

# NEONATOLOGY TODAY

News and Information for BC/BE Neonatologists and Perinatologists

Volume 8 / Issue 2

February 2013

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#### 2<sup>nd</sup> Evidence-Based Neonatology Conference

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www.ebneo2013.com

#### 1<sup>st</sup> Conference of the Egyptian Neonatal Network (EGNN)

Apr. 4-6, 2013; Cairo, Egypt  
www.cme-group.net

#### First Coast Neonatal Symposium

Apr. 17-19, 2013; Augustine, FL USA  
www.neonatalSYMPOSIUM.com

#### 24<sup>th</sup> Annual Meeting of the European Society of Pediatric and Neonatal Intensive Care - ESPNIC 2013

Jun. 12-15, 2013; Rotterdam, Netherlands  
www.kenes.com/espnic

#### 8<sup>th</sup> International Neonatal Nursing Conference 2013 - COINN 2013

Sep. 5-8, 2013; Belfast, Northern Ireland  
www.coinn2013.com

### NEONATOLOGY TODAY

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ISSN: 1932-7129 (print); 1932-7137 (online).  
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#### Corporate Offices:

8100 Leaward Way,  
Nehalem, OR 97131 USA

#### Mailing Address:

PO Box 444  
Manzanita, OR 97130 USA

#### Editorial and Subscription Offices

16 Cove Rd., Ste. 200  
Westerly, RI 02891 USA

[www.NeonatologyToday.net](http://www.NeonatologyToday.net)

Neonatology Today (NT) is a monthly newsletter for Neonatologists and Perinatologists that provides timely news and information regarding the care of newborns and the diagnosis and treatment of premature and/or sick infants.

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## Total Anomalous Pulmonary Venous Connection in the Neonate

By Claudeen K. Whitfield, MD;

P. Syamasundar Rao, MD

### Introduction

In the previous issues of this publication, we focused on several general topics on Congenital Heart Disease (CHD) in the neonate.<sup>1-5</sup> More recently, we began addressing individual cardiac lesions, namely: Transposition of the Great Arteries<sup>6</sup> and Tetralogy of Fallot,<sup>7</sup> Hypoplastic Left Heart Syndrome<sup>8</sup> and Tricuspid Atresia.<sup>9</sup> In this issue of *Neonatology Today*, we will discuss Total Anomalous Pulmonary Venous Connection (TAPVC). Other conditions with similar embryological and clinical findings, as well as therapeutic implications, such as atresia of the common pulmonary vein, cor triatriatum and stenosis/atresia of the individual pulmonary veins will not be reviewed in this paper.

### Total Anomalous Pulmonary Venous Connection

In TAPVC, all the pulmonary veins drain into systemic veins; most commonly they drain into a common pulmonary vein which is then connected to the left innominate vein, superior vena cava, coronary sinus, portal vein or other rare sites. Occasionally, individual veins drain directly into the right atrium.

TAPVC is the fifth most common cause of cyanotic congenital heart disease (CHD), and the twelfth most common CHD in critically ill infants. TAPVC occurs in 0.6 to 1.2 per 10,000 live births. Sixty-eight percent are diagnosed as neonates.<sup>10</sup> TAPVC is an isolated lesion in approximately two-thirds of patients and occurs in association with other CHD, as well as hetero-

taxia syndromes in the remaining one-third of patients. The male to female ratio in the Baltimore-Washington infant study was 18:23.<sup>10</sup> In other reports, a strong male preponderance of 3:1 was observed in patients with infra-diaphragmatic connection. If left unrepaired, 50% of the babies may survive up to 3 months, and 20% up to 1 year of age, depending on the type and degree of obstruction.<sup>11</sup>

### Embryology

During normal development, the lung buds are outgrowths of the primitive foregut, and early in fetal life venous drainage from the lungs is via the splanchnic plexus to the cardinal and umbilicovitelline venous systems. The common pulmonary vein arises from the posterior left atrium as a small pouch that enlarges and connects with the pulmonary venous component of the splanchnic plexus. When pulmonary venous drainage via the common pulmonary vein is established, the connections to the cardinal and umbilicovitelline venous systems involute and eventually disappear. The common pulmonary vein is incorporated into the posterior left atrial wall by differential growth, and the pulmonary veins then connect directly to the left atrium.

*“In this issue of Neonatology Today, we will discuss Total Anomalous Pulmonary Venous Connection (TAPVC).”*

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If the common pulmonary vein fails to develop or fails to connect to the splanchnic plexus, the primitive venous connections persist, and result in total anomalous pulmonary venous connection. The type of TAPVC is determined by which of the connection to the cardinal or umbilicovittelline venous system persists. Drainage of the pulmonary veins may be into the right atrium, the right common cardinal system (superior vena cava or azygos vein), the left common cardinal system (left innominate vein or coronary sinus), or the umbilicovittelline system (portal vein, ductus venosus, etc.).<sup>12</sup>

### **Classification**

Darling et al<sup>13</sup> proposed a TAPVC classification system based on the site of pulmonary venous drainage: Type I in which there is a supra-cardiac connection and all four pulmonary veins are connected to the common pulmonary vein, which is then drained by a connecting anomalous vein into the right superior vena cava, left superior vena cava, or their tributaries; Type II where there is a cardiac connection and the common pulmonary vein is connected directly to the right heart (coronary sinus or the right atrium); Type III is characterized by an infra-cardiac connection and the common pulmonary vein is drained by an anomalous channel which travels caudally anterior to the esophagus through the diaphragm to connect to the portal venous system; and Type IV where there are mixed connections, and the right and left pulmonary veins drain to different sites (for example, left pulmonary veins into the left vertical vein and then into the left innominate vein and right pulmonary veins directly into the right atrium or coronary sinus).<sup>13</sup> Supra-cardiac connection is the most common (45%), followed by cardiac (25%), infra-cardiac (25%) and mixed (5%).<sup>14-18</sup>

A simpler classification was proposed by Smith and associates:<sup>19</sup> supra-diaphragmatic without pulmonary venous obstruction and infra-diaphragmatic with obstruction. Although the supra-diaphragmatic forms are generally non-obstructive, obstruction can also occur in these as well, as reviewed elsewhere.<sup>20</sup> However, the infra-diaphragmatic forms are almost always obstructive. Connection to the left innominate vein is the most common type of TAPVC.<sup>21-23</sup> Infra-diaphragmatic type is most common form in neonates.<sup>21-23</sup>

### **Pathophysiology**

In all types of TAPVC, entire pulmonary venous blood eventually returns to the right atrium. Intra-cardiac mixing of systemic and pulmonary venous returns occurs. Therefore, right-to-left shunt across the atrial septum (patent foramen ovale or atrial septal defect) must be present for survival. A restrictive atrial communication is not uncommon. If atrial communication is restrictive, the amount of blood reaching the left atrium is limited, and systemic blood flow (cardiac output) is reduced. If there is wide-open atrial communication, the flow distribution to systemic and pulmonary circuits is dependent on relative compliances of the atria and ventricles; these compliances are eventually linked to pulmonary and systemic vascular resistances.

In babies with a non-obstructive type of TAPVC, as the pulmonary vascular resistance decreases (with age), there is progressive increase in pulmonary blood flow. This causes pulmonary over-circulation and eventually congestive heart failure. Right atrial and right ventricular enlargement and dilatation of main and branch pulmonary arteries are usually seen. If untreated, increased pulmonary blood flow will result in pulmonary arteriolar medial hypertrophy and intimal proliferation, and the patients will develop pulmonary hypertension and eventually pulmonary vascular obstructive disease.

In babies with obstructive types of TAPVC, because of high pulmonary venous pressure, reflex pulmonary arteriolar constriction occurs resulting in high pulmonary artery pressure and decreased pulmonary blood flow. When the osmotic pressure of the blood exceeds the hydrostatic pressure in the capillaries, pulmonary edema develops. This is partly compensated for by increased pulmonary lymphatic drainage, develop-

ment of alternative pulmonary venous bypass channels and altered capillary permeability.

Obstruction to pulmonary venous return is uniformly present in the infra-diaphragmatic type. It may be extrinsic at the level of the diaphragm as the connecting vein passes through it, constriction of the ductus venosus, high resistance to the passage of the blood through the hepatic sinusoids, intrinsic stenosis of the connecting vein or a combination thereof.<sup>20</sup> The long connecting vein itself may offer impedance to the pulmonary venous return.<sup>20</sup> In the supra-diaphragmatic types, the obstruction can also occur and it may be at multiple sites and with varying degrees of severity. It may be intrinsic, within the connecting vein itself or extrinsic by compression (of the vertical vein) between the left bronchus and left pulmonary artery. The intrinsic stenosis of the anomalous connecting vein may be at its junction with the common pulmonary vein, at its entry into the left innominate vein, superior vena cava, azygos vein or right atrium, somewhere within the vein itself or a combination thereof. Also, the left innominate vein, superior vena cava or azygos vein may themselves be narrowed. For further details, the reader is referred elsewhere.<sup>20</sup> Obstruction is least likely to occur when the pulmonary veins drain into the coronary sinus. The potential for obstruction at the atrial septal defect level has already been mentioned above.

### **Clinical Features**

Clinical features are largely determined by the degree of pulmonary venous obstruction. If obstruction is present, the majority (~75%) of patients will present within the first few days of life and the remainder at a later time. The presentation is shortly after the first 12 hours of life; this is in contradistinction to Respiratory Distress Syndrome which usually presents at birth. These babies are acutely ill and manifest tachypnea, dyspnea, hypoxemia and metabolic acidosis. These signs and symptoms appear to be related to severe pulmonary venous congestion. Physical examination is significant for rales and rhonchi in both lung fields. Cardiovascular findings include widely split second heart sound with an accentuated pulmonary component and no murmurs. Sometimes a non-specific ejection systolic murmur along the left sternal border may be heard. Hepatomegaly is usually present. Obstructive TAPVC is present in almost all infra-diaphragmatic types and in only 50% of supra-diaphragmatic types.

In the absence of pulmonary venous obstruction, the presentation is within the first month of life in more than half of the patients and the remainder during the first year of life. They usually present with signs of congestive heart failure. Tachypnea, tachycardia, feeding difficulties and failure to thrive are usual presenting symptoms. Findings on physical examination are similar to those in patients with a secundum atrial septal defect in that there is a prominent right ventricular impulse (hyperdynamic), widely split and fixed second heart sound, an ejection systolic murmur at the left upper sternal border and a mid-diastolic flow rumble at the left lower sternal border. In addition, pulmonary component (P2) of the second heart sound is accentuated, and an ejection systolic click plus third and/or fourth heart sounds (multiple cardiac sounds) may be present. Cyanosis is minimal and may not be clinically detectable because of markedly increased pulmonary blood flow. Signs of cardiac failure are usual. Another clinical feature is a venous hum heard at the left or right upper sternal borders or in the infraclavicular regions in the supra-cardiac types of TAPVC; the venous hum is not altered by changes in the position of the patient.

### **Non Invasive Evaluation**

#### **Chest X-ray**

In the obstructive type, the size of the heart is small and normal or mildly enlarged. There is evidence of marked pulmonary edema with stippled densities and reticular pattern in the lung parenchyma, partially obscuring the cardiac borders (Figure 1). The reticular pattern may sometimes be mistaken for Respiratory Distress Syndrome or group B strep-

tococcal infection. In the non-obstructive type where there is unrestricted pulmonary blood flow, there is cardiomegaly and increased pulmonary vascular markings, but usually no pulmonary edema is seen. In the supra-cardiac type draining into the left innominate vein, a snowman-type of cardiac silhouette may be seen; however, this may take several weeks/months to develop and may not be obvious in the neonatal period.



Figure 1. Chest x-ray of a neonate with total anomalous pulmonary venous connection of an infra-diaphragmatic type demonstrating severe pulmonary venous congestion. Mild cardiac enlargement is also seen.

### Electrocardiogram

Electrocardiogram reveals right ventricular hypertrophy in the obstructive type; however, it may be difficult to distinguish it from normal neonatal right ventricular preponderance. In the non-obstructive type, right axis deviation, right atrial enlargement as seen by tall P waves in lead II and right precordial leads and right ventricular hypertrophy, manifested tall R waves in right precordial leads, sometime with rSR pattern are usually seen.

### Echocardiogram

Echocardiographic studies are useful in confirming the diagnosis, and in defining various issues germane to the management of these sick babies. Inability to easily visualize the entry of pulmonary veins into the left atrium by two-dimensional (2D) and color flow mapping should arouse the suspicion of the diagnosis of TAPVC. Enlargement of the right atrium, right ventricle and pulmonary artery is seen in all types of TAPVC (Figure 2). The left atrium and left ventricle usually appear relatively small compared to the very large right ventricle.<sup>25,26</sup> The enlarged right ventricle encroaches onto the left ventricle, compressing it posteriorly (Figure 2 A & C) and to the left (Figure 2D). The left atrium is smaller than normal (because of lack of contribution of the common pulmonary vein), but is easily seen (Figure 2 A, B & D).

The right ventricular and pulmonary artery pressures are elevated, as demonstrated by high tricuspid valve regurgitant velocity (Figure 3A). The right ventricular and pulmonary artery systolic pressure may be estimated by modified Bernoulli equation:

$$\text{Right ventricular and pulmonary artery systolic pressure} = 4V^2 + 5 \text{ mmHg}$$

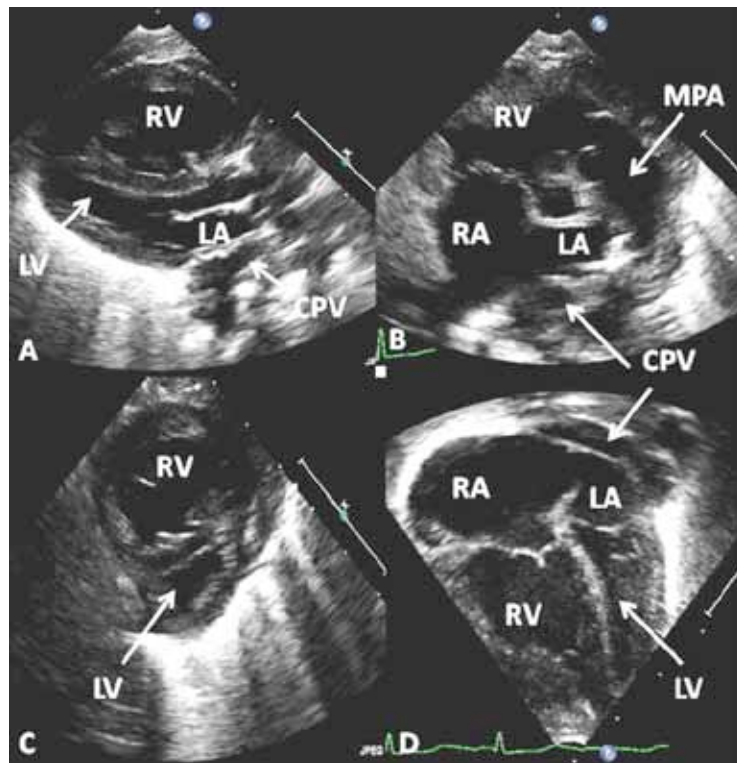


Figure 2. Selected video frames of a 2-dimensional echocardiogram in parasternal long (A) and short (B & C) axis and apical four chamber (D) views demonstrating a large right atrium (RA), right ventricle (RV) and main pulmonary artery (MPA) in an infant with total anomalous pulmonary venous connection. Note that the enlarged RV encroaches onto the left ventricle compressing it posteriorly (A & C) and to the left (D). Common pulmonary vein (CPV) is located behind (A & B) and superior to the left atrium (LA) (D).

Where V is peak velocity of the regurgitant tricuspid jet, and 5 is the estimated right atrial pressure.

Right to left shunt across the patent foramen ovale is also seen in all types of TAPVC (Figure 3B).

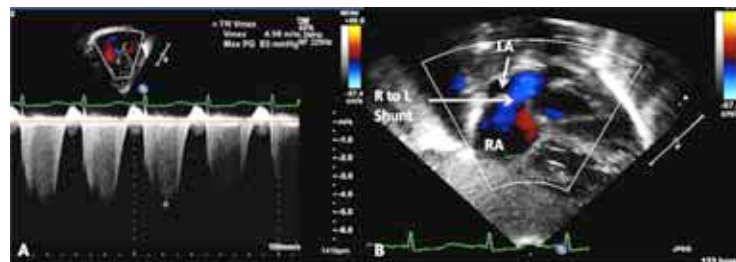


Figure 3. A. High tricuspid regurgitant Doppler flow velocity is shown and is suggestive of elevated pulmonary artery pressure in a neonate with an infra-diaphragmatic type of total anomalous pulmonary venous connection. B. Color Doppler flow mapping demonstrating right to left shunting across the atrial septum. RA, right atrium; LA, left atrium.

The common pulmonary vein is seen behind the left atrium (Figure 2 A & B) and every effort should be made to demonstrate the entry of all pulmonary veins into this chamber by using a combination of 2D imaging and color flow mapping (Figures 4 & 5) in multiple views. Para-sternal, subcostal and supra-sternal notch views are most helpful in this regard. The size and orientation (horizontal or vertical) of the common pulmonary vein should also be determined. Careful color flow imaging should be used to demonstrate the anomalous connecting vein and the site of its drainage.

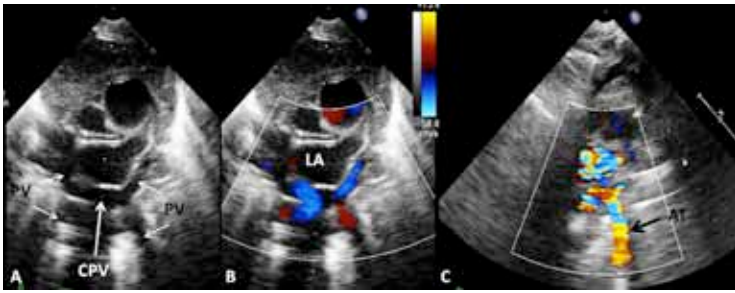


Figure 4. Selected video frames from suprasternal notch views in a baby with infra-diaphragmatic type of total anomalous pulmonary venous connection showing pulmonary veins (PV) draining into a common pulmonary vein (CPV) which is located adjacent to the left atrium (LA); 2-dimensional (A) and color flow mapping (B) images are shown. Anomalous trunk (AT) traversing towards the diaphragm is shown in C.

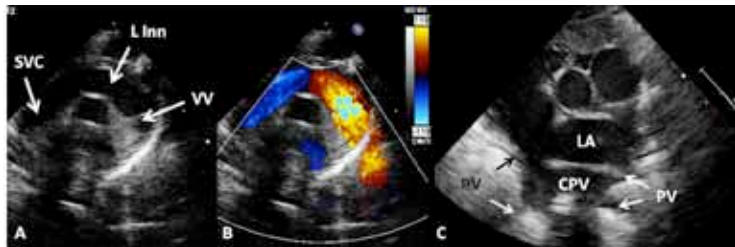


Figure 5. Selected video frames from suprasternal notch views in a baby with supra-diaphragmatic type of total anomalous pulmonary venous connection showing dilated vertical vein (VV), left innominate vein (L Inn) and superior vena cava (SVC); 2-dimensional (A) and color flow mapping (B) images are shown. 2-dimensional images of pulmonary veins (PV) draining into a common pulmonary vein (CPV) which is located adjacent to the left atrium (LA) are also shown (C).

Examples of TAPVC with connection to infra-diaphragmatic (Figure 4), left innominate (Figure 5) and coronary sinus (Figure 6) sites are shown. Stenosis of the connecting vein can occur and may be demonstrated by imaging actual narrowing, by dilated proximal portion of the connecting vein, by turbulent, continuous and increased Doppler flow velocity (Figure 7) or a combination thereof.

If the ductus arteriosus is patent, right to left shunt across it is usually seen, particularly in patients with obstructed TAPVC; this might partially bypass pulmonary circuit with high pulmonary vascular resistance in the obstructed TAPVC and support the cardiac output.

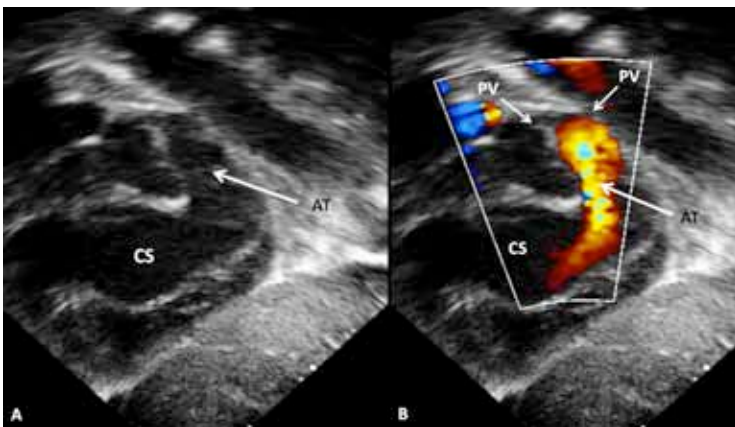


Figure 6. Two-dimensional (A) and color flow mapping (B) images in a baby with total anomalous pulmonary venous connection to coronary sinus (CS) demonstrating dilated CS. An anomalous trunk (AT) connects the pulmonary veins (PV) to the CS.

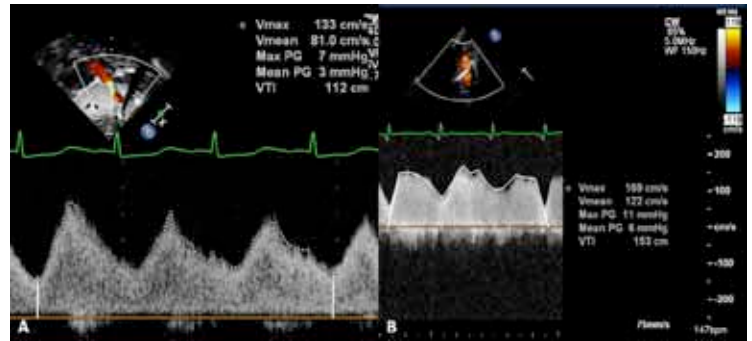


Figure 7. Continuous wave Doppler recordings from the obstructed anomalous trunks demonstrating high velocities in two different patients with total anomalous pulmonary venous connection, infra-diaphragmatic (A) and supra-diaphragmatic (B).

### Magnetic Resonance Imaging

Because precise anatomic details are often outlined by echocardiographic studies in the neonate, there is little need for MRI in this age group irrespective of pulmonary venous obstruction. When echo-Doppler studies can't, for certainty, demonstrate all pulmonary veins,<sup>26</sup> particularly when connection to multiple sites (mixed type of TAPVC) is suspected or in patients with poor echo windows, MRI can provide vital anatomic information.

### Cardiac Catheterization

Cardiac catheterization is not usually necessary to confirm the diagnosis in the neonate. However, beyond infancy, it may be indicated in order to measure the pulmonary vascular resistance and study its responses to vasodilators.

### Management

The initial management of neonates with TAPVC is similar to that of any cyanotic/distressed infant with suspected serious heart disease and is discussed in depth elsewhere<sup>4</sup> and will not be detailed here. Maintenance of neutral thermal environment, normal acid-base status, normoglycemia, and normocalcemia should be undertaken by appropriate monitoring and correction as needed.<sup>4</sup> No more than 0.4 FIO<sub>2</sub> is necessary unless Pulmonary Parenchymal Disease is present. Metabolic acidosis, defined as pH < 7.25 should be corrected with sodium bicarbonate (usually 1-2 mEq/kg diluted half and half with 5% or 10% dextrose solution) immediately. In the presence of respiratory acidosis, appropriate suctioning, intubation and assisted ventilation should be undertaken.

Almost all patients have a large pulmonary venous confluence behind the left atrium. This structure is horizontal in babies with supra-cardiac and cardiac connection and vertical in those with infra-diaphragmatic connection. The surgical repair usually involves making an anastomosis between this pulmonary venous confluence and the posterior wall of the left atrium under cardiopulmonary bypass and/or hypothermia. In TAPVC connected to coronary sinus, surgical excision of the common wall between the coronary sinus and left atrium is performed along with closure of orifice of the coronary sinus and the PFO.

In the obstructive type, initial stabilization by intubation and ventilation with high airway pressure should be initiated. Prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) infusion to open the ductus may decompress the pulmonary vascular bed and augment systemic blood flow. In addition, it may open the ductus venosus, thus decreasing pulmonary venous obstruction. This effect is not as certain as with ductus arteriosus and is not reliable. Intravenous infusion of PGE<sub>1</sub> may be started at a dose of 0.05 to 0.1 µg per kilogram of body weight per minute and the rate of infusion is reduced

to 0.02 µg per kilogram once the ductus is open. This lower dose has been most helpful in reducing the incidence and severity of some of the drug's bothersome side effects, namely, apnea and hyperpyrexia. It is important to emphasize, however, that most patients with infra-diaphragmatic type have severe obstruction and the main treatment mode is surgical correction. After initial stabilization, emergent surgical correction by anastomosis of the common pulmonary vein to the left atrium is mandatory. High mortality seen in early years with surgery has decreased over the years.<sup>27</sup>

In non-obstructive type, elective surgery is recommended after control of cardiac failure is achieved and the patient is stabilized. Congestive heart failure is managed with inotropic support and diuretics. The entire systemic flow must pass through the patent foramen ovale (PFO) and therefore, if the PFO is restrictive, systemic perfusion is significantly reduced. These patients with supra-diaphragmatic type of TAPVC with a restrictive PFO will benefit from a balloon atrial septostomy.<sup>28,29</sup> Surgical correction involves anastomosis of the common pulmonary vein with the left atrium. Ligation of the connecting vein is routinely performed. Depending on surgical preference, the PFO is usually, but not always, closed.

In the presence of mixed type of TAPVC, a single large posterior pulmonary venous confluence is absent. Therefore, if the patient is stable and without significant pulmonary hypertension or pulmonary venous obstruction then one management option is to follow these patients medically until individual anomalous veins are large enough to be anastomosed to the left atrium.<sup>26</sup>

Clinical and echocardiographic follow-up is recommended to detect development of pulmonary venous obstruction.

### Summary and Conclusions

In TAPVC, all pulmonary veins drain into systemic veins, most commonly they drain into a common pulmonary vein which is then connected to the left innominate vein, superior vena cava, coronary sinus, portal vein or other rare sites. TAPVC is the fifth most common cyanotic CHD and occurs in 0.6 to 1.2 per 10,000 live births. Irrespective of the type, all pulmonary venous blood eventually gets back into right atrium, mixes with systemic venous return, and gets redistributed to the systemic (via patent foramen ovale) and pulmonary (via tricuspid valve) circulations. The TAPVC is classified based on the anatomic location to which the connecting veins drain, namely, supra-diaphragmatic (supra-cardiac and cardiac) or infra-diaphragmatic and physiologic based on obstruction to the pulmonary venous return, namely, obstructive or non-obstructive. The supra-diaphragmatic forms are generally non-obstructive, and the infra-diaphragmatic forms are almost always obstructive. Connection to the left innominate vein is the most common type of TAPVC. Infra-diaphragmatic type is most common form in the neonate.

The obstructive types present within the first few hours to days of life with signs of severe pulmonary venous congestion and manifest severe tachypnea, tachycardia and cyanosis. Examination reveals rales in the lung fields and a loud pulmonary component of the second heart sound. The non-obstructive TAPVC patients, on the other hand, usually present with symptoms of congestive heart failure later in the first month of life. On examination, they have very mild or no visible cyanosis and may have clinical signs of heart failure. Other findings on ex-

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## ***“Follow-up to detect development of pulmonary venous obstruction is recommended.”***

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amination are similar to those seen in patients with secundum atrial septal defect. Clinical and chest x-ray findings are suggestive of the diagnosis and can be confirmed by echocardiographic studies.

In the obstructive type, initial stabilization by intubation and ventilation with high airway pressure should be undertaken. This is followed by emergent surgical correction by anastomosis of the common pulmonary vein with the left atrium. In the non-obstructive type, control of congestive heart failure and stabilization of the patient, followed by elective or semi-elective surgery is recommended. Follow-up to detect development of pulmonary venous obstruction is recommended.

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## NT

*Claudeen K. Whitfield, MD  
Pediatric Cardiology Fellow  
The Division of Pediatric Cardiology,  
Department of Pediatrics  
University of Texas-Houston Medical  
School/Children's Memorial Hermann  
Hospital  
Houston, TX USA*

### Corresponding Author

*P. Syamasundar Rao, MD  
Professor of Pediatrics and Medicine  
Director, Pediatric Cardiology Fellowship  
Programs  
Emeritus Chief of Pediatric Cardiology  
University of Texas-Houston Medical  
School  
Children's Memorial Hermann Hospital  
Houston, Texas*

*UT-Houston Medical School  
6410 Fannin St.  
UTPB Suite # 425  
Houston, TX 77030 USA  
Phone: 713-500-5738  
Fax: 713-500-5751*

*P.Syamasundar.Rao@uth.tmc.edu*

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# Medical News, Products & Information

## A Complete Digital Eye Exam – Part of a Routine Newborn Examination (White Paper)

### New Perspectives on Newborn Eye Imaging

Recently, an international group of Pediatric Ophthalmologists gathered in Kunming, China to hold a clinical discussion and debate on the value of universal newborn eye imaging. This clinical recap shares insights from that event. The physicians in attendance included: Lihong Li, MD, Director of Ophthalmology Department, Maternal and Children's Hospital, Kunming, China; Peiquan Zhao, MD, Director of Ophthalmology Department, Shanghai Xinhua Hospital, Shanghai, China; Xin Song, MD, Pediatric Ophthalmologist, Ministry of Health, Children's Eye Care Center, China; Lijun Shen, MD VP of Wenzhou Eye Hospital, Wenzhou, China; Paul J. Rychwalski, MD, Pediatric Ophthalmologist, Cole Eye Institute at the Cleveland Clinic Foundation; and Helen A. Mintz-Hittner, MD, Pediatric Ophthalmologist, University of Texas Health Science Center.

### What is the Value of Newborn Eye Imaging?

One of the questions the participants explored is whether newborn eye imaging reveals potentially serious conditions. The answer is "Yes," based on studies conducted in China and presented to the group.

In Kunming, Lihong Li, MD, Director of the Ophthalmology Department of Maternal and Children's Hospital undertook a study in response to the Vision 2020 initiative. All babies examined were full-term, healthy infants. The results of this study (see Figure 1) showed significant numbers of clinically important eye abnormalities. Of particular note are the two cases of retinoblastoma. One of those cases represented the earliest detection of retinoblastoma ever recorded in China. Other notable results are the detection of 15 cases of FEVR and 67 cases of macular hemorrhages (1.9%), a more serious condition and potentially clinically significant.

Results of a 2009 clinical study headed by Zhan Li, MD, Director of Ophthalmology at Zhuhai Maternal and Children's Hospital, Zhuhai, China were also reported to the group. This study supported Dr. Lihong Li's findings that imaging of all newborns provides early detection of potentially harmful eye diseases.

Dr. Li's results are as follows:

- A total of 4,283 newborns were imaged.
- 3,812 were normal babies and 471 were premature.
- Abnormalities (including retinal hemorrhage) were found in 14.5% of the newborns.
- The incidence of abnormalities was 1.4% when excluding retinal hemorrhage.

Looking at the data presented by Drs. Li and Li, it is clear that newborn eye imaging helps physicians diagnose significant abnormalities, many of which warrant follow-up. Comparing the rate of eye abnormalities found in newborns (1:70 in Dr. Lihong Li's study) to the rate of hearing abnormalities (1:300-500),<sup>1</sup> eye imaging of all newborns should be as much a part of standard newborn care as hearing screening.

Using RetCam imaging, physicians can diagnose many conditions that result in vision impairment, if not blindness. Early detection can lead to appropriate treatment, and preservation of vision. Because vision accounts for 83% of human sensory input,<sup>2</sup> the importance of good eyesight cannot be overstated. A child with good vision has better social, educational and psychological development and is more capable throughout life.

Number of newborns imaged:	3,573 (100.0%)
Abnormalities found: (including retinal hemorrhage)	769 (21.5%)
Retinal hemorrhage in both eyes:	509 (14.3%)
Level 3 retinal hemorrhage:	215 (6.0%)
Macular hemorrhage:	67 (1.9%)
<b>Other abnormalities:</b>	
FEVR:	15 cases
Retinoblastoma:	2 cases
(one case was the earliest ever found in China)	

Figure 1.

Dr. Hittner suggested that a patient's family can also benefit from newborn eye imaging. For infants found with an eye disease, other siblings can be evaluated to determine whether they also have a similar eye condition. As more healthy newborns are imaged, the accumulated data may help answer questions about the causes and effects of retinal hemorrhage and other eye diseases. For instance, Dr. Li in Kunming is investigating why the incidence of retinal hemorrhage seems to be higher in Kunming than in other parts of China, and whether preventive measures can be taken. Dr. Li is also hoping to learn whether macular hemorrhage in infants is related to amblyopia later in childhood.

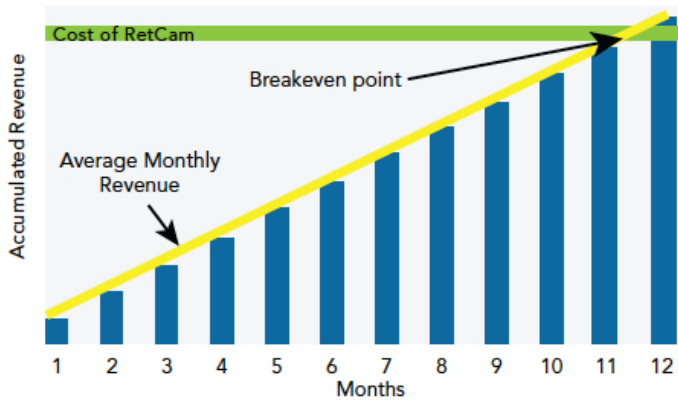
### What is the Value of Newborn Eye Imaging?

The existing data about cost is encouraging. In Zhuhai, the hospital charged the equivalent of US\$65 per patient. In Kunming, the charge equated to US\$45 per infant. Based on the number of patients and the fees, a hospital would recover the cost of a RetCam device in about one year. After that, the device could generate a profit for the hospital. Efficient workflows for the imaging equal to about 3,000 patients imaged annually for each RetCam device. The procedure takes 10 minutes or less and can be done along with the other typical newborn tests. Trained professionals can capture the RetCam images. Pediatric Ophthalmologists or other physician specialists can then evaluate the images and make diagnoses. In Wenzhou, China, Lijun Shen, MD works in a hospital that specializes in ophthalmology. She chose RetCam as the tool to capture images used to evaluate and diagnose eye disease. Dr. Shen has been able to diagnose several different newborn eye diseases, thus offering a better chance for early treatment. Dr. Shen has established a relationship with children's hospitals in the Wenzhou area, and actively encourages newborn imaging. The medical college and hospital now provide skilled staff to visit local children's hospitals several times a week. The visiting staff acquired images of all newborns with RetCam, and electronically sends patient images to a central site database for evaluation and diagnosis by eye specialists. This protocol demonstrates that patients can benefit from RetCam eye imaging without placing an undue burden on the patient, hospital staff or medical specialists.

**Is Newborn Eye Imaging Safe?** Another area discussed by the participating physicians was patient safety during newborn eye imaging. Here, the data is positive. In a patient population of approximately 8,000 newborns (from Drs. Li and Li studies) who were imaged using the RetCam, there were no reports of infections or corneal damage, and no adverse effects from dilation or aesthetic drops. These favorable results reflect a well-designed and careful protocol for patient imaging. First, imaging is not done for a patient with an existing infection. Practitioners use dilation drops. And, the test is done close to the new-



### Example of Newborn Eye Imaging Revenue Stream



born intensive care unit for added safety. When these practices are followed, physicians believe the imaging is safe.

**Do Parents Accept the Procedure?** Parents intuitively understand the importance of their child's eye-sight. When they learn that imaging with RetCam is brief, safe, and non-invasive, the majority willingly accept and appreciate the procedure as an important part of their infant's care and are willing to pay for it.

#### References

1. A hearing test (called brain-stem evoked-response audiometry) is performed routinely with newborn babies in all states. Source: Hearing Loss Fact Sheet: [www.cdc.gov/ncbddd/actearly/pdf/par-ents\\_pdfs/HearingLossFactSheet.pdf](http://www.cdc.gov/ncbddd/actearly/pdf/par-ents_pdfs/HearingLossFactSheet.pdf)
2. Oklahoma Cooperative Extension Service [www.oces.okstate.edu/washita/uploaded\\_files/4h\\_Lear-ing\\_Styles.doc](http://www.oces.okstate.edu/washita/uploaded_files/4h_Lear-ing_Styles.doc)

The RetCam Systems are FDA cleared for the following indications:

- General ophthalmic imaging including retinal, corneal, and external imaging
- Photo documentation of pediatric ocular diseases including retinopathy of prematurity (ROP).
- Screening for Type 2 pre-threshold ROP (zone 1, stage 1 or 2, without plus disease, or zone 2, stage 3, without plus disease) or treatment-requiring ROP, defined as Type 1 ROP (zone 1, any stage, with plus disease; zone 1, stage 3 without plus disease; or zone 2, stage 2 or 3, with plus disease) or threshold ROP (at least 5 contiguous or 8 non-contiguous clock hours of stage 3 in zone 1 or 2, with plus disease)\* in 35-37 week postmenstrual infants.

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### NEONATOLOGY

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## Benefits of Higher Oxygen, Breathing Device Persist after Infancy - Preterm Infants still Better off as Toddlers, NIH Network Study Confirms

By the time they reached toddlerhood, very preterm infants originally treated with higher oxygen levels continued to show benefits when compared to a group treated with lower oxygen levels, according to a follow-up study by a research network of the National Institutes of Health that confirms earlier network findings. Moreover, infants treated with a respiratory therapy commonly prescribed for adults with obstructive sleep apnea fared as well as those who received the traditional therapy for infant respiratory difficulties, the new study found.

In the original 2010 study, of infants born between 24 to 27 weeks of gestation, investigators in the Neonatal Research Network found:

- Infants were more likely to survive if they had received higher oxygen levels, although they were at higher risk of an eye condition that can impair vision or lead to blindness.
- Continuous positive airway pressure (CPAP), a treatment typically reserved for adults with obstructive sleep apnea, was as effective as standard therapy with a ventilator and surfactant (a sticky substance that coats the inside of the lungs).
- For the current study, the researchers checked on the children's progress, comparing the groups' survival rates and cognitive and motor development 18 to 22 months after they were originally due to be born. The re-evaluation of the original study treatment groups examined:
  - Children treated with oxygen saturation levels that were either low (85% to 89%) or high (91% to 95%).
  - Children treated with CPAP therapy and those treated with a ventilator and surfactant.

The researchers compiled the results of their analysis in terms of a combined primary outcome. This primary outcome took into account two possibilities: whether an infant either died in the first or second year of life or had a neurodevelopmental impairment—any of a number of conditions affecting the nervous system; these included: cerebral palsy, blindness, hearing loss or low scores on tests of infant mental and motor development. The researchers selected this outcome because infants who died before 18 months of age, could not be classified as having a neurodevelopmental impairment.

In terms of the primary outcome, the researchers found no differences between the groups.

When the researchers looked at outcome measures separately, however, they did observe differences. The researchers documented higher survival rates among children who received oxygen with higher saturation rates. The study's original findings showed that survivors in this group also had a greater risk of developing retinopathy of prematurity, an eye condition that can impair vision or cause blindness. Although those receiving higher oxygen levels were more likely to have had corrective eye surgery, by the time the children reached 18 to 22 months corrected age -- their age had they been born at the approximate time they were due. The researchers found that there was no difference in the rate of vision problems between the two groups.

"CPAP for infants has been available since the 1970s. This is the first study to compare surfactant treatment to CPAP in a large group of infants, and these results reassure us that CPAP is as good a choice in the first hour of life as traditional methods for very preterm babies who need help breathing," said senior author Rosemary D. Higgins, MD, of the Pregnancy and Perinatology Branch of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), one of two NIH institutes supporting the study. "We've also confirmed that higher oxygen targets improve survival and don't appear to threaten survivors' vision in the longer term."

The study also received funding from the National Heart, Lung and Blood Institute.

Their findings appear in the *New England Journal of Medicine*.

The research was conducted at hospitals affiliated with the NICHD-funded Neonatal Research Network.

More than 1,300 preterm infants born between 2005 and 2009 were included in the study. Between 18 and 22 months after the infants' original due date, researchers assessed whether the children had cerebral palsy and evaluated their vision, hearing, physical mobility and cognitive development.

The researchers found that 60% of the children showed typical physical and cognitive development for their age.

"Although these findings can give delivery room practitioners confidence in a suitable approach, they can't help predict how these children will grow or how well they'll do in school," Dr. Higgins said. "Our group will continue to monitor the health of a subset of these children through childhood, to determine if there are any major differences between the groups."

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) sponsors research on development, before and after birth; maternal, child, and family health; reproductive biology and population issues; and medical rehabilitation. For more information, visit the Institute's website at <http://www.nichd.nih.gov/>.

The National Institutes of Health (NIH), the nation's medical research agency, includes 27 Institutes and Centers and is a component of the US Department of Health and Human Services. NIH is the primary federal agency conducting and supporting basic, clinical, and translational medical research, and is investigating the causes, treatments, and cures for both common and rare diseases. For more information about NIH and its programs, visit <http://www.nih.gov>.

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# Global Neonatology Today Monthly Column - China and the Millennium Development Goals

By Dharmapuri Vidyasagar, MD, FAAP, FCCM

China, the country with the largest population in the world and the fastest growing economy is still considered a developing country! Despite its size and rapid development, China has many serious health, social and environmental issues that need to be addressed. However, China has made great strides in eliminating poverty, both within its borders and without.

After being one of the most insular and ideologically rigid communist countries in the world, China started to emerge into the modern economic system in early 1980s. A change in national policy resulted in China formulating development goals and identifying indicators of progress aimed at achieving a "Xiaokang society" (a moderately prosperous society). In 2002, the government made further plans to extend its policy of building a Xiaokang society in an inclusive way. In 2007, the Government integrated the Millennium Development Goals (MDGs) into overall national plans. The overall positive effectiveness of these changes is showing in many spheres of China's life. Here, we outline a few of the findings in relation to Poverty, MDG #1.

Using the poverty line set by the Chinese Government, the number of poor people in China's rural areas fell from 85 million people in 1990 (9.6% of the total rural population) to 35.97 million people in 2009 (only 3.8% of the total rural population). China is the first developing country to achieve the MDG poverty reduction target before its proposed deadline.

Measured against the international poverty standard of proportion of people earning less than US \$1/day, the share of China's rural population living in poverty was reduced from 46% in 1990 to 10.4% in 2005, which also meets the MDG target well-ahead of schedule of reaching target by 2015.

Another indicator used is the "poverty gap ratio," which reflects, not only the number of poor people, but also how far below the poverty line their incomes are. China has achieved good results against this indicator, with the ratio falling 75% between 2000 and 2005.

Because China has one sixth of the global population, the positive effects of progress in China have had a far greater impact on global poverty levels.

From 1990 to 2005, the number of people worldwide living on less than US \$1 per day fell by 418 million, or 23%, to 1.4 billion.

The population of global poor actually rises when China is taken out of the equation; the global poor population actually rose by 58 million people!

During the global financial crisis in 2009, 100 million people entered into poverty, and the number of people without sufficient food amounted to 1 billion. China, however, made remarkable progress by addressing the financial crisis with active financial policies, and a moderately loose monetary policy, as well as a stimulus plan that focused on the expansion of domestic demand. Employment opportunities, the price of agricultural products, and the operation and management of enterprises all remained stable.

With the introduction of the minimum subsistence guarantee system for urban and rural residents, the basic needs of the poor in both urban and rural environments were largely met. The net income of farmers in China nationwide increased by 8.5%.

More interestingly, China is also aggressively assisting in global poverty reduction in poor states, particularly in Africa, by providing assistance, social development, and promoting international cooperation.

Finally China's marked achievements in poverty alleviation have laid a solid foundation within the country, and are helping other developing countries in achieving the MDG #1.

*SOURCE: China's Progress towards the Millennium Development Goals; 2010 Report; Ministry of Foreign Affairs of the People's Republic of China; United Nations System in China*

**The Clock is Ticking !!!**

**NT**

Dharmapuri Vidyasagar, MD, FAAP, FCCM  
University of Illinois at Chicago  
Professor Emeritus Pediatrics  
Division of Neonatology  
Chicago, IL USA  
Phone: +312.996.4185  
Fax: 312.413.7901  
dvsagarmd@yahoo.com

## NEONATOLOGY TODAY

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ISSN: 1932-7129 (print); 1932-7137 (online).

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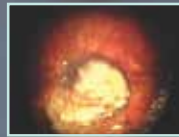


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