Short Review

Acute effects of pre-exercise voluntary hypocapnic hyperventilation on exercise performance and metabolic responses during high-intensity exercise

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ABSTRACT

High-intensity exercise induces the accumulation of hydrogen ions, resulting in a decrease in plasma and muscle pH (i.e., metabolic acidosis), a key mechanism contributing to fatigue. Alleviating metabolic acidosis is crucial for improving high-intensity exercise performance. Voluntary hyperventilation increases carbon dioxide (CO_2) elimination, reduces arterial CO_2 partial pressure (hypocapnia), and an increase in plasma pH (i.e., respiratory alkalosis). Pre-exercise voluntary hypocapnic hyperventilation is a potentially effective intervention for alleviating metabolic acidosis and has been proposed to enhance exercise performance during cycling and resistance exercise. Furthermore, this technique may reduce aerobic metabolism while increasing anaerobic metabolism by decreasing active skeletal muscle blood flow and inhibiting oxidative phosphorylation during subsequent exercise. According to the overload principle, stimulating the anaerobic energy system during each high-intensity training session can improve its capacity, ultimately enhancing high-intensity exercise performance. High-intensity exercise performed under hypoxic conditions such as using hypoxic chambers or hypoxic gas inhalation, has traditionally been employed to stimulate anaerobic metabolism more effectively than normoxic environments. However, such hypoxic interventions are often inaccessible to many athletes due to logistical constraints.

55 This short review highlights recent findings on the acute effects of pre-exercise voluntary
56 hypocapnic hyperventilation on exercise performance and metabolic responses during
57 high-intensity exercise.
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59 **Keywords:** Anaerobic metabolism, Aerobic metabolism, Respiratory alkalosis,
60 Ergogenic aid
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タイトル: 動脈血二酸化炭素分圧低下を伴う運動前自発的過換気が高強度運動中の運動パフォーマンスおよび呼吸代謝応答に及ぼす急性的影響

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要旨: 高強度運動は水素イオンの蓄積を誘発し、血漿および筋の pH の低下 (すなわち代謝性アシドーシス) をもたらし、これが疲労のメカニズムのひとつであると考えられる。自発的過換気を行うと、二酸化炭素 (CO_2) の排出を増加させ、動脈血 CO_2 分圧の低下 (低カプニア) と血漿 pH の上昇 (すなわち呼吸性アルカローシス) をもたらす。したがって、自発的過換気は高強度運動の代謝性アシドーシスを緩和する戦略となる。この点から、自発的な過換気が自転車運動パフォーマンスや、レジスタンス運動時の挙上回数を向上させる可能性が示唆されている。

さらに、運動前の自発的過換気は骨格筋血流量の減少や、酸化的リン酸化の阻害により、その後の運動中の酸素摂取量を減少させ、それに伴って無酸素性代謝を

90 増加させる。過負荷の原則に基づけば、毎トレーニングセッションを通じて無酸
91 素性エネルギー系を刺激すればその能力が向上し、最終的に高強度運動パフォ
92 ーマンスの向上につながる。同様の効果は、低酸素環境下での高強度運動 (低酸
93 素チャンバー、低酸素ガス吸入) によって得られるが、低酸素環境へのアクセス
94 が限られているため、低酸素介入はすべてのアスリートにとって現実的な方法
95 ではない。本 short review では、動脈血 CO_2 分圧低下を伴う運動前の自発的過換
96 気が、高強度運動時の運動パフォーマンスおよび呼吸代謝応答に及ぼす急性的
97 影響に関する最新の研究を紹介する。

Introduction

High-intensity sporting events, such as 100–200 m sprints, 50–100 m swims, and ball games (e.g., basketball, soccer, tennis) require anaerobic energy supply, including the ATP-PCr and glycogen-lactic acid systems at a rate substantially greater than that of endurance exercises [1-3]. These energy systems are crucial in generating high power output. However, energy production via the glycogen-lactic acid system leads to the accumulation of hydrogen ions (H^+), leading to a decrease in plasma and muscle pH levels (i.e., metabolic acidosis). Metabolic acidosis may inhibit the activity of glycolytic enzymes [4, 5] and impair excitation-contraction coupling mechanisms [6-8], ultimately contributing to fatigue. To enhance performance during high-intensity exercise, alleviating metabolic acidosis is crucial. One effective strategy is to increase plasma pH (alkalosis) before exercise. Voluntary hyperventilation, which increases carbon dioxide (CO_2) elimination, can reduce arterial CO_2 partial pressure ($PaCO_2$) (hypocapnia), thereby inducing respiratory alkalosis [9, 10].

Studies suggest that pre- and inter-set voluntary hypocapnic hyperventilation may acutely enhance exercise performance during anaerobic activities, including the 30-second Wingate anaerobic test [11], the initial phase of the 3-minute all-out cycling test [12], high-intensity intermittent cycling [10], and resistance exercise repetitions [13]. Conversely,

other studies have reported that pre-exercise voluntary hypocapnic hyperventilation did not enhance performance during high-intensity exercise [14-18], potentially due to hypocapnia-induced cerebral hypoperfusion [19], which may impair motor performance [20].

Sodium bicarbonate ($NaHCO_3$) ingestion increases plasma bicarbonate ion (HCO_3^-) levels and plasma pH, thereby inducing metabolic alkalosis. Consequently, $NaHCO_3$ ingestion has long been utilized as an ergogenic aid to mitigate metabolic acidosis induced by high-intensity exercise, as described by the equilibrium reaction [21]:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$$

Previous studies have demonstrated that $NaHCO_3$ ingestion (0.3–0.5 g/kg of body weight) enhances exercise performance in various activities, including combat sports tasks [22], single and repeated high-intensity cycling [23, 24], running [25, 26], and swimming [27]. However, the positive effects of $NaHCO_3$ ingestion remain debatable due to reported gastrointestinal side effects, such as bloating, nausea, vomiting, and abdominal pain [24, 28, 29], as well as uncertainties surrounding its optimal dosage and timing [24, 30, 31]. Moreover, ingesting $NaHCO_3$ in doses exceeding 0.3 g/kg of body weight may significantly increase the body's sodium load, potentially surpassing the Tolerable Upper Intake Level for sodium specified in dietary guidelines [32]. Excessive sodium intake has been linked to increased serum sodium levels, which positively correlate with mean arterial pressure [33],

134 thereby heightening cardiovascular strain. In contrast, hypocapnic hyperventilation offers
135 an alternative approach to alleviating metabolic acidosis without the adverse effects
136 associated with $NaHCO_3$ ingestion.

137 In addition to enhancing exercise performance, acute pre-exercise voluntary
138 hypocapnic hyperventilation stimulates anaerobic metabolism, increasing anaerobic
139 energy supply during subsequent exercise. According to the overload principle [34)],
140 repeated stimulation of the anaerobic energy system during high-intensity training
141 sessions can enhance its capacity, ultimately improving high-intensity exercise
142 performance.

143 High-intensity exercise in normobaric hypoxia, such as hypoxic gas inhalation or
144 hypoxic chamber training, has been shown to effectively stimulate anaerobic metabolism.
145 Hypoxia reduces arterial O_2 partial pressure [35)] and inhibits the activation of
146 mitochondrial pyruvate dehydrogenase (PDH), limiting oxidative phosphorylation [36)].
147 This restriction in oxygen supply and utilization in active skeletal muscles reduces oxygen
148 uptake ($\dot{V}O_2$) while increasing anaerobic metabolism without compromising performance
149 during supramaximal exercise [37-39)]. However, hypoxic training requires specialized
150 equipment, such as hypoxic chambers, which may not be accessible to all athletes. As an
151 alternative, the acute effects of pre-exercise voluntary hyperventilation have garnered

152 attention for their potential to stimulate some benefits of hypoxia. This short review
153 provides an overview of the acute effects of voluntary hypocapnic hyperventilation on
154 exercise performance, its associated metabolic responses during high-intensity exercise.
155
156 ***Effects of voluntary hypocapnic hyperventilation on exercise performance***
157 Over the past decade, voluntary hypocapnic hyperventilation has been investigated
158 as an alternative to $NaHCO_3$ ingestion for enhancing exercise performance [10, 15, 40].
159 Voluntary hyperventilation increases CO_2 elimination from the body, resulting in a
160 decrease in H^+ and HCO_3^- [9, 10], as outlined in the equilibrium reaction. Unlike $NaHCO_3$
161 ingestion, voluntary hypocapnic hyperventilation can be initiated and terminated instantly
162 without the need for external devices.
163 Sakamoto et al. (2014) demonstrated that 30 s of voluntary hypocapnic
164 hyperventilation (~130 L/min of minute ventilation and ~25 mmHg of end-tidal CO_2
165 partial pressure [($P_{ET}CO_2$), an index of $PaCO_2$] performed before each cycling bout
166 attenuated power decrement during 10 sets of 10-s maximal pedaling, interspersed with
167 60-s recovery periods [10]. Subsequent studies have reported that pre-exercise voluntary
168 hypocapnic hyperventilation (30–120 L/min of minute ventilation, ~25 mmHg of
169 $P_{ET}CO_2$) enhanced performance during the subsequent high-intensity exercise protocols,

including 30-s Wingate anaerobic test [11], the initial phase of the 3-min all-out cycling test [12], and total repetitions in bench and leg presses [13] compared with control (pre-exercise spontaneous breathing) trial. In these studies, the pH decline associated with high-intensity exercise was attenuated by voluntary hypocapnic hyperventilation [10-13], suggesting that alleviating metabolic acidosis may contribute to improved performance during high-intensity exercise.

Conversely, other studies reported that pre-exercise voluntary hypocapnic hyperventilation, characterized by minute ventilation of 30–120 L/min of and $P_{ET}CO_2$ of 20–25 mmHg, does not affect performance during high-intensity intermittent exercise [14, 15] or the 30-s Wingate anaerobic test [16-18]. Moreover, Johnson et al. (2021) reported that 15-min bout of pre-exercise voluntary hypocapnic hyperventilation (40–60 L/min of minute ventilation) impaired power output during the final 30-s of a 3-min all-out cycling test. Consistent with previous research [14, 16-18, 41], a recent systematic review and meta-analysis suggested that pre-exercise and/or inter-set voluntary hypocapnic hyperventilation does not enhance sports performance during high-intensity exercise [42]. Two potential mechanisms underlying these observations are hypocapnia and a reduction in HCO_3^- (respiratory alkalosis). Cerebral blood flow is highly sensitive to changes in $PaCO_2$ [19], and hypocapnia induces cerebral vasoconstriction, resulting in reduced

188 cerebral blood flow [19]. This reduction in cerebral perfusion has been shown to impair
189 motor performance [20]. Consistent with this, a positive correlation has been observed
190 between power output improvement (hyperventilation trial – spontaneous breathing trial)
191 and $PaCO_2$ immediately before the 3-min all-out cycling test where lower $PaCO_2$ values
192 corresponded to smaller improvement in power output [12]. Unlike $NaHCO_3$ ingestion,
193 hypocapnia is induced exclusively by voluntary hyperventilation. Furthermore,
194 respiratory alkalosis resulting from voluntary hyperventilation reduces not only plasma
195 H^+ but also HCO_3^- [9, 10]. The reduction in HCO_3^- is also induced exclusively by voluntary
196 hyperventilation, and not $NaHCO_3$ ingestion. Considering the equilibrium reaction, this
197 reduction in HCO_3^- may attenuate the buffering capacity of H^+ produced during high-
198 intensity exercise. Consequently, the hypocapnia and lower HCO_3^- may offset the benefits
199 of a reduction in H^+ on exercise performance. Therefore, it remains inconclusive whether
200 hypocapnic hyperventilation improves performance during high-intensity exercise.
201 Further investigations are required to identify the specific conditions under which
202 voluntary hypocapnic hyperventilation can enhance or impair physical sports
203 performance.
204
205 ***Effects of voluntary hypocapnic hyperventilation on aerobic and anaerobic metabolism***

206 Previous studies have consistently demonstrated that voluntary hypocapnic
207 hyperventilation performed, both before and during exercise at a minute ventilation rate
208 of 30 L/min, increases the anaerobic metabolic rate. This is evidenced by delayed $\dot{V}O_2$
209 kinetics during constant workload submaximal exercise [9, 43-47] and elevated
210 phosphocreatine breakdown [48], without altering the total workload. Recent studies have
211 focused on the effects of voluntary hyperventilation conducted exclusively before
212 exercise, as maintaining hyperventilation during high-intensity exercise to induce
213 hypocapnia is challenging. Consistent with earlier findings with voluntary hypocapnic
214 hyperventilation performed before and during submaximal exercise, pre-exercise
215 voluntary hypocapnic hyperventilation (~ 30 L/min of minute ventilation, ~20 mmHg of
216 $P_{ET}CO_2$) enhances anaerobic metabolism. This is reflected by reduced $\dot{V}O_2$, elevated
217 blood lactate concentrations, and increased oxygen deficit without negatively impacting
218 exercise performance [12, 14, 16-18, 41]. These findings suggest that pre-exercise voluntary
219 hypocapnic hyperventilation may be more effective in stimulating the anaerobic energy
220 system during high-intensity exercise compared to spontaneous breathing.

221 Several mechanisms have been proposed to explain the reduction in $\dot{V}O_2$ observed
222 during high-intensity exercise following pre-exercise hyperventilation (Fig. 1). First, pre-
223 exercise hyperventilation can decrease active muscle blood flow [44, 45]. Chin et al. (2010b,

2013) reported that pre-exercise voluntary hypocapnic hyperventilation (30 L/min minute ventilation) induces vasoconstriction in the femoral arteries [44, 45], which may impair oxygen delivery to active muscles. Although speculative, this hypoperfusion could also be partly attributed to pre-exercise voluntary hyperventilation itself (normocapnic hyperventilation). For example, previous studies reported that pre-exercise normocapnic hyperventilation (30 L/min minute ventilation) reduces $\dot{V}O_2$ during subsequent high-intensity exercise independently of hypocapnia [41]. Keramidas et al. (2011) observed that 30-min of pre-exercise normocapnic hyperpnea reduced active muscle blood flow index, as assessed by near-infrared spectroscopy, during subsequent intense exercise [49]. This effect may be mediated by the activation of the respiratory muscle metaboreflex, leading to vasoconstriction and reduced blood flow in active muscles [50, 51]. However, further studies are required to fully elucidate the mechanisms by which pre-exercise normocapnic hyperventilation reduces $\dot{V}O_2$ during subsequent exercise.

Second, hypocapnic hyperventilation delays the activation of mitochondrial PDH [47], a critical enzyme in oxidative phosphorylation [52], potentially impairing oxygen utilization in active muscles. Third, Dobashi et al. (2017, 2020, 2023a, b) reported that pre-exercise hypocapnic hyperventilation inhibits minute ventilation during subsequent high-intensity exercise [14, 16, 17, 41]. Elevated $PaCO_2$ considerably enhances ventilation by

altering the medullary H^+ concentration and stimulating central chemoreceptors [53-55]. However, under hypocapnic conditions, reduced central chemoreflex activation may impair pulmonary ventilation, contributing to reduced $\dot{V}O_2$ during exercise. Fourth, hypocapnia elevates blood pH [9], resulting in a leftward shift in the oxyhemoglobin dissociation curve and attenuating oxygen off-loading from hemoglobin.

Influence of hyperventilation duration on aerobic and anaerobic metabolism

Most previous studies have utilized prolonged (e.g., 15–20 min) moderate-volume hyperventilation (~30 L/min of minute ventilation). This duration is based on the observation that approximately 15 min of voluntary hyperventilation at ~30 L/min is required to eliminate 90% of the body's CO_2 [56]. Such prolonged hyperventilation induces notable physiological effects, including inhibition of PDH [47], and greater vasoconstriction of the active skeletal muscles compared to shorter durations (e.g., ~5 min) of the voluntary hypocapnic hyperventilation [44, 45]. However, employing 15–20 min of voluntary hypocapnic hyperventilation increases the overall duration of the training session.

Hayashi et al. (1999) reported that voluntary hypocapnic hyperventilation at 60 L/min of minute ventilation, performed for 2 min before and 6 min during exercise

delayed the initial increase in $\dot{V}O_2$ at the onset of submaximal exercise. Similarly, Dobashi et al. (2023b) compared the metabolic responses during high-intensity exercise after 5 min versus 20 min of pre-exercise voluntary hypocapnic hyperventilation [16]. The results revealed that 5 min of pre-exercise voluntary hypocapnic hyperventilation (~30 L/min of minute ventilation) reduced $\dot{V}O_2$ during the 30-s Wingate anaerobic test to a level comparable to that observed after 20 min of hyperventilation (Fig. 2) [16]. As with 20-min of pre-exercise hypocapnic hyperventilation, the reduction in $\dot{V}O_2$ during exercise, associated with a shorter duration of hypocapnic hyperventilation, may be partially attributed to lower minute ventilation during the exercise [16]. Moreover, femoral arterial vasoconstriction induced by hypocapnic hyperventilation was observed ~5 min after the onset of hypocapnic hyperventilation, though the magnitude of the response was smaller compared to that observed after 20-min [44, 45]. Furthermore, voluntary hypocapnic hyperventilation increased oxy-hemoglobin levels at vastus laterals for up to 5 min following the onset of hyperventilation [9, 44]. This suggests that short-term (~5 min) hypocapnic hyperventilation results in a more pronounced leftward shift in the oxy-hemoglobin dissociation curve compared to 20-min hypocapnic hyperventilation, thereby attenuating oxygen off-loading from hemoglobin. These mechanisms may contribute to the reduced $\dot{V}O_2$ observed after 5 min of hypocapnic hyperventilation.

In addition to single-bout exercise, previous studies have investigated the effect of voluntary hypocapnic hyperventilation on metabolic responses during high-intensity intermittent exercise (3 sets of 30-s exercises interspersed with 4-min recovery periods) [14]. Dobashi et al. (2017) observed that hypocapnic hyperventilation reduces aerobic energy supply during the first exercise, but not during subsequent bouts. Previous studies reported that while steady-state active muscle blood flow and $\dot{V}O_2$ remain comparable between control and hypocapnia trials, the initial rapid increase in blood flow and $\dot{V}O_2$ in response to exercise is delayed under hypocapnic conditions [44, 45]. These findings suggest that pre-exercise hypocapnic hyperventilation primarily affects the initial $\dot{V}O_2$ response by slowing it. Furthermore, the increase in $\dot{V}O_2$ in response to exercise initiation accelerates with repeated exercise bouts [57, 58]. Consequently, the $\dot{V}O_2$ increases during the second and subsequent exercises may occur too rapidly to be influenced by hypocapnia. Additionally, the unaltered $\dot{V}O_2$ during the second and subsequent exercise could be attributed to an insufficient degree of hypocapnia. Dobashi et al. (2017) employed 2-min inter-set hypocapnic hyperventilation (40 L/min minute ventilation) to induce hypocapnia. Consequently, during the recovery period, after the first and second exercise bouts, $P_{ET}CO_2$ was approximately 27 mmHg, compared to ~19 mmHg before the first bout. This difference is attributable to the exercise-induced increase in

296 metabolism and the shorter duration of hyperventilation. A threshold $P_{ET}CO_2$ level
297 between 27 and 19 mmHg may exist for reducing aerobic metabolism.
298
299 **Practical implications**
300 Pre-exercise voluntary hypocapnic hyperventilation (5–20 min) has been shown to
301 increase anaerobic energy supply to compensate for reduced aerobic energy supply during
302 short-term (i.e., < 30 s), high-intensity exercise without impairing performance. Notably,
303 a 5 min duration of pre-exercise voluntary hypocapnic hyperventilation reduces $\dot{V}O_2$
304 during high-intensity exercise to levels comparable to those observed with 20 min of
305 hyperventilation [16]. For athletes without access to hypoxic interventions, short duration
306 (e.g., 5 min) hypocapnic hyperventilation may serve as a practical method to effectively
307 stimulate anaerobic metabolism during short-term (i.e., < 30 s), high-intensity exercise
308 training. However, in the context of high-intensity intermittent exercise, pre-exercise, and
309 inter-set, hypocapnic hyperventilation appears to stimulate the anaerobic energy system
310 only during the first exercise bout.
311 Notably, existing studies have primarily investigated the acute effect of hypocapnic
312 hyperventilation. Consequently, whether high-intensity exercise training with hypocapnic
313 hyperventilation leads to greater adaptations in the anaerobic energy system than that with

314 spontaneous breathing remains unknown. This critical knowledge gap warrants direct
315 investigation in future research.
316
317 **Conclusion**
318 This short review summarizes the acute effects of voluntary hypocapnic
319 hyperventilation on exercise performance and metabolic responses during high-intensity
320 exercise. The findings suggest that: 1) pre-exercise voluntary hypocapnic
321 hyperventilation does not appear to enhance exercise performance during high-intensity
322 exercise, and 2) pre-exercise voluntary hypocapnic hyperventilation lasting 5–20 min
323 may effectively stimulate the anaerobic energy system during short-term (i.e., < 30 s),
324 high-intensity exercise compared to pre-exercise spontaneous breathing. However,
325 further research is required to elucidate the specific parameters of voluntary hypocapnic
326 hyperventilation that influence improvements or reductions in physical sports
327 performance.
328
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KD and AK drafted the manuscript. All authors have critically reviewed, revised, and approved the manuscript.

Conflicts of Interests

The authors have no conflict of interest to declare.

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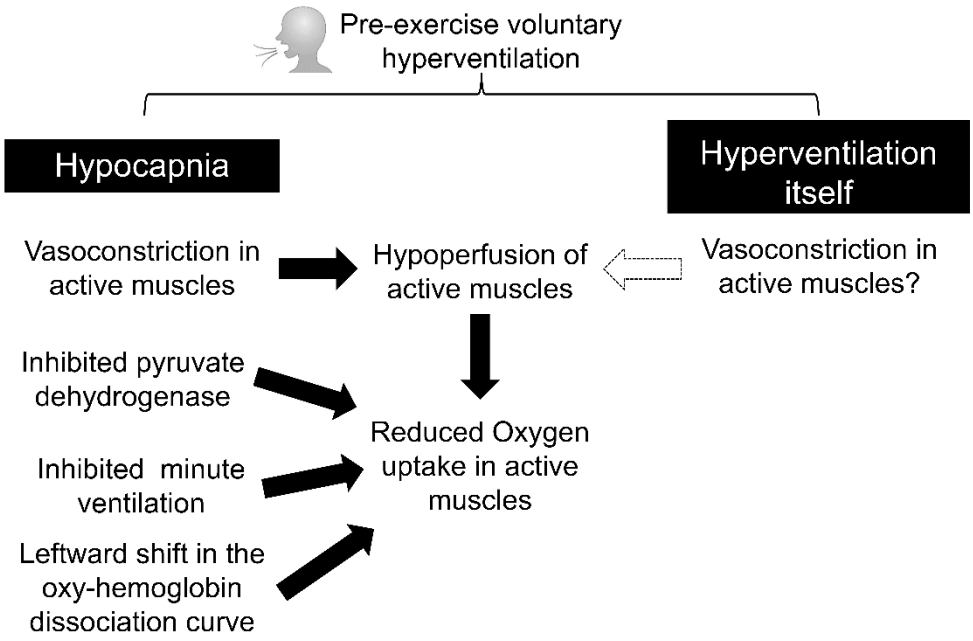
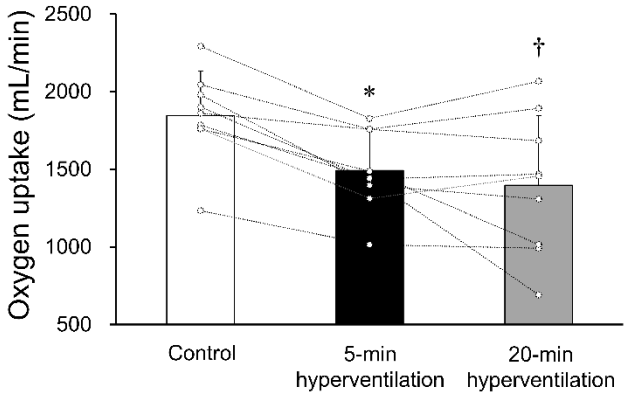
Figure legends

Fig 1. Schematic diagram illustrating the proposed mechanisms for reduced oxygen uptake in active muscles following pre-exercise voluntary hyperventilation. The dashed arrow represents a potential mechanism for reduced oxygen uptake attributed to pre-exercise voluntary hyperventilation.

Fig 2. Oxygen uptake measured during the 30-s Wingate anaerobic test. Individual data and means with standard deviations are presented (n = 9). * $P < 0.05$, Control vs. 5-min hyperventilation. † $P < 0.05$, Control vs. 20-min hyperventilation. Reproduced from Dobashi et al. 2020


Pre-exercise voluntary hyperventilation
Hypocapnia
Hyperventilation itself
Vasoconstriction in active muscles
Hypoperfusion of active muscles
Vasoconstriction in active muscles?
Inhibited pyruvate dehydrogenase
Inhibited minute ventilation
Leftward shift in the oxy-hemoglobin dissociation curve
Reduced Oxygen uptake in active muscles


Oxygen uptake (mL/min)
2500
2000
1500
1000
500
*
†
Control
5-min
hyperventilation
20-min
hyperventilation