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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.

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 Penaloza 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 (SaO_2).

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]

$$\mathrm{LVmass} = 1.04\left[(\mathrm{LVD} + \mathrm{IVS} + \mathrm{LVPW})^3 - \mathrm{LVD}^3\right] - 13.6$$
$$\mathrm{RVmass} = 1.04\left[(\mathrm{RVDd} + \mathrm{IVSd} + \mathrm{RVFWd})^3 - \mathrm{RVDd}^3\right] - 13.6.$$

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
Statistics							
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; SaO_2: arterial oxygen saturation.