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Tetralogy of Fallot: Yesterday and Today

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Abstract Tetralogy of Fallot (TOF) is a cyanotic congenital cardiac defect that was first described by Stenson in 1672 and later named for Fallot, who in 1888 described it as a single pathological process responsible for (1) pulmonary outflow tract obstruction, (2) ventricular septal defect (VSD), (3) overriding aortic root, and (4) right ventricular hypertrophy. The surgical history of TOF began with the development of the systemic to pulmonary artery shunt (BT shunt) by Blalock, Taussig, and Thomas in 1944. Ten years later complete repair of TOF was performed by Lillehei using cross-circulation and by Kirklin with a primitive cardiopulmonary bypass circuit. Notable contributions by several other surgeons including Bahnson, Ebert, Malm, Trusler, Barratt-Boyes, and Castaneda would lead us into the modern era of surgery. Today, complete repair of TOF is performed before six months of age with low mortality (<2%). In select cases a modified version of the BT shunt is still performed as the initial procedure. Long-term survival rates are excellent (85%–90%). Adult survivors with TOF are an ever-increasing population and may require reintervention, surgically or catheter based. Promising future innovations include percutaneous pulmonary valve replacement, tissue-engineered autologous valves and conduits, and genetic manipulation. This article presents a review of TOF, including the history of surgical treatment, present-day approaches, and long-term outcomes.

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"The processes of disease are so complex that it is excessively difficult to search out the laws which control them, and, although we have seen a complete revolution in our ideas, what has been accomplished by the new school of medicine is only an earnest of what the future has in store."
Sir William Osler 1895

Introduction

Anatomy

The anatomy of tetralogy of Fallot (TOF) was first described in 1671 by the Danish anatomist and naturalist Niels Stensen in a fetus with ectopia cordis [1]. Several other investigators including Edward Sandifort (1777) [2], William Hunter (1784) [3], Farre (1814) [4], and Thomas Peacock (1846) [5, 6], in turn, described similar anatomy. In 1888, Etienne-Louis Arthur Fallot published a series of reports in the *Marseille Medical Journal* describing the anatomy and the pathologic process underlying the defect. He proposed that there was one pathologic process occurring during fetal development that accounted for the nonrandom association of four anatomic features. Fallot did not use the term "tetralogy of Fallot"; he called the condition *la maladie bleue* (blue malady) or *cyanose cardiaque* (cardiac cyanosis) [1, 7]. The eponymous term "tetralogy of Fallot" was first used in 1924 by Maude Abbott, a Canadian pioneer in pediatric cardiology and pathology [8], who based the attribution on that early description by Fallot.

Tetralogy of Fallot is characterized by four distinct anatomic features: (1) pulmonary outflow tract obstruction, (2) ventricular septal defect (VSD), (3) overriding aortic root, and (4) right ventricular hypertrophy. According to

Anderson, the condition is defined on the basis of antero-cephalad deviation of the outlet septum or its fibrous remnant, with associated malformation of the septoparietal trabeculations [9]. According to Van Praagh, TOF results from underdevelopment of the subpulmonary infundibulum [1]. Both Anderson and Van Praagh agree that TOF is one abnormality or pathologic process that occurs during embryogenesis causing the first three features, plus the fourth feature, right ventricular hypertrophy, which occurs as result of the obstruction to pulmonary blood flow [1, 9]. There is a spectrum of disease from mild right ventricular outflow tract obstruction (RVOTO) to severe obstruction (i.e., TOF–pulmonary atresia). The level of obstruction may occur at one or more of the following heart structures: (1) infundibulum, (2) pulmonary valve, (3) main pulmonary artery, and/or (4) branch pulmonary arteries.

Frequent anatomical associations with TOF include right aortic arch (25%), left anterior descending (LAD) coronary artery from the right coronary artery (RCA) (5%), branch pulmonary artery anomalies (30% of infants presenting in first year of life), major aortopulmonary collaterals (<5%), foramen ovale, and atrial septal defect (10%) [10]. Noncardiac anatomical associations include forked ribs and scoliosis. Anatomical variants of TOF–pulmonic stenosis include TOF–pulmonary atresia with or without major aortopulmonary collaterals, TOF–absent pulmonary valve, TOF–double outlet right ventricle, and TOF–atrioventricular septal defect.

Epidemiology and etiology

Tetralogy of Fallot occurs in 3 of every 10,000 live births and constitutes approximately 7%–10% of all congenital defects. It is one of the most common causes of cyanotic heart disease beyond the neonatal age [11]. Males are affected slightly more often than females. The etiology is multifactorial and has been associated with maternal intake of retinoic acid, untreated maternal diabetes, and phenylketonuria. Chromosomal anomalies including trisomies 21, 18, and 13 have also been associated with TOF. More frequent, however, are microdeletions of chromosome 22 [11]. There is also an association between Alagille syndrome with *JAG1* mutations and TOF. [12]

Clinical manifestations and diagnosis

The presentation of patients with TOF will vary depending on the severity of RVOTO. The majority of patients present as neonates with some degree of cyanosis. Those patients with mild or no cyanosis may not present until months later, when the RVOTO has worsened. Approximately 50% of patients today are diagnosed antenatally by fetal echocardiography. [11]

The prominence of a systolic murmur will be inversely related to the severity of RVOTO. The second heart sound may be single and loud. Clubbing is seen in those patients with severe longstanding cyanosis. Today it is rare to see patients with clubbing (except in the developing world), because diagnosis is made early. Present-day diagnosis usually includes chest radiograph, electrocardiogram, and echocardiogram. Echocardiogram is the gold standard for diagnosis and evaluation of intracardiac anatomy. Cardiac catheterization is rarely used today. Cardiac magnetic resonance imaging (CMRI) is sometimes used to evaluate anatomy and is especially useful in adults with repaired TOF.

Patients with TOF have long been known for their "tet spells," hypercyanotic episodes that usually begin sometime in infancy or toddler age and lessen after age 4–5 years. The spells are usually precipitated by agitation or decreased hydration [13]. These acute spells are caused by an imbalance of pulmonary-to-systemic blood flow. When there is a decrease in systemic vascular resistance (i.e., dehydration) or an increase in pulmonary vascular resistance (i.e., infundibular muscle spasm and obstruction) a right-to-left shunt across the VSD and marked desaturation will be seen [14]. Untreated severe cyanosis and hypoxia can occur, followed by syncope and even death. Treatment includes calming the child, providing oxygen and hydration, increasing peripheral resistance with neosynephrine or phenylephrine, and correcting metabolic acidosis. The knees-to-chest position in infants or squatting in older children has also been shown to increase systemic pressure and help treat tet spells. The use of propranolol has been described to prevent or lessen the severity of spells through relaxation of the infundibular muscle [13].

Natural history

The natural history of TOF without major associated cardiac anomalies is variable and, like its presentation, depends on the severity of RVOTO. Twenty-five percent of infants with severe obstruction not treated surgically die within the first year. Left untreated, 40% die by age 3 years, 70% by age 10 years, and 95% by age 40 years. The hazard function, or instantaneous risk of death, is greatest in the first year of life. After the first year the risk is constant until age 25 years, but then it increases [10]. Major causes of death in surgically untreated patients include hypoxic spells (62%), cerebrovascular accidents (17%), and brain abscesses (13%) [15].

Surgical treatment—early years

Systemic to pulmonary artery shunt

By the 1900 s there were several published articles describing the anatomy of TOF, but unfortunately there was no treatment for patients born with this defect. Murphy and Cameron [16] in their JAMA Classics article, "The Blalock-Taussig-Thomas Collaboration," described the state of care for patients with cyanotic congenital heart disease in 1945 as follows: "The care of patients with cyanotic heart disease was an exercise in clinical-pathological correlation rather that therapeutic hope."

The story behind the first surgical treatment of TOF began at Johns Hopkins with Helen Taussig, director of the cardiac clinic at the Harriet Lane Home for Invalid Children, Alfred Blalock, chief of surgery, and Vivien Thomas, Blalock's laboratory surgical technician. By the early 1940 s Taussig had spent over 10 years caring for children with congenital heart disease and was one of the leading authorities. Caring for these children over many years afforded Taussig the opportunity to witness the natural history of many congenital heart defects [17]. She noted that there were some children with cyanotic heart disease who did better as long as the ductus arteriosus remained open. Those whose ductus closed early died shortly thereafter. This was confirmed on autopsy. She realized that many cyanotic babies were dying of anoxemia and not cardiac failure, as had been thought. Taussig started to think about how one could keep the ductus open. Upon reading Robert Gross's 1939 report of the first successful closure of a patent ductus arteriosus (PDA) in a child, she came up with the idea of creating a ductus [18]. Some time in 1940 or 1941 Taussig met with Dr. Gross to explain her concept of an artificial ductus. Gross was reported to have said that he was only interested in operations to close a patent ductus not open one [17].

Taussig then approached Blalock directly after he had performed a ductal ligation for the first time at Johns Hopkins. In her own words, Taussig said to Blalock, "I stand in awe and admiration of your surgical skill—but a truly great day will come when you can build a ductus for a cyanotic child, not when you close a ductus for a child who has a little too much blood going to his lungs." Blalock replied, "When that day comes, this will be child's play" [18]. Blalock and Thomas went on to create a cyanotic animal model to test Taussig's theory. They removed lobes of one or both lungs and created an anastomosis between the proximal ends of the pulmonary artery and pulmonary vein, which resulted in arterial desaturation. They then created a systemic (subclavian artery) to pulmonary artery shunt or artificial ductus, which improved the cyanosis [19].

On November 29, 1944, a very ill, cyanotic, 4 kg, 15-month-old baby girl with TOF was taken to the operating room by Dr. Blalock with Vivien Thomas by his side. Through a left anterolateral thoracotomy the divided proximal end of the left subclavian artery was anastomosed to the side of the left pulmonary artery. The operation took less than one and a half hours. The postoperative course was stormy because the child developed several pneumothoraces, but eventually she did well and was discharged home two months after the operation [20].

Blalock went on to perform two additional systemic to pulmonary artery shunts and reported the series of three patients in a landmark paper published in the *Journal of the American Medical Association* in May 1945. The case series had been presented before the Johns Hopkins Medical Society on March 12, 1945 [20]. The work of Taussig, Blalock, and Thomas served as a model for future bench to bedside investigations [16]. Between November 29, 1944, and January 1, 1951, Blalock and associates performed systemic to pulmonary artery shunts on 1,034 cyanotic patients with decreased pulmonary blood flow. Of the total number of patients treated, 779 (75%) were believed to have TOF, and 99 of those 779 patients died after operation. Helen Taussig performed two detailed long-term studies on this initial cohort of patients, and both were published: one in 1971 and the other in 1975. A little over 50% of the original patients who survived the initial operation were still alive at 20 years follow-up [18].

The development of the systemic to pulmonary arterial shunt (the Blalock-Taussig shunt—BT shunt) by Blalock, Taussig, and Thomas marked the beginning of the era of congenital heart surgery. The BT shunt quickly became acceptable palliation not only for TOF but also for other cyanotic defects associated with decreased pulmonary blood flow. By 1950, many other centers in addition to Johns Hopkins were performing the BT shunt procedure.

Other systemic to pulmonary artery shunts and modifications of the original BT shunt were later described. The Potts shunt reported in 1946 was an anastomosis between the descending aorta and the left pulmonary artery. The procedure was later abandoned because of the difficulty in closing the shunt at the time of complete repair [21]. The Waterson shunt described in 1962 was an ascending aorta to pulmonary artery anastomosis that was easy to perform and simple to close [22]. The Cooley shunt reported in 1966 was an intrapericardial anastomosis from ascending aorta to right pulmonary artery [23]. The Potts, Waterson, and Cooley shunts were all central shunts and were less likely to thrombose compared to the more peripherally placed BT shunt. The modified BT shunt used a prosthetic tube graft interposed between the systemic artery (subclavian artery) and the pulmonary artery, instead of the direct anastomosis first described [24]. Most congenital

surgeons today perform either a modified BT shunt via a posterolateral thoracotomy or a median sternotomy; or a central shunt (ascending aorta to main pulmonary artery) via a median sternotomy. Both the modified BT shunt and the central shunt today use a prosthetic graft made of polytetrafluoroethylene (PTFE).

In 1948, following Blalock's publication of the first three patients treated with a BT shunt, Brock described a procedure to relieve pulmonic stenosis. Brock's procedure was described for either infundibular or valvular pulmonic stenosis. It consisted of a right ventriculotomy through which dilatation and valvulotomy/infundibulotomy with a cutting knife would be performed. Blalock himself performed this procedure, but only in patients with pure pulmonary stenosis; he did not recommend it for patients with TOF for two reasons, which he reported. Blalock believed that pulmonary valve stenosis was rare in patients with TOF, and also that it was technically difficult to remove the infundibular stenosis with this method. Three years later, despite Blalock's comments, Downing reported using the Brock procedure for relief of pulmonary stenosis in 8 patients with TOF–pulmonary stenosis. Seven of the eight patients survived with improvement in cyanosis and exercise tolerance. Both Brock and Downing found that there was a higher than initially believed incidence of pulmonary valvular stenosis in TOF patients [25].

Early complete repair

Up until 1952 congenital heart surgery was virtually an extracardiac field, except for Brock's treatment of pulmonic stenosis. The first congenital intracardiac procedure was performed by Lewis and Taufic in 1952. They closed an atrial septal defect (ASD) under direct vision through a right atriotomy using moderate hypothermia and inflow occlusion [26]. The following year, John Gibbon, using the "mechanical heart–lung apparatus" that he developed, operated on four patients with atrial septal defects, only one of whom survived. Following Gibbon, other investigators made attempts with various heart–lung machines. However, few surgeons were interested in using those devices. The success in the animal laboratory with these first heart–lung machines was not reproducible in the operating room with humans. In addition, surgeons such as John Lewis and Henry Swan were already successfully performing intracardiac procedures on patients without mechanical heart–lung bypass. They used hypothermia and inflow occlusion (circulatory arrest) as they repaired various congenital defects [27]. Swan, in his report of direct-vision surgery using hypothermia, stated that there were three adverse characteristics of extracorporeal circulation: "(1) its complexity and expense, (2) material increase in the magnitude of the operation and (3) its failure to provide a dry field for operation" [28].

Meanwhile, Lillehei and colleagues in Minneapolis were performing experiments in the laboratory using cross-circulation in dogs. Because there was no pump oxygenator available to Lillehei and colleagues at that time, cross-circulation was being used temporarily to permit open heart work on the animals. The animals operated on with cross-circulation had better outcomes than those operated on with the heart lung machine. The cross-circulation animals recovered quickly and there was low mortality. The lack of success with the early heart–lung machines gave Lillehei's group the incentive to start performing open-heart surgery in humans using controlled cross-circulation. There was a single pump that controlled the reciprocal exchange of blood between the patient and the donor. From March 1954 to July 1955, Lillehei operated on 45 patients with controlled cross-circulation, and 22 of those patients survived 30 years or more with good quality of life. More than half of the patients were 6 months of age or younger, with various diagnoses, including VSD, TOF, atrioventricular canal defect, PDA, pulmonic stenosis, and anomalous pulmonary venous drainage [29]. Lillehei was the first to successfully perform complete repair of TOF using extracorporeal circulation. His success also provided evidence that open-heart surgery with temporary extracorporeal circulation was possible [27].

Interest resurfaced in the development of a heart–lung machine, or as we know it today a cardiopulmonary bypass circuit (CPB) circuit, and research continued. In 1955, at the Mayo Clinic, John Kirklin and associates reported the use of a modified Gibbons CPB circuit in the open repair of complex congenital heart defects including VSD and TOF. Twenty-four of their 40 patients survived (60%) [30]. Kirklin continued to employ a modified version of the original Gibbon pump called the Gibbon-Mayo pump-oxygenator, not only in the repair of VSD and TOF but also in treating other congenital defects. He published several reports over the next 10 years (more than 500 patients) on the complete repair of TOF as a primary procedure, and as a secondary procedure in patients who had previously undergone a shunt procedure [31–35].

In addition to Kirklin, surgeons from other centers were reporting on their experiences with complete repair of TOF [36–40]. Mortality in the early years of repair was as high as 60%, but by the early 1960s perioperative mortality decreased significantly to 7%–14%. Ages of these patients ranged from 15 months to 54 years. The mortality rate was higher in patients with severe cyanosis and younger age. The number of patients who had previous shunts ranged from 43% to 75% [34–40]. Conduct of CPB was relatively uniform by all centers, using a disc or vertical screen oxygenator. On bypass, patients' body temperature ranged

from 25 to 32°C. Deep hypothermic circulatory arrest (DHCA) at 15°C was used to close a Potts shunt if present. Cardiac asystole was induced by potassium citrate infusion in the early years, and then by intermittent aortic cross clamping. The left heart was vented via the apex of the left ventricle (LV) to prevent coronary and systemic air embolus. The CPB circuit was usually primed with fresh whole or reconstituted blood [34–36, 38–40]. Aminocaproic acid was used by some groups and helped with the postoperative bleeding seen especially in the severely cyanotic, polycythemic patients [38]. The operations were performed via median sternotomy. Shunts, if present, were closed prior to initiation of CPB. Depending on the RV outflow tract coronary artery anatomy and location of stenosis, a longitudinal or transverse ventriculotomy was made. Initially these incisions were quite large, but as time went on surgeons realized they did not need to be so large. The closure of VSD was accomplished through the RV ventriculotomy with a pericardial or prosthetic patch. Division and/or resection of infundibular muscle bundles and relief of pulmonary valve stenosis was performed prior to VSD closure. An infundibular patch was placed if the resection of muscle was not enough to enlarge the outflow tract, and a transannular patch was applied if the pulmonary annulus was too small. The pulmonary valve was preserved if possible. Intracardiac pressures were almost always measured, with the goal to have the systolic RV/LV pressure ratio <0.5–0.75 [34–36, 38–40]. Surgeons recognized early on that the right atrial pressures needed to be monitored carefully in the postoperative period and be kept higher than normal (18–20 mmHg) because of the noncompliance of the right ventricle after reconstruction [38]. Use of an aortic or pulmonary homograft as a right ventricle to pulmonary artery conduit for those patients with severe hypoplasia or atresia was also first described during this period [41].

Several technical issues were encountered during this time period, among them, coronary air embolism, coronary artery injury, inadequate myocardial protection, poor systemic perfusion, bleeding, postoperative low cardiac output, and pulmonary dysfunction. As advances and changes in surgical technique and conduct of cardiopulmonary bypass were achieved, there was a commensurate improvement in overall outcomes and survival. Younger age (<5 years), severity of cyanosis and obstruction to pulmonary flow, use of transannular patch, and presence of a Potts shunt were associated with higher risk for mortality in all series. The presence of a systemic to pulmonary artery shunt (occluded or open) as a risk factor for mortality varied depending on center [34–36, 38–40].

Kirklin, in his article reviewing early and late results in 337 patients operated on for TOF, also found that severe associated disease such as left pulmonary artery agenesis, aortopulmonary collaterals, coronary artery anomalies, and end-to-end BT shunts were factors that increased the mortality risk [35]. Factors associated with better probability of survival included accurate anatomic repair, decreased use of transannular patch, hemostasis, adequate systemic perfusion, maintenance of adequate blood volume, and avoidance of metabolic acidosis [34].

By the end of the 1960 s many centers were beginning to evaluate and publish follow-up on their patients who had undergone complete correction over the previous 10 years. In those patients that left the hospital, 80%–90% were functioning well [35–37, 42]. Malm and colleagues [42] found that approximately 80% of patients in their series had good to excellent hemodynamics at postoperative cardiac catheterization. The predominant late follow-up issue was pulmonary insufficiency, which most often occurred in patients who had transannular patches [35–37, 42]. A significant number of the patients with pulmonary insufficiency also had cardiomegaly. Aneurysmal dilatation of outflow tract patches was noted, usually in patients with distal outflow tract obstruction or when pericardium was used for patch material. Very few patients had significant residual RVOTO [35–37]. A small number of patients had new aortic insufficiency [37].

Results of these follow-up studies provided the basis for surgical treatment recommendations for TOF. Symptomatic disease at any age was an indication for surgical intervention. A shunting procedure was recommended in children <5 years of age because of the high mortality risk after complete repair in this age group. It was thought that placing a shunt in these patients might help to prepare the pulmonary bed for total correction. Once shunted, the patients should undergo complete correction before the second decade. Symptomatic patients greater than 5 years of age could undergo complete primary repair, and ideally, elective primary repair would be carried out between the ages 8 and 12 years [42].

The years between 1950 and 1970 were marked by an increased understanding of the anatomy of TOF, a more standardized surgical repair, technical advancements in conduct of cardiopulmonary bypass, and better postoperative management all of which translated into survival rates as high as 85%–90% by the end of the two decades.

Surgical treatment: the modern era 1970–present

In the modern era of surgical treatment there was a shift toward performing complete repair of TOF in younger age groups, including neonates. This happened not just in TOF but in other complex cardiac defects such as transposition of the great arteries [43].

Neonatal surgery

Up until the 1970s very few surgeons were performing complete repair of TOF in children younger than 3–5 years of age. The results were variable, with early mortality rates of 5%–14% [36, 44, 45]. In these early reports important observations were made. McMillan in 1965 [44] noted that patients whose VSD was closed primarily had a high incidence of heart block and death. He subsequently changed to patch closure of VSD. Bonchek and Starr [45] evaluated a series of 59 TOF patients less than two years of age. They separated their patients into six groups according to the initial severity of cyanosis and symptoms. The patients who had none or mild symptoms and cyanosis worsened with time. Waiting for complete repair until after the age of two years was a risk factor for increased mortality even if those patients underwent eventual surgical intervention. Six of 14 patients died, 3 while waiting and 3 early after surgical intervention. In the 28 patients who had severe symptoms at diagnosis and underwent immediate complete repair, the mortality was only 7%. In those patients who received shunts at diagnosis 31% died (pulmonary atresia or severe hypoplasia only). Bonchek and Starr concluded that it was advantageous to perform complete repair at an earlier age and not to wait until the child got older. Based on direct visualization and pathological examination of the RV outflow tract in those patients with mild symptoms, they also concluded that early operation would prevent worsening obstruction from fibrosis and undergrowth of the RV outflow tract. Shunts did not improve the growth of the RV outflow tract and actually may have had a negative impact on it. This study was important in that it not only compared early versus late primary repair but also examined the natural history of TOF pathophysiology.

Barratt-Boyes, Kirklin, and Castaneda's reports in the early 1970 s demonstrated that complete repair of TOF and other complex congenital heart defects could be done safely in neonates and infants with relatively low mortality. Deep hypothermic circulatory arrest or low-flow hypothermic CPB was used. In those patients with TOF the ages ranged from 1 month to 48 months. Mortality ranged from 4% to 17%. There was no heart block and no significant neurological sequelae [46–48]. There was a higher incidence of transannular patch repair (TAP) in both the Barratt-Boyes (75% in the less than 4 months age group) series [46] and the Castaneda (85% of all patients 1 day to 18 months of age) series [48]. Kirklin only used one TAP (4.5%) [47]. Barratt-Boyes compared his series of complete primary repairs with his previous series of 44 infants palliated with a BT shunt. In those patients palliated with a BT shunt there was an early mortality of 20% and late mortality of 6%. After second-stage complete repair, the mortality was 8%. He concluded that there was higher mortality risk in the two-stage patients (shunt then complete repair) than in primary repair. [46] This trend toward earlier repair continued well into the next three decades. Today, early survival after complete primary repair is reported as high as 98%–100% in large centers [49–52].

Despite the excellent survival results in neonatal and infant primary complete repair, there still remains controversy today. What is the optimal timing of complete repair? The history of surgical treatment of TOF from its inception into the 1970s clearly supports the present-day recommendation of complete repair by age 6 months (but no later than 12 months), for the nonductal dependent, asymptomatic infant diagnosed with TOF [45]. The remaining controversy surrounds the question of whether or not the symptomatic neonate should undergo a primary complete repair versus a two-stage procedure beginning with shunt placement and followed by complete repair. Most surgeons agree that the relative indications for shunt as the initial procedure in the neonatal period include those patients with severely hypoplastic pulmonary arteries, anomalous LAD from an RCA crossing the RV outflow tract, or associated non-cardiac anomalies.

The advocates for complete repair in the neonatal period believe that there are potential benefits of complete repair such as promotion of normal somatic growth and development, elimination of chronic hypoxemia, less need for extensive right ventricular muscle excision, better late ventricular function, and decreased incidence of late dysrhythmias [53]. In addition, one-stage repair may lessen parental anxiety and lower the risk of hypercyanotic spells and their sequelae [54]. Surgeons opposed to early one-stage primary repair believe that there is a higher incidence of TAP and its potential long-term consequences, especially pulmonary insufficiency. However, a long-term follow-up study from Boston did not show any significant difference between the patients with or without TAP with regard either to freedom from reintervention or to survival [55]. Proponents of the two-stage repair believe a shunt may increase the growth of the pulmonary valve and branch pulmonary arteries, thereby decreasing the chance of a TAP when it is time for complete repair. In addition, a shunt can be placed without the need for bypass in most cases, and this avoids exposing a neonate to bypass or circulatory arrest.

Fraser and colleagues devised a system to individualize the surgical treatment to the patient. Based on their institution's 40-year experience with 2,175 patients, they developed a management protocol focusing on patient size, systemic arterial saturation, and anatomy. Symptomatic patients and asymptomatic patients weighing less than 4 kg with threatened pulmonary artery isolation underwent palliation with a BT shunt followed by complete repair at

6–12 months of age. All other patients underwent primary repair at or after 6 months of age. Early mortality was 0% with 3 late deaths (2.1%). There was a 3% reoperation rate. Fraser et al. found no significant difference between the primary repair and two-staged patients with regard to time to extubation, intensive care unit (ICU) stay, or hospital length of stay (LOS). Their hypothetic "ideal" TOF management strategy sought to have no attrition while awaiting repair, appropriate organ system growth especially neurodevelopment, promotion of pulmonary artery growth, avoidance of circulatory arrest, minimal or no RV ventriculotomy, preservation of pulmonary valve, minimal need for reintervention, and minimal late morbidity [56].

Changes in operative technique

Long-term studies performed in those patients operated on during the 1950 s and 1960 s continued to find chronic pulmonary insufficiency (PI) that was associated with RV dysfunction [57], exercise intolerance [58], and ventricular dysrhythmias [59], as well as a small but real incidence in sudden death [60]. Transannular patching and ventriculotomy were thought to play a major role in PI and RV dysfunction.

Pulmonary valve sparing—the transatrial and transatrial-transpulmonary approaches

In an effort to preserve the pulmonary valve and avoid ventriculotomy the transatrial and transatrial-transpulmonary approaches were revisited in the 1990s [61–63]. The first description of a transatrial, transpulmonary repair of TOF–pulmonary stenosis was actually published by Hudspeth and colleagues in 1963. They described application of his surgical technique in 10 patients with varying degrees of cyanosis. Both the VSD and the infundibular stenosis were approached through a right atriotomy. Prior to closure of the VSD, the infundibular and pulmonary subvalvular area were evaluated and enlarged as needed through the right atriotomy. If necessary, a supravalvular incision was made above the pulmonary valve and further work was performed on the pulmonary valve itself (i.e., commissurotomy). Systolic ventricular and aortic pressures were measured post-repair, and if the RV pressure was 50% or less of the LV pressure the repair was believed to be adequate [64].

The transatrial and transatrial-transpulmonary approach is frequently used today in all age groups, including neonates, with survival >99% and a low incidence of early reintervention [56, 61–63] Stewart et al. [62] reviewed 102 patients (median age 5.9 months) comparing transatrial approaches with TAP. They found that postoperative RV outflow tract gradients were greater in the transatrial and transatrial-transpulmonary groups than in the TAP group. However, the incidence of moderate PI was higher in the TAP patients. With time (mean 34 months), the peak RV outflow tract gradient decreased in the transatrial groups, whereas there was a mean increase in the TAP group. Pulmonary insufficiency increased for both groups but was higher for the TAP group. It will be important to see if the long-term results (20–30 years) have an impact on PI, RV dysfunction, and ventricular dysrhythmias.

Pulmonary valve substitutes

Innovations such as monocusp valves to create right ventricular outflow tract competence have been reported in patients where a transannular patch is needed because the pulmonary valve/annulus is too small. The monocusp valve had initially been described by Zavanella and colleagues in 1978. Their technique used the native posterior cusp of a native bicuspid valve or two posterior cusps of a native trileaflet valve to construct a monocusp valve. This was designed to decrease or prevent PI in those patients needing a transannular patch [65]. During the 1980's there were a few small series and one animal study describing the use of monocusps or composite transannular patches [66–68]. It was not until the 1990s that the monocusp valve made from autologous or bovine pericardium, allograft pulmonary valve cusp, or polytetrafluoroethylene (PTFE) membrane became more popular [69–71]. In the early postoperative period monocusp valves have been shown to significantly reduce or prevent PI [70]. Long-term survival, freedom from reoperation (10 years), and freedom from progression to greater than moderate PI (10 years) for those patients with TOF and TOF–pulmonary atresia who received a PTFE monocusp valve were 98%, 88%, and 53%, respectively [71].

Valved right ventricle (RV) to pulmonary artery (PA) conduits have been used to reconstruct the right ventricular outflow tract in patients whose pulmonary valve/annulus is too small. These conduits are especially important in patients with TOF–pulmonary atresia and TOF patients requiring reoperation for severe PI or recurrent stenosis. Complete repair of TOF–pulmonary atresia with a homograft as a RV to PA conduit was initially reported in 1966 [41]. In the 1980 s more refined modes of cryopreservation without the use of gamma radiation were being used, and cryopreserved valved homografts gained popularity both in adult and congenital heart surgery [72]. Pulmonary homografts are still used, especially in infants, even though their freedom from reoperation is only 50% at 5 years [73]. Aortic homografts have been shown to be as durable as pulmonary homografts [72]. However, both aortic and pulmonary homografts, especially when used in neonates, have a median freedom from explantation of approximately

3 years [74]. The ideal valve and conduit replacement has yet to be found. New stentless heterograft valved conduits (i.e., bovine jugular vein graft) and autologous pericardial valved conduits are promising alternatives to homografts [72]. Tissue-engineered valves and conduits have future potential, and if they are successful may be the closest to an ideal conduit, especially in children.

Adults with tetralogy of fallot

Recent estimates suggest that there are more adults than children living with congenital heart disease, and this population is growing by 5% per year [75]. This may be underestimating the real number, as many adult patients with congenital heart disease (ACHD) are not routinely followed. Pediatric cardiologists and congenital heart surgeons are just beginning to appreciate the magnitude of new issues that adult congenital heart disease (ACHD) bring to their prospective fields.

Tetralogy of Fallot is the oldest surgically treated complex congenital heart defect and has well documented long-term follow-up [76]. Kirklin reported a 32-year actuarial survival rate of 88% in 163 patients surviving 30 days after complete surgical repair of TOF that was performed during 1955–60. Predictors of late mortality were older age at operation, previous heart failure, and high > 0.5 RV:LV systolic pressure [77]. In an inception cohort of adults with repaired TOF evaluated by Hickey et al., the late risk of death was approximately 0.5% per year 30 years after correction, with a gradual increase with age. Incremental risk factors for death in the late hazard phase included anatomic subtype TOF–atrioventricular canal and TOF–double outlet right ventricle, branch pulmonary artery stenosis, and Trisomy 21 [78].

Many of the questions raised by surgeons during the early years of TOF repair regarding the effects of surgical repair are being answered today through long-term studies. Despite excellent early outcomes in survival, a number of patients are left with both anatomic and functional abnormalities and will need further intervention. Postoperative residua seen long term in repaired TOF patients include right ventricular volume overload from PI, RV outflow tract obstruction, right ventricular aneurysm from outflow tract patch or from ventriculotomy, distal pulmonary artery obstruction, atrial and ventricular incisional scars, ventricular septal defects (recurrent or residual), ventricular hypertrophy, chamber enlargement, biventricular dysfunction, aortic insufficiency, and aortic root dilatation [76, 79]. Arrhythmia, heart failure, and complications from reoperation are the three most common late causes of death in repaired TOF adults [77]. Risk of sudden cardiac death increases with time. Thirty years after surgery the risk is reported to be approximately 6%–9% [59]. Identified risk factors for sudden death include electrocardiographic QRS duration >180 ms, older age at repair, significant pulmonary valve or tricuspid valve regurgitation, history of syncope, cardiothoracic ratio >0.6 on chest radiograph, multifocal premature ventricular contractions, clinical ventricular tachycardia, and a positive programmed ventricular stimulation study [59].

The most common indication for reoperation is PI [76]. Chronic, severe PI, which can cause right ventricular dilatation and heart failure, has been a focus of many investigations recently, and the timing of surgical intervention especially in the asymptomatic patient remains a controversial issue [79]. It is important to balance the benefits of pulmonary valve replacement (decrease in RV volume overload and RV remodeling) needed before irreversible dysfunction occurs versus the disadvantages of valve failure and the need for future reintervention.

Criteria for pulmonary valve replacement have been developed based on severity of PI as measured by regurgitant fraction on CMR or CT scan; right and left ventricular end-systolic and end-diastolic volume indices, ejection fractions, and presence of RVOT aneurysm. Clinical criteria include exercise intolerance, symptoms and signs of heart failure, cardiac medications, syncope, and sustained ventricular tachycardia. Additional criteria to be considered are hemodynamically significant lesions, such as moderate or severe tricuspid regurgitation, residual left-to-right shunts at the atrial or ventricular level, severe aortic regurgitation, and TOF repair at later age (greater than 3 years) [79].

In addition to pulmonary valve replacement, there are preliminary data to support resection of right ventricular outflow tract aneurysms and RV remodeling. This work is based on the concepts of ventricular remodeling developed for the left ventricle. Initial studies have demonstrated improved RV function. A prospective randomized trial is in progress to determine if this treatment improves RV volumes and function [80].

Further development in valve technology (bioprosthetic and prosthetic valves, tissue-engineered valves) and transcatheter techniques for valve replacement will have an impact on the timing and indications for pulmonary valve replacement in the future [79].

Future innovations

Tissue-engineered valves and valved conduits

Successful in vitro creation of tissue-engineered heart valves based on allograft matrices reseeded with human venous endothelial cells was reported in 2002. Shortly thereafter, successful implantation of tissue-engineered

human heart valves using autologous progenitor cells into two pediatric patients was reported. At 3.5 years follow-up both patients are free from pulmonary dilatation or stenosis, valve degeneration, cusp thickening or reduction in mobility, and trivial to mild PI [81]. Valved conduits have also been created in animal models [82]. This is promising work and has potential in providing infants and children with not just TOF but other congenital defects with alternative valve and tissue replacement that has the capacity to grow and remodel along with the somatic growth of the child [59, 81].

Percutaneous valves

Percutaneous implantation of valves is a rapidly growing field, with human trials in progress. This therapy has the potential to lower both morbidity and mortality in adult patients with repaired TOF who are in need of reoperation for pulmonary valve replacement. Initial results with this therapy are encouraging [83].

Genetic manipulation

A number of genes have recently been identified that are involved in cardiogenesis. In addition, large-scale mutation screenings of congenital heart patients have identified several important genes that may become valuable in diagnosis. Animal model systems have been developed, in particular the mouse heart model, which is similar to the human heart and amenable to genetic manipulation. These models provide the framework for future research with the potential for genetic manipulation as a therapeutic tool for congenital heart disease [84].

Summary

The history of the surgical treatment of TOF is over 60 years old. The Blalock-Taussig shunt introduced in 1944 was lifesaving for thousands of patients for whom there was no hope. Its development marked the beginning of surgical treatment of congenital heart disease and served as a model for future bench-to-bedside innovations. Complete repair of TOF and the development of cardiopulmonary bypass quickly followed. Advances in surgical techniques, cardiopulmonary bypass, and postoperative care over the past 6 decades have brought us today to where survival after complete repair is greater than 98% in large congenital heart surgery programs. Two major changes in the surgical treatment of TOF were prompted by the results of long-term studies of the patients treated operatively in the early era. With such re-evaluation came a shift away from palliation to early primary repair, and new surgical techniques were developed aimed at preservation of right ventricular function. Because of the excellent early and late survival rates after repair of TOF, there is an ever-growing population of adults with repaired TOF. It is in this adult population that we will ultimately determine whether the changes in our surgical treatment will have a positive impact on late RV dysfunction.

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