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Iloprost improves running performance at 5,000 m in Han but not in Tibetans

Bengt Kayser[1,*], Jui-Lin Fan[1], Liya Nan[2], Wang Liang Bang[2], Bianba[3] & Tianyi Wu[2]

1 Institute of Sport Sciences, University of Lausanne, Lausanne, Switzerland
2 National Key Laboratory of High Altitude Medicine, Department of Hypoxic Physiology and Mountain Medicine, High Altitude Medical Research Institute, Xining, Qinghai, P. R. China.
3 Tibet University Medical College, Lhasa, Tibet, P. R. China
* Corresponding author: Prof. Dr. Bengt Kayser, Institute of Sport Sciences, University of Lausanne, Synathlon Uni-Centre, 1015 Lausanne, Switzerland
E-Mail: bengt.kayser@unil.ch

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ABSTRACT

Background: Tibetans lose less aerobic exercise capacity in hypoxia compared to lowland Han. We tested if inhalation of iloprost (to counter hypoxic pulmonary vasoconstriction) and furosemide (to decrease afferent vagal traffic from pulmonary receptors) improve performance in hypoxia in Han compared to Tibetans. **Methods**: 8 Tibetans and 8 Han, living at 2,260 m, did incremental uphill treadmill running to exhaustion at ambient pressure on day 1, followed by three runs at 5,000 m (hypobaric chamber) after inhalation of iloprost (ILO), furosemide (FUR) or placebo (PLA), on different days in a counter-balanced order. **Results**: In Han the performance decrement from 2,260 m to 5,000 m was greater than in Tibetans ($p<0.05$). In Han iloprost improved performance at 5,000 m compared to placebo ($p<0.05$ vs. PLA); furosemide had no effects. In Tibetans there were no treatment effects. Peripheral O_2 saturations at peak exercise at 5,000 m, were higher by ~8 % in the Tibetans ($p<0.05$ vs. Han). Maximum heart rate was lowered by 13±6 bpm in Han at 5,000 m regardless of treatment compared to 2,260 m ($p<0.05$). Tibetans reached similar maximum heart rates ~200 bpm at 5,000 m and 2,260 m, independent of treatment. Conclusions: The blunting of the exercise impairment in severe hypoxia in Han during maximal exercise after inhalation of iloprost suggests that hypoxic pulmonary vasoconstriction and right ventricular function are potential performance limiting factors in Han in hypoxia.

Keywords:
altitude – cardiac – pulmonary – right ventricle – heart rate – performance

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Introduction

Exercise-induced arterial hypoxemia impairs maximum aerobic capacity (Dempsey & Wagner, 1999; Nielsen, 2003). This effect is exacerbated at high altitude because of lower inspiratory oxygen tension (PiO_2) (Amann & Calbet, 2008). Up to altitudes ~4,000 m the loss of aerobic capacity in hypoxia is determined by a decrease in arterial oxygen saturation (SaO_2) and thus arterial oxygen concentration (CaO_2) and mass arterial oxygen flux (CaO_2 x cardiac output = QaO_2) (Amann & Calbet, 2008; Chapman, Emery, & Stager, 1999; Chapman, Stager, Tanner, Stray-Gundersen, & Levine, 2011; Ferretti, Moia, Thomet, & Kayser, 1997). However, during exercise in more severe hypoxia (above ~4,000 m), when SaO_2 drops below 80 % (Wagner, 2000), there are unexplained reductions in both maximum heart rate and cardiac output (Amann & Kayser, 2009; Boushel et al., 2001; Kayser, Narici, Binzoni, Grassi, & Cerretelli, 1994; Mourot, 2018). The impaired maximal cardiac function at peak exercise in hypoxia is restored rapidly by increasing PiO_2 to normoxic levels, enabling heart rate and cardiac output to further increase with increasing exercise intensity. The underlying mechanisms of the impaired maximum heart rate and associated reduction in cardiac output in severe hypoxia remain uncertain.

A possible explanation for the drop in cardiac output in hypoxia is the development of hypoxic pulmonary vasoconstriction (HPV) (Naeije & Chesler, 2012; Naeije et al., 2010) . Whilst controversy remains, HPV-induced pulmonary hypertension would lead to right ventricular over-load, limiting cardiac output and impairing maximum aerobic capacity (Anholm & Foster, 2011; Naeije, 2011). Among Han lowlanders acutely exposed to an altitude of 3,700 m, 61% developed borderline or confirmed HPV and had impaired right ventricular function at high altitude. This compromised their cardiorespiratory fitness in relation to their mean pulmonary arterial pressure (PAP) (Yang et al., 2014). Tibetans, a well-adapted high altitude population (Wu & Kayser, 2006), have a blunted HPV (Groves et al., 1993) , maintain higher arterial oxygen saturation (Marconi et al., 2004; Wu & Kayser, 2006), reach higher peak heart rates and show less performance decrement during hypoxic exercise compared to Han lowlanders (Marconi et al., 2004; Niu, Wu, Li, Chen, & Song, 1995; Sun et al., 1990; Wu & Kayser, 2006; Zhou, Zhuang, Wu, Zhang, & Cherdrungsi, 2008; Zhuang et al., 1993). If the greater loss of aerobic performance in hypoxia of Han compared to Tibetans is due to more HPV, the inhalation of iloprost, a prostacyclin analogue which decreases pulmonary vascular resistance (Olschewski et al., 2002; Waxman & Zamanian, 2013) and improves endurance exercise performance in primary pulmonary hypertension patients (Wensel, Opitz, Ewert, Bruch, & Kleber, 2000) could potentially improve endurance exercise performance in hypoxia in Han as compared to Tibetans.

Another possible explanation for the observed decrease in lower peak heart and cardiac output in lowlanders exercising in severe hypoxia is increased parasympathetic activity (Boushel et al., 2001). A potential origin for increased parasympathetic activity is activation of pulmonary vagal afferents caused by subclinical interstitial pulmonary oedema from hypoxia and exercise-induced increased PAP (Anholm, Milne, Stark, Bourne, & Friedman, 1999; Bhagat et al., 2011; Cremona et al., 2002; Lee & Pisarri, 2001; Paton, 1998). Inhaled furosemide alleviates dyspnoea and improves endurance exercise performance under certain pathological conditions, possibly through pulmonary vagal afferent inhibition (Jensen, Amjadi, Harris-McAllister, Webb, & O'Donnell, 2008; Newton, Davidson, Macdonald, Ollerton, & Krum, 2008; Parshall et al., 2012). We hypothesized that inhalation of furosemide by preventing activation of pulmonary vagal receptors would increase peak heart rate and improve endurance exercise performance in hypoxia in Han but not in Tibetans.

We therefore assessed endurance exercise performance in Tibetans and Han living at 2,260 m during incremental uphill treadmill running, first at ambient pressure and then in a hypobaric chamber at a simulated altitude of 5,000 m. We compared the effect of inhaled iloprost , furosemide and placebo on running performance at 5,000 m expecting that iloprost and furosemide would improve performance during incremental treadmill running in severe hypoxia in Han but not in Tibetans.

Methods

Participants

Two groups of eight healthy non-smoking Han and Tibetan men volunteered to participate (Table 1). The Han were born and raised in Xining (2,260 m) and had lived there for most of their lives. The Tibetans (and their parents) were born at altitude (3,778±196 m, mean±SD) and were studying in Xining (2,260 m) since 1-3 yr, spending their summer and winter holidays at home (3,750 to 4,280 m). They were recruited by word of mouth from the local student population.

All participants were seen by a physician for a medical history and a physical examination. Inclusion criteria were age 18-25 years, parents and grandparents of exclusively Tibetan or Han ethnicity, respectively, and no contra-indications for exercise stress testing. The protocol was approved by the Qinghai High

Table 1: Participant characteristics.

	Tibetan	Han
N	8	8
Age (yr)	20±2	20±1
Height (cm)	171±5	179±4*
Body mass (kg)	59±8	77±18*
Time spent at altitude (yr)	19±2	19±1
ABP (sys/dia, mmHg)	116±10 / 72±6	128±11 / 77±10
SaO_2 (%)	94±1	94±2
Hb (g/L)	158±9	164±9[1]
Ht (%)	47±2	49±2

*p<0.05; [1]p=0.09; ABP: arterial blood pressure; SaO_2: pulse oximetry; Hb: haemoglobin; Ht: haematocrit

Altitude Medical Science Institutional Committee on Human Research. Written informed consent was obtained from all participants, in accordance with the Declaration of Helsinki.

Resting measurements

At ambient pressure, after 5-10 min rest sitting, blood pressure was measured by auscultation using a sphygmomanometer, and heart rate and saturation (SaO_2) with a finger oximeter (Nonin, Plymouth, MN, USA) in triplicate with 2 min intervals and averaged. A supine resting ECG was then recorded. A venous blood sample was taken from a cubital vein for the determination of haemoglobin concentration ([Hb]) and haematocrit (Hct) (Sysmex 2000i, Siemens, Munich, Germany).

Exercise test

The participants performed incremental exercise tests on a treadmill (h/p/Cosmos, Rome, Italy), first walking and then running, according to a modified Bruce protocol (3 min stages at the following speeds and slopes: 2.7 km/h at 0 % (warm-up), 2.7 km/h at 10 % (stage 1), 4.0 km/h at 12 % (stage 2), 5.4 km/h at 14 % (stage 3), 6.8 km/h at 16 % (stage 4), 8.0 km/h at 18 % (stage 5), until voluntary exhaustion under strong verbal encouragement. We chose running over cycling in order to allow the participants to engage in a type of large muscle group effort they were well-accustomed to. Ear pulse oximetry and 12 lead pre-cordial ECG were continuously monitored (Masterscreen, Carefusion, Höchberg, Germany).

Simulated altitude measurements

The exercise testing at a simulated altitude of 5,000 m was done in a hypobaric chamber with no blinding to the condition (High Altitude Medical Research Institute, Xining, Qinghai, China). The pressure was gradually lowered over 40 min to reach the final altitude. Fractions of oxygen and carbon-dioxide were monitored by the chamber's control system and kept at their normal ambient values. Total exposure time lasted 3 to 4 hr per session. The intervention consisted of iloprost (5 µg in saline, Roche, Switzerland), furosemide (40 mg in saline, Mepha, Basel, Switzerland) or placebo (saline only), inhaled over 10-15 min with an ultrasound nebulizer (AeronebGO, Galway, Ireland) each on a different day. After decompression the participants inhaled the intervention substance, according to a between-group counter-balanced randomization scheme to prevent bias from repeated simulated altitude exposure. The sequence list for the participants was identical in the two groups: 1-3-2, 2-1-3, 3-2-1, 1-3-2, 2-1-3, 3-2-1, 1-3-2, 2-1-3, where 1 was placebo, 2 furosemide and 3 iloprost. Participants and experimenters were blinded to the substances. The participants then mounted the treadmill. After a standing resting measurement they started exercising until they reached voluntary exhaustion under strong verbal encouragement. At the completion of the exercise test the participant was gradually decompressed to the ambient atmospheric pressure over 30 min.

Analysis and statistics

Resting measurements at ambient pressure and at 5,000 m in the chamber were compared with t-tests. We analysed the effects of ethnicity and treatment (i.e. placebo, furosemide or iloprost) during exercise using a two-way (ethnicity and treatment) ANOVA. Pairwise comparisons (Tukey HSD) were then performed between means. Data are presented as mean ± SD or 95% confidence interval (CI). An α-level of 0.05 was used to interpret our findings. Analysis was done with SPSS (22, IBM, NY, USA) and Prism (6.0f, Graphpad, La Jolla, CA, USA).

Results

Resting variables at ambient pressure (2,260 m)

Participant characteristics and resting values are shown in Table 1. Han and Tibetans were similar with the exception of the slightly higher stature and body mass of the Han.

Simulated altitude of 5,000 m

Exposure to 5,000 m was well tolerated; none of the participants reported signs of acute mountain sickness. There were no side effects reported of the inhalation of placebo, iloprost or furosemide. Resting ECG was normal in all conditions, with sinus tachycardia during exposure to 5,000 m. Two out of eight Han and two out of eight Tibetans had slight right axis deviations. On average acute exposure to 5,000 m lowered total (placebo) exercise time by 127±64 sec (P<0.001 vs. 2,260 m).

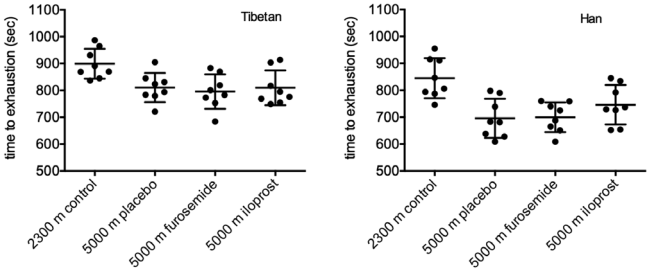

Figure 1: Time to exhaustion during incremental uphill running. Dots indicate individuals. Bars and flankers indicate means±SD.

Regardless of the altitude, exercise time was consistently better in Tibetans (P=0.020 vs. Han). Compared to 2,260 m, exercise time at 5,000 m was shortened by 10% for Tibetans (P<0.001) and by 18% for Han (P<0.001), the Tibetans exercising significantly longer than the Han (P=0.006). Compared to placebo, furosemide inhalation did not change exercise time in Tibetans (P=0.399) or Han (P=0.823). Meanwhile, iloprost

inhalation improved exercise time in Han (P=0.008) but not in Tibetans (P=0.419). As a result, no significant difference in exercise time was observed anymore between the Han and Tibetan upon iloprost inhalation.

Saturation

Ascent to 5,000 m lowered SaO_2 in both Tibetans and Han (P<0.001), an effect exacerbated with exercise (P=0.001). A smaller reduction in SaO_2 was observed in the Tibetans during exercise compared to Han (interaction: P=0.040). As a result SaO_2 during exercise was consistently higher in Tibetans compared to Han (P=0.008). Accordingly, CaO_2 during exercise was lowered at 5,000 m (P<0.001), with lesser reduction observed in the Tibetans compared to Han (interaction: P=0.013). Regardless of the ethnicity, there were no effects of inhaled furosemide or iloprost on SaO_2 at exhaustion, i.e. exhaustion was reached at similar SaO_2.

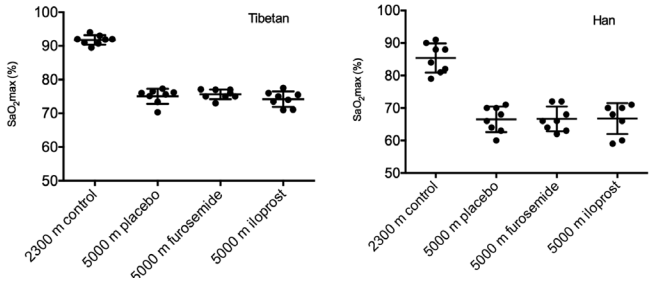

Figure 2: Saturation at maximum exercise effort. Dots indicate individuals. Bars and flankers indicate means±SD.

Maximum heart rate

No difference in maximum heart rate was observed between Tibetan and Han during exercise at 2,260 m (P=0.361). During exercise at 5,000 m, for any given submaximal exercise intensity, HR was higher compared to at 2,260 m (P=0.035). The absolute increase in HR during exercise was greater in Tibetans (interaction: P=0.009), due to the higher maximal exercise intensity achieved compared to Han. In Han, maximum heart rate was decreased by 13±6 bpm during exercise at 5,000 m with placebo (P<0.001). Compared to placebo, neither iloprost nor furosemide influenced maximum heart rate in the Han. In Tibetans, exercise at 5,000 m lowered maximum heart rate by 5±3 bpm (P=0.027) with placebo. Meanwhile, no difference in maximum heart rate was observed with furosemide and iloprost compared to placebo in Tibetans during exercise at 5,000 m.

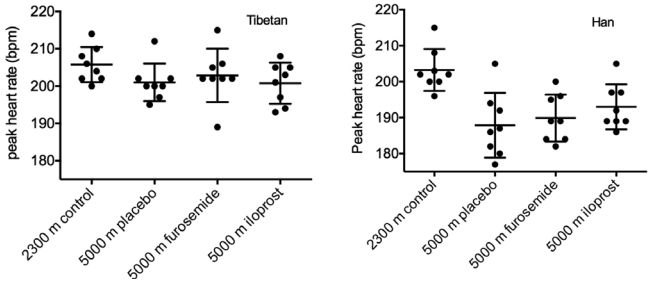

Figure 3: Heart rate at maximum exercise effort. Dots indicate individuals. Bars and flankers indicate means±SD.

Discussion

This study examined the effects of inhalation of iloprost and furosemide on incremental inclined treadmill running performance at 5,000 m in Han and Tibetans. We report three unique findings: 1) Inhalation of iloprost improved running performance by ~50 sec (95% CI, 15 to 86 sec) in Han Chinese at 5,000 m, while it had no effect in the Tibetans (95% CI, -35 to 36 sec); 2) Inhalation of furosemide had no significant effects in either Han or Tibetans; and 3) During maximal exercise at 5,000 m, the Tibetans were able to reach very high maximum heart rates (~200 bpm), not yet reported before at such altitude, while maintaining a significantly better arterial saturation as compared to the Han.

Iloprost

Prostacyclin is a potent pulmonary vasodilator synthesized in the endothelium. It targets the IP receptor in the smooth muscle cells of the pulmonary vasculature. IP recepter activation triggers conversion of ATP to cyclic-AMP, which increases protein-kinase-A activity, leading to downstream effects including vasodilation (Humbert & Ghofrani, 2015). Iloprost is a prostacyclin analogue. When inhaled its pulmonary vasodilatory potency is similar to that of prostacyclin, but the effects last longer (30 to 90 min, vs. 15 min for prostacyclin (Olschewski et al., 2002; Waxman & Zamanian, 2013)). In our iloprost-naïve participants we used the recommended initial dose of 10 microgram, which was inhaled over a period of about 10-15 min prior to the start of the resting measurements. The full testing sequence was completed within an hour, so that our results were obtained inside the therapeutic window of inhaled iloprost. We found that iloprost inhalation improved performance in Han at 5,000 m, while no effect was observed in the Tibetans (Table 3). Wensel et al.(2000) reported that iloprost inhalation decreased pulmonary vascular resistance and improved exercise time by 16% in primary pulmonary hypertension patients. Therefore, whilst speculative, we attribute the improvement in running performance we found in the Han to an attenuation of hypoxia-induced pulmonary hypertension during maximum exercise with iloprost. However, since we were unable to measure PAP during exercise, strong conclusions cannot be drawn. Our findings would seem to support recent observations of a relationship between borderline pulmonary hypertension and aerobic exercise performance in young otherwise healthy Chinese lowlanders in conditions of acute and chronic altitude exposure (Yang et al., 2014). Our data also corroborate reports of partial improvements (10–25 %) in maximal exercise

capacity in hypoxia with other specific pulmonary vasodilating interventions (Ghofrani et al., 2004; Naeije & Dedobbeleer, 2013). Since iloprost had no effect in the Tibetans, our results would then suggest that HPV is not a limiting factor for exercise performance in the Tibetan population. Nevertheless, our data provide only limited evidence supporting a role for HPV in limiting performance in Han at high altitude.

Furosemide

Others proposed that the decrease in maximum heart rate at altitude is due to increased parasympathetic activity (Bao et al., 2002; Boushel et al., 2001). Furosemide is a loop diuretic which inhaled can alleviate symptoms of dyspnea (Newton et al., 2008; Parshall et al., 2012), perhaps through pulmonary vagal receptor inhibition, decreasing vagal afferent traffic (Lee & Pisarri, 2001; Newton et al., 2008). We therefore hypothesized that heart rate during maximal exercise in hypoxia would increase under inhalation of furosemide because of less parasympathetic activity. In the present study, maximum heart rate was not significantly different in the Han after furosemide inhalation compared to placebo (+2 bpm [95% CI, -2 to +6]). Accordingly, this finding refutes our hypothesis of pulmonary receptor stimulation causing increased parasympathetic activity limiting maximum heart rate during hypoxic exercise. However, pulmonary receptors and their role in limiting maximum heart rate in severe hypoxia are still not yet well understood (Widdicombe, 2009). In rabbits basal rapid adapting pulmonary receptor (RAR) activity increases during prolonged exposure to hypoxia accompanied by pulmonary congestion (Bhagat et al., 2011). In humans, exposure to high altitude is accompanied by pulmonary congestion and subclinical interstitial pulmonary edema (Anholm et al., 1999; Cremona et al., 2002). It therefore remains possible that increased PAP (from altitude and exercise) and interstitial oedema would stimulate vagal pulmonary receptors, leading to increased parasympathetic activity, in turn leading to decreased peak heart rates, even though the absence of an effect of inhaled furosemide in our study would argue against this contention.

Maximum heart rates in Tibetans

Strikingly, on average our Tibetan participants reached peak heart rates above 200 bpm, independently of the altitude or the intervention, contrary to what was expected from the extant literature (Mourot, 2018). Our participants were young (20±2 yr) and heart rates around 200 bpm were therefore expected in normoxic conditions, but not necessarily at 2,260 m, and certainly not at 5,000 m. More important, the Tibetans reached similar peak heart rates in all conditions. This finding is contrary to the prevailing view of decreased peak heart rates above about 4,000 m (Bao et al., 2002; Boushel et al., 2001; Wagner, 2000). At lower altitudes peak heart rate remains similar to that observed at sea level, but beyond 4,000 m peak heart rate progressively decreases with increasing altitude, while chronic exposure to hypoxia decreases it even further, because of the increased CaO_2 from the increased haemoglobin. For example, Danish climbers attempting Mt Everest, who prior to departure had mean peak heart rates of 186 bpm in normoxia, and 170 bpm in acute hypoxia (10 % O_2 in N_2), after acclimatization at 5,400 m reached peak heart rates of only 155 bpm (Lundby & van Hall, 2001). In that study, in two climbers heart rate was monitored during ascent to 8,750 m (without supplementary O_2), with peak rates of only 144 and 148 bpm, respectively.
The reasons for the decrease in peak heart rate in acute and chronic severe hypoxia are unknown (Mourot, 2018). In lowlanders, after 9 weeks at 5,260 m, vagal blockade with glycopyrrolate restored maximum heart rate to sea level values, but had no influence on cardiac output or performance, which remained reduced, while acutely normalizing FiO_2 at peak exercise restored cardiac output and power output to sea level values (Boushel et al., 2001). Those authors concluded that enhanced parasympathetic neural activity accounts for the lowering of heart rate during exercise at altitude, but could not explain why blocking parasympathetic activity did not improve performance. Bao et al. (2002) investigated the effects of beta-blockade with propranolol and para-sympathetic blockade with glycopyrrolate and reported that increased parasympathetic neurotransmitter release and decreased beta-adrenoreceptor activity account for the decreased peak heart rates, despite enhanced sympathetic activity. An acute increase in FiO_2 rapidly counteracted the parasympathetic, but not the sympathetic hyperactivity that occurred at high altitude (Bao et al., 2002). Favret and Richalet hypothesized that the drop in maximum heart rate in severe hypoxia would prevent mismatching between myocardial O_2 demand and supply (Favret & Richalet, 2007). They reasoned that compensation of decreased CaO_2 in severe hypoxia by increasing coronary blood flow would not be possible anymore above a certain altitude. Only by capping maximal heart rate, which would decrease myocardial O_2 demand, would cardiac integrity be protected. Our results suggest that this would not be the case for Tibetans exercising maximally at 5,000 m, but leaves the hypothesis to be tested in even more severe hypoxia such as found close to the summit of Mt Everest (8848 m).

Limiting factors of exercise performance in hypoxia

The impairment of aerobic power and exercise performance in severe hypoxia (SaO_2<80 %) is still not well understood. Lack of oxygen is obviously the reason, but the underlying mechanisms that lead to an earlier disengagement from an exercise challenge in hypoxia compared to normoxia remain unknown (Fan & Kayser, 2016). According to Verges et al. (2012) active locomotor muscle metabolic fatigue cannot be the main cause of the impaired whole body exercise performance in severe hypoxia. Upon reaching exhaustion in hypoxia, participants can continue cycling when surreptitiously switched to normoxia (Amann et al., 2006; Boushel et al., 2001; Kayser et al., 1994; Koglin & Kayser, 2013), which also argues in favour of a

supra-spinal limitation of exercise performance (Fan & Kayser, 2016). Amann et al. (2007) reported that the degree of hypoxia influences the relative role of muscle fatigue in the cessation of dynamic exercise with large muscle groups. Those authors proposed a threshold of SaO_2 for a 'switch' from a predominant effect of peripheral fatigue to one of a supra-spinal limitation. They found similar levels of muscle fatigue at task failure from constant load exercise to exhaustion in different conditions of inspiratory oxygen tension, when SaO_2 averaged 94 %, 82 %, or 76 % (FiO_2 0.21–0.12), but not at a SaO_2 of 67 % (FiO_2 0.10) when apparently supra-spinal limitation led to early disengagement of the effort. When reaching exhaustion at 5,000 m our Han Chinese participants had on average saturations of about 67 %, similar to that of Amann's participants. This would suggest that limitation of exercise at 5,000 m in our Han participants may have been less from peripheral muscle fatigue as compared to 2,260 m and that supra-spinal effects would have played a predominant role. By contrast, our Tibetan participants had significantly higher saturations as compared to the Han participants, on average remaining higher than 74 % at maximum exercise, i.e. at or just above the supposed 'switch' value between 76 and 67 % as suggested by Amann et al. (2007). It therefore remains possible that the 'switch' from predominantly peripherally determined fatigue towards a supra-spinal mechanism could exist in the Tibetans too, but at higher altitudes, when their SaO_2 could drop below 67 %. One other feature with regard to SaO_2 made the Tibetans stand out. Apart from being higher, their saturations were all very similar; variance was lower as compared to that of the Han, as can be clearly seen in Figure 1. We do not have an explanation for the better saturations of the Tibetans as compared to the Han Chinese, nor for the reduced variance. An increased affinity for oxygen of haemoglobin could play a role. Simonson et al. (2014) reported lower haemoglobin P50 in Han Chinese and Tibetans at 4,200 m in comparison with low altitude data, but no difference between the two groups, excluding a role for P50.

Tibetans and altitude

It is beyond the scope of this study to comprehensively review what is known about the Tibetans' better adaptation to altitude as compared to other ethnic groups. But with regard to exercise performance there is sufficient research suggesting that Tibetans do indeed fare better [see e.g. (Wu & Kayser, 2006)]. Tibetans do not have very high aerobic capacity, but are able to reach a higher fraction of their low-altitude aerobic capacity in hypoxia as compared to lowlanders (Marconi et al., 2004; Niu et al., 1995) . Since this characteristic is also present in Tibetans born at low altitude this suggests a trait for better altitude adaptation (Marconi et al., 2004). Recent work suggests that hypoxic exposure over many generations indeed led to the selection of specific alleles in Himalayan (Simonson, McClain, Jorde, & Prchal, 2012), but also Andean (Brutsaert et al., 2004), and East-African highlanders (Scheinfeldt et al., 2012).

Limitations

Several important methodological limitations should be considered when interpreting our findings. First, iloprost was expected to alleviate HPV and thus lower PAP, but we were not able to measure PAP. Our results, even though compatible with a role for HPV in limiting performance in the Han, should therefore be completed with new data including measurements of PAP during exercise, e.g. with echo-doppler. Second, since we did not measure stroke volume or cardiac output, we could only infer cardiovascular changes from observing changes in heart rates. However, since there was a clear difference between the Han and the Tibetans with regard to heart rate it seems likely that they did differ for cardiac output, but this remains to be tested, e.g. with acetylene rebreathing, echo-doppler or transthoracic impedancemetry. Third, we were unable to recruit participants of similar stature, resulting in slightly smaller and lighter Tibetan participants compared to their Han Chinese counterparts. Our results should therefore be completed with measurements in more participants and with similar build. Fourth, because of calibration problems of our gas exchange apparatus upon decompression to 5,000 m we could not obtain reliable gas exchange data. Fifth, we cannot present any rates of perceived exertion for leg and breathing effort since the participants did not understand the instructions. Sixth, we cannot ascertain maximality of the running effort with usual criteria such as high RPE, a plateau in VO_2, and an RER > 1.1. And finally, since we used the actual living altitude of 2,260m of our participants as our control condition, and not (acute) sea level conditions, we cannot exclude some effect of partial acclimatization to high altitude.

Conclusions

We report conserved maximum heart rate and less desaturation during maximum exercise in acute severe hypoxia (5,000 m) in Tibetans compared to Han, allowing the Tibetans to outperform the Han. Since inhalation of iloprost blunted the exercise impairment in Han during maximal exercise in severe hypoxia but had no effect in Tibetans, HPV possibly plays a role in the greater impact of hypoxia on maximum exercise capacity in Han as compared to Tibetans.

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Competing Interests

The authors have declared that no competing interests exist.

Data Availability Statement

The datasets used can be made available from the corresponding author on reasonable request.

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