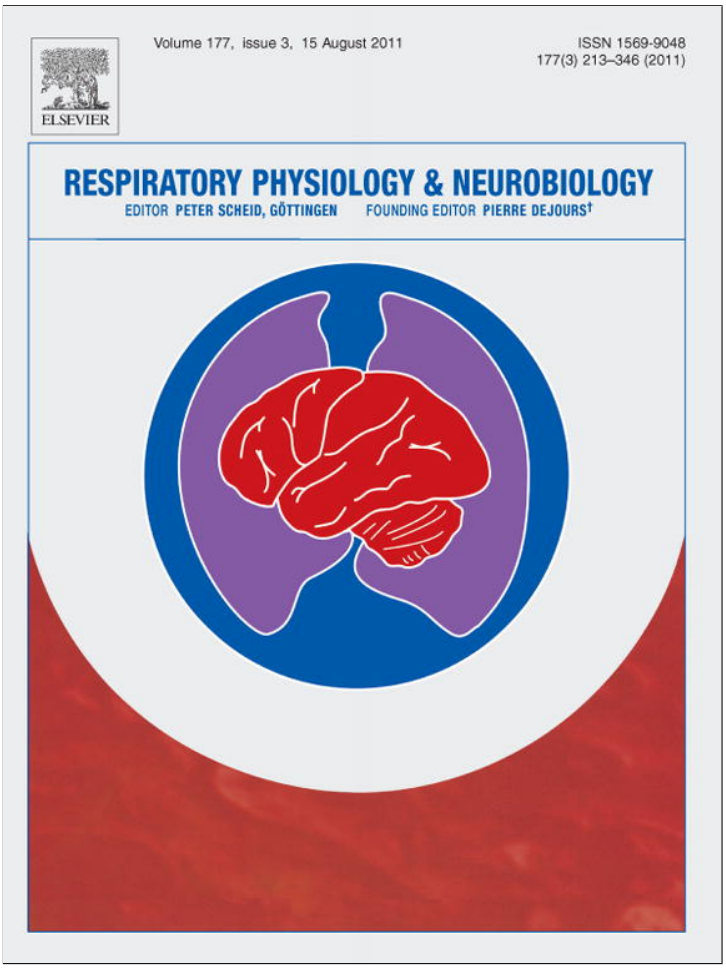

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Exercise intolerance at high altitude (5050 m): Critical power and W'

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ABSTRACT

The relationship between work rate (WR) and its tolerable duration (t_{LIM}) has not been investigated at high altitude (HA). At HA (5050 m) and at sea level (SL), six subjects therefore performed symptom-limited cycle-ergometry: an incremental test (IET) and three constant-WR tests (% of IET WR_{max}, HA and SL respectively: WR_1 70 ± 8%, 74 ± 7%; WR_2 86 ± 14%, 88 ± 10%; WR_3 105 ± 13%, 104 ± 9%). The power asymptote (CP) and curvature constant (W') of the hyperbolic WR–t_{LIM} relationship were reduced at HA compared to SL (CP: 81 ± 21 vs. 123 ± 38 W; W': 7.2 ± 2.9 vs. 13.1 ± 4.3 kJ). HA breathing reserve (estimated maximum voluntary ventilation minus end-exercise ventilation) was also compromised (WR_1: 25 ± 25 vs. 50 ± 18 l min^{-1}; WR_2: 4 ± 23 vs. 38 ± 23 l min^{-1}; WR_3: −3 ± 18 vs. 32 ± 24 l min^{-1}) with near-maximal dyspnea levels (Borg) (WR_1: 7.2 ± 1.2 vs. 4.8 ± 1.3; WR_2: 8.8 ± 0.8 vs. 5.3 ± 1.2; WR_3: 9.3 ± 1.0 vs. 5.3 ± 1.5). The CP reduction is consistent with a reduced O_2 availability; that of W' with reduced muscle–venous O_2 storage, exacerbated by ventilatory limitation and dyspnea.

1. Introduction

The ability to sustain high-intensity exercise is widely acknowledged to be impaired on acute ascent to high altitude (HA), as evident in a reduced whole-body maximum O_2 uptake ($\dot{V}_{O_2\,max}$) (Hansen et al., 1967) and muscle $\dot{V}_{O_2\,max}$ (Calbet et al., 2003; Lundby et al., 2006). This reflects, in part at least, a limitation to muscle O_2 delivery and/or utilization rates consequent to the low arterial O_2 content and reductions in maximal cardiac output ($\dot{Q}_T$), stroke volume (SV) and heart rate (HR) (Vogel et al., 1974) and maximal muscle blood flow ($\dot{Q}_M$) (Calbet et al., 2003; Lundby et al., 2006). Furthermore, as the lactate threshold (or gas exchange threshold, GET) is also reduced at HA, at least acutely (Grassi et al., 1996; Myers et al., 2008), the metabolic stress associated with a particular supra-GET work rate (WR) is functionally elevated.

For exercise at sea-level (SL), WRs that lie immediately above GET are relatively sustainable as $\dot{V}_{O_2}$ and the elevated blood lactate and proton concentrations ($[L^-]$, $[H^+]$) are each able to stabilize (Poole et al., 1988; Whipp, 1994). The upper demarcator of this "heavy" intensity domain is the "critical power" (CP) (Whipp and Rossiter, 2005), all higher WRs being characterized by $\dot{V}_{O_2}$ and blood [La] and $[H^+]$ continuing to increase to, or towards, their maximum attainable values (Poole et al., 1988; Whipp, 1994; Jones et al., 2008). In this "very heavy" (or "severe"): (Jones et al., 2010) intensity domain (Whipp and Rossiter, 2005), the tolerable duration (t_{LIM}) declines with increasing WR in a fashion that has been well described by a hyperbolic function both for small muscle groups (Monod and Scherrer, 1985) and for larger muscle-group exercise such as cycling (Moritani et al., 1981; Whipp et al., 1982; Poole et al., 1988):

$$WR = \frac{W'}{t_{LIM}} + CP \quad (1)$$

where the curvature constant, termed the anaerobic work capacity (Monod and Scherrer, 1985) or W' (Whipp et al., 1982; Poole et al., 1988), is equivalent to a constant amount of work that can be performed above CP, regardless of the imposed WR (Moritani et al., 1981; Whipp et al., 1982; Monod and Scherrer, 1985; Poole et al., 1988). As CP is generally agreed to represent the highest sustainable WR for which steady states of $\dot{V}_{O_2}$, blood $[L^-]$ and $[H^+]$ (Poole et al., 1988; Whipp and Rossiter, 2005) and muscle $[H^+]$

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(Jones et al., 2008) can be attained, it is assumed to reflect a rate of aerobic energy-pool reconstitution whose magnitude sets the maximum WR that can be sustained without a progressively increasing anaerobic contribution (Moritani et al., 1981; Poole et al., 1988; Whipp and Rossiter, 2005; Jones et al., 2010). The constitution of W' is less certain, but is typically proposed to reflect an intramuscular anaerobic energy store composed of phosphagens such as phosphocreatine (PCr) and sources linked to anaerobic glycolysis, in addition to utilization of stored O_2. t_{LIM} is reached when this store becomes depleted, its rate of depletion being proportional to the supra-CP power requirement (Moritani et al., 1981; Poole et al., 1988). There could also be an involvement of factors related to the accumulation of fatigue-related metabolites such as H^+, inorganic phosphate (Pi) and potassium ions (K^+) (Fitts, 2008) to some collective "limit" at a rate proportionally coupled to the rate at which W' is being utilized (Coats et al., 2003), at which point the WR can no longer be sustained (Coats et al., 2003; Poole et al., 1988).

However, little is known about how CP and W' contribute to exercise intolerance on ascent to HA, as studies to date have typically been confined to incremental and/or single constant-WR protocols, which do not lend themselves to such considerations. Extrapolating from SL findings, we propose that a compromised t_{LIM} at HA is likely to involve a reduction in CP, as CP has been reported to be decreased at SL when hypoxic gas mixtures are breathed acutely (Moritani et al., 1981; Whipp et al., 1982). In contrast, W' in these SL studies was unaffected (Moritani et al., 1981; Whipp et al., 1982). Whether a similar lack of effect for W' might be expected at HA is harder to ascertain. Resting and peak exercise muscle [ATP] and [PCr] levels have been reported to be essentially unaffected by ascent to HA (van Hall et al., 2009). Likewise, maximum blood [L^-] has been reported to be similar to SL values on immediate ascent (despite the lower $\dot{V}_{O_2\,max}$), and although this is widely reported to decline as acclimatization proceeds (the "lactate paradox") (Cerretelli and Samaja, 2003; Reeves et al., 1992; West, 1986), no blunting was evident in arterial [L^-], muscle [L^-] or leg net lactate release during incremental exercise for moderate HA exposure (i.e. two weeks at 4100 m) compared to acute hypoxia at SL (van Hall et al., 2009). However, we speculate that a HA-related reduction in the volume of O_2 stored in muscle and venous blood could cause W' to be reduced relative to SL values.

It was therefore the purpose of this investigation to evaluate the effects of acute HA exposure on the parameters of the WR–t_{LIM} relationship (i.e. CP and W'), as well as key parameters of aerobic function (i.e. functional $\dot{V}_{O_2}$ gain $\left(\Delta\dot{V}_{O_2}/\Delta WR\right)$, GET and $\dot{V}_{O_2\,max}$) at an altitude of 5050 m in healthy lowlanders participating in a trek to the Pyramid Laboratory, near Mount Everest base camp. We hypothesized that t_{LIM} at a given work rate would be reduced at HA, consequent to a reduced CP and W'.

2. Methods

2.1. Subjects

Six recreationally active, healthy non-smoking residents (two females and four males) who were born and permanently resident at SL (Table 1) provided written informed consent to participate in the study. The procedures and protocols were approved by the National Research Council (CNR, Italy) as part of the Ev-K2-CNR research program, and were conducted in accordance with the Declaration of Helsinki.

2.2. Protocols

The HA phase of the study was conducted at the CNR Pyramid Laboratory, Lobuche, Khumbu, Nepal (5050 m; barometric pressure ~410 Torr) over a 3-day period, and the SL phase 3 months later (Rome, Italy; ~100 m). Timing constraints with relation to the availability of the HA testing facility precluded the entire SL phase being performed prior to the HA ascent; however, prior to departure, each subject completed a single maximal incremental exercise test. The SL phase was delayed for 3 months so as to minimize any effects of acclimatization, with subjects maintaining their pre-HA activity patterns over this period. The subjects travelled by plane to Katmandu (1340 m), where they stayed for 4 days before being flown to Lukla (2860 m) for a 10-day trek to the Pyramid Laboratory with intermediate stops of 3 days at Namche Bazaar (3450 m) and then 2 days at Pheriche (4252 m) to allow for acclimatization. During ascent and throughout the stay at the Pyramid Laboratory, symptoms of acute mountain sickness and resting arterial O_2 saturation (SpO_2) were monitored. On day 1 at the Pyramid Laboratory, the subjects rested. On day 2, they performed standard pulmonary function tests and then completed a familiarization, which included a maximal incremental exercise test and a resting blood sample for hematocrit measurement. Standard pulmonary function tests consisted of three maximal expiratory maneuvers each lasting 6 s, performed at rest and in the standing position; the best of these was recorded and utilized for statistical analysis. Calibration of the spirometer (photoelectric digital turbine, diameter 28 mm; resolution 4 ml, Micro Kit, COSMED, Rome, Italy) was performed prior to each test, using a 3 l syringe.

On day 3, the formal testing began, with a second maximal incremental exercise test. On the immediately following days, each subject completed three high-intensity constant-WR tests to the limit of tolerance. A recovery period of at least 12 h was allowed between tests, so that no subject performed more than two tests per day and the protocol was completed in 3 days. Just prior to departing for HA, each subject performed an incremental exercise test. Three months after returning to SL, all the tests were repeated.

2.2.1. Incremental exercise test

Incremental exercise tests were performed to the limit of tolerance from an initial 20 W baseline (at least 4 min), with a WR incrementation rate of 15 W/min at HA and 25 W/min at SL, and a final 20 W recovery (at least 6 min). This allowed determination of peak $\dot{V}_{O_2}$ ($\dot{V}_{O_2\,peak}$) and $\Delta\dot{V}_{O_2}/\Delta WR$, and non-invasive estimation of GET using standard and directly validated ventilatory and pulmonary gas exchange criteria, i.e. the "V-slope" criterion as the $\dot{V}_{O_2}$ at which a systematic increase in the slope of the CO_2 output ($\dot{V}_{CO_2}$) to $\dot{V}_{O_2}$ relationship occurred (Beaver et al., 1973), in conjunction with the ventilatory equivalent for O_2 and end-tidal PO_2 starting to increase with no concomitant increase in the ventilatory equivalent for CO_2 $\left(\dot{V}_E/\dot{V}_{CO_2}\right)$ or decrease in end-tidal PCO_2 (e.g. ATS/ACCP, 2003). To allow comparison with CP, the steady-state WR equivalent of the GET for each condition was derived by correcting the measured WR at GET for the influence of the fundamental $\dot{V}_{O_2}$ time constant (τ'); i.e. at a given $\dot{V}_{O_2}$ (in this case, that corresponding to GET), the steady-state WR equivalent will be less than the measured WR by an amount equal to the product of the ramp WR incrementation rate (W/min) and τ' (min) (Whipp, 1994).

2.2.2. Constant-WR test

Constant-WR tests were performed to the limit of tolerance, again from an initial 20 W baseline (at least 4 min) and with a final 20 W recovery (at least 6 min), each at different WRs chosen to induce exhaustion over a range of times from ~2 to 15 min (e.g. Poole et al., 1988; Whipp, 1994; Jones et al., 2008) and to provide a relatively even point distribution along the $1/t$ axis The order in which these tests was imposed was randomized for each subject.

Table 1
Subject characteristics.

Subject	Age (yr)	Ht (m)	BMI (kg m^{-2})	FVC (SL) (l) (% pred)	FEV_1 (SL) (l) (% pred)	HCT (SL) (%)	FVC (HA) (l) (% pred)	FEV_1 (HA) (l) (% pred)	HCT (HA) (%)
1	36	1.87	21.6	5.55 (106)	4.17 (108)	44	5.44 (104)	4.57 (94)	58
2	56	1.78	25.6	4.46 (95)	3.33 (98)	40	4.51 (94)	3.02 (96)	50
3	25	1.72	19.6	3.61 (83)	3.14 (90)	43	3.32 (76)	3.25 (93)	40
4	32	1.78	22.7	5.55 (104)	4.92 (117)	44	5.67 (106)	5.2 (124)	60
5	34	1.57	24.3	3.69 (107)	2.95 (108)	38	3.53 (102)	2.67 (98)	55
6	62	1.72	27.7	5.31 (125)	4.09 (136)	42	5.07 (119)	4.01 (133)	50
Mn ± SD	41 ± 15	1.74 ± 0.10	23.6 ± 2.9	4.70 ± 0.90 (103 ± 14)	3.77 ± 0.75 (109 ± 16)	41.8 ± 2.4	4.59 ± 0.99 (100 ± 14)	3.79 ± 0.98 (106 ± 17)	50.5 ± 7.6*

BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; HCT, hematocrit; SL, sea level; HA, high altitude.
* $P < 0.05$ vs. SL.

2.3. Equipment

Subjects exercised on a mechanically braked cycle ergometer (828 E, Monark Exercise AB, Varberg, Sweden), with pedaling frequency being maintained at 60 ± 5 rpm (with subjects following an electronic audio signal generated each second). Prior to each test, the zero-load setting on the ergometer was checked and a calibration was performed with a 4 kg weight. Ventilatory and pulmonary gas exchange variables were measured breath-by-breath in all tests using a portable system (K4b^2, COSMED, Italy), which has previously been used at HA (Pattinson et al., 2004). The system comprised a face mask, analyzer unit (containing O_2 and CO_2 gas analyzers), heart-rate monitor and battery. The analyzer unit with battery pack, face-mask and tubing (weight 0.8 kg) was attached to the subject with a harness and connected to a personal computer by an Ethernet cable connection. The face-mask contained a turbine for measurement of volume and flow; calibration was performed with a 3 l syringe (Hans Rudolph, Kansas City, MO, USA) over a range of different flow profiles. Respired gas, sampled continuously from a port within the turbine via a Nafion polymer capillary (Permapure©), was analyzed at 100 Hz using rapid-response O_2 (polarographic) and CO_2 (infrared) analyzers (mean response time 120 ms); calibration was performed using two precision-analyzed gas mixtures spanning the respired range. The gas analyzers were automatically thermostated and compensated for ambient variations in barometric pressure, humidity and environmental temperature. The volume and gas concentration signals were sampled and digitized every 10 ms, and time-aligned; i.e. correcting for the transport delay between the turbine and gas analyzers and for the analyzer rise time (Beaver et al., 1973). The accuracy of the telemetric system has been previously established (Palange et al., 2000; Pattinson et al., 2004). Heart rate was calculated beat-by-beat, and SpO_2 was monitored non-invasively using finger pulse oximetry (Masimo Rad-5, Masimo Corporation, Irvine, CA, USA). Capillary blood samples were taken (~25 μl) from the finger-tip of the hand, heated by an infrared lamp, at rest, after 2 min of exercise at 20 W and within the first 10 s of recovery (i.e. end-exercise), and analyzed immediately post-test for [L^-] using an automated analyzer (Lactate-Pro, Arkray, Inc., Japan); calibration was performed before the analysis of each set of blood samples using the manufacturer's calibration strip. Subjects were also asked to rate "shortness of breath" and "leg effort" at end-exercise in an alternating sequence using the 0-to-10 Borg category-ratio scale (Borg, 1982).

2.4. Analyses

Breath-by-breath data were edited to exclude occasional outlying breaths (>±4 SD of the local mean), which were the result of coughs, swallows, sighing or gasping, etc. Baseline $\dot{V}_{O_2}$ for the initial 20 W warm-up phase was calculated as the mean $\dot{V}_{O_2}$ over the final 60 s. $\dot{V}_{O_2\,peak}$ was calculated as the average $\dot{V}_{O_2}$ for an integral number of breaths over the last ~20 s of the incremental phase. t_{LIM} was calculated as the interval between the imposition of the WR step and the point at which the subject could no longer maintain the required pedaling rate (60 rpm) despite active encouragement from the same observer. The subjects were not told for how long they had exercised or at what WR. CP and W' were estimated as the WR-intercept and slope, respectively, by least-squares linear regression from the WR–t_{LIM}^{-1} relationship (Poole et al., 1988). Breathing reserve (BR) was estimated as the difference between the estimated maximum voluntary ventilation (MVV) and the end-exercise ventilation ($\dot{V}_{E_{peak}}$) (ATS/ACCP, 2003); MVV being estimated as $FEV_1 \cdot 40$ (Campbell, 1982) and FEV_1 being measured at SL and at HA.

Differences among measured responses were determined by a Student's paired *t*-test. Two-way repeated measures analysis of variance (ANOVA), with a Bonferroni post hoc test, was used to evaluate differences between variables at each WR within groups (i.e. HA and SL). Pearson's Product–Moment correlation coefficient (R^2) was used to identify correlations between criterion variables. The level of statistical significance was set at $P < 0.05$. Group data are presented as mean ± SD.

3. Results

Ascent to HA resulted in a significant arterial desaturation at rest (Tables 2 and 3), SpO_2 averaging 83.8 ± 4.6% at HA vs. 97.7 ± 1.0% at SL (Tables 2 and 3).

3.1. Incremental exercise

The key findings for incremental exercise (Table 2) are that at HA, SpO_{2peak} (72.8 ± 7.3 vs. 98.0 ± 1.4%, $P < 0.001$), WR_{peak} (138 ± 26 vs. 208 ± 44 W, $P < 0.01$), $\dot{V}_{O_{2\,peak}}$ (1690 ± 353 vs. 2227 ± 511 ml min^{-1}, $P < 0.01$) and GET (1015 ± 222 vs. 1302 ± 241 ml min^{-1}, $P < 0.01$) were each lower compared to SL, but with no change in $\Delta\dot{V}_{O_2}/\Delta$WR; it should be noted that these SL $\dot{V}_{O_{2\,peak}}$ values did not differ from those measured in the single incremental test prior to HA ascent (2221 ± 607 ml min^{-1}, coefficient of variation: 27.3% vs. 22.9%, respectively pre- and post-HA). Peak HR was also lower at HA (147 ± 13 vs. 168 ± 12 beat min^{-1}, $P < 0.001$), as was peak O_2 pulse $\left(\dot{V}_{O_{2\,peak}}/HR\right)$ (11.5 ± 2.5 vs. 13.4 ± 3.2 ml beat^{-1}, $P < 0.05$). Despite no change in resting blood [L^-] with HA ascent, end-exercise [L^-] at HA was appreciably reduced compared to SL. Despite the lower $\dot{V}_{O_{2\,peak}}$ and $\dot{V}_{CO_{2\,peak}}$ at HA, $\dot{V}_{E_{peak}}$ at HA was appreciably higher than at SL, as was the slope of the linear phase of the $\dot{V}_E - \dot{V}_{CO_2}$ relationship $\left(\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}\right)$ and $\dot{V}_E/\dot{V}_{CO_2}$ at GET, reflective of the lower end-tidal PCO_2 ($P_{ET}CO_2$) at HA. Consequently, in contrast to SL, the end-exercise breathing reserve (BR) at HA was not significantly higher or lower than

Table 2
Group-mean responses (±SD) to incremental exercise at high altitude and sea level.

	High altitude	Sea level	*P*-value
$\dot{V}_{O_2\,peak}$, ml min^{-1}	1690 ± 353	2227 ± 511	0.007
WR_{peak}, W	138 ± 26	208 ± 44	0.005
GET, ml min^{-1}	1015 ± 222	1302 ± 241	0.006
$\Delta\dot{V}_{O_2}/\Delta WR$, ml W^{-1}	10.2 ± 1.2	9.4 ± 0.75	0.2
HR_{rest}, beat min^{-1}	83 ± 18	74 ± 16	0.0003
HR_{peak}, beat min^{-1}	147 ± 13	168 ± 12	0.0009
O_2 $pulse_{rest}$, ml beat^{-1}	3.7 ± 1.2	3.6 ± 1.6	0.8
O_2 $pulse_{peak}$, ml beat^{-1}	11.5 ± 2.5	13.4 ± 3.2	0.05
$[La^-]_{rest}$, mmol l^{-1}	1.7 ± 0.5	1.9 ± 0.7	0.6
$[La^-]_{peak}$, mmol l^{-1}	5.8 ± 1.7	9.5 ± 3.0	0.03
$\dot{V}_{CO_2\,peak}$, ml min^{-1}	2059 ± 573	2816 ± 780	0.02
RER_{peak}	1.21 ± 0.13	1.26 ± 0.18	0.6
$\dot{V}_{E_{peak}}$, l min^{-1}	121 ± 35	94 ± 30	0.07
BR, l min^{-1}	31 ± 28	57 ± 20	0.1
f_{Rpeak}	51.2 ± 7.9	38.5 ± 6.6	0.04
$\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}$	44 ± 5	24 ± 2	0.0001
$\dot{V}_E/\dot{V}_{CO_2}$ at GET	45 ± 4	29 ± 2	0.000009
$P_{ET}CO_{2rest}$, mm Hg	25 ± 1	33 ± 3	0.0003
$P_{ET}CO_{2peak}$, mm Hg	20 ± 2	37 ± 2	0.00003
SpO_{2rest}, %	85.0 ± 4.3	97.7	0.0009
SpO_{2peak}, %	73 ± 7	98 ± 2	0.0005
Dyspnea	9.3 ± 1.0	5.3 ± 1.8	0.005
Leg fatigue	7.8 ± 1.5	9.2 ± 0.8	0.2

$\dot{V}_{O_2}$, O_2 uptake; WR, work rate; GET, gas exchange threshold; HR, heart rate; $[La^-]$, lactate concentration; $\dot{V}_{CO_2}$, CO_2 output; RER, respiratory exchange ratio; $\dot{V}_E$, ventilation; $P_{ET}CO_2$, end-tidal PCO_2; SpO_2, arterial O_2 saturation.

the estimated limiting value of 0 ($P = 0.19$; 2-tailed paired *t*-test). In addition, the end-exercise dyspnea at HA was greater than for SL, attaining the limiting value of 10 ($P = 0.17$; 2-tailed paired *t*-test). Leg fatigue was slightly reduced at HA, although this was not statistically significant.

3.2. Constant-WR exercise

For each subject, $1/t_{LIM}$ was directly correlated with WR both at SL and HA, and the data were well fit to a linear regression of WR vs. $t_{LIM}{}^{-1}$ (Fig. 1), with R^2 values typically being at least 0.98, and the mean SE of the CP estimation being 5 W. However, CP and W' were significantly reduced at HA compared to SL (CP: 81 ± 21 vs. 123 ± 38 W, $P = 0.04$; W': 7.2 ± 2.9 vs. 13.1 ± 4.3 kJ, $P = 0.02$).

The constraints placed on WR selection for the constant-WR tests (i.e. with t_{LIM} falling in the range ~2–15 min: see Section 2) resulted in the absolute WRs at HA being appreciably lower than those at SL (Table 3). This precluded iso-WR comparisons of response. However, in all subjects, end-exercise $\dot{V}_{O_2}$ met the criterion for $\dot{V}_{O_2\,max}$ by being independent of WR (Fig. 2, Table 3), averaging 1583 ± 358 ml min^{-1} at HA and 2232 ± 520 ml min^{-1} at SL, which was not significantly different from the corresponding $\dot{V}_{O_2\,peak}$ obtained on the incremental test (Table 2). As was the case for the incremental tests, end-exercise SpO_2 was lower at HA (averaging 73.3 ± 6.4 vs. 97.6 ± 1.0%, $P < 0.00001$), end-exercise HR was lower (averaging 148 ± 14 vs. 168 ± 12 beat min^{-1}, $P < 0.0002$) as was end-exercise O_2 pulse (11 ± 2 vs. 13 ± 3 ml beat^{-1}, $P < 0.00002$) (Table 3). End-exercise $[L^-]$ was significantly reduced at HA (7.5 ± 2.5 mmol vs. 9.7 ± 2.1 mmol, respectively; $P < 0.001$), although independent of WR (Table 3) and not significantly different from the corresponding values at the limit of tolerance on the corresponding incremental test (Table 2).

As was the case for the incremental tests, end-exercise $\dot{V}_E$ at HA was higher than at SL, averaging 143 ± 41 vs. 111 ± 23 l min^{-1} ($P < 0.001$), respectively, despite the applied WRs at HA being less than at SL (Table 3, Fig. 3). Also, end-exercise $\dot{V}_E$ for the individual constant-WR tests was greater the higher the WR at HA and also at SL (Table 3, Fig. 3). However, FEV_1 and therefore MVV at HA were not significantly changed on average (Table 1), although increases were evident in some subjects and decreases in others consistent with the variable responses reported in the literature (Mansell et al., 1980; Gautier et al., 1982; Welsh et al., 1993). Consequently, the reduction in breathing reserve was more marked as WR increased (Table 3, Fig. 3) and, in contrast to SL, attained the estimated limiting value of 0 at HA ($P = 0.015$, 0.33 and 0.34 for WR_1, WR_2 and WR_3, respectively). Similarly, dyspnea at HA was progressively exacerbated with increasing WR, also attaining maximal values at WR_3 ($P = 0.0001$, 0.006 and 0.02 for WR_1, WR_2 and WR_3, respectively). In contrast, leg fatigue was significantly lower at HA, averaging 5.5 ± 1.2 vs. 7.6 ± 0.9 ($P < 0.00008$).

Both at SL and HA, CP was correlated with GET, expressed as the steady-state WR-equivalent of the $\dot{V}_{O_2}$ value at GET ($R^2 = 0.68$, $P < 0.05$ and 0.76, $P < 0.05$, respectively). Furthermore, the individual reductions in CP at HA, relative to SL, correlated with the corresponding reductions in GET, expressed as the steady-state WR-equivalent of the $\dot{V}_{O_2}$ value at GET ($R^2 = 0.77$, $P < 0.05$), with the

Table 3
Group-mean end-exercise responses (±SD) to exhausting constant-load exercise at high altitude and sea level.

	High altitude			Sea level		
	WR_1	WR_2	WR_3	WR_1	WR_2	WR_3
WR, W	99 ± 24	114 ± 25*	142 ± 26$^{*,\#}$	152 ± 37§	175 ± 44*,§	208 ± 48$^{*,\#,\S}$
WR, % WR_{peak}	72 ± 13	83 ± 14*	104 ± 13*	73 ± 6	83 ± 6*	100 ± 5*
t_{LIM}, s	378 ± 142	242 ± 59*	117 ± 22$^{*,\#}$	523 ± 198	249 ± 30*	156 ± 20$^{*,\#}$
$\dot{V}_{O_2}$, ml min^{-1}	1548 ± 370	1651 ± 382	1550 ± 380	2280 ± 587§	2227 ± 540§	2189 ± 527§
HR, beat min^{-1}	148 ± 17	150 ± 14	147 ± 12	169 ± 12§	169 ± 10§	165 ± 16§
O_2 pulse, ml beat^{-1}	10 ± 2	11 ± 3	11 ± 2	14 ± 4†	13 ± 4†	13 ± 4†
$[La^-]$, mmol l^{-1}	6.2 ± 1.8	7.1 ± 1.7	9.1 ± 3.1	10.7 ± 2.2 §	9.9 ± 1.9 §	8.4 ± 1.7
$\dot{V}_{CO_2}$, ml min^{-1}	1888 ± 404	2170 ± 567	2134 ± 514	2382 ± 505	2747 ± 657*,§	2932 ± 732$^{*,\#,\S}$
RER	1.23 ± 0.19	1.32 ± 0.14*	1.38 ± 0.03*	1.06 ± 0.7	1.24 ± 0.08*	1.34 ± 0.04*
$\dot{V}_E$, l min^{-1}	126 ± 49	147 ± 42	155 ± 32*	101 ± 17§	113 ± 22§	119 ± 29§
BR, l min^{-1}	25 ± 25	4 ± 23	−3 ± 18	50 ± 18§	38 ± 23§	32 ± 24§
$\dot{V}_E/\dot{V}_{CO_2}$	66 ± 14	68 ± 7	73 ± 9	43 ± 7§	42 ± 5§	41 ± 7§
$P_{ET}CO_2$, mm Hg	20 ± 3	20 ± 2	20 ± 2	31 ± 2§	34 ± 5§	35 ± 5§
SpO_{2rest}, %	82.7 ± 5.1	84.0 ± 6.0	83.5 ± 3.9	97.2 ± 0.8§	98.2 ± 1.2§	97.7 ± 0.5§
SpO_{2peak}, %	71 ± 6	74 ± 8	75 ± 5	98 ± 1§	97 ± 1§	98 ± 2§
Dyspnea	7.2 ± 1.2	8.8 ± 1.2*	9.3 ± 1.0*	4.8 ± 1.3§	5.3 ± 1.2§	5.3 ± 1.5§
Leg fatigue	6.0 ± 1.3	5.2 ± 1.2	5.3 ± 1.0	7.7 ± 0.8†	7.2 ± 0.8†	7.8 ± 1.0†

* $P < 0.05$ vs. WR_1.
$^{\#}$ $P < 0.05$ vs. WR_2.
§ $P < 0.01$ vs. HA.
† $P < 0.05$ vs. HA.

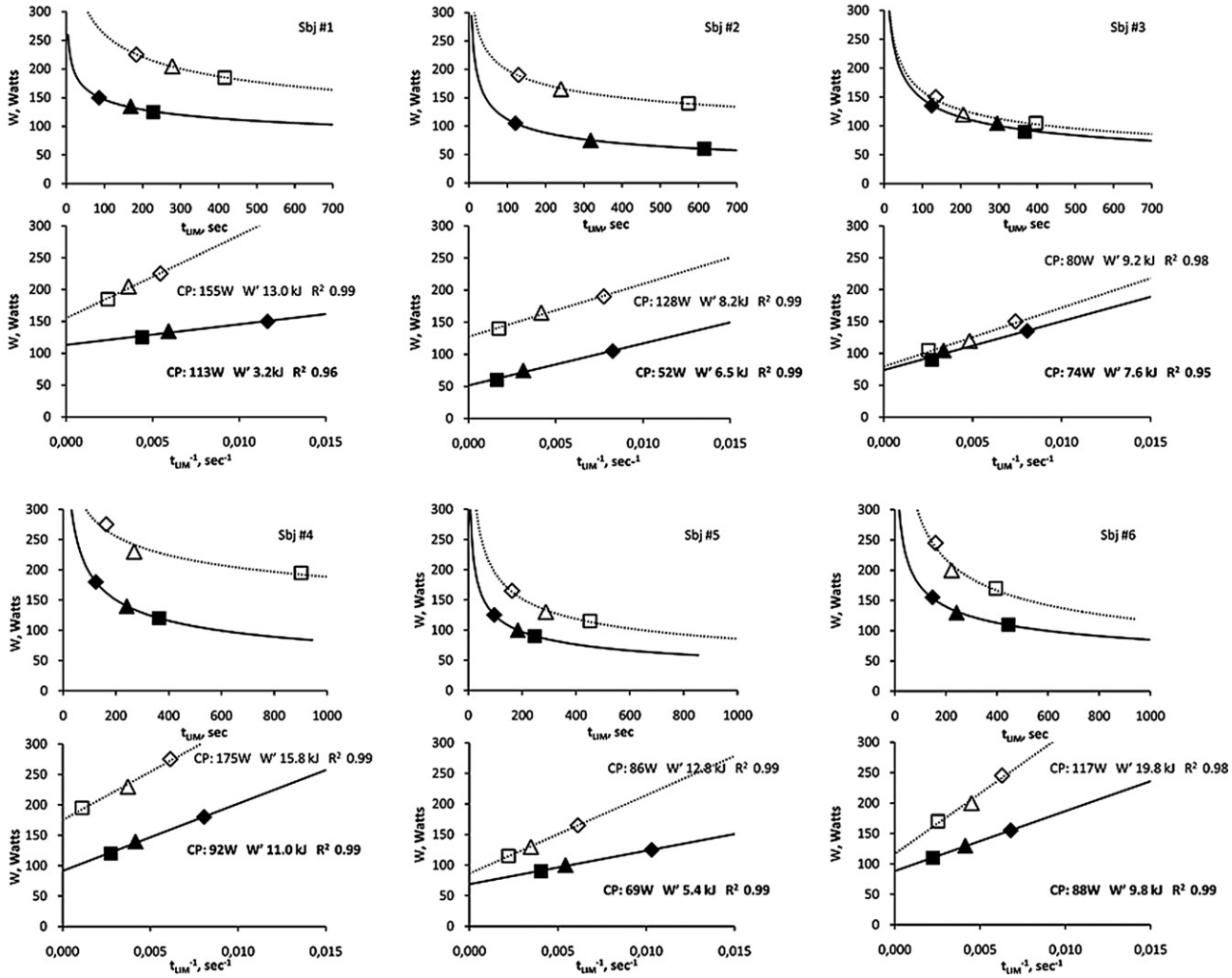

Fig. 1. Individual WR–t_{LIM} (above) and WR–t_{LIM}^{-1} (below) relationships for all subjects at sea level (open symbols, thin text) and high altitude (closed symbols, bold text). Linear regression on the WR–t_{LIM}^{-1} relationship yields CP (y-intercept) and W' (slope).

linear regression of ΔCP on ΔGET having a slope not significantly different from unity (1.134 ± 0.251; $P = 0.011$) and a ΔCP-intercept not significantly different from zero (-1.25 ± 11.2; $P = 0.916$) (Fig. 4, left panel). In contrast, there was no correlation between the corresponding reductions in W' and those of GET (Fig. 4, right panel).

4. Discussion

In this first study to characterize the power–duration (WR–t_{LIM}) relationship for high-intensity constant-WR exercise following ascent to HA (5050 m) in lowlanders (sufficient to lower SpO_2 at end-exercise to slightly above 70%: Tables 2 and 3), we demonstrated the relationship to be well-described by a hyperbolic function after 14 days at HA, as has been extensively documented at SL. The impaired exercise tolerance at HA in this intensity domain was the result of reductions in the associated parameters, CP and W'.

4.1. Decreased critical power

Our demonstration of a reduced CP on ascent to HA, in conjunction with reductions in $\dot{V}_{O_2\,max}$, GET, and peak O_2 pulse (Figs. 1 and 2; Tables 2 and 3) is consistent with CP reflecting a limiting rate of aerobic energy-pool reconstitution (Moritani et al., 1981; Whipp et al., 1982; Poole et al., 1988), and coheres with the effects of acute hypoxic exposures at SL (Moritani et al., 1981; Whipp et al., 1982). Further support for this view is that CP was highly correlated with θ_L both at SL and at HA - although it should be noted that validation of the non-invasive GET estimation against directly-measured arterial [L^-] at HA has not yet formally been undertaken. Indeed, the HA-related reduction in CP was essentially equal to that of the WR-equivalent of GET. The likely cause of the reduced CP would therefore seem to favor a reduced O_2 availability to and/or utilization by the exercising muscles, rather than impaired pulmonary gas exchange. For example, while acute simulated HA exposures of similar equivalent height to the present study have been reported to result in a widened alveolar-to-arterial PO_2 difference during exercise consequent to increased ventilation–perfusion inequality and diffusion limitation (e.g. Wagner et al., 1986), later studies following a 2-week altitude exposure at 3800 m arrived at rather different conclusions. The period of acclimatization returned the alveolar-to-arterial PO_2 difference to SL values (Bebout et al., 1989) which, as $\dot{Q}_T$ at a given $\dot{V}_{O_2}$ was lower at HA, was proposed to reflect the influence of a longer pulmonary capillary vascular transit time; ventilation–perfusion status was unchanged, however.

With regard to the possibility of impaired convective O_2 transport into the exercising muscles, arterial O_2 delivery and mean muscle end-capillary PO_2 at maximal exercise have been reported to be reduced following a 2-week HA exposure at 4100 m, although no submaximal responses were measured (Lundby et al.,

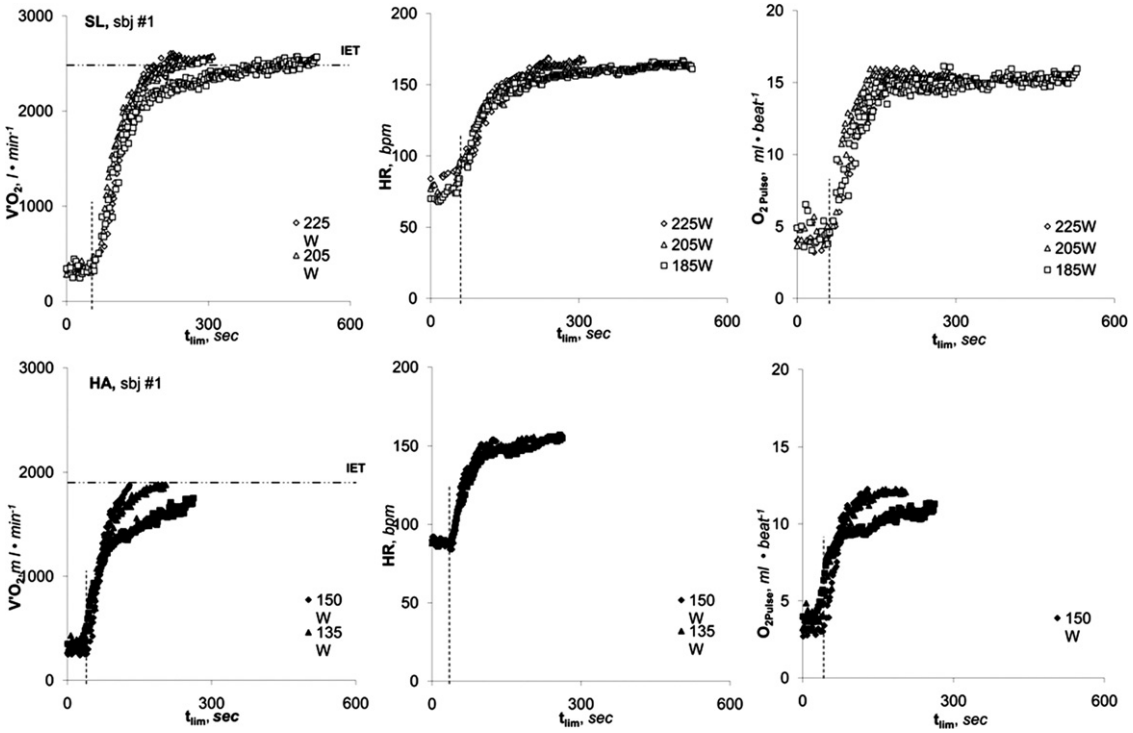

Fig. 2. $\dot{V}_{O_2}$, HR and O_2 pulse response profiles for a representative subject for three constant-WR tests performed to the limit of tolerance at sea level (open symbols) and high altitude (closed symbols) from unloaded pedaling. The vertical dashed line indicates exercise onset. IET indicates $\dot{V}_{O_{2\,peak}}$ from ramp tests. WR_1: 185 W (square); WR_2: 205 W (triangle); WR_3: 225 W (circle).

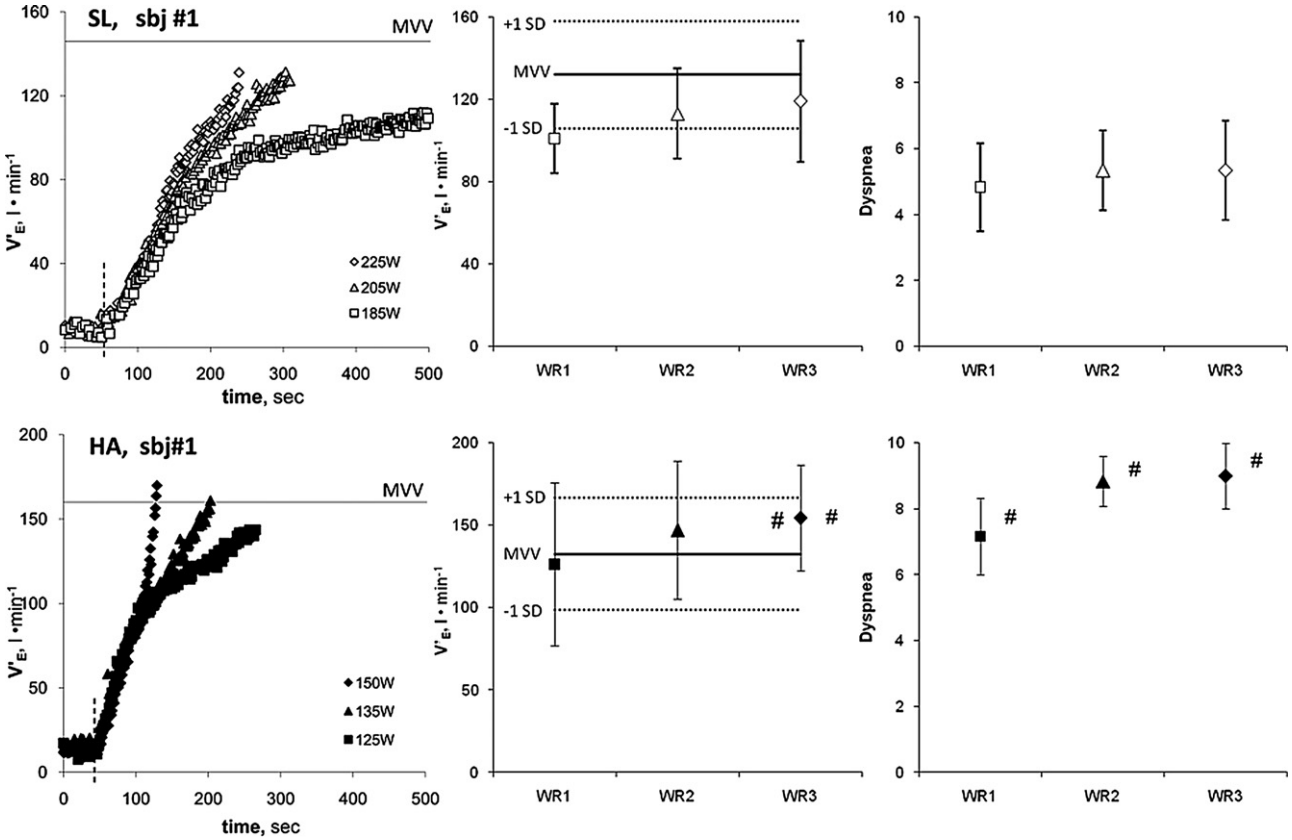

Fig. 3. Left panel: $\dot{V}_E$ response profiles for a representative subject for three constant-WR tests performed to the limit of tolerance at sea level (open symbols) and high altitude (closed symbols) from unloaded pedaling. The vertical dashed line indicates exercise onset. Center and right panels: Group-mean end-exercise responses for $\dot{V}_E$ and dyspnea for the three constant-WR tests (WR_1, WR_2 and WR_3).

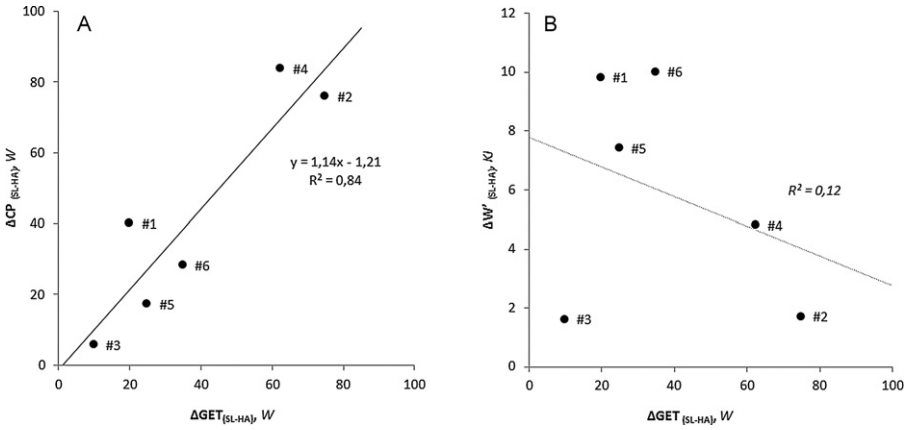

Fig. 4. Left panel: individual reductions in CP at HA, relative to SL ($\Delta CP_{(SL\text{-}HA)}$) as a function of the corresponding individual reductions in GET at HA ($\Delta GET_{(SL\text{-}HA)}$). Right panel: individual reductions in W' at HA, relative to SL ($\Delta W'_{(SL\text{-}HA)}$) as a function of the corresponding Individual reductions in GET at HA ($\Delta GET_{(SL\text{-}HA)}$). Lines are best-fit linear regressions.

2006). And, in our study, the already-low resting SpO_2 fell further throughout both the incremental and the constant-WR tests (Tables 2 and 3). The HA-related increase in hematocrit that we observed was presumably consequent to plasma volume decline and possibly also an increasing red cell mass (although the latter is generally agreed to be of far slower onset), coupled with hypoxia-induced hyperventilation (Tables 1–3, Fig. 3). This would be expected to provide some measure of compensation for the initially reduced arterial O_2 content (CaO_2) (reviewed in Grover et al., 1986; Schoene, 2000). However, this could well have been offset by a lower $\dot{Q}_T$ and $\dot{Q}_M$ at the HA CP, compared to the SL CP, because of the lower WR and presumably $\dot{V}_{O_2}$. For example, $\dot{Q}_T$ at a given submaximal WR (or $\dot{V}_{O_2}$) has been shown to be lower at HA (after 10 days at 4350 m) than at SL, largely consequent to a reduced SV despite HR still tending to be slightly elevated (Vogel et al., 1974) (our demonstration of a reduced peak HR is consistent with this: Tables 2 and 3, Fig. 2); it is only at substantially higher altitudes that the submaximal $\dot{Q}_T - \dot{V}_{O_2}$ relationship returns to the SL characteristic (Reeves, 2002). Also, a smaller fraction of $\dot{Q}_T$ appears to be preferentially distributed to the working muscles at HA than at SL (Calbet et al., 2003) which, interestingly, might reflect greater perfusion demands of the respiratory muscles at HA because of the higher $\dot{V}_E$'s (Table 3; Fig. 3) (Dempsey et al., 2006). Finally, Lundby et al. (2004) have demonstrated no increase in the expression of either hypoxia inducible factor 1a or vascular endothelial growth factor mRNA in muscle after 2 week at a similar altitude to our investigation, and no increase in capillary-to-muscle fibre ratio after 8 week.

We therefore speculate that $\dot{Q}_M$ at CP was lower at HA than at SL and therefore that arterial O_2 delivery was also lower. However, we were unable to incorporate these technically demanding measurements into constant-WR tests at CP in order to test this proposal. How muscle mitochondrial PO_2 at CP is affected by the HA ascent also can only speculated upon. It has been argued, from studies at a slightly lower altitude (4100 m) than the present study (Wagner et al., 1986; Lundby et al., 2006), that O_2 diffusive conductance may be more important than convective O_2 transport in limiting maximal performance; whether this is also the case at CP, with its lower $\dot{V}_{O_2}$, can only be speculated on. Regardless, it seems unlikely that oxidative enzyme activities are affected (Young et al., 1984; Mizuno et al., 2008).

It is of interest that the fundamental (or phase II) kinetics of the $\dot{V}_{O_2}$ response to constant-WR exercise has been reported to be slowed with acute normobaric hypoxia below GET (Murphy et al., 1989) and above GET (Engelen et al., 1986). Were this to occur also at HA, it would imply an increase in the magnitude of the O_2 deficit at a given WR, and, depending on how the "slow component" of the $\dot{V}_{O_2}$ response were to be influenced by the HA exposure, this would have the potential to constrain the range of WRs that could be accommodated by the limiting aerobic energy-pool reconstitution rate without incurring a progressively increasing anaerobic contribution (Moritani et al., 1981; Whipp et al., 1982; Poole et al., 1988). However, the single constant-WR transitions used in the present study precluded any formal kinetic analysis of the $\dot{V}_{O_2}$ responses, because of sub-optimal signal:noise considerations compounded by complexities related to the influence of the $\dot{V}_{O_2}$ slow component and the exact value of the asymptotic $\dot{V}_{O_2}$ value at these supra-CP WRs (Whipp and Rossiter, 2005).

4.2. Decreased W'

Our demonstration of a reduced W' at HA (Fig. 1) is at odds with the effects of acute hypoxic exposures at SL (Moritani et al., 1981; Whipp et al., 1982), which suggest that some sequellae related to acclimatization may be involved which would not be evident with acute hypoxia at SL. With regard to anaerobic energy stores, it is likely that O_2 stores (e.g. in muscle and venous blood) were lower at HA consequent to the hypoxic conditions, although we were not able to quantify this. As muscle–venous O_2 content (Cv,MO_2) changes can reasonably be assumed to dominate the "anaerobic" O_2 stores, the stores contribution to W' can be viewed as the extent to which these stores become depleted above CP: i.e. the difference between the product of Cv,MO_2 and the effective muscle–venous volume at CP and at maximal exercise (all supra-CP WRs leading to $\dot{V}_{O_2\,max}$). The study of Lundby et al. (2006) provides some insight in this context: from their primary $\dot{V}_{O_2}$, $\dot{Q}_M$ and arterial O_2 delivery data, it is evident that Cv,MO_2 at maximal exercise is lower at HA than at SL ($\sim$1.5 ml 100 ml^{-1} vs. $\sim$2.0 ml 100 ml^{-1}). Even were simplifying assumptions to be made regarding the effective venous volume, the lack of information about the corresponding Cv,MO_2 values at CP hinders any further analysis, however.

In contrast, muscle glycogen stores and their breakdown during exhausting exercise are not compromised for comparable HA exposures (van Hall et al., 2009); neither is the activity of key glycolytic enzymes (hexokinase, glycogen phosphorylase) affected (Young et al., 1984). Similarly, intramuscular PCr stores have been reported to be depleted to a similar extent for exhaustive exercise at HA as at SL (van Hall et al., 2009). However, were the associated $\dot{V}_{O_2}$ kinetics to be slower (see above), this suggests (based on ^{31}P-NMR measurements) a correspondingly slowed time-course of [PCr] depletion and therefore a more marked [PCr] fall (Rossiter et al., 2002); a

contention which is supported by the observations of Haseler et al. (1998) for normobaric hypoxic plantar flexion exercise.

An involvement of fatigue-related metabolite accumulation should also be considered. Muscle [Pi] during exhausting exercise at HA has been reported to be no different from SL, for short-duration exposures (van Hall et al., 2009). However, interpreting the consequences of the lower end-exercise arterial [L^-] (e.g. Tables 2 and 3) (Reeves et al., 1992; but c.f. van Hall et al., 2009) and muscle [L^-] at HA (Brooks et al., 1998; but c.f. ref. van Hall et al., 2009) is challenging for considerations of W'. That is, it has been demonstrated that, for submaximal exercise following ascent to HA (as at SL), exercising muscles simultaneously produce and oxidise L^-, with a reduced L^- clearance suggesting that other tissues contribute to the elevated arterial [L^-] (Brooks et al., 1998). Whether this is the case also for fatiguing exercise has not, to our knowledge, been explored.

The consequences for H^+ status in our study are also largely uncertain. Although the respiratory alkalosis that develops on immediate HA ascent (e.g. Tables 2 and 3) would be expected to temper the deleterious consequences of developing acidosis in the exercising muscles, subsequent renal compensation compromises the bicarbonate-related buffer capacity (Cerretelli and Samaja, 2003). However, the extent to which whole-body buffer capacity might be affected in our study is uncertain.

One factor that has the potential to influence W' at HA is exercising-muscle mass, a significant correlation having been reported between W' for cycle ergometry and thigh circumference (Miura et al., 2002). A further factor relates to muscle activation. It has been reported that Group III and IV muscle fiber discharge is reduced in experimental animals, both in acute and chronic hypoxia (e.g. Dousset et al., 2003). Others, however, have argued for an increase (e.g. Hill et al., 1992; Amann and Kayser, 2009). The extent to which such influences might impact on W' (or CP) is unclear, however.

Altitude exposure is well known to lead to weight loss, consequent to factors such as loss of appetite, loss of body water, increased basal metabolic rate, increased activity levels and sarcopenia. However, as our subjects showed no reduction in body mass at HA (70.8 ± 10.7 kg vs. 69.7 ± 11.5 kg at SL), it seems unlikely that an altitude-related loss of exercising-muscle mass is a significant contributor to the reduced W'.

A component of central fatigue is possible, however. That is, for comparable HA exposures, exercise tolerance was improved by breathing hyperoxic inspirates; an effect that was considered to be related to the improved cerebral reoxygenation (reviewed in Amann and Kayser, 2009).

4.3. Ventilatory limitation and dyspneic sensation

What is evident from our study is that $\dot{V}_{E_{peak}}$ for both the incremental and constant-WR tests at HA was likely to be contributing to the limitation, i.e. with little or no breathing reserve remaining, such that t_{LIM} at a given supra-CP WR was prematurely truncated. This clearly contrasted with the SL findings (Tables 2 and 3; Fig. 3). Arterial hypoxemia, acting at the carotid chemoreceptors, is likely to be a major contributor to the exaggerated $\dot{V}_E$ responses we observed at HA. This raises the issue that a significant contributor to exercise intolerance above CP could be the associated intensity of dyspneic sensation, which in contrast to leg fatigue, attained limiting values at HA (Tables 2 and 3; Fig. 3). In this context, observations from the 2004 Everest-K2 Italian Expedition are of interest. That is, those climbers who reached the summit without oxygen evidenced a lower resting $\dot{V}_E$ and hypoxic ventilatory responsiveness (HVR, $\Delta\dot{V}_E - \Delta SpO_2$) during acclimatization (Bernardi et al., 2006); it being proposed that a less sensitive HVR at HA might increase BR and therefore reduce dyspnea to allow sustainable $\dot{V}_E$'s in the extreme hypoxia at the summit. It should be noted that the observations of Bernardi and coworkers are in contrast those of Schoene et al. (1984) who observed a better climbing performance in those subjects with a higher HVR at HA. However, the techniques used for estimating HVR at HA in these two studies were different: Schoene et al. using Dejours-type transient N_2 and O_2 tests, while Bernardi et al. used the more traditional progressive isocapnic hypoxia approach. The Dejours approach is designed, because of its transient nature, to "isolate" the primary peripheral chemoreceptor component of the hypoxic $\dot{V}_E$ response, whereas the sustained progressive exposure allows time for additional influences of the altered PO_2 on $\dot{V}_E$ to be expressed (e.g. CNS actions on pH via the hemoglobin dissociation curve and cerebral blood flow) (for discussion, see Ward, 1994). A further point to be considered is that the "high performing" subjects studied by Bernardi et al. also evidenced a slow, deep pattern of breathing which could have contributed to the reported improvement in pulmonary gas exchange efficiency in these subjects. Even so, there is not a ready explanation for the observed differences. The factors contributing to the dyspnea at HA are likely to be complex, however, involving also factors such as respiratory work and respiratory muscle fatigue (Cilbella et al., 1995) and an amplifying effect of the hypoxic condition (Ward and Whipp, 1989).

Finally, there may also be a contribution to the compromised exercise tolerance above CP at HA, consequent to the possibility that the demands of the respiratory muscles at these high WRs diverted a proportion of the perfusion away from the involved locomotor muscles (Calbet et al., 2003), predisposing to locomotor muscle fatigue (reviewed in Dempsey et al., 2006). End-exercise $\dot{V}_E$ clearly encroached on BR, implying respiratory flow limitation (Table 3; Fig. 3).

4.4. Conclusion

The reduction in CP on acute ascent to HA (5050 m) is consistent with a reduced O_2 availability to the exercising muscle. In contrast, the associated reduction of W' is less easily explained, but could be the consequence, at least in part, of reduced muscle–venous O_2 storage and limiting levels of dyspnea consequent to ventilatory limitation.

Disclosure

Authors G. Valli, A. Cogo, C Passino, D. Bonardi, G. Morici, V. Fasano, M. Agnesi, L. Bernardi, A.M. Ferrazza, S.A. Ward and P. Palange have no conflicts of interest or financial ties to disclose.

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