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Tetralogy of Fallot: Origins, Management and Outcomes

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Abstract

Tetraology of Fallot (TOF) is the most common of the cyanotic congenital heart diseases. It is characterized by four anatomical lesions all of which have a spectrum of severity. Clinically the presentation of the neonate depends on the degree of Right Ventricular Outflow Tract (RVOT) obstruction and the patency of the ductus arteriosus with common symptoms including paroxysms of irritability, diaphoresis, hyper cyanotic spells and heart failure. Physicians currently use a multitude of investigations in order to demonstrate the complex physiology of TOF including sonography (in utero), Doppler echocardiography, cardiac catheterization, Multidetector CT (MDCT) and MRI. When used in combination these allow for planned surgical management of this otherwise life limiting condition which can be technically challenging due to variable anatomy. Currently patients should have curative surgery between 3-6 months with surgical approaches including VSD closure through a transaterial-transpulmonary approach and Transannular Patch (TAP) placement to limit RVOT. Currently, 97% TOF patients can expect to survive one year however they require very close follow up with cohort studies revealing high risks of ventricular arrhythmia and sudden cardiac death.

Keywords: Heart diseases; Tetraology of fallot; Surgical approaches

Introduction

Tetralogy of Fallot (TOF) first described in 1671 and fully anatomically described in 1784 is currently the most common cyanotic congenital heart defect (prevalence-2.8-3.9/10,000) [1,2]. This condition is characterized by the presence of four key anatomical features each of which may vary in severity **(Figure 1)** [3,4]. In addition to this a number of associated cardiac malformations are noted in ~40% of affected individuals **(Table 1)** [5,6]. Historically, 50% of patients with TOF died within a year of birth however now 97% patients may expect to survive one year and of these 98% will be alive at 20 years [7,8]. Established risk factors for this condition include DiGeorge/Down syndrome, foetal Rubella infection and maternal diabetes [9].

The aims of this review is to consider the pathophysiology of TOF and current approaches to managing the plethora of disease states this encompasses and consider the long-term sequalae of this common condition for the appreciation of the general physician.

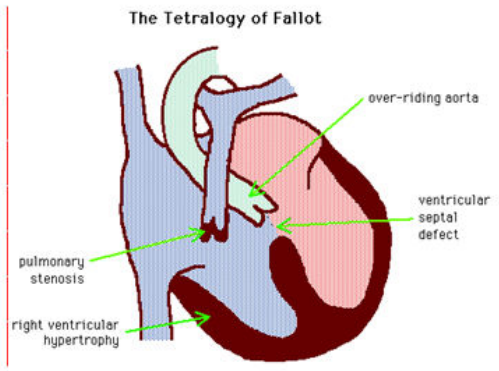

Figure 1: The anatomical lesions found in classical TOF [9].

Table 1: Common anatomical variants associated with TOF [4,5].

Anatomical Variant	Frequency
Right Sided Aortic Arch	12.50%
Atrial Septal Defect	0.7%-9%
Anomalous Coronary Arteries	5%-12%
PDA	4%-5.4%
Bilateral SVC	6.20%
Additional VSD	2.4%-5.4%

Pathophysiology and Spectrum of Disease

The pathophysiology of TOF is one where normal heart development beginning in the 3rd week of gastrulation is

impaired. In particular, there is antero-cephalad deviation of the developing ventricular septum which yields a misalignment Ventricular Septal Defect (VSD). This deviation furthermore results in incomplete transfer of the developing aorta leading to an overriding aorta; while Pulmonary Stenosis (PS) particularly present at the infundibulum is achieved by unequal partitioning of the truncus arteriosus and deviation of the aorticopulmonary septum. The haemodynamic consequences of the above results in compensatory Right Ventricular Hypertrophy (RVH). Depending on the degree of Right Ventricular Outflow Tract (RVOT) obstruction the significance of the VSD is gauged. If the level of obstruction is low then a small Left-Right shunt may form and be of little consequence however if large then a right-left shunt may form leading to hypoxia. While this will provoke a polycythaemia this will not correct the underlying hypoxia and will instead predispose to thromboses [3,10,11].

The most serious variant of TOF is TOF with Pulmonary Atresia (TPA). In this instance the Pulmonary Valve (PV) is now imperforate with the pulmonary arteries either confluent or absent [12]. As such there is no connection between the right ventricle and the pulmonary artery leading to an obligatory right to left shunt and pulmonary circulation entirely derived from either the Patent Ductus Arteriosus (PDA) ± Major-Aorto Pulmonary Collaterals (MAPCAs) **(Figure 2)**. Such dependency on the PDA is disadvantageous as upon closure rapid hypoxia and death may ensue. Moreover, MAPCAs while not dependent on prostaglandin to remain patent may become stenosed over time and are incredibly variable concerning their origin and course. This makes repair very difficult and their utility as a stable blood supply to the lungs questionable [12,13]. Prior to surgical repair therefore as in all cases of TOF; 64-MDCT angiography must be performed to determine local pulmonary and coronary anatomy [14].

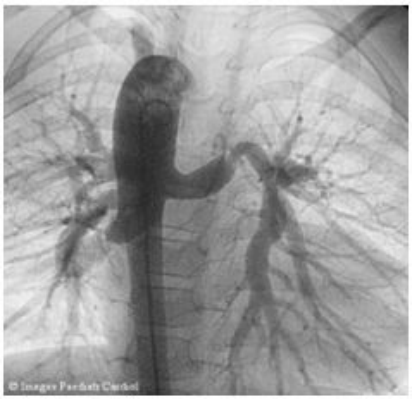

Figure 2: Aortogram showing two large MAPCAS one to each lung [12].

Other rarer TOF variants include absent pulmonary valve syndrome and double outlet right ventricle. The former of these present in only 3%-6% of TOF diagnoses involves complete absence of the PV. This characteristically produces volume overloading of the RV due to regurgitation and dilatation of the Pulmonary Artery (PA) which compresses the developing bronchial tree resulting in bronchomalacia [15]. In double-outlet however, the right ventricle supplies both the aorta and PA predominantly/entirely meaning that the LV only contributes to the systemic circulation through the VSD present [16].

Diagnosis of TOF

Currently, the prenatal diagnosis of TOF through sonography is suboptimal. This is due to the modalities inherent dependency on the operator's skill and a lack of consensus regarding the sonographic features of TOF [17]. This is reflected by recent estimates that the detection rate of Atrioventricular Septal Defects (AVSD) by sonography is only 42% [18]. Proposed sonographic features include however thickened nuchal translucency, polyhydramnios, VSD and an enlarged aortic diameter [19,20]. If clinical suspicion of TOF exists prenatal echocardiography and Doppler should be performed. The outcomes of TOF in the developing foetus are good, in one study of TOF foetuses a 77% survival rate was noted in continued pregnancies with worse outcomes observed in those children with underlying chromosomal abnormalities and complex disease [8].

Upon birth, a more detailed examination must be performed to delineate the type of TOF lesion present and plan the necessary surgical management. Transthoracic 2D and Doppler echocardiography are the favoured techniques for this purpose [1]. The earlier such investigations take place the sooner prostaglandin therapy can be initiated in order to preserve ductal patency. Chest X-Ray while not essential in the diagnostic workup of TOF has been used historically for diagnostic purposes. Classically, a 'boot shaped' heart is seen formed by the upturned cardiac apex and concavity of the pulmonary conus. Electrocardiogram in TOF will demonstrate right axis deviation and RVH with the former of these unlike in the normal new-born failing to normalize [10]. Other investigations such as cardiac catheterization has utility in determining local vascular anatomy in order to plan treatment although as mentioned MDCT and MRI are emerging as alternatives [21].

Clinical Presentation and Management

The clinical presentation of the neonate depends on the degree of RVOT obstruction and the patency of the ductus arteriosus [22]. Typically symptoms of TOF develop months after birth and are characterized by decreased exercise tolerance and hyper cyanotic spells. However, in patients with rare TOF variants symptoms may occur within days of birth and the closing of the ductus [3,8]. As such continued patency of the ductus arteriosus achieved by prostaglandin infusion is a key step in the management of TOF as it can increase PaO_2 levels by 20 mmHg-30 mmHg enabling clinical stabilization until surgical repair [23]. Upon examination neonates will exhibit a systolic thrill at the lower left sternal border (VSD), systolic ejection murmur (PS) which decreases during hyper cyanotic periods and clubbing of the fingers and toes [10].

Hyper cyanotic spells are an episodic central cyanosis due to increasing RVOT obstruction in a person with pre-existing congenital heart disease. These episodes are characterized by paroxysms of hyperpnoea, prolonged cry and irritability and are precipitated by defecation, fever, anemia and breastfeeding in the neonate. If not treated rapidly these events will progress to seizure, syncope and death [24]. Management of these episodes include knee-chest positioning (↑venous return; ↓systemic vascular resistance), judicious oxygen administration, use of Subcutaneous Morphine to depress respiration and relax pulmonary outflow, sodium bicarbonate for acidosis correction, vasopressors and in refractory cases emergency surgery [25].

Surgical management of TOF has been performed since 1954 and initially involved cross circulation and cardiopulmonary bypass but had a high mortality rate [26]. Currently, TOF repair is two staged in asymptomatic individuals and single in symptomatic patients. In the initial management of asymptomatic individual's palliative surgery aims to improve lung perfusion and buy time until correctional repair is optimal. Palliative methods include shunt insertion e.g. Blalock-Taussig operation whereby a shunt connects the ipsilateral subclavian vein to the pulmonary artery. The timing of curative surgery stands at 3 months-6 months old allowing those with severe symptomatic disease to be operated on first [1,27]. Currently, overall mortality rate of this approach is currently <5%. This cut-off is such so as to minimize the sequelae of delayed correction which include continued RVH and future risk of ventricular arrhythmia. It must be noted however corrective surgery has been linked to detrimental effects on brain development and lower follow up IQ levels. This is as a result of the hypoxic effects of hypothermic cardiopulmonary bypass and cardiac arrest employed during surgery [28,29].

This repair may however be complicated by features such as the Left anterior descending artery branching from the Right Coronary Artery. This anomalous vessel travels anterior to infundibulum of the RVOT which is a site of surgical incision and as such must be avoided through pre-operative imaging [10]. Presently a transatrial-transpulmonary approach for patch closure of the VSD is preferred as unlike right ventriculotomy incision is not associated with significant tissue scarring. RVOT obstruction is managed by PV dilation and Transannular Patch (TAP) placement. This patch however does predispose to volume overload, subsequent RV dysfunction and pulmonary regurgitation. Through allowing of residual PS these may be avoided [1]. In addition the issues remains that frequent revisions may be needed to enlarge it as the developing neonates heart continues to grow. In those individuals with pulmonary the use of a TAP and VSD closure may still be performed. In those with MAPCAs and Pulmonary Arteries their contribution to pulmonary blood flow must be determined as must the importance of the patent ductus. In those who are ductal dependent a shunt insertion should be used and in the absence of significant MAPCAs complete repair by age 1 year. In those with large MAPCAs detailed angiography must be undertaken in a staged manner to allow for staged unifocalization whereby collaterals are removed from the aorta and surgically attached to the pulmonary artery [26]. Absent pulmonary valve syndrome also has a similar surgical management to classical TOF however it remains controversial as to whether a pulmonary valve should be inserted and the now dilated PA reduced. Currently, surgical correction is made in two stages by firstly addressing the correction of TOF and then secondly decompressing the lungs which is classically performed by plication of the proximal pulmonary arteries and reduction of the distal pulmonary arteries [15,30].

Surgical complications of TOF repair include RV diastolic restriction which while often transient may become chronic in nature. While this may be beneficial in concomitant Pulmonary Regurgitation (PR) there is retrograde blood flow into the Superior Vena Cava which is undesirable. Management of this acutely is through inotropic support and high dose diuretics [31]. Long term outcomes that patients should be aware of regarding TOF repair include progressive PR, RV failure (RHF), atrial/ventricular arrhythmias and sudden cardiac death. In particular PR/RHF incidence is high [32]. This regrettable complication is due to usually unavoidable damage made to the PV upon relieving the RVOT obstruction. However, an increasingly difficult thing to assess is the best time and indications for performing pulmonary valve replacement. This is because replaced valves do not grow with the patients meaning that repeat surgery is usually required as is the issue regarding the longevity of the valve itself which maximally is 10 years. PV replacement has been proven to reduce RV end-diastolic volume, improve LV systolic function, reduce arrhythmia risk and improve symptomology [33]. Recent recommendations suggest that the presence of symptoms is the most important factor in determining timing of PV replacement. In asymptomatic disease however PV replacement is indicated in patients with a decreased exercise tolerance, a RV End diastolic volume of ≥ 170 ml/m^2 and presence of moderate Tricuspid Regurgitation (TR) [34]. Other long term complications of repair include Exercise intolerance. This is often due to myocardial damage, the presence of residual defects and progressive valvular abnormalities. This decrease in exertion is due to abnormal RV haemodynamics and may be restricted to those individuals who did not undergo previous shunt palliation and whom had a high preoperative NYHA classification [35].

Long-term follow-up of repaired TOF patients has revealed that patients 0 years-20 years at the age of repair and who survived 1 year postoperatively have an excess mortality that persists for the next three decades of life [36]. This excess mortality is namely from ventricular arrhythmia and sudden cardiac death. In one multicenter cross sectional study 43.3% of studied patients had present or past arrhythmia of which atrial arrhythmias were predominant and was found to be associated with the number of cardiac surgeries (OR:1.4) and right atrial enlargement (OR 6.2) while Ventricular arrhythmias were associated with number of cardiac surgeries (OR 1.3) and LV diastolic dysfunction (OR 3.3) [37]. In addition, patients who suffer PR are at high risk of sudden death through ventricular tachycardia while those with TR are at risk of atrial tachyarrhythmia [38]. As such continued revision of surgical

technique in TOF must be made if we are to avoid the risk of myocardial fibrosis and valve damage which predispose to arrhythmias. In light of these numerous serious complications diligent follow up of all patients should be performed with at least yearly echocardiogram, MRI imaging, ECG and exercise tolerance testing.

Conclusion

The management of TOF has improved greatly from previous decades and patients may now expect a near normal life expectancy. This success however has been coupled with increasing observations of late complications including arrhythmia, PR and sudden cardiac death. While studies have revealed risk factors for the above complications improved understanding is required if we are to be able to provide the high provision of care required in this population.

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