UNIVERSITY OF CALIFORNIA,
IRVINE

# Undiagnosed Congenital Heart Disease in Children in Rural Yunnan, China

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Public Health

by

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Dissertation Committee:
Professor Robert C. Detrano, Chair
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2020

# DEDICATION

To

My parents, for their love and encouragement

My husband, for his unwavering support

My son, for so much happiness and joy he brings to our lives

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# ACKNOWLEDGMENTS

I would like to express my deepest appreciation to my committee chair, Professor Robert C. Detrano, who has the attitude and the substance of a genius: he continually and convincingly conveyed a spirit of adventure in regard to research. Without his guidance and help this dissertation would not have been possible.

I would like to thank my committee members, Professor Scott M. Bartell and Professor Nathan Wong, whose suggestions and comments made this dissertation better; and Professor Oladele Ogunseitan and Professor Guiyun Yan, who provided valuable comments on my dissertation proposal.

I would like to thank Professor Songyuan Tang of Kunming Medical University and Dr. Tao Guo of Yunnan Fuwai Cardiovascular Hospital, who helped connect me with Yunnan rural hospitals.

I would like to thank my colleagues in Yunnan, China. They are Ms. Shanshan Chen, Dr. Yani Li, Ms. Rui Zhang, Dr. Yun Li, and Mr. Daniel Zhang. Without your help, my research projects would not have been finished smoothly.

I also would like to thank staff of Obstetrics and Pediatrics departments of Yunnan county-level hospitals in Zhaotong, Honghe, Dali, Yuxi, Baoshan, and Banna prefectures. Without your collaboration, this dissertation would not be possible.

Finally, I would like to thank everyone else who helped contribute to this dissertation; and to my friends Joann Yuan, Tamara Jimah, Yao Li, Qiujie Li, and Jie Cui, thank you for keeping me company on this long walk.

Financial support was provided by the University of California, Irvine, Program in Public Health and Department of Radiological Sciences, Ping and Amy Chao Family Foundation and China California Heart Watch.

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# ABSTRACT OF THE DISSERTATION

Undiagnosed Congenital Heart Disease in Children in Rural Yunnan, China

By

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Doctor of Philosophy in Public Health

University of California, Irvine, 2020

Professor Robert C. Detrano, Chair

The aims of this dissertation were to investigate the distribution of congenital heart disease (CHD) and its catastrophic outcome -- Eisenmenger syndrome in children in Yunnan Province, China, and to discuss the optimal method to implement newborn CHD screening in rural Yunnan.

CHD is one of the most common birth defects that occurs in around 8 per 1000 live births. Repairing a heart defect early in life can prevent the development of its inoperable outcome -- Eisenmenger syndrome. In the first part of this dissertation, I reported my retrospective medical record review of 1301 children in rural Yunnan who were diagnosed with a CHD between 2006 and 2016. I used the methods of descriptive analysis and logistic regression to analyze data and concluded that ventricular septal defect, atrial septal defect, and patent ductus arteriosus were the three most common CHDs. Two in every 100 pediatric cardiac patients had developed Eisenmenger syndrome, and age is the most important risk factor for developing Eisenmenger syndrome in children with CHD.

The second part of this dissertation is a report of a program to train Yunnan Province obstetric doctors and nurses regarding proper exam of the hearts of newborn babies. Newborn CHD screening, including pulse oximetry screening and heart auscultation, can identify critical and major CHDs early in life with very high sensitivity and specificity. In rural Yunnan, newborn CHD screening was not previously practiced. We, therefore, designed an on-site, one-day training program to educate Yunnan obstetric and pediatric staff on proper CHD screening. The training program, which started in July 2015 and lasted through 2016, trained 2,175 medical staff. I used pre- and post- training questionnaires and behavior checklists to evaluate the training. Evaluation results showed that after training, trainees demonstrated improved knowledge and practice of CHD screening.

Since most of residents in Yunnan live at mild and moderate altitudes (between 500 and 2500 meters), and high altitude affects pulse oximetry screening results, the cut off values of pulse oximetry screening should be adjusted in most of Yunnan. In the third part of my dissertation, I investigated the relationship between pulse oximetry screening result (blood oxygen saturation) and altitude in 41,097 newborn babies. Study results showed that every 1,000-meter increase in altitude was associated with a 1.54 percent decrease in mean $SpO_2$. I recommended new cut-off values of pulse oximetry screening at mild and moderate altitudes.

In conclusion, a great number of pediatric CHD patients in rural Yunnan did not receive timely diagnosis or treatment early in life. Newborn CHD screening was an effective

method to prevent late diagnosis of CHD, and due to our efforts, this kind of screening has been routinely implemented in rural Yunnan, China.

# CHAPTER 1 BACKGROUND

Congenital heart defects (CHD), also known as congenital heart diseases are problems in the structure of the heart that develop in utero during the development of the cardiovascular system and are present at birth. CHDs are the most common types of birth defects.[1]

CHDs have many subtypes and the problems can range from simple to complex or critical. Simple defects, such as small ventricular septal defects, may have no signs or symptoms and may not need any treatment. Complex or critical CHDs such as complete transposition of the great arteries may present severe or life-threatening symptoms, such as cyanosis and shortness of breath. These patients need surgical correction or other treatments early in life.[2]

## 1.1 Embryology of the cardiovascular system

The heart is the first functional organ that develops in human embryos. It starts to beat and pump blood around 3 weeks after fertilization.[3]

The heart forms from the mesoderm, the middle layer of an embryo in early development (between the endoderm and ectoderm). The heart begins to develop near the head of the embryo, the cardiogenic area. Under the regulation of multiple factors, the cardiogenic area begins to form two endocardial tubes. The two tubes join together and fuse to form a single primitive cardiac tube. Initially, the cardiac tube is a single chambered structure, composed

of five distinct regions. They are from head to tail, the truncus arteriosus, bulbus cordis or conus, primitive ventricle, primitive atrium and the sinus venosus.[3]

The single chambered heart initially is a straight tube positioned in the pericardial cavity (Figure 1.1 (a)). The bulb ventricular region grows much more rapidly than the pericardial cavity (Figure 1.1 (b)). As a consequence, extension in a longitudinal direction is blocked and the heart tube is forced to bend (Figure 1.1 (c)). The cranial ventricular component of the tube bends in a caudal and ventral direction to the right; the caudal atrial component moves in an opposite direction to the left (Figure 1.1 (d)). Eventually, the atrial region is superior to the ventricular region and the cardiac apex points toward the left side of the body (Figure 1.1 (e)).[3]

The primitive heart tube eventually forms a fully developed four-chambered heart. The truncus arteriosus eventually divides and forms the aorta and pulmonary trunk. The primitive ventricle develops into the major part of the left ventricle, and the bulbus cordis develops into the major part of the right ventricle. The primitive atrium becomes the anterior portions of both atria. The sinus venosus develops into the superior portion of the atria, coronary sinus and oblique vein of left atrium .[3]

The fetal lungs are filled with fluid and not inflated. The placenta supplies oxygen and removes carbon dioxide and other metabolites. Oxygenated blood enters the right side of the heart via the placenta.[4] Most of the blood from the right side of the heart bypasses the

lung through the foramen ovale and ductus arteriosus.[4] The two structures normally close shortly after birth.

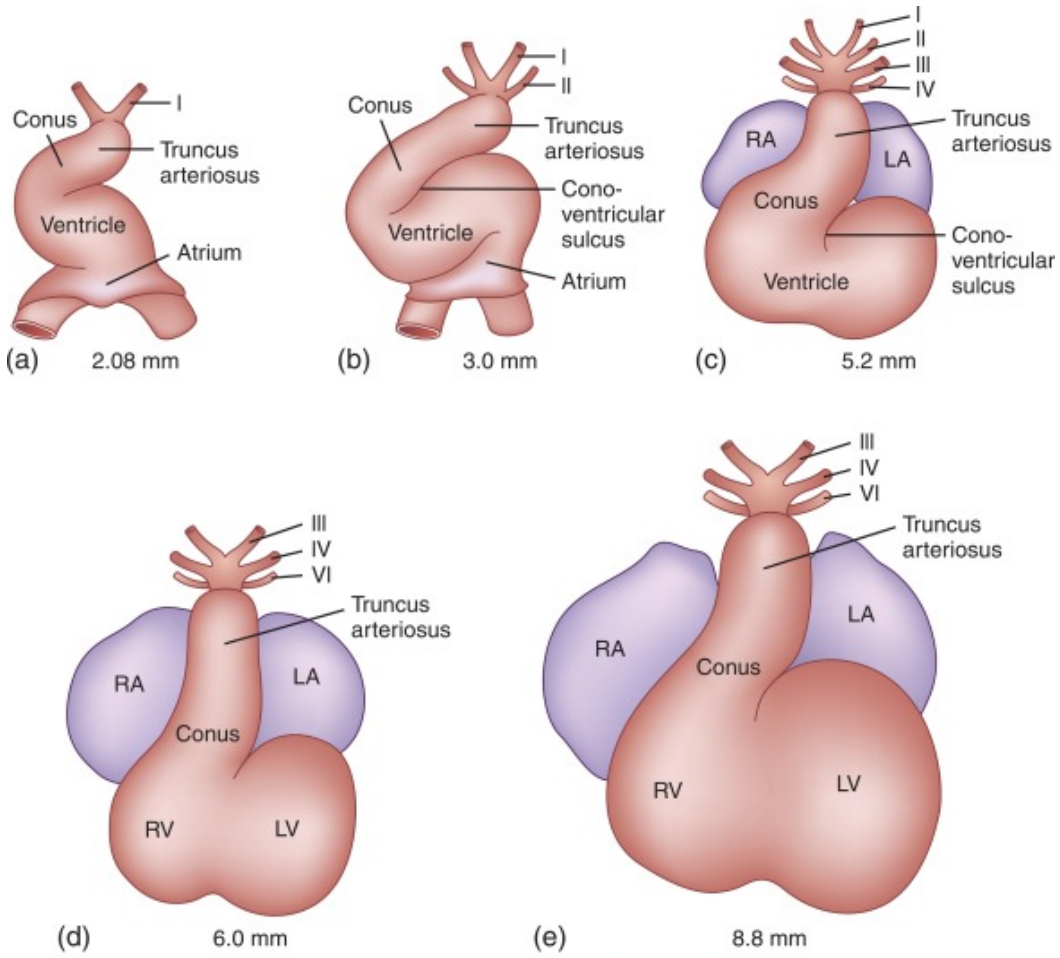


Figure 1.1. Bending of cardiac tube establishing major regional divisions. I, II, III, IV, VI are aortic arches; millimeters (mm) refer to the human embryo's crown-rump length; LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle. Note: Reprint from "Chapter 15 - Congenital Heart Disease: Pathology, Natural History, and Interventions. In: Buja LM, Butany J, eds. Cardiovascular Pathology (Fourth Edition)" by Ottaviani G, Buja LM (2016). *San Diego: Academic Press*, 611-647. Copyright © 2016 Elsevier Inc.

When a newborn takes the first breath, the lung starts to expand, and the ductus arteriosus and the foramen ovale both close. The baby's cardiac circulation now functions

as an adult. If the ductus arteriosus does not close after 24 hours of birth, it is a type of CHDs called patent ductus arteriosus (PDA).[5] If a wall between chambers has a hole, vessels or heart valves are narrow or arteries are not positioned properly, CHDs occur.

## 1.2 Classification

There are many different types of congenital heart defects. Based on different criteria, they fall into different categories.

### 1.2.1 According to the flow of the blood

The two major pathophysiological types of CHD are shunts and obstructions. [3] A shunt is an abnormal communication between the left and right sides of the heart or between the systemic and pulmonary vessels.[6] An obstruction occurs when blood vessels or heart valves are narrow. With an obstruction, the heart has to pump harder to get blood pass the blockage. Depending on the flow of the blood, shunts can be classified into two major categories: left-to-right shunts and right-to-left shunts (Table 1.1).

Left to right shunts are the most common forms of CHDs, which are initially acyanotic and less severe. Right-to-left shunts allow deoxygenated blood to bypass the lung and return back to the body. Right-to-left shunts are more severe and most of them cause cyanosis (bluish color of skin and mucous membranes from decreased blood oxygen).

### 1.2.2 According to oxygen saturation level

According to the oxygen saturation in the body, CHDs can be classified as cyanotic CHDs or acyanotic CHDs.[3] In cyanotic CHDs, oxygen-poor blood reaches systemic circulation through the aorta. This results in a bluish tone to the skin, lips, and nail beds (cyanosis).[7] Acyanotic CHDs do not affect the oxygen saturation level in the blood. A bluish tone of the skin is not common in babies with acyanotic CHDs. However, it may occur during activities when the child needs more oxygen. CHD classification based on blood flow and oxygen saturation is shown in Table 1.1.

| **Acyanotic** | | **Cyanotic /right to left shunts** |
|---|---|---|
| **Left-to-right shunts** | **Obstructions** | • Tetralogy of Fallot<br>• Transposition of the great arteries |
| • Ventricular septal defect<br>• Patent ductus arteriosus | • Pulmonary valve stenosis<br>• Aortic valve stenosis | • Pulmonary atresia<br>• Total anomalous pulmonary venous return |
| • Atrial septal defect<br>• Atrioventricular defect | • Coarctation of the aorta | • Truncus arteriosus<br>• Hypoplastic left heart syndrome<br>• Double Outlet Right Ventricle<br>• Ebstein's Anomaly |

Table 1.1 Classification of CHDs

1.2.3 According to severity

On the basis of the severity classification of CHD recommended by Ewer,[8] all newborns with a CHD can be classified into four groups:

1. Critical CHDs, which can cause death and need intervention before 28 days of age, include hypoplastic left heart, pulmonary atresia with intact ventricular septum, simple transposition of the great arteries, interruption of the aortic arch, coarctation of the aorta, aortic valve stenosis, pulmonary valve stenosis, tetralogy of Fallot, pulmonary atresia with ventricular septal defect, and total anomalous pulmonary venous connection. About one-fourth of CHDs are critical.[9] Critical CHD is one of the main targets of newborn screening programs.
2. Serious CHDs, which need intervention within 1 year of age
3. Significant CHDs, which persist longer than 6 months of age, but were not classified as critical or serious
4. Non-significant CHDs, which are not physically appreciable and not persisting after 6 months of age.

### 1.2.4 Common defects

Ventricular septal defect, atrial septal defect, and patent ductus arteriosus are the most common types of CHDs. They account for more than 50% of all CHDs.[10]

#### 1.2.4.1 Ventricular Septal Defect (VSD)

VSD is the most common type of CHDs. It affects 3.6 per 1000 births, accounting for about 40% of all CHDs.[10] It characterized by an opening in the ventricular septum allowing the blood to flow from the left to the right ventricle. VSD may occur in isolation or in association with other CHDs, including atrial septal defects, patent ductus arteriosus, right aortic arch, pulmonic stenosis, tetralogy of Fallot, complete atrioventricular canal defects, and (corrected) transposition of great arteries.[11]

The size and location of the defect determine the severity of the anomaly. Small VSDs can close spontaneously in childhood. Some of the large-sized VSDs are considered critical and life-threatening, which have to be surgically closed in the first year of life. Because VSDs are usually close spontaneously or identified and repaired in childhood, the prevalence is much lower in adults.[12]

VSDs have 4 types.[11] They are Membranous VSD (most common), infundibular VSD, Inlet or atrioventricular canal VSD, and Muscular VSD.

1.2.4.2 Atrial Septal Defect (ASD)

ASD is the second most common type of CHDs. It affects 0.9 per 1000 births, accounting for about 10% of all CHDs.[10] It characterized by an opening in the interatrial septum allowing the blood to flow from the left to the right atrium. Most of the ASDs are isolated -- with no other associated conditions. Depending on the size of the shunt and associated anomalies, ASD can result in a spectrum of disease ranging from no signs and symptoms to pulmonary arterial hypertension and even Eisenmenger syndrome. Many patients with ASD are asymptomatic during the first 1-3 decades of life, which results in a delay in diagnosis until adulthood. Closure of ASD early in life, using a catheter-based or surgical procedure can prevent complications. Patients underwent ASD closure in childhood showed good long-term survival (97%) and low morbidity.[13]

ASDs based on the anatomic location, are classified into four types: Secundum ASD (75%), primum ASD (15%), sinus venous ASD (10%), and coronary sinus ASD (very rare).[3]

1.2.4.3 Patent ductus arteriosus (PDA)

Ductus arteriosus is a fetal blood vessel that connects aorta and the pulmonary artery, which normally closes soon after birth. In a PDA, the ductus arteriosus fails to close but remains open. As a result, a portion of oxygenated blood abnormally transmits from the aorta to the pulmonary artery. Premature newborns are more likely to have PDA due to under-development of the heart and lungs.[14]

Most of newborns who have PDA are asymptomatic at birth and shortly thereafter. Symptoms, such as a bounding pulse and poor growth start to emerge in the first year of life. With time, an uncorrected large PDA can lead to pulmonary hypertension and Eisenmenger syndrome.[5] If a transposition of the great arteries is present in addition to a PDA, the PDA cannot be surgically corrected since it is the only way to have blood oxygenated.[15]

## 1.3 Etiology and risk factors

About 20% of CHDs are attributed to known causes such as genetic syndromes and teratogens.[16] However, the etiologies of the remaining 80% of CHDs are unknown.[16] It is generally accepted that the causes of CHDs with unknown etiology follow a multifactorial model, in which both genetic and environmental factors are involved in disease development.[17] A genetic variation may contribute a small amount to an individual's

susceptibility to a CHD. Variations interact with each other and with environmental factors which may raise the likelihood to have a CHD.

### 1.3.1 Genetic factors

Chromosomal abnormalities are associated with some CHDs. Down syndrome, in which individuals have an additional chromosome 21, is the most common chromosomal anomaly seen in patients with CHD, followed closely by velocardiofacial syndrome (VCFS), which is caused by loss of part of chromosome 22. About 40%–50% of patients with Down syndrome have a CHD,[18] and 80% of patients with VCFS have a CHD.[19(p11)]

Copy number variants also contribute to CHDs. The copy number variations of del22q11, which presents in DiGeorge syndrome and VCFS and del17q11, which causes William syndrome, are proven to be associated with the development of CHDs.[20,21]

Single point mutations including transcription factors(NKX2.5, TBX1, TBX5, and MEF2), ZIC3, the NOTCH1 gene and related NOTCH signaling genes are also causes of CHDs.[21,22]

### 1.3.2 Non-genetic factors

Numerous nongenetic factors are associated with CHDs. Folate deficiency is a well-documented risk factor for CHDs.[23] Folic acid supplement (400 micrograms per day) during pregnancy is routinely recommended during pregnancy, and it is associated with a decreased risk for CHDs.[24,25] Maternal smoking is another well-defined risk factor. Smoking during the first trimester of pregnancy is associated with an increased risk of

CHDs.[26–28] Exposure to secondhand smoke is also a risk factor for CHDs.[29] Besides, maternal diabetes, maternal rubella infection[30], maternal alcohol ingestion[31], maternal obesity[32], and exposure to air pollutants[33] are also been implicated as risk factors.

## 1.4 Epidemiology

CHDs are the most common types of congenital anomalies, which account for one-third of congenital anomalies.[1] CHD occurs in about 8 per 1000 live births.[10]

### 1.4.1 Incidence

The incidences of specific defects are shown in Table 1.2. VSD, ASD, and PDA are the most common types of CHDs, the incidences of which are about 3.6/1000, 0.9/1000, and 0.8/1000, respectively. About 1 in 4 congenital heart diseases are critical.[9] Babies with a critical congenital heart disease need surgery in the first year of life. Based on the study by Hoffman (Table 1.2), the most common types of CCHDs are the Coarctation of the Aorta, Tetralogy of Fallot, and d-Transposition of the Great Arteries.

The incidence of CHD also varies in different geographic areas. The incidence of CHD is commonly reported as being between 4 and 10 per 1000 in the United States,[34] as 8.2 per 1000 births in Europe, as 9.3 per 1000 in Asia, as 1.9 per 1000 in Africa,[35] and as 13.3 per 1000 live births in india.[36]

| Lesion | Number of Studies | Mean | SD | Lower Quartile | Median | Upper Quartile | NERICP 1975–1977 |
|---|---|---|---|---|---|---|---|
| VSD | 43 | 3,570 | 2,878 | 1,757 | 2,829 | 4,482 | 345 |
| PDA | 40 | 799 | 1,399 | 324 | 567 | 782 | 135 |
| ASD | 43 | 941 | 1,043 | 372 | 564 | 1,059 | 65 |
| AVSD | 40 | 348 | 165 | 242 | 340 | 396 | 110 |
| PS | 39 | 729 | 731 | 355 | 532 | 836 | 73 |
| AS | 37 | 401 | 543 | 161 | 256 | 388 | 41 |
| Coarc | 39 | 409 | 246 | 289 | 356 | 492 | 165 |
| Tetralogy | 41 | 421 | 188 | 291 | 356 | 577 | 196 |
| d-TGA | 41 | 315 | 115 | 231 | 303 | 388 | 218 |
| HRH | 32 | 222 | 199 | 105 | 160 | 224 | — |
| Tricuspid atresia | 11 | 79 | 52 | 24 | 92 | 118 | 56 |
| Ebstein's anomaly | 5 | 114 | 138 | 38 | 40 | 161 | 12 |
| Pul Atresia | 11 | 132 | 123 | 76 | 83 | 147 | 69 |
| HLH | 36 | 266 | 216 | 154 | 226 | 279 | 163 |
| Truncus | 30 | 107 | 71 | 61 | 94 | 136 | 30 |
| DORV | 16 | 157 | 103 | 82 | 127 | 245 | 32 |
| SV | 23 | 106 | 70 | 54 | 85 | 136 | 54 |
| TAPVC | 25 | 94 | 46 | 60 | 91 | 120 | 58 |
| All cyanotic | 37 | 1,391 | 590 | 1,078 | 1,270 | 1,533 | 888 |
| All CHD* | 43 | 9,596 | 7,484 | 6,020 | 7,669 | 10,567 | 2,033 |
| BAV | 10 | 13,556 | 13,049 | 5,336 | 9,244 | 13,817 | — |

Table 1.2. Incidence of CHD per Million Live Births. *Excluding bicuspid nonstenotic aortic valves, isolated partial anomalous pulmonary venous connection and silent ductus arteriosus. VSD = ventricular septal defect; PDA = patent ductus arteriosus; ASD = atrial septal defect; AVSD = atrioventricular septal defect; PS = pulmonic stenosis; AS = aortic stenosis; Coarc = coarctation of the aorta; Tetralogy = Tetralogy of Fallot; d-TGA = complete transposition of the great arteries; HRH = hypoplastic right heart; Pul atresia = pulmonary atresia; HLH = hypoplastic left heart; Truncus = truncus arteriosus; DORV = double outlet right ventricle; SV = single ventricle; TAPVC = total anomalous pulmonary venous connection; BAV = bicuspid aortic valve; CHD=congenital heart disease; Coarc = coarctation of the aorta; NERICP = New England Regional Cardiac Program. Note: Reprint from "The incidence of congenital heart disease." By Hoffman, J. I., & Kaplan, S. (2002). *Journal of the American college of cardiology*, *39*(12), 1890-1900. by. 

### 1.4.2 Survival

CHD is a leading cause of infant death. It accounts for 4.2% of neonatal deaths in the United States.[37] For infants that were diagnosed with CHD, 1-year survival was 87%, 5-year survival was 85% and 10-year survival was 81%.[38] One-year survival was 75.2% for those

with CCHDs. [9] 69% of patients with CCHDs survived to adulthood. Overall, simple CHDs have a better survival compared with critical CHDs. A 25-year comparison of survival probability between critical and simple CHDs is shown on Figure 1.2.

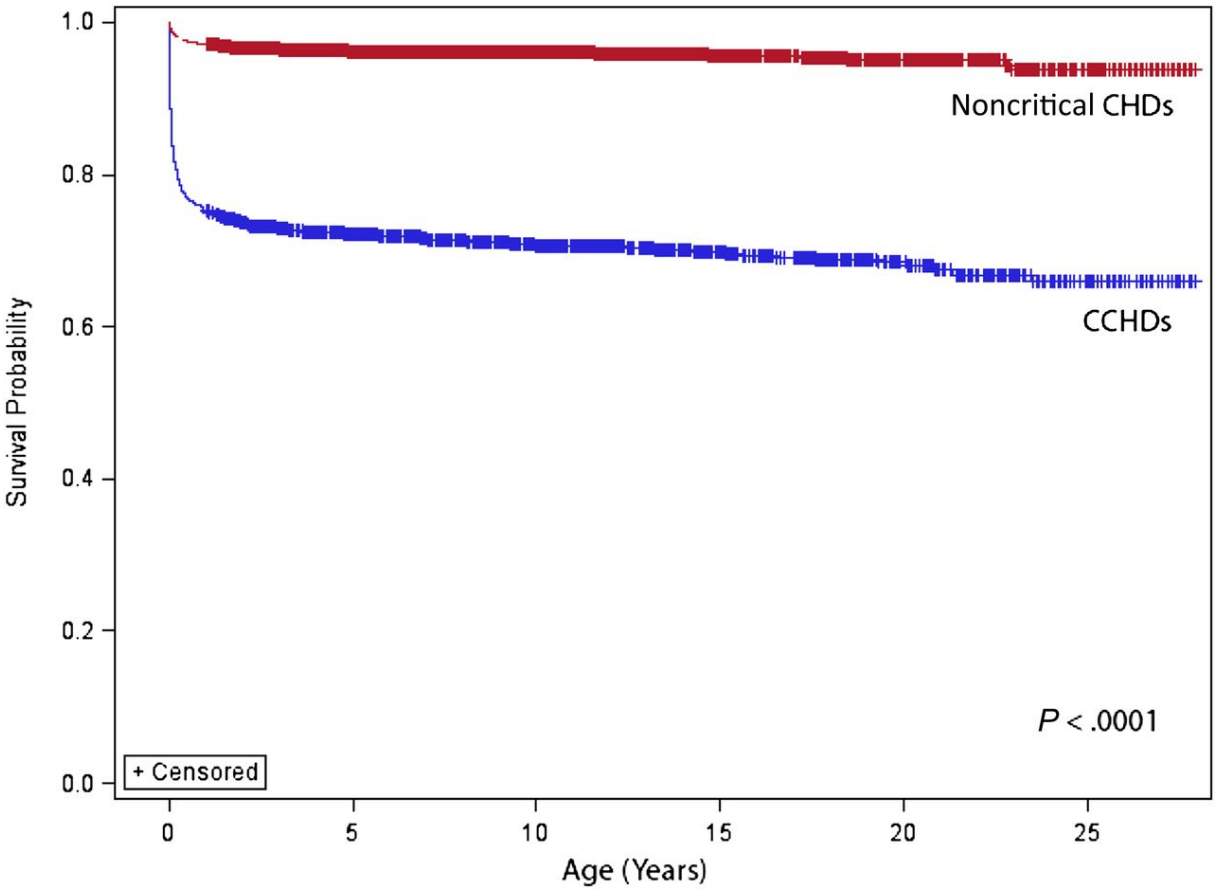


Figure 1.2 Survival for persons with critical versus noncritical CHDs: Atlanta, Georgia, 1979–2005. Note: reprint from "Temporal trends in survival among infants with critical congenital heart defects." By Oster, M. E., Lee, K. A., Honein, M. A., Riehle-Colarusso, T., Shin, M., & Correa, A. (2013). *Pediatrics*, *131*(5), e1502-e1508. Copyright © 2013 by the American Academy of Pediatrics

### 1.4.3 Prevalence

In the general population, the prevalence of CHD is 5.78 per thousand.[39] As a consequence of advances in CHD treatment in these decades, the mortality of CHD is decreasing, and many pediatric CHD patients now reach adulthood.[39] The prevalence of CHD is estimated to be 3 to 4 per thousand in adults[12,39], and 11.89 per thousand in children.[39] The prevalence of CCHD is about 0.4 per thousand in adults and 1.5 per thousand in children.[39] ASD, VSD, and PDA are the most common lesions for both pediatric and adult CHD patients. Gender differences were observed in CHD patients of all ages. CHD is more prevalent in females (4.8 per thousand) than males (3.9 per thousand).[39]

## 1.5 Diagnosis and Treatment

1.5.1 Diagnosis

Echocardiography is the primary imaging tool for diagnosing and assessing congenital heart disease. In recent years, it has been the gold standard for noninvasive imaging for CHD.[40] However, echocardiography has limitations. It may not be sufficient for evaluating extracardiac structures, such as pulmonary arteries.[41] Cardiac catheterization[42], cardiac computed tomography (CT) and magnetic resonance imaging (MRI) are important complementary diagnostic tools that were performed as needed.[43]

Some of CHDs can be detected prenatally.[44] The prenatal detection rate for CHD varies from 20% to 90%,[45–54] depending on the subtypes of the diseases and the skills of a sonographer. The detection rates of major heart defects in 29,460 fetuses are shown in Table 1.3. The current prenatal screening strategy for heart disease in most countries is a standard

anomaly scan at 20 weeks of gestation, using a four-chamber view of the fetal heart, plus outflow-tract, if technically feasible.[55] For high-risk mothers, a fetal echocardiography test will be ordered.[56] The detection rate of fetal echocardiography is higher than a standard anomaly scan. The detection rate of the former can be as high as 90%.[51–54] Early detection for CHD can largely benefit families for enough time for counseling and the best preparation for timely treatment.

| | | | *Prenatally detected* | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | *Time of detection* | | | | | | | | | |
| | | | *Early* | | *Routine scan* | | *Late* | | *Total* | | *Not detected* | |
| *Defect* | n | % | n | % | n | % | n | % | n | % | n | % |
| AVSD, total | 21 | 22 | 4 | 19 | 10 | 48 | 1 | 5 | 15 | 71 | 6 | 29 |
| AVSD, simple | 18 | 19 | 3 | 17 | 8 | 44 | 1 | 6 | 12 | 67 | 6 | 33 |
| AVSD, complex | 3 | 3 | 1 | 33 | 2 | 67 | | | 3 | 100 | | |
| TGA, total | 17 | 18 | | | 8 | 47 | 2 | 12 | 10 | 59 | 7 | 41 |
| TGA, simple | 7 | 7 | | | 3 | 43 | | | 3 | 43 | 4 | 57 |
| TGA, complex | 7 | 7 | | | 4 | 57 | 1 | 14 | 5 | 71 | 2 | 29 |
| TGA, corrected | 3 | 3 | | | 1 | 33 | 1 | 33 | 2 | 67 | 1 | 33 |
| HLHS, total | 10 | 11 | 3 | 30 | 3 | 30 | | | 6 | 60 | 4 | 40 |
| HLHS, simple | 8 | 9 | 2 | 25 | 2 | 25 | | | 4 | 50 | 4 | 50 |
| HLHS, complex | 2 | 2 | 1 | 50 | 1 | 50 | | | 2 | 100 | | |
| Coarctation of aorta, total | 9 | 9 | | | 3 | 33 | 1 | 11 | 4 | 44 | 5 | 56 |
| Coarctation of aorta, simple | 7 | 7 | | | 3 | 43 | | | 3 | 43 | 4 | 57 |
| Coarctation of aorta, complex | 2 | 2 | | | | | 1 | 50 | 1 | 50 | 1 | 50 |
| Ventricular septal defect | 9 | 9 | | | 2 | 22 | 1 | 11 | 3 | 33 | 6 | 67 |
| Tetralogy of Fallot | 7 | 7 | | | 1 | 14 | 2 | 29 | 3 | 43 | 4 | 57 |
| Pulmonary stenosis | 4 | 4 | | | | | 1 | 25 | 1 | 25 | 3 | 75 |
| Pulmonary atresia | 3 | 3 | | | 2 | 67 | 1 | 33 | 3 | 100 | | |
| Primum ASD | 3 | 3 | 1 | 33 | | | | | 1 | 33 | 2 | 67 |
| Single ventricle | 3 | 3 | | | 3 | 100 | | | 3 | 100 | | |
| DORV | 3 | 3 | | | 2 | 67 | | | 2 | 67 | 1 | 33 |
| TAPVR | 2 | 2 | | | | | | | | | 2 | 100 |
| Tricuspid atresia/critical stenosis | 2 | 2 | 1 | 50 | | | | | 1 | 50 | 1 | 50 |
| Common arterial trunk | 1 | 1 | | | | | 1 | 100 | 1 | 100 | | |
| Aortic valve stenosis | 1 | 1 | | | | | | | | | 1 | 100 |
| Mitral stenosis | 1 | 1 | | | 1 | 100 | | | 1 | 100 | | |
| Ebstein's anomaly | 1 | 1 | | | 1 | 100 | | | 1 | 100 | | |
| Total | 97 | 100 | 9 | 9 | 36 | 37 | 10 | 11 | 55 | 57 | 42 | 43 |

ASD, atrial septal defect; AVSD, atrioventricular septal defect; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries.

Table 1.3 Major heart defects in a non-selected population of 29460 fetuses, detection rate and time of detection. Note: Reprint from "Prenatal detection of heart defects in a non-selected population of 30149 fetuses—detection rates and outcome." By Tegnander, E., Williams, W., Johansen, O. J., Blaas, H. G., & Eik-Nes, S. H. (2006). *Ultrasound in Obstetrics &*

### 1.5.2 Treatment

The treatment for CHDs depends on the type and severity of the disease. A patient's age and general health also determine what treatment is needed. Children who have a mild congenital heart disease and were diagnosed early in life may not need any treatment. For moderate and critical congenital heart diseases, medicines, catheter-based interventions or surgical procedures are probably needed. Because of the dramatic improvement in CHD treatment, survival through childhood is currently common even in complex CHD patients such as hypoplastic left heart syndrome.[57]

## 1.6 Delayed Diagnosis

Even though most infants with CHD can benefit from early detection and intervention, many infants are discharged from the hospital without a CHD diagnosis.[58,59] CHD diagnosis after postpartum discharge is defined as delayed diagnosis. As medical technology is fast developing, the rate of delayed diagnosis is decreasing these years.[59,60] However, recent literature still showed a CCHD delayed diagnosis rate of 10% - 30% in developed countries.[60,61] In developing countries, the rates of delayed diagnosis of CCHD are believed to be much higher. Delayed diagnosis is associated with delivery outside a tertiary hospital, birth hospital nursery level, and CCHD type.[60,61] A delayed CCHD diagnosis can lead to heart failure, cardiovascular collapse and even death.[62,63] Newborn cardiac screening is an effective method to avoid the late diagnosis of CHDs.

### 1.7 Screening

Disease Prevention includes a wide range of activities aimed at reducing risks or threats to health. In public health, there are three levels of prevention. Primary prevention aims to prevent the initial development of a disease. Secondary prevention includes the early detection of existing disease to reduce severity and complications. Tertiary prevention is reducing the impact of the disease. Newborn cardiac screening for CHDs is an example of secondary prevention, which can identify CHDs early in life and prevent catastrophic complications.

The pulse oximeter is widely used in newborn cardiac screening. Pulse oximetry screening is a non-invasive measurement of blood oxygen saturation. Using pulse oximeter to screen newborns 24 hours after birth and before hospital discharge can help detect most of the major CHDs and CCHDs.[64] The rationale of this method is that hypoxemia is present in most potentially life-threatening CHDs. With the addition of clinical examination (assessment of pulses and heart sounds and inspection for cyanosis), the pulse oximeter can help detect most of the CHDs.[2,8,62] This combined method has a high sensitivity (93%) and specificity (97%) for the detection of major CHDs and CCHDs.[2,8]

Based on the CCHD screening algorithm endorsed by the American Academy of Pediatrics (AAP),[65,66] every newborn baby should undergo pulse oximetry screening after 24 hours of age or shortly before the hospital discharge. The screening should occur on the right hand and either foot. The baby passes CCHD screening if the oxygen saturation is equal to or greater than 95% and the difference between hand and foot is no greater than 3%. If the

oxygen saturation is less than 90% on hand or either foot, the screening will immediately fail. If the screening is between 90% and 95% or the difference between hand and foot oxygen saturation is greater than 3%, then repeat the whole procedures of screening in one hour. A baby who cannot pass the screening for 3 times will be considered to have failed the screening (Figure 1.3).

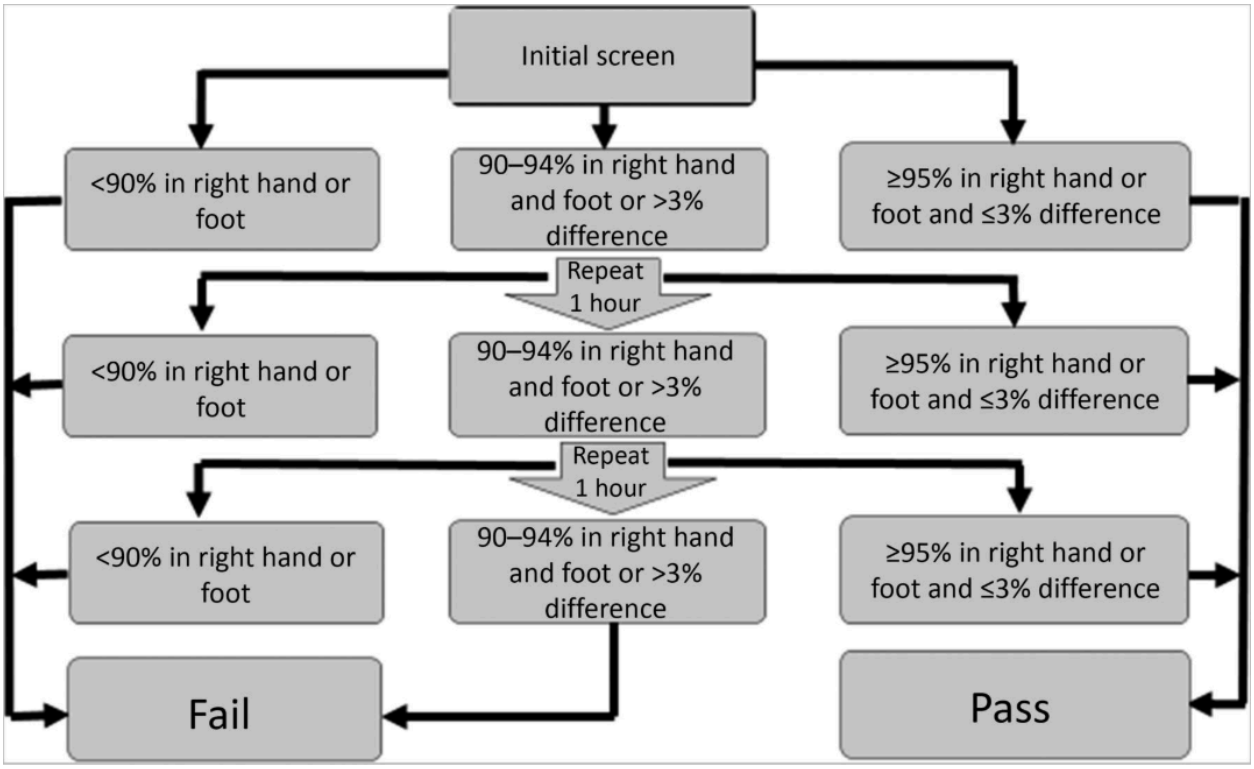


Figure 1.3. AAP CCHD screening algorithm. The screening is for the well-baby nursery at ≥ 24 hours of age or just before discharge. Note: Reprint from "A modified algorithm for critical congenital heart disease screening using pulse oximetry." by Diller, C. L., Kelleman, M. S., Kupke, K. G., Quary, S. C., Kochilas, L. K., & Oster, M. E. (2018). *Pediatrics, 141*(5). 

Currently, the pulse oximetry screening is being performed routinely in most of the hospitals in the developed countries and regions. However, many developing countries

don't have routine CCHD screening. Even though a number of medical centers measure babies' oxygen saturation, they do not follow a standard screening algorithm. The criteria for pass and fail are usually unclear.

### 1.8 Congenital Heart Diseases in Yunnan

Yunnan Province is located in the southwest of China. It is situated in a mountainous area, with high altitudes in the northwest and low altitudes in the southeast. Yunnan is ranked the fourth poorest province among 34 Provinces in China,[67] with an estimated average annual family income of 37,734 CNY (5,474 USD) in 2012.[68]

Yunnan is one of the provinces that have the greatest number of non-profit organizations in China. The main reason that so many organizations choose to help Yunnan is that a great number of people in Yunnan reside in rural and remote mountainous areas. They do not see doctors until very sick. Heart charity organizations such as Ai You Foundation, Children's Heart Link and China California Heart Watch all have been dedicated in Yunnan helping children with congenital heart diseases for more than 10 years. An epidemiological study conducted in 2006 by Dr. Jiang presented that the prevalence of CHDs in Yunnan is 5%, and significant regional and ethnic differences were observed. The prevalence is higher in low-income regions than high-income regions in Yunnan.[69] Through the published study and communications with nonprofit organizations, I realized that a large underserved population with CHD exists in Yunnan. Improvement is needed regarding screening, early diagnosis, referral, and treatment for congenital heart diseases. I summarized the following public health problems that are of my top points of concern.

1. More severe pediatric CHD cases were seen in Yunnan than in developed countries/regions. Many children with CHD are undiagnosed or untreated until adulthood.
2. As mentioned in the Screening section (1.7), newborn CHD screening is not a routine practice in most developing regions including Yunnan province. Almost all hospitals in Yunnan don't conduct CHD screening for newborns, which can largely result in late diagnosis of CHD.
3. Yunnan's altitude varies from sea level to above 5000 meters. High altitudes can cause low oxygen saturation levels. Thus, the pass/fail criteria for newborn CHD screening should be adjusted in most of the places of Yunnan province.

In the next three chapters, I will describe the three problems in detail and discuss potential solutions.

# CHAPTER 2 EISENMEGER SYNDROME IN PEDIATRIC PATIENTS WITH CONGENITAL HEART DEFECTS IN YUNNAN

## 2.1 Introduction

Congenital heart defects (CHD) affect 0.8% of the general population.[35,39,70] Pulmonary arterial hypertension (PAH) is a common complication of CHD, particularly in patients with systemic-to-pulmonary shunts.[71] PAH associated with congenital heart defects (PAH-CHD) accounts for 30% of all types of PAH.[72] An estimated 4 - 10% of adult CHD patients have PAH.[73] Eisenmenger syndrome (ES) is the most advanced form of PAH-CHD, in which the systemic to pulmonary shunt becomes bi-directional, PAH is irreversible and surgical repair cannot be safely performed.[3,74] About 1% of adult CHD patients have ES.[73] PAH and ES are probably less common in children but what percentages of pediatric CHD patients have PAH and ES are unknown.

In the developed world, most patients with CHD are identified early and their defects are repaired in childhood.[59,75] Pediatric Eisenmenger syndrome is thus rare. However, in the developing world, many young patients have cardiac lesions unrepaired until adulthood, and some may develop ES in childhood making them not eligible for repair.[76,77]

An epidemiologic description of PAH and ES in pediatric CHD patients is needed to inform physicians for better strategies of early detection and prevention. We assessed CHD data from Yunnan, China for a 10-year period spanning 2006 through 2016. Our objectives were to 1) investigate the percentages of PAH and ES among pediatric patients with unrepaired

CHD and in different CHD subgroups, 2) investigate the factors that contribute to the development of PAH or ES, and 3) discuss the role that age plays on the course of Eisenmenger syndrome.

## 2.2 Methods

### 2.2.1 Patients

This is a retrospective study, using the database collected by China California Heart Watch (China Cal) in Yunnan Province, China. Yunnan Province, consisting of 16 prefectures is situated in the southwest of China, with high altitudes in the northwest and low altitudes in the southeast. It is ranked the fourth poorest province among 34 Provinces in China,[67] with an estimated average annual family income of 37,734 CNY (5,474 USD) in 2012.[68] China Cal is a non-profit organization with missions of diagnosing, referring and financially supporting children with congenital heart defects in underserved and impoverished areas in Yunnan Province, China. Working with local personnel, every year since 2006, China Cal volunteer cardiologists traveled to rural villages and towns of every Yunnan prefecture to examine self-referred or elementary school children for congenital heart defects. Children who were diagnosed with CHD were then referred to provincial medical centers for treatment.

A medical intake profile was created to record every patient's demographics, family history, symptoms, heart rate, pulse oximetry, blood pressure, detailed cardiac ultrasound findings, final diagnosis, and referral information. This study reviewed China Cal's intake records from 2006 to 2016. Patients satisfying the following criteria were included in this

study: 1) under 19-year old on the first China Cal visit; 2) diagnosed with one or multiple types of the CHDs listed in Table 2.1; and 3) no prior surgical or percutaneous intervention (patients with unrepaired CHD) before the first China Cal visit.

| |
|---|
| Category I |
| • Tricuspid regurgitation or mitral regurgitation/ aortic valve regurgitation |
| • Pulmonary stenosis (PS) |
| • Aortic stenosis (AS) |
| • Atrial Septal defects (ASD) |
| • Patent ductus arteriosus (PDA) |
| • Ventricular septal defects (VSD) |
| Category II |
| • Persistent truncus arteriosus |
| • Atrioventricular septal defect or endocardial cushion defect |
| • Tetralogy of Fallot |
| • Double outlet right ventricle |
| • Tricuspid atresia |
| • Ebstein's anomaly of the tricuspid valve |
| • Single (double inlet) ventricle with pulmonary stenosis |
| • Partial anomalous pulmonary venous drainage |
| • Coarctation of the aorta |
| • Primary pulmonary hypertension |
| • Pulmonary atresia |
| • Aortic or mitral atresia |
| • Interrupted or atretic aortic arch |
| • Complete transposition of the great arteries |
| • Anomalous connection/obstruction of the pulmonary veins |
| • Congenital anomalies of coronary arteries |
| • Coronary artery fistula |
| • Congenitally corrected transposition of the great arteries |
| • Cardiomyopathy |

Table 2.1. Underlying cardiac defects

2.2.2 Identification of pulmonary artery hypertension and Eisenmenger syndrome

We carefully reviewed each patient's first clinic visit record. The following data collected in the medical record were used: age, sex, geographic region, altitude, patient source (self-referred or school screening), family annual income, oxygen saturation, presence or absence of clinical Down syndrome, systolic pulmonary artery pressure (sPAP), detailed ultrasound findings and final diagnosis.

In our study, PAH was detected by echocardiography. PAH was considered present when "pulmonary arterial hypertension" was one of the diagnoses in ultrasound findings, or the pulmonary artery systolic pressure exceeded 35 mm Hg. [78]

Based on Wood's definition, Eisenmenger syndrome is defined as "pulmonary hypertension due to a high pulmonary vascular resistance with reversed or bidirectional shunt at aortopulmonary, ventricular, or atrial level." [74] Patients with the following ultrasound findings were provisionally considered as ES presence on the first round of data review: 1) presence of PAH and 2) presence of right to left or bi-lateral shunting through a shunt defect (VSD, ASD, PDA) or 3) significant pulmonary and systemic venous blood mixing at the ventricular or atrial level (single ventricle, truncus arteriosus, etc.). Dr. Robert Detrano then carefully reviewed ultrasound findings and CT and/or catheter results of the suspicious patients and eventually identified ES status.

2.2.3 Underlying defects

Patients were divided into two groups -- simple CHD and complex CHD, based on the defect type and the number of defects. Simple CHD was defined as the presence of a single type of the following defects: ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA), aortic, pulmonic, or mitral stenosis, or regurgitation (Category I defects in Table 2.I). Complex CHD was defined as the presence of at least two Category I defects and/or at least one Category II defects in Table 2.1.

### 2.2.4 Statistical analysis

Baseline characteristics were presented as count and percentage for categorical variables and mean and standard deviation (SD) for continuous variables. Chi-square tests were performed to compare categorical variables between groups; two-tailed t-tests were performed to compare continuous variables between groups. Annual family income, a continuous variable not normally distributed, was presented as median with the 1$^{st}$ to 3$^{rd}$ quartiles and compared with the Mood's median test. Multivariable logistic regression models were fitted to investigate the relationship between ES or PAH with age, sex, the presence of Down Syndrome, underlying groups, patient source, and altitude. *P values* <0.05 were considered as significant for all tests. All statistical analyses were performed using R version 3.5.3.

## 2.3 Results

### 2.3.1 Baseline characteristics

Our study included 1,301 patients, who had at least one of the CHD defects listed in Table 2.1. The patients came from all 16 prefectures in Yunnan Province. Table 2.2 shows the

baseline characteristics of the study population. Fifty-three percent were female. The age range of study patients was from 2-day old to 18.9-year old, with a mean of 5.7 years. 83.2% of study population were self-referred, and 16.8% were from school screening. The altitudes that patients resided at ranged from 110 to 3282 meters, with a mean of 1497 meters. The median annual family income of the study population was 10,000 CNY and the mean was 17,286 CNY (2,542 USD). Eighteen (1.4%) of the study population had Down syndrome. Patients with PAH were older than patients without PAH (mean: 7.0 vs 5.5 years; $p < 0.0001$); and patients with ES were older than the patients without ES (mean: 11.8 vs 5.6 years; $p<0.05$). The mean oxygen saturation in ES patients was significantly lower than that in non-ES patients (88.3% vs 93.5%; $p<0.05$). The annual family income was lower in PAH patients compared with non-PAH patients ($p<0.05$). ES and non-ES patents did not show a significant difference in family income ($p=0.98$).

2.3.2 Underlying defects

Of 1,301 total population, 1,007 (77.4%) had one congenital heart defect, 205 (15.8%) had two defects, and 89 (6.8%) had three to five defects. Simple defects were present in 902 (69.3%), and complex defects were present in 399 (30.7%) patients (Table 2.2). VSD (n = 467, 51.8%) was the most frequent underlying defect among patients with simple CHD. It was followed by ASD (n=228, 25.3%) and PDA (n=115, 12.7%). Tetralogy of Fallot (TOF) was the most frequent underlying complex CHD (n = 64, 16.0%). Other frequent underlying complex CHDs included: pulmonary atresia (PA) (n = 36, 9.0%), atrioventricular septal defect (AVSD) (n = 26, 6.5%), complete transposition of great arteries (TGA) (n = 24, 6.0%)

and double outlet right ventricle (DORV) (n = 21). In 73.7% patients with complex CHD, there was at least one other heart defect present.

| | Total n=1,301 | PAH | | ES | |
|---|---|---|---|---|---|
| | | Yes (n=214) | No (n=1087) | Yes (n=19) | No (n=1282) |
| Sex | | | | | |
| Female | 53% | 48.6% | 53.8% | 52.6% | 53.0% |
| Defects | | | | | |
| Simple CHD | 902 | 125 | 777 | 9 | 893 |
| *PDA* | *115* | *12* | *103* | *1* | *114* |
| *ASD* | *228* | *24* | *204* | *0* | *228* |
| *VSD* | *467* | *87* | *380* | *8* | *459* |
| *PS* | *35* | *0* | *35* | *0* | *35* |
| *AS* | *23* | *0* | *23* | *0* | *23* |
| *Regurgitation* | *26* | *2* | *24* | *0* | *26* |
| *AI* | *6* | *0* | *6* | *0* | *6* |
| Complex CHD | 399 | 89 | 310 | 10 | 389 |
| Mean Age, yrs (SD) | 5.7 (4.7) | ***7.0 (4.9)*** | ***5.5 (4.6)*** | ***11.8 (5.7)*** | ***5.6 (4.6)*** |
| Patient source | | | | | |
| Self-referred | 83.2% | 80.8% | 83.7% | 89.5% | 83.2% |
| Mean altitude, meters (SD) | 1497 (492) | 1517 (482) | 1493 (494) | 1380 (605) | 1499 (490) |
| Mean hand $SpO_2$, % (SD) | 93.5 (7.0) | 92.6 (7.4) | 93.6 (6.8) | ***88.3 (7.5)*** | ***93.5 (6.9)*** |
| Median annual family income, CNY (Q1,Q3) | 10000 (4900, 20000***)*** | ***10000 (5000, 15000)*** | ***10000 (4500, 20000)*** | 10000 (5750, 27500) | 10000 (4800, 20000) |

Table 2.2 Baseline characteristics in 1,301 pediatric CHD patients. PAH = pulmonary artery hypertension, ES = Eisenmenger syndrome, CHD = congenital heart defects, PDA = patent ductus arteriosus, ASD = atrial septal defects, VSD = ventricular septal defects, PS = pulmonary stenosis, AS = aortic stenosis, Regurgitation = tricuspid or mitral or aortic valve regurgitation, $SpO_2$ = oxygen saturation, CNY = Chinese Yuan, Q1–Q3 = 1st–3rd quartiles

### 2.3.3 PAH and ES

Among all study patients, 214 (16.4%) had PAH and 19 (8.9%) of the PAH patients had ES. The ES patients accounted for 1.5% of all patients. 125 (58.41%) of the PAH patients had simple CHD, and 9 (47.37%) of ES patients had simple CHD.

Of the patients with simple CHD, 13.9% and 1.0% had PAH and ES. The percentages of PAH in PDA, ASD, and VSD patients were 10.4%, 10.5%, and 18.6%, respectively. The percentages of ES in those patients were 0.9%, 0%, and 1.8%, respectively. Of patients with complex CHD, 22.3% had PAH and 2.5% had ES. The percentages of PAH and ES were 7.8% and 0 among patients with TOF, 8.3% and 5.6% among patients with PA, 50% and 11.5% among patients with AVSD, 25% and 8.3% among patients with TGA, and 33.3% and 9.5% among patients with DORV.

### 2.3.4 Age

Most of the study population were in the age group of 5 to 10 years old (Table 2.3). VSD was the predominant underlying defect in all age groups (Figure 2.1). Figure 2.2 shows the percentages of PAH and ES among unrepaired-CHD patients by age group. The percentage of PAH increased with age throughout the entire childhood, as did the percentage of ES. Infants aged <1 showed the lowest percentage of PAH (10.3%) and no infant was diagnosed with ES. The percentage of PAH increased linearly with age up to the age of 15 years, then plateaued. The percentage of ES increased slowly with age up to age 15 years. However, from age 15 to 19 years, the percentage of ES showed a sharp increase. Children

aged 15 – 19 years had the highest percentage of PAH (23.1%) and ES (11.5%), i.e., almost 50% of the PAH patients of age between 15 and 19 years had developed ES.

| Age group (yrs.) | No. Total n=1301 | With PAH n (%) | With ES n (%) |
|---|---|---|---|
| <1 | 223 | 23 (10.3%) | 0 (0%) |
| 1 – 5 | 473 | 63 (13.3%) | 3 (0.6%) |
| 5 – 10 | 322 | 63 (19.6%) | 3 (0.9%) |
| 10 – 15 | 231 | 53 (22.9%) | 5 (2.2%) |
| 15 – 19 | 52 | 12 (23.1%) | 6 (11.5%) |

Table 2.3. PAH & ES by Age Group**.** PAH = pulmonary artery hypertension, ES = Eisenmenger syndrome

| | OR | 95% CI | P-value |
|---|---|---|---|
| Dependent variable: PAH | | | |
| Age | 1.07 | (1.03, 1.10) | <0.0001 |
| Complex CHD | 1.68 | (1.22, 2.29) | 0.001 |
| Down present | 9.17 | (3.46, 26.97) | <0.0001 |
| Sex Female | 0.81 | (0.60, 1.09) | 0.16 |
| Self-referred | 1.01 | (0.66, 1.55) | 0.98 |
| Altitude | 1.00 | (1.00, 1.00) | 0.45 |
| Dependent variable: ES | | | |
| Age | 1.28 | (1.18, 1.43) | <0.0001 |
| Complex CHD | 2.23 | (0.85, 6.03) | 0.10 |
| Down present | 14.40 | (2.64, 61.86) | <0.001 |
| Sex Female | 1.14 | (0.43, 3.11) | 0.79 |
| Self-referred | 2.97 | (0.75, 20.15) | 0.17 |
| Altitude | 1.00 | (1.00, 1.00) | 0.70 |

Table 2.4. Logistic Regression Analysis of PAH and ES with Risk Factors**.** PAH = pulmonary artery hypertension, ES = Eisenmenger syndrome, CHD = congenital heart defects, altitude = the altitude of patient residences

2.3.5 Other risk factors

Table 2.4 displays the results of the multivariate logistic regression analysis of PAH and ES, with independent variables including patients' age, sex, underlying groups, patient source, and altitude. Age (OR: 1.07; 95% CI: (1.03, 1.10)), presence of complex CHDs (OR: 1.68; 95% CI: (1.22, 2.29)), and presence of Down syndrome (OR: 9.17; 95% CI: (3.46, 26.97))

were positively associated with the presence of PAH. Sex, patient source, and altitude were not significantly associated with the presence of PAH. Age (OR: 1.28; 95% CI: (1.18, 1.43)) and presence of Down syndrome (OR: 14.40; 95% CI: (2.64, 61.86)) were positively associated with ES. Specifically, if Down syndrome presents, or when a patient is getting old, the odds of getting ES will increase. The presence of a complex CHD, sex, patient source, and altitude were not significantly associated with the presence of ES.

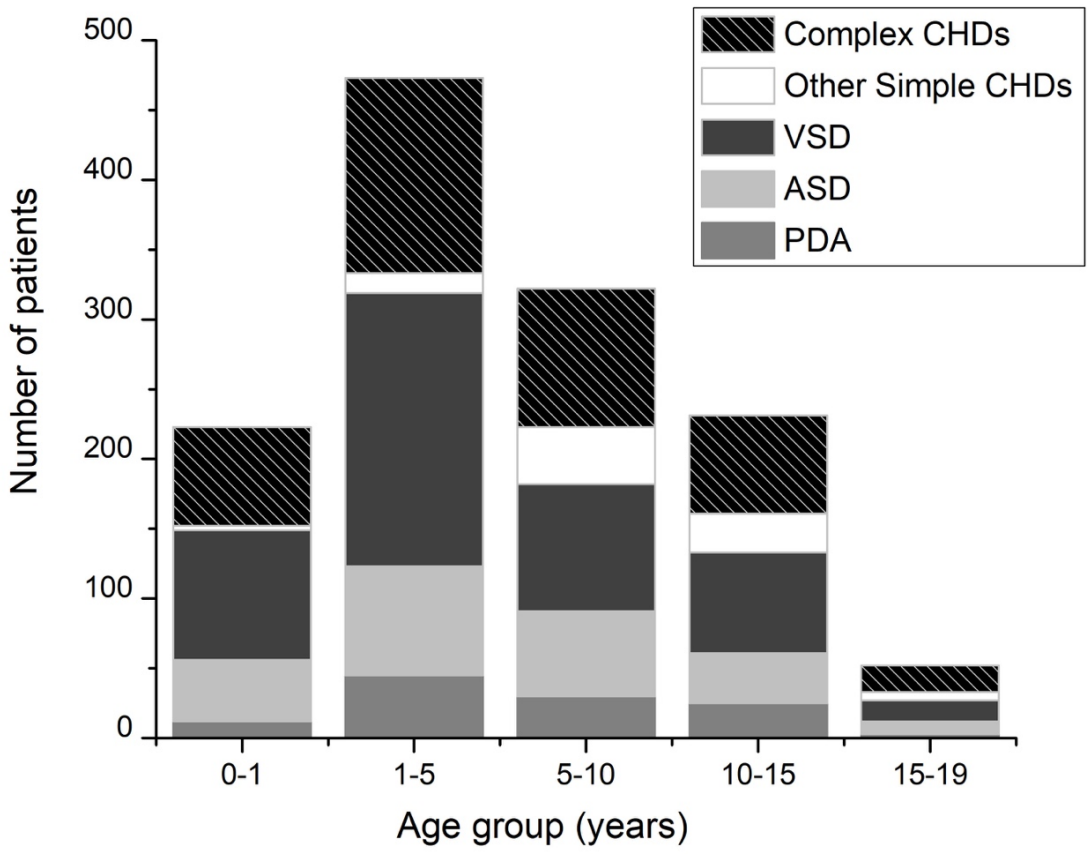


Figure 2.1. Age distribution and underlying defects of CHD patients.

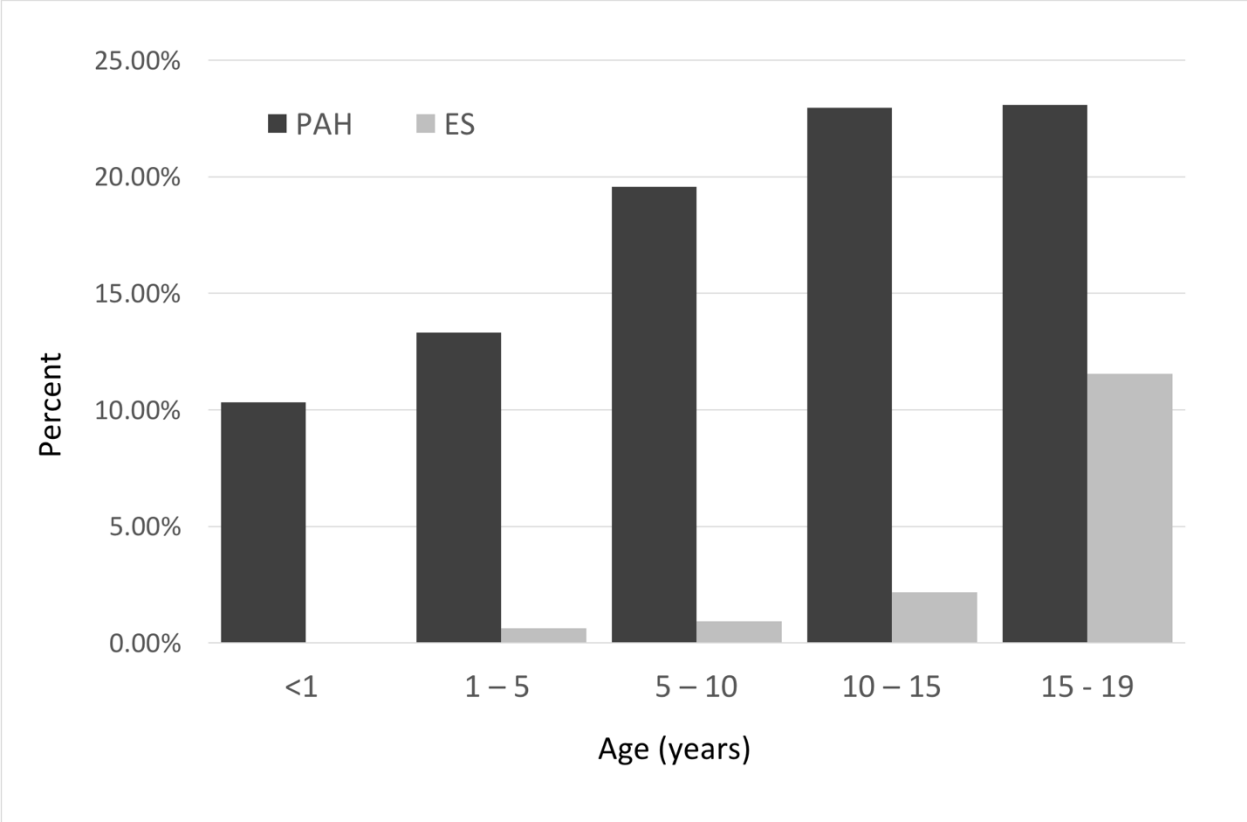


Figure 2.2. Prevalence of PAH and ES among CHD Patients by Age Group

## 2.4 Discussion

Our study shows the distribution of underlying defects among children with unrepaired CHD in Yunnan Province, China, and reveals the percentages of Eisenmenger syndrome and pulmonary artery hypertension in these patients. Importantly, this is the first study showing the percentages of ES and PAH among pediatric CHD patients by age group. Our study finds that the percentages of PAH and ES are 16.4% and 1.5% among pediatric patients with unrepaired CHD in Yunnan Province, China. The percentages of PAH and ES increase with age. For CHD patients with age between 15 and 19 years, the percentages of PAH and ES are the highest (23.1% and 11.9%, respectively). Age, presence of complex

CHD and presence of Down syndrome are associated with increased risk of developing PAH or ES.

### 2.4.1 Data

Our study participants were from all 16 prefectures in Yunnan Province. Most of the participants (83.2%) were self-referred CHD patients. Study results show that VSD, ASD, and PDA were the top 3 most common lesions among pediatric CHD patients; and TOF is the most common complex congenital heart defect. The results are consistent with Dr. Jiang's CHD prevalence study in Yunnan in 2005.[69] Our findings are also compatible with the findings of pediatric CHD studies in other regions of China[79–81] and in other developing countries.[10,34,60,76,82,83(p109)] Our study population was children with unrepaired CHD, which were not uncommon in rural Yunnan. However, such large numbers of unrepaired cases of CHD might not be present in developed countries.

### 2.4.2 PAH and ES

The percentages of PAH and ES in pediatric patients with unrepaired CHD have not been previously reported. However, the percentages of PAH in adult CHD patients have been studied. In the CONCOR study, the authors reported percentages of 4.2% and 1% for PAH and ES among adults with CHD, but the authors explained that a PAH prevalence of 4.2% was likely an underestimation and adjusted the result to 10%,[73] which is consistent with the estimate of other researchers.[84,85] The study using the Euro Heart Survey reported percentages of 28% and 5.2% for PAH and ES among adult CHD patients,[86] but that study only included patients with VSD and ASD.

The percentages of PAH and ES are higher in patients with complex CHDs (22.3%, 2.5%) compared to patients with simple CHDs (13.9%, 1.0%). For simple CHDs, children with VSD have the highest percentages of PAH (18.6%) and ES (1.8%), which is consistent with adult ES studies.[73,85,87] The most recent study, the CONCOR study, finds that 28% patients with unrepaired VSD have PAH, and of the PAH-VSD patients, 79% developed ES.[73] Different from the increased risk among VSD patients, ASD patients have a lower risk of ES. Our results show that none of the ASD patients with PAH have developed ES, which may have to do with the relatively long asymptomatic period for ASD patients compared with patients with other cardiac lesions.[73,85] For complex CHD, patients with AVSD show the highest percentage of PAH (50%) and ES (11.5%). The CONCOR study also reported high prevalence of PAH and ES in adult patients with AVSD.[73]

2.4.3 Age and other risk factors

Age plays an important role in the course of pulmonary artery hypertension and Eisenmenger syndrome. No children under age 1 year have Eisenmenger syndrome, and only a small percentage (10.3%) has PAH. The percentages of PAH and ES increase with age. At ages between 15 and 19 years, the percentages of PAH and ES are 23.1% and 11.5% respectively. The rates are comparable with rates reported in adult patients with unrepaired CHD (28%-34% and 3-19%).[86]

Early detection of CHD and timely surgical or interventional correction can prevent the development of ES in most patients. In the developed world, the incidence of ES has

decreased.[75] In the developing world, there is urgent need for early detection and intervention. For children with unrepaired CHD, the longer the defect is unrepaired, the higher the risk that ES and PAH will develop.

Besides age, complex CHD and Down syndrome increase the risk of developing PAH or ES. For CHD patients, every one-year increase in age, the odds of developing PAH will be multiplied by 1.07. Patients with complex CHD are 1.68 times as likely to develop PAH compared to those with simple CHD. Patients with Down's syndrome are 9.17 times as likely to develop PAH compared with non-Down patients. As for Eisenmenger syndrome, every one-year increase in age, the odds of developing ES will be multiplied by 1.28. The odds of developing ES is 14.40 fold higher in Down syndrome patients compared to non-Down patients. High altitude is believed to be associated with an increased incidence of CHD.[88] However, we do not find an association between altitude and PAH or ES. Besides, self-referred patients and patients identified by school screening have similar prevalence of both PAH and ES.

### 2.4.4 Study limitation

Our data were collected in rural, underdeveloped areas. Study subjects were mostly from a low-income population. The average annual family income of our study population was 17,286 CNY, lower than the average in China and also lower than the estimated annual family income in Yunnan Province (37,734 CNY). Even though previous studies have shown that the incidence of CHD in different regions did not differ significantly,[10] developing or underdeveloped areas with insufficient resources for pediatric cardiac services could have

more PAH and ES patients. No similar pediatric ES or PAH studies in developed countries or high-income populations have been reported before, which makes comparing results impossible. Future PAH and ES studies in both developed and developing regions are warranted.

Due to the limited resources of our study region, it was very difficult for the children to get cardiac catheterization. As a result, Invasive (catheterization) data for direct sPAP measurement were not available. SPAP was therefore estimated by echocardiogram.

Our study focused on unrepaired CHD in children. The risk of developing PAH and ES will rapidly decrease after the defects are repaired.[73,86] Caution, therefore, should be taken when apply the study results to children with repaired cardiac defects.

### 2.4.5 Future

As mentioned previously, most children with CHD, if diagnosed and treated early in life, are very likely to be cured. When the optimal timing for surgical repair is missed, and ES develops, the disease is not reversible. These patients are medically treated with PAH-specific therapies, such as oral Bosentan for symptom relief.[89] Development of ES is associated with increased mortality.[86]

While PAH and ES can occur in the patients with repaired CHD, the prevalence of ES is much lower compared with patients with unrepaired CHD.[73,86] Thus, early repair may prevent the development of PAH and ES. In the developing world, however, there are some

barriers to surgical repair of CHD. First, poverty is one of the greatest barriers. Treatment of CHD, especially complex CHD, is costly. It is a significant burden for low-income families to pay surgery expenses out of pocket. Second, the resources to treat CHD may be inadequate. The ratio of cardiac surgeons/cardiovascular centers to population is much lower in developing countries compared with developed countries.[90] Third, after diagnosis, it shows a delay in referral to a cardiovascular center.[77,91] Such delay might be due to inadequate training of pediatric personnel and lack of awareness of the need for early referral.[92] Fortunately, overcoming these barriers is not impossible. Some approaches have shown to be effective in rural Yunnan Province. The Chinese government is continuously improving health care services in rural areas. By 2014, about 99 % of rural residents in China had joined the new rural cooperative medical system (NCMS), which can reimburse about 60%- 80% pediatric cardiac surgery cost for rural residents.[93] There are also charitable foundations such as Ai You Foundation to financially support children with CHD from poor families in Yunnan. Beyond that, the successful implementation of training programs at rural Yunnan hospitals has provided an effective way to improve the health care providers' awareness of the critical need of CHD early diagnosis and referral.[94] With early detection and timely intervention of CHD, one may expect that a decrease in the prevalence of PAH and ES in the future is likely.

### 2.5 Conclusion

Our study findings show that 16.4% and 1.5% of pediatric patients with unrepaired CHD have PAH and ES, respectively. PAH and ES occur more frequently in CHD patients aged 15 to 19 years. The probability of developing PAH and ES increases with age.

# CHAPTER 3 THE IMPLEMENTATION OF NEWBORN CARDIAC SCREENING IN RURAL YUNNAN

## 3.1 **Introduction**

Congenital heart defects (CHD) are the most common and severe types of congenital anomalies.[95] The incidence of CHD, as reported by Hoffman et al. [10], is 12-16 per thousand live births. Critical Congenital Heart Diseases (CCHD) can cause death or request invasive intervention in the neonatal period.[59] About one to two per thousand newborn babies have CCHD, [59] which along with large shunt lesions are the most severe types of CHDs. Large shunt lesions are ventricular septal defects (VSD) and patent ductus arteriosus (PDA) that require surgery in order to prevent death from irreversible pulmonary vasculature disease. The incidence of VSD and PDA is approximately 4.4 per thousand live births.[10] We estimated that one-fourth of the VSDs and PDAs are large shunt lesions, so an estimated one in every thousand neonates are born with large shunt lesions. Most of these heart defects are curable if discovered early in life.[59]

Nevertheless, many infants with CCHD or large shunt lesions are not diagnosed and are directly discharged from the hospital.[58,59] Many of them die in infancy and some develop incurable pulmonary vascular disease and Eisenmenger's syndrome and then die in young adulthood. Thus, hospitals should improve the method of screening for CCHD and large shunt lesions. Pulse oximetry screening is effective for early detection of CCHD and large shunt lesions.[2,8,96–99] In most developed countries, this method has been added to the uniform newborn screening panel. However, according to the results of our preliminary study, many

rural hospitals in Yunnan, China did not implement pulse oximetry screening on newborn babies.

By contrast, in large hospitals of developed countries, many educational programs for newborn pulse oximetry screening have been successfully implemented.[100–103] One of the largest such programs, TxPOP, successfully and quickly trained neonatal nurses in Texas in the proper use of pulse oximetry.[101] Despite the success of such programs, there has been no effort to disseminate pulse oximetry screening method to rural areas in developing countries.

A large study conducted in Shanghai has reported that newborn cardiac screening using pulse oximeter and stethoscope is feasible and reliable for the detection of CCHD with a sensitivity of 93.2% and a specificity of 97.1%. Cardiac screening using pulse oximeter alone lead to an approximately 10% decrease of sensitivity.[2] Based on our preliminary study in rural areas of Yunnan, hospitals did not conduct proper cardiac auscultation on every newborn baby. Hence, training rural hospital personnel in the proper use of stethoscope is also imperative.

We designed and implemented a training program for newborn pulse oximetry and stethoscope screening for obstetric doctors and nurses working in rural areas of Yunnan Province. The aims of this study are 1) to test if the training program will result in trainees' improvement in knowledge of cardiac screening and the proper use of pulse oximeter and stethoscope, 2) to test if the training program will lead to high newborn cardiac screening

rates in the participating hospitals, and 3) to discuss the best practices in educating rural obstetric personnel on newborn cardiac screening.

Yunnan is a socio-economically depressed province of China (per capita annual income of $1,222). An estimated 592,000 neonates are born in Yunnan province each year.[104] Assuming a CCHD incidence of two per thousand, and a large shunt lesion incidence of one per thousand, approximately 1,800 Yunnan infants are affected per year. These affected infants can benefit from an effective cardiac screening program.

## 3.2 **Methods**

### *3.2.1 Training Strategy*

In China's rural county hospitals, where most birthing occurs, obstetricians and obstetric nurses take responsibility for the care of all asymptomatic neonates, pediatricians are only consulted for infants with signs or symptoms of disease. We therefore designed a training program—the Newborn Cardiac Screening Training Program (NCASTP)—for obstetricians and obstetric nurses in Yunnan rural county hospitals. We established a training team in June 2015, which included three core members (a cardiologist, a Ph.D. student in Public Health and a research assistant) and a number of volunteers. All members in the training team spoke fluent Chinese. The team visited every rural county hospital which was interested in the training program and trained the obstetric personnel in office/classrooms near the neonatal units.

Using the donated Masimo Rad 5 pulse oximeter from Irvine California, we implemented the training according to the following steps:

- pre-training quiz and behavior assessment
- 30-minute lecture on newborn cardiac screening
- one-on-one pulse oximeter practice training
- one-on-one stethoscope practice training
- post-training quiz test
- quiz test and a second behavior assessment

In the practical training, the trainers modeled the correct use of a pulse oximeter to measure pre- and post-ductal oxygen saturation on a plastic model and then on real babies. Then obstetricians and obstetric nurses practiced measuring on the plastic model. When the trainers verified that trainees demonstrated proper use, the trainees moved on to the stethoscope practice training. The stethoscope practice training was elective for the obstetric nurses. In this part, the cardiac specialist trainer used a plastic infant model designed by the General Doctor Company in Shanghai to show the trainees normal and abnormal sounds at four auscultatory sites. The training team would not leave until the cardiac specialist verified that the trainees were able to distinguish normal from the abnormal sounds and knew where the four sites were located.

The pulse oximetry screening algorithm we used was a variation of Granelli's method.[97] The neonates were measured 24 hours after birth on their right hand and on either foot. The neonate was provisionally considered as screen-positive if both pre- and post-ductal oxygen

saturation were less than the cut-off value or the difference between the two was greater than 3%. If the first screening was abnormal, a repeat measurement was performed before hospital discharge. Neonates with two repeated positive measurements were finally regarded as screen-positive and were referred for an immediate cardiac ultrasound exam.

By the end of 2016, NCASTP had trained 2,175 obstetric nurses and doctors (on average 21 per hospital) in 13 of the 16 Yunnan prefectures including 104 of the 125 Yunnan counties (91.2%) (Figure 3.1).

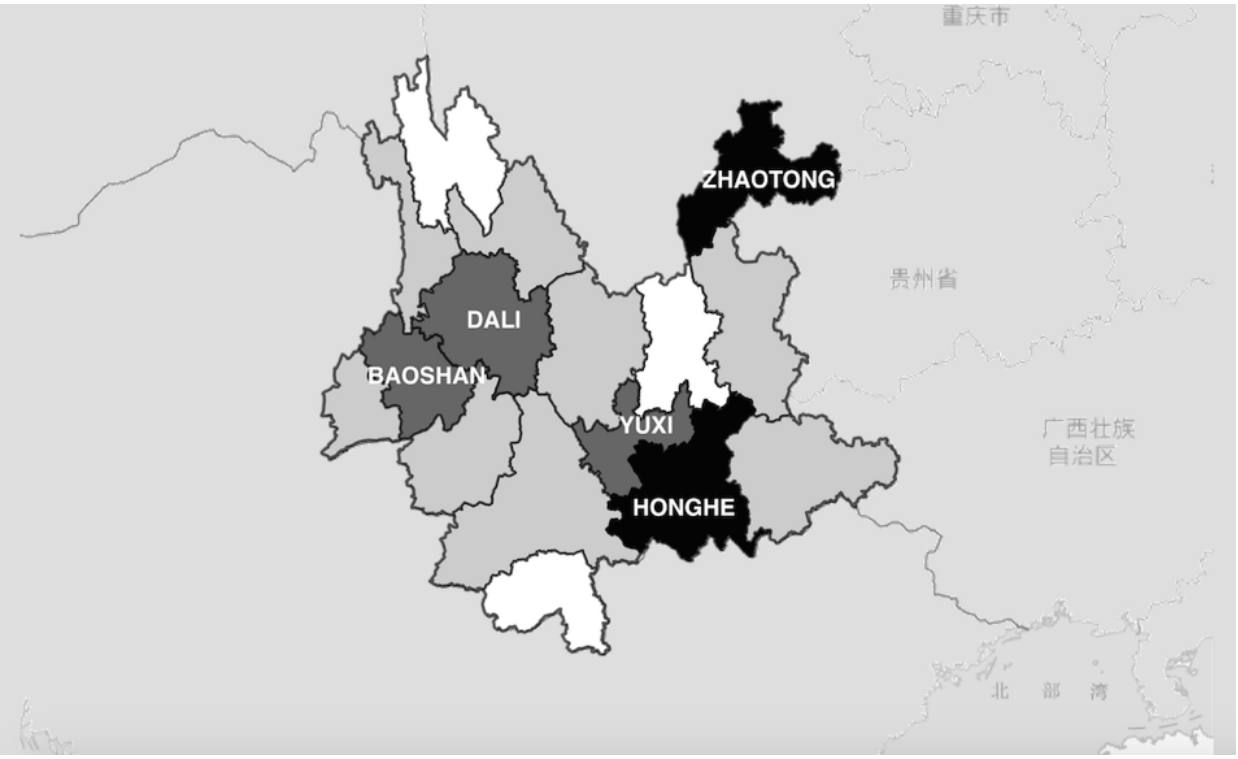


Figure 3.1. Training Map in Yunnan. This is a map of Yunnan Province of China. Areas in black are the prefectures where we trained and implemented the first and second phases of evaluation. Areas in dark grey are the prefectures where we trained and implemented the second phase of evaluation. Areas in grey are the prefectures that we trained but did not evaluate. Areas in white are the prefectures that we have not trained yet.

### *3.2.2 Evaluation Strategy*

*Phase I: Knowledge Improvement and Behavior Change of Trainees.* Trainees in 22 hospitals in Zhaotong and Honghe prefectures (Figure 3.1) participated in the first phase of training evaluation. First, a 19-item multiple-choice quiz was implemented before, immediately after and three months after training. The quiz included ten questions on newborn cardiac screening, three questions on patho-physiology, two questions on treatment, two questions on communicating with parents, one question on the symptoms of CCHD and one question on CCHD incidence. In addition, before training and three months after training, we assessed each of the trainees regarding usage of stethoscope and pulse oximeter. We interviewed them based on a behavior checklist, which included questions such as:

(1)'Have you ever applied this device (pulse oximeter/stethoscope) on newborn babies?'
(2)'How often do you use this device?' and
(3)'Do you use the device on every newborn baby?'

Finally, we asked each of the trainees to use the devices on a doll and we observed and recorded their performance.

*Phase II: Assessment of Screening Rate.* We evaluated the screening rates by collecting monthly cardiac screening data from 36 hospitals (Figure 3.1), which received our training in 2015. We provided a data entry sheet to the obstetric directors and chief nurses of those hospitals and instructed them on how to record screening results. The items on the data entry sheet included the number of neonates born in the hospital every month and each

baby's randomized ID, birth month, pre- and post-ductal oxygen saturation and auscultation results (with/without murmur) measured at 24 hours of age and before hospital discharge.

### *3.2.3 Statistical Analysis*

We summarized the number of correct answers on knowledge quizzes and the behavior scores on the use of stethoscope and pulse oximeter at three points of time (before training, immediately after training and three months after training). We applied independent two-sample t-tests to compare mean correct scores before training and immediately after training as well as before training and three months after training. Because quizzes were anonymous, matched analysis was not possible. We used Chi-square tests to compare the frequency before and three months after training and the proper use of pulse oximeter and stethoscope as well as for the same period. Statistical tests were performed with the level of significance set at 0.05.

## 3.3 Results

### *3.3.1 Phase I: Knowledge Improvement and Behavior Change of Trainees*

A total of 332 trainees from 22 hospitals of Zhaotong and Honghe prefectures enrolled in the evaluation of knowledge improvement. All of them participated in the pre-training quiz, 313 (94.3%) in the immediate post-training quiz, and 200 (60.8%) in the 3-month post-training quiz. Participants answered 45.3%, 81.9% and 64.9% of questions correctly in the pre-, post- and 3-month quizzes, respectively. Trainees showed significant knowledge improvement immediately after and three months after training ($p<0.001$).

Before our training, 180 nurses participated in the evaluation of pulse oximeter use. None of them had neonatal pulse oximeters available. Three months after the training, 99 nurses took part in the evaluation. Fifteen nurses (15.2%) reported they never used the pulse oximeter; 23 (23.2%) used it sometimes; 61 (61.6%) used it frequently. For those 61 nurses who reported using pulse oximeter frequently, all demonstrated proper use. We assessed the proper use of stethoscopes on 107 doctors before training and 61 doctors three months after the training. Before training, 32.7% of the doctors performed cardiac auscultation on every newborn baby. After, this increased to 72.1% ($p < 0.001$). Before training, 80.4% of doctors used the stethoscope improperly. After training, this dropped to 3.3% ($p<0.001$).

### *3.3.2 Phase II: Assessment of Screening Rate.*

From September 2015 to May 2016, the trained obstetricians and nurses from 36 hospitals applied cardiac screening on a total of 44,614 newborn babies. Screening rates in those hospitals were between 90.6% and 98.0%.

## 3.4 Discussion

The NCASTP is the first training program to focus on newborn cardiac screening in rural China. This program resulted in significant knowledge improvement and behavior change for rural obstetric personnel. It also resulted in a large number of newborn screenings in the participating hospitals. Before training, none of the obstetrics departments of the participating hospitals implemented proper newborn cardiac screening. Three months after training, all these hospitals had mastered and applied the cardiac screening.

The NCASTP is both efficient and practical. Similar to the results of TxPOP conducted in Texas,[101] the results of NCASTP showed that a one-day training was sufficient for rural obstetric doctors and nurses to understand the importance of cardiac screening and to master the screening skills. Additionally, NCASTP has proven to be highly cost-effective. The cost of providing NCASTP trainers was about US$300 per hospital, which includes transportation and lodging.

Despite being unable to directly train all obstetric personnel, we still found the program to be effective and successful. A small portion of the trainees (less than 6%) had to leave at various times throughout the training when their patients needed immediate care. We compared the pre-test scores of trainees who attended all of the training sessions with those who left partway through the training, and we observed no significant difference. In addition, we gave all the training materials to the directors and chief nurses of each obstetrics department. During the month after our visit, these local directors organized a second training for the obstetric personnel who did not attend the first training.

We think the approach of on-site training might be the best practice for educating rural obstetric personnel. Prior to the training program, we attempted a traditional training approach by inviting obstetric personnel from three different counties to a central location and training all participants on newborn cardiac screening. The training procedures were the same as the procedures used in the later on-site training. The only difference was that the trainees in the centralized training were told to disseminate training to their respective departments. This method failed in that the newborn cardiac screening was not

implemented in any of the participating hospitals. Comparing the results of the centralized training approach with those from the on-site training approach, we concluded that the latter approach would provide better training results for rural doctors and nurses.

Newborn CCHD screening is not one of the items on the uniform newborn screening in rural China. However, the Chinese government is continuously improving health insurance options for pediatric heart surgery and resources such as charitable foundations exist to correct heart defects in babies born to poor families. Given these improvements in Chinese healthcare, it is time to institute newborn cardiac screening throughout rural China.

### 3.4.1 The CCHD Incidence

One of the aims of this study was to investigate the incidence of CCHD in rural Yunnan. However, due to abundant missing data, this aim was not successfully accomplished. There were 4 CCHD cases found in our study, which finally resulted in an incidence of 0.1/1000, which was much lower than that hypothesized -- 2/1000. In 2016 summer, so as to understand the potential reasons for the low CCHD incidence, we traveled to 20 of the trained hospitals to investigate potential reasons for this disappointing result. At these hospitals, we discussed with obstetric staff about their difficulties in conducting cardiac screening. I summarize here the conclusions of this sub-study.

**3.4.1.1 Too sick to Screen**. This screening training program focused on rural county hospitals. These hospitals frequently do not have pediatrics departments and are not capable of treating critically ill newborns. Therefore, they transfer very ill infants to more specialized hospitals immediately after birth. In their rush to

prepare and transfer these infants, they do not perform the newborn heart screening. Since these patients are critically ill, their probability of having CCHD is high.

**3.4.1.2 Forget to Screen**. Many medical staff members have long work hours and high workloads. Occasionally, medical staff forgot cardiac screening when they were taking care of other urgent patients. This problem may also affect the result of CCHD incidence.

**3.4.1.3 Lost to Follow-up.** In order to know whether or not a baby with a positive screening result has CCHD, the research team required nurses' cooperation. Local nurses had to follow up with each baby with a positive screening result to record their diagnostic examination results. However, we only received under 50% of follow-up reports. It was either because doctors/nurses did not call every patient, did not relay the results of these calls to the research team, or the patent's families did not answer their phone calls.

**3.4.1.4 Family refuses surgery.** Though this problem does not directly relate to our research aims, it is very important. As of June 2016, four babies with CCHD were identified in Zhaotong and Honghe prefectures. Earlier surgical repair would have benefitted these newborns. However, three of the four families refused surgical treatment. Treatment for CCHD involves multiple costly, traumatic and time-consuming surgeries. All four families are from rural Yunnan. The Chinese rural health insurance system can reimburse only a relatively small part of this CCHD surgery fee. Charity organizations such as China California Heart Watch offered to pay part of the surgery fees. Despite this possibility for assistance and the knowledge that

their infants would probably succumb to their unoperated defects, these families chose not to have operations done on their children.

To solve the problems of "too sick to screen", "forgot to screen", and "lost to follow-up", in 2017, we proposed three potential solutions. First was to increase the incentive to medical staff from $0.5 to $1.5 per screening, and we gave extra incentive $5 for a follow-up case. This solution was aiming at the problems of "forgot to screen" and "lost to follow-up". In addition, we planned to involve pediatrics departments. The pediatricians would perform cardiac screening for the sick babies who were transferred to pediatrics after birth. This was aimed to solve the "too sick to screen" problem. Third, we enhanced supervision to promote screening. We planned to have a research assistant visit every hospital every two weeks to review the screening results and discuss with the responsible people for feedback or questions.

In order to test if the proposed solutions are effective. From July 2017 to Sep. 2017, we conducted a pilot study at 3 county hospitals in Banna prefecture, Yunnan Province. During the two months, 792 babies were born at the three hospitals; medical staff performed cardiac screening on 780 of them; and 14 were abnormal. Three of the 14 underwent cardiac ultrasound. No CCHD was detected.

The screening rate of this pilot study was 98.5%, higher than that in all hospitals of NCASTP. Twelve newborns were not screened because of the "too sick to screen" problem, described above. There were 11 out of 14 babies with positive screening results who did not undergo

a cardiac ultrasound or lost contact with us. These results indicated that the proposed solutions cannot completely solve the problems. The problem of “forgot to screen” was solved, but “Lost to follow-up” and “too sick to screen” were still barriers against successful conduction of CCHD incidence studies in rural hospitals.

### 3.5 Conclusion

In conclusion, study results indicated that one-day training was sufficient for rural obstetric doctors and nurses to understand the medical knowledge and master the skills regarding newborn cardiac screening. More importantly, the participating hospitals achieved very high newborn cardiac screening rates. Given the success of this training program, we recommended similar programs be implemented in other developing areas.

# CHAPTER 4 REVISED THRESHOLD VALUES FOR NEONATAL OXYGEN SATURATION AT MILD AND MODERATE ALTITUDES

## 4.1 **Introduction**

Pulse oximetry is a non-invasive method for measuring blood oxygen saturation ($SpO_2$). Pediatricians use pulse oximetry for screening neonates for heart and lung disease, allowing for early life-saving treatment. This screening method is cost-effective and the standard of care in most developed nations. In China, a developing country, the Ministry of Health also approved a program dictating mandatory pulse oximetry screening of all neonates for critical congenital heart disease in 2018. [105]

Most practitioners use 95% oxygen saturation as a reference value, below which practitioners should suspect either congenital heart disease or respiratory illness. This cutoff value was based on data collected at or near sea level. Approximately 25% of the world's population resides at altitudes higher than 500 meters above sea level. [106] The lower partial pressure of atmospheric oxygen at higher altitudes is responsible for a decrease in $SpO_2$. The $SpO_2$ reference value for this 25% of the world population therefore should be adjusted.

Studies have reported that the mean $SpO_2$ of healthy neonates measured at least 24 hours after birth is between 95% and 98.5% at mild altitude (500 – 1,500 meters), [107,108] and between 91% and 96% at moderate altitude (1,500 – 2,500 meters). [108–112] Most of those studies have focused on a single altitude stratum with a sample size between 30 and 6,011.

The sample sizes of those studies are insufficiently large to represent the true distribution in the population. Hoffman, in 2016 has suggested that a fairly large sample size is needed for accurately recommending the reference values at high altitudes. [113] In 2017, Rojas-Camayo et al. have provided reference ranges for $SpO_2$ measurements in people from 1 to 80 years from sea level to 5000 meters. [114] One limitation of this study is that it does not include infants. The objective of our study is to define threshold values for oxygen saturation in neonates from sea level to 2,202 meters.

### 4.2 Methods

Data were collected in Yunnan Province, China. Yunnan is located in the southwest of China, and it is situated in a mountainous area, with high altitudes in the northwest and low altitudes in the southeast (Figure 4.1).

In rural Yunnan province, all well neonates are cared for in the obstetrics rather than pediatrics department. Obstetric personnel take responsibility for the care of all asymptomatic neonates, including those with non-critical chromosomal defects (E.g. Down syndrome) and malformations (E.g. Mild scoliosis); pediatricians are only consulted for neonates with significant signs or symptoms of a disease. This study involved obstetrics departments of 35 county-level hospitals from 33 locations with altitudes varying from 267 to 2,202 meters. Three hospitals are located at low altitudes (0 – 500 meters), 15 hospitals at mild altitudes (500 – 1,500 meters), and 17 hospitals at moderate altitudes (1,500 to 2,500 meters). We provided each hospital with a Masimo RAD5 pulse oximeter (Masimo Corp, Irvine, CA, USA) and a reusable sensor for neonatal screening use. In order to

standardize the screening procedure, we trained obstetric nurses on the proper use of this device before the start of screening. [115]

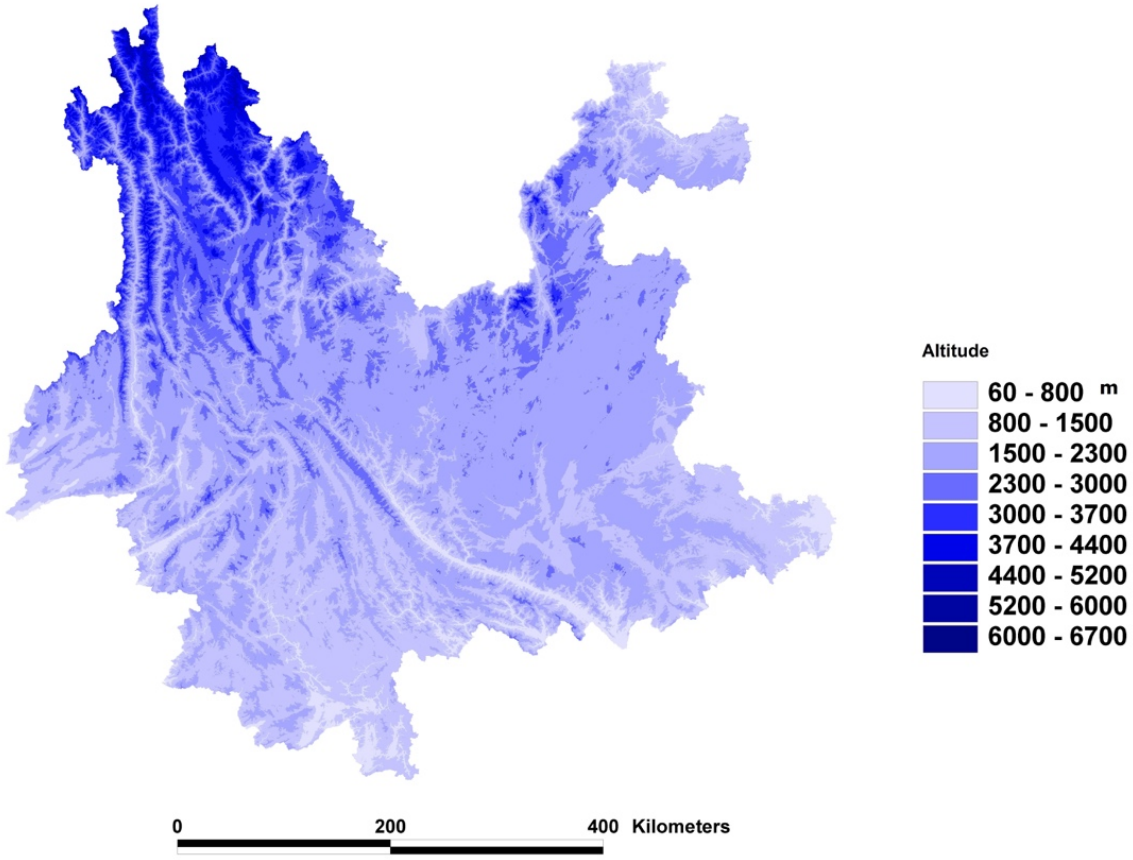


Figure 4.1. Altitude Map of Yunnan Province. Note: Reprint from "Geographical patterns of Yunnan seed plants may be influenced by the clockwise rotation of the Simao-Indochina geoblock." by Zhu, H. (*2015), Front Earth Sci, 3,* p. 2. Copyright 2015 by Zhu.

Between August 2015 and June 2016, the trained obstetric nurses recruited and measured 41,097 consecutively born, asymptomatic neonates. Neonates with low birth weight (< 2 kg), or < 35 weeks of gestational age (early preterm birth), or 5-minute Apgar score < 7, or with clinical signs or symptoms of a disease (e.g. cyanosis, respiratory distress, heart murmurs, etc.), were transferred to the neonatal intensive care unit (NICU) or the

department of pediatrics and were not included in this study. Neonates, who were discharged from the hospital within 24 hours after birth were also excluded from the study. Nurses measured each neonate the pre-ductal (right hand) and post-ductal (either foot) oxygen saturation at 24-hour after birth and most neonates were measured a second time before hospital discharge. Institutional Review Board office at the University of California, Irvine approved this study.

### *4.2.1 Data analysis*

Oxygen saturations were presented as mean and standard deviation (SD). A linear regression model was fitted to investigate the relationship between altitude and $SpO_2$. We categorized all neonates into three altitude groups (low, mild and moderate). Paired t-test was used to compare pre-ductal and post-ductal $SpO_2$, and ANOVA was used to compare $SpO_2$ among three altitude groups. We displayed the distribution of oxygen saturation for each altitude group. The $SpO_2$ values at the $2.5^{th}$ percentile were our suggested cutoff values. P values <0.05 were considered statistically significant, and all tests were 2-sided. R 3.5.1 was used for data analysis.

## 4.3 Results

Of the 41,097 study population, 20, 994 (51.08%) were females. The average length of hospital stay were 3.5 days. The hospital name, number of screened neonates, mean and standard deviation (SD) of pre- and post-ductal $SpO_2$ for each altitude stratum were recorded in Appendix 1. Figure 4.2 displayed the mean $SpO_2$ at each altitude stratum. This figure showed that for all four measurements, as altitude increased, $SpO_2$ decreased. At

altitudes closed to sea level, the mean pulse oximetry readings were between 97 - 98%. At altitudes higher than 2,000 meters, the mean $SpO_2$ decreased to between 95 - 96%. Altitude and neonatal $SpO_2$ showed a strong inverse relationship in linear regression analysis. The analysis result indicated that for the pre-ductal measurements at 24 hours after birth, every 1,000-meter increase in altitude was associated with a 1.54 (95% CI: 1.49, 1.59) percent decrease in mean $SpO_2$ ($p<0.001$).

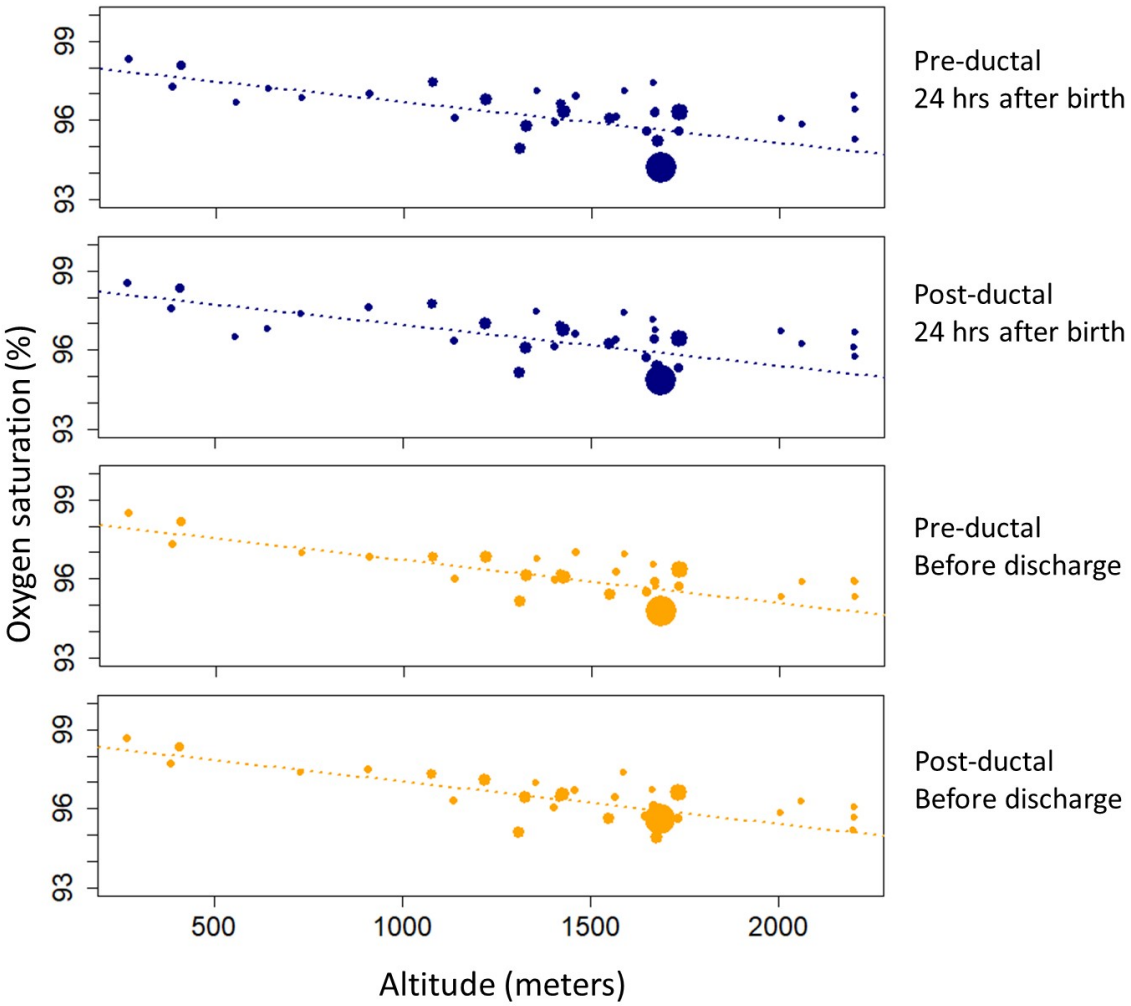


Figure 4.2. Mean Oxygen Saturation and Altitude. The coordinates of the center of a circle are the altitude and the mean oxygen saturation of the subjects in that location. The size of the circle indicates the number of observations.

Table 4.1 showed the means and SDs of pre- and post-ductal $SpO_2$ measured at 24 hours after birth and before hospital discharge for 3 altitude groups (low, mild and moderate). The table indicated that neonatal $SpO_2$ decreased with altitude. There were significant differences of means of $SpO_2$ between altitude groups ($p<0.001$). For all groups, the means of post-ductal $SpO_2$ were slightly higher than the pre-ductal ones ($p<0.001$). The SDs of the mean of $SpO_2$ were increasing as altitude increased.

| $SpO_2$ (%) | | 24 hours after birth | | *p value* | Before hospital discharge | | *p value* |
|---|---|---|---|---|---|---|---|
| Altitude group | | Pre-ductal | Post-ductal | | Pre-ductal | Post-ductal | |
| Low (N = 2,871) | Mean (SD) | 97.9 (1.4) | 98.2 (1.4) | *<0.001* | 98.0 (1.4) | 98.2 (1.4) | *<0.001* |
| Mild (N=16,437) | Mean (SD) | 96.4 (1.8) | 96.7 (1.8) | *<0.001* | 96.3 (1.7) | 96.6 (1.7) | *<0.001* |
| Moderate (N=21,789) | Mean (SD) | 95.5 (2.1) | 95.8 (2.0) | *<0.001* | 95.5 (1.9) | 95.9 (1.9) | *<0.001* |
| *p value* | | *<0.001* | *<0.001* | | *<0.001* | *<0.001* | |

Table 4.1 Oxygen Saturation by Altitude Group.

Table 4.2 showed the distribution of neonatal oxygen saturation by altitude group measured at 24 hours after birth. As shown in the table, the $SpO_2$ at the $97.5^{th}$ percentile was the same (100%) for all 3 altitude groups; however, as the percentile decreased, the value differences between 3 groups were increasing. At the $2.5^{th}$ percentile, the $SpO_2$ of 3 groups were 95%, 93% and 92% respectively. Figure 4.3 showed the histograms of $SpO_2$ for three altitude groups. It was evident that all values obtained at mild altitudes shifted leftward compared with low altitudes, and values at moderate altitudes shifted further to the left.

| Altitude group | Low | Mild | Moderate |
|---|---|---|---|
| N | 2,871 | 16,437 | 21,789 |
| Mean | 97.9% | 96.4% | 95.5% |
| Mode | 98% | 96% | 95% |
| Median | 98% | 96% | 95% |
| 2.5$^{th}$ percentile | 95% | 93% | 92% |
| 5$^{th}$ percentile | 95% | 93% | 92% |
| 25$^{th}$ percentile | 97% | 95% | 94% |
| 75$^{th}$ percentile | 99% | 98% | 97% |
| 95$^{th}$ percentile | 100% | 99% | 99% |
| 97.5$^{th}$ percentile | 100% | 100% | 100% |

Table 4.2 Distribution of Neonatal Oxygen Saturation by Altitude Group Measured at 24 Hours After Birth.

At sea level, 2.5% of asymptomatic infants had $SpO_2$ below 95%.[113] We used the value of the 2.5$^{th}$ percentile as the cutoff threshold in each of three altitude categories. We, therefore, defined the cutoff threshold values of 95% for low altitudes (0 -- 500 meters), 93% for mild altitudes (500 – 1,500 meters), and 92% for moderate altitudes (1,500 – 2,202 meters).

### 4.4 Discussion and conclusion

This is the largest study to date reporting the reference range of neonatal oxygen saturation at mild and moderate altitudes. Our study results indicate that the mean $SpO_2$ in neonates is 97.9% at low attitude; 96.4% at mild altitude; and 95.5% at moderate attitude. Other studies focusing on asymptomatic neonates 24 hours of age or older had similar findings. Hoffman pooled neonatal $SpO_2$ studies and found a mean between 92.5 - 97% at moderate altitudes.[113] A similar meta-analysis study conducted by Subhi et al. concluded an

equation to predict mean $SpO_2$ at a given altitude: $SpO_2\ (\%) = 100.5 - 1.374 \times e^{0.5906 \times \text{altitude(km)}}$. [116] Based on this equation, the mean $SpO_2$ was 97.1% at 1,500 meters and 94.5% at 2,500 meters. Unfortunately, this meta-analysis did not involve studies at mild attitudes. In addition, Levesque et al. found a mean $SpO_2$ of 97.1% at sea level; [117] Samuel et al. reported a mean $SpO_2$ between 98.3 -98.9% at sea level and between 97.8-98.5% at 780 meters; [107] Ravert et al. found a mean of 95-96.7% at 1,370 meters and a mean between 93.9 -95.4% at 2,072 meters; [108] and Ahmad et al. reported a mean $SpO_2$ of 95.4% at 1,640 meters. [109] We also found that the SDs of the mean of $SpO_2$ were increasing as altitude increased. Other studies also reported similar findings. [113,114]

Our study results also indicate that the mean $SpO_2$ measured at 24 hours after birth and that measured before hospital discharge do not show a significant difference, which suggests that after 24 hours after birth, the second $SpO_2$ measurement may not be necessary if the first measurement is normal.

We apply the 2.5 percentile to determine the cutoff values and revised neonatal $SpO_2$ cutoff values from lower than 95% to lower than 93% for mild altitudes and to lower than 92% for moderate altitudes. We do not apply a correction for altitudes lower than 500 meters. A large number, (833) neonates have $SpO_2$ of exactly the cutoff value of mild altitude (93%); an even larger number, (2,347) have $SpO_2$ of exactly 92%, the moderate altitude cutoff. In order to reduce the potential for false-negative screening results, we recommend that, at mild altitudes, $SpO_2$ ≤93% be considered abnormal and at moderate altitudes, ≤92% be

designated as abnormal. The cutoff values for each group are drawn in broken lines in figure 4.3.

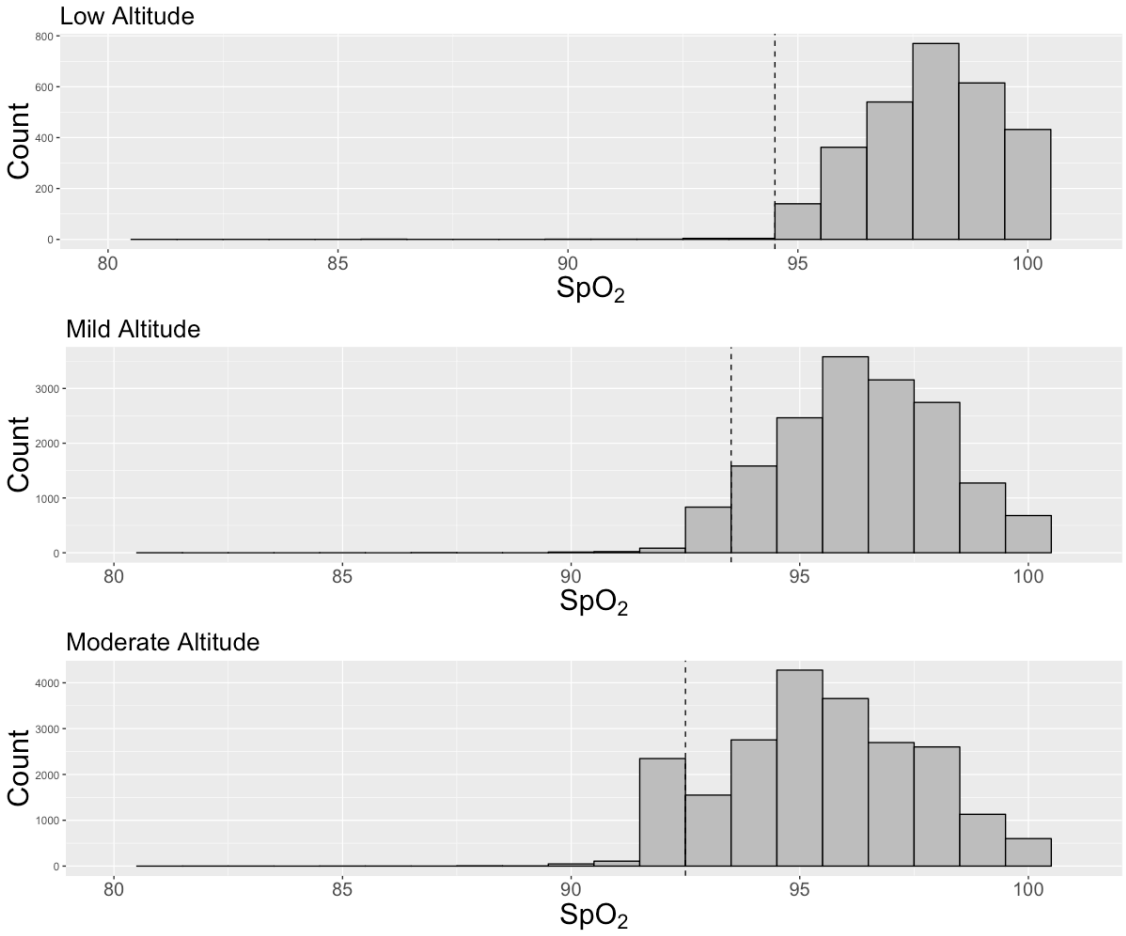


Figure 4.3. Histograms of Pre-ductal Oxygen Saturation Measured at 24 Hours After Birth at Low, Mild and Moderate Altitudes. The revised thresholds are identified with broken lines. (Note: the $SpO_2$ readings fall on the left side of the threshold line are abnormal)

Table 4.3 shows the number and percent of neonates below the old and new cutoff thresholds. Under the old cutoff threshold (95%), there are 15.4% and 31.3% neonates have abnormal screening results at mild and moderate altitudes; while the percentages drop about 10% and 20%, respectively when the new thresholds (mild: ≤ 93%; moderate:

≤ 92%) are applied. This change will result in a decrease in false positive rate. It will also increase the specificity and positive predictive value of the $SpO_2$ screening test.

| Altitude Group | Old cutoff | No. (%) abnormal | New cutoff | No. (%) abnormal |
|---|---|---|---|---|
| Low | <95% | 12 (0.4%) | *No adjustment is needed* | |
| Mild | <95% | 2541 (15.4%) | ≤93% | 958 (5.8%) |
| Moderate | <95% | 6828 (31.3%) | ≤92% | 2524 (11.5%) |

Table 4.3. Number and Percent of Neonates Below The Old and New Cutoff Thresholds

Our study has limitations. We only included full-term and late preterm (> 35 weeks of gestational age) neonates. We did not investigate the $SpO_2$ difference between full and late preterm neonates since the $SpO_2$ between healthy term and healthy near-term neonates did not show a significant difference in previous studies. [110,118] However, future research on early preterm neonates born at mild and moderate altitudes may be needed. Second, we did not compare the $SpO_2$ in different delivery methods (vaginal birth or caesarean section). The delivery method probably did not impact the explanation of our study results since previous studies showed that the method of delivery had no association with newborn $SpO_2$. [119–121] In addition, all our subjects were Chinese ethnicity and care should, therefore, be taken in applying the results to other ethnicities.

We conclude that the neonatal oxygen saturation decreases as altitude increases. The cutoff threshold for normal oxygen saturation should vary across altitudes. We recommend a cutoff value of ≤93% for mild altitudes (500 – 1,500 meters) and ≤92% for moderate altitudes (1,500 – 2,202 meters).

# CHAPTER 5 SUMMARY AND CONCLUSION

In this dissertation, I investigated what percentage of pediatric CHD patients missed the optimal treating time in rural Yunnan and highlighted the importance of CHD early detection. Then I presented a training model of newborn CCHD screening, which had been successfully implemented in rural Yunnan. Last, I discussed the revised pulse oximetry screening cut off values at mild and moderate altitudes.

In 2018, 4 years after we initially proposed CCHD screening program, the Ministry of Health in China officially approved mandatory CCHD screening in newborns in 24 provinces, including Yunnan province.[105] Hundreds of thousands of babies with the disease will benefit from this big public health decision.

In the face growing burden to overcome cardiovascular diseases, including congenital heart diseases in Yunnan. China's biggest cardiovascular hospital - Fu Wai Cardiovascular Hospital based in Beijing opened a branch in Kunming, Yunnan in 2017. The new hospital has more than 700 beds, which offers residents more convenient access to cardiology care.

Although many efforts have been done, there are still problems that need to be resolved in the future. First, medical staff shortage in rural Yunnan is a barrier against comprehensive and advanced cardiac care. When our team was training the rural medical staff on newborn pulse oximetry screening, most of the rural doctors and nurses indicated that they were handling a very heavy workload and they concerned they might have no time to screen all

babies. In China, most of the doctors and nurses prefer to work at urban hospitals. The rural hospitals cannot find sufficient doctors and nurses to fill open positions. In rural China, the number of licensed doctors is 16 per 10,000 citizens, compared to 39 doctors per 10,000 citizens in urban China.[122] The strategies of addressing the staff shortage should be discussed in the future.

Second, Yunnan rural hospitals do not have public health social workers to help patients to solve social and economic problems. The doctors and nurses are doing social workers' job – discussing insurance coverage with patients, following up with the referred patients for diagnosis and prognosis, and assisting patients in applying for financial help. Establishing a social worker group to take responsibility for assisting patients and responding to their inquiries can reduce doctors' and nurses' burdens. More investigations are needed regarding a good solution to this problem. Addressing these health care problems will be a long-term goal in public health that need authorities' support and policy change.

In conclusion, a large underserved population with CHD exists in Yunnan province. They were either undiagnosed or untreated until late childhood or even adulthood. Pulse oximetry screening is an effective method to identify CHD quickly and accurately. Practicing the screening routinely on newborns can benefit hundreds of thousands of children every year.

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**Appendix 1 Mean and standard deviation of four measurements of oxygen saturation at 35 hospitals.** At three hospitals, Jinghong, Mengla and Mengla Southern hospitals, nurses screened only once at 24 hours after birth. At all other hospitals, the neonates were screened twice.

| Altitude (meters) | Hospital Name | N | 24h $SpO_2$ (%) | | Before discharge $SpO_2$ (%) | |
|---|---|---|---|---|---|---|
| | | | Hand Mean (SD) | Foot Mean (SD) | Hand Mean (SD) | Foot Mean (SD) |
| 267 | Shuifu | 832 | 98.3 (1.2) | 98.6 (1.2) | 98.5 (1.2) | 98.7 (1.1) |
| 383 | Suijiang | 868 | 97.3 (1.4) | 97.6 (1.4) | 97.3 (1.3) | 97.7 (1.4) |
| 408 | Yanjin | 1171 | 98.1 (1.5) | 98.3 (1.5) | 98.1 (1.5) | 98.3 (1.5) |
| 553 | Jinghong | 406 | 96.7 (1.5) | 96.5 (1.6) | NA | NA |
| 640 | Mengla & Mengla Southern | 293 | 97.2 (1.4) | 96.8 (1.4) | NA | NA |
| 730 | Yongshan | 462 | 96.8 (1.8) | 97.4 (1.7) | 97.0 (1.2) | 97.4 (1.3) |
| 907 | Qiaojia | 856 | 97.0 (1.8) | 97.6 (1.9) | 96.9 (1.7) | 97.5 (1.8) |
| 1077 | Kaiyuan | 1587 | 97.4 (1.6) | 97.8 (1.6) | 96.8 (1.4) | 97.3 (1.4) |
| 1135 | Daguan | 1003 | 96.1 (2.0) | 96.4 (1.9) | 96.0 (1.8) | 96.3 (1.8) |
| 1217 | Jinping | 1969 | 96.8 (1.6) | 97.0 (1.5) | 96.8 (1.4) | 97.1 (1.3) |
| 1308 | Mengzi | 1822 | 94.9 (1.5) | 95.1 (1.5) | 95.1 (1.5) | 95.1 (1.4) |
| 1323 | Jianshui | 1925 | 95.8 (1.4) | 96.1 (1.4) | 96.2 (1.5) | 96.4 (1.5) |
| 1356 | Pingbian | 623 | 97.1 (1.5) | 97.5 (1.6) | 96.7 (1.4) | 97.0 (1.4) |
| 1401 | Nanjian | 863 | 96.0 (1.8) | 96.1 (1.7) | 96.0 (1.7) | 96.1 (1.6) |
| 1417 | Shiping | 1452 | 96.6 (1.9) | 96.9 (1.9) | 96.2 (1.9) | 96.4 (1.8) |
| 1427 | Mile | 2371 | 96.3 (1.6) | 96.7 (1.6) | 96.1 (1.6) | 96.6 (1.6) |
| 1457 | Binchuan | 805 | 96.9 (1.8) | 96.6 (1.8) | 97.0 (1.7) | 96.7 (1.7) |
| 1547 | Lvchun | 1890 | 96.0 (1.8) | 96.2 (1.7) | 95.4 (1.5) | 95.6 (1.6) |
| 1565 | Longling | 850 | 96.2 (1.7) | 96.4 (1.7) | 96.3 (1.6) | 96.4 (1.6) |
| 1588 | Yimen | 445 | 97.1 (1.9) | 97.4 (1.9) | 96.9 (1.7) | 97.4 (1.6) |
| 1647 | Yuxi | 1165 | 95.6 (2.2) | 95.7 (2.1) | 95.5 (2.0) | 95.7 (2.0) |
| 1665 | Yunlong | 381 | 97.4 (2.0) | 97.1 (2.0) | 96.5 (1.8) | 96.7 (1.8) |
| 1667 | Tengchong & Yongping | 1054 | 96.3 (2.0) | 96.4 (2.0) | 95.9 (1.8) | 96.1 (1.8) |
| 1670 | Midu | 619 | 96.4 (2.1) | 96.7 (2.0) | 95.7 (2.0) | 96.0 (1.9) |
| 1673 | Baoshan | 2044 | 95.2 (2.1) | 95.4 (2.0) | 94.8 (1.7) | 94.9 (1.7) |
| 1683 | Zhenxiong | 6625 | 94.2 (1.9) | 94.9 (1.8) | 94.8 (2.0) | 95.6 (2.0) |
| 1733 | Gejiu | 1167 | 95.6 (1.8) | 95.3 (1.8) | 95.7 (1.6) | 95.6 (1.5) |
| 1734 | Luxi | 3255 | 96.3 (1.8) | 96.5 (1.8) | 96.3 (1.6) | 96.6 (1.6) |
| 2005 | Xiangyun | 455 | 96.1 (2.1) | 96.7 (2.1) | 95.3 (1.9) | 95.8 (2.0) |
| 2060 | Eryuan | 681 | 95.9 (2.0) | 96.3 (2.1) | 95.9 (1.9) | 96.3 (1.9) |
| 2199 | Jianchuan | 481 | 96.9 (1.9) | 96.1 (2.1) | 95.9 (2.1) | 95.2 (2.1) |
| 2201 | Huaning | 289 | 95.3 (2.4) | 95.7 (2.3) | 95.3 (1.9) | 95.7 (2.0) |
| 2202 | Heqing | 388 | 96.4 (2.3) | 96.7 (2.2) | 95.9 (2.1) | 96.1 (2.0) |
| | Total | 41097 | 96.02 (2.1) | 96.30(2.0) | 95.97(1.9) | 96.30(1.9) |