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L-Arginine Improves Endurance to High-Intensity Interval Exercises in Overweight Men

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The effects of acute consumption of L-Arginine (L-Arg) in healthy young individuals are not clearly defined, and no studies on the effects of L-Arg in individuals with abnormal body mass index undertaking strenuous exercise exist. Thus, we examined whether supplementation with L-Arg diminishes cardiopulmonary exercise testing responses, such as ventilation (VE), VE/VCO_2, oxygen uptake (VO_2), and heart rate, in response to an acute session of high-intensity interval exercise (HIIE) in overweight men. A double-blind, randomized crossover design was used to study 30 overweight men (age, 26.5 ± 2.2 years; body weight, 88.2 ± 5.3 kilogram; body mass index, 28.0 ± 1.4 kg/m^2). Participants first completed a ramped-treadmill exercise protocol to determine VO_2max velocity (vVO_2max), after which they participated in two sessions of HIIE. Participants were randomly assigned to receive either 6 g of L-Arg or placebo supplements. The HIIE treadmill running protocol consisted of 12 trials, including exercise at 100% of vVO_2max for 1 min interspersed with recovery intervals of 40% of vVO_2max for 2 min. Measurements of VO_2 ($ml{\cdot}kg^{-1}{\cdot}min^{-1}$), VE (L/min), heart rate (beat per min), and VE/VCO_2 were obtained. Supplementation with L-Arg significantly decreased all cardiorespiratory responses during HIIE (placebo+HIIE vs. L-Arg+HIIE for each measurement: VE [80.9 ± 4.3 L/min vs. 74.6 ± 3.5 L/min, $p < .05$, ES = 1.61], VE/VCO_2 [26.4 ± 1.3 vs. 24.4 ± 1.0, $p < .05$, ES = 1.8], VO_2 [26.4 ± 0.8 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$ vs. 24.4 ± 0.9 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$, $p < .05$, ES = 2.2], and heart rate [159.7 ± 6.3 beats/min vs. 155.0 ± 3.7 beats/min, $p < .05$, $d = 0.89$]). The authors conclude consuming L-Arg before HIIE can alleviate the excessive physiological strain resulting from HIIE and help to increase exercise tolerance in participants with a higher body mass index who may need to exercise on a regular basis for extended periods to improve their health.

Keywords: heart rate, strenuous exercise, ventilation

Increased body fat negatively impacts gas exchange during exercise (Gläser et al., 2013); that is, individuals with obesity/overweight require higher increases in ventilation (VE), oxygen uptake (VO_2), and heart rate (HR) during exercise (Nora et al., 2010). Furthermore, obese persons have increased ventilation/perfusion (V/Q) inequalities so that the VE/carbon dioxide (CO_2) production ratio (VE/VCO_2) impairs work efficiency during exercise. These factors are related to respiratory dysfunction and mechanical inefficiency in obese individuals (O'Donnell et al., 2012). Excess adipose tissue also reduces cardiovascular function and aerobic capacity during exercise as HR responses are decreased during maximal exercise, resulting in diminished oxygen (O_2) transport (Harten, 2018).

One form of exercise that is gaining popularity, and which has been shown to reduce body weight and body fat as well as obesity-related risk factors, is high-intensity interval exercise (HIIE; Keating et al., 2017), defined as repeated intermittent near-maximal to maximal bouts of exercise that are separated by short periods of recovery (Buchheit & Laursen, 2013). The evidence clearly supports the idea that high-intensity interval training significantly improves body composition variables and increases VO_2max and insulin sensitivity in both healthy and clinical populations (Francois & Little, 2015; Khammassi et al., 2018). Evidence supports the idea that high-intensity interval training provides superior benefits on glycemic control and cardiorespiratory fitness compared with moderate-intensity continuous exercise (Jelleyman et al., 2015). The HIIE also decreases dyspnea during exercise more than a moderate-intensity exercise in patients with cardiac disease (Bernhardt & Babb, 2016). The lack of breathlessness experienced by overweight participants during exercise (Bernhardt & Babb, 2016) may motivate them to participate in high-intensity interval training, as they likely would have greater tolerance to HIIE, compared with moderate-intensity exercise, for at least two reasons: (a) HIIE has built-in recovery periods between bouts of exercise (as such, allowing for a reduction in VE) and (b) HIIE does not require sustained exercise periods above VT (Guiraud et al., 2012).

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The endogenous synthesis of nitric oxide (NO) is impaired in individuals with obesity, and NO concentrations decrease with high-intensity exercise (Shan et al., 2013). The combination of these two factors can cause significant decreases in exercise tolerance, suggesting that individuals with obesity could benefit from supplementation with L-arginine (Tousoulis et al., 2002). That is, L-arginine is a precursor of NO synthesis and is found in red meats, poultry, and fish. Release of NO influences the cardiovascular and respiratory systems in humans at rest and during exercise (Tousoulis et al., 2002). Studies report consuming 6 g of L-arginine 80 min prior to exercise significantly increased muscle blood flow by increasing vasodilation and improving hematological factors (such as red blood cell deformability and aggregation; Álvares et al., 2012; Connes et al., 2010). However, some studies suggested that L-arginine does not affect the oxygen (O_2) cost of moderate-intensity cycling and submaximal running (Vanhatalo et al., 2013). There is an inverse relationship between body mass index (BMI) and the bioavailability of NO, suggesting that body fat can alter hemodynamic responses (Toda & Okamura, 2013). The production and bioavailability of NO under physiological conditions are dependent on the amount of exogenous L-arginine (Tousoulis et al., 2002). For example, ingesting L-arginine reverses the effects of endothelial NO-synthase (eNOS) inhibition (Nosarev et al., 2015). Inhibition of eNOS increases VO_2 consumption during exercise (Nosarev et al., 2015), and a lower L-arginine/ADMA (endogenously produced eNOS inhibitor) ratio is associated with decreased forced expiratory volume (Holguin, 2013).

Several factors can influence the efficacy of L-arginine supplementation during exercise, including the mode of delivery, different types of commercial supplement and its ingredients, dosage, the timing of consumption before exercise, exercise intensity, and mode of exercise (resistance vs. running and high intensity vs. moderate intensity) and participants characteristics (athlete vs. inactive and healthy vs. individuals with disease; Bailey et al., 2010; Bescós et al., 2009; Koppo et al., 2009; Meirelles et al., 2019; Vanhatalo et al., 2013). Recently, Meirelles et al. (2019) found no beneficial effects of 6-g L-arginine in improving VO_2 consumption during exercise in healthy young active males (Meirelles et al., 2019). In accordance with this, Andrade et al. (2018) showed that the same dosage of L-arginine (6 g) does not improve muscle function during recovery following strength exercise in recreationally active healthy young adults (Andrade et al., 2018).

To our knowledge, the benefits of L-arginine supplementation in overweight individuals completing an acute bout of HIIE have not been investigated. Understanding the influences of L-arginine supplementation in individuals with an abnormal BMI is important not only for future studies on the acute effects of low doses of L-arginine in clinical populations but also for studies in such individuals relative to their exercise tolerance. Thus, we investigated the acute effects of consuming 6 g of L-arginine on some cardiorespiratory factors (such as VE, VE/VCO_2, and VO_2, as well as HR) during HIIE in individuals who were overweight, and hypothesized that such men receiving supplementation with L-arginine would have an enhanced exercise tolerance through HIIE (Álvares et al., 2012; Bailey et al., 2010; McKnight et al., 2010), as measured by various markers of ventilatory function.

Methods

Participants

Thirty healthy overweight men (age, 26.5 ± 2.2 years; body weight, 88.2 ± 5.3 kg; BMI, 28 ± 1.4 kg/m^2; body fat percentage, 24.1 ± 2.3; and VO_2max, 36.1 ± 3.2 ml·kg^{-1}·min^{-1}) participated in this study. Inclusion criteria included individuals who were nonsmokers; who had no history of chronic diseases, including cardiovascular and pulmonary diseases; who had a BMI of 25.0–29.9 kg/m^2, and who were not participating in any exercise programs. Before the two HIIE sessions, the Sport Sciences Research Institute approved the exercise protocol (IR.SSRC.REC.1398.089). All participants were fully informed about the aims and experimental procedures and provided written informed consent. Participant number was determined through power calculations (G*Power software, G*Power, version 3.1.9.7).

Experimental Design

Participants reported to our laboratory on three separate occasions, with 1 week separating each session. During the first session, height (Seca, Birmingham, United Kingdom) and body mass (Seca, United Kingdom) were measured to determine BMI (weight [kilogram] divided by height [meters] squared), and participants then completed a VO_2max treadmill test. During the second and third sessions, all participants performed HIIE after consuming either L-arginine or placebo, which was randomly assigned in a double-blind manner (Figure 1). Participants were asked not to engage in any vigorous exercise for at least 48 hr before each test and to abstain from consuming products containing L-arginine (e.g., chicken, red meats, nuts/seeds, legumes, dairy products, beetroot, etc.).

Maximal Oxygen VO_2max Test

A computer-based metabolic cart system (Metalyazer 3B, Germany) was used to collect ventilatory expired gases and measure maximal HR, maximal velocity, and oxygen uptake (VO_2). The equipment was calibrated according to the manufacturer's recommendations before the start of the measurements. The participants were verbally encouraged to provide their maximal efforts and to do so throughout the test. The protocol started with a 1-min warm-up at the speed of 1.5 km/hr; the speed of the treadmill (h/p/cosmos pulsar 3p, made in Germany) was progressively increased to 2 min (Manfredini et al., 2004). The incline of the treadmill remained at a 0% grade throughout the warm-up, following which they completed stretching exercises. Immediately after the warm-up, each participant was fitted with a facemask, and a ramp protocol was initiated, where the incline of the treadmill remained at a 0% grade, and the speed increased every 2 min by 2 km/hr until the participants reached volitional exhaustion. The HR (beats/min) of participants was continuously recorded throughout the test using an HR monitor (Polar Electro Oy, Kempele, Finland). Participants reported their rating of perceived exertion using the Borg scale (6–20) during the last 10 s of each 2-min stage of the test (Borg, 1970). The criteria used for gauging the achievement of a maximal effort were: (a) a plateau in VO_2 (or failure to increase VO_2 by 150 ml min^2), (b) RER ≥ 1.10, (c) a rating of perceived exertion of 17 on a 6–20 rating of perceived exertion scale, and (d) peak HR ≥ 95% of age-predicted maximal HR (208 – 0.7 × Age; Pescatello et al., 2014). A maximal effort was considered attained if at least three out of these four criteria were met. When the treadmill was stopped following maximal exhaustion, the final velocity was determined as the velocity at VO_2max ($v\dot{V}O_2$max) and was used as the work rate for the two subsequent HIIE sessions.

HIIE Sessions and L-Arginine Supplementation

All sessions were performed in the morning (between 8:00 and 9:00 a.m.) following an 8-hr overnight fast. Each participant

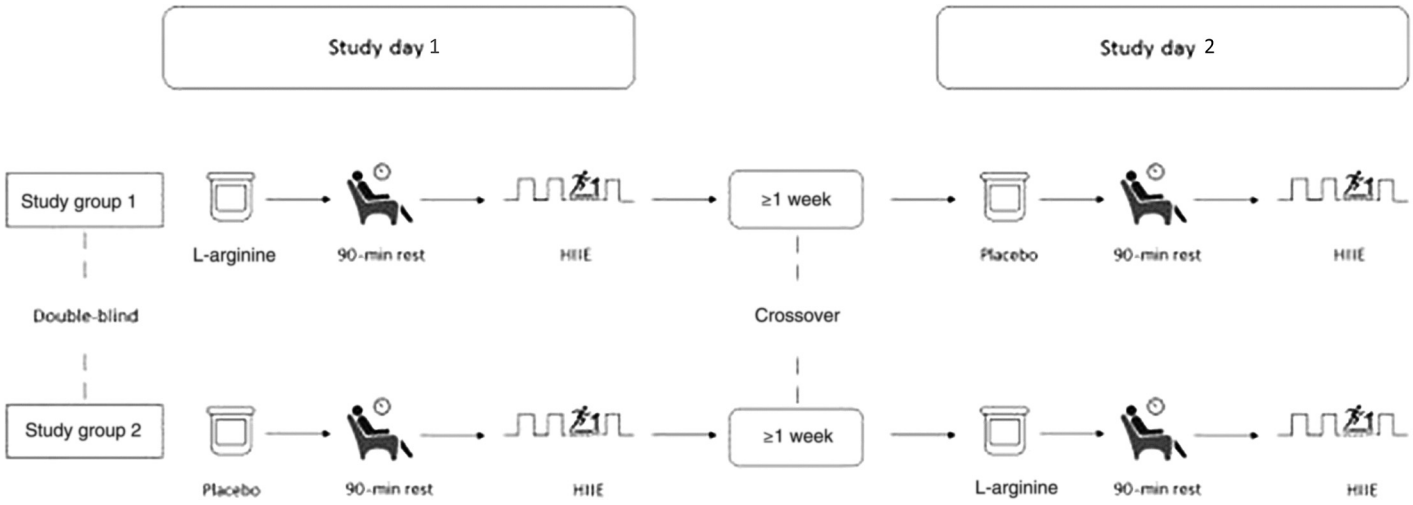

Figure 1 — Study design. HIIE indicates high-intensity interval exercise.

scheduled two HIIE sessions at approximately the same time each day to control for diurnal variations. After arriving at the laboratory, participants were asked to remain seated for 10 min before consuming 6 grams of either L-arginine (L-arginine HCL [70%] +L-citrulline malate [16.7%], Body Attack, Germany) or placebo (Maltodextrin MD 18, Karen Company, Yazd, Iran). The subjects remained seated for an additional 90 min. We used a double-blind crossover design, with a 7-day washout period between the two treatment conditions, implying that after the 1-week washout period, participants who originally consumed the L-arginine supplement in the first part of the study then consumed the placebo before undertaking HIIE and vice versa. This dosage of L-arginine is well-tolerated when consumed orally by healthy participants (Álvares et al., 2012). Both L-arginine and placebo were dissolved in 250-ml water, and both drinks had the same color and flavor. The pharmacokinetics of L-arginine supplementation was used to optimize its effects; that is, 90 min was required to reach peak plasma levels (Bode-Böger et al., 1998). The supplement was independently analyzed and verified for its safety and the presence of the active compound and the absence of contaminants by Ghahari Azarmidakht Laboratory, Mazandaran, Iran.

The HIIE Protocol

Following 90 min of rest, participants undertook progressive warm-ups consisting of stretching exercises. The HIIE protocol consisted of 12 trials, including active intervals at 100% of vVO_2max for 1 min interspersed by 2-min recovery periods of 40% of vVO_2max. Immediately thereafter, participants were allowed to sit. Regardless of the warm-up and the recovery after exercise, the HIIE protocol always lasted 36 min. All participants (L-arginine+HIIE or placebo +HIIE groups) performed two different sessions separated by a 1-week interval to avoid the stress of testing. All sessions were supervised by an exercise physiologist, and environmental conditions, including ambient temperature (25 ± 2 °C) and time of day (08:00–09:00 a.m.), were constant for each session.

During both HIIE sessions, the ventilatory expired gas analysis was performed by a computer-based system (Metalyazer 3B) during the following stages: during the 3-min rest period, the 3- to 5-min warm-up period, during HIIE, and during 3-min recovery period. Measurements of VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$), VE (L/min), and HR (beats/min), as well as VE/VCO_2, were obtained breath by breath (averaged for 10-s intervals; Antoine-Jonville et al., 2012). The VE/VCO_2 ratio was determined by using a least-squares regression analysis ($y = mx + b$; where m = slope) of VE and VCO_2 responses and age-predicted maximal HR defined as 208 – 0.7 × age (years). Borg scale data were collected after each interval. We used a filter to analyze the ventilatory gas data, as previously described (Antoine-Jonville et al., 2012).

Statistical Analysis

All data are presented as the mean ± SD. All statistical analyses were completed using IBM SPSS statistical software (version 18.0; SPSS, Inc., Chicago, IL). A normal distribution of data was assessed using the Kolmogorov–Smirnov test. A two-way analysis of variance with repeated measure (2 × 25; session vs. time) was used to analyze the responses of all variables. A Bonferroni post hoc test was used to determine significant changes between groups; that is, (a) averages of all the active intervals+L-arginine versus averages of all the active intervals+placebo, (b) averages of all the recovery intervals+L-arginine versus averages of all the recovery intervals+placebo, and then (c) averages of all the active+recovery intervals of both sessions by using paired t test in order to define the total physiological strain of HIIE+L-arginine versus HIIE+placebo. Effect sizes (ES) were assessed from the analysis of variance output by partial eta-squared. Statistical significance was established at $p \leq .05$.

Results

The VE significantly increased during HIIE regardless of which supplement was consumed, $F(24, 504) = 68.56$, $p = .0001$, ES = 0.76. The interaction of time and session indicated that increases in VE (L/min) were greater in the placebo+HIIE group than in the L-arginine+HIIE group, $F(24, 504) = 48.81$, $p = .0001$, ES = 0.70 (Figure 2a). The Bonferroni post hoc test revealed that significant improvement in VE occurred after the fourth interval during L-arginine+HIIE (Figure 2b). Additionally, the paired t test revealed that changes in VE were higher in placebo+HIIE both during active (95.7 ± 5.1 [placebo+HIIE] vs. 87.2 ± 2.1 [L-arginine+HIIE]) and recovery intervals (66.2 ± 3.5 [placebo+HIIE] vs. 62.0 ± 5.0 [L-arginine+HIIE]) ($p < .05$, ES = 1.61).

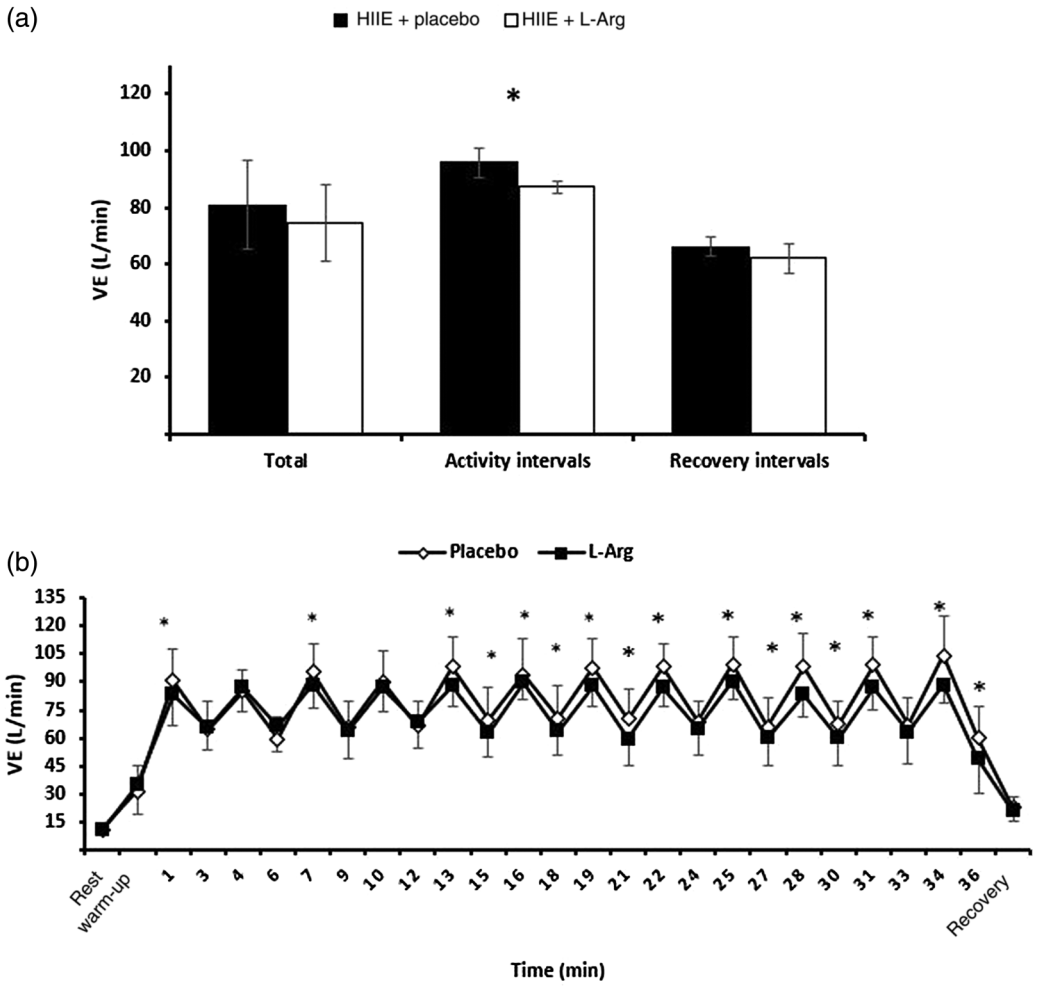

Figure 2 — (a) Mean (±SD) of VE during two sessions, active intervals, and recovery intervals. (b) Time course of the mean (±SD) changes in VE during two sessions, active intervals, and recovery intervals. Abbreviations: L-Arg = L-arginine; VE = ventilation; HIIE = high-intensity interval exercise. *Significant ($p < .05$) effects of supplementation with L-arginine ($N = 30$).

The VE/VCO_2 ratio significantly increased during HIIE regardless of which supplement was consumed, $F(24, 648) = 18.13$, $p = .0001$, ES = 0.40. Similarly, the interaction of times and sessions showed that the VE/VCO_2 ratio was greater in the placebo + HIIE group compared with the L-arginine+HIIE group, $F(24, 648) = 6.53$, $p = .0001$, ES = 0.19 (Figure 3a). The Bonferroni post hoc test revealed that significant improvement in VE/VCO_2 occurred after the third interval during L-arginine+HIIE (Figure 3b). The paired t test revealed that the VE/VCO_2 ratio was greater during active intervals in the placebo+HIIE group (32.0 ± 1.7) versus the L-arginine+HIIE group (29.3 ± 1.1; $p < .05$, ES = 1.8); the VE/VCO_2 ratio in recovery intervals was significantly shorter ($p < .05$, ES = 1.68) in the L-arginine group (19.5 ± 0.9) compared with the placebo-treated group (20.8 ± 1.0).

The VO_2 significantly increased during HIIE with either supplement condition, $F(24, 648) = 264.0$, $p = .0001$, ES = 0.90. The interaction of times and sessions showed that VO_2 consumption was significantly higher in the placebo+HIIE group compared with the L-arginine+HIIE group, $F(24, 648) = 8.68$, $p = .0001$, ES = 0.24 (Figure 4a). The Bonferroni post hoc test revealed that significant improvement in VO_2 occurred in all active intervals (except the eight intervals) and four of the recovery intervals during L-arginine+HIIE (Figure 4b). In addition, the paired t test showed significant higher VO_2 consumption in placebo+HIIE both during active (32.0 ± 0.8 $ml \cdot kg^{-1} \cdot min^{-1}$ [placebo+HIIE]) vs. (29.3 ± 0.8 $ml \cdot kg^{-1} \cdot min^{-1}$ [L-arginine+HIIE]) and recovery intervals (20.9 ± 0.9 [placebo +HIIE] vs. 19.5 ± 1.0, [L-arginine+HIIE]) ($p < .05$, ES = 2.2).

Finally, HR significantly increased during HIIE with either supplement condition, $F(24, 600) = 53.36$, $p = .0001$, ES = 0.68. Moreover, the interaction of times and sessions showed that HR was higher in the placebo + HIIE group compared with the L-arginine +HIIE group, $F(24, 600) = 1.94$, $p = .005$, ES = 0.07 (Figure 5a). Bonferroni post hoc test revealed that significant improvement in HR occurred in the active intervals of the first, third, seventh, eighth, ninth, 10th, 11th, and the 12th and two of the recovery intervals during L-arginine+HIIE (Figure 5b). Also, the paired t test showed that changes in HR (beats/min) were higher in placebo+HIIE both during active (172.6 ± 6.7 [placebo+HIIE] vs. 167.3 ± 4.7 [L-arginine+HIIE]) and recovery intervals (146.8 ± 5.9 [placebo +HIIE] vs. 142.8 ± 2.8 [L-arginine+HIIE]) ($p < .05$, ES = 0.89).

Discussion

We studied the effects of L-arginine supplementation on cardiopulmonary responses for VE, VE/VCO_2, VO_2, and HR in an acute session of HIIE in overweight adults and found that the increases

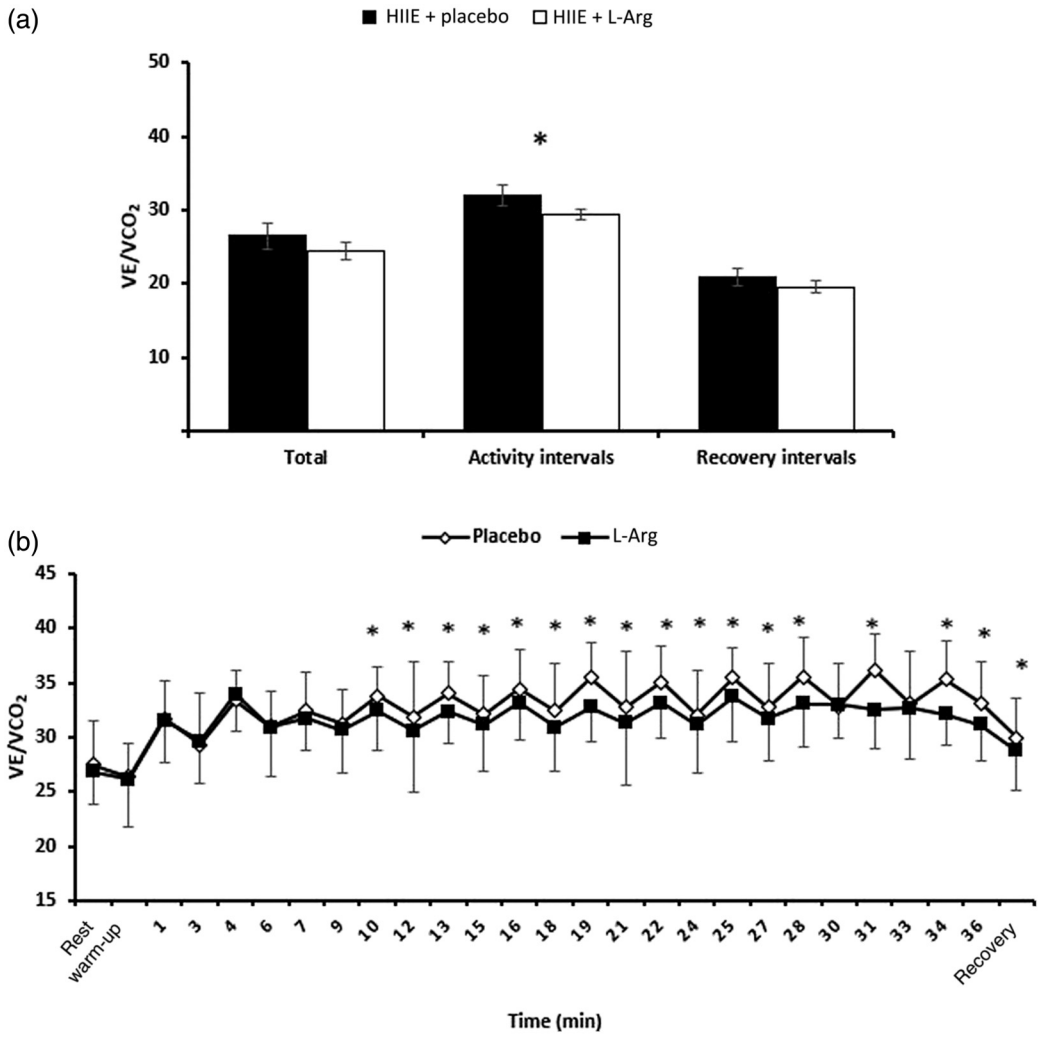

Figure 3 — (a) Mean (±SD) values of VE/VCO_2 during two sessions, active intervals, and recovery intervals. (b) Time course of the mean (±SD) changes in VE/VCO_2 during two sessions of active and recovery periods. Abbreviations: L-Arg = L-arginine; HIIE = high-intensity interval exercise; VE = ventilation; VCO_2 = carbon dioxide production. *Significant ($p < .05$) effects of supplementation with L-arginine ($N = 30$).

in VE in the L-arginine+HIIE treatment were lower than in the placebo treatment (placebo+HIIE) during active exercise and recovery intervals. Our findings are in contrast with those of another study, reporting no differences in the effects of L-arginine and placebo on VE in response to high-intensity exercise (Bailey et al., 2010). A potential explanation for these divergent findings is that the latter study (Bailey et al., 2010) used an HIIE protocol lasting only 6 min. We also reported the differences in VE values just after the second half of our exercise protocol (after the 13th min). We also found significantly lower responses of VE in 83% and 50% of active exercise intervals and recovery intervals, respectively, during the L-Arginine+HIIE treatment. This suggests that an increase in bioavailability of NO (following consumption of L-Arginine) during exercise might depend on the intensity and duration of exercise sessions (Meirelles et al., 2019). There were also differences in the BMI of our participants and those of Bailey et al., which is an important consideration as vital capacity and total lung capacity decrease with greater BMI, which can lead to dyspnea during exercise (O'Donnell et al., 2012), suggesting that overweight individuals have inefficient respiratory responses during exercise.

We reported a steeper VE/VCO_2 ratio increase during both active and recovery intervals in the L-arginine+HIIE group. To be more accurate, we found a steeper VE/VCO_2 ratio increase in 75% of active intervals and almost 60% of recovery intervals in the L-arginine+HIIE group, which is in agreement with the study by (Banning & Prendergast, 1999). That is, these researchers reported that short-term L-arginine supplementation decreased VE/VCO_2. There are several reasons for changes in VE/VCO_2, which can stem from muscle-like changes in anaerobic glycolysis (peripheral factors) or cardiovascular and respiratory systems, such as changes in cardiac output and pulmonary vasoconstriction (central factors) during exercise (Prado et al., 2016). Nevertheless, a reduction in VE/VCO_2 is associated with improvements in hemodynamic parameters in the pulmonary system (Mezzani et al., 2015). The L-arginine, by augmenting vasodilation, decreases physiological pulmonary dead space and increases cardiac output, so improving ventilation/perfusion (V/Q) inequalities and VE/VCO_2 (Nagaya et al., 2001). In addition, L-arginine improves endothelial function during exercise and increases blood flow to exercising muscle (Álvares et al., 2012; Tousoulis et al., 2002) and so augments O_2 uptake and also delays the reductions in VE/VCO_2 caused by metabolites (Schaefer et al., 2002).

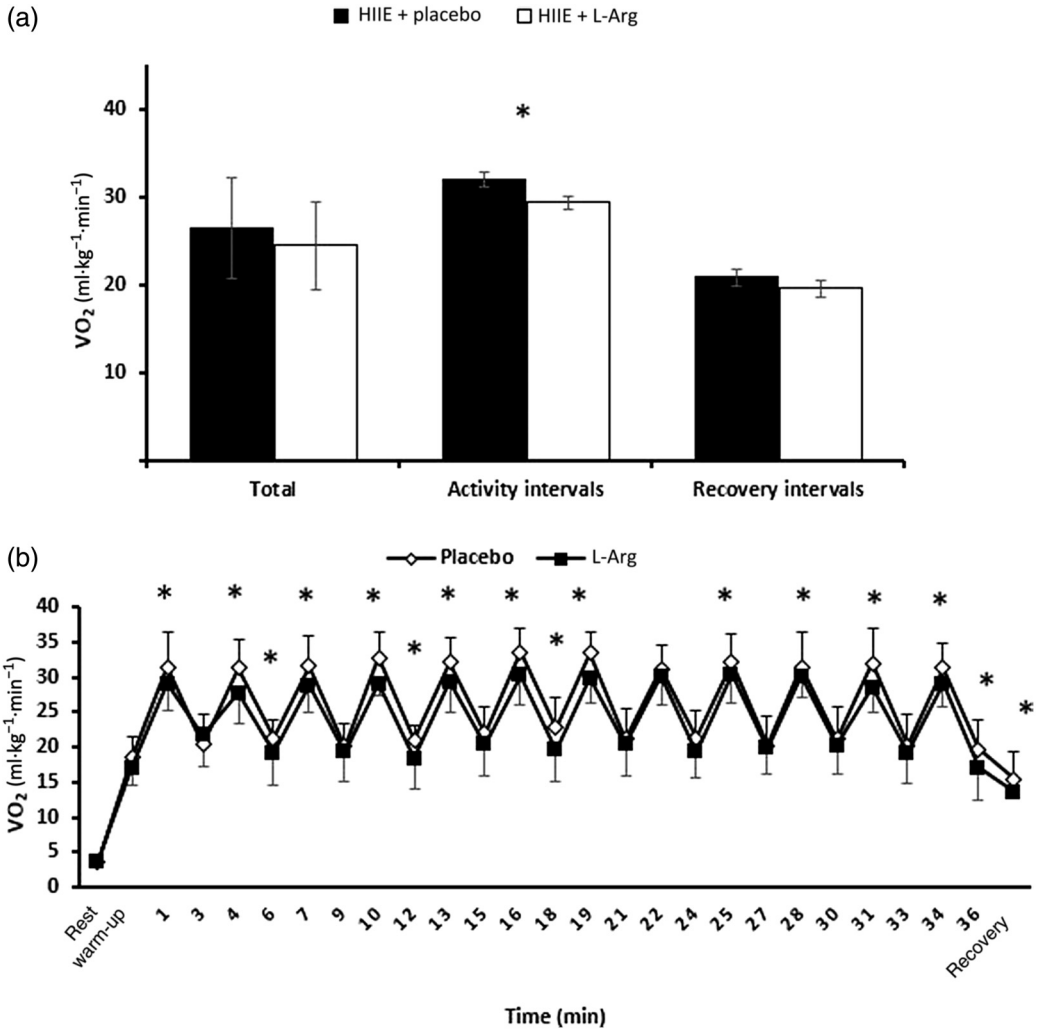

Figure 4 — (a) Mean (±SD) of VO_2 during two active and recovery intervals. (b) Time course of the mean (±SD) changes in VO_2 during active recovery intervals. *Significant ($p < .05$) effects of supplementation with L-arginine (N = 30). Abbreviations: L-Arg = L-arginine; HIIE = high-intensity interval exercise; VO_2 = oxygen uptake.

We also found lower VO_2 responses during both the active and recovery periods in the L-arginine+HIIE group. Several studies reported that L-arginine administration did not influence VO_2 during moderate-intensity cycling (Vanhatalo et al., 2013) or during submaximal running (Bescós et al., 2009), while other studies demonstrated that such interventions alter NO bioavailability, which can increase VO_2 during exercise (Jones et al., 2004). It is likely that increased shear stress experience during high-intensity exercise induces a greater release of NO (Connes et al., 2010). Also, red blood cells exposed to excess L-arginine are also able to release NO (Connes et al., 2010). Thus, a combination of these two effects is potential secondary mechanisms that improve VO_2 consumption during exercise. In line with this, we found significant changes in VO_2 responses after the ninth minute of L-Arginine +HIIE. Moreover, NOS inhibition with $N(\omega)$-nitro-L-arginine methyl ester (L-NAME) increases VO_2 during moderate-intensity cycling (Jones et al., 2004). Thus, a possible reason for the lower VO_2 responses we observed during the L-arginine+HIIE treatment could be related to increases in NO bioavailability (Jones, 2014), which improves microvascular diffusion in skeletal muscles, leading to increased O_2 consumption. The participants in our study were able to work at a lower O_2 requirement (mainly after the ninth minute of exercise), leading to a lower VO_2 for the same exercise work rate in the placebo+HIIE treatment. More recently, Meirelles et al. (2019) showed that 6 grams of L-arginine did not change the O_2 cost during the running treadmill test in healthy active males (Meirelles et al., 2019); the potential reason for this discrepancy could be, in part, due to the fact that only individuals with poor NO synthesis could benefit from L-arginine supplementation (Alvares et al., 2012). However, endogenous NO production is impaired in individuals with abnormal BMI (Toda & Okamura, 2013; Tousoulis et al., 2002).

We also report an attenuated HR response in the L-arginine +HIIE group, both during the active and recovery periods, in agreement with other studies reporting that L-arginine decreases HR during exercise (Banning & Prendergast, 1999). The L-arginine reduces left ventricular afterload to cause increases in stroke volume and cardiac output (Nagaya et al., 2001). Other mechanisms, such as reduced β-adrenergic agonist-induced chronotropic responses and increases in parasympathetic activity, are also thought to mediate decreased HR responses during exercise (Michael et al., 2017). Additionally, there was a faster recovery

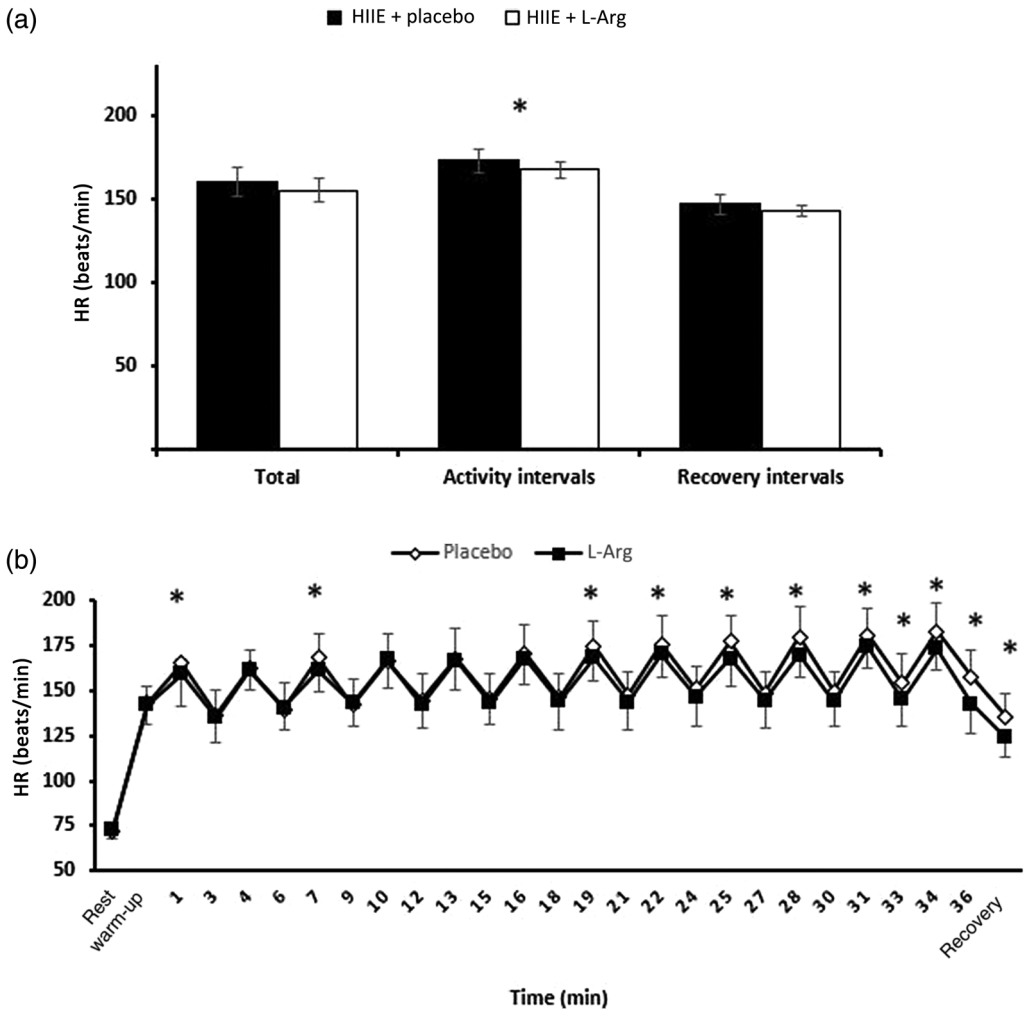

Figure 5 — (a) Mean (±SD) of HR during active and recovery intervals. (b) Time course of mean (±SD) changes in HR during active and recovery intervals. *Significant ($p < .05$) effects of supplementation with L-arginine (N = 30). Abbreviations: L-Arg = L-arginine; HIIE = high-intensity interval exercise; HR = heart rate.

of HR at the end of exercise (3-min recovery phase), possibly related to the increased vagal activity; however, further investigations are required to clarify the actual mechanism.

Previous studies investigated the effects of acute consumption of L-arginine in healthy (Alvares et al., 2012), active (Andrade et al., 2018), and elite runners (Boorsma et al., 2014)—individuals with a normal BMI. The divergent outcomes found in the literature might, in part, originate from using an inappropriate dosage of L-arginine for these active individuals (Alvares et al., 2012). Our study also has some potential limitations affecting our outcomes. First, participants took only 6 g of L-arginine, which might be a suboptimal dosage to achieve the maximal physiological supplementation effects. Thus, it is possible that we would have observed greater benefits with L-arginine if either the participants consumed higher doses of L-arginine (e.g., more than 10 grams) or consumed a smaller dosage for longer periods of time (e.g., consuming 6 g of L-arginine, three times/day for a week). Secondly, we did not use pure L-arginine in this study; the supplement we used contained L-arginine (70%) and L-citrulline malate (17%), and we are unable to exclude the distinct effects due only to L-arginine present in the supplement. Although L-citrulline malate can act synergistically with L-arginine, we presume that the limited amount of L-citrulline malate in the supplement had a minimal effect in improving cardiopulmonary exercise testing variables during HIIE, as supported by another study conducted by Bailey et al. (2010) (Bailey et al., 2010). In addition, we did not use the near-infrared spectroscopy technique for measuring muscle oxygenation/deoxygenation throughout the HIIE. This technique would have enhanced our sensitivity of detection. Thirdly, we did not measure plasma nitrite levels; however, the dose of L-arginine we used is known to increase blood flow (Alvares et al., 2012) and cause vasodilation (Bode-Böger et al., 1998) in humans. Finally, we delimited our study to men; future research to compare the acute effects of L-arginine in both males and females with various levels of BMI (normal, overweight, and obesity) would be of importance.

Conclusion

Consuming L-arginine before HIIE alleviates excess physiological cardiorespiratory strain, making exercise more tolerable for overweight men who wish to meet their regular physical activity needs as set by current health and wellness guidelines.

Acknowledgment

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References

Álvares, T.S., Conte, C.A., Jr., Paschoalin, V.M.F., Silva, J.T., Meirelles, C.D.M., Bhambhani, Y.N., & Gomes, P.S.C. (2012). Acute L-arginine supplementation increases muscle blood volume but not strength performance. *Applied Physiology, Nutrition, and Metabolism, 37*(1), 115–126. PubMed ID: 22251130 doi:10.1139/h11-144

Alvares, T.S., Conte, C.A., Jr., Silva, J.T., & Paschoalin, V.M.F. (2012). Acute L-Arginine supplementation does not increase nitric oxide production in healthy subjects. *Nutrition & Metabolism, 9*(1), 54. PubMed ID: 22691607 doi:10.1186/1743-7075-9-54

Andrade, W.B., Jacinto, J.L., da Silva, D.K., Roveratti, M.C., Estoche, J.M., Oliveira, D.B., … Aguiar, A.F. (2018). L-Arginine supplementation does not improve muscle function during recovery from resistance exercise. *Applied Physiology, Nutrition, and Metabolism, 43*(9), 928–936. PubMed ID: 29544063 doi:10.1139/apnm-2017-0594

Antoine-Jonville, S., Pichon, A., Vazir, A., Polkey, M.I., & Dayer, M.J. (2012). Oxygen uptake efficiency slope, aerobic fitness, and V (E)-VCO_2 slope in heart failure. *Medicine & Science in Sports & Exercise, 44*(3), 428–434. PubMed ID: 21808213 doi:10.1249/MSS.0b013e31822f8427

Bailey, S.J., Winyard, P.G., Vanhatalo, A., Blackwell, J.R., DiMenna, F.J., Wilkerson, D.P., & Jones, A.M. (2010). Acute L-arginine supplementation reduces the O_2 cost of moderate-intensity exercise and enhances high-intensity exercise tolerance. *Journal of Applied Physiology, 109*(5), 1394–1403. PubMed ID: 20724562 doi:10.1152/japplphysiol.00503.2010

Banning, A.P., & Prendergast, B. (1999). Intravenous L-arginine reduces VE/VCO_2 slope acutely in patients with severe chronic heart failure. *European Journal of Heart Failure, 1*(2), 187–190. PubMed ID: 10937929 doi:10.1016/S1388-9842(99)00013-6

Bernhardt, V., & Babb, T.G. (2016). Exertional dyspnoea in obesity. *European Respiratory Review, 25*(142), 487–495. PubMed ID: 27903669 doi:10.1183/16000617.0081-2016

Bescós, R., Gonzalez-Haro, C., Pujol, P., Drobnic, F., Alonso, E., Santolaria, M.L., … Galilea, P. (2009). Effects of dietary L-arginine intake on cardiorespiratory and metabolic adaptation in athletes. *International Journal of Sport Nutrition and Exercise Metabolism, 19*(4), 355–365. PubMed ID: 19827461 doi:10.1123/ijsnem.19.4.355

Bode-Böger, S.M., Böger, R.H., Galland, A., Tsikas, D., & Frölich, J.C. (1998). L-Arginine-induced vasodilation in healthy humans: Pharmacokinetic–pharmacodynamic relationship. *British Journal of Clinical Pharmacology, 46*(5), 489–497. PubMed ID: 9833603 doi:10.1046/j.1365-2125.1998.00803.x

Boorsma, R.K., Whitfield, J., & Spriet, L.L. (2014). Beetroot juice supplementation does not improve performance of elite 1500-m runners. *Medicine & Science in Sports & Exercise, 46*(12), 2326–2334. PubMed ID: 24781895 doi:10.1249/MSS.0000000000000364

Borg, G. (1970). Perceived exertion as an indicator of somatic stress. *Scandinavian Journal of Rehabilitation Medicine, 2*(2), 92–98. PubMed ID: 5523831

Buchheit, M., & Laursen, P.B. (2013). High-intensity interval training, solutions to the programming puzzle. *Sports Medicine, 43*(10), 927–954. PubMed ID: 23832851 doi:10.1007/s40279-013-0066-5

Connes, P., Frank, S., Martin, C., Shin, S., Aufradet, E., Sunoo, S., … Messonnier, L. (2010). New fundamental and applied mechanisms in exercise hemorheology. *Clinical Hemorheology and Microcirculation, 45*(2-4), 131–141. PubMed ID: 20675893 doi:10.3233/CH-2010-1291

Francois, M.E., & Little, J.P. (2015). Effectiveness and safety of high-intensity interval training in patients with type 2 diabetes. *Diabetes Spectrum, 28*(1), 39–44. PubMed ID: 25717277 doi:10.2337/diaspect.28.1.39

Gläser, S., Ittermann, T., Koch, B., Schäper, C., Felix, S.B., Völzke, H., … Hansen, J.E. (2013). Influence of smoking and obesity on alveolar-arterial gas pressure differences and dead space ventilation at rest and peak exercise in healthy men and women. *Respiratory Medicine, 107*(6), 919–926. PubMed ID: 23510666 doi:10.1016/j.rmed.2013.02.013

Guiraud, T., Nigam, A., Gremeaux, V., Meyer, P., Juneau, M., & Bosquet, L. (2012). High-intensity interval training in cardiac rehabilitation. *Sports Medicine, 42*(7), 587–605. PubMed ID: 22694349 doi:10.2165/11631910-000000000-00000

Harten, M.V. (2018). *The association of BMI with peak heart rate and peak oxygen pulse in apparently healthy adults* [Master's thesis, Utrecht University, The Netherlands]. Utrecht University Repository. Retrieved from http://dspace.library.uu.nl/handle/1874/366281

Holguin, F. (2013). Arginine and nitric oxide pathways in obesity-associated asthma. *Journal of Allergy, 2013,* 714595. doi:10.1155/2013/714595

Jelleyman, C., Yates, T., O'Donovan, G., Gray, L.J., King, J.A., Khunti, K., & Davies, M.J. (2015). The effects of high-intensity interval training on glucose regulation and insulin resistance: a meta-analysis. *Obesity Reviews, 16*(11), 942–961. PubMed ID: 26481101 doi:10.1111/obr.12317

Jones, A.M. (2014). Dietary nitrate supplementation and exercise performance. *Sports Medicine, 44*(S1), 35–45. doi:10.1007/s40279-014-0149-y

Jones, A.M., Wilkerson, D.P., Wilmshurst, S., & Campbell, I.T. (2004). Influence of L-NAME on pulmonary O_2 uptake kinetics during heavy-intensity cycle exercise. *Journal of Applied Physiology, 96*(3), 1033–1038. PubMed ID: 14657038 doi:10.1152/japplphysiol.00381.2003

Keating, S., Johnson, N., Mielke, G., & Coombes, J. (2017). A systematic review and meta-analysis of interval training versus moderate-intensity continuous training on body adiposity. *Obesity Reviews, 18*(8), 943–964. PubMed ID: 28513103 doi:10.1111/obr.12536

Khammassi, M., Ouerghi, N., Hadj-Taieb, S., Feki, M., Thivel, D., & Bouassida, A. (2018). Impact of a 12-week high-intensity interval training without caloric restriction on body composition and lipid profile in sedentary healthy overweight/obese youth. *Journal of Exercise Rehabilitation, 14*(1), 118. PubMed ID: 29511662 doi:10.12965/jer.1835124.562

Koppo, K., Taes, Y.E., Pottier, A., Boone, J., Bouckaert, J., & Derave, W. (2009). Dietary arginine supplementation speeds pulmonary VO2 kinetics during cycle exercise. *Medicine and Science in Sports and Exercise, 41*(8), 1626–1632. PubMed ID: 19568197 doi:10.1249/MSS.0b013e31819d81b6

Manfredini, F., Conconi, F., Malagoni, A.M., Manfredini, R., Mascoli, F., Liboni, A., & Zamboni, P. (2004). Speed rather than distance: A novel graded treadmill test to assess claudication. *European Journal of Vascular and Endovascular Surgery, 28*(3), 303–309. PubMed ID: 15288635 doi:10.1016/j.ejvs.2004.05.005

McKnight, J.R., Satterfield, M.C., Jobgen, W.S., Smith, S.B., Spencer, T.E., Meininger, C.J., … Wu, G. (2010). Beneficial effects of L-arginine on reducing obesity: Potential mechanisms and important implications for human health. *Amino Acids, 39*(2), 349–357. PubMed ID: 20437186 doi:10.1007/s00726-010-0598-z

Meirelles, C.M., Matsuura, C., Silva, R.S., Jr., Guimarães, F.F., & Gomes, P.S.C. (2019). Acute effects of L-Arginine supplementation on oxygen consumption kinetics and muscle oxyhemoglobin and deoxyhemoglobin during treadmill running in male adults. *International Journal of Exercise Science, 12*(2), 444. PubMed ID: 30899346

Mezzani, A., Giordano, A., Moussa, N.B., Micheletti, A., Negura, D., Saracino, A., … Carminati, M. (2015). Hemodynamic, not ventilatory, inefficiency is associated with high VE/VCO_2 slope in repaired, noncyanotic congenital heart disease. *International Journal of Cardiology, 191,* 132–137. PubMed ID: 25965620 doi:10.1016/j.ijcard.2015.04.285

Michael, S., Graham, K.S., & Davis, G.M. (2017). Cardiac autonomic responses during exercise and post-exercise recovery using heart rate variability and systolic time intervals—A review. *Frontiers in Physiology, 8,* 301. PubMed ID: 28611675 doi:10.3389/fphys.2017.00301

Nagaya, N., Uematsu, M., Oya, H., Sato, N., Sakamaki, F., Kyotani, S., … Miyatake, K. (2001). Short-term oral administration of L-arginine improves hemodynamics and exercise capacity in patients with precapillary pulmonary hypertension. *American Journal of Respiratory and Critical Care Medicine, 163*(4), 887–891. PubMed ID: 11282761 doi:10.1164/ajrccm.163.4.2007116

Nora, T., Bicescu, G., Enache, R., Dragoi, R., & Cinteza, M. (2010). Cardiopulmonary exercise testing in differential diagnosis of dyspnea. *Maedica, 5*(3), 214–218. PubMed ID: 21977155

Nosarev, A.V., Smagliy, L.V., Anfinogenova, Y., Popov, S.V., & Kapilevich, L.V. (2015). Exercise and NO production: Relevance and implications in the cardiopulmonary system. *Frontiers in Cell and Developmental Biology, 2,* 73. PubMed ID: 25610830 doi:10.3389/fcell.2014.00073

O'Donnell, D.E., O'Donnell, C.D., Webb, K.A., & Guenette, J.A. (2012). Respiratory consequences of mild-to-moderate obesity: impact on exercise performance in health and in chronic obstructive pulmonary disease. *Pulmonary Medicine, 2012,* 818925. PubMed ID: 23097698 doi:10.1155/2012/818925

Pescatello, L.S., Riebe, D., & Thompson, P.D. (2014). *ACSM's guidelines for exercise testing and prescription*. Philadelphia, PA: Lippincott Williams & Wilkins.

Prado, D., Rocco, E., Silva, A., Rocco, D., Pacheco, M., & Furlan, V. (2016). Effect of exercise training on ventilatory efficiency in patients with heart disease: A review. *Brazilian Journal of Medical and Biological Research, 49*(7), e5180. PubMed ID: 27332771 doi:10.1590/1414-431x20165180

Schaefer, A., Piquard, F., Geny, B., Doutreleau, S., Lampert, E., Mettauer, B., & Lonsdorfer, J. (2002). L-Arginine reduces exercise-induced increase in plasma lactate and ammonia. *International Journal of Sports Medicine, 23*(6), 403–407. doi:10.1055/s-2002-33743

Shan, L., Wang, B., Gao, G., Cao, W., & Zhang, Y. (2013). L-Arginine supplementation improves antioxidant defenses through L-arginine/nitric oxide pathways in exercised rats. *Journal of Applied Physiology, 115*(8), 1146–1155. PubMed ID: 23950164 doi:10.1152/japplphysiol.00225.2013

Toda, N., & Okamura, T. (2013). Obesity impairs vasodilatation and blood flow increase mediated by endothelial nitric oxide: An overview. *The Journal of Clinical Pharmacology, 53*(12), 1228–1239. PubMed ID: 24030923 doi:10.1002/jcph.179

Tousoulis, D., Antoniades, C., Tentolouris, C., Goumas, G., Stefanadis, C., & Toutouzas, P. (2002). L-Arginine in cardiovascular disease: Dream or reality? *Vascular Medicine, 7*(3), 203–211. PubMed ID: 12553744 doi:10.1191/1358863x02vm434ra

Vanhatalo, A., Bailey, S.J., DiMenna, F.J., Blackwell, J.R., Wallis, G.A., & Jones, A.M. (2013). No effect of acute L-arginine supplementation on O2 cost or exercise tolerance. *European Journal of Applied Physiology, 113*(7), 1805–1819. PubMed ID: 23423302 doi:10.1007/s00421-013-2593-z