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Individual variations and sex differences in hemodynamics and percutaneous arterial oxygen saturation (SpO_2) in Tibetan highlanders of Tsarang in the Mustang district of Nepal

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Abstract

Background: Many studies have indicated specific low-hemoglobin (Hb) adaptation to high altitude in the Tibetan population, but studies focusing on physiological variations within this population are limited. This study aimed to investigate the relationships between SpO_2 and related factors, including individual variations and sex differences, to assess the generality of high-altitude adaptation in the Tibetan population of Tsarang.

Methods: The participants were 31 male and 41 female community-dwelling people aged ≥18 years living in Tsarang, in the Mustang district of Nepal. Height, weight, SpO_2, Hb concentration, finger temperature, heart rate, and blood pressure were measured. Lifestyle information was obtained by interview.

Results: Men had significantly higher systolic blood pressure ($p = 0.002$) and Hb ($p < 0.001$) than women. There was no significant correlation between SpO_2 and other parameters in men. In women, SpO_2 was negatively correlated with heart rate ($p = 0.036$), Hb ($p = 0.004$), and finger temperature ($p = 0.037$). In multiple regression analysis, a higher SpO_2 was marginally correlated with lower age ($\beta = -0.109$, $p = 0.086$) and higher Hb ($\beta = 0.547$, $p = 0.053$) in men. In women, higher SpO_2 was significantly correlated with lower heart rate ($\beta = -0.045$, $p = 0.036$) and Hb ($\beta = -0.341$, $p = 0.018$). Mean hemoglobin (95% confidence interval) was 13.6 g/dl (13.1–14.0 g/dl), which is lower than that found previously in Andeans and almost equal to that in Japanese lowlanders measured using the same device. In some participants of both sexes, hemoglobin was >17.0 g/dl.

Conclusion: Higher SpO_2 was marginally correlated with younger age and higher Hb in men and with lower heart rate and lower Hb in women. Hemoglobin concentration was similar to that found previously in lowlanders, but higher in some individuals. These results indicate individual variation and sex differences in the hemodynamics of high-altitude adaptation in Tibetan highlanders of Tsarang, as well as low-Hb adaptation to high altitude equal to that of other Tibetans.

Keywords: High-altitude adaptation, SpO_2, Individual variation, Sex difference, Tibetan highlanders

Background

High-altitude adaptation has been researched and discussed for over 100 years. Previous studies have revealed specific populational differences in high-altitude adaptations among such as Andean, Tibetan, and Ethiopian populations [1–5]. It is well known that Tibetan

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highlanders have lower hemoglobin (Hb) and SpO_2 levels than Andean highlanders [2, 4, 5]. Recent genomic analysis has clarified the mechanism of low-Hb adaptation to high altitude in Tibetans [1, 6–8], who were termed 'King of the Mountains' by Edward et al. [9] because of their ability to live and reproduce successfully at high altitude.

Although populational differences have been well discussed, there is limited knowledge of physiological variations in highlanders [3, 10]. From the perspective of physiological anthropology, various studies have conducted field research to investigate variation in physiological response from the perspective of acute hypobaric hypoxia in lowlanders [11, 12] or of physiological variation in highlanders [6, 13, 14]. In our previous field research, we investigated the health status of Tibetans in Tsarang village (altitude, 3570 m) [6]. The Tsarang village is highly preserved due to its location in Mustang district, neighboring the Tibetan area of China. Physiological data from this region are limited because the Mustang district was isolated from other parts of Nepal until 1992 [15–17]. We have also investigated individual variations and sex differences in the percutaneous arterial oxygen saturation (SpO_2) of young Andean highlanders in Bolivia (altitude, 3700–4000 m). As these studies share common measurement devices and protocols [6, 14], the physiological states can be compared between these two populations.

Therefore, the aim of the study was to investigate individual variation and sex differences in SpO_2 and related factors, to assess the generality of high-altitude adaptation in the Tibetan population of Tsarang.

Methods

This cross-sectional study was conducted in Tsarang village (altitude, 3570 m), Dhaulagiri zone, in the Mustang district of Western Nepal in July 2017. We recruited 188 participants (85 men and 103 women, age $\geq$ 18 years). To enable comparison with our previous study of highlanders in Bolivia, we selected those aged 18–40 years from this group and analyzed the data of a final total of 31 men and 41 women.

After explaining the experiment and obtaining informed consent, each participant's height, weight, SpO_2, Hb concentration, finger temperature, heart rate, and blood pressure were measured. All parameters were measured at room temperature (22–24 °C) with the participants wearing traditional clothes.

After anthropometric measurements for height and weight, SpO_2 was measured by a finger pulse oximeter (Masimo Radical V 5.0; Masimo Corp, Irvine, CA). Hb concentration and finger temperature were measured on the inner surface of the index finger using an ASTRIM FIT health monitoring analyzer (Sysmex; Kobe, Japan). Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate were measured in the left arm in the resting condition by a digital automatic blood pressure monitor (HEM-7210, OMRON; Kyoto, Japan).

Height (cm) and weight (kg) were measured with clothing and without shoes, and body mass index (BMI) was calculated as weight/height squared (kg/m^2). Information about physical activity (walking or doing any equivalent amount of exercise activity more than 30 min per day: yes/no), current smoking (having one or more cigarettes per day: yes/no), and alcohol use (some alcohol consumption one or more days per week: yes/no) was obtained by interview. Details of the research and data collection methods have been described elsewhere [6, 15].

Statistical analysis

Variables are presented as the mean and 95% confidence interval (95% CI). Student's t-test and Fisher's exact test were used for comparisons between men and women. Pearson's correlation analysis was used to assess correlations between SpO_2 and other parameters for men, for women, and for total participants. Multiple regression analysis was used to assess correlations between SpO_2 and related parameters (sex, age, heart rate, DBP, Hb, and finger temperature) for men, for women, and for total participants. These parameters were added to the above model because their p values were <0.15 in a simple correlation analysis between SpO_2 and other parameters in each sex. Finger temperature data were missing in 1 man and 1 woman, and Pearson's correlation analysis and multiple regression analysis omitted data of 1 man and 1 woman. All analyses were performed using the Statistical Analysis System software package version 9.4 (SAS Institute, Cary, NC).

Results

Table 1 summarizes the characteristics of the 72 participants. Height and weight were significantly higher in men than women (p < 0.001), but there was no significant difference in BMI. SBP and Hb were also significantly higher in men than women (p = 0.002 and p < 0.001, respectively). There was no significant difference between men and women in terms of SpO_2, heart rate, DBP, or finger temperature. Regarding lifestyle factors, men had significantly higher rates of smoking and alcohol use (p = 0.043 and p < 0.001, respectively).

In men, there was no significant correlation between SpO_2 and other parameters (Fig. 1, Table 2). In women, SpO_2 was negatively correlated with heart rate, Hb, and finger temperature (Fig. 1, Table 2).

In multiple regression analysis, higher SpO_2 was marginally correlated with lower age and higher Hb in men (Table 3). In women, higher SpO_2 was significantly

Table 1 Characteristics of the study population

	Total ($n = 72$)	Men ($n = 31$)	Women ($n = 41$)	*P*-value
	Mean (95% *CI*)			
Age (y)	31.2 (29.7–32.7)	32.5 (30.5–34.6)	30.1 (28.1–32.3)	0.113
Height (cm)	158.4 (156.2–160.5)	165.2 (162.7–167.8)	153.2 (151.0–155.4)	< 0.001
Weight (kg)	56.7 (54.4–59.1)	62.2 (59.4–65.0)	52.6 (49.5–55.6)	< 0.001
BMI (kg/m^2)	22.6 (21.8–23.4)	22.9 (21.7–24.0)	22.4 (21.2–23.5)	0.544
Heart rate (bpm)	81.0 (78.4–83.6)	79.2 (75.5–82.9)	82.3 (78.6–86.1)	0.241
SBP (mmHg)	117.6 (114.6–120.6)	123.0 (118.4–127.6)	113.6 (109.9–117.2)	0.002
DBP (mmHg)	75.6 (73.1–78.0)	77.7 (74.0–81.3)	74.0 (70.6–77.3)	0.138
SpO_2 (%)	92.4 (92.0–92.8)	92.5 (91.8–93.2)	92.4 (91.9–92.9)	0.820
Hemoglobin (g/dl)	13.6 (13.1–14.0)	14.6 (14.1–15.1)	12.7 (12.2–13.4)	< 0.001
Finger temperature (°C)	33.8 (33.1–34.6)	34.4 (33.4–35.5)	33.4 (32.3–34.5)	0.179
	% (95% *CI*)			
Current smoking (yes)	22.5 (13.5–34.0)	35.5 (18.6–52.3)	12.5 (2.3–22.8)	0.043
Alcohol drinking (yes)	16.9 (8.2–25.6)	35.5 (18.6–52.3)	2.5 (0.0–7.3)	< 0.001
Physical activity (yes)	74.6 (64.5–84.8)	67.7 (51.3–84.2)	80.0 (67.6–91.0)	0.279

95% CI 95% confidence interval, *BMI* Body mass index, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *SpO_2* Saturation of percutaneous oxygen

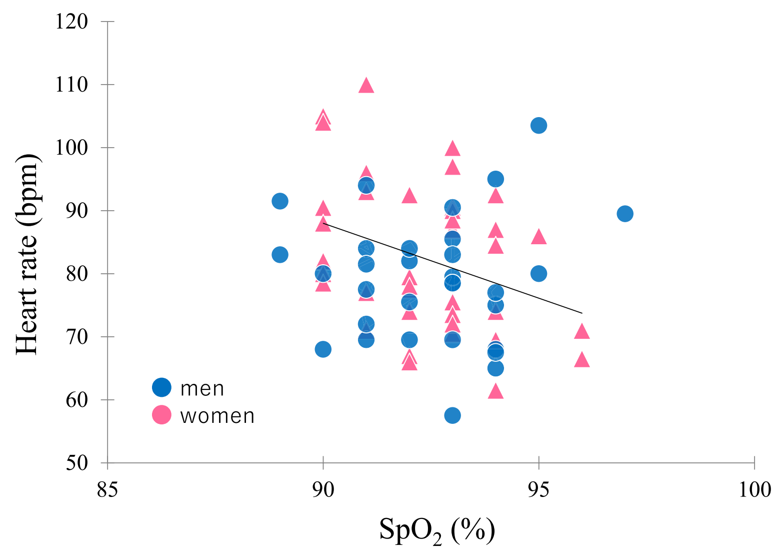

Fig. 1 Scatter plot of SpO_2 and heart rate in Tibetan highlanders living in Tsarang. SpO_2 was negatively correlated with heart rate ($r = -0.329$, $P = 0.036$) in women. The solid line indicates the trend for women

correlated with lower heart rate and Hb (Table 3). Higher SpO_2 was marginally related to higher age in all participants and in men (Table 3).

Discussion

Previous studies have indicated low-Hb adaptation to high altitude in Tibetans [1–5, 10, 18–22]. In the present study, we present physiological data of hemodynamic parameters (focusing primarily on SpO_2) and individual variation and sex differences in isolated Tibetan highlanders living in Tsarang village.

The present study found no significant difference in SpO_2 between men and women (Table 1). Beall et al. [23] reported lower SpO_2 in male than female Tibetans living at an altitude of 3800–4200 m (mean SpO_2: 90.2% at 3800 m, 89.2% at 3850 m, 88.7% at 4065 m, 88.9% at 4200 m) and sex differences in SpO_2 tended to be greater at higher altitudes. SpO_2 was relatively higher (92.4% at 3570 m) in the present study, and a similar study reported no sex

Table 2 Simple correlation coefficients between SpO_2 and other parameters

	Total ($n = 72$)		Men ($n = 31$)		Women ($n = 41$)	
	r	*p*-value	*r*	*p*-value	*r*	*p*-value
Age (y)	−0.259	0.028	−0.247	0.180	−0.289	0.067
BMI (kg/m^2)	−0.047	0.698	−0.197	0.288	0.060	0.710
Heart rate (bpm)	−0.171	0.150	0.054	0.773	−0.329	0.036
SBP (mmHg)	−0.134	0.263	−0.075	0.689	−0.226	0.155
DBP (mmHg)	−0.100	0.403	0.086	0.645	−0.259	0.102
Hemoglobin (g/dl)	−0.128	0.283	0.252	0.172	−0.433	0.004
Finger temperature (°C)[a]	−0.156	0.196	0.082	0.667	−0.332	0.037

SpO_2 Saturation of percutaneous oxygen, *BMI* Body mass index, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure

[a] Men ($n = 30$), women ($n = 40$)

Table 3 Multiple regression analysis between SpO_2 and other parameters

	Total ($n = 70$)			Men ($n = 30$)			Women ($n = 40$)		
	β (95% *CI*)	*p*-value	r^2	*β* (95% *CI*)	*p*-value	r^2	*β* (95% *CI*)	*p*-value	r^2
Sex (women/men)	−0.385 (−1.356, 0.585)	0.431		–	–		–	–	
Age (y)	−0.060 (−0.131, 0.011)	0.094		−0.109 (−0.235, 0.017)	0.086		−0.016 (−0.094, 0.062)	0.676	
Heart rate (bpm)	−0.027 (−0.070, 0.011)	0.204		−0.012 (−0.120, 0.095)	0.813		−0.045 (−0.087, −0.003)	0.036	
DBP (mmHg)	−0.003 (−0.048, 0.041)	0.885		0.048 (−0.055, 0.151)	0.349		−0.010 (−0.058, 0.038)	0.672	
Hemoglobin (g/dl)	−0.099 (−0.360, 0.162)	0.450		0.547 (−0.007, 1.102)	0.053		−0.341 (−0.619, −0.063)	0.018	
Finger temperature (°C)	−0.051 (−0.190, 0.089)	0.472		0.102 (−0.161, 0.365)	0.433		−0.089 (−0.241, 0.064)	0.247	
			0.120			0.223			0.365

β Standardized regression coefficient, *95% CI* 95% confidence interval, *DBP* Diastolic blood pressure, r^2 Coefficient of determination for model

differences in Tibetans at 3658 m [24]. Accordingly, sex differences in SpO_2 might not be apparent in the Tibetan population at altitudes below 3700 m.

Higher Hb and blood pressure in men compared with women have been reported in a sea-level environment [25–27]. Similarly, Hb and SBP were both significantly higher in men than in women in the present study (Table 1), consistent with the result for Hb reported in a previous study of Tibetan and Andean highlanders [3]. These results suggest that the same sex differences in Hb and SBP are present in both highlanders and lowlanders.

The present results found no significant correlation between SpO_2 and heart rate in men, but that SpO_2 negatively correlated to heart rate in women (Fig. 1, Table 2). In women, multiple regression analysis showed that lower SpO_2 was significantly correlated with higher heart rate after adjusting for covariates (Table 3). Heart rate decreases after long-term high-altitude exposure [28]; however, the present results indicate that lower SpO_2 potentially evoked a higher heart rate for greater oxygen delivery even in Tibetan highlanders, and especially in women. This sex difference may indicate that in the case of higher Hb in men than women and higher blood flow for oxygen delivery in Tibetans [29, 30], lower SpO_2 is not necessary to evoke a higher heart rate in men. Thus, although the association between SpO_2 and heart rate is similar between Tibetan men and women, further studies that add men's data and blood flow measurements are required to assess this complex association.

In men, multiple regression analysis revealed that lower SpO_2 was marginally correlated with lower Hb after adjusting for covariates (Table 3). In contrast, in women, lower SpO_2 was significantly correlated with higher Hb after adjusting for covariates (Table 3). This negative correlation in women is reasonable because higher Hb enables higher oxygen delivery, even if SpO_2 is lower. However, as there was a weak positive correlation between SpO_2 and Hb in men, the inverse result is difficult to explain. As men had higher Hb than women, this positive correlation might indicate better hemodynamic adaptation to high altitude or increasing pulmonary arterial pressure in men. Contrary to the present results, Beall et al. [3] reported a negative correlation between SpO_2 and Hb in Tibetan men but not in Tibetan women at 3800–4065 m. This inconsistency in sex differences might be due to inconsistency in the studied high-altitude environments and population differences between TAR (Tibet autonomous region) and Tibetans living in Tsarang. In addition, Beall et al. [23] also suggested the effect of age and sex interactions on SpO_2 in Tibetans in TAR, and they also recently reported aging changes of SpO_2 in Tibetan women in Tsarang [31]. Similarly, our results also showed an aging effect of SpO_2, in men and overall (Table 3). Taken together, the present results and those of previous studies suggest sex differences in hemodynamics and SpO_2 in Tibetan highlanders of Tsarang. Further studies are necessary to clarify the biological mechanism of this complex association in greater detail.

We have previously reported sex and individual differences in hemodynamics and SpO_2 in young Andean highlanders in Bolivia (altitude, 3700–4000 m) in a study of a similar duration, using the same protocol [14]. SpO_2 was higher in the present study (mean [95 % *CI*], 92.4% [92.0–92.8%]) compared with the Andean highlanders (91% [90.0–91.0%]). Although previous studies have reported lower SpO_2 in Tibetans than in Andeans at similar altitudes [1, 3], Tsarang is located at 3570 m and the environment is moderately hypoxic compared with Bolivia (3700–4000 m), which might be the reason why Tibetan in Tsarang could maintain higher SpO_2.

Typically, among lowlanders, men have higher skin temperature and peripheral blood flow than women, in a thermoneutral environment [32, 33]. Another study found higher finger temperature in Andean men than in Andean women [14]. Interestingly, there was no significant sex difference in finger temperature in the present study, and it was slightly higher in Tibetans than in Andeans in our previous studies [14]. Previous studies have reported that Tibetan highlanders had high nitric oxide (NO) concentration and blood flow for oxygen delivery [29, 30], which suggests that Tibetan highlanders in Tsarang also have higher blood flow as a high-altitude adaptation, similar to other Tibetans. In addition, the mean (95% CI) Hb of Tibetans in the present study was 13.6 g/dl (13.1–14.0 g/dl), which is clearly lower than that of Andeans and almost equal to that of Japanese lowlanders measured using the same device [34]. This finding might indicate that Tibetans living in Tsarang have a low-Hb adaptation to high altitude; however, as some of the present individuals had higher Hb (≥17.0 g/dl) (Fig. 2), it is necessary to assess the mechanism for individual differences in more detail. In the total regression analysis, 22.3% of the variation in SpO_2 was explained in men and 36.5% in women, but the remaining variation was unclear. Recent studies have reported that the physiological status of highlanders is affected by *EPAS1* and *EGLN1* genes [7, 8, 11, 18, 35–37]. The effect of these genetic variations and other underlying factors on individual variations requires further investigation.

The present study has several limitations. First, the results do not necessarily show a causal relationship because of the cross-sectional design of the study. Second, the sample size was limited and also information on other determinants (e.g., ventilation, nutritional status, or menstrual cycle) contributing to SpO_2 was not obtained. Third, because Hb concentrations were

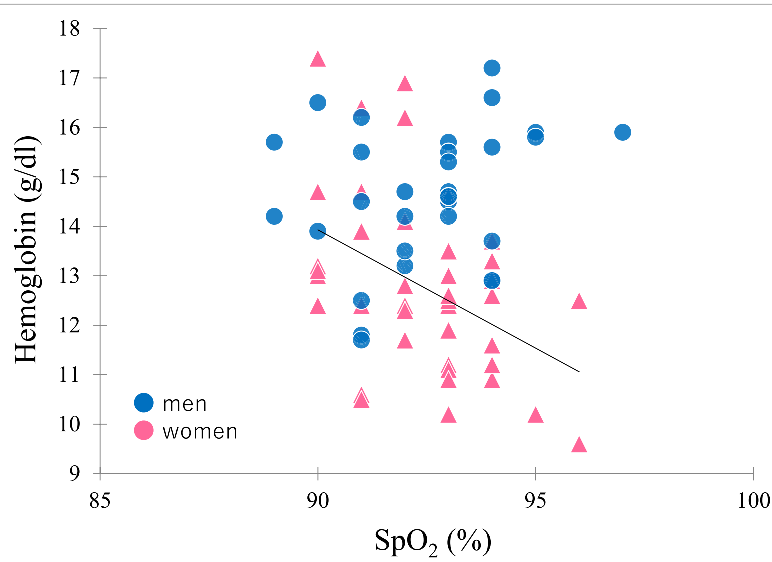

Fig. 2 Scatter plot of SpO_2 and hemoglobin in Tibetan highlanders living in Tsarang

estimated values, they are difficult to compare with values reported in other studies.

Conclusion

Among Tibetan highlanders of Tsarang village, higher SpO_2 showed a weak correlation with lower age and higher Hb in men, and higher SpO_2 was related to lower heart rate and lower Hb in women. Those living in Tsarang have a low-Hb adaptation to high altitude similar to that of other Tibetans, but Hb was higher in some individuals. These results suggest the presence of individual variations and sex differences in the hemodynamics of high-altitude adaptation in this population.

Abbreviations

95% CI: 95% confidence interval; BMI: Body mass index; DBP: Diastolic blood pressure; EGLN1: Egl-9 family hypoxia-inducible factor 1; EPAS1: Endothelial PAS domain-containing protein 1; Hb: Hemoglobin; SBP: Systolic blood pressure; SpO_2: Percutaneous arterial oxygen saturation; TAR: Tibet autonomous region.

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Authors' contributions

TN and TY designed and performed the research. TN, HA, SK, HI, and TY contributed to data acquisition, data analysis, or interpretation. All authors approved the final version of the manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

This study was approved by the ethical committees of the Nepal Health Research Council (approval no. 142/2016) and the Institution of Tropical Medicine, Nagasaki University (approval no. 150226137-3). Each participant in the study was given detailed information about the research objectives, data collection procedures, benefits, risk, and confidentiality before written informed consent was obtained. If a participant was unable to write, a thumb impression was obtained.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Bigham AW, Wilson MJ, Julian CG, Kiyamu M, Vargas E, Leon-Velarde F, et al. Andean and Tibetan patterns of adaptation to high altitude. Am J Hum Biol. 2013;25:190–7.
2. Beall CM. Andean, Tibetan, and Ethiopian patterns of adaptation to high-altitude hypoxia. Integr Comp Biol. 2006;46:18–24.
3. Beall CM, Brittenham GM, Strohl KP, Blangero J, Williams-Blangero S, Goldstein MC, et al. Hemoglobin concentration of high-altitude Tibetans and Bolivian Aymara. Am J Phys Anthropol. 1998;106:385–400.
4. Beall CM, Reichsman AB. Hemoglobin levels in a Himalayan high altitude population. Am J Phys Anthropol. 1984;63:301–6.
5. Beall CM. Tibetan and Andean contrasts in adaptation to high-altitude hypoxia. Adv Exp Med Biol. 2000;475:63–74.
6. Koirala S, Nakano M, Arima H, Takeuchi S, Ichikawa T, Nishimura T, et al. Current health status and its risk factors of the Tsarang villagers living at high altitude in the Mustang district of Nepal. J Physiol Anthropol. 2018;37:20.
7. Bigham AW, Lee FS. Human high-altitude adaptation: forward genetics meets the HIF pathway. Genes Dev. 2014;28:2189–204.
8. Beall CM, Cavalleri GL, Deng L, Elston RC, Gao Y, Knight J, et al. Natural selection on EPAS1 (HIF2alpha) associated with low hemoglobin concentration in Tibetan highlanders. Proc Natl Acad Sci U S A. 2010;107:11459–64.
9. Gilbert-Kawai ET, Milledge JS, Grocott MP, Martin DS. King of the mountains: Tibetan and Sherpa physiological adaptations for life at high altitude. Physiology (Bethesda). 2014;29:388–402.
10. Beall CM, Almasy LA, Blangero J, Williams-Blangero S, Brittenham GM, Strohl KP, et al. Percent of oxygen saturation of arterial hemoglobin among Bolivian Aymara at 3,900-4,000 m. Am J Phys Anthropol. 1999;108:41–51.
11. Yasukochi Y, Nishimura T, Motoi M, Watanuki S. Association of EGLN1 genetic polymorphisms with SpO2 responses to acute hypobaric hypoxia in a Japanese cohort. J Physiol Anthropol. 2018;37:9.
12. Motoi M, Nishimura T, Egashira Y, Kishida F, Watanuki S. Relationship between mitochondrial haplogroup and physiological responses to hypobaric hypoxia. J Physiol Anthropol. 2016;35:12.
13. Yasukochi Y, Nishimura T, Ugarte J, Ohnishi M, Nishihara M, Alvarez G, et al. Effect of EGLN1 genetic polymorphisms on hemoglobin concentration in Andean highlanders. Biomed Res Int. 2020;2020:3436581.
14. Nishimura T, Ugarte J, Ohnishi M, Nishihara M, Alvarez G, Yasukochi Y, et al. Individual variations and sex differences in hemodynamics with percutaneous arterial oxygen saturation (SpO2) in young Andean highlanders in Bolivia. J Physiol Anthropol. 2020;39:31.
15. Arima H, Nakano M, Koirala S, Ito H, Pandey BD, Pandey K, et al. Unique hemoglobin dynamics in female Tibetan highlanders. Trop Med Health. 2021;49:2.
16. Jeong C, Witonsky DB, Basnyat B, Neupane M, Beall CM, Childs G, et al. Detecting past and ongoing natural selection among ethnically Tibetan women at high altitude in Nepal. PLoS Genet. 2018;14:e1007650.
17. Cho JI, Basnyat B, Jeong C, Di Rienzo A, Childs G, Craig SR, et al. Ethnically Tibetan women in Nepal with low hemoglobin concentration have better reproductive outcomes. Evol Med Public Health. 2017;2017:82–96.
18. Beall CM. Adaptation to high altitude: phenotypes and genotypes. Annu Rev Anthropol. 2014;43:251–72.
19. Cueto M. Andean biology in Peru. Scientific styles on the periphery. Isis. 1989;80:640–58.
20. Beall CM, Decker MJ, Brittenham GM, Kushner I, Gebremedhin A, Strohl KP. An Ethiopian pattern of human adaptation to high-altitude hypoxia. Proc Natl Acad Sci U S A. 2002;99:17215–8.
21. Alkorta-Aranburu G, Beall CM, Witonsky DB, Gebremedhin A, Pritchard JK, Di Rienzo A. The genetic architecture of adaptations to high altitude in Ethiopia. PLoS Genet. 2012;8:e1003110.
22. Beall CM, Brittenham GM, Macuaga F, Barragan M. Variation in hemoglobin concentration among samples of high-altitude natives in the Andes and the Himalayas. Am J Hum Biol. 1990;2:639–51.

23. Beall CM. Oxygen saturation increases during childhood and decreases during adulthood among high altitude native Tibetians residing at 3,800-4,200m. High Alt Med Biol. 2000;1:25–32.
24. Zhuang J, Droma T, Sun S, Janes C, McCullough RE, McCullough RG, et al. Hypoxic ventilatory responsiveness in Tibetan compared with Han residents of 3,658 m. J Appl Physiol (1985). 1993;74:303–11.
25. Joyner MJ, Wallin BG, Charkoudian N. Sex differences and blood pressure regulation in humans. Exp Physiol. 2016;101:349–55.
26. Reckelhoff JF. Sex differences in regulation of blood pressure. Adv Exp Med Biol. 2018;1065:139–51.
27. Smetana P, Batchvarov V, Hnatkova K, John Camm A, Malik M. Sex differences in the rate dependence of the T wave descending limb. Cardiovasc Res. 2003;58:549–54.
28. Mazzeo RS, Bender PR, Brooks GA, Butterfield GE, Groves BM, Sutton JR, et al. Arterial catecholamine responses during exercise with acute and chronic high-altitude exposure. Am J Physiol. 1991;261:E419–24.
29. Beall CM, Laskowski D, Erzurum SC. Nitric oxide in adaptation to altitude. Free Radic Biol Med. 2012;52:1123–34.
30. Hoit BD, Dalton ND, Erzurum SC, Laskowski D, Strohl KP, Beall CM. Nitric oxide and cardiopulmonary hemodynamics in Tibetan highlanders. J Appl Physiol (1985). 2005;99:1796–801.
31. Beall CM, Childs G, Craig SR, Strohl KP, Quinn E, Basnyat B. Repeatability of adaptive traits among ethnic Tibetan highlanders. Am J Hum Biol. 2021:e23670. [Epub ahead of print].
32. Daanen HA. Finger cold-induced vasodilation: a review. Eur J Appl Physiol. 2003;89:411–26.
33. Cooke JP, Creager MA, Osmundson PJ, Shepherd JT. Sex differences in control of cutaneous blood flow. Circulation. 1990;82:1607–15.
34. Saigo K, Imoto S, Hashimoto M, Mito H, Moriya J, Chinzei T, et al. Noninvasive monitoring of hemoglobin. The effects of WBC counts on measurement. Am J Clin Pathol. 2004;121:51–5.
35. Simonson TS, Yang Y, Huff CD, Yun H, Qin G, Witherspoon DJ, et al. Genetic evidence for high-altitude adaptation in Tibet. Science. 2010;329:72–5.
36. Yang J, Jin ZB, Chen J, Huang XF, Li XM, Liang YB, et al. Genetic signatures of high-altitude adaptation in Tibetans. Proc Natl Acad Sci U S A. 2017;114:4189–94.
37. Yang Y, Du H, Li Y, Guan W, Tang F, Ga Q, et al. NR3C1 gene polymorphisms are associated with high-altitude pulmonary edema in Han Chinese. J Physiol Anthropol. 2019;38:4.

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