Cyanotic Heart Disease: An Overview of Tetralogy of Fallot

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ABSTRACT

Tetralogy of Fallot (TOF) is the most common cyanotic heart disease with anomalies consist of: ventricular septal defect (VSD), overriding aorta, pulmonary stenosis and hypertrophic of the right ventricular. It also has various anomalies type such as TOF with absent pulmonary valve, TOF with pulmonary atresia, TOF with atrioventricular septal defect, TOF with coronary artery anomalies, etc which will be discussed in detail. Proper diagnosis is required when dealing with the TOF continue with radiological examination. Adequate history taking and correct physical examination are necessary in dealing with congenital heart defects, especially TOF case. In this overview, we also discuss about the comprehensive management, from tet spell management, palliative management of TOF that required shunt with various technique, and surgical total corrective of TOF with many approach such as transannular accompany with right ventriculotomy or transatrial with transpulmonary or beating heart surgery technique to prevent reperfusion injury complication.

Keywords: Tetralogy of Fallot, Cyanotic heart disease, Anomaly anatomy

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1. INTRODUCTION

Tetralogy of Fallot is a complex congenital heart defect consisting of a **ventricular septal defect (VSD)**, **overriding aorta or aortic dextroposition**, **pulmonary stenosis/ infundibular/ valvular/ both**, and **right ventricular hypertrophy**(1) **(Figure 1).** Etienne Fallot first described this complex anomaly in 1888, which was found by Nils Stensen in 1671(2). TOF is the most common type of cyanotic congenital heart disease with approximately found in 4-5/100.000 live births and 7%-10% of all congenital heart disease (3). In Indonesia, there are no specific data that represent TOF. Still, data collected from Harapan Kita National Heart Center Indonesia showed that more than 40.000 babies are born with a congenital heart defect (8/1000 live births), 25% is cyanotic, and 75% is acyanotic.

If ASD accompanies the TOF, it is called as Pentalogy of Fallot. TOF is a congenital heart defect with an R->L shunt. The presence of a VSD and pulmonary stenosis alone is usually called Pink Fallot; wherein there is no R->L shunt (cyanotic). According to Kirklin, TOF must meet the requirements of 1) A large VSD with size as large as the aortic orifice or bigger; 2) High-grade pulmonary stenosis, until the right ventricular pressure is equal or greater than the left ventricle(4).

In the past, TOF patients could only reach 12 with mortality related to hypoxemia, brain abscess, endocarditis, and cerebral vascular accident. Cyanotic conditions in TOF required surgery, and this was done palliatively in 1945 by Alfred Blalock and Hellen B. Taussig, who later became known as Blalock-Taussig Shunt(5). Today, most TOF patients can undergo total correction in early infancy or early childhood with a success rate of 90% since discovering an extracorporeal circulation/heart-lung machine. Lillehei first performed total TOF correction in 1955 with controlled cross circulation(6).

2. ANATOMY

2.1 VENTRICULAR SEPTAL DEFECT

The septal defect in TOF can be caused by the anterior and cephalad malalignment of the outlet portion of the muscular ventricular septum. Another cause of this VSD is fibrous remnant cushions failing to muscularized during the embryonic phase. The VSD in TOF is usually single, malaligned, perimembranous with extension defect into subpulmonary region, and muscular VSD may be present(7). The location of the VSD on TOF is just below the aorta, more anterior or ventral than the normal VSD position. VSD has a variety of size. It is usually large/unrestrictive in TOF and allows bidirectional shunting. Both ventricular systolic pressures are equal, so the ventricle act as one functional chamber(1). Blood flow to the systemic and pulmonary circuits depends on the resistances. In most cases of TOF, right to left shunt across the VSD can be caused by pulmonary stenosis that more than the systemic vascular tone. Rotation of the aorta in TOF causes a connection between the anterior mitral valve and the left coronary valve of the aorta. The non-coronary aortic valve confronts the VSD and the right coronary aortic valve. The surgeon needs to know at the time of

VSD closure with a patch to avoid iatrogenic damage to the aortic valve(8,9).

2.2 DEXTROPOSITION OF THE AORTA/ OVERRIDING AORTA

In TOF, the aorta receives blood flow from both ventricles depending on right ventricle outflow tract obstruction (RVOTO). This also can be caused by the displacement of the aorta to the right and overrides the malaligned VSD. The difference from the double outlet right ventricle is that in TOF, the aorta arises predominantly from the left ventricle with only some origin from the right ventricle. In contrast, in DORV, the aorta arises predominantly from the right ventricle(10,11).

2.3 RIGHT VENTRICLE OUTFLOW TRACT OBSTRUCTION (RVOTO)

The key feature of TOF is the obstruction to pulmonary flow at the level of the right ventricle outflow tract (RVOTO). It can occur at multiple levels, such as infundibular, valvar, and/or supravalvar. Muscular band hypertrophy in the region of the subpulmonal from the anterior and cephalad deviation of the VSD can cause infundibular obstruction. The bicuspid pulmonary valve and hypoplastic annulus can cause valvar obstruction. In contrast, narrowing the main pulmonary artery, the stenotic proximal branch of pulmonary arteries, or hypoplastic branch pulmonary arteries can cause supravalvar obstruction. The degree of Presence of unrestrictive VSD with worsening RVOTO leads to RV pressure rise, causes a right to left shunt, reduces pulmonary blood flow, ends with the hypoxemia condition(12,13).

Measurement of pulmonary artery diameter in preparation for total TOF correction is an important parameter. One of the methods used is McGoon Ratio. **McGoon ratio** is calculated by measuring the sum of the diameter of the Right Pulmonary Artery (RPA) and Left Pulmonary Artery (LPA) divided by the diameter of descending aorta at the level above the diaphragm. An average value of 2 is normal, so there are no restrictive right and left pulmonary arteries. If the ratio is above 1.2, then it is acceptable postoperative right ventricle systolic pressure in the total correction of TOF. If the ratio is below 0.8, it is inadequate for the complete repair of TOF. Another method that can be used is Nakata Index. **Nakata Index** is calculated from the diameter of pulmonary arteries measured immediately proximal to the origin of upper lobe branches. The sum of the cross-sectional area of right and left pulmonary arteries are divided by the patient's body surface area. An average value of 330 mm^2/m^2 is normal. A Nakata index of >150 mm^2/m^2 is acceptable for the complete repair of TOF, whereas a Nakata index <150 mm^2/m^2 shows a narrow pulmonary artery(14,15).

$$\text{McGoon Ratio: } \frac{\text{D RPA + D LPA}}{\text{D Ao}}$$

$$\text{Nakata Index: } \frac{\text{CSA of RPA + CSA of LPA}}{\text{BSA (Body Surface Area)}}$$

2.4 RIGHT VENTRICLE HYPERTROPHY

Right ventricle hypertrophy usually appeared at the severe degree of TOF. It develops as a consequence of RVOTO.

As mentioned before, RVOTO raises the RV pressure to maintain pulmonary flow. Large RV cavity size is an important issue after TOF repair(7,16).

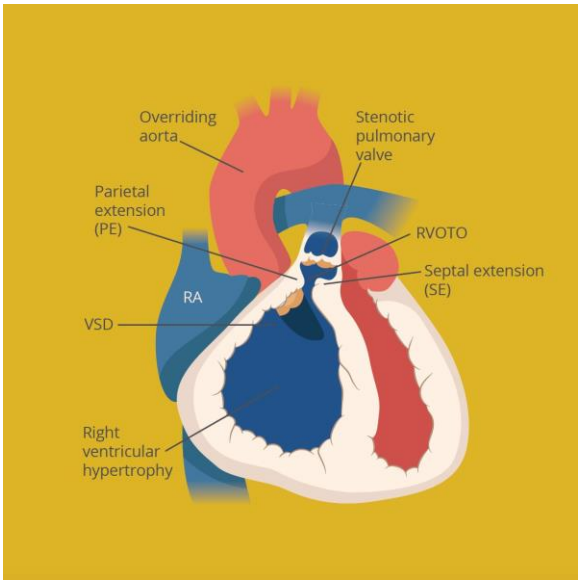


Figure 1. Tetralogy of Fallot Scheme Shows VSD, RVOTO, Overriding Aorta, RVH

3. DIAGNOSIS

Early TOF diagnosis can be made using prenatal ultrasound, and it is useful for postdelivery therapy in duct-dependent pulmonary blood flow cases. Still, the gold standard for TOF diagnosis and its anomaly is the postnatal echo. In physical examination, the presence of murmur and cyanotic signs are not specific to TOF. The presence of a murmur and its degree depend on the size of VSD. The cyanotic symptoms of TOF depend on the severity of the pulmonary stenosis. If the degree of pulmonary stenosis is mild, the symptoms may not be present until late childhood. If the stenosis is present, the cyanotic symptom may be present in early infancy. Usually, the cyanotic symptom will develop between 2 to 6 months(10,17).

One of the dangerous characteristic symptoms of TOF is tet spell or described as hypercyanotic spells, blue spells, tetralogy spells, hypoxic spells, etc. This condition can occur between 1-12 months, with high frequency in 2-3 months old. It is usually induced by crying, feeding, defecation, and it usually happens in the morning. It causes convulsion or even death. The spell incident can be caused by increased catecholamines, which stimulate hyperapnea. Parents can do things at home with children suffering spells by putting their children in the knee-to-chest position to increase systemic vascular resistance and systemic venous return to the right heart, leading to an increase of intracardiac left to right shunting increase right ventricle preload. In-hospital treatment, intravenous fluid is needed to increase right ventricle preload followed by oxygen administration to decrease pulmonary vasoconstriction. If this therapy doesn't work, intubation is needed(8,18–21).

X-ray examination shows a "boot-shaped" appearance due to right ventricle hypertrophy, and right axis deviation can be seen on ECG. Postnatal echo is useful for TOF diagnosis, determining the VSD location, and assessing RVOTO. The severity of RVOTO can be assessed by measuring the anatomic appearance and estimation of pressure gradient using Doppler. The associate anomaly of TOF, such as atrial septal defect (ASD), can be seen in this examination(22,23).

In this modern era, non-invasive imaging such as CT angiography or MRI for TOF diagnosis is more popular than cardiac catheterization due to complications such as initiating hypercyanotic spells. Cardiac catheterization is indicated only for patients with coronary artery anomalies or the presence of MAPCAs with pulmonary atresia. Catheterization can be used for diagnostic tools and therapeutic modalities such as balloon pulmonary valvuloplasty and occasionally RVOT stenting(24,25).

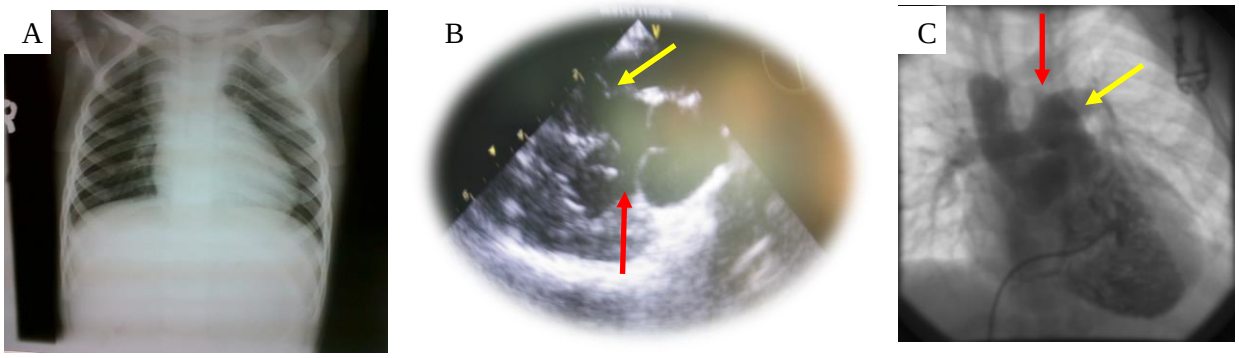


Figure 2. Radiological Examination for TOF (A) X-ray shows "boot shaped" appearance, (B) Echocardiography shows dextroposition of the aorta (yellow arrow) and VSD (red arrow) (C) Angiography shows infundibular stenosis (yellow arrow) and pulmonary artery (red arrow) (Source: Tahalele's Documentation)(26)

4. MANAGEMENT

4.1 SURGICAL CORRECTIVE

Median sternotomy cardiopulmonary bypass (CPB) with normothermia or moderate hypothermia is done during corrective surgical repair of TOF. The pericardium is opened like A ɔ letter "L," followed by installing extracorporeal circulation and aortic clamps, administration of cardioplegia and placement of a left atrial vent. Blalock – Taussig Shunt is usually ligated and divided during the cooling phase. The basic principles of TOF total correction are(12,20):

a) **VSD closure (Figure 3B)**
b) **Elimination of pulmonary infundibulum stenosis or pulmonary valvular stenosis (Figure 3A)**
c) **Widen RVOT (Figure 3C)**

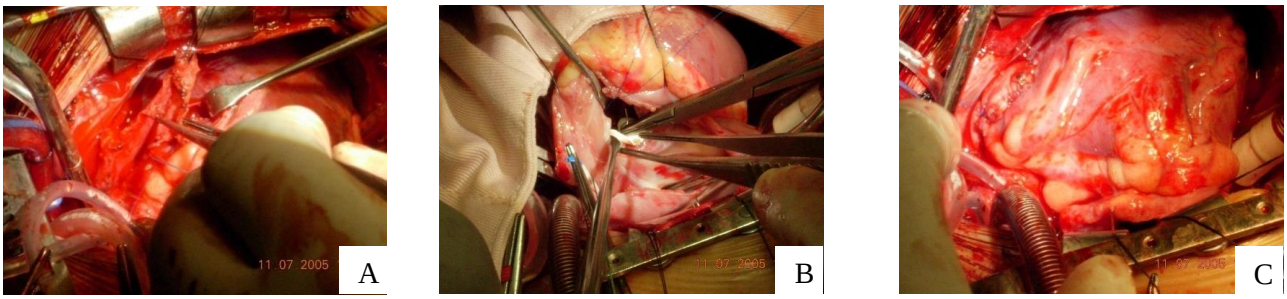


Figure 3. Surgical Picture of TOF (A) Infundibular resection (B) VSD Closure (C) Transannular patch (RVOT Widening) (Source: Tahalele's documentation)

Total correction can be done through the transannular + right ventriculotomy approach or transarterial + transpulmonary approach(3,10).

a) Transannular + right ventriculotomy approach **(Figure 4A)**

In the transannular + right ventriculotomy approach, an incision

was made in the pulmonary artery in the RVOT area above the pulmonary annulus, followed by an arteriotomy to cut the annulus. Identification of the VSD is made by observing the thickened supraventricular crest. Infundibulum resection was performed, followed by measurement of the RVOT diameter according to the McGoon ratio. The VSD using a patch (pericardial or synthetic patch material) is performed, followed by the closure of the pulmonary arteriotomy using a pericardial patch. Avoid bundle of his during VSD closure(12).

b) Transatrial + transpulmonary approach This technique is performed with an incision in the right atrium (as in normal VSD closure) followed by identifying the TOF's VSD. The infundibulum is identified to the pulmonary direction through the tricuspid valve. If necessary, a ventriculotomy is performed. Circular resection of the infundibulum followed by measurement of the RVOT. VSD closure was done through the right atrium, followed by the closure of pulmonary arteriotomy. A transarterial-transpulmonary approach implies a minimal or no ventriculotomy, and therefore it is expected to improve the right ventricular performance in the long term(12) **(Figure 4B)**.

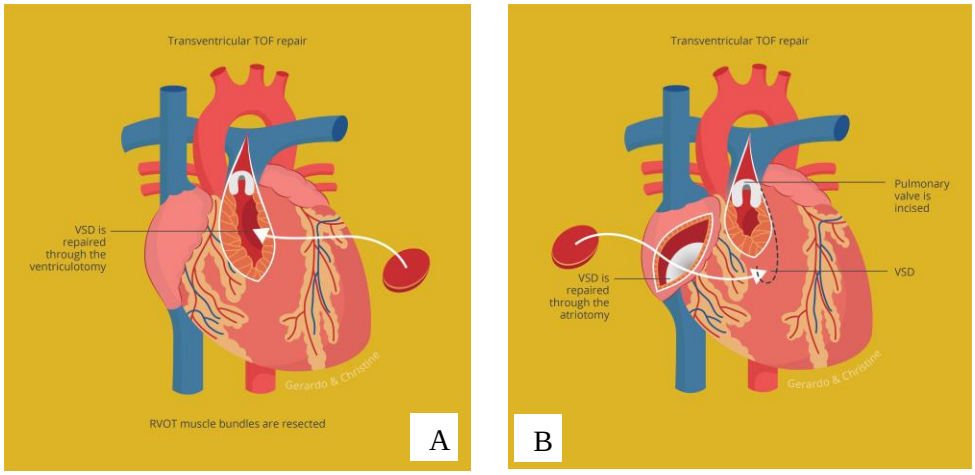


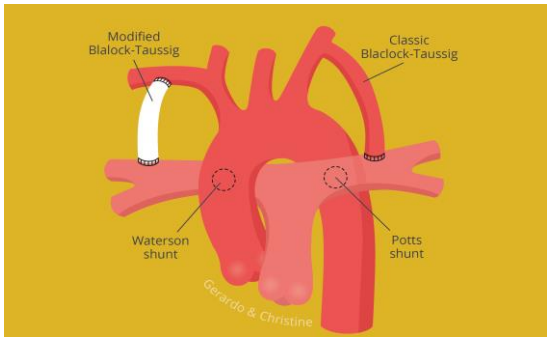
Figure 4. Surgery Approach in Total Correction of TOF (A) Transannular + right ventriculectomy (B) Transatrial + transpulmonary (Source: Adapted from F1000 research with modification)

4.2 SURGICAL PALLIATIVE

Surgical palliative therapy in TOF gives arterial blood flow to pulmonary circulation. Surgical palliative's purpose is to provide pulmonary blood flow adequately, pulmonary artery system growth and patient growth. Many surgical techniques can be used, such as(8,24,27) **(Figure 5)** :

a) Blalock-Taussig Anastomosis (BT Shunt) by connecting one of the subclavian arterie/;s with the ipsilateral branch of the pulmonary artery. The anastomosis can be done either by directly cutting the subclavian artery (classic BT Shunt) or using a prosthesis (usually Gortex) to connect the subclavian artery and pulmonary artery (modified BT Shunt).

b) Pott's anastomosis by the connecting descending aorta and the pulmonary artery's left branch(28).
c) Waterson Anastomosis by connecting ascending aorta with right pulmonary artery intra pericardial(29).



The complication of surgical palliative is the risk of recurrent laryngeal and phrenic nerve injury, shunt thrombosis, imbalance in shunt flow, inadequate or excessive, leading to cyanosis and heart failure.

Figure 5. Surgical Palliative Scheme in TOF consist of :
A) Classic Blalock-Taussig;
B) Modified Blalock-Taussig
C) Waterson Shunt
D) Potts Shunt

4.3 BEATING HEART SURGERY IN TOF

Aortic cross clamps, cardioplegia and reperfusion injury, can cause Myocardial Infarction. To reduce this complication, surgeons in some centers, including RSUD Dr. Soetomo Surabaya, use beating heart surgery to reduce the heart's workload. The main requirement to use this technique is a competent aortic valve. A recent report by Tahalele *et al*. in the total correction of TOF with beating heart technique showed a good result with no residual pulmonary stenosis and minimal (2 mm) residual VSD(26).

5. VARIANTS OF TOF ANATOMY ANOMALY

5.1 TOF WITH ABSENCE OF PULMONARY VALVE

The absent pulmonary valve in TOF is characterized by pulmonary valve dysgenesis, stenosis of the pulmonary valve and the annular that leads to pulmonary insufficiency **(Figure 6)**Tracheobronchial tree compression occurs caused by aneurismal dilatation of the main and branches of pulmonary arteries. Airway compression and trachea-bronchomalacia are common to this variant. Patients usually present in the early neonatal period with respiratory distress symptoms. Prone position to move the pulmonary arteries from tracheobronchial trees, chest physiotherapy, ventilator with intubation and PEEP are needed before early surgical repair. Administration of nitric oxide (NO) as a pulmonary vasodilator is useful to reduce pulmonary artery pressure. If the patient is stabilized, total repair of TOF can be done alongside repair of aneurysm dilated pulmonary artery(21).

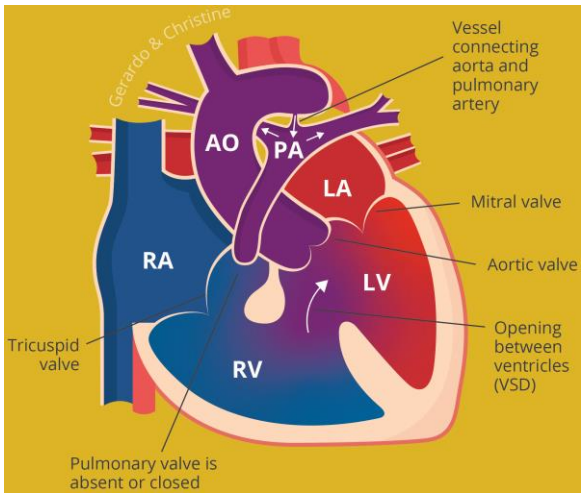


Figure 6. TOF with Absence or Closed of Pulmonary Valve Scheme

5.2 TOF WITH PULMONARY ATRESIA

TOF with pulmonary atresia (TOF-PA), also called PA with VSD. This type is an extreme form of TOF with no antegrade flow to the pulmonary artery. The presence of ductus arteriosus can feed the confluent branch of pulmonary arteries. In contrast, in the severe form where the ductus is absent, the source of pulmonary blood flow comes from major aortopulmonary collateral arteries (MAPCAs) (30,31) **(Figure 7)**.

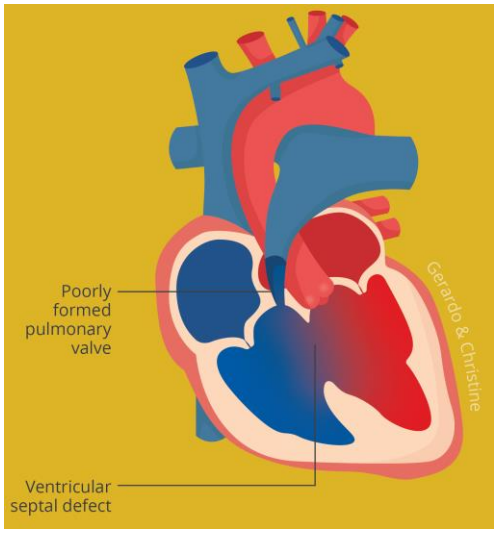


Figure 7. TOF with Pulmonary Atresia Scheme

5.3 TOF WITH MULTIPLE-MULTIFOCAL-AORTO-PULMONARY COLLATERAL ARTERIES (MAPCAs)

MAPCAs are the presence of additional vascular hyperplasia due to pulmonary stenosis or pulmonary atresia. MAPCAs cause anastomoses between the aorta and pulmonary artery branches at hilar, extrapulmonary, intrapulmonary and intraaciner levels **(Figure 8)**. These collateral vessels connect the systemic and pulmonary arterial circulations directly from the aorta or the branches from both above and below the diaphragm level. TOF with MAPCAs are diseases with complex and heterogeneous characteristics with varying severity. Maps are present in 20-25% of patients with TOF. Pulmonary blood supplies are determined alongside central pulmonary atresia and the nature of MAPCA supply by angiography or computed tomography(32).

The main goal of management TOF with MAPCAs is to return biventricular circulation with minimum surgical and catheter intervention procedures. PGE1 infusion can be used to open the ductus in a patient with low O2 saturation, or an aortopulmonary shunt may be needed. Inpatient with adequate O2 saturation between 70%-90%, no immediate intervention is necessary(20,30,33).

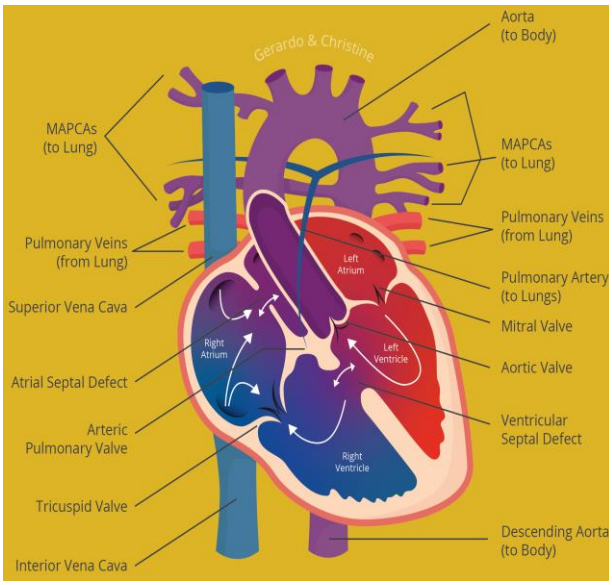


Figure 8. TOF with MAPCAs Scheme

5.4 TOF WITH ATRIOVENTRICULAR SEPTAL DEFECT (AVSD) / ATRIOVENTRICULAR CANAL DEFECT (AVCD)

TOF with complete AVSD (**Figure 9)** is usually seen in patients with down syndrome, this type of TOF is an uncommon variant. An abnormal tricuspid valve with regurgitation is usually found in this type of TOF. Surgical planning must be considered carefully when treating this combination. Uncareful surgical planning can result in pulmonary valve insufficiency or residual stenosis. Worsen tricuspid valve regurgitation can be caused by volume overload and RV hypertension, leading to PA pressure elevation and worsening pulmonary valve insufficiency, especially in those following transannular patch reconstruction(8,34,35).

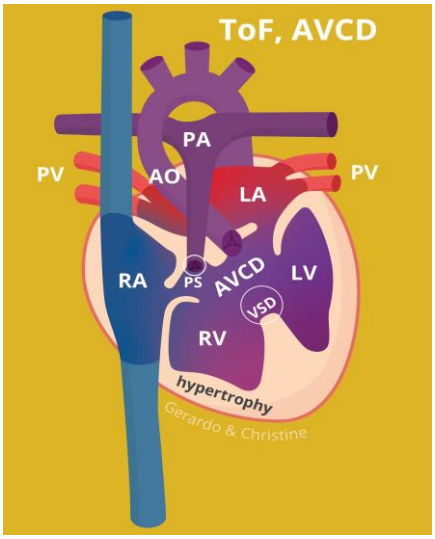


Figure 9. TOF with AVCD Scheme

5.5 TOF WITH CORONARY ARTERY ANOMALIES

Coronary artery anomalies were found in 2%-12% of patients with tetralogy of Fallot, according to Gonzalez and Sivalingam. A challenging adequate relief of RVOTO found in coronary artery anomalies which cross infundibular areas. The most common form of a coronary anomaly in TOF patients is a single left anterior descending artery (LAD) originating from RCA, followed by the first branch of the right coronary artery (RCA) (Conus branch) crossing the RVOT, RCA originates from LAD and paired anterior descending artery **(Figure 10)**. In the past, coronary artery anomalies in TOF patients push the surgeon to delay the total corrective surgery and perform palliative therapy by making systemic pulmonary shunts. But now, many surgeons choose to do the definitive repair by implantation of a right ventricle to pulmonary artery conduit (RV-PA Conduit) **(Figure 11A)**. Another method used by Bizarre *et al*. in his 36 TOF patients showed a good result by using the transarterial - transpulmonary approach with minimal transannular patch and

sufficient infundibulotomy to release the RVOTO **(Figure 11C)**. In 1976, a technique by Bonchek was used to mobilize the coronary artery anomalies and placement of a transannular patch underneath it **(Figure 11B)**. This technique was also used by Banjout *et al.* in 2020 in his 14 patients with good results. The newest technique used by Shivaprakasha is called as double barrel technique(11,36,37).

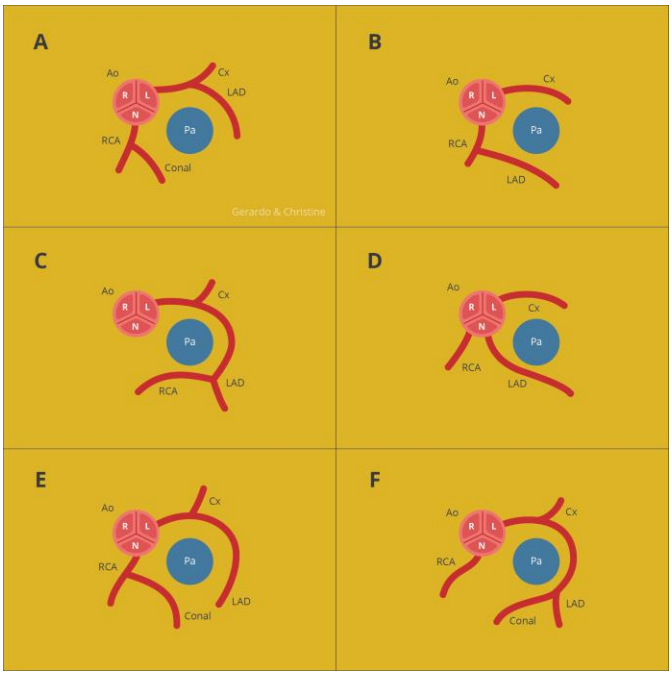


Figure 10. Coronary Artery Anomalies in TOF Scheme
(A) Normal Coronary Artery Anatomy, (B) LAD from RCA, (C) RCA from LAD, (D) LAD from right coronary sinus, (E) Large conal branch from RCA, (F) Large conal branch from LAD. LAD: Left Anterior Descending, RCA: Right Coronary Artery, Cx: Circumflex Artery, PA: Pulmonary Artery, Ao: Aorta

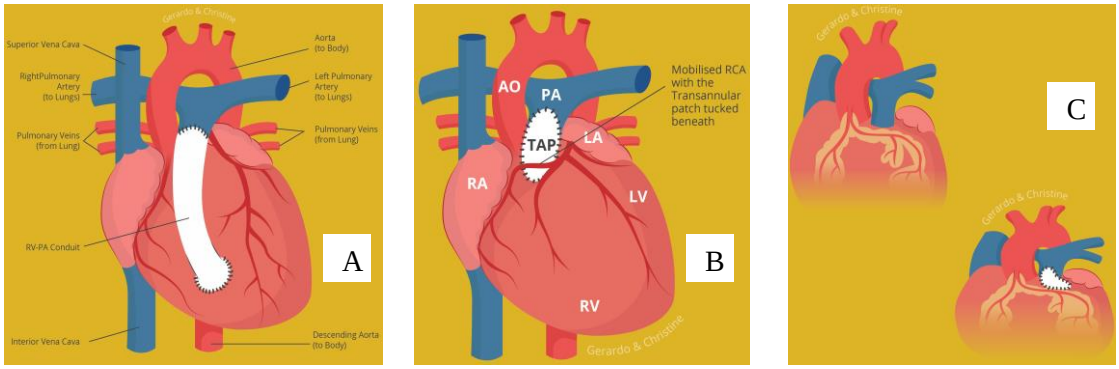


Figure 11. Surgical Repair Scheme of Coronary Artery Anomalies in TOF
(A) RV-PA Conduit, (B) Mobilize the coronary artery anomalies and placement of a transannular patch (C) Minimal transannular patch technique

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