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STATE-OF-THE-ART PAPER

Hot Topics in Tetralogy of Fallot

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Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect. We explore "hot topics" to highlight areas of emerging science for clinicians and scientists in moving toward a better understanding of the long-term management of patients with repaired TOF. From a genetic perspective, the etiology of TOF is multifactorial, with a familial recurrence risk of 3%. Cardiac magnetic resonance is the gold standard assessment tool based on its superior imaging of the right ventricular (RV) outflow tract, pulmonary arteries, aorta, and aortopulmonary collaterals, and on its ability to quantify biventricular size and function, pulmonary regurgitation (PR), and myocardial viability. Atrial re-entrant tachycardia will develop in more than 30% of patients, and high-grade ventricular arrhythmias will be seen in about 10% of patients. The overall incidence of sudden cardiac death is estimated at 0.2%/yr. Risk stratification, even with electrophysiologic testing and cardiac magnetic resonance, remains imperfect. Drug therapy has largely been abandoned, and defibrillator placement, despite its high risks for complications and inappropriate discharges, is often recommended for patients at higher risk. Definitive information about optimal surgical strategies for primary repair to preserve RV function, reduce arrhythmia, and optimize functional status is lacking. Post-operative lesions are often amenable to transcatheter intervention. In selected cases, PR may be treated with transcatheter valve insertion. Ongoing surveillance of RV function is a crucial component of clinical assessment. Except for resynchronization with biventricular pacing, no medical therapies have been shown to be effective after RV dysfunction occurs. In patients with significant PR with RV dilation, optimal timing of pulmonary valve replacement remains uncertain, although accepted criteria are emerging. (J Am Coll Cardiol 2013;62:2155–66) © 2013 by the American College of Cardiology Foundation

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect, occurring in approximately 1 in 3,500 births and accounting for 7% to 10% of all congenital cardiac malformations. This exploration of a few "hot topics" is not intended to be a comprehensive review, but to present areas of emerging science for clinicians and scientists in moving toward a better understanding of the long-term management of patients with repaired TOF. Specifically, the following topics are presented: 1) genetics; 2) the crucial role of cardiac magnetic resonance (CMR) imaging; 3) recent advances in echocardiography (ECHO); 4) arrhythmias and sudden cardiac death (SCD); 5) surgical considerations and catheter-based therapy; 6) exercise performance; 7) ventricular function and heart failure; and 8) timing of and indications for pulmonary valve replacement (PVR).

Genetics

The etiology of TOF is multifactorial. Up to 25% of patients have chromosomal abnormalities, with trisomy 21 (Online Mendelian Inheritance in Man [OMIM][1] 190685) and

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[1]OMIM (Online Mendelian Inheritance in Man) is an online catalog of human genes and genetic disorders developed by the National Center for Biotechnology Information (NCBI) (http://www.omim.org/).

Abbreviations and Acronyms

BNP = B-type natriuretic peptide
CMR = cardiac magnetic resonance
ECHO = echocardiography
EF = ejection fraction
ICD = implantable cardioverter-defibrillator
LV = left ventricular
NYHA = New York Heart Association
PR = pulmonary regurgitation
PVR = pulmonary valve replacement
RV = right ventricular
SCD = sudden cardiac death
TAPSE = tricuspid annular plane systolic excursion
TOF = tetralogy of Fallot

22q11.2 microdeletions (OMIM 188400, 192430, and 611867) most frequent. Trisomies 18 and 13, as well as other less common chromosomal abnormalities, have been reported. Chromosome 22q11.2 microdeletions occur in approximately 20% of TOF patients with pulmonary stenosis and in 40% with pulmonary atresia (1–4). DiGeorge syndrome (*DGS*; OMIM 188400), the most severe type of 22q11.2 microdeletion, also includes palatal abnormalities, dysmorphic facies, learning disabilities, immune deficiencies, and/or hypocalcemia (5). A less severe 22q11.2 microdeletion in TOF, Shprintzen (velocardiofacial) syndrome (*VCFS*; OMIM 192430), does not include the immune deficiencies or hypocalcemia of DiGeorge syndrome (5). Of the more than 40 commonly deleted 22q11.2 genes, only T-box 1 (*TBX1*) has been found in murine models to be haploinsufficient, with a phenotype convincingly similar to that of the human syndrome. *TBX1* missense and truncating mutations have been identified in up to 30% of patients with the nondeletion type and with the DGS/VCFS phenotype (6,7).

Mutations of the jagged1 gene (*JAG1*; chromosome 20p12), which cause Alagille syndrome, show clinical overlap with 22q11.2-deletion disorders and may cause isolated TOF (8). Mutations of the NK2 homeobox 5 gene (*NKX2.5*; chromosome 5q35) have been reported in 4% of nonsyndromic patients with TOF (9). Other known TOF-associated genetic variants include: zinc finger protein, multitype 2 (*ZFPM2*) (10); growth differentiation factor 1 (*GDF1*) (11); *GATA4* (12); cripto, Frl1, cryptic 1 (*CFC1*); forkhead box transcription factor 1 (*FOXH1*) (13); teratocarcinoma-derived growth factor 1 (*TDGF1*); nodal (*NODAL*) (14); and *GATA6* (15). Analysis of copy number variants has been used for identifying 11 de novo copy number variants associated with TOF (16). These regions included chromosomes 1q21.1, 3p25.1, 7p21.3, and 22q11.2. Arrington et al. (17) demonstrated that haploinsufficiency of the lipoma preferred partner protein, a member of the zyxin family of proteins, may cause TOF.

The risk for recurrence in a family is approximately 3%. If a genetic basis for TOF is identified, family members with congenital heart defects can be screened to determine the risk for passing congenital heart defects on to future children. Genetic data can also be used for risk stratification in patients regarding cardiac and noncardiac manifestations of the disease.

Screening of patients with TOF could include fluorescence in situ hybridization analysis of chromosome 22q11 microdeletions or a chromosome microarray. If the result is negative, consideration may be given to specific genetic-mutation analyses.

Cardiac Magnetic Resonance

CMR is the gold standard quantitative assessment of biventricular size and function, flow measurements, and myocardial viability (18,19). The goals of CMR in repaired TOF include: 1) quantitative assessment of left ventricular (LV) and right ventricular (RV) volumes, mass, stroke volumes, and ejection fraction (EF); 2) quantification of pulmonary regurgitation (PR), tricuspid regurgitation, cardiac output, and pulmonary-to-systemic flow ratio; 3) evaluation of regional wall motion abnormalities; 4) imaging the anatomy of the RV outflow tract, pulmonary arteries, aorta, and aortopulmonary collaterals; 5) assessment of myocardial viability, including scar tissue in the ventricular myocardium aside from sites of previous surgery; 6) evaluation for residual intra- or extracardiac shunt; 7) evaluation of the aortic valve for regurgitation and measurement of aortic size; and 8) evaluation of the coronary arteries (20,21) (Fig. 1). Despite the complex geometry and heavy trabeculations of the RV, CMR measurements of ventricular size and function in repaired TOF have shown good intra- and interobserver reproducibility (22,23).

The indications for CMR in repaired TOF vary with age. During the first decade of life, CMR is indicated only when imaging data necessary for clinical decision-making cannot be obtained on ECHO. However, if there is concern regarding the degree of RV volume load and dysfunction, CMR is preferred over computed tomography or catheterization. Beginning early in the second decade of life, CMR is indicated as a routine test for the surveillance of PR, biventricular size and function, dysfunction of other valves, and myocardial viability assessment. Little information exists regarding the optimal frequency of CMR following baseline examination. In many patients, ventricular size and function remain stable over many years. In others, the RV progressively dilates, and its function declines over a short time period. Until new data emerge to guide the frequency of CMR after baseline examination, it may be reasonable to repeat the study every 3 years, or more frequently in patients with advanced disease.

CMR has emerged as a powerful tool for risk stratification in patients with repaired TOF. In a study of 793 patients from 6 centers, Gatzoulis et al. (24) found that older age at repair and QRS duration $\geq$180 ms were independent predictors of SCD; this finding was later supported by findings from Khairy et al. (25). However, those studies lacked tools to measure RV size and function. More recently, a study utilizing CMR for measuring ventricular size and function found that severe RV dilation and RV and/or LV dysfunction were independent predictors of heart failure, sustained ventricular tachycardia, and SCD (26). In a multicenter study of 871 patients with TOF, Valente et al. (27) showed that although QRS duration $\geq$180 ms alone

Figure 1 **Cardiac Magnetic Resonance Evaluation of a Large Right Ventricular Outflow Aneurysm in Patient With Repaired Tetralogy of Fallot**

Large aneurysm of the right ventricular outflow with an associated thrombus. **(A)** Cine SSFP image in an oblique coronal plane showing the right ventricular inflow (RV) and outflow. Note the thin-walled aneurysm (An). **(B)** Oblique sagittal image of the aneurysm and the thrombus **(arrow)**. **(C)** Imaging in the axial plane demonstrates that the aneurysm fills the left superior hemithorax. The **arrow in C** is showing the same thrombus as in **B**.

was a modest predictor of death or sustained ventricular tachycardia (C = 0.676; R^2 = 0.054), the addition of CMR-measured RV mass-to-volume ratio and EF to a model of prolonged QRS duration substantially improved outcome prediction (C = 0.833; R^2 = 0.23).

Echocardiography

Recent advances in ECHO (including 3-dimensional [3D] ECHO) have improved the assessment of global and regional RV performance. Techniques for measuring RV volumes and RVEF by 3D ECHO have become available over the past decade. These tools use databases of RV shapes (generated from CMR images from many patients with TOF) to best estimate RV size in individual patients, although low resolution and an inability to perform real-time volume acquisition remain limiting factors. Findings from studies comparing the accuracy of measurements of RV volumes and RVEF between 3D ECHO and CMR have varied. In general, it has been suggested that 3D ECHO underestimates RV volumes and may overestimate RVEF (28), although the technique has not been applied to a large population of patients with TOF.

Several methods of assessing global RV function in patients with TOF have been studied. Tricuspid annular peak systolic velocity (S′) (TAPSE) has been utilized as a measure of RV systolic function and appears to correlate with CMR-measured RVEF (29). TAPSE is a simple and reproducible measure of RV systolic performance. RV fibers are primarily longitudinal (in contrast to those in the LV); TAPSE determines the longitudinal motion of the RV using 2-dimensional or M-mode ECHO for measuring the distance that the tricuspid valve moves toward the apex in systole (Fig. 2). TAPSE and RVEF have been strongly correlated in adult cohorts without TOF (30). However, a recent study suggests that the correlation between TAPSE and RVEF in children with TOF is weak, perhaps due to abnormal regional contraction, and thus, the overall value of TAPSE in this population may be limited (31).

Myocardial isovolumic acceleration may be useful for detecting early RV dysfunction. It is a relatively load-independent measure and reflects RV contractility (32,33) (Fig. 3). Reports have demonstrated that myocardial acceleration was lower in patients with severe PR than in those with mild or moderate PR (32,33). Myocardial acceleration also correlated inversely with QRS prolongation (32).

Patients with TOF have regional wall motion abnormalities such as diminished RV outflow tract contractility. Therefore, global measures of RV performance may not accurately reflect true RV function. Regional wall motion measures, which utilize strain (regional deformation) and strain rate (rate of regional deformation), may be advantageous in patients with TOF because these methods avoid geometric assumptions and allow for the measurement of individual myocardial regions. In general, strain and strain rate are globally impaired in post-operative TOF patients (34–36). Reduced regional RV strain measures have also been associated with severity of PR (35). A recent study reported that global and RV free wall longitudinal peak systolic strain continued to deteriorate in serial assessments in adults after TOF repair, whereas RVEF remained the same. These findings suggest that regional wall motion

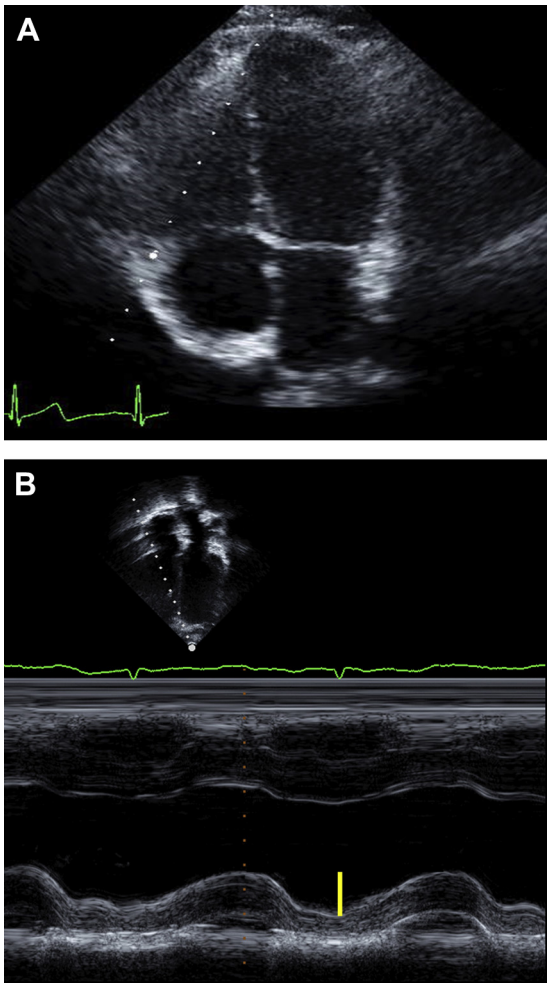

Figure 2 **Measurement of TAPSE**

(A) Apical 4-chamber view in a patient with tetralogy of Fallot. The **dotted line** indicates cursor placement at the tricuspid lateral annulus to measure tricuspid annular plane systolic excursion (TAPSE), an indicator of ventricular contractile function. **(B)** M-mode echocardiographic measurement of TAPSE, the longitudinal distance (in centimeters) that the tricuspid annulus moves during systole **(yellow line)**.

assessment may detect early, subtle RV dysfunction (36). LVEF was found to be abnormal in 21% of a large cohort of adults with TOF (37). Although associated with RV systolic dysfunction, LV systolic dysfunction was not associated with severity of pulmonary regurgitation. LV and RV diastolic dysfunction were found in 13.8% and 53.5%, respectively, of adults with repaired TOF. Ventricular arrhythmias were more prevalent in these patients (38).

Arrhythmias and SCD

The most common arrhythmogenic mechanisms in TOF involve surgical scars and natural conduction obstacles that create narrow corridors capable of supporting macro–re-entry. Atrial re-entrant tachycardia will develop during extended follow-up in more than 30% of patients, and high-grade ventricular arrhythmias will be seen in about 10% of patients (39,40). The overall incidence of SCD is estimated at 0.2%/yr of follow-up (24,41,42). Most SCD events appear to be due to sustained ventricular tachycardia, with a smaller portion related to rapidly-conducted atrial tachycardia and, rarely, abrupt atrioventricular block (43).

Efforts to define an accurate scheme for the prediction of ventricular tachycardia and SCD among patients with TOF have been ongoing (24,44–51). Numerous clinical variables have been identified (Table 1), providing reasonably strong negative predictive accuracy but only fair positive predictive accuracy. The imperfections in risk stratification in patients with TOF have become more pronounced in the modern era because therapy for individuals perceived to be at high risk typically involves invasive measures, such as implantable cardioverter-defibrillator (ICD) placement, surgery, or catheter ablation. The requirement of aggressive therapies has resulted in a growing reliance on more sophisticated testing with electrophysiologic studies and CMR to improve risk stratification (25,26,52,53). Many patients defined as high risk by the available criteria will not experience an event during intermediate-term follow-up (25,52,54), making the decision to accept the risks of invasive therapy difficult. Certain clinical variables have emerged that help to describe the clinical profile of TOF patients at highest risk for ventricular tachycardia and SCD. Multiple studies have verified that these patients are older (>20 years of age); have undergone multiple cardiac operations (including initial palliative shunting); and have a longer QRS duration and, importantly, evidence of compromised LV systolic and/or diastolic function (55). The identification of such factors has done much to improve the surgical approach to TOF. Patients now undergo definitive repair at a younger age (<2 years), with strong efforts made to avoid ventriculotomy incisions and to preserve pulmonary valve competence (48).

Potential sites for atrial macro–re-entry in patients with TOF have been defined. Two dominant circuits are recognized: 1) rotation along the edge of the tricuspid valve, with a narrow conduction corridor at the isthmus between the inferior vena cava and the tricuspid valve ring (i.e., atrial flutter); and 2) rotation around a lateral atriotomy scar, with a narrow conduction corridor between the lower edge of the incision and the inferior vena cava (i.e., "incisional" tachycardia) (56). Targeted ablation of these sites by catheter or surgical means provides an effective approach to TOF patients with frequent or highly-symptomatic recurrences (57). Catheter and surgical mapping of monomorphic ventricular tachycardia in patients with TOF has begun to illuminate the multiple macro–re-entrant pathways that can develop in the surgically-modified RV (58,59). The most common circuits include: 1) the anterior RV surface around a ventriculotomy incision (in patients with a nontransannular patch); and 2) the septal surface to RV free wall through the conal septum. The complex geometry of

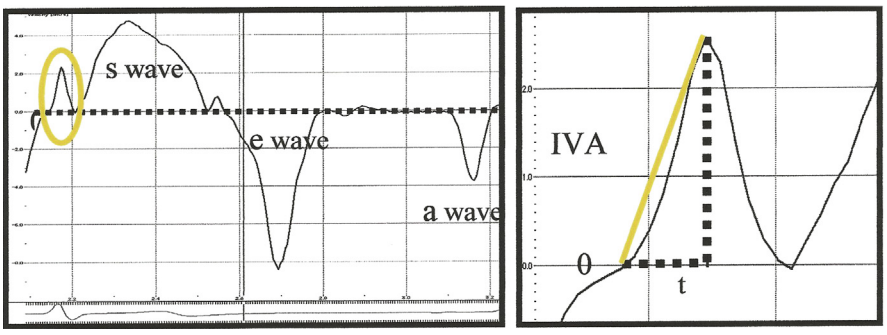

Figure 3 Measurement of Myocardial Acceleration During Isovolumic Contraction on Tissue Doppler

(Left) The **yellow outline** shows the isovolumic contraction time period. **(Right)** Enhanced image shows how the myocardial isovolumic acceleration (IVA) is measured **(yellow line)**, with the velocity of myocardial motion measured against time (t).

the RV, especially in the setting of advanced hypertrophy, also allows for other circuits.

Drug therapy has largely been abandoned as the sole treatment of TOF in patients with sustained ventricular tachycardia and/or in those considered high risk. An ICD is recommended for most patients, although catheter or surgical ablation may be useful. The acute success rate for ablation is now approximately 90%, but a 5% to 20% recurrence rate limits widespread application of the technique (59–61). Ablation is often used in ICD recipients to reduce the number of appropriate shocks.

It remains to be seen whether the risk for ventricular tachycardia can be reduced by reverse remodeling in patients with longstanding RV disease undergoing PVR and/or RV scar resection. Preliminary data suggest that there is potential for improved rhythm status if the intervention is combined with mapping and ablation of ventricular tachycardia circuits (47,62). However, surgical PVR alone does not have a major impact on the risk for ventricular tachycardia, at least when performed in TOF adults with a longstanding hemodynamic burden. Reverse remodeling and ventricular tachycardia reduction might be feasible if surgery is performed earlier in the disease course (63).

Table 1 Risk Factors for Ventricular Tachycardia and Sudden Cardiac Death

Standard clinical variables
Older age at time of repair
Prior large palliative shunts
Older chronologic age
Recurrent syncope
Pulmonary regurgitation
Residual pulmonary stenosis
Severe RV enlargement
Depressed RV function
Depressed LV function
High-grade ventricular ectopy on Holter or exercise test
Prolonged QRS duration on electrocardiogram (>180 ms)
Advanced testing
Positive ventricular stimulation at electrophysiology study
Large RV size on CMR
Large pulmonary regurgitant fraction on CMR

CMR = cardiac magnetic resonance; LV = left ventricular; RV = right ventricular.

ICDs are increasingly utilized in TOF. In a multicenter study of 121 ICD implantations in TOF patients, Khairy et al. (64) found appropriate discharges ranging from 7.7% to 9.8%/year for primary and secondary prevention indications. Independent predictors of appropriate ICD discharge included poor hemodynamics, such as increased LV end-diastolic pressures and underlying arrhythmia (ventricular tachycardia). In patients undergoing primary prevention, a 12-point risk score from 6 clinical variables (prior palliation, inducible and spontaneous ventricular arrhythmias, QRS duration, ventriculotomy, and LV end-diastolic pressure) predicted appropriate ICD discharge. However, patients had high risks for complications (30%) and inappropriate discharges (approximately 6%/year). Witte et al. (65) compared adult ICD recipients with TOF to those with dilated cardiomyopathy. The patients with cardiomyopathy were older (mean age 54SD12 vs. 25SD7 for TOF patients) and were more likely to have had the ICD implanted for secondary prevention. Interestingly, over the 2 years of follow-up, the patients with TOF were less likely to have received an appropriate discharge (5% vs. 23%) and were more likely to have received inappropriate therapy (20% vs. 4%). These findings highlight the issues of ICD therapy in this complex population.

Surgical Considerations

Increasing knowledge of morbidity associated with childhood repair of TOF mandates ongoing assessment of current surgical approaches. Given that most major centers now achieve hospital mortality rates of <2% (66), outcomes analysis should focus on long-term preservation of RV and patient functional status.

Neonatal versus non-neonatal repair. Neonatal primary repair is promoted in many centers, although this practice is

controversial (67,68). Issues include exposure of the immature brain to the deleterious effects of cardiopulmonary bypass (low flow or deep hypothermic circulatory arrest) balanced against the ongoing risks of hypoxemia (69). Proponents emphasize the unpredictable nature of hypercyanotic spells and the risk of conservative surveillance. Opponents of neonatal repair note the anatomic constraints of small-body intracardiac exploration, particularly the preservation of the crucial elements of RV function, including tricuspid valve function, conduction system trauma, pulmonary valve preservation, and avoidance of a ventriculotomy.

Neonatal palliation. Palliative shunting is still widely practiced, with variable results (70). The technical difficulties with shunt placement in newborns with small pulmonary arteries and the challenges related to post-operative management have resulted in many centers favoring complete repair when operation is indicated in the first 3 months of life. Alternative strategies for palliation, including ductal and RV outflow tract stent placement, have been described (71).

Surgical methodology. Although the conventional technique for complete surgical repair includes infundibulotomy with or without an incision across the pulmonary valve annulus, the transatrial/transpulmonary or infundibular sparing method may offer improved intermediate-term RV function and a lower risk for arrhythmia (72). Valve-sparing techniques offer the theoretic advantage of long-term pulmonary valve competence, but may be associated with persistent RV hypertension (73). Late pulmonary valve competence is lacking in monocusp repair techniques. Intraoperative pulmonary balloon angioplasty with complete transventricular repair may optimize pulmonary annular growth but requires an RV incision and is of unproven long-term benefit (74). Techniques involving an RV incision are affected by the presence of an anomalous anterior descending coronary artery; the transatrial/transpulmonary method is not affected by this anomaly (75). Definitive longitudinal outcomes data from comparisons of the various surgical approaches are lacking (76,77).

Reoperation. PR is the most common indication for late reoperation (78). The benefits of earlier reoperation (in adolescence or young adulthood) have been reported (77). Options for pulmonary prosthesis include stented bioprosthesis (porcine or pericardial); expanded polytetrafluoroethylene bivalved, homograft conduits; and other conduits (stentless porcine, polyethylene terepthalate porcine, and bovine jugular). The durability of stented porcine versus pericardial is comparable and is preferred in adults (79,80), particularly because it facilitates future percutaneous pulmonary valve replacement. Polytetrafluoroethylene bivalved prostheses are relatively new, and no late data exist (81). Percutaneous valve replacement after this procedure is not possible. Extracardiac conduits are avoided when possible; their main role is in TOF with pulmonary atresia. Relatively good durability of homograft conduit in infants and small children make it a preferred conduit in this age group (82). Homograft durability is better in an orthotopic position (i.e., inside native pulmonary artery or in the position of the native pulmonary artery) compared with an extracardiac position (right ventriculotomy to pulmonary artery). Homografts and bovine jugular conduit durability in infants and young children are similar, and given the limited availability of homografts, the bovine conduit is widely used (82). The durability of homografts in adulthood, however, is inferior to those of standard stented and stentless bioprosthetic valves (83,84). Mechanical valves in the pulmonary position are used rarely and are considered in patients who require anticoagulation with warfarin for other reasons or when there have been multiple prior operations (e.g., left-sided mechanical prosthesis) (85).

Tricuspid regurgitation may be secondary to RV dilation from PR or from a structural valve abnormality related to the ventricular septal defect patch or chordal disruption at initial repair. Tricuspid regurgitation can also be secondary to permanent pacing or ICD leads. Tricuspid repair can be accomplished with an eccentric, purse-string, or ringed annuloplasty (86). Tricuspid replacement may be required if prior repairs have failed or if there are major leaflet abnormalities. The risk of operation is greater with tricuspid replacement (86).

Surgery for arrhythmia is performed most commonly for atrial tachyarrhythmias (87). The most common are atrial re-entry tachycardia, atrial fibrillation, and flutter. Atrial flutter is treated with cryoablation or radiofrequency ablation of the right atrial isthmus. Paroxysmal atrial fibrillation is treated with right atrial maze, and continuous atrial fibrillation is best treated with biatrial maze (88,89). The most common arrhythmia following maze surgery is junctional or slow sinus rhythm, which may require permanent pacing. Prophylactic maze surgery at the time of reoperation for other reasons (e.g., PVR) is controversial. Good results of arrhythmia ablation have been reported with cut-and-sew, radiofrequency, and cryoablation techniques. The overall success of maze surgery may be determined more by the location of lesions than by energy source (90). Ventricular arrhythmias may be related to severe RV dilation, ventriculotomy scar, or both. Treatment is aimed at pre-operative mapping and percutaneous ablation. Intraoperative ablation of a tachycardia focus can be performed at the time of reoperation and is guided by mapping (pre-operative or intraoperative).

Dilated ascending aorta is common in TOF, particularly in adults. Limited natural history and treatment data are available, and the timing of aortic intervention is controversial. Dissection and aortic rupture in this patient group are rare (91). Aortic valve competence is often preserved despite aortic dilation. There are no guidelines for the management of a dilated aorta in congenital heart disease (78). In general, replacement of the ascending aorta is indicated if it is $\geq$60 mm. The sinuses are left intact (i.e., supracoronary graft) if they are $<$40 mm. Aortic root (composite graft) replacement is indicated if the sinuses are $\geq$50 mm. Valve-sparing root replacement is preferred if

root replacement is necessary and the annulus is not significantly dilated. When the sinuses are between 40 and 50 mm, the technique of operation is individualized.

Catheter-Based Therapy

Patients with repaired TOF may have residual lesions amenable to catheter intervention. Patients with residual pulmonary artery stenosis are often amenable to catheter balloon dilation, but most often require stent implantation (92,93). Those with residual RV outflow tract obstruction may be amenable to angioplasty or to RV outflow tract stenting. Caution must be exercised to ensure that RV outflow tract stenting does not cause coronary compression.

The original criteria for percutaneous Melody valve implantation (Medtronic, Inc., Minneapolis, Minnesota) for PR included RV–to–pulmonary artery conduits of ≥16 mm, balloon sizing of the narrowest area to ≥14 and ≤20 mm, and moderate-to-severe PR or conduit stenosis (gradient ≥35 mm Hg) (94).

The Sapien valve (Edwards Lifesciences Corporation, Irvine, California) can be expanded to 26 mm and is currently available only for patients participating in U.S. Food and Drug Administration (FDA) trials. Because the Melody valve has achieved approval by the FDA (Humanitarian Device Exemption), it is being used more frequently in unique situations in which a pre-existing conduit has not been placed but there is some type of circumferential landing zone—either a pre-existing tissue pulmonary valve implant, a previously implanted stent, or native narrowing of the RV outflow tract. Initial reports following Melody implantation noted potential stent fracture due to its position in the RV outflow tract (94) within the contractile area of the RV and often just under the sternum. Pre-stenting of the RV outflow tract with ≥1 stent(s) to achieve a more stable, ridged conduit prior to Melody placement has diminished the occurrence of stent fracture (95). Endocarditis following Melody valve placement has been reported (96–99) (Fig. 4). Although there is considerable practice variation with antibiotic prophylaxis, the current guidelines recommend prophylaxis for prosthetic valves (100).

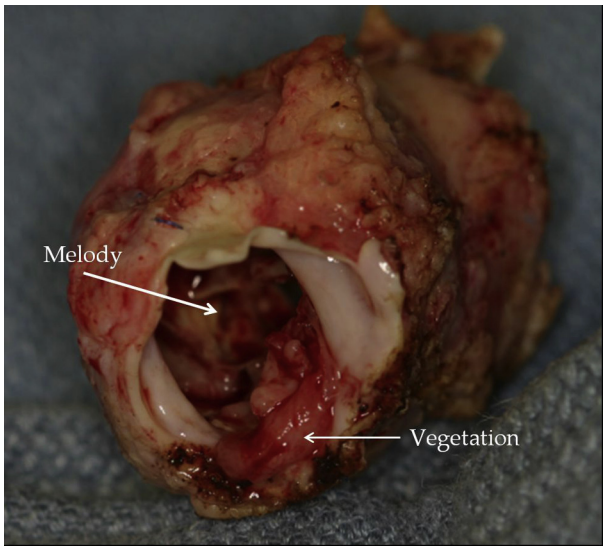

Figure 4 ***Streptococcus sanguinis* Valve Endocarditis**

Tetralogy of Fallot in a man age 20 years who underwent transcatheter implantation of a Melody bovine jugular valve (Medtronic, Inc., Minneapolis, Minnesota) with a stent system at the level of a bovine (pulmonary) valve conduit. The patient was lost to follow-up after 7 weeks. He developed chills, fatigue, and dyspnea on exertion. Echocardiography showed a large vegetation with severe pulmonary stenosis and right ventricular dysfunction. On surgery, a large vegetation was found attached to the implanted valve leaflet and to the stent wall.

Exercise Performance and Testing

There is evidence linking severe PR and RV dilation to impaired exercise performance in patients with repaired TOF. RV dysfunction leads to exercise intolerance and is associated with SCD (24). Exercise testing not only is useful in assessing overall clinical status and functional capacity, but also may help to guide the timing of PVR because RV dysfunction may manifest only during exercise and biventricular electromechanical dyssynchrony may worsen. At peak exercise, post-operative patients with TOF have lower cardiac index and stroke volume (101). Peak oxygen consumption during metabolic stress testing averages approximately two-thirds of normal (102), and low peak oxygen consumption (≤36% predicted) has been shown to correlate with mortality in adults with repaired TOF (103). Exercise testing may help to identify TOF patients with exertional arrhythmias.

Ventricular Function and Heart Failure

B-type natriuretic peptide (BNP) has been shown to be an important biomarker in patients with heart failure due to LV dysfunction. Several studies have investigated the relationship between BNP and RV dysfunction. BNP levels in TOF correlate with New York Heart Association (NYHA) functional class. In contrast to levels in patients with LV dysfunction, BNP elevations are mild. BNP has been reported to correlate with ECHO and CMR estimates of RV volume load, such as degree of PR and RV size. In a retrospective cohort study comparing plasma BNP levels during long-term follow-up in 130 children and adults with repaired TOF, Koch et al. (104) found that BNP was positively correlated with the ECHO-derived ratio of RV diastolic diameter to LV diastolic diameter as well as to severity of tricuspid regurgitation and PR. Significant correlations of BNP and measurements of PR fraction with CMR-derived RV volumes have also been reported (102). Two studies have investigated the correlation between BNP and exercise performance in TOF (BNP and exercise time

[r = 0.59, p < 0.001]). Exercise was associated with increased plasma BNP levels in both groups. A greater increase in BNP was noted in patients with TOF than in controls (37.6 ± 27.5 pg/ml vs. 11.3 ± 4.5 pg/ml, p = 0.0001). Forced vital capacity (FVC%) (84.9 ± 16.9 vs. 98.4 ± 18.2, p = 0.01) and forced expiratory volume during the first second (FEV1%) (91.5 ± 19.3 vs. 103.8 ± 16.1, p = 0.02) were decreased, exercise duration (ED) (10.1 ± 1.9 min vs. 11.4 ±1.7 min, p = 0.02), maximum heart rate (HRmax) (171.2 ± 18.9/min vs. 186.4 ± 13.9/min, p = 0.004), and maximum oxygen uptake (VO_{2max}) (1.56 ± 0.53 l/min vs. 2.1 ± 0.6 l/min, p = 0.007) were lower in patients with TOF (104,105).

With advances in transcatheter and surgical PVR, early detection of RV dysfunction has become increasingly important. RV function is affected by pre-load, afterload, and contractility, as well as by synchrony of contraction and ventricular interdependence (106). The deleterious effect of chronic afterload due to RV outflow tract obstruction on RV function is greater than that on the LV (107). Significant PR, RV outflow tract aneurysm, and akinesia can also decrease cardiac output (108). RV volume overload may negatively affect the function of both ventricles due to their interdependence (107). Even patients with "well-repaired" TOF may have residual hemodynamic abnormalities that require serial surveillance (108).

There has been interest in evaluating the treatment options for RV dysfunction in TOF (109). Babu-Narayan et al. (110) reported the findings from a randomized trial of ramipril for the treatment of RV dysfunction in adults with repaired TOF. Their 6-month study in 64 patients showed no differences in the primary and secondary endpoints of change in RVEF, change in NYHA functional class, exercise capacity, or BNP levels. Norozi et al. (111) evaluated the effects of bisoprolol in the treatment of patients with TOF and mild RV dysfunction. In their randomized study, 33 adult patients with repaired TOF were assigned to receive either bisoprolol or placebo for 6 months. No differences were seen in RVEF, NYHA functional class, or exercise capacity; BNP was increased significantly only in the bisoprolol-treated group.

Resynchronization therapy has proved to be beneficial in patients with congenital heart defects. Among children with TOF, isolated RV dysfunction, and right bundle branch block, temporary RV pacing was associated with improvements in cardiac index and RV contractility indexes (112). Among adults with TOF and poor LV function, RV pacing alone was associated with improved RV contractility, but it had no apparent effect on the LV (113); biventricular pacing was needed to increase contractility of both ventricles. Endocardial electrical mapping in adults with TOF has shown that the LV may have delayed activation patterns masked by the overlying right branch bundle block (114). Appropriate resynchronization may depend on a patient's age and underlying electrical synchrony pattern.

Timing of and Indications for PVR

There are several indicators useful for determining PVR in the TOF patient with free PR and a dilated RV. Optimal timing of PVR remains controversial because the unnatural history of TOF with PR is not well defined. Caution should be exercised in the decision of early intervention because there is a high incidence of conduit dysfunction, especially in the young (115,116). Serial increases in RV volume and worsening RVEF, along with exercise-testing measures and symptoms attributable to RV volume overload, are factors used for determining the timing of PVR (18,78). Other factors to consider are RV hypertension, moderate to severe tricuspid regurgitation, severe branch pulmonary arterial stenosis, sustained tachyarrhythmia, and large RV outflow tract aneurysm (30,78).

Ideally, PVR should occur prior to the development of frank RV dysfunction, but this prediction is difficult at times. RV function may improve in the absence of irreversible myocardial changes. Therefore, PVR should be considered in the face of significant RV dilation (117). Patients with chronic PR in whom LV dysfunction, heart failure, or syncope develops may have adverse outcomes (25,118). To date, there is no conclusive evidence that PVR improves survival. Harrild et al. (62) reported no difference in the composite outcome of ventricular tachycardia and death between patients with post-operative TOF and those who did not undergo PVR.

Discussion

Much attention has been given to evaluation and management of TOF to optimize disability-free survival. We have summarized the latest information from experts for key clinical issues to inform current practice, as follows:

1. From a genetic perspective, the etiology of TOF is multifactorial, with a familial recurrence risk of 3%. For nonsyndromic patients, fluorescence in situ hybridization for chromosome 22q11 microdeletion is a reasonable starting point.
2. CMR is the gold-standard assessment tool on the basis of its superior imaging of the RV outflow tract, pulmonary arteries, aorta, and AP collaterals, and its ability to quantify biventricular size and function, PR, and myocardial viability (18,19).
3. ECHO is the primary tool for imaging in pediatric patients. ECHO techniques that could provide reliable information for clinical decision making are being developed. Regional RV strain and strain rate may be useful for detecting early, subtle RV dysfunction (36).
4. Atrial re-entrant tachycardia will develop during extended follow-up in more than 30% of patients, and high-grade ventricular arrhythmias will be seen in about 10% of patients (39,40). The overall incidence

of SCD is estimated at 0.2%/year of follow-up (41,42). Risk stratification, even with electrophysiology testing and CMR, remains imperfect (25,26,44–53). Drug therapy has largely been abandoned, and ICD placement, despite high risks for complications and inappropriate discharges (64), is often recommended for patients at higher risk.

5. Even today, definitive information about optimal surgical strategies for primary repair to preserve RV function, reduce arrhythmia, and optimize functional status are lacking (76,77). After primary repair, reoperation for PR, tricuspid regurgitation, dilated aorta, or arrhythmia is often performed, although evidence is lacking about optimal timing and technique.
6. Post-operative lesions are often amenable to transcatheter intervention and avoid the need for reoperation. In selected cases, PR may be treated with transcatheter valve insertion.
7. Ongoing surveillance of RV function is a crucial component of clinical assessment and is a primary focus of quantitative CMR and ECHO imaging. Serum BNP has been correlated with ECHO and CMR parameters of RV function and volume, as well as with exercise performance. Current strategies to preserve RV function are primarily related to the timing of surgery or an interventional procedure. No known medical therapies have been shown to be effective once RV dysfunction occurs, although resynchronization with biventricular pacing has been shown to improve cardiac index and contractility (112,113).
8. In patients with significant PR, optimal timing of PVR remains uncertain.

Conclusions

Echocardiography and cardiac magnetic resonance imaging techniques have, in many instances, replaced cardiac catheterization as the primary diagnostic tool. They are particularly useful in the assessment of pulmonary valve function, ventricular volumes, and right ventricular performance, which are key factors for risk stratification. Genetic testing may help identify syndromic patients with additional risk factors. Surgical repair is associated with low mortality rates (<2%), but many patients will require multiple surgeries, with PR the most common indication for reoperation. Catheter-based therapy, in selected patients, may prevent additional surgeries. Optimal timing of PVR remains uncertain, although newer and revised criteria are emerging. Atrial re-entrant tachycardias are more common than ventricular tachycardia but most SCD events are associated with the latter.

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