Tetralogy of Fallot (TOF) in Children — Pathophysiology and Treatment

Tetralogy of Fallot is considered as the most common form of cyanotic congenital heart disease. The condition might be associated with other extracardiac abnormalities, such as cleft palate or facial anomalies. Echocardiography and magnetic resonance imaging studies are helpful in the assessment of the degree of the right ventricular outflow tract obstruction which is responsible for the symptoms of Tetralogy of Fallot including cyanosis. The only definitive treatment for Tetralogy of Fallot is a primary surgical correction.

Overview

Tetralogy of Fallot (TOF) is a very common congenital heart disease that is characterized by four things as the name suggests:

- Right ventricular outflow tract obstruction in the form of pulmonary stenosis that overworks the heart in a bid to pump enough blood.
- A ventricular septal defect.
- Aorta dextroposition and overrides the outlets of the heart leading to poor oxygenation of the blood.
- Right ventricular hypertrophy develops due to the high workload placed on the heart due to narrowing and the septal defect.
Epidemiology of Tetralogy of Fallot

TOF is considered as one of the most common types of congenital heart diseases with an estimated incidence of 3 to 6 for 10,000 live births. TOF is also considered as the most common cause of cyanotic congenital heart diseases.

TOF has been associated with an increased risk of cleft lip and palate, hypospadias and skeletal abnormalities. TOF has been described in familial and sporadic cases. The most likely genetic locus to be associated with TOF is 22q11.2. TOF is more common in boys and is believed to be more common in siblings of affected children. Most patients present to the clinic before 15 years of age.

The prognosis of TOF is dependent on the degree of the right ventricular outflow tract obstruction and on whether the patient is a possible candidate for surgical intervention or not. Ventricular arrhythmias and sudden cardiac death seem to be more common in this group of patients compared to the general population.

Left untreated, 90% of the patients are expected to die within the first twenty years of their life. The risk of stroke, subacute bacterial endocarditis, and pulmonary embolic disease is reported to be higher in untreated TOF. Patients with TOF and pulmonary atresia have the highest mortality rate.

Classification of Tetralogy of Fallot

There is no standard classification for Tetralogy of Fallot (TOF), but many experts use the following classification:

**Cyanotic TOF:** The infants with TOF, along with moderate to severe pulmonary obstruction, are cyanotic (bluish) at birth due to the right-to-left shunting of de-oxygenated blood across the ventricular septal defect (VSD) from the right ventricle to the body.

**A-cyanotic TOF:** The infants with TOF, along with mild pulmonary obstruction, are usually a-cyanotic because there is little or no right-to-left shunting of the blood at the ventricular level; however, these patients still undergo complete intracardiac repair.
**Pulmonary atresia/VSD**: It is also described as TOF with the pulmonary atresia and is different from other types both anatomically and physiologically. It is often associated with the malformation of the central pulmonary arteries.

**Absent pulmonary valve syndrome**: It is also described as TOF with an absent pulmonary valve. It is usually associated with tracheobronchial compression and malformation.

**Pathophysiology of Tetralogy of Fallot**

The exact etiology of TOF is unknown, but genetic predisposition has been described. Polymorphisms in the methylenetetrahydrofolate reductase gene and the VEGF gene have been linked to an increased risk of TOF from two recent studies.

The most commonly identified risk factors for TOF include maternal rubella, alcohol use during pregnancy, maternal history of phenylketonuria and maternal diabetes. Additionally, women who are older than 40 years of age are more likely to give birth to children with TOF than younger women.

Deletions on the chromosome band 22q11 have been linked to an increased risk of TOF, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcemia.

The symptomatology of TOF is dependent on the degree of the right ventricular outflow tract obstruction and on the balance between the right and left ventricular pressures. When the right ventricular pressure is significantly higher, as is seen in severe right ventricular outflow tract obstruction, right-to-left shunting might occur. When this happens, adequate oxygenation of the blood becomes dependent on the presence of a patent ductus arteriosus.

**By definition, the tetralogy of Fallot (TOF) involves four main heart malformations which present together:**

<table>
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<tr>
<th>Condition</th>
<th>Description</th>
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<tr>
<td><strong>Pulmonary Infundibular Stenosis</strong></td>
<td>It is due to the narrowing of the right ventricular outflow tract. It can occur at just below the pulmonary valve (infundibular stenosis) or at the pulmonary valve (valvular stenosis). The most common cause of the infundibular pulmonic stenosis is the overgrowth of the heart muscle wall. The degree of the stenosis is the primary determinant of the symptoms and severity.</td>
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<tr>
<td><strong>Overriding Aorta</strong></td>
<td>It is an aortic valve with a biventricular connection, i.e., it is situated above the ventricular septal defect and connected to the right and left ventricle at the same time. The degree of &quot;override&quot; is defined by the degree to which the aorta is attached to the right ventricle. The aortic root is always abnormally located to the right of the root of the pulmonary artery.</td>
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**Ventricular Septal Defect (VSD)**

It is a hole between the two bottom chambers of the heart, i.e., ventricles. The defect is usually centered on the most superior aspect of the ventricular septum, i.e., the outlet septum, and, in most of the cases, is single and large. Sometimes, the thickening of the septum, i.e., septal hypertrophy can narrow the margins of the defect.

**Right Ventricular Hypertrophy**

The right ventricle becomes more muscular than the normal, causing a characteristic boot-shaped appearance as seen by the chest X-ray. The mis-arrangement of the external ventricular septum is the main reason for the increase in the size of the right ventricular wall to deal with the increased obstruction to the right outflow tract.

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**Clinical Presentation of Tetralogy of Fallot**

The most common presentation of TOF includes a failure to thrive and difficulty feeding. Patients with TOF complicated by pulmonary atresia usually become more cyanotic 48 hours after birth, when the ductus arteriosus starts closing. Parents are likely to tell that there is something wrong with their child as a result of the feeding habit.

Tet spells are defined as the development of episodes of cyanosis. They usually happen when the child is crying or feeding. Sudden death might be due to hypoxic test spells which happen due to a sudden spasm of the infundibular septum which increases the right ventricular outflow tract obstruction.

Patients with TOF usually learn that squatting improves their symptoms and this can be an important sign on physical examination. Older children with TOF usually have exertional dyspnea.

Central cyanosis is usually evident since birth in patients with TOF. Digital clubbing can be seen at the age of 3 to 6 months.

Auscultation of the heart might reveal a systolic ejection murmur over the pulmonic area due to right ventricular outflow tract obstruction. Patients with severe right ventricular outflow tract obstruction are usually more cyanotic and have a softer systolic ejection murmur.

Due to right ventricular hypertrophy, a right ventricle impulse might be felt on chest palpation. Patients with TOF are at an increased risk of infective endocarditis.

The symptoms of Tetralogy of Fallot (TOF) vary, depending on the extent of obstruction of the blood flow out of the right ventricle and into the lungs. Signs and symptoms may include:

**Symptoms**

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<tr>
<td><strong>Tet spells</strong></td>
<td>These are the episodes of bluish pale skin during crying or feeding. The babies who have unrepaired Tetralogy of Fallot (TOF) sometimes have “tet spells”. A tet spell occurs when the level of oxygen in the blood drops suddenly. This causes the baby to become very blue due to de-oxygenation.</td>
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<tr>
<td><strong>Failure to thrive</strong></td>
<td>It is also termed as weight-faltering in pediatrics. During this symptom, the baby indicates insufficient weight gain or inappropriate weight loss.</td>
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<tr>
<td><strong>Exertional dyspnea</strong></td>
<td>Babies feel dyspnea upon exertion or hard physical activity like exercise. The main underlying reason is the decreased oxygen saturation of the blood. This condition worsens with age.</td>
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Parents should seek medical attention once they notice some of these symptoms on their children:

- Unusual irritability
- Syncope or seizures
- General body weakness
- Bluish discoloration
- Difficulty breathing

**Signs**

**Physical Examination**

The following signs will be seen on physical examination:

1. Cyanosis is the important sign of Tetralogy of Fallot (TOF). Cyanosis is actually a bluish tint to the skin, fingernails, and lips. A low oxygen level in the blood is the main cause of cyanosis
2. A systolic thrill is present on the anterior side along the left sternal border. A harsh type of systolic ejection murmur (SEM) can be heard over the pulmonic area and the left sternal border. However, an acyanotic patient with the Tetralogy of Fallot (pink tet, not blue) will have a loud, long, systolic murmur with a thrill along the RVOT (right ventricular outflow tract)
3. RV (right ventricular) predominance on palpation
4. Bulging of the left hemithorax
5. Scoliosis
6. Aortic ejection click
7. Retinal engorgement
8. Squatting position as a compensatory mechanism
9. Hemoptysis

**Diagnostic Workup for Tetralogy of Fallot**

Patients with TOF usually have polycythemia due to cyanosis. Peripheral oxygen saturation is usually between 65 and 70%. Low platelets and increased bleeding time are also commonly seen in cyanotic patients with TOF.

A chest X-ray might reveal diminished pulmonary vascular markings, especially in older children. A boot-shaped heart is a specific sign of TOF and can be seen on chest X-rays.

Imaging studies are essential for the diagnosis of TOF and usually reveal a large ventricular septal defect, an aorta that is overriding over the ventricular septum, and right ventricular outflow tract obstruction. The degree of right ventricular outflow tract obstruction.
obstruction should be assessed because it can predict the prognosis.

Magnetic resonance imaging is superior to echocardiography in the assessment of the aorta, the degree of the right ventricular outflow tract obstruction, the size of the ventricular septal defects, right ventricular hypertrophy and the status of the pulmonary artery. The test, however, requires sedation in young children and is usually not suitable for sick infants.

Patients with marked right ventricular hypertrophy might have right axis deviation on an electrocardiogram.

The assessment of the pulmonary arteries, the degree of right ventricular outflow tract obstruction, the position and size of the ventricular septal defect and the presence or absence of other coronary artery abnormalities can be done by cardiac catheterization.

**Differential Diagnosis of Tetralogy of Fallot**

The successful diagnosis of Tetralogy of Fallot (TOF) depends on the history of the patient, presentation of the symptoms by the patients and vigilant detection of signs by the clinician. Further confirmation can be done with the help of lab and imaging investigations. For the accurate diagnosis of patients with Tetralogy of Fallot, the main symptoms and signs should be considered, which have been mentioned above.

The other clinical conditions which can confuse the diagnosis of coarctation of the aorta due to a similar presentation have been named below:

<table>
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<th>Differential Diagnosis</th>
<th>Signs and symptoms</th>
<th>Severe cases</th>
<th>Physical examination</th>
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<tr>
<td>Bronchiolitis</td>
<td>Young infants may become fussy and experience difficulty feeding, have increasing coryza and congestion, low-grade fever and apnea.</td>
<td>Respiratory distress with retractions, tachypnea, nasal flaring, possibly cyanosis and irritability.</td>
<td>Tachycardia, retractions, tachypnea, fever (38-39°C), fine rales with diffuse and fine wheezing, otitis media and hypoxia.</td>
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<tr>
<td>Bronchiolitis (Pediatric Acute Respiratory Distress Syndrome)</td>
<td>Tachypnea, respiratory distress, agitation, and hypoxemia. Crackles may be audible throughout the lung fields which signify pulmonary edema, Comcomitant fever, reduction in lung compliance along with functional residual capacity, reduced lung function, muscle wasting and weakness and broncho reactivity.</td>
<td>Tachycardia, retractions, tachypnea, fever (38-39°C), fine rales with diffuse and fine wheezing, otitis media and hypoxia.</td>
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<td>Pneumothorax</td>
<td>Diaphoresis and cyanosis, Respiratory findings: Tachypnea, respiratory distress, distant or absent breath sounds, asymmetric lung expansion, hyper-resonance on percussion, and adventitious lung sounds. Cardiovascular findings: Jugular venous distention, hypotension, tachycardia, pulsus paradoxus.</td>
<td>Tachypnea, respiratory distress, distant or absent breath sounds, asymmetric lung expansion, hyper-resonance on percussion, and adventitious lung sounds.</td>
<td>Tachycardia, retractions, tachypnea, fever (38-39°C), fine rales with diffuse and fine wheezing, otitis media and hypoxia.</td>
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<td>Pulmonic Valvular Stenosis</td>
<td>Cyanosis, history of a heart murmur since birth, fatigue, dyspnea, mental retardation/developmental disorders, dizziness or syncope, chest pain. Physical examination: The 1st heart sound is normally followed by a systolic ejection click; the murmur of pulmonic stenosis is of the systolic ejection type and can be best heard at the 2nd left intercostal space. The 2nd heart sound is split. Elevated central venous pressure, pulsatile liver, hepatosplenomegaly and hepatojugular reflux.</td>
<td>Tachycardia, retractions, tachypnea, fever (38-39°C), fine rales with diffuse and fine wheezing, otitis media and hypoxia.</td>
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Pediatric Apnea

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<th>Signs on Physical examination:</th>
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<td>Head examination: Micrognathia, abnormal facial appearance, frontal bossing, low set ears, bulging fontanel suggesting raised intracranial pressure, rhinorrhea</td>
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<td>Neck examination: Nuchal rigidity is a sign of meningitis; listen to the neck for stridor which can suggest laryngotracheomalacia</td>
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<tr>
<td>Chest examination: Listen for abnormal breath sounds, chest wall deformities, exaggerated periodic breathing pattern, wheezing with stridor</td>
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<td>Abdominal examination: Hepatomegaly or splenomegaly, Hyperactive bowel signs</td>
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<td>Musculoskeletal: Rickets</td>
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<td>Neurologic examination: Seizure activity, abnormal eye movements, muscle rigidity</td>
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<td>Skin: Pallor represents poor perfusion or anemia; cyanosis represents poor perfusion or hypoxia.</td>
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Risk factors for Tetralogy of Fallot

The main cause of TOF is not known; however, there are some risk factors that can result to contraction of the disease. They comprise of:

1. A mother who uses alcohol
2. A mother who is over the age of 40
3. A woman who gets rubella during pregnancy
4. A mother who has diabetes

Treatment of Tetralogy of Fallot

Cyanotic infants should be treated as soon as possible with oxygen supplementation by an open-end cannula or a tube. Stress in infants is associated with the worsening of the cyanosis and hypoxemia; therefore, the placement of intravenous lines should be done by experienced individuals.

Once at the emergency department, the cyanotic infant should be placed on the mother’s shoulder with the knees tucked up. At this stage, the administration of morphine sulfate intramuscularly is indicated to decrease systemic venous return and suppress the respiratory drive. Patients with acidosis and hyper cyanosis should be treated with sodium bicarbonate.

Once the patient is stabilized, further medical therapy is indicated. Asymptomatic infants usually require no medical therapy. The administration of intravenous propranolol has been described to alleviate the symptoms of severe cyanosis. Propranolol mechanism of action in this scenario is the relaxation of the infundibular muscle spasm that is responsible for the acute increase in the right ventricular outflow tract obstruction. The administration of intravenous prostaglandin E is indicated in patients with TOF and pulmonary atresia to maintain the patency of the ductus arteriosus. These medical therapies are only a bridge to definitive surgical repair.

It is highly recommended that the patients undergo a complete surgical repair procedure before their second birthday. Surgical intervention before the age of 12 months has been associated with the best outcome and should be considered whenever possible.

Early primary repair of TOF eliminates right ventricular outflow tract obstruction, which prevents right ventricular hypertrophy and cyanotic spells. Patients who have a very low birth weight, small and abnormal pulmonary arteries, multiple ventricular septal defects and other intracardiac malformations should not be provided with a primary repair.

The ideal operation for the treatment of TOF includes the primary closure of the
ventricular septal effect, the resection of the stenosed area of the infundibular muscle, and the relieve of the right ventricular outflow tract obstruction. Patients should be under cardiopulmonary bypass during the procedure.

Patients who are not possible candidates for the primary repair of TOF should undergo palliative surgery to relieve cyanosis and improve the quality of life. The placement of a shunt between the subclavian artery and the pulmonary artery is successful in the relief of cyanosis and usually remains patent for years.

Surgical Treatment

The timing of the complete surgical repair depends on numerous variables, including the symptoms and associated lesions. The current trend is to perform the complete surgical procedure before 1 year of age, and preferably by the age of 2 years.

Infants with cyanosis are stabilized by the administration of prostaglandins. The use of prostaglandins decreases the need to perform surgery urgently. The procedure of a primary repair avoids the prolonged right ventricular outflow obstruction and the resultant right ventricular hypertrophy (RVH), postnatal angiogenesis and prolonged cyanosis.

The following factors increase the risk for early repair of tetralogy of Fallot (TOF):

- Pulmonary artery atresia
- Low birth weight
- Major associated anomalies
- High peak RV-to-left ventricular pressure ratio
- Severe annular hypoplasia

Complications of Tetralogy of Fallot

Additional surgery

Some young adults or teenagers need additional surgery; for instance, the pulmonary valve can narrow again with the passage of time, reducing the blood flow. The surgeon may need to replace or widen the valve.

Leaking heart valves

The most frequent problem observed after Tetralogy of Fallot repair is the pulmonary backflow or leaking from the pulmonary valve. The backflow from the aortic valve and tricuspid valve can also occur.

Arrhythmias

The arrhythmias associated with Tetralogy of Fallot include ventricular tachycardia, atrial flutter, and atrial fibrillation.

Pulmonary artery branch stenosis

The pulmonary valve can narrow again over time. This will reduce the blood flow to the lungs, making the heart to work hard. Several surgical techniques are used to fix this
Residual ventricular septal defects

Some VSDs can still leak, even after they’ve been successfully repaired. VSDs need to be repaired again if they’re large or are causing problems with the proper functioning of the right ventricle.

References


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