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## Interleukin-6 response to exercise during acute and chronic hypoxia

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**Abstract** Prolonged exercise is associated with increased plasma levels of the cytokine interleukin-6 (IL-6). Both circulating catecholamine levels and exercise intensity have been related to the exercise-derived IL-6. During hypoxia and acclimatization, changes in sympathetic activity is seen, and also a given workload becomes more intense in hypoxia. Therefore, hypoxia offers a unique opportunity to study the effect of catecholamines and intensity on exercise-derived IL-6. In the present study, eight Danish sea-level residents performed 60 min of cycle ergometer exercise at sea level (SL) (154 W, 45% maximal  $\dot{V}O_2$ max), in acute (AH) and chronic hypoxia (CH), at the same absolute (<sub>abs</sub>) ( $AH_{abs}$  = 154 W, 54%  $\dot{V}O_2$ max;  $CH_{abs}$  = 154 W, 59%  $\dot{V}O_2$ max) and same relative (<sub>rel</sub>) ( $AH_{rel}$  = 130 W, 46%  $\dot{V}O_2$ max;  $CH_{rel}$  = 120 W, 44%  $\dot{V}O_2$ max) workload. We hypothesized that the IL-6 response to exercise at the same absolute workload would be augmented during hypoxia compared with sea level, and that these changes would not correlate with changes in catecholamines. In  $AH_{abs}$  (2.35 pg·ml<sup>-1</sup>) and  $CH_{abs}$  (3.34 pg·ml<sup>-1</sup>) the IL-6 response to exercise was augmented ( $p < 0.05$ ) compared with that at sea level (0.78·ml<sup>-1</sup>). In addition, after 60 min of bicycling at sea level,  $AH_{rel}$  (1.02 pg·ml<sup>-1</sup>) and  $CH_{rel}$  (1.31 pg·ml<sup>-1</sup>) resulted in similar IL-6 responses. The augmented IL-6 response during  $AH_{abs}$  and  $CH_{abs}$  did not match changes in circulating catecholamine levels when comparing all trials. We conclude that the plasma IL-6 concentration during exercise in hypoxia is

intensity dependent, and that factors other than catecholamine levels are more important for its regulation.

**Keywords** Absolute · Altitude · Catecholamines  
Exercise · Relative

### Introduction

Prolonged exercise is associated with increased plasma levels of the cytokine interleukin-6 (IL-6) (Pedersen et al. 2001). It has been demonstrated that contracting skeletal muscle releases IL-6, and that this release can account for the systemic IL-6 increase observed during exercise (Steensberg et al. 2000). In addition, brain (Nybo et al. 2002) and peritendon tissue (Langberg et al. 2002) release small amounts of IL-6 during exercise. At rest fat tissue is responsible for up to 30% of the plasma IL-6 (Mohamed-Ali et al. 1997), and it was recently demonstrated that this release was augmented post-exercise, whereas it was not increased during exercise (Lyngsø et al. 2002). The plasma IL-6 concentration during exercise has previously been correlated with the circulating catecholamine concentration (DeRijk et al. 1994; Mazzeo et al. 2000b; Papanicolaou et al. 1996; van Gool et al. 1990), but a recent publication demonstrated that epinephrine infusion, reaching exercise epinephrine levels, only resulted in a fivefold increase in plasma IL-6 compared with a 29-fold induction during exercise (Steensberg et al. 2001a). In another study (Steensberg et al. 2000b) IL-6 differences across an exercising and a resting leg were measured, and only the exercising leg released IL-6 in spite of the fact that both legs experienced the same catecholamine concentration. In contrast, one recent study found that an  $\alpha$ -adrenergic blocker blunted the plasma IL-6 response to exercise at sea level and during hypoxia (Mazzeo et al. 2000b). Humans exposed to hypoxia experience changes in sympathetic activity with acclimatization (Mazzeo et al. 1991, 1995) and the influence of catecholamines on IL-6 concentrations can thus favourably be investigated in a

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hypoxic environment. Moreover, resting epinephrine is elevated after 2–3 days of hypoxic exposure, and thereafter gradually decreases towards sea level values, whereas a rise in norepinephrine is reported to occur more gradually, and not to return to sea level values with acclimatization (Mazzeo et al. 1991, 1995, 1998, 2000a, 2000b). When using hypoxia to study the role of catecholamines in exercise-induced changes in plasma IL-6, it must be taken into account that maximal  $\dot{V}O_2$  consumption ( $\dot{V}O_{2\max}$ ) decreases with increasing altitude, and therefore a workload performed at sea level will be relatively more intense when performed at altitude (Dill et al. 1931). This is important because studies have demonstrated that the IL-6 response to exercise is dependent on the exercise intensity. Moreover, during a marathon race a correlation between the intensity of exercise and the increase in plasma IL-6 was found (Ostrowsky et al. 2000). In support, an increase in plasma-IL-6 was demonstrated after only 6 min of intense rowing exercise (Nielsen et al. 1996), whereas exercise protocols using less intense exercise did not find an increase until 30 min of exercise (Starkie et al. 2001a, 2001b).

Also hypoxia per se is associated with an increase in plasma IL-6 in most studies (Hartmann et al. 2000; Klausen et al. 1997; Mazzeo et al. 2000b), whereas one study did not find an effect (Pavlicek et al. 2000). The increased sympathetic activity during hypoxia has been associated with the increase in plasma IL-6 (Mazzeo et al. 2000b). In addition, the development of high altitude pulmonary edema (HAPE) seems to further elevate plasma IL-6 (Maggiorini et al. 2000).

The purpose of the present study was to examine the effect of catecholamines and exercise intensity on plasma IL-6 concentrations during exercise using hypoxia as a model. We hypothesized that exercising at the same relative workload at sea level and during acute and chronic hypoxia would result in the same increases in plasma IL-6, whereas exercise at the same absolute workload would result in an increased IL-6 response during acute and chronic hypoxia compared with sea level. Furthermore, we hypothesized that the IL-6 response to exercise would be unaffected by differences in catecholamines.

## Methods

### Subjects

Eight trained (physical education college students) sea-level residents (six males and two females) [ $\dot{V}O_{2\max} = 4.2$  (0.3)  $l \cdot \text{min}^{-1}$ , height = 186 (2) cm, weight = 78 (3) kg, age = 25 (1) year, mean (SD)] took part in this study. All subjects gave their informed consent before participation. The research protocol was approved by the Ethical Committee of Copenhagen and Frederiksberg communities (KF11-050/01), and in accordance with the declaration of Helsinki II. This study was part of a large high altitude expedition to the Andes mountains of Bolivia, and the methods are described in detail elsewhere (Lundby and van Hall 2002).

### Acclimatization

The subjects were flown from Copenhagen (sea level) to La Paz (Bolivia), and spent two nights at 3800 m (Fig. 1). Hereafter they lived in the higher part of La Paz at 4100 m during the remaining time of the study. To keep a similar activity level as in Denmark, subjects were encouraged to perform outdoor activities such as cycling, soccer, basketball, hiking, and rock climbing. Food supplies were ample. All testing was performed in a nearby hospital.

### Preliminary testing of subjects

$\dot{V}O_{2\max}$  was determined by the use of a progressive exercise protocol on a cycle ergometer (Monark 824E, Sweden). Exercise started with a 15-min warm-up period of 100 W at 80 rpm, after which the workload was increased by 40 W every 2 min 30 s until exhaustion.  $\dot{V}O_{2\max}$  was defined as the value obtained when an increase in exercise intensity of 40 W did not result in any further increase in  $\dot{V}O_2$  uptake ( $\dot{V}O_{2\max}$ ; i.e. a decrease, no change, or an increase  $< 150 \text{ ml} \cdot \text{min}^{-1}$ ). This procedure resulted in a plateau in  $\dot{V}O_2$  in seven out of eight subjects; the last subject indicated that the exercise protocol elicited maximal exercise in secondary parameters, i.e. high heart rate, lactate, and respiratory exchange ratio (RER) values. Measurements were done on three separate occasions: (1) at sea level, (2) at sea level while inducing acute hypoxia by breathing 12.4%  $O_2$  in  $N_2$  (equivalent to 4100 m) from a Douglas bag (the subjects started to breathe the hypoxic gas mixture 10 min before the start of exercise) and (3) after approximately 4 weeks at 4100 m. To accustom the subjects to the exercise protocol, each subject completed the exercise protocol at sea level and in acute hypoxia before the actual maximal exercise test.

### Testing protocol

All subjects were investigated on five separate occasions and performed 60 min of ergometer cycle exercise at 50% of sea level  $\dot{V}O_{2\max}$  at sea level (SL), and again at the same absolute workload when acutely exposed to 4100 m ( $AH_{\text{abs}}$ ), and after 3.5–4.5 weeks of exposure to 4100 m ( $CH_{\text{abs}}$ ). Similarly they were investigated at 50% of acute and chronic hypoxic  $\dot{V}O_{2\max}$  in acute ( $AH_{\text{rel}}$ ) and chronic hypoxia ( $CH_{\text{rel}}$ ), i.e. eliciting the same relative work intensity as at sea level. Acute hypoxia was induced

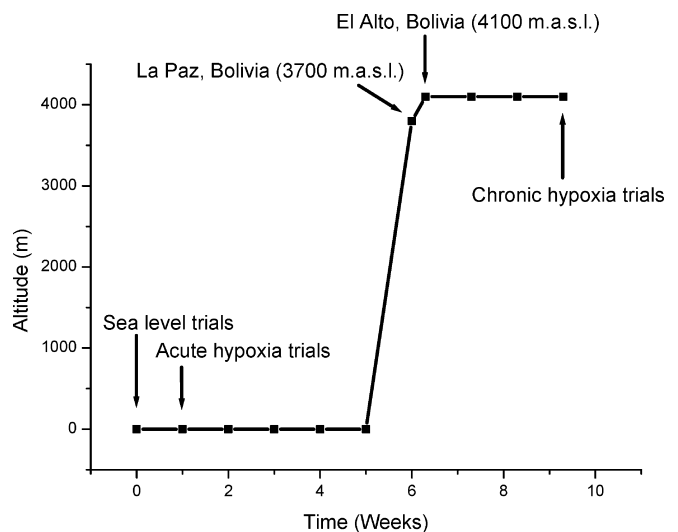


Fig. 1 Acclimatization scheme for the experiments

by letting the subjects breath 12.4% O<sub>2</sub> in N<sub>2</sub> from a Douglas bag, and was initiated 10 min before rest measurements. Chronic hypoxic measurements were completed in hospital settings at 4100 m in La Paz, Bolivia. The sea level and acute hypoxic trials were initiated in March in Copenhagen, starting with the sea level trials. The acute trials were conducted in random order. The chronic hypoxic trials were conducted randomly between days 24 and 32 at altitude, the average being 4 weeks. All trials were at least 4 days apart. Resting samples were also obtained after 8 weeks at 4100 m. On each occasion (except at 8 weeks) the subjects reported to the laboratory 12 h post-absorptive and were fed 0.7 g cornflakes/kg body weight with an unlimited amount of skimmed milk. They were allowed to drink water ad libitum. Exercise started exactly 2 h after finishing the meal. Then, 45 min before the start of exercise, a 20 G catheter was inserted in an antecubital vein, after which the subjects lay down for 15 min before measurements began. Pulmonary gas exchange, arterial oxygen saturation, and blood samples were taken at rest and after 15, 30, 45 and 60 min of exercise.

### Measurements

The same equipment was used in all experimental trials.  $\dot{V}O_2$ , CO<sub>2</sub> output ( $\dot{V}CO_2$ ), and minute ventilation ( $\dot{V}_E$ ) were measured on-line by the use of standard open-circuit techniques (Oxygen Analyzer S-3A/I, Ametek, USA; LB-2, Beckman, USA; VRDC/HC-1, Parvo Medics, USA). Before use, the system was calibrated against two gas mixtures previously measured by the micro Scholander method. Flow was calibrated with a 3 l syringe. Pulmonary gas exchange was measured over a period of 5 min on each measure point.

Blood samples obtained for determination of IL-6 were drawn over 5 s in 5 ml syringes (Becton Dickinson, Spain) and transferred to a 10 ml centrifuge tube containing EDTA and immediately centrifuged at 5000 rpm for 5 min at 4°C. The plasma was transferred to Eppendorf tubes and immediately stored at -50°C for later analysis. IL-6 was determined via commercially available high sensitivity ELISA kit (R and D systems, Minneapolis, Minn., USA) in Denmark. From the same sample also free fatty acids (FFA), glycerol, glucose, and lactate were analysed, and the results are published elsewhere (Lunbby and van Hall 2002).

Blood samples for analysis of epinephrine (E) and norepinephrine (NE) were obtained and stored in the same manner as above, but transferred to centrifuge tubes containing EGTA instead of EDTA (Lunbby and van Hall 2002). The analysis was performed by high performance liquid chromatography (HPLC) (Waters, Millipore, Mass., USA). The 15, 30, 45, and 60 min sample points were averaged. Oxygen saturation was monitored throughout the protocol by a pulse oxymeter (Datex, Instrumentarium, Finland) with the sensor attached to the fingertip of the first or second finger. Blood samples were transported from Bolivia to Denmark in dry-ice-filled containers.

### Statistics

All data are expressed as means (SE), except when stated differently. IL-6 data were log transformed to obtain a normal distribution. Statistical difference was tested by one-way ANOVA. Pair-wise differences were identified using Newman-Keuls post hoc procedure. The level of significance was set at  $p < 0.05$ .

## Results

### Maximal exercise tests

At SL maximal workload was 356 (23) W and elicited a  $\dot{V}O_2$  of 4.2 (0.3) l·min<sup>-1</sup> and a heart rate (HR) of 187 (8) beats·min<sup>-1</sup>. Compared with SL  $\dot{V}O_2$ max decreased ( $p < 0.05$ ) to 3.5 (0.2) l·min<sup>-1</sup> in acute hypoxia.  $W_{max}$  and  $HR_{max}$  decreased ( $p < 0.05$ ) accordingly to 281 (19) W and 176 (8) beats·min<sup>-1</sup>. Compared with acute hypoxia acclimatization had no further effect on the above parameters, the values being 3.2 (0.2) l·min<sup>-1</sup>, 254 (17) W, and 177 (7) beats·min<sup>-1</sup>, respectively during chronic hypoxia.

### The 60-min cycle exercise test

At sea level the 60 min of cycle exercise elicited on average 45% of  $\dot{V}O_2$ max (Table 1). In  $AH_{abs}$  and  $CH_{abs}$  this workload corresponded to 54 and 59% of  $\dot{V}O_2$ max, respectively. When correcting the workload in  $AH_{rel}$  and  $CH_{rel}$  for the decrease in  $\dot{V}O_2$ max, the exercise intensity elicited 46 and 44% of the corresponding  $\dot{V}O_2$ max. The difference in exercise intensities also elicited a higher plasma lactate and HR during  $AH_{abs}$  and  $CH_{abs}$ , but not during  $AH_{rel}$  and  $CH_{rel}$ .

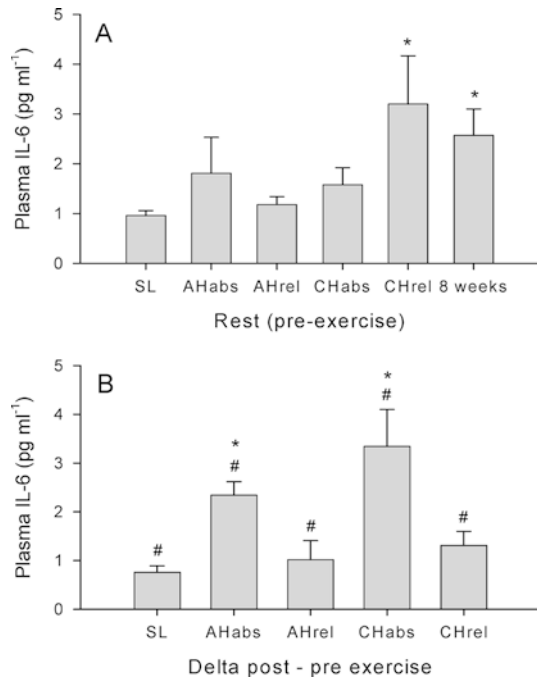
### Plasma IL-6 and catecholamines

The resting plasma IL-6 at sea level was 0.96 (0.09) pg·ml<sup>-1</sup> (Fig. 2A). The resting plasma IL-6 at acute hypoxia was not significantly different from that at sea level, being respectively 1.8 (0.72) and 1.18 (0.16) pg·ml<sup>-1</sup> before the two exercise trials. In contrast, the plasma IL-6 was augmented ( $p < 0.05$ ) at rest in the subjects before

**Table 1** Average 60-min exercise values at sea level (SL), acute (AH) and chronic (CH) hypoxia. Exercise workload (W), oxygen uptake ( $\dot{V}O_2$ , l·min<sup>-1</sup>), percentage of  $\dot{V}O_2$ max (% $\dot{V}O_2$ max, %), plasma lactate (mmol·l<sup>-1</sup>), heart rate (HR, beats·min<sup>-1</sup>), oxygen saturation (Sat, %). Values are mean (SD);  $n = 8$  in each trial

Parameter	Workload		$\dot{V}O_2$		% $\dot{V}O_2$ max		Lactate		HR		Sat	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SL	154	13	1.9	0.1	45	1	1.4	0.1	129	6	97	0
$AH_{rel}$	130*	15	1.6*	0.1	46	2	1.7	0.3	129	7	80*	1
$AH_{abs}$	154	13	1.9	0.1	54*	2	3.7*	0.8	152*	5	80*	1
$CH_{rel}$	120*	21	1.4*	0.2	44	3	1.9*	0.2	132	5	85 <sup>#</sup>	1
$CH_{abs}$	154	13	1.9	0.1	59*	2	3.4*	0.5	153*	7	84 <sup>#</sup>	1

Significant differences: \* $p < 0.05$  compared with SL, <sup>#</sup> $p < 0.05$  compared with AH



**Fig. 2** **A** Plasma interleukin-6 (*IL-6*) at rest at sea level, acute and chronic hypoxia. **B** Delta plasma *IL-6* in response to 60 min of exercise at sea level, acute and chronic hypoxia. Values are mean (SE);  $n=8$  in each trial. Significant differences: \* $p < 0.05$  compared with the other experimental trials, # $p < 0.05$  compared with rest

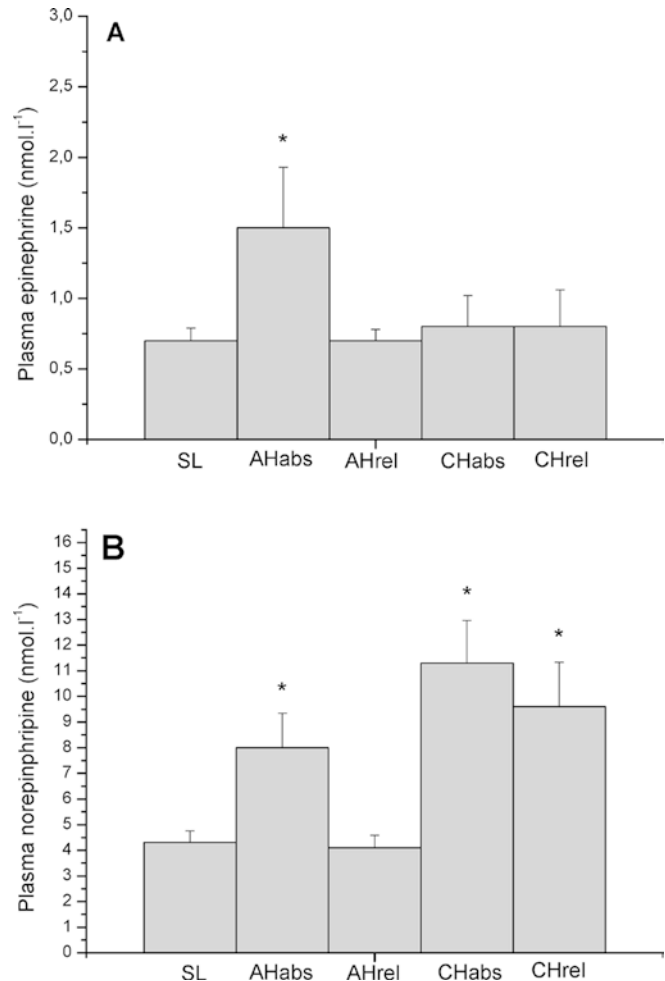
performing the relative workload exercise test at chronic hypoxia, but not before performing the absolute workload test, being 3.2 (0.98) and 1.5 (0.3)  $\text{pg}\cdot\text{ml}^{-1}$  respectively. This was the case even though the two trials were performed in a randomized order. After 8 weeks at high altitude the plasma *IL-6* was significantly elevated ( $p < 0.05$ ) compared to sea level, being 2.57 (0.54)  $\text{pg}\cdot\text{ml}^{-1}$ .

In order to present the exercise data as simply as possible, the plasma-derived parameters obtained after 15, 30, 45, and 60 min of exercise are all averaged to one exercise value, i.e. one exercise value for each experimental setting. Plasma *IL-6* increased in response to exercise in all trials (Fig. 2B). The exercise-induced change in plasma *IL-6* was 2.35 (0.28) and 3.34 (0.76)  $\text{pg}\cdot\text{ml}^{-1}$  during  $\text{AH}_{\text{abs}}$  and  $\text{CH}_{\text{abs}}$  respectively, this increase being augmented ( $p < 0.05$ ) compared to exercise at sea level,  $\text{AH}_{\text{rel}}$ , and  $\text{CH}_{\text{rel}}$ . There were no differences between changes in plasma *IL-6* during exercise at sea level,  $\text{AH}_{\text{rel}}$  and  $\text{CH}_{\text{rel}}$ , the increases being 0.78 (0.13), 1.02 (0.39) and 1.31 (0.29)  $\text{pg}\cdot\text{ml}^{-1}$  respectively.

Plasma epinephrine increased ( $p < 0.05$ ) approximately twofold during exercise in  $\text{AH}_{\text{abs}}$  compared with all other trials (Fig. 3). Norepinephrine was elevated ( $p < 0.05$ ) during exercise at  $\text{AH}_{\text{abs}}$ ,  $\text{CH}_{\text{abs}}$  and  $\text{CH}_{\text{rel}}$  by 186–263% compared to exercise in SL and  $\text{AH}_{\text{rel}}$ .

## Discussion

The major findings in this study are that: (1) submaximal exercise performed at the same relative percent of



**Fig. 3** **A** Average plasma epinephrine concentrations ( $\text{nmol}\cdot\text{l}^{-1}$ ), and **B** average plasma norepinephrine concentrations ( $\text{nmol}\cdot\text{l}^{-1}$ ) during 60 min of exercise at sea level, acute and chronic hypoxia. Values are mean (SE);  $n=8$  in each trial. Significant differences: \* $p < 0.05$  compared with the other experimental trials

$\dot{V}\text{O}_2\text{max}$  in acute and chronic hypoxia, as compared to sea level, induces similar increases in plasma *IL-6* concentrations; and (2) exercise in acute and chronic hypoxia at the same absolute workload as at sea level further increased the plasma *IL-6* concentration compared to sea level. In addition, the results support the idea that catecholamines do not play a major role in the induction of the *IL-6* release during exercise.

The limitations of the present study include the use of males and females as subjects, and the use of two different approaches to induce hypoxia in the acute and chronic situation. Firstly, there seems to be no difference in the exercise-induced increase in *IL-6* between males and females (B.K. Pedersen, personal communication). Secondly, in acute hypoxia the low  $\text{O}_2$  saturation was achieved by reducing  $\text{F}_1\text{O}_2$  and keeping barometric pressure constant, whereas the same degree of hypoxia was achieved in the chronic situation by reducing barometric pressure and keeping  $\text{F}_1\text{O}_2$  constant. This hypoxia model has been applied on numerous high altitude research expeditions. However, recently the use

of normobaric hypoxia against hypobaric hypoxia showed different physiological responses in ventilatory parameters (Savourey et al. 2003). Whether metabolic parameters are affected as well is at present unknown.

The finding that exercise at the same absolute workload during hypoxia, as compared with sea level, augments the plasma IL-6 response is in line with the recent study by Mazzeo et al. (2000b), and supports the theory that exercise intensity as such influences the IL-6 response to exercise. Of note, in the present study a difference in exercise intensity of only 45% versus 55% of  $\dot{V}O_2\text{max}$  resulted in an approximately threefold difference in the IL-6 response.

It is well documented that, as exercise intensity increases, there is a gradual shift from fat towards carbohydrate oxidation in the contracting skeletal muscle (Christensen and Hansen 1939), ultimately providing almost all of the substrate at  $\dot{V}O_2\text{max}$ . The increase in carbohydrate oxidation during exercise has been shown to result mostly from an increase in muscle glycogen utilization compared to a less increased blood glucose uptake (Febbrario et al. 2000). In the present study, no muscle glycogen measurement was obtained; however, it is reasonable to assume that, during  $AH_{\text{abs}}$  and  $CH_{\text{abs}}$ , the breakdown of glycogen must be higher than during the  $SL$ ,  $AH_{\text{rel}}$  and  $CH_{\text{rel}}$  trials, due to the relatively higher exercise intensity, ultimately resulting in a lower intra muscular glycogen content. Also, as published in our accompanying paper (Lundby and van Hall 2002), the oxidation of carbohydrates during  $AH_{\text{abs}}$  and  $CH_{\text{abs}}$  is significantly higher than during  $AH_{\text{rel}}$  and  $CH_{\text{rel}}$ . Interestingly, it was recently shown that a contracting leg with low glycogen released IL-6 1 h before the control leg (Steensberg et al. 2001b). Furthermore, the leg with the lowest glycogen content at the end of exercise expressed the highest level of IL-6 mRNA regardless of pre-exercise glycogen levels. Although no measurements of glycogen, IL-6 expression or IL-6 release in the exercising muscle were performed in this study, it is tempting to speculate that the higher carbohydrate utilization in the working muscle during  $AH_{\text{abs}}$  and  $CH_{\text{abs}}$  presumably resulting in lower glycogen levels would cause the augmented plasma IL-6 concentrations during these trials.

As previously mentioned, catecholamines have been hypothesized to be involved in the IL-6 response to exercise (DeRijk et al. 1994; Mazzeo et al. 2000b; Papanicolaou et al. 1996; van Gool et al. 1990). In contrast, other recent studies (Steensberg et al. 2000, 2001a) have not found support for catecholamines to play a major role in the exercise-induced IL-6 response. In the present study, the IL-6 response to exercise was augmented in  $AH_{\text{abs}}$  and  $CH_{\text{abs}}$  when compared to exercise at  $SL$ ,  $AH_{\text{rel}}$  and  $CH_{\text{rel}}$ . However, epinephrine was only augmented during exercise at  $AH_{\text{abs}}$ . In addition, plasma norepinephrine was similarly elevated during exercise at  $AH_{\text{abs}}$ ,  $CH_{\text{rel}}$  and  $CH_{\text{abs}}$  compared to exercise at  $SL$  and  $AH_{\text{rel}}$ , despite the demonstration that only exercise at  $AH_{\text{abs}}$  and  $CH_{\text{abs}}$  resulted in increased plasma IL-6 levels compared to exercise at  $SL$ ,  $AH_{\text{rel}}$

and  $CH_{\text{rel}}$ . Therefore, these results suggest that catecholamines are not the main regulators of the IL-6 response during exercise.

Most studies have reported augmented resting plasma levels of IL-6 at high altitude; however, the elevations are not uniform. One study has reported an effect after 4 h of hypoxic conditions (Mazzeo et al. 2000b). In the present study the resting plasma IL-6 level after ~10 min of hypoxic conditions was unchanged compared with sea level. Regarding chronic hypoxia, the present study did not demonstrate a clear picture. Thus, after 3–4 weeks of high altitude plasma IL-6 was either augmented or unchanged in the same subjects measured on two different occasions. After 8 weeks of high altitude exposure IL-6 was elevated in all subjects compared with sea level. Plasma IL-6 has not been measured after such a long period of high altitude exposure before, but the finding is in line with the observed effect of 2–12 days of high altitude exposure (Klausen et al. 1997; Mazzeo et al. 2000b). The plasma IL-6 concentrations reported in these studies were between 2.5 and 10 pg ml<sup>-1</sup>, and thus not as high as the levels seen during infections (Bruunsgaard et al. 1999). In contrast, one study found that individuals with high-altitude pulmonary edema (HAPE) after exposure to high altitude had plasma levels of IL-6 > 20 pg ml<sup>-1</sup>, whereas non-HAPE individuals did not develop an increase in plasma IL-6 (Kleger et al. 1996; Maggiorini et al. 2000). Also, the bronchoalveolar fluid of patients with HAPE contains elevated levels of IL-6 (Kubo et al. 1996). The literature therefore suggests that hypoxia is associated with non-pathophysiological elevations in plasma IL-6, whereas development of HAPE results in further elevated plasma IL-6, possibly related to inflammation.

In conclusion, this study suggests that catecholamines are not key regulators of the IL-6 response to exercise. In contrast, during exercise, the IL-6 response depends heavily on exercise intensity. Furthermore, this study confirms the observation that chronic hypoxia results in elevated plasma IL-6.

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