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Newborn screening for congenital heart disease using echocardiography and follow-up at high altitude in China

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ABSTRACT

Background: Pulse oximetry screening for critical congenital heart disease (CHD) is inapplicable to high altitude due to the variedly decreased arterial saturations and rare complex CHD. We examined the incidence and spectrum of CHD in newborns using echocardiography at high altitude and followed up their outcomes.
Methods: A total of 1337 babies were studied. Echocardiography was performed in 1002 asymptomatic newborns (3–5 days). In the same period, retrospectively studied 394 newborns (≤2 days) admitted to the NICU where echocardiograph was performed in 335. In both groups, follow-up was made at 1–3, 6 and 12–18 months.
Results: The incidence of CHD in asymptomatic newborns was 27.8%, consisting secundum atrial septal defect (ASD) [175 (62.7%)], patent ductus arteriosus (PDA) [61 (21.9%)], ventricular septal defect (VSD) [8 (2.9%)] and multiple defects [35 (12.6%)]. And 19.4% in NICU patients with similar spectrum, except for 2 with complex CHD who died before discharge. By 12–18 months of follow-up, 30% of CHD remained open. Thirteen patients developed mild to severe pulmonary arterial hypertension (PAH), and 2 of them died of heart failure.
Conclusions: The incidence of CHD in newborns at high altitude is about 20 times higher than that at low altitude, consisting mostly of simple forms with left to right shunt, with rare complex CHD. By 12–18 months, the incidence of CHD is still about 10 times higher than that at low altitude. About 8% patients developed PAH or death. Follow-up must be reinforced in order to provide early intervention and prevent from PAH or death.

1. Introduction

According to data from low altitudes, the incidence of congenital heart disease (CHD) is about 6–9‰, with critical CHD in 15%–25% [1,2]. Pulse oximetry has been recommended as a newborn screening tool for critical CHD with the cutoff $SpO_2 < 95\%$. However, this screening method is inapplicable to high altitude for a number of reasons. First, newborns at high altitude have a lower corresponding SpO_2 and wider standard deviations across different levels of altitude [3]. A recent study from moderate altitude in Aurora, Colorado, USA (1694 m) showed significantly higher failure rates of pulse oximetry screening than those at sea level, even with a cut-off value of 90% [4]. The United States workgroup has expressed concern about adapting such protocol in high altitude communities and recommended further research [5]. Second, previous studies from high altitudes have reported extremely rare incidence of critical CHD [6–9]. Almost all the CHDs are the simple forms with left to right shunt including secundum atrial septal defect (ASD), patent ductus arteriosus (PDA), and ventricular septal defect (VSD) [6–9]. Third, altitude hypoxia induces pulmonary arterial hypertension (PAH) in healthy people [10–12]. PAH may be compounded in high altitude children with left to right shunt types of CHD [13–15]. Noticeably, all the previous high altitude screening studies were conducted in older children aged from 2 to 18 years [6–9]. Many of them developed PAH, and some with severe CHD may have died before the age of screening. As such, early detection of CHD is crucial. Until now, the true picture of CHD occurrence and natural history at high altitude worldwide remains lacking.

The study aimed to examine the incidence and spectrum of CHD at high altitude using the intensive methodology with echocardiography

Abbreviations: ASD, atrial septal defect; CHD, congenital heart disease; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PDA, patent ductus arteriosus; PFO, patent foramen ovale; VSD, ventricular septal defect.

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screening newborns and follow up their outcomes, and consisted of two parts. Study 1 was to screen asymptomatic newborns for CHD in postnatal day 3–5 and follow-up their outcomes; Study 2 retrospectively examined the occurrence of CHD in newborns who were admitted to NICU within 2 postnatal days in order to depict a truer spectrum of CHD and follow-up their outcomes.

2. Patients and methods

2.1. Study population

2.1.1. Study 1

This study was prospectively conducted at the Qinghai Women and Children's Hospital in Xining (2261 m), Qinghai province from Mar, 2015 to Aug, 2017. As part of a quality initiative to implement newborn echocardiography screening and follow-up program, the study did not require approval from the Institutional Ethics Board. Consent was obtained by verbal explanations from parents. All asymptomatic newborns in postnatal day 3–5 were eligible for this study, irrespective of gestational age. The frame was chosen considering the high rate of PDA closure within postnatal day 3–4 [16] as well as the discharge time of the mothers and babies.

2.1.2. Study 2

In the same period as Study 1, newborns admitted to NICU within postnatal day 2 in the same hospital were retrospectively examined. Echocardiograph was performed when CHD was suspected. These newborns were not prospectively screened due to the limited personnel and machinery resources.

2.2. Demographic data and ethnic history of migration to Qinghai-Tibet plateau

In both studies, demographic data included gestation age, birth weight, sex, mother's age, ethnic and altitude of family's residence. In Study 2, clinical diagnosis at NICU admission was also collected.

The ethnic populations consisted of Han, Hui, Salar, Tibetan and others. Historically, Tibetans have inhabited at the Qinghai-Tibet plateau for approximately 25,000 years. Hui, Salar and some other minorities such as Tu and Mongolian migrated to Qinghai about 650 years ago. The majority of Han migrated to Qinghai about 60 years ago.

2.3. Echocardiography

Transthoracic echocardiography was performed by two technicians (Ting Dai and Hong Chen), using a Hewlett-Packard-8500 ultrasound system equipped with a 2.5 MHz transthoracic transducer (Andover, MA, U.S.A.). Two-dimensional imaging with color Doppler flow mapping depicted the location and size of the defect.

Systolic pulmonary arterial pressure (PAP) was estimated by tricuspid regurgitation. PAH was diagnosed according to the values in healthy newborns and infants at high altitude, i.e., systolic PAP >40 mm Hg [12].

2.4. Follow-up

Newborns screened positive for CHD or PFO in both studies were initially scheduled for follow-up at 1, 3, 6 and 12 months, or until complete spontaneous closure. When parents did not take the initiatives, phone calls were made repeatedly to ensure the follow-ups. As a result, the follow-up periods were divided to 1–3, 6 and 12–18 months. The infants whose CHD remained open or who had complications during the follow-up period were recommended to the Department of Cardiology in the same hospital for intervention.

2.5. Statistical analysis

Continuous data were presented as mean ± SD, and categorical data as number (%). Birth weight range was classified into low birth weight (<2500 g), normal birth weight (2500–4000 g) and macrosomia (≥4000 g). Mother's age range was classified into 15–24, 25–34 and 35–48 [17]. The ethnic was classified according to historic order of migration. Altitude was divided according to altitude medicine classification whereby altitude ≥2500 is considered to have medical significance. These variables were numbered 0, 1, or/and 2, respectively (Table 1).

Univariate logistic regression was used to identify correlation of incidence and spontaneous closure of total or each form of CHD or PFO with each demographic parameter. For some of the parameters divided into 3 groups as described above, polynomial transformation was used for the best fit. The demographic parameters achieving $p < 0.10$ were defined as significant and entered into a multiple logistic regression in which a $p < 0.05$ was considered significant. SAS 9.3 (SAS Institute, Inc., Cary, North Carolina) was used.

3. Results

3.1. Study 1. In asymptomatic newborns

There were 1396 live births during the study period. Among them, 1002 asymptomatic newborns (71.8%) underwent the screening, 101 (10.0%) babies' parents rejected the study, and 41 (4.1%) were missed due to the unavailability of personnel or devices. The remaining 394 (28.2%) babies were transferred to NICU and echocardiography was performed in 335 (see Study 2 section). Fig. 1 shows that the distribution of altitudes in 1337 babies was uneven, concentrating in Xining (2261 m) (398 babies, accounted for 29.8%) and Hualong (2848 m) (192 babies, 14.4%).

The frequency distribution of CHD and PFO across the demographic variables in 1002 asymptomatic newborns (and 335 NICU babies) are listed in Table 1. Of the 1002 newborns, CHD was diagnosed in 279 (27.8%). There were 676 babies (67.5%) with PFO. In isolated and multiple defects, the size of ASD was 2.69 ± 0.75 mm, PDA 2.15 ± 0.59 mm, VSD 2.8 ± 0.64 mm and PFO 2.21 ± 0.50 mm.

In univariate logistic regression, the incidences of CHD, ASD, multiple CHD and the size of PFO negatively correlated with ethnic classifications following polynomial transformation, that is, significantly higher in Han than Hui, and others and Tibetans ($p < 0.10$ for all), without significant difference between the latter two ethnic groups ($p > 0.40$ for all). The incidence of CHD was significantly higher in females than males ($p = 0.085$). There was significant and positive correlation between altitude and ethnics ($p = 0.030$).

Multivariate logistic regression showed the same polynomial trend in the correlations between ethnic classifications and incidences of CHD, ASD, multiple CHD and size of PFO after adjusting sex and altitude ($p < 0.05$ for all).

3.2. Study 2. In NICU

The 394 newborns admitted to NICU were diagnosed as severe pneumonia, asphyxia neonatorum or hypoxic ischemic encephalopathy, but none as CHD.

Echocardiography was performed in 335 patients (85.0%). CHD was found in 65 (19.4%) (Table 1), with simple CHD with left to right shunt in 63 (96.9%). Two patients had complex CHD. One of them had the anomalous right superior pulmonary veinous return to the right atrium with ASD and left inferior pulmonary venous stenosis. The other had transposition of the great arteries, ASD and VSD. Both patients died of pneumonia with respiratory and heart failure in NICU, in addition to another 3 deaths including 1 with ASD, 1 with PDA, and 1 with ASD and VSD. PFO was found in 84 babies (25.1%). In isolated and multiple defects, the size of ASD was 2.78 ± 0.81 mm, PDA 2.33 ± 0.61 mm, VSD 5.18 ± 2.31 mm and PFO 2.10 ± 0.41 mm.

Univariate logistic regression showed no significant correlations between the demographic variables and the incidence, forms and sizes of CHD or PFO ($p > 0.10$ for all). No significant difference was found in the sizes of ASD, PDA, VSD and PFO between asymptomatic and NICU babies ($p > 0.10$ for all).

3.3. Follow-up results

Since the sizes of CHDs and PFO at birth and their spontaneous closure rates were not significantly different between the babies in Study 1 and Study 2, they were analyzed together. The numbers of CHD and PFO babies at 1–3, 6 and 12–18 months and the spontaneous closure rates are shown in Table 2. By 12–18 months old, 29.1% CHD and 39.6% PFO remained open, making the incidence of 10% and 25%, respectively. The follow-up rate negatively, linearly and significantly correlated with ethnic classifications [Han 51.2% (128/250), Hui, and others 44.7% (306/685) and Tibetans 32.8% (22/67)] ($p = 0.020$).

Table 1
Frequency distribution and statistical results of CHD and PFO across the demographic variables in 1002 asymptomatic newborns and 335 newborns admitted in the NICU (%).

Demographic variables	Asymptomatic babies ($n = 1002$)							NICU babies ($n = 335$)							
	Total Number	Number of CHD					Number of PFO	Total Number	Number of CHD						Number of PFO
		ASD	PDA	VSD	Multiple	Total			ASD	PDA	VSD	Multiple	Complex	Total	
Gestation age (weeks)															
28–37	68(6.8)	7(10.3)	2(2.9)	2(2.9)	4(5.9)	15(22.1)	49(72.1)	163(48.7)	18(11.0)	5(3.1)	0	4(2.5)	0	27(16.6)	41(25.2)
37–42	934(93.2)	168(18.0)	59(6.3)	6(0.6)	31(3.3)	264(28.3)	627(67.1)	172(51.3)	19(11.0)	9(5.2)	1(0.6)	7(4.1)	2(1.2)	38(22.1)	43(25.0)
Birth weight(g)															
1300–2500	126(12.5)	16(12.7)	9(7.1)	2(1.6)	6(4.8)	33(26.2)	92(73.0)	155(46.3)	18(11.6)	4(2.6)	0	6(3.9)	0	28(18.1)	50(32.3)
2500–4000	852(85.1)	156(18.3)	51(6.0)	6(0.7)	26(3.1)	239(28.1)	569(66.8)	173(51.6)	19(11.0)	10(5.8)	1(0.6)	5(2.9)	2(1.2)	37(21.4)	32(18.5)
4000–5950	24(2.4)	3(12.5)	1(4.2)	0	3(12.5)	7(29.2)	15(62.5)	7(2.1)	0	0	0	0	0	0	2(28.6)
Newborn sex															
Male	543(54.1)	84(15.5)	34(6.3)	3(0.6)	18(3.3)	139(25.6)*	379(69.8)	176(52.5)	14(8.0)	11(6.3)	0	4(2.3)	1(0.6)	30(17.0)	47(26.7)
Female	459(45.8)	91(19.8)	27(5.9)	5(1.1)	17(3.7)	140(30.5)*	297(64.7)	159(47.5)	23(14.5)	3(1.9)	1(0.6)	7(4.4)	1(0.6)	35(22.0)	37(23.3)
Mother's age (y)															
15–24	392(39.1)	70(17.9)	25(6.4)	3(0.8)	12(3.1)	110(28.1)	262(66.8)	112(33.4)	14(12.5)	2(1.8)	0	7(6.3)	1(0.9)	24(21.4)	25(22.3)
25–34	512(51.2)	87(17.0)	31(6.1)	5(1.0)	18(3.5)	141(27.5)	343(67.0)	149(44.5)	12(8.1)	9(6.0)	1(0.7)	2(1.3)	0	24(16.1)	42(28.2)
35–48	98(9.7)	18(18.4)	5(5.1)	0	5(5.1)	28(28.6)	71(72.4)	74(22.1)	11(14.9)	3(4.1)	0	2(2.7)	1(1.4)	17(23.0)	17(23.0)
Ethnic															
Han	250(25.0)	51(20.4)*†	17(6.8)	2(0.8)	14(5.6)*†	84(33.6)*†	159(63.6)	130(38.8)	18(13.8)	6(4.6)	1(0.8)	4(3.1)	0	29(22.3)	34(26.2)
Hui, Salar and others	685(68.4)	112(16.4) *†	40(5.8)	6(0.9)	21(3.1)*†	179(26.1)*†	469(68.5)	175(52.2)	17(9.7)	7(4.0)	0	5(2.9)	2(1.1)	31(17.7)	41(23.4)
Tibetan	67(6.7)	12(17.9) *†	4(6.0)	0	0*†	16(23.9)*†	48(71.6)	30(9.0)	2(6.7)	1(3.3)	0	2(6.7)	0	5(16.7)	9(30.0)
Altitude (m)															
<2500	586(58.5)	92(15.7)	36(6.1)	5(0.9)	20(3.4)	153(26.1)	409(69.8)	190(56.7)	22(11.6)	10(5.3)	0	2(1.1)	0	34(17.9)	52(27.4)
≥2500	416(41.5)	83(20.0)	25(6.0)	3(0.7)	15(3.6)	126(30.3)	267(64.2)	145(43.3)	15(10.3)	4(2.8)	1(0.7)	9(6.2)	2(1.4)	31(21.4)	32(22.1)

ASD, atrial septal defect; CHD, congenital heart disease; PDA, patent ductus arteriosus; PFO, patent foramen ovale; VSD, ventricular septal defect.

* p value < 0.1 by univariate logistic regression.

† p value < 0.05 by multivariate logistic regression.

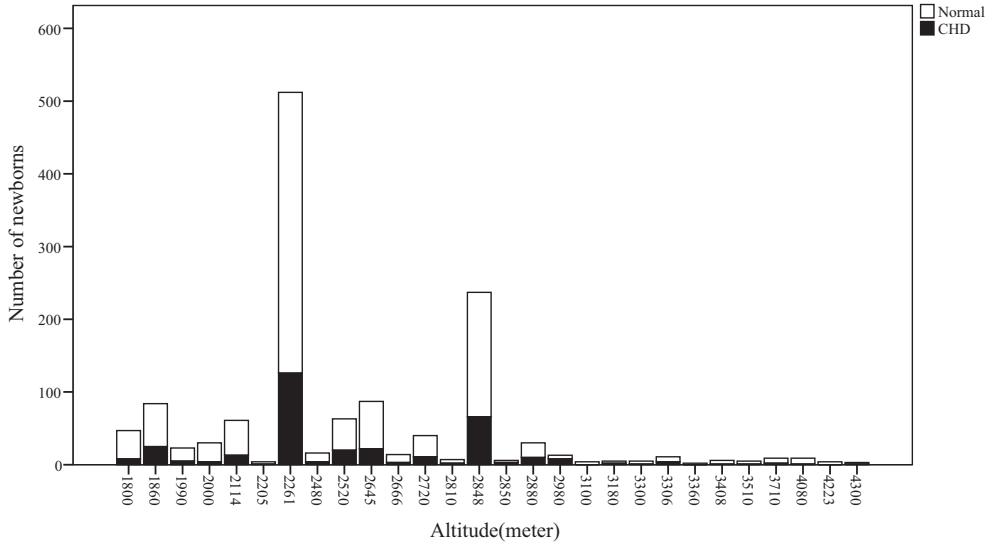

Fig. 1. The altitude distribution of parents' residing places in 1337 newborns screened for congenital heart disease (CHD). White bar indicates babies without CHD. Black bar indicates those with CHD.

In univariate logistic regression, the spontaneous closure rate of CHD was significantly higher in term infants than preterm infants ($p = 0.046$), and in males than females ($p = 0.002$). It positively correlated with ethnic classifications ($p = 0.041$), following polynomial transformation, that is, significantly lower in Han than Hui and others, and Tibetans ($p = 0.041$) without significant difference between the latter two groups of ethnics ($p > 0.50$). (Table 3).

In multivariable logistic regression after adjusting for gestational age, the same polynomial trend was also found in the correlations between ethnic classifications and the spontaneous closure rate of CHD ($p < 0.049$). It was significantly higher in males than females ($p = 0.002$). No correlation was found between other demographic variables and individual forms of CHD or PFO ($p > 0.10$ for all). (Table 3).

In Study 1, 6 babies developed PAH, including 3 with ASD, 1 with PDA, 1 with ASD and PDA, and 1 with ASD, PDA and VSD at 12–18 months follow-up (systolic PAP 54, 50, 41, 50, 43 and 65 mmHg, respectively). Two babies with multiple defects (ASD + PDA + PFO and ASD + PDA + VSD) died of pneumonia at 4 and 6 months, respectively. In Study 2, 5 babies with ASD and PDA developed PAH (systolic PAP 57, 78, 54, 88 and 95 mmHg, respectively). The patient with the highest PAP was diagnosed as Eisenmenger syndrome. One baby with large VSD (5.8 mm) lost follow-up.

4. Discussion

The incidence of CHD varies and is usually expressed as per thousand live births [1,2]. Hoffman and Kaplan in 2002 examined the incidences reported in 62 studies published after 1955 and determined the reasons for the variability. The incidence of CHD depended primarily on the number of small VSDs and this number in turn depended upon how early the diagnosis was made [2]. They suggested that any assessment of the incidence of CHD must take into account of the ages of the patients with special reference to the increased use of echocardiography in neonates [2]. A recent meta-analysis by van der Linde et al. found significant geographical differences in the incidence and forms of CHD, with Asia being the highest (9.3‰), followed by Europe (8.2‰) and North America (6.9‰) [1]. They concluded that the observed differences may be of genetic, environmental, socioeconomic or ethnic origin, and there needs further investigation to tailor the management of this global health problem. It must be noted that all the studies included in the meta-analyses were from low altitude regions.

High altitude represents a combination of all the distinctive environmental (altitude hypoxia in particular), socioeconomic, genetic and ethnic factors. The incidence of CHD at high altitude is usually expressed as per hundred and progressively increases with increased altitudes. There have been several screening studies from high altitudes, all using physical examination screening first followed by echocardiography. In 1962, Marticorena et al. from Peru screened 5000 school children at altitude between 3500 m and 5000 m [9]. The incidence of PDA was 0.72%, which was 18 times greater than the average of sea levels (0.04%). In a later study in 1988 in Qinghai province, the same region as our study, 763 Tibetan and Han children of 2–16 years old were screened at three levels of altitude of 2260 m, 3000 m and 4500 m. The incidence of CHD was 2.2%, 3.4% and 5.2%, respectively, without significant difference between Han and Tibetans. The CHD comprised mostly ASD and PDA, with rare other mild forms, including bicuspid aortic valve

Table 2
Numbers and spontaneous closure rates in 831 babies with CHD or PFO at different periods of follow-ups (%).

Follow-up age	ASD	PDA	VSD	$Total_{CHD}$	PFO
1–3 months					
Number of follow-up	88(34.2)	43(38.4)	7(29.2)	121(35.2)	235 (30.9)
Number of closure	12(13.6)	36(83.7)	1(14.3)	33(27.3)	34(14.5)
6 months					
Number of follow-up	78(31.8)	15(19.7)	7(30.4)	96 (30.9)	170 (23.4)
Number of closure	39(50.0)	7(46.7)	3(42.9)	54(56.3)	87 (51.2)
12–18 months					
Number of follow-up	84(40.8)	23(33.3)	7(35.0)	105(40.9)	190 (29.7)
Number of closure	55(65.5)	17(73.9)	6(85.7)	83(79.0)	125 (65.8)
Total number of follow-up	**160/257(62.3)**	**68/112(60.7)**	**13/24(54.2)**	**213/344(61.9)**	**407/760(53.6)**
Total number of closure	**106(66.3)**	**60(88.2)**	**10(76.9)**	**151(70.9)**	**246(60.4)**

ASD, atrial septal defect; CHD, congenital heart disease; PDA, patent ductus arteriosus; PFO, patent foramen ovale; VSD, ventricular septal defect.

Table 3
Numbers and spontaneous closure rates in 831 babies with CHD or PFO across the demographic variables by 12–18 months of follow-up (%).

Demographic variables	Number of follow-up					Number of closure				
	ASD	PDA	VSD	$Total_{CHD}$	PFO	ASD	PDA	VSD	$Total_{CHD}$	PFO
Gestation age (weeks)										
28–37	9(56.3)	4(5.9)	2(15.4)	14(6.6)	21(5.2)	4(3.8)	3(5.0)	2(20.0)	6(4.0)*	11(4.5)
37–42	151(43.7)	64(94.1)	11(84.6)	199(93.4)	386(94.8)	102(96.2)	57(95.0)	8(80.0)	145(96.0)*	235(95.5)
Birth weight(g)										
1300–2500	15(9.4)	9(13.2)	4(30.8)	22(10.3)	38(9.3)	10(9.4)	5(8.3)	3(30.0)	15(10.0)	23(9.3)
2500–4000	140(87.5)	55(80.9)	9(69.2)	183(85.9)	356(87.5)	91(85.9)	51(85.0)	7(70.0)	129(85.4)	217(88.2)
4000–5950	5(3.1)	4(5.9)	0	8(3.8)	13(3.2)	5(4.7)	4(6.7)	0	7(4.6)	6(2.5)
Newborn sex										
Male	77(48.1)	42(61.8)	6(46.1)	109(51.2)	232(57.0)	60(56.6)	39(65.0)	5(50.0)	89(58.9)*†	148(60.2)
Female	83(51.9)	26(38.2)	7(53.9)	104(48.8)	175(43.0)	46(43.4)	21(35.0)	5(50.0)	62(41.1)*†	98(39.8)
Mother's age (y)										
15–24	57(35.6)	24(35.3)	5(38.5)	76(35.7)	152(37.3)	39(36.8)	23(38.3)	4(40.0)	58(38.4)	81(32.9)
25–34	86(53.8)	38(55.9)	8(61.5)	114(53.5)	211(51.9)	57(53.8)	32(53.3)	6(60.0)	92(60.9)	138(56.1)
35–48	17(10.6)	6(8.8)	0	23(10.8)	44(10.8)	10(9.4)	5(8.4)	0	1(0.7)	27(11.0)
Ethnic										
Han	46(28.8)	21(30.9)	5(38.5)	61(28.6)	101(24.8)	26(24.5)	18(30.0)	3(30.0)	9(6.0)*†	61(24.8)
Hui, Salar and others	107(66.9)	43(63.2)	8(61.5)	142(66.7)	284(69.8)	74(69.8)	38(63.3)	7(70.0)	106(70.2)*†	168(68.3)
Tibetan	7(4.3)	4(5.9)	0	10(4.7)	22(5.4)	6(5.7)	4(6.7)	0	36(23.8)*†	17(6.9)
Altitude (m)										
<2500	93(58.1)	44(64.7)	7(53.9)	127(59.6)	272(66.8)	68(64.2)	38(63.3)	4(40.0)	95(62.9)	173(70.3)
≥2500	67(41.9)	24(35.3)	6(46.1)	86(40.4)	135(33.3)	38(35.8)	22(36.7)	6(60.0)	56(37.1)	73(29.7)

ASD, atrial septal defect; CHD, congenital heart disease; PDA, patent ductus arteriosus; PFO, patent foramen ovale; VSD, ventricular septal defect.
* p value < 0.1 by univariate logistic regression.
† p value < 0.05 by multivariate logistic regression.

($n = 1$) and prolapsing mitral valve (n = 1) [6]. In a study in 2008 also in Qinghai screening 32,578 Tibetans of 4–18 years old, the incidence was 7.2‰, comprising ASD, PDA and VSD [7]. In the most recent study from Tibet in 7088 children of 4–17 years, the incidence of CHD was 4.6‰, 10.8‰ and 13.4‰ at altitudes 2800–4200 m, 4200–4700 m and > 4700 m, respectively. In the second part of their study with focus on critically ill patients ($n = 383$), complex CHDs were found in 3.9%, including tetralogy of Fallot, double-outlet right ventricle etc. [8]. There were also some other mild forms of CHD in 2.3%, including aortic valve and pulmonary valve abnormalities, etc. This was the only study that reported the occurrence of complex and a few mild forms of CHD. Noticeably, in the latest two studies [7,8], the incidence was surprisingly lower comparing to earlier reports [6,9].

In our study, the incidence of CHD was 27.8% in asymptomatic newborns, and 19.4% in NICU. The overall incidence is about 20 times higher than previously reported values from low altitude in newborns [18], and 5 to 10 times higher than those at high altitude data in older children [6–9]. The very high incidence of CHD found in our study is clearly as a result of the intensive methodology using echocardiography screening at birth. As Hoffman and Kaplan have pointed out, the use of echocardiography and at birth are the two main factors to 'inflate' the incidence of CHD [2]. Echocardiographic diagnoses are so accurate that few misdiagnoses are made. Previous screenings at high altitude were performed in older children using physical examination first, followed by echocardiography. This approach may underestimate the incidence of CHD. For example, ASD, which has the highest incidence at high altitude, is usually asymptomatic and has murmurs that are soft, many of these subjects may be missed at physical examination, but later present in adult life [19]. Another reason for the higher incidence in newborns is that spontaneous closure of these defects occurs when growing older. In our patients, by 12–18 months of age, nearly 70% of CHD spontaneously closed, leaving the incidence of 10%, which is still >10 times higher than that at low altitude, and at least two times higher than previously reported values from high altitude. Finally, some of the children with CHD may have died of complications such as pneumonia, PAH or cardiac failure during infancy under the relatively poor economic and medical conditions in high altitude regions. In our study, 5 patients died during the stay in NICU. PAH happened in 11 of our patients including 1 with Eisenmenger syndrome even with close follow-up. The two patients who died of pneumonia and cardiac failure in Study 1 may have well developed PAH. Our previously study from the same region has shown that healthy children from birth to 14 years old living at high altitude have significantly high PAP, right ventricular dilatation and hypertrophy, with reduced systolic and diastolic function of both ventricles [11,12], indicating the susceptibility to PAH and heart failure. We have further reported that much severer PAH, as compared to low altitude reports, may occur at the onset of pneumonia in high altitude children [20].

In consistency with previous high altitude reports [6–9], the spectrum of CHD in our study consists mostly of simple CHD with ASD and PDA being the majority, a few VSD, and rare complex CHD. This is different from low altitude regions where VSD is the commonest accounting for about 40% of all forms of CHD, and critical CHD occurs in about 15%–25% [1,2]. Altitude hypoxia is known to induce the postnatal delayed descent of pulmonary and right heart pressure, inhibiting the closure of ASD [15]. As for PDA, failure of lower oxygen tension to constrict the ductus is the mechanism [21]. Indeed, it has been reported that the incidence of ASD and PDA is positively related to the level of altitude approximately in parabolic curve. This pattern is similar to the parabolic tendency observed when other physiologic (SpO_2 and PAP) and anatomic parameters (right ventricular hypertrophy and structural changes of pulmonary vessels) are correlated with the level of altitude [10,22]. This pattern was not shown in our data, however, attributable to the design of our study. The screening was performed in the hospital in Xining where came patients from a wide spread of regions in Qinghai, instead of screening at specific altitudes as in previous studies [6–9]. The distribution of parents' residing places was uneven (Fig. 1), thus unable to detect the relation between altitude and the incidence of CHD. However, the strikingly high incidence of ASD and PDA that consists of persistence of a fetal pathway, strongly suggests a postnatal, i.e., altitude hypoxia, rather than a fetal teratogenic mechanism.

All the previous studies, except one [8], from high altitudes reported only mild forms of CHD mostly with left to right shunt [6,7,9]. This is different from our clinical observations in which complex CHD are occasionally seen. In order to depict a better spectrum of CHD at high altitude, we added Study 2 to include newborns transferred to NICU before echocardiography screening could be performed. We found two complex CHD cases. One had partial anomalous pulmonary venous return with ASD and left lower pulmonary venous stenosis. The other had transposition of the great arteries with ASD and VSD. Both patients

died of pneumonia with respiratory and heart failure in NICU. The rare occurrence of complex CHD in our study is consistent to the latest report in the critically ill patients from Tibet [8]. None of the babies admitted to NICU was initially diagnosed as CHD. Noticeably, the size of VSD, but not other defects, in NICU patients was considerably larger than the asymptomatic babies although without achieving statistical significance likely due to the small number of patients ($n = 4$). Our data suggest the necessity of routine echocardiography to examine CHD in all the babies in NICU at high altitude.

The natural history of these defects is different at high altitude. In low altitude regions, PDA almost always closes by 3–4 days after birth [16], and 85% to 90% of ASD [23] and muscular VSD [24] close spontaneously by one year of age. In our study in newborns in postnatal 3–5 days, the incidence of PDA was more than twice of that at sea level [1] and closed much later, 83.7% by 3 months. By 12–18 months, 33.7% ASD, 11.8% PDA and 23.1% VSD remained open (Table 2). Additionally, our data revealed that the spontaneous closure rate of CHD was significantly higher in males as compared to females ($p < 0.05$). This, together with the tendency of higher incidence of CHD in females, is consistent to data from the old textbook showing that the incidence of ASD and PDA were more common in females [25].

Uncorrected CHD is the predominant etiology of PAH and heart failure in the pediatric population at high altitude [14]. In our patients during the relatively short follow-up period of 12–18 months, 13 patients developed mild to severe PAH even Eisenmenger syndrome, accounting for 7.9%, including 2 deaths. A retrospective study from Qinghai province showed that among 1178 patients of 1–69 years old with simple CHD with left to right shunt, moderate to severe PAH occurred in 58%, with progressive morbidity and severity with increased altitude and age [26]. Unfortunately, at high altitude worldwide, only a small fraction of CHD patients are offered surgical or interventional repair timely.

Globally, PAH associated with CHD may be the most preventable cause of PAH and related morbidity and fatal sequelae [27]. Early detection of CHD and access to treatment is critical. As such, implementation of newborn screening for CHD using echocardiography at high altitude is much needed, yet challenging. Medical resources remain much limited. Even more difficult is that many parents of the patients lacked the health knowledge and refused to participate the screening. Even after the diagnosis of CHD, many were reluctant to return to the follow-ups. This problem was more serious in Hui, Tibetan, and other minor ethnics than Han. Mobile population, low educational level and income are the significant causes for not actively using medical care service in resource-constrained communities in China and likely in other high-altitude regions worldwide. In peculiar, Tibetans have 'cool' attitude towards to death, in part because they believe in samsara. From a health perspective, it is of great importance to increase awareness about the disease and improve medical care resources at high altitude.

An important finding in the present study is the relation between ethnics and the incidence and spontaneous closure rate of CHD. It has been well documented that the Tibetans have the most optimal genetic adaptation to high altitude following a process of natural selection through millennia in an environment of chronic hypoxia [10]. Our study further demonstrated the advantageous adaptation in the ethnics with longer history at high altitude in terms of CHD. The incidence of total CHD as well as ASD and multiple CHD in Han tended to be higher than Hui, and others and Tibetans, whereas the spontaneous closure rate of CHD significantly lower. This is different from the study by Miao et al. [6], showing comparable incidence of CHD between Tibetans and Han, which might be due partly to the older age of screening in 4–18 years. It has been reported that Han may develop severer PAH even without CHD [28] and have higher incidence of subacute infantile mountain disease that may lead to death [29] although not happened in any of our patients. Surprisingly, the difference in the incidence and spontaneous closure rate of CHD was insignificant between Tibetans and Hui, and others, given the fairly short history of latter ethnic populations migrating to Qinghai-Tibet plateau for about 650 years. Nonetheless, taken together with previous findings from high altitude regions, there are indeed much fewer other forms of CHD, mild or severe [6–9]. The etiology for this striking predisposition at high altitude may involve interaction between environmental and genetic factors which warrants further studies.

The incidence of PFO was 67.5% at birth in our study. By 12–18 months, about 40% of them remained open. This figure is close to those values from low altitudes [30]. There has been mounting evidence that PFO is not benign but frequently associated with ischemic stroke, migraines, decompression sickness, peripheral embolism and obstructive sleep apnea [31]. Given the higher pulmonary and right heart pressure in high altitude residents, the presence of PFO may have particular implications. It might be functionally, rather than anatomically closed, although no contrast echocardiography was performed in our study. Those with PFO may be more susceptible to have reversal of flow across the defect at strenuous exercise and pneumonia [20]. It has been reported that the presence of PFO in high altitude residents is ~~was~~ associated with right ventricular enlargement and an exaggerated increase in PAP and right ventricular dysfunction at mild exercises [32].

5. Limitations

First, our hospital is located in area where the main habitats are Hui and Han, with considerably less Tibetans. The proportion of ethnics in our study population was 28.4% Han, 64.3% Hui, Salar and others and 7.3% Tibetan. This figure does not represent the overall population composition in Qinghai which includes 53.0% of Han, 22.5% Hui, Salar and others and 24.4% Tibetan. This might, to some degree, limited us to detect the relation between the incidence and spontaneous closure rate of CHD and some of the ethnics (e.g. Hui, Salar and others vs Tibetan). Second, despite of the original design of the longitudinal study to follow-up each CHD baby until spontaneous closure, our study became cross-sectional given the difficulties in following up. There were nearly 60% of patients coming to the follow-ups, but only 9% repeatedly returned to the follow-ups until closure. This problem was more significant in Tibetans, Hui and other ethnics as compared to Han. Therefore, the natural history of CHDs in these high-altitude babies remains an estimate. Third, echocardiography was not routinely performed in all the NICU patients. Therefore, our data could not provide a precise incidence of CHD and its correlation with demographic variables in the NICU population.

6. Conclusion

The incidence of CHD in newborns at high altitude is about 20 times higher than the reported values from low altitude regions, consisting mostly of simple forms of ASD and PDA, and rare complex CHD. The spontaneous closure of the simple defects occurs much later as compared to the low altitude figures. By 12–18 months of age, about 30% CHD remain open, leaving the incidence of 10%, which is still about 10 times higher than that at low altitude. Longer history of migration is associated with lower incidence of CHD and higher rate of spontaneous closure. About 8% patients developed PAH or died of heart failure. Routine CHD screening using echocardiography should be implemented in newborns at high altitude. Follow-up must be reinforced in order to provide early intervention and prevent from significant PAH or death.

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Disclosures

None.

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