



Anatomical and hemodynamic evaluations of the heart and pulmonary arterial pressure in healthy children residing at high altitude in China ☆☆☆



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ABSTRACT

Objectives: Altitude-hypoxia induces pulmonary arterial hypertension and altered cardiac morphology and function, which is little known in healthy children at high altitude. We compared the cardiopulmonary measurements between the healthy children at 16 m and those at 3700 m in China and between the Hans and the Tibetans at 3700 m.

Methods: Echocardiography was assessed in 477 children (15 day–14 years) including 220 at 16 m and 257 at 3700 m. The dimensions and wall thickness of the left- and right-sided heart, systolic and diastolic functions including cardiac output index (CI) were measured using standard methods. Mean pulmonary arterial pressure (mPAP) was estimated by the Doppler waveforms in the main pulmonary artery.

Results: Compared to the 16 m-group, 3700 m-group had higher mPAP, increasing dilatation of the right heart, and slower decrease in right ventricular hypertrophy in 14 years ($p < 0.05$). The left heart morphology was not different ($p > 0.20$). Systolic and diastolic functions of both ventricles were significantly reduced, but CI was higher ($p < 0.0001$). There was no difference in any measurement between the Hans and the Tibetans ($p > 0.05$).

Conclusions: Children living at high altitude in China have significantly higher mPAP, dilated right heart and slower regression of right ventricular hypertrophy in the first 14 years of life. Systolic and diastolic functions of both ventricles were reduced with a paradoxically higher CI. There was no significant difference in these features between the Hans and the Tibetans. These values provide references for the care of healthy children and the sick ones with cardiopulmonary diseases at high altitude.

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1. Introduction

The heart and pulmonary circulation in people living at high altitude exhibit important physiological and morphologic characteristics in adaptation to chronic hypoxia. Knowledge in this field has been progressed over the past 5 decades, especially in the 1960s by the Peruvian investigators. The first direct measurement of increased pulmonary arterial pressure by cardiac catheterization was in the Andeans in Peru (4540 m) in 1956 [1]. It remained to 1962 for Penalosa et al. to make the crucial connection between chronic hypoxia and pulmonary hypertension [2]. Subsequently, Arias-Stella and others reported morphological alterations of the right heart. Right

ventricular hypertrophy was found from the heart specimens of children and adults at high altitude when compared to those at sea level [3,4]. Subnormal cardiac output was also noted in adults at rest and during exercises [5]. It is not until recently that myocardial function has been studied in details using echocardiography in healthy adults living at high altitude, showing altered diastolic function and preserved systolic function of both ventricles [6]. In addition, it has been realized that the genetic adaptation through varied number of generations and millennia of life at high altitude is an important determinant of the cardiopulmonary alterations [7]. It has been documented that the Tibetans, with the oldest altitude ancestry in the world, have the most optimal adaptations with normal pulmonary arterial pressure and exercise capacity [8]. However, paucity of data exists about the developmental changes of the cardiac morphology and function and pulmonary arterial pressure in children born and living at high altitude during the early years of life [9,10], none in the Tibetan children. Jiuzhi County in Qinghai Province, China is located at 3700 m and has a population mixed with the migrated Hans in the past 50–60 years and the native Tibetans. Therefore,

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this study aimed, first, to obtain cross-sectional evaluation of the cardiac morphology and function and pulmonary arterial pressure using echocardiography in children from neonates to 14 years old in Jiuzhi County in comparison to children living at 16 m in Shanghai; second, to compare these measurements between the Han children and the Tibetan children at 3700 m.

2. Methods

2.1. Subjects

The study was prospectively conducted in accordance with research protocols approved by the institutional Research Ethics Boards at Qinghai Women's and Children's Hospital and Shanghai Children's Medical Center. The subjects were enrolled from the local child healthcare clinics, nursery and primary schools during the period of 1998–2002. Physical examination, electrocardiography (ECG) and chest X-ray were performed to exclude any child with cardiopulmonary diseases. A total of 477 healthy children (age: 15 days–14 years, median: 6.5 years) were studied, including 220 children in the sea-level group (SLG) at 16 m in Shanghai (133 boys and 87 girls) and 257 in the high altitude group (HAG) at 3700 m in Jiuzhi County (142 boys and 115 girls, $p < 0.05$ for gender distribution). All the children in Shanghai were Hans, whereas there were 117 Hans and 140 native Tibetans in Jiuzhi County. Children in the two altitude groups were divided into 7 age groups (1 month, ~6 months, ~1 year, ~3 years, ~6 years, ~10 years and ~14 years) (Table 1). A pulse oximeter was placed at the big toe of each child to measure arterial oxygen saturation (SaO₂).

2.2. Echocardiographic assessments of the cardiac morphology and function and pulmonary arterial pressure

One experienced echocardiographer (H-Y Q) from Qinghai Women and Children's Hospital performed two-dimensional color Doppler echocardiography in all the children, sequentially in Jiuzhi County and then in Shanghai. Images and ECG were acquired using Hewlett-Packard-8500 and 2.5, 3.5 or 5.0-MHz transthoracic transducer (Andover, MA, U.S.A.) when children were awake and quiet, or sedated by 10% hydrochloride occasionally if necessary. All echocardiographic studies were recorded and measurements were taken in triplicate and averaged. Analysis of the measurements was made in the digital storing program Xcelera (Philips, Amsterdam, The Netherlands) offline by the echocardiographer (H-Y Q).

2.3. Cardiac morphology

The dimensions of the cardiac chambers and main arteries were obtained using standard views including right atrium (RA), right ventricle (RVD) and right ventricular outflow tract (RVOT), main pulmonary artery (PA), left ventricle in systole and diastole (LVs and LVd) and aortic root (AO). PA and AO ratio (PA/AO) was calculated. The thickness of the ventricular walls was also obtained including right ventricular anterior wall (RVAW), interventricular septum (IVS) and left ventricular posterior wall in systole and diastole (LVPWs and LVPWd) using left ventricular long axis wall. The masses of left and right ventricles (LV_{MASS}, RV_{MASS}) were calculated by the following equations: [11]

$$LV_{mass} = 1.04 [(LVD + IVS + LVPW)^3 - LVD^3] - 13.6$$

$$RV_{mass} = 1.04 [(RVDd + IVSd + RVFWd)^3 - RVDd^3] - 13.6.$$

2.4. Cardiac function

2.4.1. Right ventricle

Systolic function – the areas of the right ventricle during systole and diastole in standard apical four-chamber view were measured to estimate the right ventricular ejection fraction (RVEF) without including RVOT. *Diastolic function* – a pulsed Doppler sample volume was placed at the tip of tricuspid valve leaflets to measure tricuspid E (VE_{TV}) and A (VA_{TV}) wave peak velocities, E/A_{TV} ratio and E wave deceleration time (EDT_{TV}). Isovolumic relaxation time (RIRT) was measured by subtracting the interval between the initiation of QRS complex of the ECG and the cessation of right ventricular outflow from the interval between the initiation of QRS complex wave and the initiation of E wave.

2.4.2. Left ventricle

Systolic function – the left ventricular length was measured from the apical four-chamber view. Left ventricular area was measured at the levels of the mitral valve and papillary muscles from a parasternal short axis view. All the measures were obtained during systole and diastole to estimate left ventricular ejection fraction (LVEF), cardiac output (CO) and cardiac output index (CI) using the modified Simpson method, without including the left ventricular outflow tract. Left ventricular long axis view was used to measure the fractional shortening (LVFS) and the mean velocity of circumferential fiber shortening (mVCF). Ejection time

Table 1
Mean ± SD values of demographic variables in the sea level and high altitude groups.

Age	Altitude	Number of patients	Weight (kg)	Height (cm)	BSA (m ²)	SaO ₂ (%)	Heart rate (bpm)
<1 m	16 m	19	3.5 ± 1.2	51 ± 5	0.21 ± 0.04	99 ± 1	149 ± 10
	3700 m	13	3.1 ± 0.6	50 ± 4	0.20 ± 0.02	91 ± 5	147 ± 19
1–6 m	16 m	23	6.9 ± 1.7	62 ± 4	0.34 ± 0.05	100 ± 0	140 ± 13
	3700 m	7	6.9 ± 0.9	63 ± 3	0.35 ± 0.02	89 ± 5	121 ± 16
7–12 m	16 m	19	9.3 ± 1.5	73 ± 3	0.44 ± 0.04	99 ± 2	123 ± 12
	3700 m	4	9.1 ± 1.0	75 ± 5	0.44 ± 0.04	90 ± 1	124 ± 21
13 m–3 y	16 m	26	11.7 ± 2.0	85 ± 6	0.53 ± 0.06	99 ± 1	111 ± 15
	3700 m	14	11.1 ± 2.5	82 ± 8	0.51 ± 0.08	90 ± 4	109 ± 12
4–6 y	16 m	45	17.5 ± 3.0	106 ± 7	0.72 ± 0.09	99 ± 2	102 ± 12
	3700 m	44	16.6 ± 3.1	105 ± 9	0.70 ± 0.09	90 ± 2	102 ± 16
7–10 y	16 m	50	25.2 ± 5.5	126 ± 9	0.94 ± 0.13	99 ± 1	86 ± 16
	3700 m	97	22.4 ± 3.7	122 ± 7	0.87 ± 0.10	91 ± 3	97 ± 15
11–14 y	16 m	30	42.9 ± 12.2	145 ± 23	1.36 ± 0.25	100 ± 1	82 ± 11
	3700 m	69	32.5 ± 6.4	140 ± 10	1.13 ± 0.15	91 ± 2	78 ± 12
<i>Statistics</i>							
P _{age}			<0.0001	<0.0001	<0.0001	0.79	<0.0001
P _{altitude}			0.80	0.99	0.82	<0.0001	0.29
P _{age * altitude}			0.038	0.53	0.036	0.87	0.11

BSA: body surface area; SaO₂: arterial oxygen saturation.

(LVET) was calculated by the time interval between aortic valve opening and closing. *Diastolic function* – a pulsed Doppler sample volume was placed at the tip of mitral valve leaflets to measure mitral E (VE_{MV}) and A (VA_{MV}) wave peak velocities and E/ A_{MV} and E wave deceleration time (EDT_{MV}). The isovolumic relaxation time (LIRT) was measured from the apical five-chamber view by simultaneous recording of the aortic and mitral flows.

2.4.3. Pulmonary arterial pressure

The mean pulmonary arterial pressure (mPAP) was estimated by the right ventricular systolic time interval (RSTI) that was derived from the Doppler waveforms in the main pulmonary artery, including pre-ejection period (PEP), acceleration time (AT), ejection time (ET), AT/ET ratio, right ventricular pre-ejection period (PEP) and acceleration time ratio (PEP/AT). The mean pulmonary arterial pressure (mPAP) was estimated using the following equation: [12]

$$\text{mPAP} = 27.79 + 35.42 \times \text{PEP/AT} - 50.85 \times \text{AT/ETc}$$

where AT/ETc indicates AT/ET corrected by the square root of R–R interval from the ECG.

3. Statistical methods

Data were described as mean \pm standard deviation. Chi-squared test was used to examine the difference in gender distribution between the two groups. Multivariate linear regression was used to examine the difference in demographic, cardiac morphological and functional, and pulmonary arterial pressure variables as dependent variables in relation to altitude, age groups and age altitude interactions as independent variables. The multivariate linear regression analysis of cardiac morphological and functional, and pulmonary arterial pressure variables was adjusted by body surface area (BSA) and gender. For some measures, various transformations of time (logarithmic and polynomial) were tested regarding the best fit for the age course. Additionally, the analysis of the variables related to time was adjusted by heart rate. The probability values of the altitude effect (P_{altitude}) indicated the difference in the overall levels of each variable between the two altitude groups. The probability values of the age group (P_{age}) effect indicated the overall change of each variable over the 7 age groups in the two altitude groups. The probability values of the interaction of altitude and age group ($P_{\text{altitude} \times \text{age}}$) indicated the difference in trends of each variable between the two altitude groups over the 7 age groups. Un-paired *t*-test was used to compare the variables between the Hans and the Tibetans at 3700 m. All data analyses were performed using SAS statistical software version 9.3 (SAS Institute, Inc., Cary, NC). A *p* value < 0.05 indicated a statistical significance.

4. Results

4.1. Comparison of demographic variables between the sea-level and high altitude groups

Compared to SLG, SaO_2 in HAG was significantly and consistently lower ($p < 0.0001$) without significant change with age in the two groups ($p = 0.79$). Weight, height and BSA increased significantly with age in both groups ($p < 0.0001$ for all). The increase in weight and BSA was significantly slower in HAG ($p = 0.038$ and $p = 0.036$, respectively), but not in height ($p = 0.53$). Heart rate decreased significantly with age ($p < 0.0001$), without significant difference between the two groups ($p = 0.29$). In addition, weight and BSA were significantly greater ($p = 0.001$ and $p = 0.04$, respectively), and heart rate was significantly slower in boys than in girls ($p = 0.005$). Height and SaO_2 were not significantly different between boys and girls ($p = 0.49$ and $p = 0.87$, respectively) (Table 1).

4.2. Comparison of pulmonary arterial pressure variables between the sea-level and high altitude groups

After adjusted by heart rate and gender, AT, ET, AT/ET and PEP significantly increased with age in both groups ($p < 0.0001$ for all). PEP/AT did not change significantly with age in either of the two groups ($p = 0.38$). Compared to SLG, AT and ET in HAG were significantly lower ($p = 0.0008$ and $p = 0.039$, respectively). PEP, PEP/AT and mPAP were significantly higher ($p < 0.0001$ for all). AT/ET was not significantly different between the two groups ($p = 0.11$). mPAP was significantly higher in the 14 years ($p < 0.0001$) with different trends during the 14 years. In HAG, mPAP was the highest in the neonatal period (35.1 ± 8.9 mm Hg), then rapidly decreased within 6 months (27.3 ± 11.8 mm Hg), followed by a gradual decrease thereafter ($p = 0.003$). mPAP in SLG did not change significantly with age ($p = 0.09$). No significant difference was found in any of the variables between boys and girls ($p = 0.35$ to $p = 0.82$ for all) (Table 2).

4.3. Comparison of cardiac morphological variables between the sea level and high altitude groups

4.3.1. Right heart

The analysis of the cardiac morphological variables was adjusted by BSA and gender. RA, RV, RVOT and PA significantly increased with age in both groups ($p = 0.05$, $p = 0.048$, $p = 0.01$ and $p < 0.0001$, respectively). RVAW and PA/AO did not change significantly with age in the two groups ($p = 0.15$ – 0.72). RVmass and RVmass/LVmass significantly decreased with age in both groups ($p < 0.0001$ for both). Compared to SLG, the increase in RA, RV and RVOT with age was significantly faster ($p = 0.0008$, $p = 0.035$ and $p < 0.0001$, respectively). PA and PA/AO were significantly larger throughout the 14 years ($p = 0.040$ and $p < 0.0001$, respectively). RVAW tended to be thinner (0.055). The overall RVmass and RVmass/LVmass were not significantly different between the two groups ($p = 0.34$ and $p = 0.80$, respectively). But the decrease in RVmass was significantly slower ($p = 0.005$) and the decrease in RVmass/LVmass trended to be slower ($p = 0.10$) (Table 3).

4.3.2. Left heart

After adjusted by BSA and gender, all the variables of the left heart significantly increased with age ($p < 0.05$ for all), except for LVPWd and IVS ($p = 0.75$ and $p = 0.99$, respectively). There was no significant difference in any of these variables between the two groups ($p = 0.20$ – 0.70 for all) (Table 4).

In addition, the dimensions of the right and the left heart were significantly greater in boys than in girls ($p < 0.03$ for all). The thickness of ventricular walls was not significantly different between boys and girls ($p > 0.3$ for all).

4.4. Comparison of cardiac functional variables between the sea level and high altitude groups

4.4.1. Right ventricle

Systolic function – RVEF did not change significantly with age ($p = 0.20$) and was significantly lower in HAG compared to SLG in the 14 years ($p < 0.0001$). *Diastolic function* – VE_{TV} was significantly related to time after polynomial transformation and showed a significant increased until 1 year ($p < 0.0001$), followed by a gradual decrease thereafter in both groups ($p < 0.0001$). VA_{TV} and EDT_{TV} significantly decreased with age in both groups ($p < 0.0001$ for both). E/ A_{TV} and RIRT significantly increased with age ($p < 0.0001$ and $p = 0.007$, respectively). Compared to SLG, VA_{TV} and RIRT were significantly higher ($p = 0.041$ and $p = 0.044$, respectively), VE_{TV} and E/ A_{TV} were significantly lower in the 14 years ($p < 0.0001$ and $p = 0.002$, respectively). EDT_{TV} trended to be shorter ($p = 0.058$) with a significantly slower decrease ($p = 0.002$) (Table 5).

Table 2
Mean ± SD values of pulmonary arterial pressure variables in the sea level and high altitude groups.

Age	Altitude	PEP (ms)	AT (ms)	ET (ms)	PEP/AT	AT/ET	mPAP (mm Hg)
<1 m	16 m	36 ± 6	78 ± 15	205 ± 25	0.49 ± 0.14	0.38 ± 0.06	14.5 ± 8.6
	3700 m	40 ± 10	52 ± 15	196 ± 14	0.79 ± 0.14	0.26 ± 0.08	35.1 ± 8.9
1–6 m	16 m	37 ± 6	82 ± 11	226 ± 24	0.45 ± 0.11	0.37 ± 0.06	15.4 ± 7.5
	3700 m	50 ± 12	80 ± 21	213 ± 32	0.69 ± 0.35	0.37 ± 0.08	27.3 ± 11.8
7–12 m	16 m	40 ± 7	92 ± 13	234 ± 27	0.44 ± 0.06	0.39 ± 0.05	14.8 ± 5.2
	3700 m	53 ± 10	83 ± 19	235 ± 13	0.68 ± 0.24	0.35 ± 0.08	25.1 ± 15.2
13 m–3 y	16 m	42 ± 8	97 ± 15	260 ± 27	0.44 ± 0.10	0.37 ± 0.06	17.7 ± 6.9
	3700 m	49 ± 11	81 ± 19	239 ± 29	0.65 ± 0.26	0.34 ± 0.07	26.8 ± 12.9
4–6 y	16 m	42 ± 7	115 ± 19	287 ± 22	0.38 ± 0.08	0.40 ± 0.06	14.8 ± 6.5
	3700 m	49 ± 11	96 ± 17	261 ± 25	0.53 ± 0.19	0.37 ± 0.06	24.1 ± 8.2
7–10 y	16 m	46 ± 9	123 ± 25	300 ± 30	0.39 ± 0.11	0.41 ± 0.07	16.6 ± 7.5
	3700 m	56 ± 13	104 ± 16	274 ± 25	0.56 ± 0.18	0.38 ± 0.05	23.1 ± 8.5
11–14 y	16 m	49 ± 10	131 ± 19	301 ± 25	0.38 ± 0.10	0.44 ± 0.06	15.3 ± 5.8
	3700 m	59 ± 12	116 ± 19	295 ± 25	0.52 ± 0.15	0.39 ± 0.06	23.3 ± 7.8
<i>Statistics</i>							
P _{age}		<0.0001	<0.0001	<0.0001	0.38	<0.0001	0.09
P _{altitude}		<0.0001	0.0008	0.039	<0.0001	0.11	<0.0001
P _{age * altitude}		0.12	0.63	0.69	0.01	0.99	0.003

AT, acceleration time; ET, ejection time; mPAP, mean pulmonary arterial pressure; PEP, pre-ejection period.

4.4.2. Left ventricle

Systolic function – LVEF was significantly related to age after logarithmic transformation. It showed a fast decrease until 1 year of age, followed by a slow decrease thereafter (p = 0.037). LVEF was not significantly different between the two groups (p = 0.40). LVFS did not change significantly with age (p = 0.69) and was significantly lower in HAG compared to SLG in the 14 years (p = 0.003). mVCF significantly decreased with age (p < 0.0001) and was significantly lower in HAG in the 14 years (p = 0.003). *Diastolic function* – VE_{MV}, VA_{MV} and EDT_{MV} were related to time after polynomial transformation, being significant increased until 1 year (p < 0.0001 for VE_{MV}, p = 0.004 and p = 0.032 for VA_{MV} and EDT_{MV}, respectively), followed by a gradual decrease thereafter (p < 0.0001 for all). Compared to SLG, VE_{MV} was significantly lower in the 14 years (p < 0.0001). VA_{MV} and EDT_{MV} were significantly lower before 6 month of age (p < 0.0001 and p = 0.010, respectively) and was not significantly different thereafter. E/A_{MV} and LIRT significantly increased with age (p < 0.0001 and p = 0.041, respectively) without significant difference between the two groups (p = 0.74 and p = 0.60, respectively). CI was related to time

after polynomial transformation and showed an increase until 1 year (p < 0.0001), followed by a gradual decrease thereafter in both groups (p < 0.0001). CI was significantly higher in HAG compared to SLG in the 14 years (p < 0.0001) (Table 6).

None of the cardiac functional variables was significant different between boys and girls (p > 0.10 for all). CI was significantly higher in boys than in girls (p = 0.042).

4.5. Comparison of demographic and cardiopulmonary variables between the Hans and the Tibetans in the high altitude group

No significant difference was found in any of the variables between the Han children and the Tibetan children at 3700 m (p > 0.10 for all).

5. Discussion

Our study demonstrated the developmental characteristics of cardiac morphology and function and pulmonary arterial pressure during the first 14 year of life in the healthy Han and Tibetan children born and

Table 3
Mean ± SD values of the right heart morphology in the sea level and high altitude groups.

Age	Altitude	RA (cm)	RV (cm)	RVOT (cm)	PA (cm)	PA/AO	RVAW (cm)	RVmass (g)	RVmass/LVmass
<1 m	16 m	0.9 ± 0.1	0.8 ± 0.1	1.0 ± 0.1	0.9 ± 0.1	0.94 ± 0.08	0.2 ± 0.0	1.79 ± 0.43	0.28 ± 0.07
	3700 m	0.9 ± 0.1	0.7 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.02 ± 0.08	0.2 ± 0.1	1.40 ± 0.40	0.25 ± 0.04
1–6 m	16 m	1.0 ± 0.1	0.9 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	0.96 ± 0.05	0.2 ± 0.0	2.20 ± 0.34	0.23 ± 0.06
	3700 m	1.3 ± 0.1	1.0 ± 0.2	1.7 ± 0.3	1.3 ± 0.1	1.09 ± 0.10	0.2 ± 0.1	2.70 ± 1.11	0.24 ± 0.07
7–12 m	16 m	1.2 ± 0.1	0.9 ± 0.1	1.4 ± 0.2	1.3 ± 0.1	0.94 ± 0.08	0.2 ± 0.0	2.46 ± 0.57	0.18 ± 0.05
	3700 m	1.2 ± 0.2	1.1 ± 0.2	1.7 ± 0.2	1.5 ± 0.2	1.07 ± 0.06	0.2 ± 0.0	2.93 ± 0.55	0.24 ± 0.05
13 m–3 y	16 m	1.3 ± 0.1	1.0 ± 0.2	1.5 ± 0.1	1.4 ± 0.1	0.99 ± 0.06	0.2 ± 0.0	2.69 ± 0.79	0.16 ± 0.04
	3700 m	1.4 ± 0.2	1.2 ± 0.2	1.8 ± 0.2	1.6 ± 0.2	1.08 ± 0.10	0.2 ± 0.1	3.95 ± 1.29	0.22 ± 0.05
4–6 y	16 m	1.4 ± 0.1	1.2 ± 0.2	1.8 ± 0.2	1.7 ± 0.2	0.96 ± 0.06	0.2 ± 0.1	3.80 ± 0.97	0.16 ± 0.05
	3700 m	1.6 ± 0.2	1.2 ± 0.2	1.9 ± 0.2	1.8 ± 0.1	1.08 ± 0.09	0.2 ± 0.1	4.07 ± 1.27	0.17 ± 0.05
7–10 y	16 m	1.5 ± 0.2	1.3 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	0.96 ± 0.07	0.2 ± 0.0	5.00 ± 1.48	0.15 ± 0.05
	3700 m	1.8 ± 0.2	1.3 ± 0.2	2.2 ± 0.2	2.0 ± 0.2	1.05 ± 0.10	0.2 ± 0.1	5.33 ± 1.85	0.16 ± 0.05
11–14 y	16 m	1.7 ± 0.3	1.5 ± 0.2	2.2 ± 0.3	2.1 ± 0.2	0.93 ± 0.06	0.3 ± 0.0	6.91 ± 2.46	0.14 ± 0.04
	3700 m	1.9 ± 0.2	1.5 ± 0.2	2.4 ± 0.2	2.2 ± 0.2	1.01 ± 0.12	0.3 ± 0.1	7.36 ± 2.48	0.16 ± 0.04
<i>Statistics</i>									
P _{age}		0.05	0.048	0.01	<0.0001	0.72	0.47	<0.0001	<0.0001
P _{altitude}		0.77	0.37	0.34	0.040	<0.0001	0.055	0.34	0.80
P _{age * altitude}		0.0008	0.035	<0.0001	0.05	0.18	0.06	0.005	0.10

AO, aortic root; LVmass, the mass of the left ventricles; PA, pulmonary artery; RA, right atrium; RV, right ventricular; RVAW, right ventricular anterior wall; RVmass, the mass of the right ventricles; RVOT, right ventricular outflow.

Table 4
Mean \pm SD values of the left heart morphology in the sea level and high altitude groups.

Age	Altitude	LA (cm)	LVD (cm)	LVs (cm)	AO (cm)	LVPWd (cm)	LVPWs (cm)	LVmass (g)	IVS (cm)
<1 m	16 m	1.0 \pm 0.1	1.8 \pm 0.3	1.0 \pm 0.2	1.0 \pm 0.1	0.3 \pm 0.0	0.5 \pm 0.1	6.83 \pm 2.41	0.26 \pm 0.05
	3700 m	0.9 \pm 0.1	1.8 \pm 0.1	1.1 \pm 0.1	1.0 \pm 0.1	0.2 \pm 0.1	0.5 \pm 0.1	5.78 \pm 1.71	0.25 \pm 0.05
1–6 m	16 m	1.2 \pm 0.1	2.3 \pm 0.3	1.1 \pm 0.3	1.2 \pm 0.1	0.3 \pm 0.0	0.6 \pm 0.1	10.21 \pm 2.65	0.28 \pm 0.04
	3700 m	1.3 \pm 0.1	2.3 \pm 0.4	1.2 \pm 0.3	1.2 \pm 0.1	0.3 \pm 0.0	0.7 \pm 0.1	11.55 \pm 4.12	0.31 \pm 0.04
7–12 m	16 m	1.3 \pm 0.3	2.6 \pm 0.2	1.2 \pm 0.2	1.4 \pm 0.1	0.3 \pm 0.1	0.6 \pm 0.1	14.28 \pm 3.31	0.32 \pm 0.04
	3700 m	1.4 \pm 0.3	2.5 \pm 0.1	1.4 \pm 0.1	1.4 \pm 0.1	0.3 \pm 0.0	0.7 \pm 0.1	12.18 \pm 0.41	0.30 \pm 0.00
13 m–3 y	16 m	1.5 \pm 0.1	2.8 \pm 0.3	1.5 \pm 0.2	1.5 \pm 0.1	0.3 \pm 0.1	0.7 \pm 0.1	17.37 \pm 4.37	0.31 \pm 0.05
	3700 m	1.5 \pm 0.1	2.7 \pm 0.3	1.5 \pm 0.2	1.5 \pm 0.1	0.4 \pm 0.1	0.8 \pm 0.1	18.35 \pm 4.94	0.36 \pm 0.05
4–6 y	16 m	1.8 \pm 0.1	3.3 \pm 0.3	1.8 \pm 0.4	1.7 \pm 0.2	0.4 \pm 0.1	0.7 \pm 0.2	24.48 \pm 5.25	0.35 \pm 0.05
	3700 m	1.7 \pm 0.2	3.1 \pm 0.3	1.8 \pm 0.2	1.7 \pm 0.2	0.4 \pm 0.1	0.8 \pm 0.1	23.90 \pm 5.87	0.38 \pm 0.07
7–10 y	16 m	1.9 \pm 0.2	3.6 \pm 0.4	2.0 \pm 0.3	1.9 \pm 0.2	0.4 \pm 0.1	0.9 \pm 0.1	35.25 \pm 9.58	0.40 \pm 0.05
	3700 m	1.9 \pm 0.2	3.5 \pm 0.3	2.1 \pm 0.3	1.9 \pm 0.2	0.4 \pm 0.1	0.9 \pm 0.1	33.72 \pm 9.17	0.41 \pm 0.08
11–14 y	16 m	2.2 \pm 0.3	4.1 \pm 0.5	2.2 \pm 0.4	2.3 \pm 0.2	0.5 \pm 0.1	1.0 \pm 0.2	50.69 \pm 15.95	0.45 \pm 0.08
	3700 m	2.1 \pm 0.2	3.9 \pm 0.3	2.1 \pm 0.3	2.2 \pm 0.2	0.5 \pm 0.1	1.0 \pm 0.1	46.53 \pm 10.39	0.47 \pm 0.07
<i>Statistics</i>									
P_{age}		<0.0001	<0.0001	<0.0001	<0.0001	0.99	0.004	0.049	0.75
P_{altitude}		0.90	0.28	0.38	0.50	0.16	0.54	0.32	0.65
$P_{\text{age} + \text{altitude}}$		0.94	0.87	0.85	0.61	0.08	0.20	0.09	0.10

AO, aortic root; IVS, interventricular septum; LA, left atrium; LVD, left ventricular in diastole; LVmass, the mass of the left ventricles; LVPWd, left ventricular posterior wall in diastole; LVPWs, left ventricular posterior wall in systole; LVs, left ventricle in systole.

living at 3700 m in Jiuzhi County, Qinghai Province, China. Compared to children at the sea level in Shanghai, children at 3700 m had a consistently lower SaO₂, slower growth in body weight and BSA, higher pulmonary arterial pressure, larger right heart, and less regressed right ventricular hypertrophy. The left heart morphology was not significantly different. Systolic and diastolic functions of both ventricles were reduced. Paradoxically, CI was significantly greater. Surprisingly, none of the variables was significantly different between the Han children and the Tibetan children living at high altitude.

People living in high altitude environments are exposed to an environment of hypobaric hypoxia with low ambient partial pressure of oxygen. An atmospheric pressure of 500 mm Hg at 3700 m leads to the partial pressure of oxygen of 105 mm Hg, representing 66% of that at the sea level, limiting oxygen supply in the air and the blood. SaO₂ reduced to 90% in the high altitude group of children in our study. Altitude adaptation implies a series of physiological changes in the oxygen transport system to maintain optimal oxygen supply to meet oxygen consumption of the tissues, including polycythemia, lung and tissue diffusion capacity, systemic vascular resistance and cardiac output. The

role of pulmonary arterial hypertension in this process has not been clearly established.

The classic and pioneer studies on altitude related pulmonary arterial hypertension emerged in the 1960s in the Andeans at 4540 m by the Peruvian investigators. The first report of direct measurements of pulmonary arterial hypertension using cardiac catheterization was in 7 healthy adult volunteers [1]. This work was extended to include 32 children 1 to 14 years of age [13] and 38 adults 17 to 38 years of age [13]. Later, an additional group of newborns was studied [14]. Thus, a complete profile is depicted about the development of pulmonary arterial hypertension from neonate to adulthood in healthy highlanders, specifically speaking, the Andeans in Peru. mPAP of 60 mm Hg was found in the newborns, similar to that at the sea level. After birth, the rapid decline seen in the sea level residents is slowed, and a mild to moderate degree of pulmonary arterial hypertension remained through adulthood. mPAP was 45 mm Hg in children 1 to 5 years of age and 28 mm Hg in adolescents and adults (12 mm Hg in sea level residents). Similar pattern, but to a lesser degree, was observed in children at 3700 m in our study using echocardiography. mPAP was

Table 5
Mean \pm SD values of the right ventricular systolic and diastolic functional variables in the sea level and high altitude groups.

Age	Altitude	RVEF (%)	E _{TV} (cm/s)	A _{TV} (cm/s)	E/A _{TV} (cm/s)	RIRT (s)	EDT _{TV} (ms)
<1 m	16 m	63 \pm 9	43 \pm 11	53 \pm 10	0.84 \pm 0.23	31 \pm 17	5.34 \pm 2.24
	3700 m	60 \pm 6	40 \pm 8	57 \pm 7	0.69 \pm 0.07	29 \pm 10	6.29 \pm 1.53
1–6 m	16 m	60 \pm 8	55 \pm 13	53 \pm 13	1.09 \pm 0.33	28 \pm 9	6.56 \pm 1.55
	3700 m	50 \pm 8	49 \pm 6	62 \pm 8	0.78 \pm 0.08	46 \pm 21	5.33 \pm 1.40
7–12 m	16 m	59 \pm 7	60 \pm 14	52 \pm 15	1.22 \pm 0.30	32 \pm 6	5.62 \pm 1.43
	3700 m	53 \pm 4	44 \pm 9	58 \pm 15	0.77 \pm 0.05	40 \pm 8	4.90 \pm 1.77
13 m–3 y	16 m	58 \pm 6	63 \pm 15	41 \pm 10	1.56 \pm 0.37	32 \pm 11	6.07 \pm 2.47
	3700 m	50 \pm 16	45 \pm 7	53 \pm 13	0.92 \pm 0.29	51 \pm 12	5.02 \pm 0.90
4–6 y	16 m	61 \pm 7	63 \pm 12	40 \pm 8	1.58 \pm 0.29	37 \pm 11	5.05 \pm 1.28
	3700 m	56 \pm 7	54 \pm 12	48 \pm 11	1.18 \pm 0.38	53 \pm 16	5.11 \pm 1.24
7–10 y	16 m	61 \pm 7	59 \pm 11	34 \pm 8	1.80 \pm 0.47	43 \pm 15	4.24 \pm 1.32
	3700 m	55 \pm 6	59 \pm 11	43 \pm 11	1.46 \pm 0.47	55 \pm 16	5.25 \pm 1.25
11–14 y	16 m	62 \pm 8	57 \pm 11	31 \pm 8	1.90 \pm 0.36	44 \pm 15	3.87 \pm 0.93
	3700 m	54 \pm 9	58 \pm 13	37 \pm 10	1.65 \pm 0.47	51 \pm 15	4.92 \pm 1.17
<i>Statistics</i>							
P_{age}		0.20	<0.0001 ^a	<0.0001	<0.0001	0.007	<0.0001
P_{altitude}		p < 0.0001	<0.0001	0.041	0.002	0.044	0.058
$P_{\text{age} + \text{altitude}}$		0.30	<0.0001	0.83	0.72	0.36	0.002

A_{TV}, tricuspid valve A wave peak velocity; EDT_{TV}, tricuspid E wave deceleration time; E_{TV}, tricuspid valve E wave peak velocity; RIRT, right ventricular isovolumetric relaxation time; RVEF, right ventricular ejection fraction.

^a Related to time after logarithmic transformation.

Table 6

Mean ± SD values of the left ventricular systolic and diastolic functional variables and cardiac index in the sea level and high altitude groups.

Age	Altitude	LVEF (%)	LVFS (%)	mVCF (circ/s)	E _{MV} (cm/s)	A _{MV} (cm/s)	E/A _{MV} (cm/s)	LIRT (ms)	EDT _{MV} (ms)	CI (L/min * m ²)
<1 m	16 m	69 ± 6	46 ± 6	2.28 ± 0.31	61 ± 23	54 ± 15	1.13 ± 0.25	37 ± 7	8.65 ± 4.55	2.58 ± 0.54
	3700 m	65 ± 5	39 ± 5	2.03 ± 0.29	52 ± 11	44 ± 9	1.21 ± 0.20	37 ± 6	7.02 ± 2.93	2.60 ± 0.75
1–6 m	16 m	59 ± 8	46 ± 5	2.13 ± 0.35	88 ± 14	65 ± 17	1.42 ± 0.33	36 ± 5	9.36 ± 3.62	2.68 ± 0.46
	3700 m	60 ± 8	46 ± 9	1.93 ± 0.33	78 ± 23	62 ± 10	1.27 ± 0.31	47 ± 16	7.32 ± 1.61	3.24 ± 0.60
7–12 m	16 m	60 ± 5	48 ± 5	2.04 ± 0.28	90 ± 17	63 ± 16	1.45 ± 0.29	40 ± 7	9.25 ± 3.30	3.13 ± 0.58
	3700 m	63 ± 2	45 ± 5	1.83 ± 0.22	89 ± 19	70 ± 19	1.30 ± 0.12	47 ± 8	10.26 ± 5.67	3.83 ± 0.70
13 m–3 y	16 m	58 ± 5	47 ± 5	1.97 ± 0.28	90 ± 17	58 ± 11	1.59 ± 0.39	42 ± 6	8.05 ± 2.05	2.71 ± 0.43
	3700 m	59 ± 5	45 ± 4	1.76 ± 0.25	88 ± 14	56 ± 15	1.67 ± 0.54	47 ± 11	8.29 ± 2.35	3.57 ± 0.60
4–6 y	16 m	61 ± 6	47 ± 7	1.85 ± 0.38	92 ± 11	50 ± 11	1.92 ± 0.43	44 ± 8	7.16 ± 1.28	3.17 ± 0.63
	3700 m	60 ± 6	42 ± 5	1.68 ± 0.26	87 ± 12	51 ± 12	1.80 ± 0.57	49 ± 14	7.53 ± 2.42	3.74 ± 0.95
7–10 y	16 m	63 ± 5	46 ± 6	1.72 ± 0.30	89 ± 17	42 ± 11	2.23 ± 0.66	45 ± 8	6.24 ± 1.90	2.80 ± 0.59
	3700 m	56 ± 7	41 ± 6	1.53 ± 0.30	87 ± 13	48 ± 11	1.91 ± 0.43	56 ± 13	6.96 ± 1.89	3.27 ± 0.74
11–14 y	16 m	64 ± 5	47 ± 7	1.64 ± 0.30	85 ± 14	41 ± 11	2.18 ± 0.60	46 ± 7	5.92 ± 1.82	2.70 ± 0.55
	3700 m	59 ± 5	44 ± 6	1.50 ± 0.32	88 ± 12	43 ± 11	2.13 ± 0.47	53 ± 9	6.14 ± 1.08	3.26 ± 0.65
<i>Statistics</i>										
P _{age}		0.037 ^a	0.69	<0.0001	age <0.0001 ^b age ² < 0.0001	age 0.04 ^b age ² < 0.0001	<0.0001	0.041	age 0.04 age 20.0001	age <0.0001 ^b age ² < 0.0001
P _{altitude}		0.10	0.003	0.003	<0.0001	0.004	0.74	0.60	0.032	<0.0001
P _{age * altitude}		0.97	0.49	0.60	<0.0001	<0.0001	0.18	0.040	0.012	0.58

A_{MV}, mitral valve A wave peak velocity; CI, cardiac output index; EDT_{MV}, mitral valve E wave deceleration time; E_{MV}, mitral valve E wave peak velocity; LIRT, left ventricular isovolumetric relaxation time; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; mVCF, the mean velocity of circumferential fiber shortening.

Age indicates the early trend; age² indicates the later trend.

^a Related to time after logarithmic transformation.

^b Related to time after polynomial transformation.

from 35 to 27 mm Hg from neonatal period to 6 month, then gradually decreased to 25 mm Hg thereafter, whereas it remained at about 15 mm Hg throughout infancy and childhood in the sea level group.

Pulmonary arterial hypertension leads to right ventricular hypertrophy in similar patterns, as observed in the studies of heart specimens obtained from the Andeans. The rapid decline in right ventricular hypertrophy seen in the sea level newborns is also slowed and mild to moderate right ventricular hypertension is persistent throughout life [15, 16]. A recent echocardiographic study has also confirmed the persistent thickness of the right ventricular wall in the Bolivian infants at 3800 m [10]. The left heart is normal [3,17,18]. Our data also showed the comparable morphology of the left heart to the sea level group. However, the right heart was different from the previous studies in terms of the following. Right ventricular hypertrophy was not a prominent feature in the high altitude group in our study. These children only showed a slower decrease in RVmass, but the overall RVmass, RVmass/LVmass and RVAW in the 14 years were not significantly different from the sea level group. Instead, increasing dilatation of the right heart is more prominent from RA, RV, RVOT to PA over the 14 years. This is an unusual finding in healthy highlanders, but has been reported in those diagnosed as chronic mountain sickness who did not have overt heart failure symptoms or myocardial dysfunction except for an increased RV Tei index [18].

Chronic high altitude exposure may be associated with altered myocardial function, which is generally considered right-sided and diastolic [7,18,19]. Huez et al., using echocardiographic and tissue Doppler imaging, reported altered right and left ventricular diastolic function in the Bolivian adults as indicated by the decreased tricuspid annular plane excursion, tricuspid annular S waves, increased RV Tei indexes, and decreased EMV and E/AMV. The systolic function of RV and LV was preserved [6]. Maignan et al. also reported increased RV Tei index in the Andean adults. Paucity of data exists in healthy children born and living at high altitude. The only pediatric study, to our knowledge, was conducted by Huicho et al. in healthy children from 2 months to 19 years living at Tintaya, a mining camp, located in the Andean plateau (4100 m). They found that the right and left heart morphologic and functional echocardiographic measurements were comparable to sea-level reference populations [9]. Those children were not typical natives, however, as explained by the investigators. Although they had high-

altitude genetic ancestry, most of them spent a few months at lower altitudes in summer holidays. The nutritional status and the life conditions were relatively good in Tintaya children [20]. Our study found different features of cardiac function from the previous findings, showing reduced diastolic as well as systolic function of both ventricles in healthy children at 3700 m. The reduced left ventricular function may be due, at least partly, to the adverse impact of the pressure-loaded right ventricle via ventricular–ventricular interactions [21]. It should be noted that in the presence of left ventricular dysfunction, left atrial and consequently pulmonary venous pressure could also be increased. Although no data of pulmonary venous pressure in our current study, this might be a potential component contributing to the higher pulmonary arterial pressure in the high altitude group. The implication of the dilated right heart in combination with reduced systolic and diastolic function of both ventricles is unclear in the presence of paradoxically higher CI.

Indeed, CI was higher in the high altitude children than those at sea level in our study. This is again different from the previous findings showing comparable cardiac output to the sea level residents [13,18]. The reason might be plausible. It has been reported that high altitude adults, Tibetans, at 4200 m have substantially higher circulating concentrations of bioactive NO and its products, including nitrate and nitroso proteins, which control vascular resistance, blood flow and cellular respiration. Consequently, they have lower systemic vascular resistance and greater systemic blood flow to offset the low arterial oxygen content and enable oxygen delivery [22]. Additionally, NO has well established effects to decrease oxygen consumption through improved efficiency of energy production during cellular respiration, via enhancing coupled respiration and ATP content and increasing mitochondrial numbers through biogenesis [23,24]. The chronic reduction in oxygen consumption is in consistency with the slower physical growth as an adaptation mechanism to high altitude, which was found in our study and others' [22]. This mechanism may contribute to maintain the optimal balance of oxygen transport in this chronically hypoxia population. It should be mentioned that our study included the Hans and the Tibetans. The NO mechanism found in the Tibetan adults might be also applicable to the Han children at high altitude, given the comparable cardiac morphology and function and pulmonary arterial pressure between the Han children and the Tibetan children in our study.

The last finding of our study, i.e., the comparable cardiopulmonary features between the Hans and the Tibetans, was a surprise. The Tibetans are known to have the most optimal genetic adaptation to high altitude following a process of natural selection through millennia and numerous generations of life in an environment of chronic hypoxia since prehistoric times [7]. The Hans have migrated to the high altitude region in Qinghai within the past 50–60 years. It has been documented that the Tibetans have minimal elevation of pulmonary artery pressure, no hypoxic pulmonary vasoconstriction and non-muscularized pulmonary resistance arterioles [8,25,26]. Previous Chinese investigators reported a lower pulmonary pressure response to exercise in the Tibetan natives than in the Han immigrants [26]. It should be noted that the studies mentioned above were exclusively obtained from adults. A previous pediatric study may support our finding showing the comparably high prevalence of right ventricular strain on electrocardiography between the Tibetan children and the Han children [27]. As such, it appears that the advantageous adaptations found in the Tibetan adults might have not been developed yet by 14 years of age.

Our study has important implications. More than 140 million people worldwide live above 2500 m altitude. Of them, 80 million live in Asia who are considerably less studied. The echocardiographic values of cardiac morphology and function and pulmonary arterial pressure in healthy children born and living at high altitude can be used as reference values in the care of healthy children during normal growth and in clinical management and research in sick children with congenital or acquired cardiopulmonary diseases.

6. Limitations

There are several limitations in this study as the following. Firstly, one echocardiographer performed all echocardiograms and she was not blinded. This might introduce a certain degree of “observer bias”, but should not affect the results of the significance in the comparisons between the two groups, given that the echocardiographer is very experienced and disciplined. Secondly, the estimation of mean pulmonary arterial pressure used a method that was developed in China [12] and has not been compared to other estimating methods. Nonetheless, this method was validated against the direct cardiac catheterization assessments in the original study and was used in both SLG and HAG groups. Therefore, the comparison of mPAP between the two altitudes is considered valid. Second, there are other differences between the two populations, such as socioeconomic and life conditions may well be present and potentially confounding to our findings, e.g., myocardial function. These factors were not included in our study, but are considered unlikely to have more significant effect on pulmonary arterial pressure than altitude-related hypoxia. Lastly, the cardiopulmonary development after 14 years remains to be explored in both the Hans and the Tibetans at high altitude.

7. Conclusions

Children born and living at 3700 m in China, when compared to the sea level children, have a significantly higher pulmonary arterial pressure, dilated right heart and slower regression of right ventricular hypertrophy in the first 14 years of life. The morphology of the left heart was not significantly different. Systolic and diastolic functions of both ventricles were reduced with a paradoxically higher CI. There was no significant difference in the cardiopulmonary features between the Han children and the Tibetan children. These values provide references for the care of healthy children during normal growth and the clinical management and research in sick children with congenital or acquired cardiopulmonary diseases at high altitude. Further systematic studies are warranted to extend the age range to define the developmental characteristics from newborn to adulthood and to examine the potential differences between the Han adolescents and the Tibetan adolescents and adults in adaptations to high altitude.

Conflict of interest

There are no conflicts of interest.

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