J.G.; López-Gullón, J.M.; López-Samanes, Á.; Fernández-Elías, V.E.; Ortega, J.F. Improvements on neuromuscular performance with caffeine ingestion depend on the time-of-day. *J. Sci. Med. Sport.* **2015**, *18*, 338–342. [CrossRef] [PubMed]
22. Riebe, D.; Ehrman, J.K.; Liguori, G.; Magal, M.; American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*; Wolters Kluwer: Amsterdam, The Netherland, 2018.
23. Williams, T.D.; Langley, H.N.; Roberson, C.C.; Rogers, R.R.; Ballmann, C.G. Effects of short-term golden root extract (*Rhodiola rosea*) supplementation on resistance exercise performance. *Int. J. Environ. Res. Public Health* **2021**, *18*, 6953. [CrossRef] [PubMed]
24. Toledo-Ibelles, P.; Gutiérrez-Vidal, R.; Calixto-Tlacomulco, S.; Delgado-Coello, B.; Mas-Oliva, J. Hepatic accumulation of hypoxanthine: A link between hyperuricemia and nonalcoholic fatty liver disease. *Arch. Med. Res.* **2021**, *52*, 692–702. [CrossRef] [PubMed]
25. Nixon, K.M.; Parker, M.G.; Elwell, C.C.; Pemberton, A.L.; Rogers, R.R.; Ballmann, C.G. Effects of music volume preference on endurance exercise performance. *J. Funct. Morphol. Kinesiol.* **2022**, *7*, 35. [CrossRef]
26. Karow, M.C.; Rogers, R.R.; Pederson, J.A.; Williams, T.D.; Marshall, M.R.; Ballmann, C.G. Effects of preferred and nonpreferred warm-up music on exercise performance. *Percept. Mot. Ski.* **2020**, *127*, 912–924. [CrossRef]
27. Hoffman, J.R.; Kang, J.; Ratamess, N.A.; Hoffman, M.W.; Tranchina, C.P.; Faigenbaum, A.D. Examination of a pre-exercise, high energy supplement on exercise performance. *J. Int. Soc. Sports Nutr.* **2009**, *6*, 2. [CrossRef]
28. Wei, J.; Carroll, R.J.; Harden, K.K.; Wu, G. Comparisons of treatment means when factors do not interact in two-factorial studies. *Amino Acids* **2012**, *42*, 2031–2035. [CrossRef]
29. Fritz, C.O.; Morris, P.E.; Richler, J.J. Effect size estimates: Current use, calculations, and interpretation. *J. Exp. Psychol. Gen.* **2012**, *141*, 2–18. [CrossRef]
30. Cohen, J. *Statistical Power Analysis for the Behavioral Sciences*, 2nd ed.; Erlbaum Associates: Hillsdale, MI, USA, 1988.
31. Teo, W.; Newton, M.J.; McGuigan, M.R. Circadian rhythms in exercise performance: Implications for hormonal and muscular adaptation. *J. Sports Sci. Med.* **2011**, *10*, 600.
32. Knaier, R.; Qian, J.; Roth, R.; Infanger, D.; Notter, T.; Wang, W.; Cajochen, C.; Scheer, F.A. Diurnal variation in maximum endurance and maximum strength performance: A systematic review and meta-analysis. *Med. Sci. Sports Exerc.* **2022**, *54*, 169. [CrossRef]
33. Lambert, E.A.; Chatzivlastou, K.; Schlaich, M.; Lambert, G.; Head, G.A. Morning surge in blood pressure is associated with reactivity of the sympathetic nervous system. *Am. J. Hypertens.* **2014**, *27*, 783–792. [CrossRef] [PubMed]
34. Chtourou, H.; Driss, T.; Souissi, S.; Gam, A.; Chaouachi, A.; Souissi, N. The effect of strength training at the same time of the day on the diurnal fluctuations of muscular anaerobic performances. *J. Strength. Cond. Res.* **2012**, *26*, 217–225. [CrossRef]
35. Hassler, C.; Burnier, M. Circadian variations in blood pressure: Implications for chronotherapeutics. *Am. J. Cardiovasc. Drugs* **2005**, *5*, 7–15. [CrossRef] [PubMed]
36. Kario, K.; Pickering, T.G.; Hoshide, S.; Eguchi, K.; Ishikawa, J.; Morinari, M.; Hoshide, Y.; Shimada, K. Morning blood pressure surge and hypertensive cerebrovascular disease: Role of the alpha adrenergic sympathetic nervous system. *Am. J. Hypertens.* **2004**, *17*, 668–675. [CrossRef] [PubMed]
37. Roatta, S.; Arendt-Nielsen, L.; Farina, D. Sympathetic-induced changes in discharge rate and spike-triggered average twitch torque of low-threshold motor units in humans. *J. Physiol.* **2008**, *586*, 5561–5574. [CrossRef] [PubMed]
38. Jabir, N.R.; Firoz, C.K.; Zughaibi, T.A.; Alsaadi, M.A.; Abuzenadah, A.M.; Al-Asmari, A.I.; Alsaieedi, A.; Ahmed, B.A.; Ramu, A.K.; Tabrez, S. A literature perspective on the pharmacological applications of yohimbine. *Ann. Med.* **2022**, *54*, 2849–2863. [CrossRef] [PubMed]
39. Sun, H.; Green, T.A.; Theobald, D.E.; Birnbaum, S.G.; Graham, D.L.; Zeeb, F.D.; Nestler, E.J.; Winstanley, C.A. Yohimbine increases impulsivity through activation of cAMP response element binding in the orbitofrontal cortex. *Biol. Psychiatry* **2010**, *67*, 649–656. [CrossRef] [PubMed]
40. Reilly, T.; Atkinson, G.; Coldwells, A. The relevance to exercise performance of the circadian rhythms in body temperature and arousal. *Biol. Sport.* **1993**, *10*, 204.
41. Delp, M.; Manning, R.; Bruckner, J.; Armstrong, R. Distribution of cardiac output during diurnal changes of activity in rats. *Am. J. Physiol.-Heart Circ. Physiol.* **1991**, *261*, H1487–H1493. [CrossRef]
42. Fritzsche, R.G.; Switzer, T.W.; Hodgkinson, B.J.; Coyle, E.F. Stroke volume decline during prolonged exercise is influenced by the increase in heart rate. *J. Appl. Physiol.* **1999**, *86*, 799–805. [CrossRef]
43. Spina, R.J.; Ogawa, T.; Martin, W., 3rd; Coggan, A.R.; Holloszy, J.; Ehsani, A. Exercise training prevents decline in stroke volume during exercise in young healthy subjects. *J. Appl. Physiol.* **1992**, *72*, 2458–2462. [CrossRef] [PubMed]
44. Garb, S. Inotropic Action of Epinephrine, Nor-epinephrine, and N-Isopropyl-Norepinephrine on Heart Muscle. *Proc. Soc. Exp. Biol. Med.* **1950**, *73*, 134–135. [CrossRef] [PubMed]
45. Zinoubi, B.; Zbidi, S.; Vandewalle, H.; Chamari, K.; Driss, T. Relationships between rating of perceived exertion, heart rate and blood lactate during continuous and alternated-intensity cycling exercises. *Biol. Sport.* **2018**, *35*, 29–37. [CrossRef] [PubMed]
46. Costello, J.T.; Bieuzen, F.; Bleakley, C.M. Where are all the female participants in sports and exercise medicine research? *Eur. J. Sport. Sci.* **2014**, *14*, 847–851. [CrossRef] [PubMed]

47. Bushman, B.; Masterson, G.; Nelsen, J. Anaerobic power performance and the menstrual cycle: Eumenorrheic and oral contraceptive users. *J. Sports Med. Phys. Fit.* **2006**, *46*, 132.
48. Wiecek, M.; Szymura, J.; Maciejczyk, M.; Cempla, J.; Szygula, Z. Effect of sex and menstrual cycle in women on starting speed, anaerobic endurance and muscle power. *Acta Physiol. Hung.* **2016**, *103*, 127–132. [CrossRef]
49. Ghazel, N.; Souissi, A.; Chtourou, H.; Aloui, G.; Souissi, N. The effect of music on short-term exercise performance during the different menstrual cycle phases in female handball players. *Res. Sports Med.* **2022**, *30*, 50–60. [CrossRef]
50. Cowley, E.S.; Olenick, A.A.; McNulty, K.L.; Ross, E.Z. "Invisible sportswomen": The sex data gap in sport and exercise science research. *Women Sport. Phys. Act. J.* **2021**, *29*, 146–151. [CrossRef]