Cardiac structure and function in lowlanders at high altitude: short-term adaptation and chronic remodeling

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Abstract

Aims: The purpose of this study was to examine cardiac structure and function in lowlanders at high altitude(HA) to investigate short-term adaptation and long-term cardiac remodeling.

Methods: In total of 301 healthy subjects included in this study, short-term exposed (STE) and acclimatized lowlanders (AL) at HA, native Tibetans(NT) and sea level residents(SLR) were comprised of 75,77,69 and 80 participants, respectively. Standard echocardiography was performed on all groups, subjects at HA were examined after return to sea level in <24 hours.

Results: SBP and HR did not increase significantly after short-term exposure to HA in STE, but increased after long-term exposure in AL, which could be detected even after returning to the plain. Exposure to HA enlarged right heart, widened pulmonary artery and reduced left ventricular(LV) diastolic function in lowlanders. The degree of

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diastolic dysfunction was more obvious in AL. LV wall thickness increased even after short-term exposure to HA in lowlanders. Ejection fraction did not change significantly in STE, but decreased in AL.

Conclusions: Exposure to HA could enlarged the right heart and decrease the diastolic function of LV in lowlanders. The LV systolic function was preserved after short-term HA exposure, but decreased after long-term HA exposure.

Keywords: echocardiography; high altitude; lowlanders; Tibetan

1. Introduction

Barometric pressure falls as altitude increases, the concentration of oxygen in air remains constant so, as the barometric pressure decreases, the partial pressure of oxygen decreases proportionately[1]. This condition is referred to as hypobaric hypoxia, which makes it difficult for oxygen to diffuse into the lung capillaries[2]. The hypoxia environment has a series of consequences for the heart. Sudden exposure of an unacclimatized lowlander to high altitude(HA) raises pulmonary artery systolic pressure and decreases left ventricular(LV) volumes[3], which result in an increase in heart rate and cardiac output compared to sea level as a compensatory mechanism to maintain cardiac performance[4]. Acclimatization describes the physiologic changes that help maintain tissue oxygen delivery and human performance in response to continued hypobaric hypoxia[5]. Studies conducted over the past 25 years in Andeans, Tibetans, and, less often, Ethiopians show varied but distinct O2 transport traits from those of acclimatized newcomers, providing indirect evidence for genetic adaptation to HA[6]. Previous findings have been demonstrated that Sherpa to have higher maximal heart rates and only moderate pulmonary hypertension compared with lowlanders at HA[3]. However, neither the acute nor lifelong effects of HA on cardiac structure and function have been fully assessed in lowlanders. Hence, in order to examine the time course of adaptation, we compared echocardiographic parameters of short-term exposed(STE) and acclimatized lowlanders (AL) at HA with native Tibetans(NT) and sea level residents(SLR). Great number of researchers measured echocardiographic parameters always at HA, while we evaluated these data at sea level hospital. The only reason we have decided to do like this is the poor medical conditions at HA areas compelled the patients to hospitals at sea level. We would like to imitate the process of a patient coming into the hospital and compare echocardiographic parameters with previous studies to investigate the structure and function alterations of heart.

2. Methods

2.1 Study populations and design

This was a randomized study complied with the Declaration of Helsinki, and its protocol was approved by the Chengdu Office of People's Government of Tibetan Autonomous Region Hospital Ethics Committee. Written informed consent was obtained from each participant.

In total of 301 healthy subjects included in this study. Lowlanders were born at sea level (Han ethnicity) but worked at Tibet. All the lowlander participants flew to Lhasa(3700m) from Chengdu(500m) and went to their work destination by car, and returned to sea level in the same way. Group STE worked at HA less than 1 month, while group AL worked at HA throughout the year except for the Spring Festival more than 20 years. Highlanders were the native Tibetans born and lived at Tibet all the time. SLR was residents born and lived at sea level and never been to plateau.

Subjects at HA were examined after return to sea level in <24 hours in our hospital in Chengdu. The data, including basic information, a physical examination, an echocardiogram, and blood tests were collected too. The inclusion criteria were normal physical examination results. The exclusion criteria were a self-reported and verified history of any of the following conditions: coronary artery disease, structural heart disease and heart failure, any endocrine disease, and abnormal liver function.

2.2 Echocardiographic information acquisition

Standard echocardiography was performed for each participant by the same sonographer using a commercially available ultrasound system (Philips iE33). A 1 to 5 MHz phased array transducer was used to collect echocardiographic images in the parasternal long-axis, short-axis, and apical four chamber views, with three consecutive cardiac cycles recorded in order to calculate the mean values.

All two-dimensional parameters were measured in accordance with the American Society of Echocardiography(ASE) guidelines and a Chinese nationwide multicenter study[7,8]. Left atrium(LA) anteroposterior linear dimension was assessed from the parasternal long-axis view at end-ventricular systole. Interventricular septal end-diastolic thickness (IVSd), LV posterior wall end-diastolic thickness (LVPWd), the diameter of LV at end-diastole (LVEDD)and end-systolic(LVESD), the fractional shortening(FS) of LV were measured from the parasternal long-axis view at the level of the mitral valve leaflet tips. The stroke volume(SV) and ejection fraction (EF) were derived from M-mode using the Teichholz formula for participants without regional abnormalities of wall motion. The right ventricular(RV) anteroposterior dimension were determined from the parasternal long-axis view at end-diastole. The minor-axis dimension of the right atrium (RA)should be taken in a plane perpendicular to the long axis of the RA and extends from the lateral border of the RA to the interatrial septum at end systole. The pulmonary artery(PA)was measured between the valve and the bifurcation point at end-diastole from a short axis of great artery. The Doppler echocardiographic measurements were guided by another Chinese nationwide multicenter study[9]. From the mitral inflow spectra, we acquired the peak velocities of early diastolic (E), late diastolic (A) waves and E/A ratio. The peak systolic flow velocity at level of pulmonary valve (PV-v) were measured. The annular velocities at early diastole (e′) and late diastole(a′) at septal site of the mitral annulus were also measured. Ratio of septal E/e′was derived. The grade and assessment of tricuspid regurgitation(TR) by Doppler were performed as recommended by the American Heart Association[10]and ASE[11], separately. Peak TR velocity(TR-v) was measured by continuous wave Doppler across the tricuspid valve. Trans-tricuspid gradient and systolic pulmonary artery pressure(SPAP) could be reliably determined from peak TR-v, using the simplified Bernoulli equation and combining this value with an estimate of the RA pressure which was estimated from diameter inferior vena cava and respiratory changes. During the echocardiographic examinations, heart rate(HR) was continuously monitored.

2.3 Statistical methods

Statistical analysis was performed using SPSS 23.0 Statistical software. The continuous variables were expressed as mean ± SD. The quantitative data were tested by one-way ANOVA. Multiple comparisons between groups were compared with LSD analysis of variance. The enumeration data were expressed as frequencies and compared using the chi-square test, continuity correction, or Fisher's exact test. The P-values < 0.05 (two tailed) were considered to be significant.

3. Results

3.1 Comparison of demographic features

The demographic features are presented in Table 1. The comparisons between different groups showed no statistical difference in gender, age and BMI. SBP in STE group was not significantly higher than that in SLR group(P>0.05), while SBP in AL group was higher than that in STE and NT groups (P<0.05; Figure 1). We also observed that AL and NT had higher hemoglobin than STE and SLR, only NT had higher RBC than other groups(P<0.05). There were no differences in DBP and hematocrit between groups(P>0.05).

3.2 Comparison of the echocardiographic parameters

Comparisons of the echocardiographic parameters between different groups are shown in Table 2. In this study, although there was no significant difference in HR between STE and SLR, HR in STE and AL group was higher than that of NT group (P<0.05; Figure 2). LVEDD, LVESD, EDV and ESV in STE group were not significantly different from those in SLR group(P>0.05), but lower than those in AL and NT groups (P<0.05; Figure 3). There was no significant difference in SV between the groups(P>0.05). E/A of AL and NT group was lower than that of STE(P<0.05), while there was no significantly difference between STE and SLR(P>0.05). E/e′and LA were larger in the HA population than in SLR, and LA in AL and NT groups was larger than that in STE group(P<0.05;Figure 4). we found that EF had no significant change between STE and SLR group(P>0.05), but EF in SLR and STE was higher than in AL and NT groups (P<0.05; Figure 5). At the same time, we also observed that the LV wall thickness was thicker in the HA population than that of SLR(P<0.05).

For the right heart, we observed that RA, RV and PA in HA exposure groups, including STE, AL and NT, were greater than SLR. Furthermore, PA in NT group was smaller than that in AL group, whereas PV-v was the highest (P<0.05; Figure 6). We measured all the TR that can be sampled. The maximum reflux degree of each group was mild. There was no significant difference in TR and SPAP between groups(P>0.05).

4. Discussion

The purpose of this study was to examine cardiac structure and function in lowlanders at HA to investigate short-term adaptation and long-term cardiac remodeling. Hence, we compared echocardiographic parameters of short-term exposed and acclimatized lowlanders at HA with native Tibetans and sea level residents. However, standard echocardiography was performed on subjects at HA after return to sea level in <24 hours. The only reason we have decided to do like this is the poor medical conditions in the plateau compelled the patients to hospitals at sea level. We would like to imitate the process of a patient coming into the hospital and get the most realistic results. And we also aimed to explore the differences between this research method and other researches carried out at HA.

In this study, subjects exposed to HA, including STE, AL and NT groups, were about 3700 meters above sea level. The exposure time at high altitude was about 24 days, 30 years and 48 years, respectively. Hypoxia directly affects the vascular tone of the pulmonary and systemic resistance vessels and increases ventilation and sympathetic activity via stimulation of the peripheral chemoreceptors, then blood pressure and systemic vascular resistance rise over at least 3 to 4 weeks[12]. This study found that SBP in STE group was not significantly higher than that in SLR group, while SBP in AL group was higher than that in STE and NT groups. We speculated that the exposure time and measurement of blood pressure in plain were the influencing factor of SBP not significantly increased in STE group. Previous study showed acclimatized lowlanders with 15 to 18 months stayed at above 3500m had persistent sympathetic dominance with significantly reduced parasympathetic response as compared to SLR and HA natives[13]. This may help to explain the increase of SBP in AL group. Even in the plains we can detect this rise, which indicates that the duration of elevated blood pressure is related to the time of exposure to HA. The results above indicate that the blood pressure measured within 24 hours in plain can still reflect the true state of acclimatized lowlanders. The HA natives exhibited no changes in autonomic function, which could be attributed to their genetic adaptation in HA environment[13]. Thus, SBP in NT group was lower than that in AL group.

To cope with acute hypoxia, in addition to increasing the pulmonary ventilation and sympathetic activity, the cardiac output(CO) can also be increased by increasing HR[14]. In this study, although there was no significant difference in HR between STE group and SLR group, HR in STE and AL group was higher than that of NT group. There was no significant difference in SV between the groups. Research implemented by Maufrais et al found that HR increased at 4350m and remained higher during 6 days on the top of Europe even after return to sea level, but SV was unchanged[15]. The exposure time of STE was longer than the previous research. Therefore, we believed that adaptation to short-term exposure, but not acclimatized as NT was the reason for the change in HR. LVEDD, LVESD, EDV and ESV in STE group were not significantly different from those in SLR group, but lower than those in AL and NT groups. We considered that no change in LV volume between STE and SLR was the reason for no difference in SV. Sudden exposure of an unacclimatized lowlander to HA raises pulmonary artery systolic pressure and decreases left ventricular volumes[3]. There is no contradiction between reduced volume and no change in SV, because the systolic and diastolic capacity decreases synchronously, so no change in SV is understandable.

It has been speculated that reduced oxygen availability may impair diastolic relaxation at HA[16]. According to our results, E/A of AL and NT groups were lower than that of STE, while there was no significantly difference between STE and SLR. E/e′and LA were larger in the HA population than in the SLR, and LA in AL and NT groups was larger than that in STE group. In short, exposure to HA reduces LV diastolic function, and the degree of damage increases with exposure time. Sareban et al found E/A ratio decreased significantly after arrival at 4559m and LV EF did not change[17]. Boussuges et al conducting the experiment in a hypobaric chamber to assess the consequences of altitude-induced hypoxia also found EF remained the same or slightly increased[18]. Consistent with previous studies, we found that EF had no significant change between STE and SLR group, but EF in SLR and STE was higher than in AL and NT groups. Lowlanders demonstrate rapid changes in systolic mechanics after ascent to HA in response to altered hemodynamics to optimize efficiency and equalize fiber stress across the myocardium[3,19]. As mechanical stress is linearly related to myocardial oxygen demand, changes in LV mechanics could represent altered myocardial efficiency. We believed that this was the reason for the increase of EF in STE group.

At the same time, we also found that the LV wall thickness was thicker in the HA population than that of SLR. Yang et al had similar finding that the interventricular septum was thicker in the HA population than in the low-altitude population[20]. Researchers propose that HA natives experience chronic systolic functional remodeling that restores the mechanical reserve that can be used to increase SV during incremental exercise[21]. This may be the cause of LV wall thickening in NT and AL group. Whether LV wall remodeling also occurred in STE group needs further study. Unfortunately, we did not find any positive findings for left ventricular morphology and function between AL and NT groups. But we just observed basic cardiac parameters, maybe new tools, such as strain, will make new discoveries in AL and NT.

For the right heart, we observed that RA, RV and PA in HA exposure groups, including STE, AL and NT, were greater than SLR. Furthermore, PA in NT group was smaller than that in AL group, whereas PV-v was the highest. A previous study revealed that neither PA nor RA had any relationship with altitude, the effects of hypoxia seemed to be limited to the RV[21]. However, the results of this study indicated that the morphology of RA and PA could also be changed even after short-term exposure to HA. The difference in PA between AL and NT may be due to different regulatory mechanisms among races[22]. Although the morphology of the right heart had changed, it was regrettable that we had not observed the so-called elevation of PASP in lowlanders at HA and native highlanders[23]. In this study, there were only mild TR because all the subjects were healthy people, so the sample size used to evaluate PASP was too small. Previous study had shown that a wide range of PASP was observed (mean 25 mm Hg, range 18–36 mm Hg) in lowlanders at 4250m over a 10-

week period; however, unlike previous reports, they found such increases to be mild[24]. We considered that the small sample size and an insignificant increase were the causes of no increase of PASP in our results. There was a tendency toward lower PASP in Aymara native highlanders[24], and unexpectedly normal PASP was found in NT[25]. NT have higher pulmonary nitric oxide(NO) concentrations than other populations which might explain a low prevalence of HA pulmonary hypertension[26].

5. Limitations and Future Directions

The sample size of this study was small, so there were some differences between this research results and previous studies. Since the data of this study were all measured in plain, the accuracy of the conclusion needed to be further confirmed by other research tools. In the future, we will continue the design and method of this study, and use three-dimensional echocardiography and strain to further explore the cardiac changes of lowlanders exposed to HA, hence further confirm the conclusions of this research.

6. Conclusions

In order to examine cardiac structure and function in lowlanders at HA to investigate short-term adaptation and long-term cardiac remodeling, we compared echocardiographic parameters and drew the following main conclusions. First, SBP and HR did not increase significantly after short-term exposure to HA in lowlanders, but increased after long-term exposure, which could be detected even after returning to the plain. Second, exposure to HA enlarged right heart, widened pulmonary artery and reduced LV diastolic function in lowlanders. The degree of diastolic dysfunction was more obvious in the long-term exposure group. Third, LV wall thickness increased even after short-term exposure to HA in lowlanders. EF did not change significantly after short-term exposure to HA in lowlanders, but decreased after long-term exposure.

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Disclosures

No conflicts of interest, financial or otherwise, are declared by the author(s).

[1]References

. Grocott M, Montgomery H, Vercueil A. High-altitude physiology and pathophysiology: implications and relevance for intensive care medicine. *Crit Care*. 2007;11(1):203.

[2] . Leissner KB, Mahmood FU. Physiology and pathophysiology at high altitude: considerations for the anesthesiologist. *J Anesth*. 2009;23(4):543−553.

[3] . Stembridge M, Ainslie PN, Hughes MG, *et al*. Ventricular structure, function, and mechanics at high altitude: chronic remodeling in Sherpa vs. short-term lowlander adaptation. *J Appl Physiol (1985)*. 2014;117(3):334−343.

[4] . Davis P, Pattinson K, Mason N, *et al*. High Altitude Illness. *BMJ Military Health.* 2011;157:12-17.

[5] . Palmer BF. Physiology and pathophysiology with ascent to altitude. *Am J Med Sci*. 2010;340(1):69−77.

[6] . Moore LG. Measuring high-altitude adaptation. *J Appl Physiol (1985)*. 2017;123(5):1371−1385.

[7] . Lang R M , Bierig M , Devereux R B , *et al*. Recommendations for Chamber Quantification: A Report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, Developed in Conjunction with the European Association of Echocardiography, a Branch of the European Society of Cardiology[J]. Journal of the American Society of Echocardiography, 2005, 18(12):1440-1463.

[8] . Yao G H, Deng Y, Liu Y, *et al*. Echocardiographic Measurements in Normal Chinese Adults Focusing on Cardiac Chambers and Great Arteries: A Prospective, Nationwide, and Multicenter Study[J]. Journal of the American Society of Echocardiography, 2015, 28(5):570-579.

[9] . Yao G H, Zhang M, Yin L X , *et al*. Doppler Echocardiographic Measurements in Normal Chinese Adults (EMINCA): A prospective, nationwide, and multicentre study[J]. European Heart Journal Cardiovascular Imaging, 2016, 17(5):512-522.

[10] . Nishimura RA, Otto CM, Bonow RO, *et al*. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.*J Am Coll Cardiol*. 2014;63(22):e57-e185.

[11] . Rudski L G , Lai W W , Afilalo J , *et al*. Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from the American Society of Echocardiography[J]. Journal of the American Society of Echocardiography Official Publication of the American Society of Echocardiography, 2010, 23(7):685-713.

[12] . Bärtsch P, Gibbs JS. Effect of altitude on the heart and the lungs. Circulation. 2007 Nov 6;116(19):2191-202.

[13] . Dhar P, Sharma VK, Das SK, *et al*. Differential responses of autonomic function in sea level residents, acclimatized lowlanders at >3500 m and Himalayan high altitude natives at >3500 m: A cross-sectional study. Respir Physiol Neurobiol. 2018 Aug;254:40-48.

[14] . Bilo G, Caravita S, Torlasco C, *et al*. Blood pressure at high altitude: physiology and clinical implications. Kardiol Pol. 2019 Jun 25;77(6):596-603.

[15] . Maufrais C, Rupp T, Bouzat P, *et al*. Heart mechanics at high altitude: 6 days on the top of Europe. Eur Heart J Cardiovasc Imaging. 2017 Dec 1;18(12):1369-1377.

[16] . Stembridge M, Ainslie PN, Hughes MG, *et al*. Impaired myocardial function does not explain reduced left ventricular filling and stroke volume at rest or during exercise at high altitude. J Appl Physiol (1985). 2015 Nov 15;119(10):1219-27.

[17] . Sareban M, Perz T, Macholz F, *et al*. Impairment of left atrial mechanics does not contribute to the reduction in stroke volume after active ascent to 4559 m. Scand J Med Sci Sports. 2019 Feb;29(2):223-231.

[18] . Boussuges A, Molenat F, Burnet H, *et al*. Operation Everest III (Comex '97): modifications of cardiac function secondary to altitude-induced hypoxia. An echocardiographic and Doppler study. Am J Respir Crit Care Med. 2000 Jan;161(1):264-70.

[19] . Vendelin M, Bovendeerd PH, Engelbrecht J, *et al*. Optimizing ventricular fibers: uniform strain or stress, but not ATP consumption, leads to high efficiency. Am J Physiol Heart Circ Physiol. 2002 Sep;283(3):H1072-81.

[20] . Yang Y, Zha-Xi DJ, Mao W, *et al*. Comparison of Echocardiographic Parameters Between Healthy Highlanders in Tibet and Lowlanders in Beijing. High Alt Med Biol. 2018 Sep;19(3):259-264.

[21] . Stembridge M, Ainslie PN, Shave R. Short-term adaptation and chronic cardiac remodelling to high altitude in lowlander natives and Himalayan Sherpa. Exp Physiol. 2015 Nov;100(11):1242-6.

[22] . Stembridge M, Ainslie PN, Donnelly J, *et al*. Cardiac structure and function in adolescent Sherpa; effect of habitual altitude and developmental stage. Am J Physiol Heart Circ Physiol. 2016 Mar 15;310(6):H740-6.

[23] . Huez S, Faoro V, Guénard H, *et al*. Echocardiographic and tissue Doppler imaging of cardiac adaptation to high altitude in native highlanders versus acclimatized lowlanders. Am J Cardiol. 2009 Jun 1;103(11):1605-9.
[24] . Dubowitz G, Peacock AJ. Pulmonary artery pressure in healthy subjects at 4250 m measured by Doppler echocardiography. Wilderness Environ Med. 2007 Winter;18(4):305-11.
[25] . Penaloza D, Arias-Stella J. The heart and pulmonary circulation at high altitudes: healthy highlanders and chronic mountain sickness. Circulation. 2007 Mar 6;115(9):1132-46.
[26] . Mirrakhimov AE, Strohl KP. High-altitude Pulmonary Hypertension: an Update on Disease Pathogenesis and Management. Open Cardiovasc Med J. 2016 Feb 8;10:19-27.

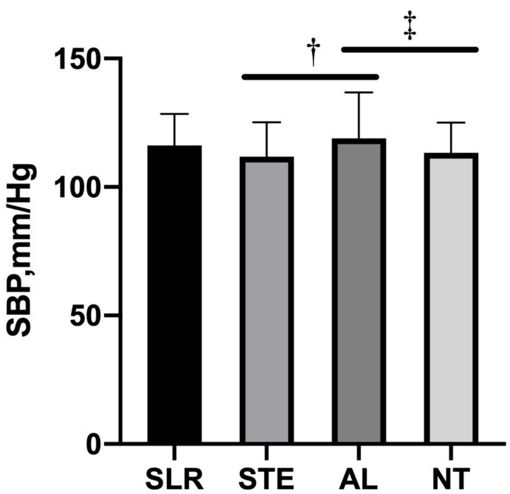

Figure 1. SBP in lowlanders at sea level residents and at high altitude and in native Tibetans. SBP in AL group was higher than that in STE and NT groups. SBP, systolic blood pressure; SLR, sea level residents; STE, short-term exposed; AL, acclimatized lowlanders; NT, native Tibetans. †*P*<0.05 *vs*. STE. ‡ *P*<0.05 *vs*. AL.

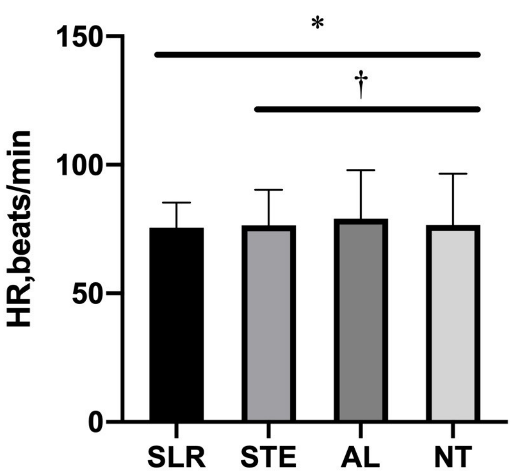

Figure 2. HR in lowlanders at sea level residents and at high altitude and in native Tibetans. HR in STE and AL groups were higher than that of NT group. HR, heart rate; SLR, sea level residents; STE, short-term exposed; AL, acclimatized lowlanders; NT, native Tibetans. **P*<0.05 vs. SLR. †*P*<0.05 vs. STE.

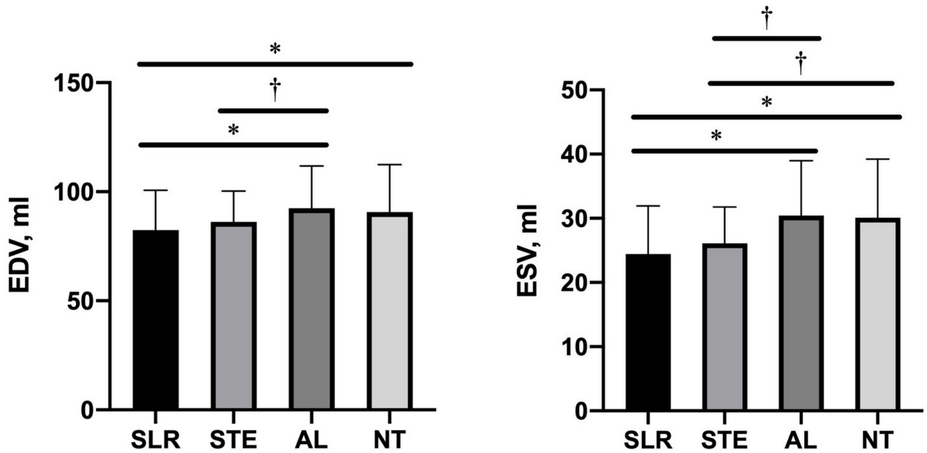

Figure 3. EDV(left) and ESV(right) in lowlanders at sea level residents and at high altitude and in native Tibetans. EDV and ESV in STE group were lower than those in AL and NT groups. EDV, end-diastolic volume; ESV, end-systolic volume. SLR, sea level residents; STE, short-term exposed; AL, acclimatized lowlanders; NT, native Tibetans. **P*<0.05 vs. SLR. †*P*<0.05 vs. STE.

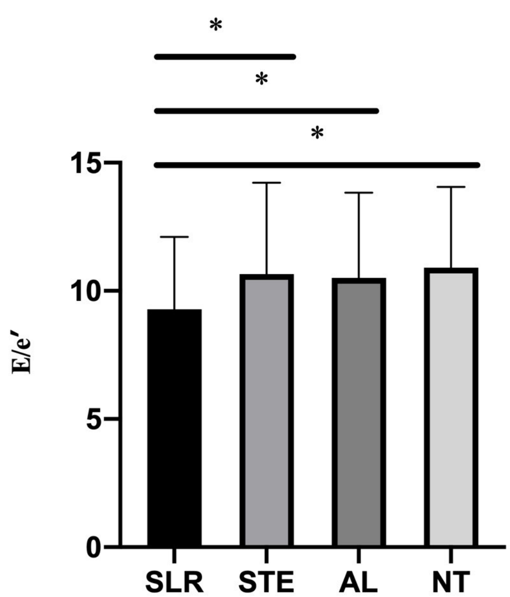

Figure 4. E/e′in lowlanders at sea level residents and at high altitude and in native Tibetans. E/e′ was larger in the HA population than in SLR. E/e′, ratio of E and e′. SLR, sea level residents; STE, short-term exposed; AL, acclimatized lowlanders; NT, native Tibetans. **P*<0.05 vs. SLR.

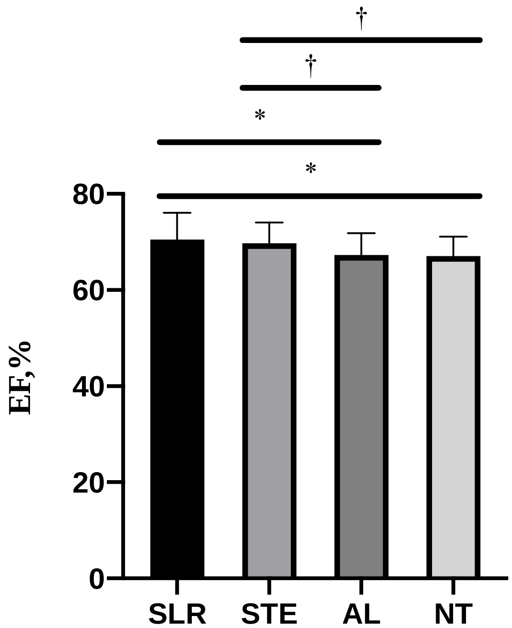

Figure 5. EF in lowlanders at sea level residents and at high altitude and in native Tibetans. EF in SLR and STE was higher than in AL and NT groups. EF, ejection fraction. SLR, sea level residents; STE, short-term exposed; AL, acclimatized lowlanders; NT, native Tibetans. **P*<0.05 vs. SLR. †*P*<0.05 vs. STE.

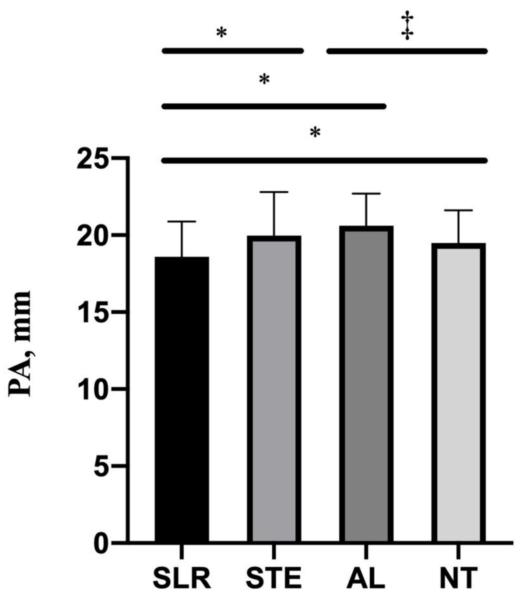

Figure 6. PA in lowlanders at sea level residents and at high altitude and in native Tibetans. PA in HA exposure groups, including STE, AL and NT, was greater than SLR. Furthermore, PA in NT group was smaller than that in AL group. PA, pulmonary artery. SLR, sea level residents; STE, short-term exposed; AL, acclimatized lowlanders; NT, native Tibetans. **P*<0.05 vs. SLR. ‡ *P*<0.05 *vs*. AL.

Table 1 Comparison of demographic features

Features	SLR	Lowlanders exposed to HA		NT
		STE	AL	
	n=80	n=75	n=77	n=69
Average altitude, m	532.87±94.22	3721.46±335.68*	3730.00±499.37*	3673.91±419.26*
Average time at plateau	/	23.56±9.00(days)	29.54±6.97(years)†	47.60±9.37(years)†‡

HA, high altitude; SLR, sea level residents; STE, short-term exposed; AL, acclimatized lowlanders; NT, native Tibetans. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; RBC, red blood cell. * *P*<0.05 *vs*. SLR. †*P*<0.05 *vs*. STE. ‡ *P*<0.05 *vs*. AL.

Table 2 Comparisons of the echocardiographic parameters

Features	SLR	Lowlanders exposed to HA		NT
		STE	AL	
	n=80	n=75	n=77	n=69
Left heart				
HR, beats/min	68.62±13.22	66.64±10.94	65.62±10.23	62.41±9.47*†
LVEDD, mm	42.80±3.76	43.37±3.19	45.14±3.04*†	44.88±3.58*†
LVESD, mm	25.60±3.06	26.08±2.55	28.21±2.77*†	28.04±3.25*†
EDV, ml	82.45±18.27	86.21±14.09	92.42±19.40*†	90.73±21.71*
ESV, ml	24.42±7.53	26.12±5.63	30.45±8.52*†	30.10±9.11*†
SV, ml	58.03±13.22	60.09±10.66	62.79±10.59	60.63±13.97
EF, %	70.48±5.54	69.72±4.33	67.29±4.56*†	67.07±4.02*†
FS, %	39.76±4.62	38.96±4.11	37.37±3.68*†	38.00±5.66*
IVSd, mm	7.91±1.13	8.69±1.56*	8.34±0.95	8.46±0.95*
LVPWd, mm	7.85±1.07	8.44±1.25*	8.28±0.86*	8.46±0.85*
LA, mm	28.29±2.95	29.73 ±3.15*	31.36±3.61*†	30.99±3.61*†
E, m/s	0.71±0.16	0.83±0.20*	0.73±0.19†	0.76±0.18†
A, m/s	0.63±0.14	0.69±0.17*	0.75±0.19*†	0.75±0.17*†
e′, cm/s	8.21±2.46	8.44±2.84	7.03±1.95*†	7.68±2.49
a′, cm/s	8.55±1.79	8.57±2.11	8.79±1.94	8.38±1.85
E/A	1.18±0.37	1.26±0.40	1.00±0.33*†	1.07±0.38†
E/e′	9.28±2.83	10.65±3.57*	10.51±3.32*	10.91±3.14*
Right heart				
RA, mm	30.00±3.68	31.37±3.65*	32.32±3.79*	32.13±4.33*
RV, mm	19.15±2.27	20.72±2.03*	20.26±2.06*	20.06±2.11*
PA, mm	18.60±2.28	19.97±2.83*	20.62±2.08*	19.49±2.13*‡
PV-v, m/s	0.85±0.13	0.92±0.18*	0.89±0.15	0.98±0.16*†‡
TR, mild/total	3/14	6/12	4/15	3/4
SPAP, mmHg	24.17±3.39	24.88±6.08	23.84±5.96	27.85±8.39

HR, heart rate; LVEDD, left ventricle diameter at end-diastole; LVESD, left ventricle diameter at end-systolic; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction; FS, fractional shortening; IVSd, interventricular septal end-diastolic thickness; LVPWd, left ventricle posterior wall end-diastolic thickness; LA, left atrium; E, Trans-mitral peak velocity at early-diastolic (E); A, Trans-mitral peak velocity at late-diastolic; e′, mitral annulus velocity at early- diastole; a′,mitral annulus velocity at late diastole; E/A, ratio of E and A; E/e′, ratio of E and e′;RA, right atrium; RV, right ventricle; PA, pulmonary artery; PV-v, the peak systolic flow velocity of pulmonary valve; TR, tricuspid

regurgitation; TR-v, Peak TR velocity; SPAP, systolic pulmonary artery pressure.
*$P<0.05$ *vs.* SLR. †$P<0.05$ *vs*. STE. ‡ $P<0.05$ *vs*. AL.