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Expert Review

Tetralogy of Fallot: Perioperative Management and Analysis of Outcomes

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TETRALOGY OF FALLOT (TOF) is one of the most common congenital cardiac disorders, accounting for roughly 10% of all congenital heart malformations and representing the most prevalent form of cyanotic congenital cardiac disease. Estimates from the Centers for Disease Control and Prevention suggest that TOF occurs in approximately 1 in every 2,518 births, resulting in approximately 1,657 new patients with TOF born in the United States each year.[1] In the current era, studies evaluating both immediate and long-term follow-up of TOF demonstrate dramatic improvements in survival since the first operations performed in the 1950s. Early surgical repair in the first year of life now is performed commonly at most major centers, with an operative mortality of less than 2%.[2,3] Long-term survival is the expectation following repair, as current outcomes data suggest a 90% survival rate beyond 30 years of age.[2,4,5] Importantly, the increased life expectancy for patients with TOF has resulted in significant demographic changes in this patient population as well. According to Marelli et al., the prevalence of TOF increased at a higher rate in adults compared with children from 1985 to 2000, with their results also suggesting that the prevalence of severe congenital heart disease, such as TOF, had yet to peak in adults.[6] A follow-up study of this same North American population (Quebec Congenital Heart Disease Database) confirmed this predicted trend, with data showing that adults accounted for nearly two-thirds of all patients with congenital heart disease in 2010.[7] Importantly, repaired TOF has become the most common form of cyanotic congenital heart disease seen in the adult population.

As more and more patients continue to survive into adulthood, many will require subsequent interventions and reoperations. Post-repair, most patients are left with residual anatomic, hemodynamic, and functional abnormalities. Most notably, these include right ventricular dilatation from chronic pulmonary regurgitation (PR), pulmonary artery stenosis, right ventricular outflow tract aneurysm, tricuspid regurgitation (TR), and residual ventricular septal defects (VSDs). These abnormalities typically are tolerated well through adolescence; however, beginning in the third decade the incidence of exercise intolerance, dysrhythmias, heart failure symptoms, and death begins to rise.[3] Thus, this rapidly growing patient population is one with significant comorbidities. To be leaders in the perioperative care of these patients, it is essential that anesthesiologists understand the complexities and challenges uniquely associated with TOF. To that end, the focus of this

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review is to provide an update on TOF for the cardiovascular anesthesiologist, highlighting important considerations for the perioperative management of this condition in both pediatric and adult patients.

Anatomy and Current Classification

The classic description of TOF includes 4 distinct morphologic abnormalities: a VSD, rightward shifting ("override") of the aorta directly above/across the ventricular septum, right ventricular outflow obstruction, and right ventricular hypertrophy. The first 3 features are due to an anterior and cephalad displacement of the infundibular (outflow) septum during fetal development, resulting in malalignment of the outflow portion of the septum with the inlet and muscular portions.[8] The VSD is perimembranous, large, and unrestrictive; override of the aorta above the VSD leads to a biventricular origin of aortic flow with an enlarged aorta and smaller pulmonary artery. The fourth feature, right ventricular hypertrophy, develops secondary to right ventricular outflow obstruction and exposure of the right ventricle to the systemic pressure. Right ventricular outflow tract obstruction can occur at the subvalvular, valvular, or supravalvular (ie, main pulmonary artery and/or branch pulmonary arteries) levels. It has been thought that all 4 features of TOF arise from a single morphogenetic defect: failed expansion of the subpulmonary conus.

Several additional anatomic abnormalities, with important clinical implications, frequently are associated with TOF. Coronary artery abnormalities may be present with the most concerning occurring when the left anterior descending artery originates anomalously from the right coronary artery. In this scenario, the artery may course across the right ventricular outflow tract and is at risk for injury during a transannular patch repair. This typically requires an alternative surgical approach. Multiple VSDs are present in ~10% of patients, while some may have an atrial septal defect (ASD), commonly referred to as the "pentalogy of Fallot." Branch pulmonary artery stenosis can occur, either naturally at the insertion site of the ductus arteriosus or secondary to palliative shunt placement (especially in older patients). Vascular abnormalities (ie, right aortic arch, abnormal origin of the subclavian arteries), when present, may have implications on the surgical approach for palliative shunt placement.

There is a spectrum of disease in TOF, as these classic features manifest with varying degrees of severity. Additionally, there are several variant forms of the disorder. A classification scheme created by the Congenital Heart Surgery Nomenclature and Database Project, in an attempt to establish a unified reporting system for congenital heart disease, suggests the following general categories of TOF: classic TOF with varying degrees of pulmonary stenosis (the most common variant), TOF with common atrioventricular (AV) canal defect (the least common variant), and TOF with absent pulmonary valve syndrome.[9] An additional fourth category, TOF with pulmonary atresia, is considered by many to be the most severe form of TOF; however, it frequently is classified under the separate category of pulmonary atresia-VSD.[9,10]

The incidence of TOF with common AV canal defect is rare, occurring in 5%-10% of patients with AV canal defects and in 1.7% of patients with TOF.[11] The presentation involves a common AV valve, primum ASD, inlet VSD, and right ventricular outflow obstruction. In TOF with absent pulmonary valve syndrome, a dysplastic pulmonary valve leads to significant PR in utero. Marked aneurysmal dilation of the developing main and branch pulmonary arteries results from the increased flow and pulsatility related to the PR. These enlarged vessels may cause airway compression, with the potential for tracheobronchomalacia and severe neonatal respiratory compromise. This rare variant is estimated to occur in 3%-6% of patients presenting with TOF.[12] The last variant, TOF with pulmonary atresia, presents with a plate-like pulmonary valve and severe hypoplasia (or absence, in the most extreme case) of the central pulmonary arteries due to the lack of forward flow from the right ventricle to the pulmonary circulation. Pulmonary blood flow depends upon a ductus arteriosus and/or major aortopulmonary collateral arteries.[8]

An additional congenital cardiac lesion closely related to, and often confused with, TOF is double outlet right ventricle (DORV). Features common to both conditions include a VSD and varying degrees of biventricular aortic origin; however, there is continued controversy regarding the relationship/distinction between TOF and DORV.[10] According to the Congenital Heart Surgery Nomenclature and Database Project, DORV is defined as a type of ventriculoarterial connection in which both great vessels arise either entirely or predominately from the right ventricle.[13] The degree of aortic override is one potential criteria used to distinguish the 2 conditions, with a DORV present when more than 50% of the aortic valve overlies the right ventricle and a normally related pulmonary artery. Other descriptions ignore the degree of aortic override in the diagnosis, instead defining DORV by the presence of fibrous discontinuity between the aortic and adjacent atrioventricular valve (in contrast to fibrous continuity of the valves in TOF).[10]

Multi-Modality Imaging

Indications for imaging in TOF vary with age, history of prior interventions, and disease severity. Although echocardiography is typically adequate for initial diagnosis, as well as evaluation following repair, in infants and young children, cardiac magnetic resonance (CMR) has become the standard imaging modality of choice for serial imaging assessment of the anatomic and functional sequelae seen in patients with repaired TOF starting in the second decade of life.[14] In particular, it is used to monitor for the deleterious effect of chronic PR on right ventricular size and function. CMR allows for superior quantification of right ventricular size (ie, mass and volumes) and function (both global and, in particular, regional ventricular function), as well as the severity of PR via calculation of pulmonary regurgitant fraction.[14,15] Additionally, CMR allows assessment of myocardial viability, flow measurements (ie, cardiac output, pulmonary-to-systemic flow ratios), and detailed imaging of

intra- and extra-cardiac structures (ie, vascular conduits, branch pulmonary arteries). This has allowed CMR to emerge as an important tool for risk stratification, as well as in guiding clinical decision-making, in patients with repaired TOF. Specifically, CMR data have become increasingly important in determining indications and timing for pulmonary valve replacement.

Two-dimensional and Doppler echocardiography remain useful for the evaluation of most anatomic and hemodynamic abnormalities in patients with repaired TOF.[3] Compared to CMR, echocardiography is relatively inexpensive, widely available, not associated with potential harmful ionizing radiation, and portable.[3] Echocardiography provides important information regarding valvular disease, and this provides important indirect information regarding the estimated right ventricular systolic pressure. In those with right ventricle-pulmonary artery conduits and nontransannular patch repairs, echocardiography is useful in quantitating residual pulmonic stenosis and, sometimes when needed, estimating right ventricular pressure by TR jet. This is very useful in select TOF patients. CMR is dependent on angle of interrogation used in setting up sequencing, which can be variable. Although recent advances in 3-dimensional echocardiography have improved the ability to measure ventricular volumes and ejection fraction, echocardiography has demonstrated a systematic bias in underestimating right ventricular volumes and may also overestimate right ventricular ejection fraction compared w CMR.[16,17] Additional limiting factors of echocardiography include lower resolution (compared to CMR), as well as the inability to perform live, real-time volume acquisition of cardiac chambers.

Multimodal imaging guidelines for patients with repaired TOF from the American Society of Echocardiography, in collaboration with the Society for Cardiovascular Magnetic Resonance and the Society for Pediatric Radiology, recommend the following as essential imaging data to periodically obtain using a combination of imaging modalities[3]:

- Right ventricular size and function, regional right ventricular wall motion abnormalities, right ventricular pressure
- Degree of PR
- Assessment of the main and branch pulmonary arteries
- Presence of systemic-to-pulmonary collateral vessels
- Evaluation of the right ventricular outflow tract for obstruction and/or aneurysm
- TR (degree and mechanism)
- Residual intra- and extra-cardiac shunts
- Left ventricular size and function
- Size of the aortic root and ascending aorta, aortic arch sidedness
- Degree of aortic regurgitation
- Origin and proximal course of the left and right coronary arteries
- Assessment of myocardial viability
- Associated abnormalities (ie, anomalies of systemic and/or pulmonary veins)

Pathophysiology

The physiology of TOF varies per patient age and the interventions used to treat the condition. Rationales for when, how, and what palliative and corrective interventions to use still are evolving. Surprisingly, the management of this congenital lesion still presents immense challenges to cardiologists, surgeons, critical care physicians, and anesthesiologists. The old mantra still holds true even today: “never trust a tet.”

For the purposes of this review the authors will focus on the physiology of non-ductal dependent TOF with pulmonary stenosis, as opposed to other variant forms of this disorder. An important anatomic distinction between the outflow tracts of the left and right ventricles is that the right ventricle circumferentially is composed of cardiac muscle. The right ventricular hypertrophy element of this lesion affects all parts of the right ventricle, including the outflow tract. After birth, right ventricular hypertrophy increases over time due to pulmonary stenosis and exposure of the right ventricle to systemic pressures because of the VSD. Driven by sudden spikes of circulating catecholamine molecules that increase cardiac contractility, these patients have a predisposition for sudden, severe, and sometimes difficult-to-treat diminution or complete absence of pulmonary blood flow. This causes a right-to-left shunting of the blood from the systemic venous return across the VSD, bypassing flow through the lungs. This is known colloquially as a “tet spell.” At birth, most patients have adequate blood flow to the lungs and do not require an immediate palliative and correctional intervention. This is because the right ventricular hypertrophy usually is not severe enough to cause a significant decrement to pulmonary blood flow. Over the course of the months and years following birth, growing right ventricular hypertrophy may cause recurrent right ventricular outflow tract obstruction and an increasing number of “tet spell” bouts. These sudden episodes of pulmonary outflow tract obstruction can occur at any time after birth, and the incidence can increase during the first year of life if left untreated.[18] These hypoxic spells used to be the major cause of mortality during the first 3 years of life.[19] Heretofore, the instantaneous risk of death was highest in the first year of life.[20] Contemporary surgical management, which has gravitated to doing primary repairs, has produced low morbidities and mortalities.[21]

Pulmonary blood flow obstruction is caused not only by the fixed elements of pulmonary artery and pulmonary valve stenosis but also by the dynamic element of increasing right ventricular outflow tract hypertrophy prior to surgical correction. An organized thought process as to the medical management of this acute pulmonary blood flow obstruction is vital. In the neonatal patient, there are potentially 3 levels of impediment to pulmonary blood flow. First, neonatal patients tend to have higher pulmonary vascular resistance (PVR) than older patients. Therefore, the use of a high inspired oxygen tension and the incorporation of a higher minute ventilation to promote hypocarbia will lower PVR and promote pulmonary blood flow. Curiously, it has been noted previously that hyperoxia also can serve as a systemic vasoconstrictor, which

could be potentially helpful during a "tet spell."[22] Pulmonary artery and pulmonary valvar atresia presents a second level of obstruction, which, unfortunately, cannot be manipulated except with direct surgical intervention. The third level of obstruction is the muscular subpulmonary conus or right ventricular outflow tract. Muscular spasm at this level is the dynamic component mentioned earlier, which often worsens with age. This may be brought on by increases in circulating catecholamine levels caused by stress. Relaxation of the muscular infundibulum and forcing more flow through this outflow tract will relieve the acute hypoxia during one of these potentially lethal crises. The first-line treatments of a "tet spell" are an infusion of volume to increase preload and the use of phenylephrine to increase the systemic afterload (phenylephrine has the added benefit of increasing preload by causing vasoconstriction of the venous capacitance vessels). Unlike other agents, such as dopamine and norepinephrine, which also can increase the systemic vascular resistance (SVR), phenylephrine does not have a direct effect on cardiac contractility. Therefore, it is an ideal agent for use as a primary therapy to increase pulmonary blood flow during a hypercyanotic spell, as phenylephrine will not cause an increase in the dynamic obstruction of the muscular right ventricular outflow tract. Increasing left ventricular afterload (by raising SVR) will elevate left ventricular end-diastolic pressure and decrease right-to-left shunting through the VSD in hypercyanotic episodes. One can also increase preload and afterload by "squatting" the patient. This can be performed taking both legs and thrusting them into the abdomen. If these treatments are not effective, then agents that decrease contractility, such as a beta-blocker, should be employed. Esmolol is probably the most logical agent to use in the acute phase of care because of its short half-life and an ability to titrate with the use of an infusion. Other second-line agents for use during a "tet spell" under anesthesia that decrease contractility include volatile anesthetics. These inhaled agents (such as sevoflurane and isoflurane) also decrease SVR and hence must be employed with caution. Sedation is an important adjuvant therapy in awake patients; it serves to decrease the levels of circulating catecholamine agents and help decrease right infundibular spasm. Opiates (such as morphine and fentanyl), benzodiazepines, and dexmedetomidine can be useful sedative agents. Midazolam administered using the intranasal route can be effective.[23] Treatment of metabolic acidosis (possibly with sodium bicarbonate) caused by hypoxia also can lower PVR. A neonate presenting with cyanosis and previously undiagnosed TOF can be given a prostaglandin E1 infusion. It even is recommended that the infusion should be started in any neonate with cyanosis before a complete diagnosis is made.[24] After reviewing these therapies, the reader might recall that these treatments also apply to the management of acute left ventricular outflow tract obstruction seen with hypertrophic obstructive cardiomyopathy. Severe, dynamic outflow tract narrowing or obstruction of the left ventricular outflow tract or right outflow tract with a ventricular septal defect caused by spasm of the muscular subvalvular components is treated, initially, in a similar manner.

Management Options

The historical evolution in treatment for TOF is of importance to the current management of patients with cyanotic congenital heart disease. Alfred Blalock, Helen B. Taussig, and Vivien Thomas developed the first Blalock-Taussig-Thomas (BTT) shunt as a palliative procedure to augment pulmonary blood flow in a 4 kg, 15-month-old girl with TOF at Johns Hopkins in 1944.[25] The operation involved the formation of a systemic (left subclavian artery) to pulmonary artery shunt, creating an artificial ductus arteriosus. Taussig previously had observed the benefits of an open ductus arteriosus in children with cyanotic heart disease (in addition to the fatal effects of early ductal closure in this same patient population), recognizing that these cyanotic babies were dying of anoxemia and not cardiac failure, as previously believed.[26] The original BTT shunt was the first attempt to build an "artificial ductus" in a cyanotic child to restore pulmonary blood flow and improve cyanosis. Perhaps even more importantly, it began the era of congenital cardiac surgery, with the BTT shunt soon being used across numerous different centers and as palliation for other cyanotic defects associated with diminished pulmonary blood flow.[26]

Over time, several alternative approaches and modifications to the original BTT shunt were developed, including a number of central shunts: Potts (descending aorta to left pulmonary artery anastomosis), Waterson (ascending aorta to pulmonary artery anastomosis), and Cooley (intrapericardial anastomosis from ascending aorta to right pulmonary artery) shunts.[26–29] The original direct systemic to pulmonary artery anastomosis of the BTT shunt has evolved into the current modified BTT shunt, in which a prosthetic tube graft is interposed between the subclavian and pulmonary arteries. In current practice, if a palliative shunt is indicated, the most common approach is by either a modified BTT shunt or a central shunt from the ascending aorta to main pulmonary artery. Both approaches utilize a polytetrafluoroethylene prosthetic graft. The modified BTT shunt can be performed by either a posterolateral thoracotomy or median sternotomy approach, while a central shunt requires a median sternotomy.[26] A post-procedure saturation of ~80%-85% is the goal, with the hope this will allow the infant to develop adequately in preparation for later surgical repair. A modified BTT shunt also may aid in growth of small pulmonary arteries. Although palliative shunting still is performed commonly in many centers, reported results are highly variable.[30,31] Alternative catheter-based approaches, particularly for premature and low birth weight infants, include balloon dilation (with or without stenting) of the right ventricular outflow tract and stenting of a patent ductus arteriosus.[30,32–34]

Key Management Issues in TOF

Controversy remains regarding the optimal timing, surgical technique, and role of aortopulmonary shunt palliation prior to repair in TOF. Primary surgical repair in the first year of life has become the prevailing management strategy in many centers.[2] Opposition to this approach points to concerns regarding

the effects of cardiopulmonary bypass (CPB) on the immature brain and other vital organs, as well the surgical challenges of small-body intracardiac exploration. Meanwhile, advocates for early surgical repair argue that continuing risks of hypoxemia, the unpredictable nature of hypercyanotic spells, and risks of conservative surveillance are more significant.[2,30,35–40] Factors such as cumulative ventricular hypertrophy and the avoidance of acute and chronic hypoxia have led many surgical groups to advocate for neonatal repair. Some surgeons, for several decades, also have promoted early repair to avoid the need for the added step of initial palliation with an arterial to pulmonary artery connection to guarantee pulmonary blood flow. Indeed, at centers that have encouraged so, such as Boston Children's Hospital, Children's National Medical Center, Stanford, and Columbia, the mortality rates are seemingly low.[35,38–40] Woldu et al. at Columbia found that their cohort of patients repaired as neonates had higher weight-for-age scores at 1 year of age compared to patients who had later TOF repairs.[41] However, these seemingly optimistic results do not seem to be reproducible in many other centers. A retrospective analysis of pooled data from 43 tertiary level children's hospitals in North America (through the Pediatric Health Information System) found that patients repaired at less than 30 days had significantly higher in-hospital mortality and total hospital and intensive care lengths of stays, and longer need for mechanical ventilation, blood pressure support, and extracorporeal membrane oxygenation support.[42] A meta-analysis of 8 studies of 3,858 patients found that neonatal repair was associated with a higher mortality, longer length of intensive care unit stays, and longer length of hospital stays.[43] A further study from Kanter et al. at Emory concluded that using a surgically created shunt palliation or complete repair as a first operation offered equivalent survival. When amalgamated together, the total length of stays for patients who underwent aortopulmonary palliation at first and then later repair was equivalent to patients who underwent primary complete repair during the neonatal period.[44] The possible insight is that high-volume centers simply might have more success. The approach to this group of patients probably will have to be tailored to an individual center's level of experience with neonatal repair and postoperative management.

Outcomes Following Surgical Repair

Surgical TOF repair has 2 primary goals: closure of the VSD (to eliminate intracardiac shunting) and the provision of adequate pulmonary blood flow. Relief of right ventricular outflow tract obstruction and pulmonary stenosis using a ventriculotomy combined with a transannular patch procedure remains the most common technique employed.[2] Interestingly, patients who received repairs after 6 months of age were more likely to receive a transannular patch and have longer cross-clamp and total bypass time periods.[45] There is now a trend to preserve the pulmonary valve anatomy whenever possible in an attempt prevent the effects of severe pulmonary insufficiency and not condemn the patient to a lifetime of pulmonary valve replacements. A thought-provoking, recently presented abstract found that a strategy promoting annular preservation may convey more advantages than a practice promoting a more liberal use of transannular patches. The authors compared several cardiac physiologic indices in 107 patients on average at a little over a decade after repair (mean = 13.1 ± 2.3 years). What made this study unique was its attempt to directly compare results of the 2 techniques by matching patients with what they termed "anatomic equivalency." As expected, patients who had annulus preservation had lower right ventricular end-diastolic volumes and right ventricular end-systolic volumes, but they also had better left ventricular ejection fractions as measured by magnetic resonance imaging. There was no significant difference in the right ventricular outflow tract gradients as measured by Doppler echocardiography. Importantly, the maximum attainable oxygen consumption was significantly higher in patients who underwent an annulus-sparing surgery.[46] Although intriguing, a large, longitudinal, and randomized control study would be needed to validate these conclusions.

The vast majority of patients will survive surgical repair and live to adulthood, and roughly half of these patients will require some form of reoperation within 30 years with pulmonary valve replacement (due to PR) representing the most common reintervention.[47,48] In fact, pulmonary valve replacement is the most frequently performed reoperation in adult congenital cardiac surgery.[49] During surgical TOF repair, pulmonic valve integrity often is disrupted in the attempt to relieve right ventricular outflow obstruction, leading to chronic PR. The consequence is chronic volume overload of the right ventricle, eventually leading to right ventricular dilation and dysfunction. Ultimately, biventricular dysfunction, dysrhythmias, exercise intolerance, heart failure symptoms, and death may follow.[50,51] Pulmonic valve replacement to restore pulmonic valve competency treats right ventricular volume load to decrease right ventricular volume and size, reduce the propensity for dysrhythmia, and decrease the risk of sudden cardiac death.[52] Pulmonic valve replacement also can be used as a treatment for patients with left ventricular dysfunction in some circumstances.

Pulmonic Valve Replacement—Indications and Outcomes

Pulmonary valve replacement clearly is indicated in patients experiencing symptoms of heart failure secondary to chronic PR; however, controversy remains regarding indications and timing for valve replacement in asymptomatic patients.[52] Current evidence appears to support strategies favoring early intervention, fearing the development of irreversible right ventricular dysfunction if volume overload is not addressed. Decision-making involves an assessment of electrophysiologic data, imaging, and exercise testing to include increased right ventricular size by CMR, new or worsening TR, severe PR, development of ventricular dysrhythmias, and QRS duration >180 ms.[52,53] Frigiola et al. suggested that valve replacement in an asymptomatic patient be undertaken once CMR demonstrates a right ventricular end-diastolic volume index of

>150 mL/m^2, a pulmonary regurgitant fraction of ≥35%, and/or an right ventricular to left ventricular end-diastolic ratio ≥2.[54] A later study by Geva recommends valve replacement for the following criteria: right ventricular end-diastolic volume >160 mL/m^2, right ventricular end-systolic volume >70 mL/m^2, pulmonary regurgitant fraction >25%, and right ventricular ejection fraction <45%.[51] Although right ventricular ejection fraction often is diminished after ventriculotomy, some providers do not refer for intervention until right ventricular ejection fraction <35%. Electrophysiologic considerations also exist regarding pulmonary valve replacement. QRS duration of >180 ms is associated with increased risk for ventricular dysrhythmias and sudden cardiac death, with evidence demonstrating an improvement in QRS duration following pulmonic valve replacement.[52,53] Operative mortality for pulmonary valve replacement is low (<1%); however, an important consideration is that the functional integrity of all bioprosthetic valves (the overwhelming choice of prosthesis) deteriorates over time, requiring a significant number of patients to undergo repeat valve replacement within ~10 years.[51]

Transcatheter Options in TOF

The durability issues inherent with prosthetic valves means that many patients may require multiple pulmonic valve replacements over the course of a lifetime, making a nonsurgical option for valve replacement an attractive option. Options for percutaneous pulmonary valve replacement include the Medtronic Melody valve (Medtronic, Inc., Minneapolis, MN) and Edwards SAPIEN valve (Edwards Lifesciences Corporation, Irvine, CA). The Medtronic Melody valve is a bovine jugular valve mounted in a stent, first approved in 2010 for placement within a circumferential right ventricle-pulmonary artery conduit. The valve is available in 3 sizes: 18, 20, and 22 mm. The Edwards SAPIEN valve is available in larger sizes (23, 26, and 29 mm) and is a stent-mounted bovine pericardial valve. It was approved for use in 2011 but only for transcatheter aortic valve replacement. At the time of publication, it is only available for pulmonary valve replacement in patients participating in Food and Drug Administration trials.[30] Although the Melody valve has achieved Food and Drug Administration approval, its indication for implantation within a circumferential conduit limits its use in patients with native or patched noncircular right ventricular outflow tracts.[49] Prestenting within a native outflow tract to create an artificial, "circumferential" conduit to serve as a landing zone in which to anchor the valve provides an alternative approach to overcome this limitation. Complications of percutaneous pulmonary valve implantation include stent fracture, coronary artery compression, infective endocarditis, and conduit rupture. New valves in different sizes likely are forthcoming as this field continues to grow.

Perioperative Management

The unique cardiac physiology of the neonate presents with anesthesiologist with some intense challenges. Cardiac compliance is reduced compared to the adult heart and therefore is less tolerant of increases in preload. There is a sharp rise in the ventricular end-diastolic pressure in response to volume. This means that the neonatal heart has a limited ability to increase cardiac output with increases in stroke volume along the Frank-Starling curve. Therefore, the neonate must rely on the heart rate to produce an adequate cardiac output to match a level of oxygen consumption that is on average 2× to 3× (5-8 mL/kg/min) that of an adult (2-3 mL/kg/min).[55] Neonates with congestive heart failure can have a higher level of oxygen consumption than a heathy newborn (mean = 9.4 ± 1.6 mL/kg/min).[56] Additionally, sensitivity to beta-adrenergic receptor stimulation is diminished after CPB and cardioplegic arrest. This may be due to an "uncoupling" of the beta-adrenergic receptor from activation of the G-stimulatory protein adenylate cyclase complex.[57] Post-bypass, after relief of the outflow tract obstruction, the phosphodiesterase enzyme inhibitor milrinone can be a valuable agent in the neonatal population. Milrinone improves myocardial relaxation by increasing the intracellular concentration of second messenger, cyclic AMP, which leads to the phosphorylation of phospholamban, which augments the rate of uptake of calcium into the sarcoplasmic reticulum.[58] This increase in the level of cyclic AMP may actually restore the effectiveness of inotropic agents and enhance systolic function.[59] In a pig model, milrinone helps to improve ventricular relaxation and load-dependent systolic performance following myocardial stunning.[60] This can be particularly helpful in newborns who have a narrower range of normal diastolic and systolic function. Milrinone is the most commonly used inotropic agent in patients with congenital heart disease undergoing cardiac surgery.[61] Milrinone often is combined with a catecholamine to enhance the effect on systolic function, working synergistically with agents that act as beta-adrenergic agonists, such as epinephrine, norepinephrine, and dopamine. A porcine model study examined combining milrinone with either epinephrine or dopamine approximately 80 days after the surgical creation of severe PR. The addition of epinephrine or dopamine further improved preload recruitable stroke work and cardiac index, in a dose-dependent manner, over milrinone alone.[62]

Neonates also can develop adrenal insufficiency in the postoperative period, which can lead to a low cardiac output state. A small randomized control study of post-bypass neonatal cardiac surgery patients found that 32.5% developed adrenal insufficiency after CPB. Patients who developed adrenal insufficiency and received a continuous infusion of hydrocortisone had a significantly lower incidence of low cardiac output syndrome. The group of patients who received the steroid infusion also had a significantly more negative fluid balance at 48 hours and better urine output and were weaned off catecholamines sooner.[63]

A major impact upon perioperative management of the patient depends on the surgical approach. The acute management of a patient with severe pulmonary insufficiency after a ventriculotomy and transannular patch focuses on maintaining forward flow through the pulmonary vascular bed to the left side of the heart. Maintenance of adequate preload and

keeping the regurgitant fraction as low as possible by maintaining high-normal heart rate are important principals. As mentioned above, the augmentation of contractility with milrinone alone, or combined with epinephrine, can be used. The lowering of PVR with hyperoxia, mild hypocarbia, or other drugs such as sildenafil, milrinone, or inhaled nitric oxide will promote forward flow from the right ventricle. If the patient has developed significant right ventricular hypertrophy, then the resultantly raised right ventricular end-diastolic pressure will impede forward flow through the right ventricle. A surgical approach to dealing with this physiologic obstruction to right ventricular outflow is the creation of a small ASD as part of the repair. Any right ventricular hypertrophy present at the time of a TOF repair and relief of the outflow tract obstruction will take many weeks to recede. Due to the raised right ventricular end-diastolic pressure, Doppler echocardiographic examination of flow through the surgically created ASD often reveals bidirectional flow. This indicates that there is a significant amount of right ventricular preload being shunted right to left through the atrial defect. Although this is blood flow that bypasses the lungs and therefore is not oxygenated, preload to the left ventricle is assured and systemic stroke volume is maintained. Without this atrial level shunt, patients with significant right ventricular hypertrophy can struggle to maintain an adequate systemic perfusion and blood pressure in the postoperative period. Oxygen saturation is sacrificed for hemodynamic stability.

When a decision is made to preserve the pulmonary valve, the surgeon endeavors to relieve the obstruction below and above the pulmonary valve as much as possible through the resection of hypertrophied muscle bundles in the right ventricular infundibulum and, if necessary, patch augmentation of the supravalvular main pulmonary artery trunk. This does leave the patient with a degree of pulmonary stenosis. Management of the patient again focuses on promoting forward blood flow to the lungs. Preservation of preload, satisfactory contractility, and low pulmonary vascular resistance are essential, but in this case, maintenance of a low-normal heart rate will allow a sufficient period to fill the ventricle with adequate preload.

Relief of the pulmonary obstruction after several months to years of blockage can trigger a reperfusion injury of the lungs, which manifests as potentially life-threatening pulmonary edema.[64] This can be seen in patients who are neither repaired surgically nor catheter-palliated until after a year of age. This injury also can be seen in any patient who undergoes balloon angioplasty for pulmonary branch stenosis and may be isolated to 1 lung if the stenosis only affected 1 side. This pulmonary edema usually is not detected until several hours after the procedure. The anesthesia practitioner should not be rushed to extubate any patient with long-standing main or branch pulmonary stenosis.

Arrythmias in TOF

Following neonatal repair of TOF, the patient is vulnerable to rhythm disturbances. Over the course of 11 years, one institution found that their incidence of junctional ectopic tachycardia was 5%-14% and persistent complete heart block was 1%.[65] One of the principals of junctional ectopic tachycardia treatment is rate control by minimizing catecholamines, using sedation, and employing tight temperature regulation to cool the patient to 35˚C to 36˚C, thus lowering the metabolic state. Chemical conversion to a sinus rhythm is then possible utilizing antiarrhythmic agents, such as amiodarone and procainamide. Dexmedetomidine might also be useful as a sedative and negative chronotropic agent. Dexmedetomidine is a selective brain and spinal cord α_2-adrenoreceptor agonist, which can inhibit neuronal firing and cause sedation and bradycardia. Bolus of any of these drugs must be used cautiously as they can cause hypotension.

As early as the second decade of life, some TOF patients have ventricular tachycardia, which typically emanates from the ventriculotomy site in the right ventricle for those patients who underwent transannular patch repair. Surgical or catheter-based ablation in the right ventricular outflow tract often is used to treat this dysrhythmia when pulmonary valve replacement is undertaken.[66–68] In other instances, however, electrophysiologic studies may be performed to ablate this arrhythmia along with implantable cardioverter-defibrillator placement independent of pulmonary valve replacement.

Outcomes Assessment

As previously discussed, early survival following TOF repair is excellent. Follow-up in the first 10- to 20-year period also is encouraging; however, the Kaplan-Meier curve drops off starting in the third decade post-repair related to progressively worsening exercise tolerance, dysrhythmias, right ventricular failure, and sudden death. Morbidity and mortality further increase in the fourth decade with contributing factors related to chronic PR, right ventricular hypertrophy, ventricular scarring, and declining left- and right ventricular function.[69] Older age at primary repair and prior shunt are independent predictors of both late morbidity and death, although these may reflect a bygone surgical era.[69–71] Although long-term survival is the expectation following repair with 90% of patients still alive after 30 years, this survival rate is still lower than the general population.[2,4,5] Additionally, data on outcomes, functional status, and life expectancy beyond 30 years are limited. Cuypers et al. attempted to address this issue with a longitudinal follow-up study aiming to provide data on survival, clinical course, and sequelae in survivors up to 40 years after initial surgical correction.[70] Their longitudinal cohort, consisting of 144 patients undergoing TOF repair between 1968 and 1980, demonstrated a cumulative survival after repair of 83% after 10 years, 81% after 20 years, 78% after 30 years, and 72% after 40 years. Heart failure and arrhythmia were the most common causes of late death, which the study authors point out is consistent with other data in the literature.[53,72–76] Although late mortality was low, cumulative event-free survival began to worsen in the third decade and declined to only 25% of patients surviving 40 years without a major event (eg, death, cardiac reintervention, symptomatic dysrhythmia, stroke, heart failure,

and/or endocarditis). Cardiac reinterventions were required in 44% of patients, mostly for pulmonary valve replacement. An important caveat, however, is that planned surgical pulmonary valve replacement no longer is considered a complication but rather a component of the overall palliative treatment plan for TOF. While prior eras routinely experienced the problems of right and left ventricular dysfunction as patients aged, current therapy revolves around performing planned pulmonary valve replacement to prevent the onset of ventricular dysfunction. Systolic right ventricular function was impaired in >75% and systolic left ventricular function in 50% of the patients. Additionally, almost half (49%) of all patients in the cohort had been hospitalized at least once in the past decade.

Discussions of the substantial morbidity encountered in adults with repaired TOF must address the issue of decompensated right ventricular volume overload leading to the progression of ventricular dysfunction, late dysrhythmia, and death. An editorial by Bichell raises this issue as a framework to question the proper timing for pulmonary valve replacement in patients with chronic PR.[69] Current criteria for pulmonary valve replacement have moved toward supporting earlier intervention. Because a QRS duration >180 ms predicts ventricular tachycardia, and QRS stabilization has been shown following pulmonary valve replacement, some suggest now moving criteria for replacement from 180 to 140 ms. Additionally, since functional recovery of the right ventricle after pulmonary valve replacement is less likely if the preoperative right ventricular end-diastolic volume is >170 mL/m^2, there is support for moving the threshold toward 150 mL/m^2.[69,77] Importantly, Bichell notes that long-term data on the effect of earlier, proactive intervention in the asymptomatic patient with PR remains incomplete. Although mortality for PR is low and an improvement in symptoms/functional class after valve replacement has been shown, a survival advantage still has not been proven.[69,78,79]

Ferraz Cavalcanti et al. performed a meta-analysis and meta-regression of 3,118 patients from 48 studies published around the world reporting data about the effect of pulmonary valve replacement in patients with repaired TOF who developed PR through December 2012.[80] Across all studies, they found a pooled 30-day mortality following pulmonary valve replacement of 0.87%, a pooled 5-year mortality of 2.2%, and a pooled 5-year need for repeat pulmonary valve replacement of 4.9%. In addition to these low rates of mortality and need for repeat valve replacement, the results of this analysis also demonstrated that after surgical pulmonic valve replacement there were significant decreases in right ventricular volumes, improvement of both right and left ventricular systolic function, decrease in QRS duration, and improvement in functional class and symptoms.

Further support for pulmonary valve replacement as a safe and appropriate intervention with a low rate of reintervention has been offered by Sabate Rotes et al. In this study, the 40-year experience with pulmonary valve replacement following repaired TOF at the Mayo Clinic was reviewed.[79] Early mortality was 1.4%, whereas survival at 5, 10, and 15 years was 93%, 83%, and 80%, respectively. Older age at initial repair, history of multiple (≥3) prior cardiac surgeries, advanced heart failure symptoms (NYHA class III/IV at time of valve replacement), and large body surface area were all independent risk factors for mortality. Overall freedom from a need for repeat pulmonary valve replacement at 5, 10, and 15 years was 97%, 85%, and 75%, respectively. McKenzie et al. also have presented data suggesting that the contemporary results of surgical pulmonary valve replacement are excellent.[49,81] Their study demonstrated median intensive care unit stay of 2 days and median hospital length of stay of 5 days, with no in-hospital or 30-day mortality reported. Freedom from pulmonary valve replacement at 1, 3, and 5 years was 99%, 99%, and 94%, respectively.

Despite these results, significant enthusiasm for alternative approaches, such as transcatheter valve replacement, exists based on concerns related to the risks of open surgical repair. Kogon highlights the important need to utilize outcomes data from surgical pulmonary valve replacement as a benchmark for comparison with these emerging alternative technologies.[49] He highlights the fact that even in sponsor-supported post-approval studies of the Melody valve, results were suboptimal compared to the surgical standard. In 116 patients followed for 8 months, although there were no reported deaths, the morbidity was significant at 17.2% of patients. Complications included conduit rupture (6 patients), endocarditis (2), arrhythmia (2), venous thrombosis (2), pulmonary artery perforation, coronary artery compression, sepsis, valve regurgitation, hemorrhage, valve thrombosis, central nervous system paresthesias, and respiratory distress. Within the 8-month follow-up period, 9% of patients required reintervention (5 repeat transcatheter pulmonary valves, 2 covered stents, 3 surgical conduit placements). Additionally, 2 large studies have shown a combined stent fracture rate of 23 per 100 person-years, with only a 77.8% freedom from fracture rate at 14 months in one study.[49,82,83] The reintervention rate was high at 14% at 2 years, which increased to 51% at 2 years if an associated major stent fracture had occurred. The risk for infection also has been shown with percutaneous pulmonary valve replacement, with data from 1 large study showing that 10% of patients developed a bloodstream infection and with 3% further developing endocarditis.[84]

Conclusions

TOF continues to be one of the most common forms of congenital heart disease encountered by cardiovascular anesthesiologists. Advances in the care of neonates born with this condition have been dramatic, although questions remain regarding the exact timing and approach for definitive surgical repair. Despite these lingering questions, early mortality at major centers is quite low and survival into adulthood has become the expectation for the vast majority of patients. Residual hemodynamic and functional abnormalities resulting from the post-repair state, however, will eventually lead to significant morbidity in the adult patient with repaired TOF. Although some progress has been made in the management of

issues unique to these patients, the shifting demographics of this rapidly growing patient population will continue to present both significant challenges and opportunities for advancing the care of the patient with repaired TOF.

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