FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2009/2010

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Tetralogy of Fallot: from fetus to adult

Abril, 2010

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UNIVERSIDADE DO PORTO

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Mestrado Integrado em Medicina

Área: Cardiologia Pediátrica

Trabalho efectuado sob a Orientação de:

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Abril, 2010

De acordo com as normas de submissão da revista: *International Journal of Cardiology*

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR
PROJECTO DE OPÇÃO
DISSERTAÇÃO/MONOGRAFIA/RELATÓRIO DE ESTÁGIO

Projecto de Opção do 6º ano - DECLARAÇÃO DE REPRODUÇÃO

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Título da Dissertação/Monografia/Relatório de Estágio: Tetralogy of Fallot: from fetus to adult

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Ano de conclusão: 6º ano

Designação da área do projecto de opção: Cardiologia Pediátrica

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Tetralogy of Fallot: from fetus to adult

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Abstract

Tetralogy of Fallot (TOF) is a congenital heart disease that consists of four anatomical abnormalities: ventricular septal defect, overriding of the aorta, right ventricular outflow obstruction and right ventricular hypertrophy.

Its prevalence ranges from 2,8 to 3,9 per 10.000 live births and accounts for 3,5% to 10% of all congenital heart diseases. In circa 40% of the patients, TOF appears associated with other congenital cardiac abnormalities.

The etiology is multifactorial and includes both environmental and genetic factors.

Clinical presentation depends upon the degree of pulmonary stenosis. The most usual modes of presentation in the first months of life are an asymptomatic murmur, cyanosis, hypercyanotic spells, and decreased exercise tolerance.

Several diagnostic tests can be used, although echocardiogram usually establishes the definitive diagnosis and normally provides sufficient information for treatment planning.

The goal of management of TOF patients is to allow total surgical correction with minimal mortality and morbidity. Before the advent of surgical intervention, about 50% of patients with TOF died in the first three years of life. Nowadays, almost all those born with this disease can expect to survive surgical correction and reach adult life. This brought up attention on long-term follow up because many patients with repaired TOF are now middle-aged. These adults now face chronic issues such as pulmonary regurgitation with consequent right ventricle dilation, systolic dysfunction, exercise intolerance and cardiac arrhythmias. Recognition of these problems is being used as feed back to improve a multidisciplinary care from the fetus to the elderly of those affected by TOF.

Objective:

The aim of this work is to make an overview of the Tetralogy of Fallot pathology, from fetal life to adulthood, emphasizing the adverse outcomes, their monitoring and management.

1. Introduction/ Historical aspects

Tetralogy of Fallot (TOF) is the most common form of cyanotic Congenital Heart Disease (CHD).

In 1671 Niels Stenson described TOF for the first time. However, only in 1784 its precise anatomical description was illustrated by William Hunter. The description of this pathology was refined several years later, in 1888, by Etienne-Louis Fallot in "*L'anatomie pathologique de la maladie bleu*". Even so, the term tetralogy of Fallot is attributed to Canadian Maude Abbott in 1924. This term is due to a tetrad of anatomic lesions being them: ventricular septal defect; overriding of the aorta; right ventricular outflow obstruction; right ventricular hypertrophy. [1]

We now regard TOF as a family of diseases. These are all characterized by a similar intracardiac anatomy, but highly variable in terms of pulmonary artery anatomy, associated abnormalities and outcomes.

The clinical spectrum is also diverse. Symptoms can range from no cyanosis, in the setting of modest pulmonic stenosis, to profound cyanosis resulting from severe pulmonic stenosis, pulmonary artery hypoplasia and resultant right-to-left ventricular shunting.

Before 1944, there was no treatment for children with TOF beyond supplemental oxygen and supportive care. Palliative treatment, in the form of a surgically created systemic-to-pulmonary arterial shunt, became available through the work of Helen Taussig, Alfred Blalock and Vivian Thomas. The first surgical shunt procedure was performed in November 1944. [2] ''Complete'' repair became available in the 1950s after the advent of controlled cross circulation, an early form of cardiopulmonary bypass. [3]

2. Epidemiology

The CHD occurs in about 1% of live births. A number of studies indicate that the prevalence of TOF ranges from 2.8 to 3.9 per 10.000 live births with males and females being affected equally. Between 3,5% and 10% of the patients with CHD have TOF. The CHD in general and TOF in particular appear to be equally prevalent in populations of different race or ethnic background. [4-9]

Without surgical treatment, the estimated 1 year survival rate is 66% and the estimated 30 year survival rate is 6%. With surgical treatment over 85% of children survive to adulthood. [10] The patients who survive into adulthood without surgical treatment require unique management based on their individual anatomy and physiology.

3. Embryology/Anatomy

The aorta and pulmonary artery form from septation of the distal bulbus cordis and truncus arteriosus and rotate to overlie the ventricles. An antero-cephalad deviation of the outlet septum with incomplete transfer of the aorta to a position above the left ventricle results in a malalignment ventricular septal defect (VSD) and an aorta that ‘‘overrides’’ the interventricular septum. This VSD is always large and non-restrictive and is located in the membranous septum in the subaortic region. Right ventricular (RV) outflow obstruction is variable in severity and nature of obstruction. It may be mild resulting in initial left-to-right shunt at ventricular level or severe causing severe cyanosis even in the neonatal period. The obstruction may be infundibular,

valvar or supravalvar in nature or may involve branch pulmonary arteries. The stenotic component may be at a single site or may involve multiple sites. Infundibular obstruction is the most common obstruction in TOF. The valvar stenosis may be due to valve leaflet fusion and/or due to valve ring hypoplasia. The RV hypertrophies as a result of the outflow tract obstruction. Thus, the characteristic four features of TOF are an overriding aorta, RV outflow tract obstruction, malalignment VSD, and RV hypertrophy (Figure 1). [1, 4-5, 8]

The anatomy of TOF explains much of the pathophysiology seen. The RV outflow tract obstruction together with the non-restrictive VSD results in equal pressures in the right and left ventricles and, typically, a right-to-left through the VSD. [1] The desaturated blood passing into the aorta results in central cyanosis. The cyanosis and hypoxemia stimulate bone marrow (*via* kidney and erythropoietin) and produce polycythemia. While the polycythemia is helpful in increasing oxygen carrying capacity, it becomes counter-productive when the hematocrit is excessive (between 60% and 70%). [11]

In addition, the pressure loaded RV becomes hypertrophied and may develop diastolic dysfunction. Aortic regurgitation may result from the dilation of the aorta or the abnormal flow caused by the overriding aorta and VSD. [10]

4. Anatomical variants of TOF and associated anomalies

TOF is associated with other congenital cardiac abnormalities in about 40% of patients. Some of the more common anomalies are a right sided aortic arch (13–34%), TOF with pulmonary atresia (~20%), atrial septal defect (~15%), atrioventricular septal defect (1.7–7%), anomalous coronary arteries (2–10%), TOF with absent pulmonary

valve (~5%), TOF with double outlet right ventricle (~3%) aortic regurgitation (<1%) and persistent ductus arteriosus (<1%). [10]

4.1. Aortic arch anomalies:

In TOF, the aortic arch is right-sided in approximately 25 % of cases. [8] There may be an associated aberrant origin of the ipsilateral subclavian artery from the descending aorta. Rare patients have an isolated origin of the left subclavian artery from the pulmonary artery. These variants are important when determining the surgical approach shunt palliation. A right or a left aortic arch with abnormal branching pattern is diagnosed with great frequency when there is associated chromosome 22q11.2 deletion. [8]

4.2. TOF with pulmonary atresia:

The pulmonary atresia is the most severe variant in the spectrum of antero-cephalad deviation of the outlet septum. The intracardiac findings are similar to those found in classic TOF, but there is no forward flow through the pulmonary artery. There may be atresia on the pulmonary valve alone, with a visible right ventricular outflow tract, infundibular atresia, or long-segment atresia in which the proximal main pulmonary artery is entirely absent. In approximately half of patients with pulmonary atresia, the right and left pulmonary arteries are confluent, with blood to the pulmonary arteries flowing through the persistently patent arterial duct. In the other half, the pulmonary arterial supply is multifocal (by multiple aorta-to-pulmonary collateral arteries (Figure 2) and patent arterial duct). [7]

4.3. Atrioventricular septal defect:

A patent foramen ovale or a true atrial defect may be present in 15% of patients with TOF in which case it may be called pentalogy of Fallot. [8]

Coexistence of TOF and atrioventricular septal defect is often seen in children with trisomy 21. [12-13] The anatomy in this scenario combines three anatomic alterations: the deviation of the outlet septum, perimembranous and muscular VSD, and common atrioventricular valve morphology. In these cases the presentation and initial medical management usually remain unchanged, but surgical repair and post-operative care are more complex. In trisomy 18, there may be a large subaortic VSD, often without pulmonary outflow tract obstruction and a frequent finding of redundant and dysplastic atrioventricular valves. [13]

4.4. Anomalous coronary arteries:

One of the most significant variations is the origin of the anterior descending artery from the right coronary artery with subsequent anterior course across the right ventricular outflow tract. [4-5, 14] The surgical importance of this variation relates to the course of the vessel anterior to the infundibulum, in the area where surgical relief of obstruction is required. Pre-operative echocardiographic studies should detail the origin and branching of the main coronary arteries and determine if any large vessels are crossing the subpulmonic region anteriorly. If uncertainty persists, then either aortic root or selective coronary angiography may be used to clarify the anatomy.

4.5. TOF with absent pulmonary valve:

Malalignment of the outlet septum with rudimentary formation of the leaflets of the pulmonary valve, so-called absent pulmonary valve syndrome, is seen in around one-twentieth of those alleged to have TOF. [15] The presence of rudimentary valvar leaflets arrayed in circular fashion at the RV outflow tract results in free pulmonary regurgitation throughout fetal life. The end result is that the chronic volume load of the right ventricle (RV) is transmitted to the pulmonary arteries. This leads to a concomitant dilation of both, the RV and pulmonary arteries. In severe cases, patients present

inspiratory and expiratory stridor due to compression of the airways by the aneurysmal pulmonary arteries and develop evidence of congestive heart failure. Although compression and obstruction of the airways are partly responsible for cyanosis, there is also focal narrowing at the RV outflow tract, contributing to the hypoxemia. The arterial duct is typically absent in this situation. [13]

4.6. TOF with double outlet right ventricle:

With pronounced aortic override, the aorta becomes more committed to the RV than to the left ventricle. In many instances this results in the ventriculo-arterial connection of double outlet RV. Although the physiology on presentation may not be altered, there are important implications for surgical repair. Patients with the aorta originating predominantly from the RV are at greater risk of developing obstruction of the newly created left ventricular outflow tract, the latter produced by the patch which closes the VSD while tunneling the left ventricle to the aorta. This patch is appreciably longer than the patch used when the aorta arises mostly from the left ventricle. [16]

5. Etiology

The etiology of TOF is multifactorial and includes both environmental and genetic factors that most likely interact with each other in certain cases.

During pregnancy, several environmental causes have been shown to increase the risk of developing TOF, such as untreated maternal diabetes, the uncontrolled dietary intake of phenylalanine in mothers with phenylketonuria, the ingestion of retinoic acid and the maternal treatment with trimethadione or paramethadione. [4]

Associated chromosomal anomalies can include trisomies 21, 18 and 13, but recent experiences points to the much more frequent association of microdeletions of

chromosome 22. Twelve percent of these patients will have chromosomal abnormalities, such as trisomy 21, 18, or 13. Up to 20% of patients with classic TOF, and 40% of those with TOF with pulmonary atresia, will have microdeletions of chromosome 22q11.2. [17-18] The deletion, manifested by varying degrees of palatal abnormalities, dysmorphic facies, learning disabilities, immune deficiencies, and hypocalcaemia, is frequently referred to as the DiGeorge Syndrome. This chromosomal abnormality is more frequent in those cases with absent pulmonary valve, right aortic arch and anomalous origin of the branch pulmonary arteries. [13]

Children of patients with TOF have a risk of CHD about three times higher than the general population (3,1% versus 1%, respectively). [4]

6. Antenatal diagnosis

A fetal echocardiography is important both for the diagnosis of TOF and for the precise characterization of fetus cardiac anatomy, since the TOF associated anatomical variations have different outcomes. As the four-chamber view usually appears normal, TOF is easily missed in a routine ultrasound. [13] Women with fetal cardiac anomaly increased risks should be offered a more detailed scan. Note, that the origin of these risk factors can be both maternal and fetal. The most common indications for fetal echocardiography are summarized in Table 1. [19]

TOF can be diagnosed antenatally as soon as cardiac anatomical details can be satisfactorily visualized, usually after 12 weeks of gestation. [20] In the classic form of TOF the echocardiography is often characterized by a normal four-chamber view, a subaortic VSD (seen in a long-axis view of the left ventricle), an aortic dilatation and override, an infundibular narrowing (normally seen in later pregnancy), a decreased

pulmonary artery/aorta ratio, a forward flow in pulmonary artery and a aortic flow originated from the both ventricles. [13]

However, other echocardiographic findings may be present according to the anatomical variations found in TOF. For example, in TOF with pulmonary atresia there are no forward flow in pulmonary arteries, the duct presents reverse flow, there are aorta-to-pulmonary collateral arteries and the pulmonary artery branches are small or even impossible to identify. [13]

In TOF with absent pulmonary valve, there are also some echocardiographic findings that allow us to differentiate from the classic TOF. The four-chamber view is abnormal due to right ventricular dilation. The pulmonary valve is dysplasic and may not be identified. Although the pulmonary annulus may be restrictive, the main pulmonary arteries and their branches are very dilated and pulsatile. By color flow mapping it´s possible to identify significant pulmonary regurgitation and the arterial duct is usually absent. [13] Progressive RV and main pulmonary artery dilatation may occur and fetalis hydrops may develop if the RV function is poor. [13, 21]

It is also important to identify the side of the aortic arch, which is easier to do in a prenatal than in a postnatal echocardiography. Such characterization is important in any fetus with diminished pulmonary blood flow, as this may be useful if surgical palliation is necessary postnatally. [13]

Extracardiac abnormalities, such as midline defects, central nervous system and renal abnormalities may be found in fetuses with TOF. These extracardiac defects are associated with chromosomal abnormalities. [13]

When TOF is diagnosed, serial antenatal studies at 6-week intervals are recommended in order to follow the growth of the pulmonary arteries, to reassess the direction of main pulmonary artery and ductal flow and to evaluate, if present, the extracardiac abnormalities. [13]

7. Prenatal counseling and management

Definition of TOF anatomical variants is very important, since the prenatal counseling and planning of perinatal management depend upon the severity of TOF encountered and the significance of extra-cardiac defects.

Survival during pregnancy varies according to anatomical variations and associated extra-cardiac anomalies. *Azancot et al* [22] reported a series of 44 cases of pre-natally diagnosed TOF. They subdivided the cases into those with major extracardiac abnormalities and those with “isolated” TOF. The survival in the two groups was 10% and 84%, respectively. This confirms the profound influence of extra-cardiac malformations on prognosis. In other study [23], the survival rate in the continuing pregnancies was 60% in the classic form of TOF, 45% in the cases with pulmonary atresia and 18% in TOF with absent pulmonary valve. Chromosomal testing should be offered to all mothers with fetuses prenatally diagnosed with TOF, due to the high incidence of chromosomal abnormalities and its association with death. [24]

Delivery of fetus with a more severe variant of TOF should always take place at a care center where neonatologists, cardiologists, and cardiovascular surgeons can appropriately manage the infant. [13] The post natal treatment can be planned according to the echocardiographic findings.

The ratio between pulmonary artery and aorta along with the pulmonary valve size and flow dynamics are valuable indicators in predicting the use of prostaglandins at birth and the surgical approach. *Hirji et al [24]* suggested that a ratio between pulmonary and aorta valve sizes of less than 0,65 was associated with the fetus being more likely to receive a transannular patch repair after birth. Furthermore a smaller ratio, an abnormal flow in the ductus arteriosus and a smaller pulmonary valve size were found to be prenatal predictors of the use of prostaglandins at the time of delivery. In other study [25], fetuses with reversal of flow in the arterial duct went on to develop

acquired pulmonary atresia and required shunting in the neonatal period. They also state that fetuses with lower pulmonary valve diameter and pulmonary arterial to aorta size ratio require early intervention.

Perinatal prognosis is worse when the TOF can be identified in a pre-natal period compared to those which diagnosis is only made postnatally. This is likely to be related to the fact that patients referred for fetal echocardiography usually showed much more severe phenotypes of TOF or other associated extra-cardiac abnormalities. [5]

8. Clinical features

8.1. Symptoms:

The degree of pulmonary stenosis (PS) is directly responsible for great variations of the clinical presentation. A patient with a mild degree of PS may not present any symptoms until late childhood, whereas one with severe PS has high probability to present symptoms in the first moths of life.

Commonly, the infants show no presence of cyanosis at birth, developing such symptom between the 2nd and 6th moth. The most usual modes of presentation are asymptomatic murmur and bluish color (cyanosis). These may be discovered on routine auscultation and observed by the parent or primary physician respectively. [1, 4-5, 8]

Hypercyanotic spells can also occur in TOF patients. These are caused by alteration on the degree of RV outflow tract obstruction and by paroxysmal hyperpnea. [14] Such spells can occur any time between 1 month and 12 years of age but the peak incidence is between the 2nd and 3rd months. In what concerns to the time of the day occurrence, these are most commonly seen after awakening from sleep. It is also

observed that crying, defecation and feeding are common precipitating factors. Spells are characterized by increasing rate and depth of respiration (hyperpnea) with increasing cyanosis. Such episodes can progress to limpness and syncope, occasionally terminating in convolutions, cerebrovascular accidents or death. [4, 8, 14]

Related to the issue of pulmonic-to-systemic blood flow ratio, but clinically distinct from hypercyanotic spells is the squatting posture commonly described in children with uncorrected TOF. Children may assume a knee-chest position, typically following exercise. The posture is thought to be instinctive and results in an improved arterial saturation. The mechanism is likely related to an increase in systemic vascular resistance and to the compression of the femoral vessels. [1, 4-5, 8]

Note that these hypercyanotic episodes were more common prior to the availability of safe and effective surgery. In the current era, evidence of such episode provides the impetus for surgical intervention, and as a result these often life-threatening episodes are less common. [8]

8.2. Physical examination:

Central cyanosis is observed in most cases of TOF. However, it should be noted that mild arterial desaturation may not cause clinically detectable cyanosis. Clubbing of fingers and toes is observed beyond the first few months of life. Also, note that signs of congestive heart failure are unusual, except in the case of severe pulmonary regurgitation when the patient has TOF with absent pulmonary valve. Prominent right ventricular impulse may be present. A systolic thrill may be present at the left upper sternal border. The first heart sound may be normal or slightly increased. The second heart sound is single without an audible pulmonary component. A grade III-IV long ejection systolic murmur caused by blood flow through the stenotic right ventricular outflow tract is usually heard at the left upper sternal border. In contrast to PS with intact ventricular septum, the TOF murmur becomes shorter and less intense

with increasing severity of PS. During hypercyanotic spell the murmur disappears or becomes very soft. Similarly in the situation of TOF with pulmonary atresia, there will be no obstructive precordial murmurs because there is a complete absence of antegrade flow across the right ventricular outflow tract. The flow across the interventricular communication is usually not turbulent, and therefore not audible. Early diastolic murmurs do not occur except in TOF with absent pulmonary valve. Continuous murmur of associated patent ductus arteriosus is rarely heard. Older children may have an audible continuous murmur of aorta-to-pulmonary collateral arteries flow into the lungs, usually heard on the back. [1, 4-5, 8, 14]

9. Diagnostic studies:

The chest radiography usually presents a “boot-shape” heart (Figure 3). This form is caused by an upturned cardiac apex and by a concavity in pulmonary conus region, due to RV hypertrophy and RV outflow tract stenosis, respectively. The pulmonary vasculature is usually diminished and, if present, a right sided aortic arch is visible. The presence of all these features is enough to diagnosis TOF. [4, 8]

Hemoglobin and hematocrit should be monitored periodically in all children with cyanotic CHD including TOF. The level of hemoglobin depends upon the degree and duration of hypoxemia. In the absence of adequate iron intake, relative anemia with hypochromia and microcytosis may develop. Since this situation can lead to cerebrovascular accidents, the relative anemia should be treated with oral supplemental iron. [8]

The electrocardiogram (ECG) will demonstrate right axis deviation and prominent right ventricular forces, with large R waves in the anterior precordial leads and large S waves in the lateral precordial leads. Although the electrocardiogram is

similar to that of a normal newborn, the right ventricular hypertrophy and right axis deviation will not normalize in a patient with TOF. [8, 14]

Echocardiogram is very helpful in confirming the diagnosis and in evaluating several of the issues related to TOF. Enlargement of the RV, large VSD, aortic override and right ventricular outflow tract obstruction can be imaged (Figure 4). Shunting across the VSD and increased Doppler flow velocity across the right ventricular outflow tract can be demonstrated. Size of the main and proximal branch pulmonary arteries and any additional sources of flow to the lungs can be evaluated. Although, the distal pulmonary arteries cannot easily be seen by echocardiogram. [4-5, 8] The Doppler velocity across the pulmonary valve increased with posnatal age and weight. The acute change in doppler velocity from prenatal to postnatal life reflects the initial decrease in pulmonary vascular resistance, permitting a larger flow across the pulmonary valve. [25]

Computerized tomography and magnetic resonance imaging (MRI) are useful in defining issues that could not be addressed by conventional echocardiography. This could be particularly important when defining vascular anatomy alterations. [14]

The catheterization is not routinely required. However, it could be performed when the necessary data for surgical correction decision making cannot be obtained by other exams. It is important to obtain oxygen saturation data since the systemic and arterial desaturations are related with the RV outflow tract stenosis. Although the left atrial and pulmonary venous saturations tend to be normal, the left ventricle and aortic saturations are usually reduced. This is due to the right-to-left ventricular shunt. Even so, the aortic saturation can be used to provide better information about blood desaturation than the one provided by left ventricle catheterism. Such is due to a better distally mixing. Note that, the right ventricular pressure curve top must be flat in comparison to the triangular shape present in patients with PS and no VSD. It can be

found a peak systolic gradient across the RV outflow tract. Also, the pulmonary arterial pressure values are low to normal. [4, 8, 14]

Angiography is an integral part of cardiac catheterization. With a selective left ventricular angiography it is possible to demonstrate the size and function of the left ventricle and the size and location of the VSD. This allows to exclude muscular VSD. A selective right ventricular angiography is recommended. This allows to study the RV size and function, and to evaluate the RV outflow stenosis. It also should be obtained a pulmonary angiography. With this, one could visualize the size of the main and branch pulmonary arteries and to exclude branch pulmonary artery stenosis. Aortic root angiography is also necessary to visualize coronary artery anatomy, especially to exclude coronary arteries crossing the right ventricular infundibulum. [1, 8, 14]

10. Differential diagnosis

The differential diagnosis of any cyanotic patient with a murmur will include persistent pulmonary hypertension of the newborn, as well as other cyanotic lesions. Such lesions can be critical PS, Ebstein's malformation, transposed arterial trunks, common arterial trunk, totally anomalous pulmonary venous connection, and tricuspid atresia. [4, 14, 26]

11. Management

The goal of management of TOF patients is to allow total surgical correction with minimal mortality and morbidity and to prevent or treat complications. Depending of the severity of obstruction within the RV outflow tract, an infusion of prostaglandin

may be initiated to preserve ductal patency, and provide a stable source of flow of blood to the lungs. [4]

11.1. Hypercyanotic spells

Overcoming a hypercyanotic spell requires maneuvers to re-establish adequate balance between the systemic and pulmonary flows. Treatment must focus on decreasing pulmonary and increasing systemic, vascular resistance. This promotes left to right flow across the VSD and into the RV outflow tract.

Treatment of an infant with cyanotic spell may be summarized as follows:

- The infant should be placed in a knee-to-chest position in an effort to increase systemic vascular resistance and promote systemic venous return to the right heart. [4]
- Oxygen should be initiated to decrease peripheral pulmonary vasoconstriction. This would improve oxygenation once flow of blood to the lungs is re-established. [4]
- Subcutaneous morphine should be administered to depress the respiratory driver of central nervous system, thus reducing hyperpnea. Morphine also decreases the release of catecholamines promoting a reduction in heart rate and the relaxation of the infundibular spasm. [4]
- Once the physical examination is completed and the laboratory studies are obtained the infant should be left undisturbed and allowed to rest.
- If present, is very important at this stage the correction of metabolic acidosis (with sodium bicarbonate), anemia (by blood transfusion) and dehydration (by appropriate fluids). [14]
- If the spell continues it may be tried vasopressors to increase the systemic vascular resistance and thus increase the pulmonary blood flow. [14]

- Another option, propranolol, may be slowly administered intravenously while monitoring the heart rate (by ECG if possible). If there is marked bradycardia, propranolol should be stopped. Once it is found to be effective, the infant may be switched to oral propranolol. Note that the propranolol action mechanism may include negative inotropic effect on the right ventricular infundibular myocardium and the prevention of ventilatory response (hyperpnea) to hypoxia. [4]
- In few cases, general anesthesia may be necessary to stop these episodes. [14]
- If the anatomy is adequate and the infant does not improve with any of the aforementioned measures, it should be performed an emergency systemic-to-pulmonary artery shunt or total correction. In case the infant improves, the same surgical procedures may be delayed for the next days. [4, 14]

11.2. Surgical palliation

If it is deemed that a given patient is not suitable for total surgical correction, palliative surgery may be utilized to augment pulmonary blood flow and to allow the patients to grow into an age, size and anatomy that are more likely suitable for complete correction. Such palliative surgery can be systemic-to-pulmonary arterial shunt, balloon dilatation and placement of a stent in the RV outflow. The most common type of systemic-to-pulmonary arterial shunt is known as the modified Blalock-Taussig shunt. This consists of a communication between a subclavian and pulmonary artery on the same side. [2] Potential disadvantages of this staged approach include long-lasting pressure overload of the RV and persistent cyanosis. Note that long-term hypoxemia contributes to cardiomyocytic degeneration and interstitial fibrosis, which have been implicated in myocardial dysfunction and ventricular arrhythmias. [27]

11.3. Surgical correction

The advent of TOF surgical correction brought great benefits for those born with this decease. Before this, almost 50% of TOF patients died in the first 3 years. Furthermore, it was unusual for a patient to reach an age over 30. Currently, it is widely know that the surgical correction allows these patients to reach adult life. [3, 28]

Over the years, the age of the patients undergoing primary corrective surgery has gradually decreased. Although, some support that surgery may be performed at diagnosis, even within the first days of life, such surgery is not advised for patients below the 3 months of age. The literature [29] suggests that the optimum age of elective repair is between 3 and 6 months of age, thus, reserving earlier open-heart-surgery for those presenting severe cyanosis or hypercyanotic spells. In case this primary repair must be performed in patients with less than 3 months, further cautions must be taken such as, longer intensive care and hospitalization. Studies of neurodevelopmental outcomes demonstrate that neonates undergoing corrective surgery compared to older children present an increased risk for neurological events on follow-up and lower intelligent quotients. [30-31]

Different techniques for surgical repair should be made according to each patient anatomic variation. Generally repair includes a patch closure of the VSD and modification of the RV outflow tract to improve pulmonary flow. The outflow track can be widened through three different procedures: opening the pulmonary valve, resecting the muscle bundles and placing a transannular patch. [10]

Follows the different surgical procedures according with three different TOF presentations: TOF with Pulmonary atresia, TOF with absent pulmonary valve and an anomalous coronary anatomy.

When TOF with pulmonary atresia only affects the pulmonary valve, the placement of the transannular patch may be successfully performed. However, when the branch pulmonary arteries are also stenotic, the placement of a RV to pulmonary

artery conduit may be necessary. In this situation, the conduit typically needs dilatation, stent enlargement or surgical replacement as the child grows. [13] When multiple aorta-to-pulmonary collateral arteries provide the pulmonary blood flow, is desirable to unifocalize the collateral arteries. This procedure consists in the disconnection of the collateral arteries from the aorta and subsequent anastomose to the pulmonary artery, maintaining pulmonary blood supply by mean of a shunt. These infants and children may require repeated interventional catheterization procedures to balloon dilate hypoplastic and stenotic branch pulmonary arteries and to coil occlude additional collateral arteries.

Surgical correction in patients with mild phenotypes of absent pulmonary valve syndrome is identical to the one held in the classic form of TOF. However, when the airways are very compressed, an emergency medical and surgical management is required. In these cases it is necessary to perform a plication of the dilated proximal pulmonary arteries and a subsequent balloon dilatation of more distal pulmonary arteries. If a severe airways compression is present, their dilation and stenting may be attempted to improve the respiratory condition. Although these aggressive measures, the hospital mortality in affected infants requiring early intervention has been documented to be as high as 50%. [32]

In the case of an anomalous coronary artery crossing the RV outflow tract, the placement of a transannular patch is not possible. Instead, a RV to pulmonary artery conduit must be used.

As a final note in this topic, it should be mentioned that the right ventriculotomy performed during the intracardiac repair leads to fibrosis at the incision point and, usually, to subsequent myocardial dysfunction. To avoid this problem, improvements on a transatrial-transpulmonary approach are being developed, thus enhancing the early and middle term outcomes. [33] Also, the placement of a transannular patch

results in unobstructed flow from the RV to the pulmonary artery, but sacrifices pulmonary valve competency resulting in pulmonary regurgitation.

12. Complications

12.1. Early postoperative outcomes

A majority of the children undergoing surgical correction present no complications in the postoperative period. Also, they are usually discharge during the week after surgery. However, a small number of children develop a restrictive RV physiology, characterized by a low cardiac output syndrome. In these cases, this syndrome is characterized by an anterograde diastolic flow in the pulmonary arteries and a retrogade flow in the superior vena cava. Both flows are caused by the atrial contraction throughout the entire respiratory cycle. [34] This restrictive physiology occurs despite an apparent adequate repair with preserved biventricular systolic function. Interestingly, the restrictive physiology does not seem to be associated with the patient age at operation. It is more common when a transannular patch is applied and it directly relates with the degree of myocardial damage at the repair. [35-36]

If such occurs in an early postoperative period, precaution measures have to be taken. It is necessary to extend the inotropic support and the hospitalization period. It is also recommended the administration of higher doses of diuretics. [37] However, it is a transient phenomenon, usually resolving within 72h, although reappearance in the later postoperative follow-up period can occur.

12.2. Late outcomes:

Not long ago, residual pulmonary valve incompetence was regarded as an inevitable, but unimportant, late sequel of repair. However, during the past decade the

degree of residual pulmonary incompetence is associated with significant late morbidity and mortality.

A progressive RV enlargement and systolic dysfunction may occur in case of chronic RV volume overload. There are a number of conditions that can contribute to the abnormal RV hemodynamics. Two examples are the residual PS and the tricuspid regurgitation. [10] It is also an important fact, that these abnormal hemodynamics are, in part, responsible for the long term presentation of arrhythmias and exercise intolerance.

Adults with repaired TOF have lower long term survival rates when compared with healthy individuals (86% vs. 96% at 30 years). They also have higher rates of recurrent symptoms (23%), sudden death (6%), and arrhythmias (4.8%). [38] Abnormalities of the left side of the heart also have been increasingly recognized, including left ventricular dysfunction and aortic root dilation. [39-40] Potential long term adverse outcomes are detailed in Table 2.

12.2.1. Residual structural heart defect

Pulmonary regurgitation with consequent RV dilation and eventual systolic dysfunction is the most common residual structural defect in repaired TOF. In the physical examination a diastolic murmur of pulmonary regurgitation, a parasternal RV impulse due to RV enlargement and signs of right sided heart failure may be present. Usually the referred murmur is soft or even absent since the velocity flow characteristic of severe regurgitation is very low. [10] As stated above, the findings in the physical exam are very subtle, turning the imaging exams into essential evaluation tools.

It is possible to observe the VSD patch and the enlarged overriding aorta in adults with repaired TOF (Figure 5). Such can be done using an echocardiography exam. The existence of residual VSDs is not usual. Although the degree of aortic dilation is typically stable, there are case reports of aortic root dilatation. [39-40]

Also, pulmonary regurgitation can be calculated using Doppler echocardiography. This technique can be used instead the cardiac MRI, since both are concordant. Even so, for a full assessment of the RV it is recommended the use of the cardiac MRI. [5]

MRI velocity mapping can be used to quantify systolic and diastolic flow through the pulmonary valve. This makes the calculation of the pulmonary regurgitant fraction possible (Figure 6). When the pulmonary valve is not functional, the retrograde flow through the valve is laminar and, because of this, the regurgitant jet may not be seen.

In cases of severe aortic insufficiency, the regurgitant fraction is much higher than the one found in pulmonary insufficiency. Note that, pulmonary regurgitant fraction is typically below 40%. [41] The difference between pulmonary and aortic regurgitant fraction values can be explained by two reasons. Firstly, even in the presence of a dysfunctional RV, the pulmonary forward flow can occur due to negative pressure of the thoracic cavity, created by both inspiration and ejected blood from the left ventricle. Secondly, as the pulmonary microvascular resistance is low, the blood ejected from the RV moves into the pulmonary microcirculation and then into the low pressure pulmonary veins. Detailing, once the flow passes through alveolar capillaries it does not return during the diastole. Thus, the magnitude of the regurgitant fraction is limited, unless there are additional factors which may increase this regurgitation. [42] Some of this additional factors are: pulmonary arteries branch stenosis; wider pulmonary valve size; reduced compliance of pulmonary arterial tree and reconstructed RV outflow tract; and dysfunctional pulmonary microvasculature [41]. In the case of pulmonary arteries branch stenosis a balloon angioplasty and stenting may delay the need for pulmonary valve replacement. [42]

Much attention has been focused on structural changes of the RV. However new studies are evaluating the result of a consequent biventricular dysfunction. The right and left ventricles are anatomically connected by a shared septum and pericardial

cavity and through subepicardial myocytes bundles that run from the free wall of the RV to the anterior wall of the left ventricle. This anatomical interaction results in both right and left ventricular function alterations. [43] Since the left ventricle systole, through shared myocytes, contributes to the external mechanical contraction of the RV, a dilatation on the RV leads to a reduced performance on the left ventricle. [44] Therefore, a strong correlation between right and left ventricular ejection fractions exists in patients after repair of TOF. [45] Furthermore, those with substantial coexisting left ventricular dysfunction have higher risks of sudden death late after repair [46], possibly due to an increasing dys-synchrony between the two ventricle contraction. The pacing of the RV improves the intraventricular dys-synchrony. [47] However, since interventricular dys-synchrony is often present, a biventricular resynchronization will probably show best results. This was tested in *Kirsh et al* which reported extraordinary functional improvement after biventricular pacing in these patients. [48]

12.2.2. Exercise intolerance

A well-known problem of patients with repaired TOF is the intolerance to exercise. It is believed that this exercise intolerance is due to abnormal RV hemodynamics. [10] The literature details a study were a reduction to nearly 56.5%, in the mean peak oxygen consumption (peak VO_2), is found in patients with TOF when compared to normal subjects. Note that, this study was conducted using the cardiopulmonary exercise test (CPET). [49]

Normally, CHD patients are unaware of their exercise limitations as these may have been present for a long period. Even so, it can be found in [49] a CPET study with asymptomatic CHD patients presenting a wide range of exercise tolerance. Some of these patients have severe reduced peak VO_2, whereas others have normal to

excellent exercise tolerance. Curiously, some even participate in high level athletic competitions.

This study indicates that it is important to evaluate the exercise intolerance evolution with an objective CPET follow up. Attending to the exercise intolerance degree, one can predict necessary hospitalization and event free survival rates in CHD patients, including repaired TOF ones. From [49] can be concluded that lower values of peak VO_2 are associated with lower event free survival rates. To exemplify, some values were from [49] transcribed to Table 3.

12.2.3. Cardiac arrhythmias

An increased risk of cardiac arrhythmias and sudden death is common in repaired TOF adults, with the following reported rates: ventricular tachycardia of 12%; atrial flutter/fibrillation of 10%; and sudden death of 8%. All these values were obtained within a mean of 21.1 years of follow-up. [50] The subjacent causes for these arrhythmias are not totally understood. However, histological and MRI exams demonstrate myocardial fibrosis in the RV. The fibrosis may occur not only at the surgical incision site, which suggests the presence of another mechanism leading to fibrosis. A cardiovascular magnetic resonance study [51] demonstrates that right and left ventricle fibrosis where common after TOF repair. They also stated that higher degrees of fibrosis were related to increased rates of ventricular dysfunction, clinical arrhythmias and exercise intolerance.

Other studies [38, 50] compare the ECG alterations with the occurrence of cardiac arrhythmias. They found that a QRS duration superior than 180ms on the resting ECG was associated with higher risk ratios of ventricular tachycardia and sudden death. However, it is not yet fully comprehended how to apply this to patient care since no intervention studies have been performed based on QRS duration. Holter

monitor measurements usually demonstrate ventricular arrhythmias (40% to 50%), but there is no association between these alterations and clinically significant events. [38]

In [52] an association between the RV pressure and sudden death was found. Patients with right ventricular systolic pressure above 60 mmHg presented higher sudden death risks.

In [10] it is pointed out that ventricular arrhythmias are mostly due to pulmonary regurgitation, whereas atrial arrhythmias are mainly caused by tricuspid regurgitation.

13. Treatment for pulmonary regurgitation

Pulmonary regurgitation is the most common hemodynamic abnormality in patients with repaired TOF. Hence, it is presumable that a pulmonary valve replacement would improve the hemodynamics and outcomes.

Although the risks associated to pulmonary valve replacement procedure are low, some more details have to be taken into account before performing such surgery. It is stated in [5] a perioperative mortality of 1% to 4% and 10 years survival between 86% and 95%. Even so, the longevity of the replacing valve can be a problem since their recommended usage time has a maximum of 10 years. Besides this, the longevity of a second homograft may be shorter, hence potentiating young patients to repeatedly undergo such replacements. Another issue is the fact that such valves do not grow with the patients. Attending to these points, one can see that it is ideal to delay the time for valve replacement as long as the clinical outcomes are not compromised. Furthermore, the optimal timing of pulmonary valve replacement is an important aspect in the management of repaired TOF adult patients.

As detailed in [53-57], the pulmonary valve replacement can benefit the patient, decreasing the RV volume and consequently improving the RV function. Also, it is

shown that the postoperative improvement degree is correlated with the preoperative RV size. Attending to these studies, the RV end systolic or diastolic volume must be taken into account when scheduling the valve replacement. In [10] is presented some suggested limit values for RV end systolic and diastolic volumes index, being those 85 ml/m^2 and 170 ml/m^2, respectively. Note that these limits are not optimal for each and every patient, as some subjects presented non complete RV dilation resolution after surgery even with RV end diastolic volume index below 170 ml/m^2. Since these surgical procedures are nowadays becoming common in TOF repaired patients, outcome data is not available yet. This result in an absence of long term prognosis associated with various degrees of persistent RV dilation or dysfunction.

Another advantage of the valve replacement is the improvement of the patient exercise capacity and clinical arrhythmias. In [58-59] it is demonstrated a stabilization of the QRS duration and subsequent reduction on the incidence of ventricular tachycardia in adults submitted to this surgery. However, these results can be biased since other anti-arrhythmia procedures are usually performed in these patients. Additional procedures consist of a preoperative transcatheter ablation, an intraoperative arrhythmia mapping and cryoablation and a postoperative implantation of an automatic defibrillator. A combination of these procedures can also be used. Several studies [58, 60-61] showed a greater chance of freedom for new arrhythmia after operation when the valve replacement and the cryoablation were concomitantly performed.

Some rare patients reach the adulthood without corrective repair. To those, an individualized management based on the characteristics of each patient is required. Potential management options can be late repair, optimization of medical treatment and possible surgical optimization of palliative shunts. For the worst cases heart/lung transplant can be performed. [10]

13.1. Percutaneous pulmonary valve replacement

The percutaneous approaches to pulmonary valve replacement have gained many adepts since their first appearance. An experimental technique was firstly reported in the early 1990s. However, it was only clinically introduced in 2000 by Philip Bonhoeffer. [62-63] The device (Melody® valve, Medtronic, USA), composed by a bovine internal jugular vein with its native valve, mounted on a stent, is advanced into the right ventricular outflow conduit and fixed in the correct place by inflation of a balloon-in-balloon system (Figure 7).

Until now, the device has been implanted in about 700 patients worldwide, with encouraging early to mid-term results. [64] A case report study [65] performed in 155 patients during 7 years, presented no periprocedural mortality and very low late mortality. It also presents freedom from reoperation rates of 93%, 86%, 84% and 70% at 10, 30, 50 and 70 months, respectively.

Although all these encouraging results, this technique also presents some unwanted effects and complications. As the coronary arteries are adjacent to the RV outflow tract such procedure must be done with extreme careful. Fracture of the stent and valve failure are the most common complications, however the implantation of a second valve usually resolve these problems. [66-67]

For the most patients with a transannular patch and a highly dilated native outflow tract, it is impossible to use this procedure. To deal with this issue, new techniques are being developed. [68-69]

14. Other considerations for adults with repaired TOF

Many factors, deriving mainly from the fact that patients with surgical corrected TOF are now reaching adult age, lead such patients to inadequate follow-up. One of

these factors is the overspecialization of cardiology with the partition of cardiologists in both adult and pediatric areas. Such, end up contributing to a deficient follow-up. Although some efforts have already been made in order to counteract this problem, "even in the best developed health-care systems"[1] these patients are suffering inevitable casualties. [1]

To help controlling this situation, the patients should be explained and advised about all the major possible problems related with this condition in their adulthood. It is recommend focus in pregnancy and exercise activities besides hemodynamic consequences and associated medical problems. Resuming, it is desired to have a program with expertise from all subspecialties covering a wider age range, hence providing a better treatment and follow-up to TOF patients.

14.1. Other medical complications

Aortic root dilation is an increasingly recognized feature of late postoperative TOF. This can lead to aortic regurgitation, aortic rupture and dissection. [39-40, 70] Its prevalence ranges from 15% to 87%, depending on the method and definition used in each study. [39, 71] Right-to-left shunting before repair leads to an increased aortic flow, which, in addition with the intrinsic properties of the aortic root, can cause aortic dilation. [72] Nowadays there is no consensus about which patient and at what stage aortic surgery should be performed. However it is accepted that when the aortic root dilatation in superior than 55mm, the surgery must be done, especially when the primary indication for surgery is pulmonary valve implantation. [72]

As most of the patients with repaired TOF are now reaching adulthood, they are now facing a new risk, the coronary artery disease. [73] However, a correct evaluation

[1] Quoted from 1. Apitz, C., G.D. Webb, and A.N. Redington, *Tetralogy of Fallot.* Lancet, 2009. **374**(9699): p. 1462-71..

of the coronary anatomy and of any residual lesion should be carefully documented if elective revascularization is necessary. [74]

Bacterial endocarditis can occur in patients with TOF in four different scenarios: before surgery; post palliation; following total repair; and after pulmonary valve replacement. [8] Endocarditis prophylaxis with dental procedures is recommended in a number of situations. A list of these situations can be found in Table 4. [75]

14.2. Pregnancy and contraception

Pregnancy in TOF postoperative women may have associated risks, therefor pre-pregnancy assessment and counseling is extremely advised. Such risks depend on the woman hemodynamic state. If the patient has good underlying hemodynamics, the pregnancy risks are similar to those of a healthy patient. Although, if the patient has substantial residual obstruction across the right ventricular outflow tract, severe pulmonary regurgitation, tricuspid regurgitation and right and left ventricular dysfunction the risks can be higher. In such case, the increased volume load, due to pregnancy, can cause heart failure and arrhythmias. [76] To prevent this volume load related problem, a pulmonary valve replacement must be considered before pregnancy. [77-78]

The recommended mode of delivery to women with TOF is vaginally. Should the woman present right ventricular failure during pregnancy, the delivery must be considered before term. Note that this is an unusual situation. [79]

14.3. Exercise activities

Since TOF affects the exercise tolerance, important consideration about participation of young adults in sport activities must be taken. Moderate exercise is encouraged for cardiovascular benefit and for self-monitoring of changes in exercise tolerance. [10] The type and grade of recommended exercise may vary depending on

the symptoms and extension of residual lesions. In patients where high RV pressures (more than 50%), severe pulmonary regurgitation with RV dilation and arrhythmias are present, the exercise activity should be avoided. Still, case the patients only present minimal residual abnormalities, full exercise activity is encouraged. [80-81] However, if any symptoms of palpitations, lightheadedness or a decrease in exercise tolerance, patients should immediately contact their physician. [10]

Exercise exams can help to evaluate the patient exercise tolerance. Although, is not, yet, established a relation between such results and the recommended exercise activities.

15. Suggested recommendations for clinical monitoring

The monitoring procedure of TOF repaired patients should be done in conjunction with experts in specific areas, such as congenital echocardiography, cardiac MRI, CPET and congenital heart surgery. This way the follow-up of these patients would be ideal. Stable patients are usually once per year screened for arrhythmia or change in exercise tolerance. [10] A list of suggestions for clinical monitoring is presented in Table 5.

As mentioned before, periodic ECO or MRI imaging, resting ECG and CPET testing, are useful for monitoring the RV enlargement, the arrhythmias and the exercise capacity, respectively.

One important point for the clinical monitoring is the correct information of the patient about their condition. Well informed patients are capable to make better decisions about their medical care and to understand the necessity of a regular visit to the clinic. [10]

In case the patient present symptoms of exercise intolerance aggravation, heart failure or arrhythmias, it is suggested the observation by an experienced CHD surgeon. [49] Even if the patient presents asymptomatically, it is acceptable a surgeon consultation under some conditions. Such consult is advised when RV dilation is severe (nearing the volumes described in Table 5) or when systolic function show deterioration. [10]

16. Conclusion

The care of children with TOF and their transition to adult life has been a success of modern medicine. Most of them survive due to an early repair and have a normal childhood. However, great challenges have come with this success. Adverse outcomes are now becoming apparent, decades after the corrective surgery. Unexpected complications are now increasingly understood, and their recognition is giving important feed-back to improve care and management of patients born with this disease.

Acknowledgments

This work was performed in collaboration with Dr. Carlos Areias, Dr. Cláudia Moura, Dr. Fernando Graça and Dr. Daniel Martins.

Abbreviations and Acronyms

- TOF: Tetralogy of Fallot
- CHD: Congenital heart disease
- VSD: Ventricular septal defect
- RV: Right ventricle
- PS: Pulmonary stenosis
- MRI: Magnetic resonance imaging
- ECG: Electrocardiogram
- CPET: Cardiopulmonary exercise testing

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Table 1: Common indications for fetal echocardiography. Adapted from Lee W et al [19].

Maternal indications	Fetal indications
First-degree relative of proband (mother or father) with CHD	Increase nuchal translucency thickness
Prior child born with CHD	Abnormal ductus venous waveform
Pre-existing metabolic disease • Diabetes mellitus type 1 • Phenylketonuria	Abnormal fetal cardiac screening exam
Infections • Parvovirus B19 • Rubella • Coxsackie	Major extracardiac abnormality
Teratogen exposure • Retinoid • Trimethadione • Phenytoin • Carbamazepine • Lithium carbonate • Valproic acid • Paroxetine	Abnormal fetal karyotype
	Hydrops
	Effusion
	Fetal cardiac dysrhythmias
	Persistent bradycardia or tachycardia

CHD, congenital heart disease.

Table 2: Potential long term adverse outcomes in patients with repaired tetralogy of Fallot. Adapted from *Huehnergarth KV et al* [10].

Potential long term adverse outcomes in Tetralogy of Fallot repaired patients	
Pulmonary regurgitation leading to:	• RV dilation • RV dysfunction • Right sided heart failure • Tricuspid regurgitation • Exercise intolerance
Other right sided conditions	• RV outflow tract obstruction • Branch pulmonary artery stenosis • Endocarditis

Left sided conditions	• Left ventricular dysfunction
	• Aortic root dilation:
	  ○ aortic regurgitation
	  ○ aortic rupture
	  ○ aortic dissection

Atrial arrhythmias	• Atrial fibrillation • Atrial flutter
Ventricular arrhythmias	• Ventricular tachycardia • Sudden death
Residual ventricular septal defect	
Exercise intolerance	

RV, right ventricle.

Table 3: Relation between event free survival rates and peak VO_2 values of CHD patients. Adapted from *Huehnergarth KV et al* [10].

Peak VO_2 (ml/kg/min)	Event free survival rate (%)
< 15.5	50.5
15.5 < … < 27	63.4
> 27	97

Peak VO_2, peak oxygen consumption using in cardiopulmonary exercise testing.

Table 4: Cardiac conditions for which prophylaxis with dental procedures is recommended. Adapted from *Wilson et al* [75].

Cardiac conditions for which prophylaxis with dental procedures is recommended
Prosthetic cardiac valve or prosthetic material used for cardiac valve repair Previous bacterial endocarditis Congenital heart disease(CHD)[1]: • Unrepaired cyanotic CHD, including palliative shunts and conduits • Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure [2] • Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)

[1] Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD;

[2] Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.

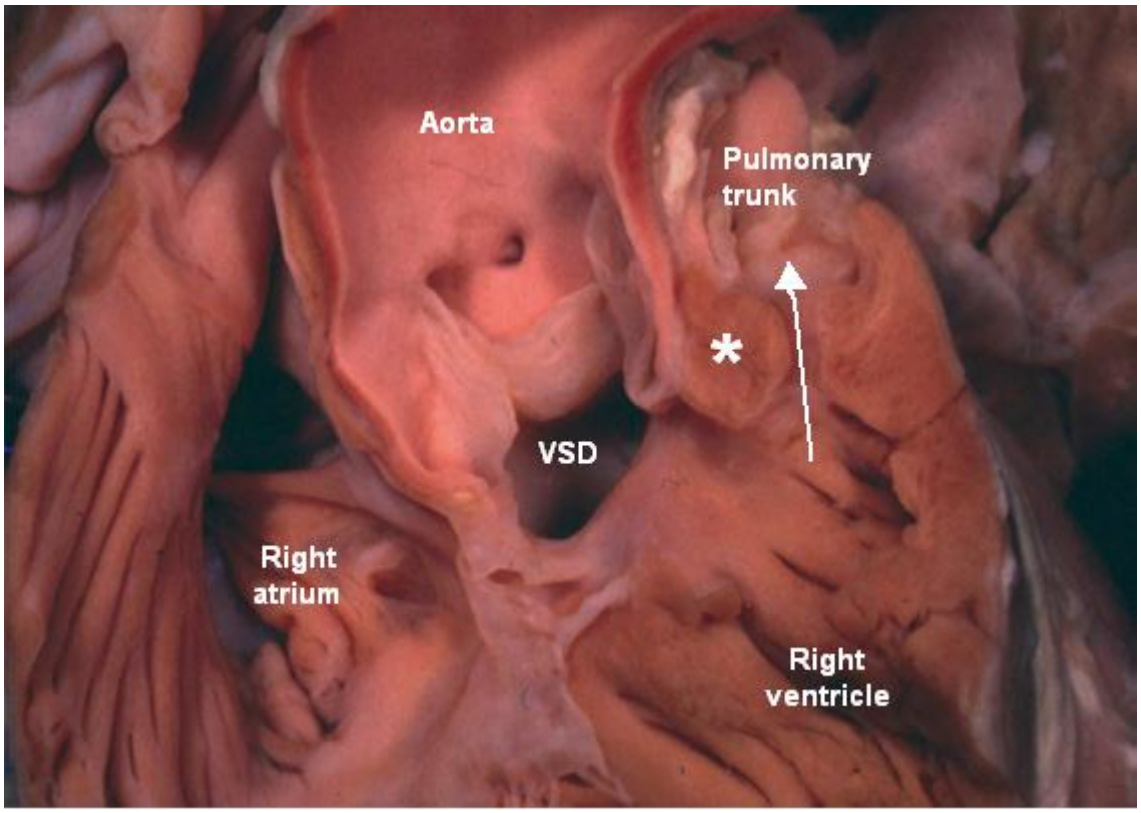
Table 5: Suggested monitoring of patients with repaired Tetralogy of Fallot. Abbreviations: Adapted from *Huehnergarth KV et al* [10].

Suggested monitoring of patients with repaired Tetralogy of Fallot	
Clinical	• Symptoms of right sided heart failure • Exercise limitation (although frequently unreliable) • Palpitations
ECG	• QRS duration .180 ms
Cardiopulmonary exercise test	• Significantly impaired exercise tolerance • Decreasing exercise tolerance as documented by serial examinations
Echocardiography	• Residual VSD • LV size and ejection fraction • Pulmonary regurgitation severity • RV size and systolic function (qualitative) • Aortic root size
Cardiac MRI[1]	• RVESVi 82–100 ml/m2 13 15 16 • RVEDVi 150 ml/m2 (in children)14 • RVEDVi 160–170 ml/m2 (in adults)15 16

[1] Cut-off values above which RV volumes may not return to normal;

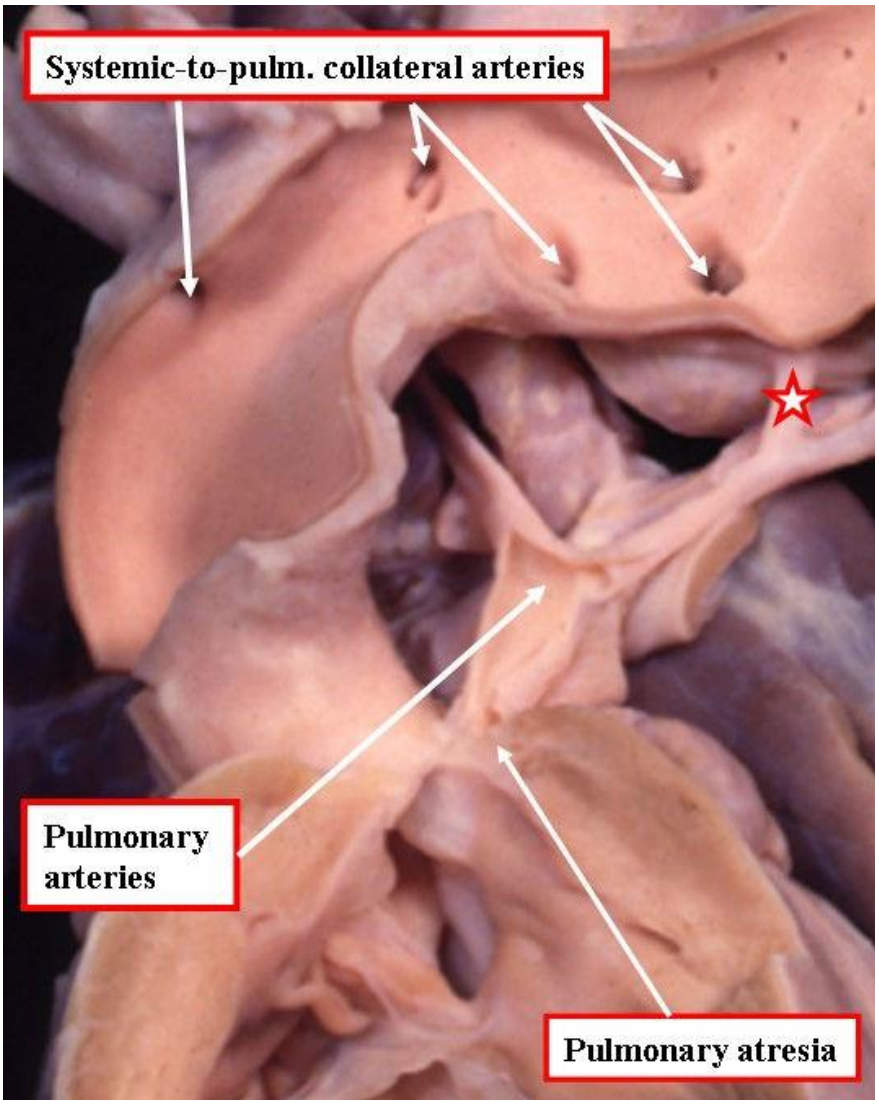
MRI, magnetic resonance imaging; LV, left ventricle; RV, right ventricle; RVEDVi, right ventricular end diastolic volume index; RVESVi, right ventricular end systolic volume index; VSD, ventricular septal effect.

Figure 1: Morphological features of tetralogy of Fallot. The subpulmonary narrowing (arrow) is formed between the malaligned muscular outlet septum (asterisk). There is a large ventricular septal defect with overriding of the aorta, which is partly committed to the hypertrophied right ventricle. Note the dysplastic and stenotic pulmonary valve. VSD, ventricular septal defect. Adapted from *Apitz C et al* [1].[2]



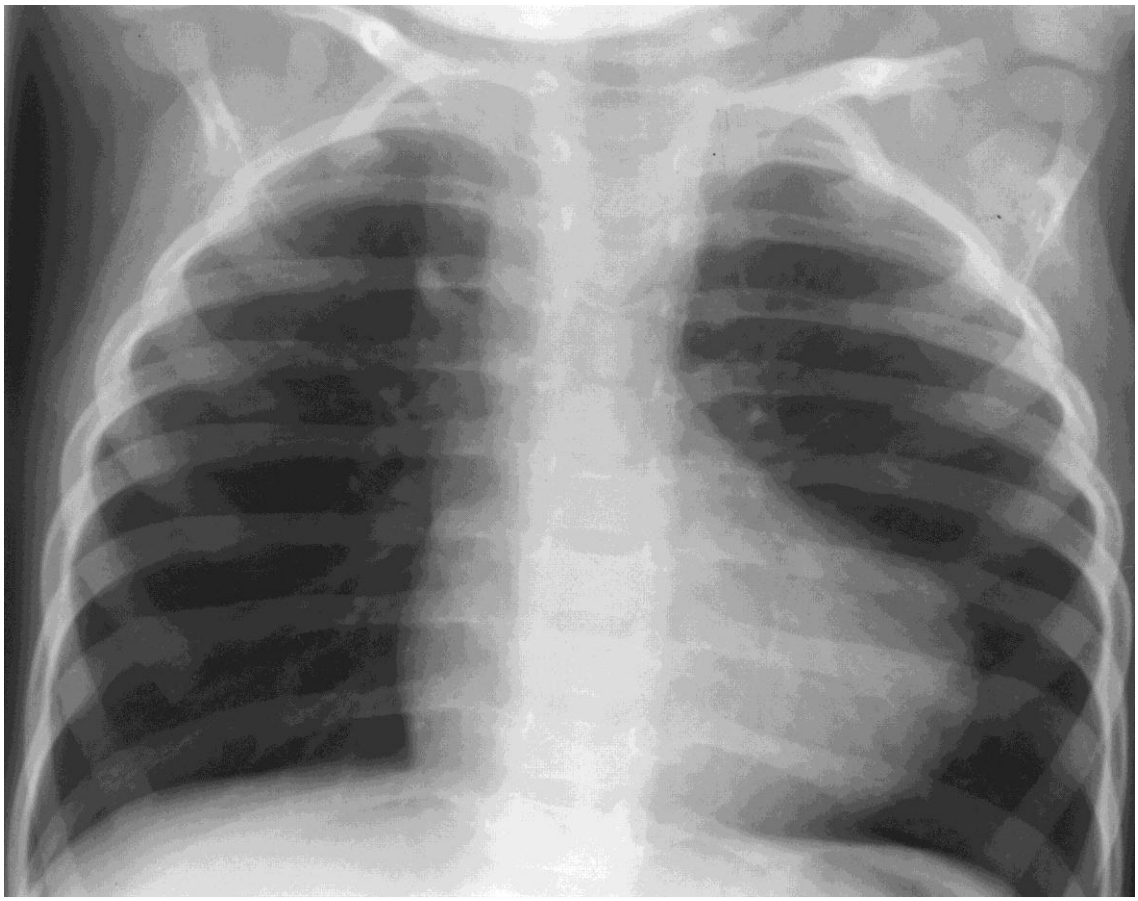
[2] See appendix 1 for copy right details

Figure 2: Tetralogy of Fallot with pulmonary atresia. The pulmonary supply is through multiple systemic-to-pulmonary collateral arteries. The star shows the connection between one of the collateral arteries and the left pulmonary artery. All the other arteries join with the pulmonary arterial supply, or else supply segments of the lung directly. Adapted from *Bailliard F et al* [4]. [3]



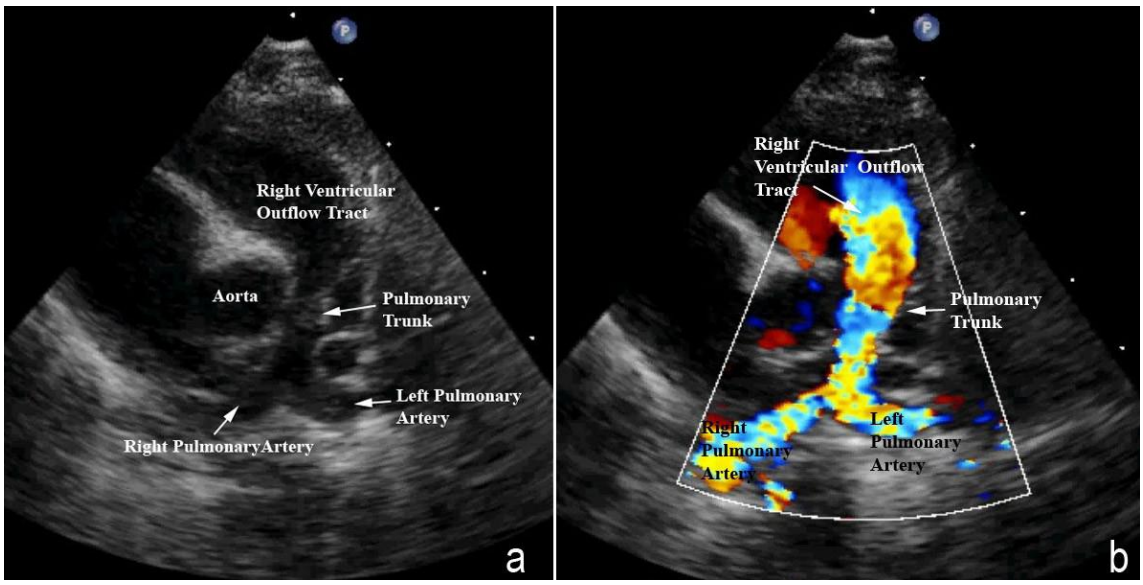
[3] See appendix 2 for copy right details

Figure 3: Frontal chest radiograph of pediatric patient with tetralogy of Fallot. It is shown the characteristic boot-shaped heart with hyperlucent lungs, diminished pulmonary vasculature, and an upturned cardiac apex. Right ventricle outflow tract is flat to concave, and right aortic arch is seen. Adapted from *Haider E et al* [82].[4]



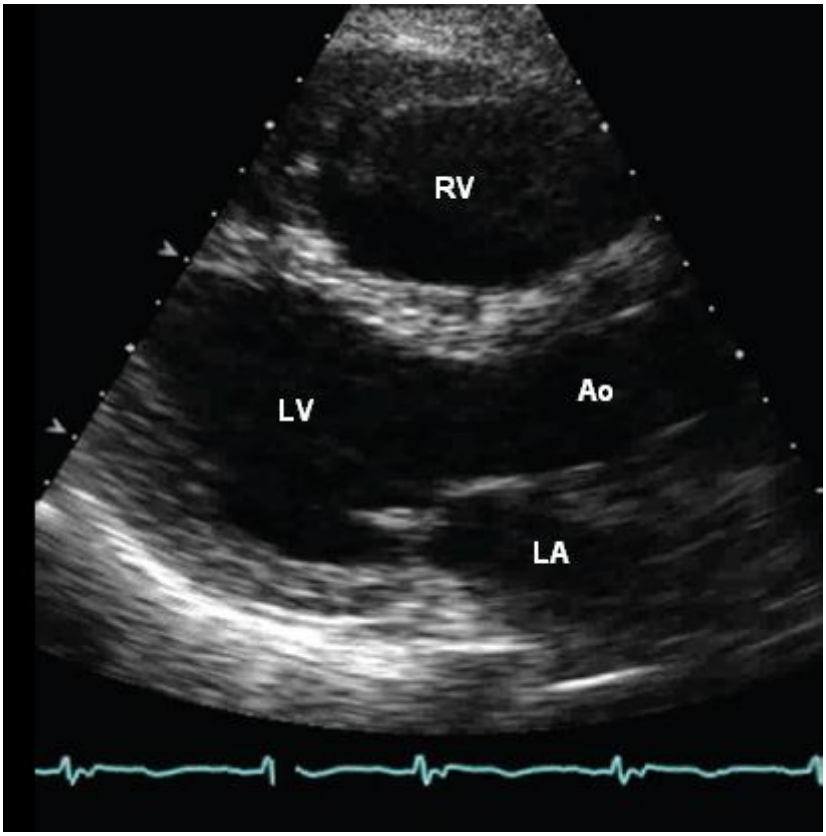
[4] See appendix 3 for copy right details

Figure 4: Image of a parasternal short axis view of the echocardiogram of a patient with tetralogy of Fallot. The image in panel a, demonstrate antero-cephalad deviation of the outlet septum into the right ventricular outflow tract and significant hypoplasia of the pulmonary trunk and the pulmonary arteries. The pulmonary valvar leaflets are not visualized. In panel b, color Doppler has been used, and demonstrates turbulence and acceleration of the flow of blood in the right ventricular outflow tract, originating at the level of the deviated outlet septum. The turbulence continues into the hypoplastic pulmonary trunk and pulmonary arteries. Adapted from *Bailliard F et al* [4].[5]



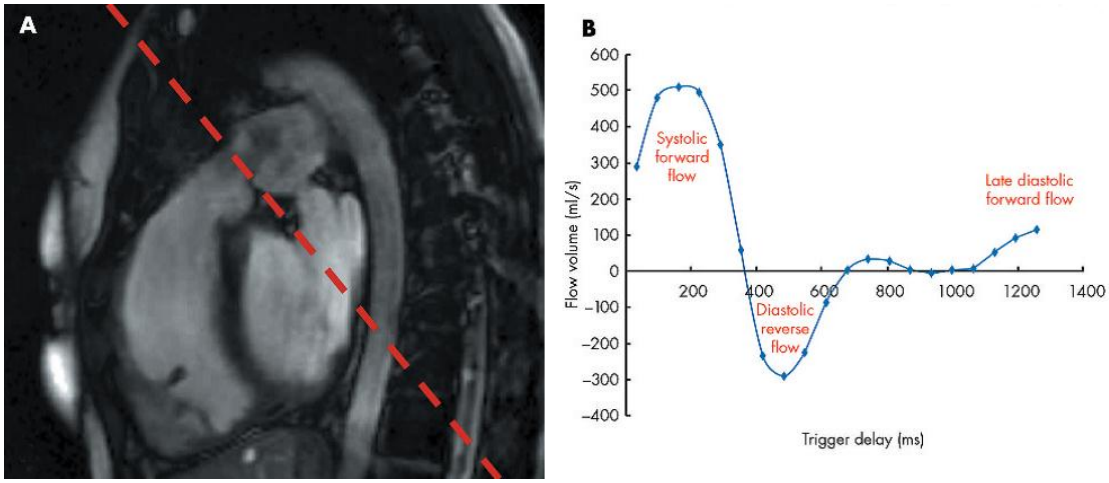
[5] See appendix 2 for copy right details

Figure 5: Echocardiogram of a 22-year-old man with repaired tetralogy of Fallot at age of 2 years. In the parasternal long axis view an overriding aorta is seen with a dilated right ventricle. Echocardiography provides quantitative assessment of left ventricle size and function and aortic root dimensions. It also allows to evaluate the presence and severity of pulmonary regurgitation, right ventricle size and systolic function, and the presence of a ventricular septal defect or any other anatomic abnormalities. Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle. Adapted from *Huehnergarth KV et al* [10].[6]



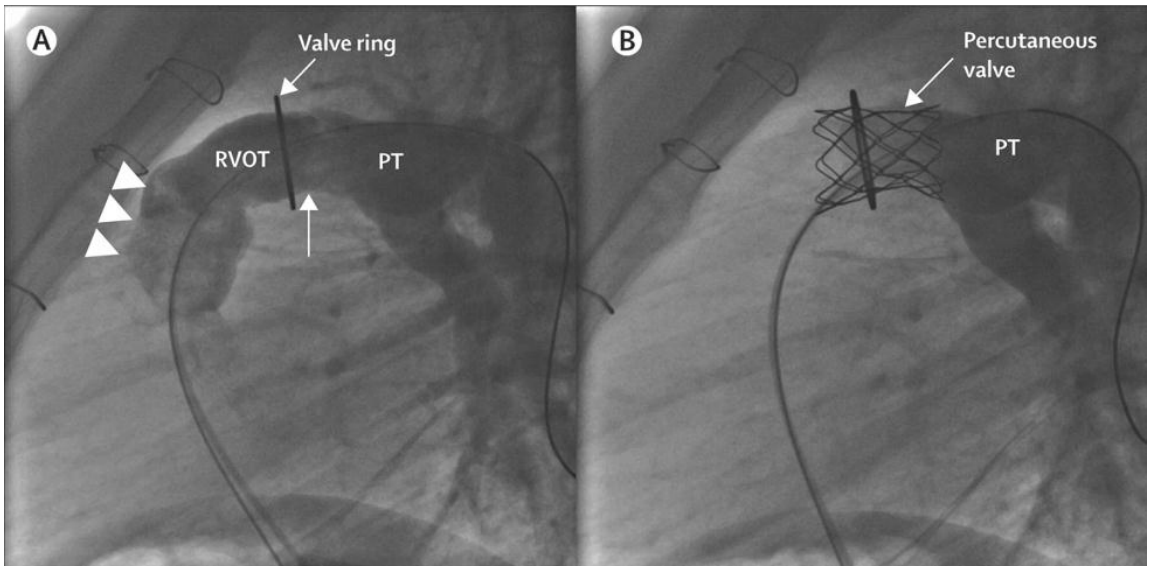
[6] See appendix 4 for copy right details

Figure 6: (A) Right ventricle outflow tract cardiovascular magnetic resonance cine image obtained from a patient with repaired tetralogy of Fallot with significant late pulmonary regurgitation. The red dotted line illustrates the through plane in which a non-breath-hold phase encoded velocity map was acquired. **(B) Flow curve obtained from the same patient.** Through integrating areas containing forward and reverse flow, a pulmonary regurgitation fraction of 34% was calculated. Adapted from *Shinebourne EA et al* [5].[7]



[7] See appendix 5 for copy right details

Figure 7: Percutaneous pulmonary valve replacement. Lateral still-frame pulmonary artery angiograms showing the pulmonary trunk (PT) and the right ventricular outflow tract (RVOT) before (A) and after (B) percutaneous pulmonary valve replacement. The patient has previously undergone surgical placement of a valved conduit between the right ventricle and the pulmonary artery. Note the residual obstruction within the valve leaflets (arrow), just above the valve ring. There is also dense opacification of the right ventricular outflow tract due to the pulmonary regurgitation (arrowheads) in the preimplantation image. The obstruction is completely relieved, and there is no residual regurgitation after percutaneous implantation of a stented valve within the previous valved conduit. Adapted from *Apitz C et al* [1].[8]



[8] See appendix 1 for copy right details

Appendix 1

Mail sent to Andrew Redington at April 19th of 2010

Dear Prof Andrew Redington:

I am a student of the 6th year of the Faculty of Medicine, University of Porto.

I am writing a review on tetralogy of Fallot and for that I used the article "*Tetralogy of Fallot",* Lancet, 2009 as a reference.

I am writing to ask for your permission to use the following figures in my review.

Figure 1: Morphological features of tetralogy of Fallot. The subpulmonary narrowing (arrow) is formed between the malaligned muscular outlet septum (asterisk), which is deviated anterocephalad relative to the limbs of the septomarginal trabeculation and the hypertrophied septoparietal trabeculations. There is a large ventricular septal defect with over-riding of the aorta, which is partly committed to the hypertrophied right ventricle. Note the dysplastic and stenotic pulmonary valve. VSD=ventricular septal defect. Image kindly provided by Robert H Anderson.

Figure 5: Percutaneous pulmonary valve replacement. Lateral still-frame pulmonary artery angiograms showing the pulmonary trunk (PT) and the right ventricular outflow tract (RVOT) before (A) and after (B) percutaneous pulmonary valve replacement. The patient has previously undergone surgical placement of a valved conduit between the right ventricle and the pulmonary artery. Note the residual obstruction within the valve leaflets (arrow), just above the valve ring. There is also dense opacification of the right ventricular outflow tract due to the pulmonary regurgitation (arrowheads) in the preimplantation image. The obstruction is completely relieved, and there is no residual regurgitation after percutaneous implantation of a stented valve within the previous valved conduit.

Yours sincerely,

Manuela Fernandes

Appendix 2

Mail sent to Frederique Bailliard at April 19th of 2010

Dear Dr. Frederique Bailliard:

I am a student of the 6th year of the Faculty of Medicine, University of Porto.

I am writing a review on tetralogy of Fallot and for that I used the article "*Tetralogy of Fallot",* Orphanet J Rare Dis, 2009 as a reference.

I am writing to ask for your permission to use the following figures in my review.

Figure 5: This specimen has tetralogy of Fallot with pulmonary atresia. The pulmonary supply is through multiple systemic-to-pulmonary collateral arteries. The star shows the connection between one of the collateral arteries and the intrapericardial pulmonary arteries. All the other arteries join with the intrapericardial pulmonary arterial supply, or else supply segments of the lung directly. The task of the clinician is to display the supply of the various collateral arteries and their communications with the intrapericardial pulmonary arteries.

Figure 7: A slightly modified view (a), angled to optimize imaging of the pulmonary arteries in the patient imaged to produce Figure 6, reveals significant hypoplasia of the pulmonary trunk and the pulmonary arteries, which result from the antero-cephalad deviation of the outlet septum.

Yours sincerely,

Manuela Fernandes

Appendix 3

Mail sent to Ehsan Haider at April 19th of 2010

Dear Dr. Ehsan Haider:

I am a student of the 6th year of the Faculty of Medicine, University of Porto.

I am writing a review on tetralogy of Fallot and for that I used the article "*The boot-shaped heart sign",* Radiology, 2008 as a reference.

I am writing to ask for your permission to use the following figure in my review.

Figure 1: Frontal chest radiograph of pediatric with tetralogy of Fallot (TOF) shows chracteristic boot-shaped heart with hyperlucent lungs, diminished central hilar pulmonary vessels, and an upturned cardiac apex. Main pulmonary artery segment is flat to concave, and right aortic arch is seen.

Yours sincerely,

Manuela Fernandes

Appendix 4

Mail sent to Kier Huehnergarth at April 19th of 2010

Dear Dr. Kier Huehnergarth:

I am a student of the 6th year of the Faculty of Medicine, University of Porto.

I am writing a review on tetralogy of Fallot and for that I used the article "*Repaired tetralogy of Fallot in the adult: monitoring and management",* Heart, 2008 as a reference.

I am writing to ask for your permission to use the following figure in my review.

Figure 3 Echocardiogram of a 22-year-old man with repaired tetralogy of Fallot at age 2 years. In the parasternal long axis view an overriding aorta is seen with a dilated right ventricle (RV). Echocardiography provides quantitative assessment of left ventricle (LV) size and function and aortic root dimensions, in addition to evaluation of the presence and severity of pulmonary regurgitation, RV size and systolic function, and the presence of a ventricular septal defect or any other anatomic abnormalities. Ao, aorta; LA, left atrium.

Yours sincerely,
Manuela Fernandes

Appendix 5

Mail sent to Elliot Shinebourne at April 19th of 2010

Dear Dr. Elliot Shinebourne:

I am a student of the 6th year of the Faculty of Medicine, University of Porto.

I am writing a review on tetralogy of Fallot and for that I used the article "*Tetralogy of Fallot: from fetus to adult",* Heart, 2006 as a reference.

I am writing to ask for your permission to use the following figure in my review.

Figure 7 (A) RVOT cardiovascular magnetic resonance cine image obtained from a patient with repaired ToF with significant late pulmonary regurgitation. The red dotted line illustrates the throughplane in which a non-breath-hold phase encoded velocity map was acquired. (B) Flow curve obtained from the same patient. Through integrating areas containing forward and reverse flow, a pulmonary regurgitation fraction of 34% was calculated.

Yours sincerely,

Manuela Fernandes
