Pathophysiology of dorv and surgical management

Advances in genetic techniques and ability to detect the chromosomal abnormalities in the cellular structures; have had a great impact on the detection of congenital cardiac defects. Although in the past congenital heart diseases have long been recognised as a constituent of complex genetic syndromes, a genetic cause for specific congenital heart diseases has less been apparent; as the sources of these defects has been believed to be multifactoral. In addition, with the advancement of the molecular genetic studies, it has come to light that in many instances, congenital heart diseases exhibit classic Mendelian transmission. It is also possible to trace the direct involvement of a gene with a particular congenital cardiac defect.

Tetrology of Fallot has been found to have genetic predisposition, it is estimated that offspring of a parent with tetrology of Fallot is more likely to suffer from the disease in comparison to offspring’s whose parents do not suffer from congenital heart disease. Studies estimated that about 1. 5% of live births will be affected by tetrology of Fallot if the parents suffer from the defect and about 0. 1% will be affected by the presence of tetrology of Fallot if parents do not suffer from congenital heart disease. In comparison in DORV chromosomal abnormalities have only been identified in some cases. In the Baltimore-Washington infant study, DORV was diagnosed in a few patients with downs syndrome and in trisomies 13 and 18, although the incidence was quite low compared with that morphologically similar lesion, tetrology of Fallot. In addition the related conotruncal abnormality, complete transposition of the great arteries, was not found in any patient with trisomy in reported study, this suggests that DORV and transposition of great

arteries may be etiologically similar and may be fundamentally different form tetrology of Fallot in terms if developmental mechanism.

Also DORV and Transposition of Great arteries are rarely found in patients with CATCH 22 syndromes, although tetrology of Fallot is not uncommon. In a large sample study of patients with conotruncal abnormalities to evaluate the frequency of 22q11 deletions, only 1of 20 patients with DORV as compared to 15. 9% of the patients with tetrology of Fallot. The studies have also reported that DORV may be a part of complex CHD in patients with DiGeorge, velocardiofacial and conotruncal anomaly-face syndrome. In a resent animal study it was reported that DORV occur in mouse embryos homozygous for the JMJ mutation, which affects the nuclear protein jmj coded by chamber-specific genes.

Surgical Management

Surgical management for the DORV and tetrology of Fallot is determined by the anatomy and physiology of the defect as well as the age at which the diagnosis is made and at which the need for surgical intervention arises. Indications for operation are similar to those for defects that lie on each side of the DORV spectrum (VSD, tetralogy of Fallot, and Transposition of great arteries). In addition the presence of associated cardiac defects may modify the approach. In DORV the position of VSD and the presence and severity of pulmonary stenosis are probably the most important considerations.

In tetralogy of Fallot most patients have satisfactory systemic arterial oxygenation saturation at birth and require no treatment. However when the oxygen saturation drops below 75-80% operative intervention becomes

imperative. Hypoxemic spells may occur from the transient reductions in pulmonary blood flow, due to sudden increase in right ventricular outflow tract obstruction and the decrease in systemic vascular resistance, so a surgical approach takes into consideration the number and location of ventricular septal defects, anatomy and severity of right outflow tract obstruction, coronary artery and aortic arch anatomy and the presence of other cardiac and non cardiac anomalies. Depending on the severity of the cyanosis two types of surgical streams are available.

There are two basic possible types of surgical strategies for newborn infants with tetralogy of Fallot. One of the strategies consists of a staged repair; where initial palliation is followed by a complete repair and other one being a complete repair in the neonatal period.

Palliative surgical correction, which often does not require the use of cardiopulmonary bypass, is the creation of systemic to pulmonary shunt. This correction is achieved by connecting systemic blood flow source to a the pulmonary blood flow, as already mentioned the main feature of this congenital defect is the reduced flow to the pulmonary system which is the basis of cyanosis. The palliative repair is done by fitting a tubular prosthesis between a systemic artery and a pulmonary artery as shown in the figure (?) (a, b and c). The commonest type of systemic-to-pulmonary arterial shunt is a modified Blalock-Taussig anastomosis which is a communication between a subclavian and pulmonary artery of the same side. Another form of palliative correction is done by creating a connection between ascending or descending aorta and the trunk of pulmonary artery. The connection which connects the posterior ascending aorta to anterior pulmonary trunk is called

Waterston shunt and connection between posterior pulmonary artery to anterior descending aorta is called potts shunt. Both of these techniques have there advantages and disadvantages (figure (S) e and f).

Figure (?) The most common types of palliative procedures for tetralogy of Fallot. The modified Blalock-Taussig shunt (MBTS) using a Gore-Tex graft either from the right subclavian artery (A) or the right innominate (INN) artery (B). C, A central aortopulmonary shunt using Gore-Tex. D, A right ventricular outflow patch without ventricular septal defect closure.

Pathophysiology of DORV

Once the anatomic variables of DORV are understood, the various physiologic manifestations become both logical and predictable, at the tetrology end of the DORV spectrum; pathophysiology is similar to that in the tetrology of Fallot. The most important variables determining the physiology of a given heart are the position of the VSD in relation to great arteries, the relation of the great arteries to each other and the presence of associated defects (in particular, outflow tract obstruction). In general patients with large VSD and no pulmonary stenosis or severe pulmonary vascular resistance are not clinically cyanotic. This is because Qp is high and the resultant mixture of blood in the right ventricle has a high enough oxygen saturation to prevent clinically evident cyanosis; however there is some arterial desaturation.

Although both great arteries arise from the right ventricle, often incomplete mixing of oxygenated and unoxygenated blood occurs at the ventricular level because of streaming. This streaming of blood within RV is usually

determined by the relationship of semilunar valves to the VSD and the position and presence of the infundibular septum. The blood in the great artery most closely related to the VSD and therefore most aligned with LV outflow tract tends to have the highest oxygen saturation. Likewise, the great artery that due to streming, preferentially receives systemic venous return, tends to have a lower saturation. This phenomema is somewhat different from true single ventricle physiology.

In DORV with subaortic VSD and no pulmonary stenosis, pulmonary blood flow will be determined by the relationship of pulmonary to systemic vascular resistance. What is usually the case after the first few weeks of life pulmonary vascular resistance is less than systemic vascular resistance, pulmonary blood flow will be greater than systemic flow, resulting in higher than normal pulmonary arterial saturation and congestive heart failure. As the pulmonary vascular resistance increases in response to this abnormal volume load, pulmonary blood flow correspondingly decreases. Eventually, if left untreated, this usually results in pulmonary vascular obstruction disease with severely and irreversible elevated pulmonary vascular resistance, causing progressive cyanosis and early mortality.

However if when the VSD is in subaortic position with pulmonary stenosis, whether valvular or subvalvular, obstruction to pulmonary blood flow is found.

Conduction System

In tetrology of Fallot the sinus and atrioventricular nodes are normal in location, and the bundle of His follows the same general course as in

patients with isolated perimembraneous and juxtatricuspid VSDs. Thus it emerges through the right fibrous trigone at the base of the noncoronary cusp of the aortic valve and courses forward toward the papillary muscle of the conus along the inferior VSD margin or slightly to the left side of the defect edge. In addition, hearts which show marked clockwise rotation of the aortic root with overriding, the right trigone is carried more rightward and superiorly and directly into VSD margin.

By contrast, the bundle of His does not lie on VSD margin when a muscle ridge is present, since the ridge projects superiorly above the right fibrous trigone.

In DORV with concordant AV connections the AV node lies in the usual position in the muscular portion of the AV septum. The bundle of His penetrates the fibrous right trigone of the central body and lies along the posteroinferior margin of the VSD in lesions that are juxtatricuspid wheter the defect is subaortic, doubly committed, or sub-pulmonary. When muscle is interposed between the defect and the tricuspid valve, this muscle protects the bundle, which no longer runs along the posteroinferior free margin of the defect.

Oxygenation

Hemodynamic representation of Tetrology of Fallot (indicating right to left shunting)

Supply of oxygen to the body

Due to the mal-alignment and deviation from the normal physiology, the main issue of the patients with tetarology of Fallot is hypoxemia due to

inadequate pulmonary blood flow caused by the inadequate pulmonary blood flow, which is determined by the right ventricular pressures and degree of obstruction. Since the right and left ventricular and aortic pressure is equalized, a drop in systemic arterial pressure will result in a reduction in pulmonary blood flow. Oxygen carrying capacity of blood depends mostly on haemoglobin concentration and greater the haemoglobin concentration in the blood that perfuses the lungs, the greater the amount of oxygen extracted per unit of blood flow. In neonates the haemoglobin concentration is relatively high (15 to 18 g/dL), however it drops to about 10 or 12g/dL by 3-4 months after birth. In neonates with tetralogy of Fallot there is an increase in blood level of erythropoietin due to hypoxemia. Iron is required to maintain or increase in haemoglobin levels; however suckling infants have very low stores of iron and food intake in early infancy provides little iron. Therefore there is a high incidence of anaemia in children with tetralogy of Fallot. On the other hand tetraology spectrum of DORV, where the great arteries lie side by side with aorta to the right of pulmonary artery and both semilunar valves lying in the same transverse and coronal plane the physiology is similar to tetralogy of Fallot. In these neonates the VSD is closer to aortic valve thus oxygenated blood form left ventricle is directed to the aorta and the deoxygenated blood is directed to pulmonary artery but the degree of pulmonary stenosis directs portion of deoxygenated blood into aorta. In addition due to the presence of large VSD both ventricles are subjected to similar pressures. Due to the pulmonary stenosis the blood flow to the lungs is restricted causing drop in the pulmonary systolic pressure, which in turn causes hypoxemia. The pulmonary stenosis is most often

infundibular, but may be valvular, with or without a small pulmonary valve ring.

In doubly committed VSD category of the DORV spectrum the conoventricular septal defect is both subaortic and sub-pulmonary owing significant conal septal mal-development and mal-position. The hemodynamics change in that case will also be determined by the presence or absence of subaortic or sub-pulmonary stenosis. Therefore cases with sub-pulmonary stenosis will have reduction in the pulmonary blood flow and will result in the hypoxemia and thereby cyanosis corresponding physiological characteristics of tetralogy of Fallot. Also in cases of non-committed DORV majority of great vessels arise form right ventricle thus right ventricle is subjected both pulmonary and aortic circulation resistance. Oxygenated blood form left ventricle gets mixed with non-oxygenated blood through VSD making systemic and pulmonary circulation equal. In addition due to left and right shunting right ventricle is volume overloaded and results in congestive heart failure.

Additionally, the stimulation for the formation of red cells continues and very high counts of red cells are achieved, but the cells are microcytic and hypochromic, since the average corpuscle volume and average corpuscle haemoglobin are markedly reduced. Also the rise above 60% increases the blood viscosity. This raised viscosity of blood leads to greater resistance to flow through the tissues and ultimately capacity to transport oxygen vanishes.

In transposition spectrum of DORV the physiology is different then described above, since the presence of large sub-pulmonary VSD and its commitment to the pulmonary artery; the course of circulation is dependent on the afterload on each ventricle, as shunting could occur in either direction. In this type of defect the oxygen saturation in the pulmonary artery is higher than in systemic circulation. The high oxygen saturation of pulmonary arterial blood will however decrease the pulmonary vascular resistance and consequently will result in right to left shunting during systole. This will result in some decrease in PO2 of blood distributed to the lungs as well as through ductus arteriosus. On the other hand during diastole a larger volume of blood will return from the pulmonary veins to the left atrium and ventricle and thus results in a left to right shunting. As a result, the oxygen saturation of the blood going to systemic circulation is increased and thus tends to limit the abnormal decrease in the upper body PO2. A characteristic of this defect is the presence of a large unrestrictive VSD with which the mixing of pulmonary and systemic blood takes. This phenomena result in a relatively large pulmonary to systemic blood flow ratio and consequently high systemic oxygen concentrations; therefore limiting the tissue hypoxia. However the inability of the ventricles to maintain the physiological normal pressures cardiac failure is often associated in infants with transposition spectrum of DORV. Infants with this type of physiology usually appear with mild cyanosis and in congestive heart failure. In addition if there is effective mixing but pulmonary flow is reduced by the presence of pulmonary stenosis or increased pulmonary vascular resistance, pulmonary to systemic flow ratio decreases and arterial saturations will be lower and subsequently will result in tetrology of Fallot type pathophysiology.

Right to Left Shunts.

Now just for a moment let us consider a large VSD assocoiated with pulmonary valve stenosis which is severe enough to have a resistance greater than systemic vascular resistance. Just like the last case, this ratio of resistances results in reversal of the shunt. This is in fact an unusual combination, but the point here is that the situation mimics the haemodynamics of tetralogy of Fallot. Also it shows how associated pulmonary stenosis can have a great influence on cardiac malformations on many sorts. We will meet it again in the commom mixing situations.

On the other hand with no pulmonary stenosis look at the difference

Right to Left Shunts.

I am making a morphological point here: tetralogy of Fallot is not a coincidence of pulmonary stenosis and VSD but the consequence of right ventricular outflow tract and central pulmonary artery hypoplasia. The diagram can be adjusted to accentuate this, as above. Tetralogy has a variable and sometimes spasmodic stenosis of the muscular right ventricular outflow tract. Sometimes, particularly early in life, the degree of obstruction is not great and the infant may present with signs of a VSD shunting left to right.

Qp: Qs (Ratios Pulmonary to systemic Ratios)

Double outlet Right ventricle hemodynamic representation (DORV -Common mixing)

In many cases of complex congenital cardiac disease it can be quite difficult to understand how the degree of systemic desaturation reflects the flows in malformed heart. It helps to realise that many of them fall into this group of “ common mixing” circulation, which is to say that all pulmonary and systemic venous blood streams are obliged to come together at some point in the circulation. They are:

- Totally anomalous pulmonary venous drainage.
- Univentricular heart.
- Double outlet right or left ventricle.
- All simple valve atresias.
- Fallot pulmonary atresia.
- Truncus arteriosus.

And any of the above in combination with any other defect.

If there is complete mixing of the systemic and pulmonary returns, it follows that pulmonary and systemic arterial saturation will be identical. Due to streaming effects, the mixing may not be quite complete but the saturations will still be nearly identical.

This all means that some degree of systemic desaturation will be present. The degree of cyanosis is dictated by the ratio of pulmonary to systemic flow as shown in the figure above, in which Qp is pulmonary flow and Qs is systemic. Often, particularly in the univentricular heart and in the double outlet ventricles, it is asssociated pumonary stenosis which determines the ratio of Qp to Qs. Some patients with a Qp high enough to keep systemic saturation above 94% or so will not be clinically cyanosed. Time and space

do not allow a full descrtiption of all the pathologies so we will take one example, double outlet right ventricle.

Double outlet right ventricle is a good example of the haemodynamic variability of this group. The figure above shows the circulation in a case where there is a large ventricular septal defect, no pulmonary stenosis and no significant rise in the pulmonary vascular resistance. Pulmonary blood flow is elevated and the radiograph will show plethora. The high ratio between pulmonary and systemic venous return means that the saturation of the mixed flow, and therefore of the aortic blood, is 90%, which is barely detectable clinically as cyanosis

INTRODUCTION –In 1888, Etienne-Louis Arthur Fallot described three cyanotic patients with four similar anatomic features [1]:

Stenosis of the pulmonary artery

Intraventricular communication

Deviation of the origin of the aorta to the right

Concentric right ventricular hypertrophy

This constellation of findings has since become known as tetralogy of Fallot (TOF). The prevalence of TOF in the United States is about 3. 9 per 10, 000 live births [2]. This defect accounts for about 7 to 10 percent of cases of congenital heart disease and is one of the most common congenital heart lesions requiring intervention in the first year of life [3]. TOF occurs equally in males and females [4].

The pathophysiology, clinical features, and diagnosis of TOF will be reviewed here. An overview of the management of this disorder, including postoperative complications and issues related to pregnancy, are discussed separately. (See “ Overview of the management of tetralogy of Fallot”.)

ANATOMY –The exact embryologic abnormality that accounts for TOF is unknown. What is recognized is that during development, there is anterior and cephalad deviation of the infundibular septum. This results in a malaligned ventricular septal defect (VSD), with the aortic root overriding the defect and leading to subsequent right ventricular outflow obstruction (figure 1). The ensuing right ventricular hypertrophy is thought to be a response to the large VSD and right ventricular outflow obstruction with resultant systemic right ventricular systolic pressure.

Ventricular septal defect – The VSD in TOF is most commonly a single large malaligned subaortic defect located in the perimembranous region of the septum (picture 1). The VSD can extend into the muscular septum. There are rarely other muscular ventricular septal defects. (See “ Pathophysiology and clinical features of isolated ventricular septal defects in infants and children”.)

Right ventricular outflow obstruction – The right ventricular outflow obstruction is often at multiple levels (picture 2):

The anterior and cephalad deviation of the infundibular septum results in subvalvar obstruction

Hypertrophy of muscular bands in this region can further accentuate subvalvar obstruction

The pulmonary valve annulus is usually hypoplastic, although in some instances it is of normal size

The pulmonary valve itself is frequently bicuspid and stenotic

In addition, it is not uncommon to identify an area of supravalvar narrowing in the main pulmonary artery at the sinotubular ridge. There may also be further obstruction at the branch pulmonary arteries. These may be diffusely hypoplastic or have focal areas of stenosis, most commonly at the proximal branch pulmonary arteries. The proximal left pulmonary artery near the site of ductal insertion is a frequent location for stenosis (picture 3A-B).

Overriding aorta – Overriding aorta is a congenital anomaly, in which the aorta is displaced to the right over the VSD rather than the left ventricle. This results in blood flow from both ventricles into the aorta.

The degree of aortic override of the VSD can vary widely and is one of the major factors used by some groups to differentiate between TOF and double outlet right ventricle. If one defines double outlet right ventricle as the presence of aortic/mitral valve fibrous continuity, then the degree of override is not relevant to diagnosis. If, however, one defines double outlet right ventricle as a condition with greater than 50 percent aortic override, then, by definition, the degree of aortic override in TOF is limited.

Associated cardiac features – There are a number of frequently associated anatomic features that are important to look for when evaluating a patient

with TOF, since they affect therapy. Associated cardiac anomalies occur in about 40 percent of patients with TOF.

Approximately 25 percent of patients have a right aortic arch. This is particularly important to identify if one is contemplating a palliative shunt.

Abnormalities of the coronary arteries, such as the left anterior descending arising from the right coronary artery, are seen in about 9 percent of patients [5]. These are important to identify prior to complete repair, since the course of the artery may run directly across the right ventricular outflow tract; inadvertent transection could have catastrophic consequences.

Occasionally, patients have significant aorticopulmonary collateral vessels that may require attention prior to or at the time of surgery.

A patent ductus arteriosus, multiple ventricular defects, and complete atrioventricular septal defects may be present.

Infrequently, aortic valve regurgitation is present due to aortic cusp prolapse.

GENETIC FACTORS –Although TOF may present as part of a known syndrome, this lesion typically occurs sporadically without other anomalies.

Surveys of patients with nonsyndromic TOF have reported the following genetic abnormalities:

In one study of 114 patients with nonsyndromal TOF, 4 percent of patients had mutations in transcription factor NKX2. 5., which appears to have a role in cardiac development [6].

In genome-wide surveys of patients with nonsyndromic TOF and their parents, de novo copy number variants were estimated to be present in about 10 percent of sporadic cases of TOF compared to less than 0. 1 percent in controls at several chromosomal locations [7].

Tetralogy of Fallot has also been reported in association with mutations in TBX1 and ZFPM2 [8-10]. Further investigation is required to determine the role of these mutations in the evolution of Tetralogy of Fallot.

Approximately 15 percent of patients with TOF present with associated syndromes, including Down syndrome (trisomy 21), Alagille syndrome (mutations in Jagged1), and DiGeorge and velocardiofacial syndromes (deletion on chromosome 22q11) [8, 11-17]. There may be susceptibility genes for TOF within the latter region of chromosome 22q11 in children without extracardiac anomalies [16, 18, 19], and 22q11. 2 deletion syndrome is unrecognized in many adult patients with TOF [20]. (See “ DiGeorge syndrome: Pathogenesis, epidemiology, and clinical manifestations” and “ Inherited disorders associated with conjugated hyperbilirubinemia”, section on ‘ Alagille syndrome’.)

PATHOPHYSIOLOGY –The physiologic consequences of TOF are largely dependent upon the degree of right ventricular outflow obstruction. Since the VSD is typically large and unrestrictive, the pressure in the right ventricle reflects that of the left ventricle. As a result, the direction of blood flow across the VSD will be determined by the path of least resistance for blood flow, not by the size of the VSD. If the resistance to blood flow across the obstructed right ventricular outflow tract is less than the resistance to flow

out of the aorta into the systemic circulation, blood will naturally shunt from the left ventricle to the right ventricle and into the pulmonary bed. In this situation, there is predominately a left-to-right shunt and the patient will be acyanotic.

As the degree of right ventricular outflow obstruction increases, the resistance to blood flow into the pulmonary bed also increases. If the right ventricular obstruction is significant enough to increase resistance, it will be easier for blood to cross the VSD from the right ventricle into the left ventricle and go out the aorta, which now becomes the path of least resistance. This right-to-left shunt across the VSD will result in a large volume of desaturated blood entering the systemic circulation and cyanosis and polycythemia will ensue (figure 1).

One of the physiologic characteristics of TOF is that the right ventricular outflow obstruction can fluctuate. An individual with minimal cyanosis can develop a dynamic increase in right ventricular outflow tract obstruction with a subsequent increase in right-to-left shunt and the development of cyanosis. In the most dramatic situation, there can be near occlusion of the right ventricular outflow tract with profound cyanosis. These episodes are often referred to as “ tet spells” or “ hypercyanotic spells”. The exact etiology of these episodes is unclear, although there have been a number of proposed mechanisms, including increased infundibular contractility, peripheral vasodilatation, hyperventilation, and stimulation of right ventricular mechanoreceptors [21].

CLINICAL PRESENTATION –The clinical presentation of the patient with TOF is dependent upon the degree of right ventricular outflow obstruction:

Children with severe obstruction and inadequate pulmonary flow typically present in the immediate newborn period with profound cyanosis

Children with moderate obstruction and balanced pulmonary and systemic flow may be noticed during elective evaluation for a murmur

Children with minimal obstruction may present with pulmonary overcirculation and heart failure

Most children with this lesion are symptomatic and cyanotic; there is a subgroup, however, with typical morphology and hemodynamics that remains clinically asymptomatic for a period of time (pink variant). In general, the earlier the onset of systemic hypoxemia, the more likely it is that severe pulmonary outflow tract stenosis or atresia is present.

Physical examination – On inspection, individuals with TOF are usually comfortable and in no distress. However, during hypercyanotic spells, they will become hyperpneic, and infants will often become agitated. If cyanosis is present, it is most easily seen in the nail beds and lips.

On palpation, one may appreciate a prominent right ventricular impulse and occasionally a systolic thrill. Hepatomegaly is uncommon. Peripheral pulses are usually normal, although the presence of prominent pulses may suggest the existence of a significant patent ductus arteriosus or aorticopulmonary collaterals.

Cardiac auscultation – On auscultation, the first heart sound is normal, and the second heart sound is most commonly single because the pulmonic component is rarely audible. Third and fourth heart sounds are uncommon. An early systolic click along the left sternal border may be heard, which is thought to be due to flow into the dilated ascending aorta. (See “ Auscultation of heart sounds”.)

Murmur – The murmur in TOF is due primarily to the right ventricular outflow obstruction, not the VSD. The murmur is typically crescendo-decrescendo with a harsh systolic ejection quality; it is appreciated best along the left mid to upper sternal border with radiation posteriorly. It can, however, have a more regurgitant quality that can be easily mistaken for a VSD. (See “ Auscultation of cardiac murmurs”.)

The murmur is due both to the degree of obstruction and to the amount of flow across the obstruction. In TOF, unlike isolated valvar pulmonary stenosis, the amount of flow across the right ventricular outflow tract will decrease as the obstruction increases, due to the shunting of blood right-to-left across the VSD. Thus, as the obstruction increases, the murmur will become softer. During severe hypercyanotic spells, the murmur may actually disappear due to the markedly diminished flow across the obstruction.