Communication

Acute Moderate Hypoxia Reduces One-Legged Cycling Performance Despite Compensatory Increase in Peak Cardiac Output: A Pilot Study

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Abstract: In severe hypoxia, single-leg peak oxygen uptake (VO_{2peak}) is reduced mainly due to the inability to increase cardiac output (CO). Whether moderate altitude allows CO to increase during single-leg cycling, thereby restoring VO_{2peak}, has not been extensively investigated. Five healthy subjects performed an incremental, maximal, two-legged cycle ergometer test, and on separate days a maximal incremental one-leg cycling test in normoxia and in moderate hypoxia (fraction of inspired oxygen (FiO_2) = 15%). Oxygen uptake, heart rate, blood pressure responses, power output, and CO (PhysioFlow) were measured during all tests. Moderate hypoxia lowered single-leg peak power output (154 ± 31 vs. 128 ± 26 watts, $p = 0.03$) and oxygen uptake (VO_2) (36.8 ± 6.6 vs. 33.9 ± 6.9 mL/min/kg, $p = 0.04$), despite higher peak CO (16.83 ± 3.10 vs. 18.96 ± 3.59 L/min, $p = 0.04$) and systemic oxygen (O_2) delivery (3.37 ± 0.84 vs. 3.47 ± 0.89 L/min, $p = 0.04$) in hypoxia compared to normoxia. Arterial–venous O_2 difference (a–vDO_2) was lower in hypoxia (137 ± 21 vs. 112 ± 19 mL/l, $p = 0.03$). The increases in peak CO from normoxia to hypoxia were negatively correlated with changes in mean arterial pressure (MABP) ($p < 0.05$). These preliminary data indicate that the rise in CO was not sufficient to prevent single-leg performance loss at moderate altitude and that enhanced baroreceptor activity might limit CO increases in acute hypoxia, likely by reducing sympathetic activation. Since the systemic O_2 delivery was enhanced and the calculated a–vDO_2 reduced in moderate hypoxia, a potential diffusion limitation cannot be excluded.

Keywords: moderate altitude; small muscle mass; exercise performance; single-leg exercise

1. Introduction

During exercise involving a large muscle mass (e.g., two-leg cycling), maximal oxygen uptake (VO_{2max}) and exercise performance are mainly limited by cardiac output (CO) and thus the ability to deliver oxygen (O_2) to the working muscles. Besides CO and the oxygen content of the arterial blood (CaO_2), blood flow to and O_2 extraction of contracting skeletal muscles are also determinants of VO_{2max} [1–4]. On the contrary, when exercising with a small muscle mass (e.g., single-leg cycling, arm or knee-extensor exercise), CO is not considered the limiting factor for VO_{2max} attainment, since maximal CO values are generally not achieved [5–7].

In acute hypoxia (e.g., high altitude) conditions, CaO_2 and arterial O_2 partial pressure (PaO_2), which constitute the driving pressure behind O_2 diffusion [8], are reduced. Thus, if not compensated by an increased CO and/or O_2 extraction, aerobic capacity may be impaired, even when exercising with a small muscle mass. Indeed, in circumstances of severe hypoxia, similar or reduced CO and leg blood flow during single-leg exercise have been observed compared to normoxic conditions, which translates into reduced leg O_2 delivery [1,9] and impaired VO_{2max}. Thus, CO, despite ample functional reserve, seems not

to be sufficiently increased to compensate for the reduced CaO_2 in acute severe hypoxia [1]. In this regard, it is important to mention that increasing CO would not only increase leg O_2 delivery, but also shorten capillary transit time and may thus limit time for O_2 diffusion [5,7,10]. O_2 extraction demonstrates a marked plateau in hypoxia and maximal values are similar in normoxia, indicating that muscle diffusive capacity plays a role in the VO_{2max} reduction at altitude [9,11]. The magnitude of this diffusion limitation is, however, controversially discussed [8,12,13]. Due to restoration of CaO_2 during altitude acclimatization and single-leg VO_{2peak}, O_2 delivery, and not diffusional limitation at the muscle level, has been suggested as the primary reason for the VO_{2peak} reduction in acute hypoxia [1].

It needs to be considered that the study design, the actual muscle mass involved, as well as the participant's fitness level may influence the physiological responses during exercise performed in hypoxia [6,9,12]. Rowell et al. [5], for instance, investigated untrained participants performing single-leg knee extension exercise at a peak workload stage, which was determined by pre-testing. Using this study design, CO and muscle blood flow reached higher values in severe hypoxia compared to normoxia [5], which is in contrast to the findings reported for well-trained athletes performing graded exercise tests to exhaustion [1,9,11].

Besides exercise setting and physical fitness levels of participants, the severity of hypoxia (altitude level) may also play a critical role when assessing factors limiting VO_{2peak} of small muscle mass in hypoxia [14]. The aforementioned studies performed exercise testing in severe hypoxia ($FiO_2 < 0.12$ corresponding to altitude levels > 4000 m), with a large impact on CaO_2 and O_2 delivery to the myocardium, respiratory muscles, and the central nervous system (CNS) [1]. Low brain O_2 delivery thus could have caused a cardioinhibitory reflex, eventually preventing a compensatory increase in CO [1]. Interestingly, to the best of our knowledge, only limited information is available on whether similar effects may occur in moderate hypoxia (i.e., $FiO_2 = 15\%$), where PaO_2 and CaO_2 are less affected. Physical activity involving small muscle mass is commonly performed at moderate altitudes, e.g., by workers, tourists, and athletes. Thus, insights on a potential loss of small muscle performance and related mechanisms when acutely exposed to rather moderate altitude is of scientific, as well as clinical/practical, relevance.

To investigate whether moderate hypoxia allows CO to increase during exercise with a small muscle mass, eventually restoring normoxic O_2 delivery and VO_{2peak}, we evaluated hemodynamic and performance parameters during maximal single-leg exercise in normoxia and at a FiO_2 of 15%. Even though muscle O_2 diffusion might be affected by a reduced transit time, we hypothesized that at a moderate altitude, small muscle performance would be preserved by compensatory increases in CO and oxygen delivery.

2. Materials and Methods

2.1. Participants

Five healthy and fit subjects (three males, age: 41 ± 13 years; two females, age: 45 ± 7 years) volunteered to participate in this pilot study. Inclusion criteria were age between 25 and 55 years, no recent health problems (checked by routine medical examination) and no exposures to hypoxia or altitude over 1500 m at least 4 weeks before exercise testing. All participants regularly participated (at least 1 h per day on 3 days per week) in various sports (e.g., running, cycling, swimming) and did not complete specific cycling training prior to their participation. Their baseline characteristics are shown in Table 1. Subjects gave their informed consent prior to their inclusion in the study, which has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki. The study was approved by the local ethics review board (University of Innsbruck, Department of Sport Science, ZI.014/2010).

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Table 1. Baseline characteristics of the participants (*n* = 5).

Variables	Mean $\pm$ SD
Age (years)	42.6 $\pm$ 10.2
Weight (kg)	62.8 $\pm$ 10.6
Height (cm)	175.6 $\pm$ 5.7
BMI (kg/m^2)	20.3 $\pm$ 2.5
HR_{max} (b/min)	180.6 $\pm$ 2.7
P_{max} (W/kg)	4.5 $\pm$ 0.7
VO_{2max} (ml/min/kg)	49.1 $\pm$ 7.0
La_{max} (mmol/l)	10.6 $\pm$ 1.6
Sport practice (h/week)	6.0 $\pm$ 0.8

Body mass index, BMI; maximal heart rate, HR_{max}; maximal lactate concentration, La_{max}; maximal power output, P_{max}; maximal oxygen uptake, VO_{2max}. Maximal values represent values during maximal two-legged cycling exercise.

2.2. Protocol

Participants visited the laboratory on three separate days: day 1 for routine medical examination, maximal (two-legged) cycle ergometer testing, and familiarization with one-leg cycling; days 2 and 3 for maximal one-legged (dominant leg) cycling tests in normoxia and hypoxia (Figure 1).
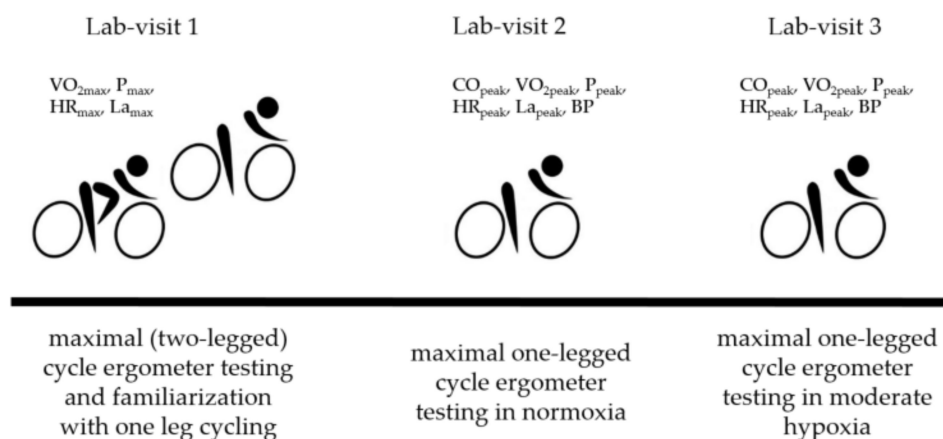

Figure 1. Experimental design. Blood pressure, BP; cardiac output, CO; heart rate, HR; lactate concentration, La; oxygen uptake, VO_2; power output, P.

2.3. One-Legged Exercise Tests

The one-legged cycle ergometer tests were conducted on an electrodynamically braked cycle ergometer (Excalibur Sport, Lode, the Netherlands). Both trials were performed in the late morning on separate days after a light breakfast at least 2 h prior to the test and a 10 min warm-up period (two-legged cycling at 40 watts). The handlebar and the saddle of the cycle ergometer were individually adjusted and remained the same in both trials. Resting measurements were performed in a sitting position (10 min) on the cycle ergometer. After this, the test started with a workload of 20 watts, which was increased by 20 watts every 2 min until the subject was unable to maintain a pedaling frequency of 30 rpm. The first test was performed in normoxia (FiO_2 = 20.9%) and the second in hypoxia (FiO_2 = 15%). Subjects were blinded to the applied FiO_2. Hypoxic air was delivered by the Hypoxico Altitude Generator (Hypoxico Europe GmbH) via a rigid mouthpiece connected to a "Y" system fixation with a double valve ensuring separate pathways between inspired and expired flow. The same valve system was applied during the normoxia setting.

2.4. Measurements and Calculation

Expired gases were analyzed for the assessment of peak oxygen uptake (VO_{2peak}) by a gas analyzer (Oxycon Alpha, Jaeger, Germany); 15 s averages of peak values were

taken for analysis. Peripheral oxygen saturation (SpO_2) was continuously measured by finger pulse oximetry (Nonin, Sanesco, Austria). Blood was taken from the hyperemized earlobe at rest and shortly before finishing the exercise test for determination of PaO_2 and hemoglobin concentration (ABL 80 Flex CO-OX OSM, Radiometer, Kopenhagen, Denmark). Lactate concentration (La) was determined at rest before starting the exercise test and 3 min after test termination (Biosen C-line, EKF diagnostic, Barleben, Germany). For continuous measurement of hemodynamic parameters (heart rate (HR), stroke volume (SV), CO, and total peripheral resistance (TPR)), the non-invasive impedance cardiograph PhysioFlow (Manatec biomedical, Poissy, France) was applied. Six electrodes were properly placed on the neck and chest, according to the manufacturer's instructions. Arterial blood pressure (BP) was measured at rest (sitting on the cycle ergometer) for calibration of the PhysioFlow before each exercise test and at the end of each stage. The signal quality and stability were checked over the entire test period.

Arterial–venous O_2 difference (a–vDO_2, $CaO_2 - CvO_2$) was calculated using the Fick equation a–$vDO_2 = VO_2/CO$ [15]. Arterial oxygen content (CaO_2) was calculated as: ($Hb \times 1.34 \times SaO_2$) + ($PaO_2 \times 0.003$), and systemic O_2 delivery as: $CO \times CaO_2$. Mean arterial blood pressure (MABP) was calculated as: 1/3 (systolic − diastolic) + diastolic BP, and total peripheral resistance (TPR) as: MABP/CO.

2.5. Statistics

Data are presented as mean values (±standard deviation, SD). Wilcoxon signed-rank tests were used to compare means recorded in normoxia and hypoxia. Spearman correlation analyses were performed to test associations between two variables. *p*-values < 0.05 are considered to indicate statistical significance.

3. Results

Resting SpO_2 values were higher in normoxia compared to hypoxia, whereas a lower resting HR was observed in normoxia (Table 2).

Table 2. Resting (sitting on the cycle ergometer) values of the normoxia and hypoxia sessions.

Variables	Normoxia	Hypoxia	*p*-Value
HR (b/min)	59.4 ± 4.6	64.4 ± 4.6	0.03
MABP (mmHg)	92.2 ± 3.9	89.7 ± 6.6	0.43
SV (mL)	78.0 ± 5.8	73.6 ± 7.8	0.18
CO (L/min)	4.63 ± 0.46	4.72 ± 0.33	0.69
SpO_2 (%)	96.5 ± 1.2	91.4 ± 1.1	0.04
CaO_2 (mL/L)	190.2 ± 34.6	178.3 ± 25.3	0.14
Systemic O_2 delivery (L/min)	0.88 ± 0.18	0.84 ± 0.15	0.35

Arterial oxygen content, CaO_2; peripheral oxygen saturation, SpO_2; cardiac output, CO; heart rate, HR; mean arterial blood pressure, MABP; stroke volume, SV; systemic O_2 delivery = $CO \times CaO_2$.

Resting BP did not differ between hypoxia and normoxia (124/76 vs. 122/74 mmHg *p* > 0.05, respectively). Peak one-legged cycling values in normoxia and hypoxia are illustrated in Table 3. During maximal single-legged exercise, peak CO was higher in hypoxia compared to normoxia, mainly due to an elevated peak HR. CaO_2 was reduced at simulated altitude (lower SpO_2 and PaO_2 and unaffected Hb). The higher CO, despite the reduced CaO_2, resulted in a higher systemic O_2 delivery in hypoxia compared to normoxia. Nonetheless, peak power output (*p* = 0.03, effect size (Cohen's d) = 4.8) and peak VO_2 (*p* = 0.04, effect size (Cohen's d) = 1.0) were lower in hypoxia compared to normoxia. In line with this, a–vDO_2 was lower in hypoxia. Peak La concentration was higher in hypoxia compared to normoxia. Differences in peak CO between the normoxia and hypoxia sessions were positively correlated with differences in peak VO_2 (r^2 = 0.91, *p* < 0.05) (Figure 2).

Table 3. Peak one-legged cycling values during the normoxia and hypoxia sessions ($n = 5$).

Variables	Normoxia	Hypoxia	*p*-Value
HR_{peak} (b/min)	142.4 ± 6.9	155.6 ± 3.6	0.03
MABP (mmHg)	97.3 ± 10.4	99.2 ± 14.9	0.89
TPR (mmHg/L/min)	5.82 ± 1.34	5.21 ± 1.71	0.09
SV_{peak} (mL)	118.2 ± 21.4	121.8 ± 23.0	0.08
CO_{peak} (L/min)	16.83 ± 3.10	18.96 ± 3.59	0.04
paO_2 (mmHg)	89.4 ± 3.2	76.8 ± 4.1	0.03
SpO_2 (%)	95.9 ± 1.8	86.9 ± 1.1	0.03
Hb (g/dL)	15.2 ± 1.2	15.4 ± 1.8	0.35
CaO_2 (mL/L)	197.9 ± 15.0	181.5 ± 19.3	0.04
a–vDO_2 (mL/L)	137 ± 21	112 ± 19	0.03
Systemic O_2 delivery (L/min)	3.37 ± 0.84	3.47 ± 0.89	0.04
P_{peak} (W)	154 ± 31	128 ± 26	0.03
P_{peak} (W/kg)	2.4 ± 0.2	2.0 ± 0.2	0.03
VO_{2peak} (mL/min)	2351 ± 719	2170 ± 706	0.04
VO_{2peak} (mL/min/kg)	36.8 ± 6.6	33.9 ± 6.9	0.04
La_{peak} (mmol/L)	8.2 ± 1.5	9.0 ± 1.6	0.04

Arterial oxygen content, CaO_2 (calculated as: $(Hb \times 1.34 \times SaO_2) + (PaO_2 \times 0.003)$); arterial–venous O_2 difference, a–vDO_2 ($CaO_2 - CvO_2$, calculated using the Fick equation a–$vDO_2 = VO_2/CO$); hemoglobin concentration, Hb; mean arterial blood pressure, MABP; peak cardiac output, CO_{peak}; peak heart rate, HR_{peak}; peak lactate concentration, La_{peak}; peak oxygen uptake, VO_{2peak}; peak power output, P_{peak}; peak stroke volume, SV_{peak}; peripheral oxygen saturation, SpO_2; systemic O_2 delivery = $CO \times CaO_2$.
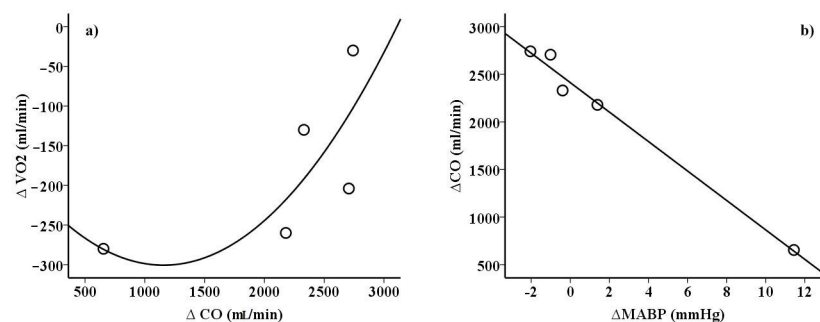

Figure 2. Relationship between changes from normoxia to hypoxia of (**a**) peak oxygen consumption (VO_2) and cardiac output (CO) ($r^2 = 0.91$, Spearman) and (**b**) CO and mean arterial blood pressure (MABP) ($r^2 = 1.0$, Spearman).

Changes (increase) of peak CO values from normoxia to hypoxia were negatively correlated with MABP in normoxia ($r^2 = 0.91$, $p < 0.05$), MABP in hypoxia ($r^2 = 0.91$, $p < 0.05$), and MABP changes ($r^2 = 1.0$, $p < 0.05$, Figure 2).

4. Discussion

The main results of the present study show reduced peak power output (P_{peak}) and VO_{2peak} values despite elevated systemic oxygen delivery during one-legged cycling in acute moderate hypoxia compared to normoxia. Data indicate that the CO increase was not sufficient to prevent the decline in P_{peak} and VO_{2peak} in hypoxia, and that the individual magnitude of VO_{2peak} reduction was closely associated with individual CO responses. This contrasts with our hypothesis, as we predicted unchanged one-leg performance due to compensation of the lower FiO_2 and SpO_2 by increased CO, eventually supported by hemoconcentration. Since systemic O_2 delivery was enhanced and a–vDO_2 reduced in moderate hypoxia compared to normoxia, a potential diffusion limitation cannot be excluded.

P_{peak} and VO_{2peak} during two-legged cycling (large muscle mass involved) are primarily limited by CO and the associated ability to deliver O_2 to the working muscles [1,16,17]. This, however, does not apply when exercising with a small muscle mass, i.e., one-legged cycling, because maximal CO in general is not attained [5–7]. In the present study, peak

values of CO and VO$_2$ are relatively (in proportion to the involved muscle mass) higher during cycling with one compared to two legs, i.e., 75% of two-legged VO$_{2peak}$. Theoretically, there is still compensatory potential for CO to increase when oxygen delivery during cycling with one leg is affected by hypoxia, i.e., oxygen desaturation, which was actually confirmed by our findings. Why compensation is insufficient to restore performance and varies considerably between individuals remains elusive.

A novel finding of the present study, besides showing a partial compensatory increase in peak CO at moderate altitude, is the observation that MABP and CO changes from normoxia to hypoxia correlate closely (r = −0.91 to −1.0). Although this result appears to be influenced by a single subject displaying a large increase in MABP, it seems intriguing to speculate that baroreceptor activity might be involved in the regulation of CO in acute moderate hypoxia (Figure 2). Baroreflex sensitivity (hypocapnia triggered) is usually reduced in acute hypoxia, potentially related to an insufficient CO elevation to compensate for the hypoxia-related loss in VO$_{2peak}$ [18,19]. A sufficient CO increase was particularly prevented in individuals with higher (but normal) values of systemic BP (and BP changes from normoxia to hypoxia), likely due to enhanced baroreceptor activity and the associated reduction in sympathetic activation and cardiac output [20]. The reduced sympathetic activation may also explain why TPR was reduced in subjects showing the highest compensatory increase in CO. However, the fact that chemoreflex activation inhibits baroreflex activation and vice versa [21,22] complicates the interpretation of these results. Furthermore, when exercising with a small muscle mass in hypoxia (compared to normoxia), accumulation of metabolites (metaboreflex) in the contracting muscle (slightly increased La concentration in hypoxia) [23] and vascular tone regulation of the non-exercising musculature [14], influencing BP response, may interact in a complex manner. Moreover, central command, a feed-forward neural mechanism that transmits impulses to the motor neurons and in parallel modulates cardiovascular responses, may have played a role in exercise performance and CO adjustments [24].

In addition to CO limitations, muscle diffusion capacity may also affect single-leg exercise performance at altitude. We found an enhanced systemic O$_2$ delivery and a lower a–vDO$_2$ in moderate hypoxia, which point towards impaired oxygen extraction by the working muscles. The impairment could potentially result from the lower O$_2$ pressure gradient and/or a shortened transit time [8,9,12]. Increased oxygen delivery to working muscles and lower a–vDO$_2$ during steady-state single-leg [5,25,26], but also double-leg [10], knee-extension exercise has previously been demonstrated, albeit in more severe hypoxia than the present study. It needs to be acknowledged that in the present study, a–vDO$_2$ was calculated and not measured, thus these data need to be interpreted with caution.

4.1. Methodological Considerations and Limitations

Certainly, our preliminary observation of a relationship between systemic BP and CO (and thus also VO$_{2peak}$) changes during exercise with a small muscle mass in acute moderate hypoxia must be interpreted with caution. As outlined, the relationship seems mainly driven by one subject and future studies involving a larger sample size are needed to confirm the present results. It also needs to be determined whether this relationship is valid under conditions of more severe hypoxia or when applying different exercise types. In this regard, it is important to mention that the type of exercise (e.g., one-legged dynamic knee extension vs. one-legged cycling), which also influences active muscle mass, may influence muscle blood flow and thus oxygen delivery. Consistent with this, it has been reported that the smaller the muscle mass (e.g., arms) and the less dynamic the exercise (e.g., intermittent isometric contraction), the more the muscular perfusion is impaired during maximal exercise [6,27]. The consequence is that maximal exercise is limited primarily by the intrinsic power of muscles rather than by O$_2$ supply [6]. Since, in the present study, a one-legged cycle exercise was applied, deviating results compared with other studies may have resulted from differences in the type of exercise (e.g., knee extension).

Sex differences in leg vasodilation during graded knee extensor exercise have been reported [28], which may have influenced the present results (males and females were included). Nonetheless, when analyzing changes from moderate altitude to sea level conditions, such differences should have little impact on the interpretation of the present data. Evidently, this only applies if there are little to no sex differences in responses to exercise in hypoxia. According to Shephard et al. [29], such differences should be minor during single-leg cycling and be most prominent when arm exercise is performed. In line with this, differences in mean VO_{2peak} and CO between altitude and sea level were similar between males and females in the present study (-2.9 mL/min/kg and 34.5 mL/min/kg for males and -2.8 mL/min/kg and 33.4 mL/min/kg for females, respectively).

The main limitation, which must certainly be acknowledged and may be considered critical, is the small sample size. Nonetheless, the uniform (in every participant) increases in CO and reductions in VO_{2peak} argue in favor of an existing compensatory increase in CO at moderate altitude, which was insufficient to restore normoxic VO_{2peak}. Furthermore, we did not monitor direct changes of cardiovascular reflexes, but the observed association between MABP, CO, and VO_{2peak} suggest involvement of those reflexes, which have to be considered in future studies involving a larger sample size.

4.2. Practical Considerations

Peak aerobic performance when exercising/working with a small muscle mass is acutely reduced even in moderate acute hypoxia. If performance is crucial, e.g., from a safety perspective, individual values of systemic BP and training involving a small muscle mass may be considered before going to altitude [30]. Additionally, acclimatization to altitude may be of importance for workers as well as athletes who have to perform with a small muscle mass (e.g., athletes with disabilities) at moderate altitude. With prolonged altitude exposure, neural adjustments change [31], which may contribute to the restoration of normoxic small muscle exercise performance, as demonstrated at higher altitudes [1]. In addition, it has been reported that acclimatization to moderate altitude may increase left ventricular muscle mass [32,33], potentially supporting compensatory increases in CO and thus performance involving a small muscle mass. Moreover, previous studies also demonstrated improved bilateral cycling performance after one-legged cycling training in normoxia [30] and hypoxia as well [34].

5. Conclusions

The present study found reduced P_{peak} and VO_{2peak}, despite elevated systemic oxygen delivery, during one-legged cycling in acute, moderate (FiO_2: 15%) hypoxia. The related CO increase was not sufficient to prevent the decline in P_{peak} and VO_{2peak}. The magnitude of VO_{2peak} reduction was associated with individual CO responses, which again were correlated with individual MABP values. These observations likely indicate the involvement of baroreceptor activity in the explanation of CO and VO_{2peak} changes when exercising with a small muscle mass in acute moderate hypoxia. Not to be ignored, the enhanced systemic O_2 delivery and the reduced a–vDO_2 in moderate hypoxia may indicate a possible diffusion limitation. These novel, yet preliminary, findings may be of clinical/practical relevance and deserve further investigation.

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Institutional Review Board Statement: The study has been approved by the local ethics review board (University of Innsbruck, Institute of Sport Science).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data are contained within the article.

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