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IN THIS ISSUE

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Neonatology Today (NT) is a monthly newsletter for BC/BE 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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Contemporary Management of Neonatal Pulmonary Disorders Conference
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Pages 2 and 11

Transposition of the Great Arteries in the Neonate

By P. Syamasundar Rao, MD

INTRODUCTION

In the previous issues of *Neonatology Today*, I discussed perinatal circulation,[1,2] an approach to the diagnosis of cyanotic neonate,[3] principles of management of the neonate with congenital heart disease[4] and neonatal cardiac emergencies[5] -- all addressing the general topics of congenital heart disease in the neonate. In this and future issues, commonly encountered cardiac defects in the neonate.

TRANSPOSITION OF THE GREAT ARTERIES

Transposition of the great arteries (TGA) is the most common cyanotic congenital heart defect (CHD) in the neonate. It constitutes 5% of all CHDs and 10% of all neonatal cyanotic CHDs.[6] A number of definitions have been used to describe TGA, but the most accurate description is "a defect in which the aorta arises from the morphologic right ventricle and the pulmonary artery from the morphologic left ventricle." In the most common form, referred to as complete transposition, the atria are normal in position (atrial situs solitus), there is atrio-ventricular concordance (right atrium connected to the right ventricle and the left atrium to the left ventricle), d loop of the ventricles (right ventricle is on the right and left ventricle on the left), ventriculo-arterial discordance (aorta arising from the right ventricle and the pulmonary artery from the left ventricle) and the aortic valve is located to the right of pulmonary valve (d-TGA). Thus the systemic venous blood from the vena cavae enters the right atrium and right ventricle and from there into the aorta while the pulmonary venous blood enters the left atrium and left ventricle and from there into the pulmonary artery (Figure 1). Therefore, the circulation is parallel instead of normal in-series circulation. There-

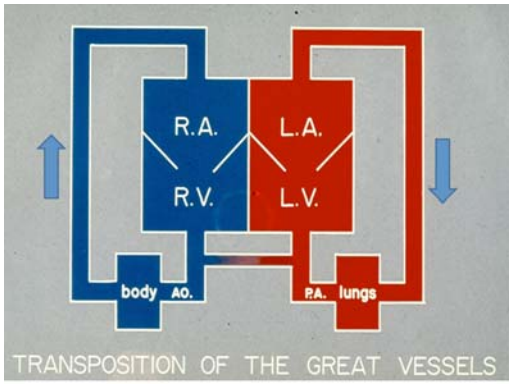

Figure 1. Box diagram of the heart showing parallel circulations in transposition of the great arteries. Note that right ventricle (R.V.) pumps into the aorta (Ao.) (because of transposition) which goes to the body and returns into right atrium (R.A.) and back into the body. Similarly left ventricular (L.V.) output goes to the pulmonary artery (PA.) and lungs and returns back to the left atrium (L.A.) and left ventricle to be pumped back into the lungs. Unless there are inter-circulatory communications via either a patent foramen ovale or patent ductus arteriosus, the infant cannot survive. Mixing across a ventricular septal defect (VSD) if such is present (not shown in the diagram) would also prevent progressive hypoxemia and death.

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fore, the pulmonary venous blood does not get delivered to the body and the systemic venous blood does not get oxygenated. Infants will not live unless there are inter-circulatory connections such as atrial or ventricular septal defect or a patent ductus arteriosus.

CLASSIFICATION

The TGA patients are arbitrarily divided into: Group I, TGA with intact ventricular septum; Group II, TGA with ventricular septal defect (VSD), and Group III, TGA with VSD and pulmonary stenosis (PS).

CLINICAL FEATURES

Clinical features depend upon the anatomic type.

Symptoms

In Group I with intact septum, infants usually present with cyanosis within the first week of life (sometimes within hours to days of life). They may otherwise be asymptomatic. However, they will, with time, develop tachypnea and respiratory distress. If they are not appropriately treated, they become acidotic and go on to become lethargic without lack of spontaneous movement, and eventually die.

Group II TGA patients with VSD present with symptoms of congestive heart failure (tachypnea, tachycardia, sweating, and poor feeding) between 4 to 8 weeks of life, but the cyanosis is minimal.

Group III patients (TGA with VSD and PS) have variable presentation, depending upon the severity of PS and the degree of intercirculatory mixing. If there is poor mixing, they may present early in life and mimic TGA with intact septum. If the PS is severe, the presentation is essentially similar to that seen with Tetralogy of Fallot (TOF).[7] With moderate PS the presentation is late with longer survival. With mild PS, congestive heart failure signs may be present, similar to Group II patients.

Physical Examination

The Group I patients with intact septum usually have severe cyanosis, but are without distress until severe hypoxemia and acidosis develop. Clubbing is not present in the newborn period and may not develop until 3 to 6 months. The right ventricular impulse is increased and the second heart sound is single. No cardiac murmurs are present; occasionally a grade I-II/VI nonspecific ejection systolic murmur may be heard along the left sternal border.

In Group II patients, tachypnea, tachycardia, minimal cyanosis, hepatomegaly, increased right and left ventricular impulses, single second sound, a grade III-IV/VI holosystolic murmur at the left lower sternal border and a mid-diastolic flow rumble (murmur) at the apex may be present.

In Group III patients, the findings are similar to TGA with intact septum, TGA with VSD, or TOF depending upon the degree of mixing and severity of PS. Most of them however, will have a long ejection systolic murmur at the left upper sternal border and/or a holosystolic murmur at the left lower sternal border; both murmurs are usually grade III to IV/VI in intensity.

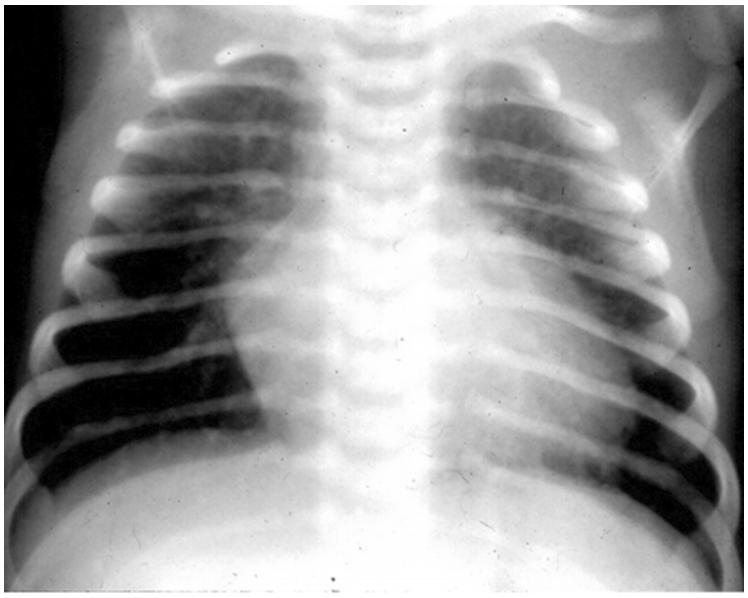

Figure 2. Chest radiograph of a two-day old infant with transposition of the great arteries demonstrating mildly enlarged size of the heart and increased pulmonary vascular markings.

NONINVASIVE EVALUATION

Chest X-ray

In Group I patients with intact ventricular septum, chest roentgenogram looks benign with normal to minimal cardiomegaly and normal to slightly increased pulmonary vascular markings (Figure 2). The shadow of the thymus rapidly involutes and a narrow pedicle (superior mediastinum) may be seen. A combination of the above signs may sometimes appear as an "egg-shaped" heart on a postero-anterior chest film. In Group II patients with VSD, moderate to severe cardiomegaly and increased pulmonary vascular markings are usually seen. In Group III patients, mild to, at worst moderate cardiomegaly may be observed. The pulmonary vascular marking may be increased, normal or decreased, dependent upon the severity of PS.

Electrocardiogram

The electrocardiogram in a neonate with TGA and intact septum (Group I) may be normal with the usual right ventricular preponderance seen at this age. In older infants clear-cut right ventricular hypertrophy becomes obvious and, in addition, right atrial enlargement may be seen. In Group II patients, biventricular hypertrophy and left atrial enlargement are usual. In Group III, right ventricular or biventricular hypertrophy is seen.

Echocardiogram

Echocardiogram is helpful in the diagnosis and assessment. Demonstration of transposition of the great arteries is somewhat difficult in view of the fact that atrial and ventricular anatomy is normal and the aortic and pulmonary valves appear similar on echocardiographic

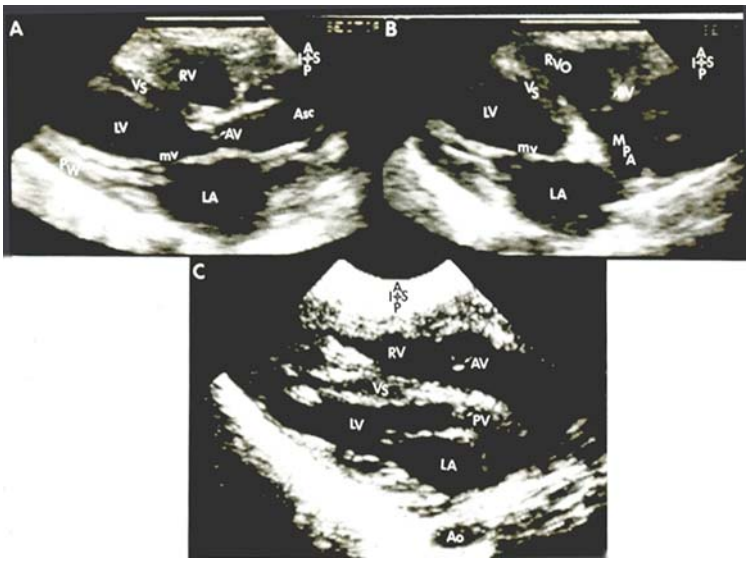

Figure 3. Precordial long axis echocardiographic views of two neonates: first (top, A & B) with normally related great arteries and the second (bottom, C) with transposition of the great arteries. In A, note that the posterior vessel arising from the left ventricle (LV) courses somewhat anteriorly, indicating that it is likely to be the aorta. In B, the anterior vessel coming off the right ventricle (RV) divides into right and left pulmonary arteries, suggesting that this vessel is main pulmonary artery (MPA). In C, the posterior vessel is coursing backward (posteriorly) after its origin from the LV and is likely to be the MPA, suggesting transposition of the great arteries. Ao, aorta; Asc, ascending aorta; AV, aortic valve; LA, left atrium; mv, mitral valve; PV, pulmonary valve; PW, posterior wall of LV; RVO, right ventricular outflow tract; VS, ventricular septum.

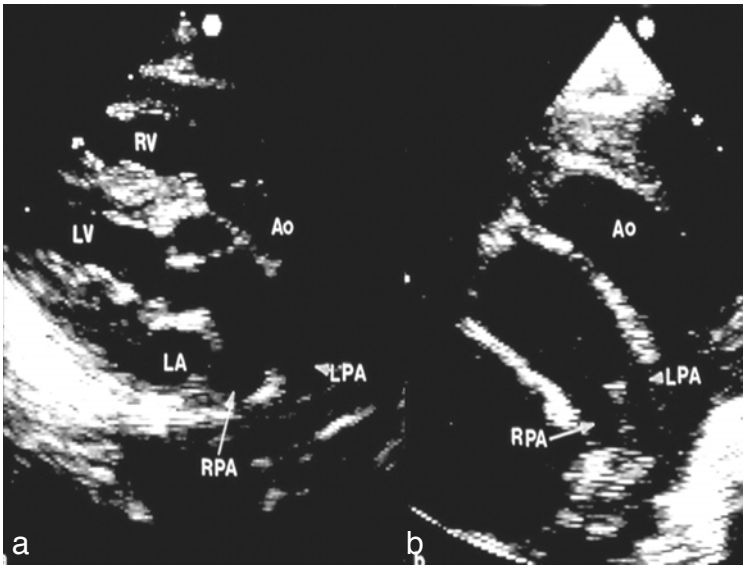

Figure 4. Selected video frames from a 2-dimensional echocardiographic view of an infant with transposition of the great arteries. In a, note the great vessel coming off of the left ventricle (LV) courses posteriorly and bifurcates into left (LPA) and right (RPA) pulmonary arteries. In b, posterior vessel is similarly seen to bifurcate. The anterior vessel is aorta (Ao). LA, left atrium; RV, right ventricle.

study. A helpful indirect sign is a somewhat posterior of the great vessel arising from the left ventricle in a precordial long axis view, indicating the vessel is pulmonary artery in contradistinction to anteriorly coursing ascending aorta (Figure 3). If one can follow the great vessel arising from the left ventricle and demonstrate its bifurcation (Figure 4), identifying it as a pulmonary artery, the diagnosis is easy. On-end visualization of both the aorta and pulmonary artery simultaneously on a precordial short axis view of the heart is also helpful in suggesting TGA. The presence of an interatrial communication and patent ductus arteriosus and shunt across them by color and pulsed Doppler should also be evaluated. In addition to these, demonstration of VSD and PS will place the patients into the respective groups.

Other Laboratory Studies

Blood gas values are useful in demonstrating the degree of hypoxemia and ventilatory status. Serum glucose (or Dexrostix), calcium, hemoglobin and hematocrit levels are useful in the overall assessment, similar to that of other cyanotic CHD in the neonate.[4]

CARDIAC CATHETERIZATION AND ANGIOGRAPHY

With the increased accuracy of echocardiographic diagnosis, invasive studies are not necessary for diagnosing TGA. Need for rapid relief hypoxemia and acidosis by balloon atrial septostomy and the need for a greater definition of coronary artery anatomy prior to arterial switch procedure may necessitate catheterization and angiography.

In Group I patients, vena caval, right atrial, right ventricular and aortic saturations are moderate to severely diminished unless atrial, ventricular or ductal shunting is present. Similarly, the pulmonary venous, left atrial, left ventricular and pulmonary arterial saturations are high with minimal, if any right-to-left shunt. In TGA, the pulmonary artery saturations are higher than those in the aorta; this is in contradistinction to higher aortic saturation in normal babies.

The left atrial pressure is usually high with a pressure gradient across the atrial septum. The right ventricular pressure is at systemic level without any gradient across the aortic valve. In TGA with intact septum, the left ventricular and pulmonary artery pressures are normal without any gradient across the pulmonary valve. However, in the early neonatal period, prior to involution of the pulmonary vasculature, these pressures are elevated, compared to normal right (pulmonary) ventricular pressure. In the presence of significant VSD and/or PS, the left ventricular pressure is elevated and this is usually proportional to the size of the VSD and/or severity of the PS. The pulmonary artery pressure is usually increased with associated VSD while with PS, it may be low to normal.

Selective right ventricular angiography (Figure 5) reveals a morphologically right ventricle with opacification of an anteriorly and superiorly displaced aorta. The aortic valve is located to the right of the pulmonary valve (d-TGA). The aorta ascends in a normal fashion and usually descends on the left side of the spine. The size and function of the right ventricle and presence of tricuspid insufficiency should be evaluated. If a VSD is present, it may be visualized. A laid-back view of the aortic root angiography along with a lateral view may be useful in demonstrating coronary artery anatomy. Aortography may, in addition, be useful in demonstrating PDA and coarctation of the aorta. Left ventricular cineangiogram (Figure 5) reveals a morphologic left ventricle with prompt opacification of the pulmonary artery. The pulmonary valve is located posterior, inferior and to the left of the aortic valve. Left ventricular angiography should be scrutinized for subvalvar and valvar PS. A VSD may be visualized, if present.

MANAGEMENT

The treatment of choice in the neonates with TGA is total surgical correction by arterial switch procedure (Jatene)[10] and will be discussed here-under. However, since the surgery is usually performed at about the age of 7 days, the infant should be cared for to ensure good clinical and metabolic state before going to surgery.

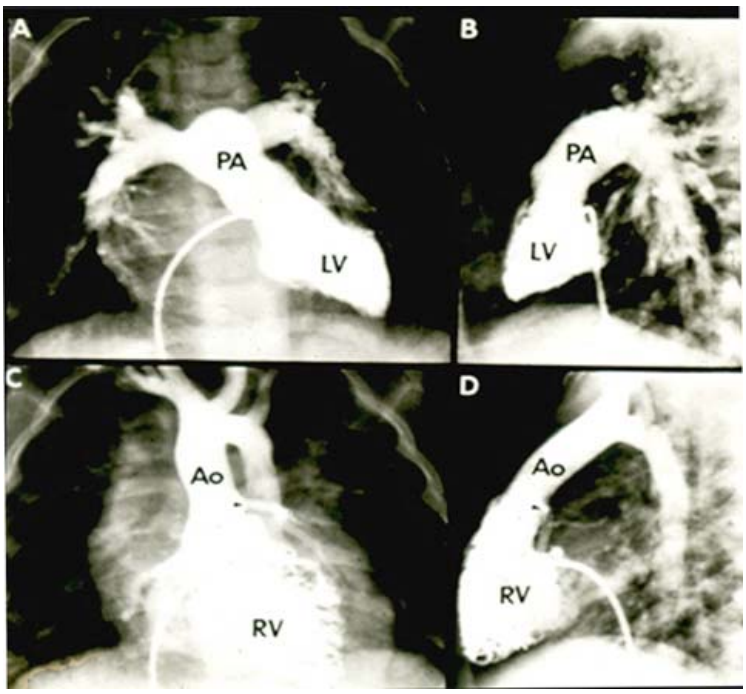

Figure 5. A & B. Left ventricular (LV) cineangiogram in postero-anterior (A) and lateral (B) views demonstrating a finely trabeculated, morphologic left ventricle with prompt opacification of the pulmonary artery (PA). The PA is inferior and posterior to its usual position. C & D. Right ventricular (RV) cineangiogram in postero-anterior (C) and lateral (D) views showing a coarsely trabeculated ventricle with opacification of the aorta (Ao). Note that the aortic valve is superior and anterior (D) to its usual position.

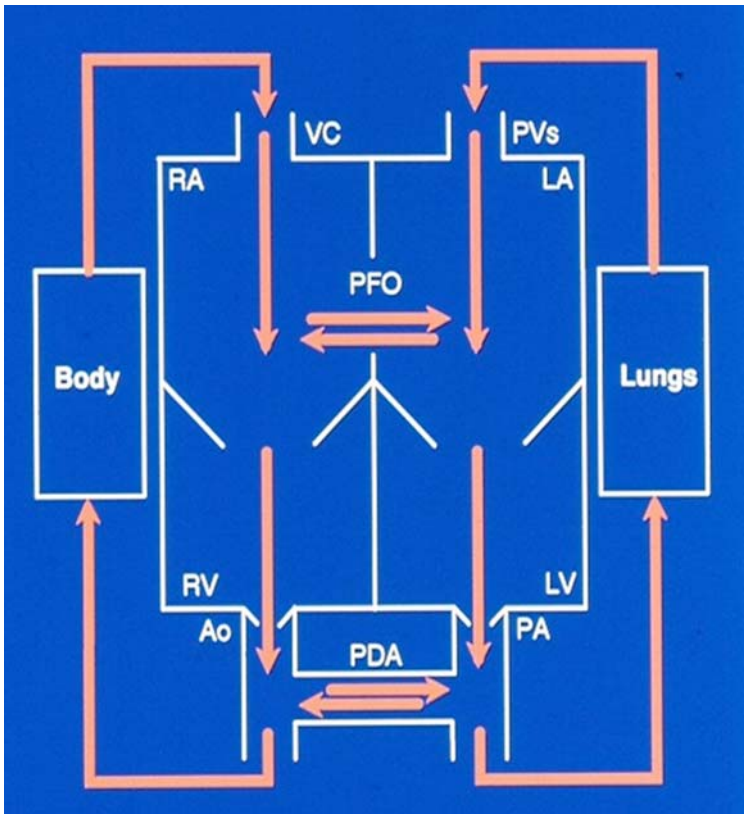

Figure 6. Box diagram of the heart showing parallel circulations in transposition of the great arteries. Unless there are inter-circulatory communications via either a patent foramen ovale (PFO) or patent ductus arteriosus (PDA), the infant cannot survive. Mixing across a ventricular septal defect, if such is present (not shown in the diagram), would also prevent progressive hypoxemia and death. Ao, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PVs, pulmonary veins; RA, right atrium; RV, right ventricle; VC, vena cavae.

General Measures

Initial management of TGA is similar to that used in other cyanotic neonates.[4] The infant's temperature should be monitored and neutral thermal environment maintained. Ambient oxygen should be administered if the infant is hypoxemic. In cyanotic CHD patients, no more than 0.4 FIO_2 is necessary; higher levels of O_2 do not increase O_2 saturation because of fixed intra-cardiac right-to-left shunting. 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. Since hypoglycemia can be a significant problem, the infant's serum glucose should be monitored. The neonates should routinely receive 10% dextrose in water intravenously. If hypoglycemia (<30 mg/100ml) is detected, 15% to 20% dextrose solution should be infused. Calcium levels should also be monitored and if hypocalcemia is detected, it should be treated.

Palliative Therapy

If untreated, *TGA with intact septum* carries a poor prognosis. Instead of having a normal in-series circulation, the TGA patients have parallel circulation (Figure 1). Without either an intra-cardiac or extra-cardiac shunt, the infants with TGA will not survive (Figure 6). The fetal circulatory pathways {patent foramen ovale (PFO) and patent ductus arteriosus (PDA)} will provide some mixing initially. However, in most neonates with TGA, the PFO and PDA tend to undergo spontaneous closure and the infant gets progressively hypoxemic. The PDA and PFO can be kept open/enlarged by pharmacological or mechanical means, respectively.

Patent Ductus Arteriosus. Intravenous infusion of prostaglandin E_1 (PGE_1) (0.05 to 0.1 mcg/kg/min) may help open the ductus, thus improving oxygenation. A small ductus may be made to dilate with PGE_1, but an already closed ductus may be difficult to reopen. Side effects include apnea, hyperthermia, muscular twitching and flushing. The side effects have not posed substantial management problems, but the neonate should be watched closely for apnea. Once the O_2 saturation improves, the dosage of the PGE_1 should be reduced stepwise downward to 0.02 to 0.025 mcg/kg/min. This may avoid the need for endotracheal ventilation because of apnea. If hypoxemia does not improve even after PGE_1, balloon atrial septostomy may become necessary.

Patent Foramen Ovale. Balloon atrial septostomy[8,9] (Figure 7) has been extensively used in the palliation of neonates with TGA with intact septum. The past experience has demonstrated that the improved mixing at the atrial level allows the neonate with transposition to grow to an age (usually 3 to 6 months) at which time a venous switch (Mustard or Senning - see surgical correction) procedure could safely be performed. With the introduction of arterial switch (Jatene) procedure which is usually performed at approximately one week of age, balloon atrial septostomy is not necessary in all babies. If naturally present PFO and/or PGE_1 infusion to dilate the PDA do not maintain reasonably good oxygen saturations (60 to 70% without metabolic acidosis), balloon atrial septostomy should be performed, preparatory to arterial switch procedure.

Septostomy Procedures. In 1966, Rashkind and Miller[8] described a technique, now called Rashkind balloon atrial septostomy, which was extensively used to improve atrial mixing in neonates with TGA. It was

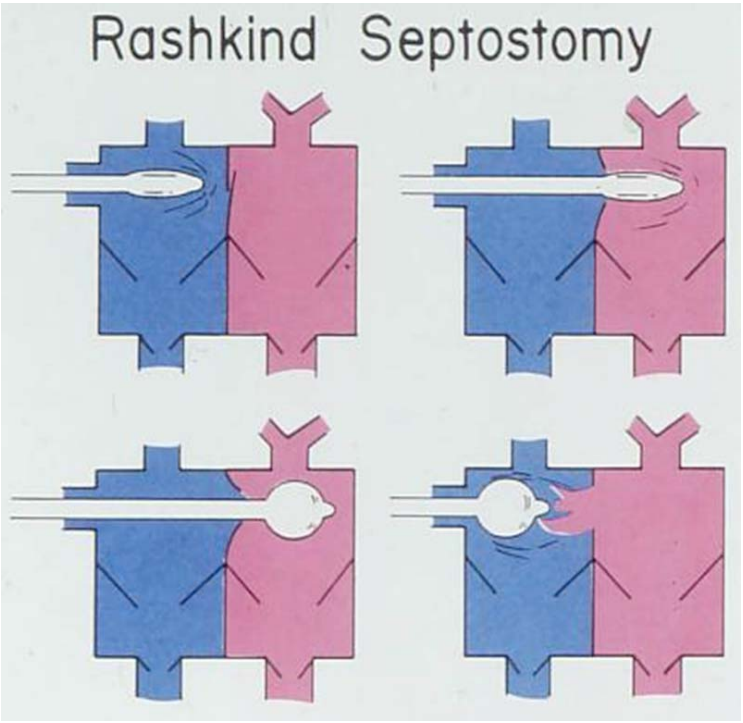

Figure 7. Diagrammatic display of the procedure of Rashkind balloon atrial septostomy. An un-inflated balloon septostomy catheter is placed in the right atrium (top left) and advanced across the patent foramen ovale into the left atrium (top right). The balloon is inflated with diluted contrast material (bottom left) and rapidly pulled back into the right atrium (bottom right), thus performing balloon atrial septostomy.

subsequently applied to many other disease entities (reviewed elsewhere[11]) in which enlarging the atrial defect is beneficial. The reason for success of balloon septostomy is a very thin and frail lower margin of the PFO (septum primum) in the newborn which can be torn by rapid withdrawal of an inflated balloon across the PFO. Some babies do have thick atria septae. To address these situations, Park and his associates, in the mid/late 1970s, extended the utility of the balloon septostomy procedure by introducing blade atrial septostomy to enlarge defects with thick atrial septae.[12] A built-in retractable blade (knife) cuts the lower margin of the patent foramen ovale (PFO) which is followed by balloon atrial septostomy. More recently, static balloon angioplasty,[11,13,14] stents,[15-17] Brockenbrough atrial septal puncture,[17] radiofrequency ablation[18-20] and cutting balloons[20] were applied to create and/or enlarge the atrial defects.[9] In most patients conventional balloon atrial septostomy is all that is necessary to palliate TGA patients until surgery. In over a 35-year experience of the author, there were only a couple of occasions when static balloon[11,14] was used in TGA neonates. Other methods of atrial septostomy[9,15-20] are not necessary in TGA patients, but may be needed in patients with Hypoplastic Left Heart Syndrome.

Rashkind Balloon Atrial Septostomy Procedure. In TGA patients who are stable, the hemodynamic (usually limited) data, including selective cine-angiography, as needed, are performed. If the infant is unstable or has extremely low oxygen saturations, one may proceed directly with balloon septostomy. In such situations, aortic saturation and pressure pullback across the atria and echocardiographic size of atrial defect are recorded. The balloon septostomy procedure involves inserting a balloon septostomy catheter, usually via a sheath percutaneously placed in the femoral vein, into the left atrium via the PFO. The balloon is inflated with diluted contrast material to a sub-maximal amount (usually 2 to 3 ml) and rapidly pulled back across the atrial septum (Figure 8) after ensuring that the catheter tip is located in the left atrium either by lateral fluoroscopy or by echocardiography. Once the catheter is pulled back to the inferior vena cava, the catheter should be rapidly advanced into the right atrium; all this is done as a single motion (Figure 8). The balloon should be deflated as the catheter is repositioned into the right atrium. This jerking motion of the contrast filled balloon catheter produces a tear in the lower margin of the PFO (septum primum) with resultant bidirectional shunt (Figure 9). We usually perform one additional septostomy following what may be considered good septostomy.

Increase in systemic arterial oxygen saturation, disappearance of pressure gradient across the atrial septum and echographic increase in the size of the atrial defect with non-restrictive Doppler

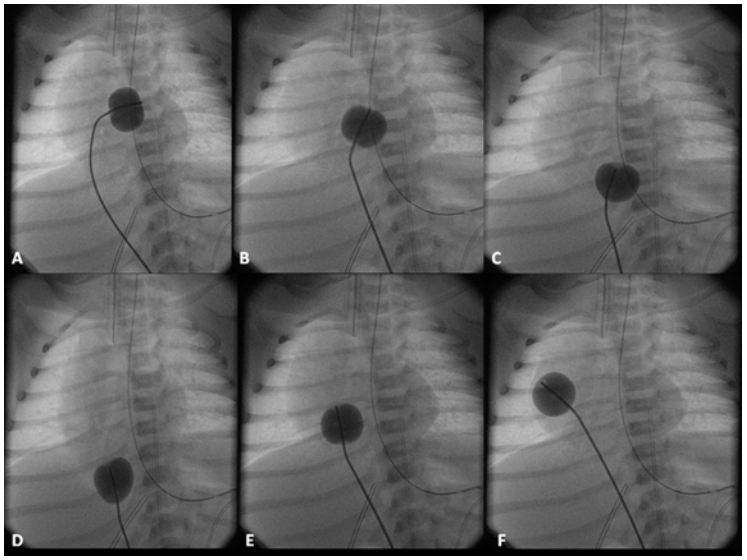

Figure 8. Selected cinfluroscopic frames of the Rashkind's balloon septostomy procedure. Note the position of the inflated balloon in the left atrium (A) and in right atrium and inferior vena cava in successive frames, as it is rapidly and forcefully withdrawn across the atrial septum (B,C, & D). After it reaches the inferior vena cava (D), it is rapidly advanced into the right atrium (E & F) in order not to inadvertently occlude the inferior vena cava in case of failure to deflate the balloon (which is quite rare).

flow across the atrial septum are demonstrated in successful procedures. Some workers balloon-size the atrial defect both prior to and following balloon septostomy, and this is another method of assessment of the result of the septostomy.

In the initial description of balloon septostomy by Rashkind and Miller,[8] the catheter was introduced into the femoral vein by cut-down. To avoid femoral venous cut-down, insertion of the catheter and performance of balloon septostomy via the umbilical vein[21] has been advocated. When percutaneous technology became available, the balloon catheter was introduced via appropriate sized percutaneously inserted femoral venous sheaths.[22,23]

Our first choice is to perform balloon septostomy via the umbilical venous route. Therefore, we encourage our neonatology colleagues to place an umbilical venous line early on, with its tip well into the right atrium, before the ductus venosus constricts. At the time of septostomy, this line is exchanged over a wire with an appropriate sized sheath.

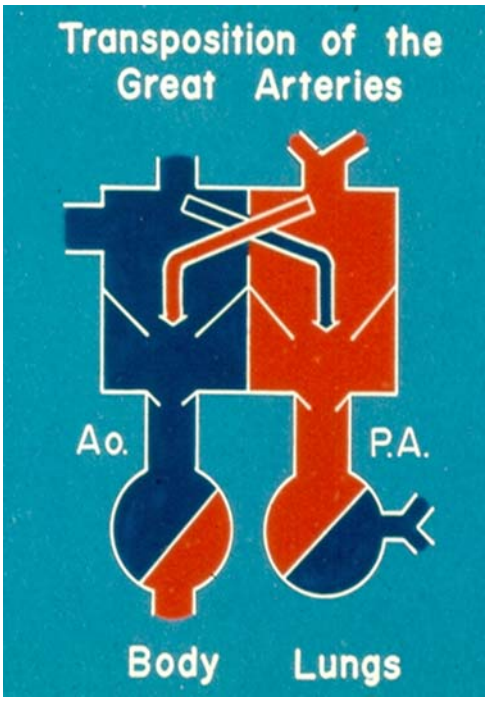

Figure 9. Diagrammatic representation of left-to-right (pink arrow) and right-to-left (blue arrow) shunt across the patent foramen ovale which has been enlarged by balloon atrial septostomy. Ao., aorta; P.A., pulmonary artery.

Initially Rashkind balloon septostomy catheters (USCI, Boston, MA) were used. Because the catheters were straight, sometimes making it difficult to advance the catheter into the left atrium, and because of the limited volume of fluid that these balloons would take, most cardiologists have switched to Edwards septostomy catheters (American Edwards Baxter, McGaw Park, IL). These catheters have a gentle curve at the tip, facilitating easy access into the left atrium and larger volume of fluid that can be injected into these balloons. More recently, atrioseptostomy catheters (B/Braun, Bethlehem, PA) have become available. There are no studies comparing the relative effectiveness of the available catheters and, therefore, the selection of the type of catheter used is at the discretion of the operator.

The feasibility of performing balloon septostomy bedside, under echo guidance, has been demonstrated.[24,25] But, most cardiologists perform the procedure in the catheterization laboratory which is preferred by the author.

TGA with VSD patients usually present with heart failure and aggressive anti-congestive measures are indeed needed. Balloon atrial septostomy may help relieve pulmonary venous congestion and improve oxygenation. These patients will require Jatene procedure along with closure of the VSD.

TGA with VSD and PS patients may have varying types of presentation. If poor mixing is the reason for hypoxemia, balloon atrial septostomy is the treatment of choice. If the hypoxemia is secondary to markedly decreased pulmonary flow, a Blalock-Taussig type of shunt[26,27] may be needed. Sometimes both transcatheter balloon atrial septostomy and balloon pulmonary valvuloplasty[28-31] may be needed to improve hypoxemia. Most of these patients eventually require a Rastelli type of repair.[32]

Surgical Correction

Two types of surgical approaches, namely atrial (venous) and arterial switch are available for use. In the venous switch procedure, the systemic venous flow is directed towards the mitral valve and the pulmonary venous flow towards the tricuspid valve by constructing an intra-atrial baffle after the removal of the atrial septum. This is a physiological (hemodynamic) correction reversing the blood flow pathways at entry to counter the congenitally reversed great arteries. But the procedure leaves the morphological right ventricle to pump against the high resistance systemic circuit. Originally described by Mustard in 1964,[33,34] the procedure was the most commonly used operation for TGA in the past. Similar venous re-directing procedures described by Senning[35] and Shumacker[36] have also been used in several centers. While post-operative complications such as arrhythmia and baffle obstruction were reduced significantly by better understanding of the conduction system and its blood supply coupled with the use of a pericardial baffle (instead of Dacron baffle), they still remained significant. Furthermore, leaving morphological right ventricle to pump into the aorta caused right ventricular failure in adolescents and adults. Jatene et al[10] described anatomical corrections for TGA in 1975; they switched the aorta and pulmonary artery with relocation of the coronary arteries to the neo-aortic root. Such procedures were initially performed for TGA with non-restrictive VSD where the left ventricular pressure was at systemic level. Subsequently the procedure was adapted to TGA with intact septum. However, arterial switch procedure must be performed in the early neonatal period prior to deconditioning of the left (pulmonary) ventricle. The arterial switch procedure has several advantages when compared with the venous switch procedure in that the arrhythmias are less frequent, and the morphological left ventricle rather than the right ventricle serves as a pump for the systemic circulation. Although there are no extensive long-term follow-up results available, the short-term and medium-term follow-up results are very encouraging and, at this time, the arterial switch procedure with or without LeCompte maneuver is considered the preferable operation for patients with TGA. Follow-up after surgery is mandatory to detect and manage residual defects.

Group III TGA patients with VSD and PS most often require Rastelli type of surgery[32] in which left ventricular blood flow is directed into the aorta with the VSD closing patch and a valved conduit (usually an aortic homograft) is inserted to connect the right ventricle to the pulmonary artery. This type of "corrective" surgery is not usually performed during the neonatal period and therefore, will not be discussed further. Palliation may be required during the neonatal period, as discussed in the preceding section.

SUMMARY AND CONCLUSIONS

Transposition of the great arteries is a congenital heart defect in which the aorta arises from the right ventricle, while the pulmonary artery comes off the left ventricle. It is the most common cyanotic CHD in the neonate. In this condition the systemic and pulmonary circulations are parallel instead of the normal circulation which is in series. This anomaly is classified into TGA with intact ventricular septum, VSD and VSD with PS. The intact ventricular septum patients present in the very early neonatal period while the other two may present with symptoms slightly later. Cyanosis is the major symptom in intact septum patients, while heart failure is the presenting symptom in patients with TGA and VSD. TGA with VSD and PS have a variable presentation. Murmurs are notably absent in intact septum babies while loud holosystolic or ejection systolic murmurs dominate in the other two groups. While the chest x-ray and ECG are helpful in the diagnosis, echocardiographic studies are confirmatory in the diagnosis and quantification of the associated defects. PGE_1 to open the ductus and/or balloon atrial septostomy to enlarge the PFO may sometimes be required for palliation. Corrective surgery by arterial switch (Jatene) procedure is necessary in TGA patients with intact septum and those with VSD whereas Rastelli procedure may be required for TGA patients with VSD and PS.

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CORRECTION: In the July 2010 issue of **Neonatology Today** - Volume 5 / Issue 7, in the lead article, "*NAVA Ventilation Allows For Patient Determination of Peak Pressures, Facilitating Weaning In Response to Improving Lung Compliance During Respiratory Distress Syndrome: A Case Report" by Howard Stein, MD.* On Page 4, **Table 2 – Average data for the 30 minutes pre-surfactant, the first 30 minutes post-surfactant, and the next 2 hours post-surfactant,** the heading in the 4th column read, "0.5-2.5 min/ post-surfactant" - it should read. "0.5-2.5 hours post-surfactant."

Global Neonatology Today: A Monthly Column

By Dharmapuri Vidyasagar, MD, FAAP, FCCM

MILLENNIUM DEVELOPMENT GOAL #5 (MDG #5)

The Problem

More than half a million women die as a result of complications during pregnancy, childbirth, and the post-partum period; consequently, high maternal mortality ratios (MMRs), number of maternal deaths/ 100,000 deliveries, are a significant problem. This amounts to one maternal death every minute of the day of the year - a great tragedy indeed. Maternal deaths are usually from preventable causes related to pregnancy, intrapartum and post partum complications. There is a large gap in MMR between rich and poor countries. Ninety nine percent of these deaths occur in resource-poor developing countries. Whereas, in rich countries the MMR it is only 9/100,000 live births, in resource-poor, underdeveloped countries, the MMR on average is 450/100,000 live births. Unfortunately, according to WHO (World Health Organization) in some countries, the MMR is as high as 1,000/ 100,000 live births! African and South Asian countries contribute to the majority of global maternal deaths. Half of all global maternal deaths occur in Sub-Saharan Africa with another third in Southern Asia.

"World bodies such as WHO and the World Bank; and philanthropic organizations such as The Gates Foundation, are making their best efforts in support of programs outlined in the Millennium Development Goals. Serious efforts are underway in most developing countries to meet the targets of all eight MDGs by 2015, but the targets seem unrealistic and too high."

MDG 5 Targets

The main aim of MDG 5 is to improve maternal health. It has two targets:

1. To reduce maternal mortality by three quarters between 1990 and 2015, and;
2. To achieve universal access to reproductive health by 2015.

Two key indicators are used to monitor the progress towards reaching MDG target. The first is reduction in MMR, and the second is to increase the proportion of births attended by skilled health personnel.

The Progress Made

Although there has been some decrease in global MMR since 1990 (MMR of 400 in 2005 vs. 430 in 1990), the progress is very slow: a mere 1% decline per year. As noted above, the decline is only 0.1% in sub-Saharan Africa, The reduction in MMR is not uniform and is unsatisfactory. A steady decrease of 5.5% per annum in MMR is required to reach the targeted goal of MDG #5 by 2015. None of the MDG priority regions have achieved a 5.5% annual decline. Globally, the proportion of assisted deliveries by a skilled attendant is increasing. (From 47% in 1990 to 61% in 2006.) However, this is far lower than the global targets of 80% by 2005, 85% by 2010 and 90% by 2015. The regions with the lowest proportions of skilled health attendants at birth were Eastern Africa (34%), Western Africa (41%) and South-Central Asia (47%), which also had the highest numbers of maternal deaths. Similarly, the targets of increased contraception, antenatal care and decrease in adolescent pregnancy are also under-achieved as of 2008.

What is to be Done

In view of the slow progress, greater emphasis is being placed on improving women's reproductive health. WHO recommends that by 2015, all primary health-care facilities should be prepared to provide, directly or through referral, the widest achievable range of:

- Safe and effective family planning and contraceptive methods;
- Essential obstetric care;
- Prevention and management of reproductive tract infections, including sexually transmitted diseases.

In addition, it is recognized that MMR is influenced by a variety of societal problems.

World bodies such as WHO and the World Bank; and philanthropic organizations such as The Gates Foundation, are making their best efforts in support of programs outlined in the Millennium Development Goals. Serious efforts are underway in most developing countries to meet the targets of all eight MDGs by 2015, but the targets seem unrealistic and too high.

For more information:
www.who.int/making_pregnancy_safer/topics/mdg/en/index.html

The Clock is Ticking!

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Children Born After Assisted Reproduction at Greater Risk of Congenital Malformations

Couples considering undergoing assisted reproductive technology (ART) treatment should be informed about the increased risk of congenital malformation posed by the use of ART. Dr. Géraldine Viot, a clinical geneticist at the Maternité Port Royal Hospital, Paris, France, speaking at the annual *Conference of the European Society of Human Genetics* says that she believed that most doctors working in ART clinics in France only told couples about such risks if they were asked specific questions.

Dr. Viot and colleagues conducted a survey in 33 French centres registered for ART, around one third of the total number of clinics registered to perform ART procedures in France. All ART births from these clinics from 2003 to 2007 were included; 15,162 children in total. The study was the largest to-date on this subject. Questionnaires were completed both by the parents and the paediatrician, and the prevalence of malformations found was compared with the data obtained from national registers and in published papers.

"We found a major congenital malformation in 4.24% of the children," said Dr. Viot, "compared with the 2-3% that we had expected from previous published studies. This higher rate was due in part to an excess of heart diseases and malformations of the urogenital system. This was much more common in boys. Among the minor malformations, we found a five times higher rate of angioma, benign tumours made up of small blood vessels on or near the surface of the skin. These occurred more than twice as frequently in girls than boys."

However, the scientists say, their results are a long way from the 11% of major malformations that have been reported by some studies. "Given that our study is the largest to-date, we think that our data are more likely to be statistically representative of the true picture," said Dr. Viot.

The average age of the parents of children born with malformations was not statistically different from the other parents in the ART group. The origins of the malformations are probably multiple, says Dr. Viot. "We need more research in order to understand the relationship between embryo culture media, timing of embryo transfer, the effects of ovarian stimulation, the use of ICSI, where sperm is injected directly into the egg, freezing of gametes and embryos and these disorders.

Dr. Viot and colleagues intend to follow-up their work analysing a further 4000 questionnaires, from children born in 2008, and to look at the motor development of children born in 2003, who are now age 7. "By following all these children we hope to understand more about not only what can go wrong after ART, but why it goes wrong," she said. "At a time when infertility is increasing and more and more couples need to use ART to conceive, it is vitally important that we find out as much as we can about what is causing malformations in these children, not only so that we can try to counteract the problem, but also in order for health services to be able to plan for their future needs."

The scientists are now trying to find out the origin of parental infertility for each child born after ART who has been affected by major malformation or epigenetic disorders. "With this knowledge, we can better establish the origin of the malformation and whether it is more likely to be related to parental infertility or the ART procedure itself", said Dr. Viot. "We already know that imprinting disorders – where the mechanism in which gene expression depends on parental origin – are clearly more frequent in our cohort than in the general population."

Imprinting disorders are all acquired because of either a maternal or paternal deletion on a chromosome, through inheritance of both chromosomes of a pair from only one parent, through mutations in some imprinted genes, or because of loss or gain of methylation (a process which is normally removed during zygote formation and re-established through successive cell divisions during development. "The prevalence of the imprinting disorder Beckwith Wiedemann Syndrome in our cohort is six times higher than we would expect in the general population, and for retinoblastoma the prevalence among ART children is 4.5 higher than in the general population," said Dr. Viot.

"These results could be due to the effect of a number of different mechanisms. They could be due to the infertility itself, the ovarian stimulation for supernumerary oocyte production, the in vitro maturation of oocytes, the use of ICSI (direct injection of sperm), the culture media, the cryopreservation of gametes and embryos – we just don't know at present. Finding this out will be a major step towards improving the health of children born after ART."

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