Tetralogy of Fallot: Case-Based Update for the Treatment of Adult Congenital Patients

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Due to advancements in surgical technique and perioperative management, the number of patients with congenital heart disease (CHD) who are surviving until adulthood is growing.[1] Tetralogy of Fallot (TOF) is the most common form of cyanotic CHD, with an estimated overall prevalence of 3,000 per one million births[2] and is considered to be one of the first congenital defects to be successfully repaired by cardiovascular surgeons.[3] As the outcomes of babies born with CHD, and specifically TOF, continue to improve, many countries have more adults living with TOF than children. With surgical correction, the 30- to 40-year survival rate is 85%-90%.[1] Consequently, new issues have emerged, including the assessment, diagnosis, and management of medical complications related to the CHD or surgical correction as well as issues found in the average aging population. For these reasons, it will become increasingly important for physicians, especially adult cardiologists, to understand adult CHD.

TOF is a congenital cardiac anomaly associated with 4 presenting components: (1) perimembranous ventricular septal defect, (2) right ventricular outflow tract (RVOT) obstruction, (3) an over-riding aortic root, and (4) right ventricular (RV) hypertrophy (Fig 1). These findings are postulated to be caused by the anterior and cephalad migration of the infundibular septum. This displacement of the septum results in a misalignment of the infundibular septum with respect to the trabecular septum, narrowing the RVOT and creating a larger, over-riding aorta and perimembranous ventricular septal defect. RV hypertrophy develops as a consequence of the pressure overload caused by the RVOT and an over-riding aorta.

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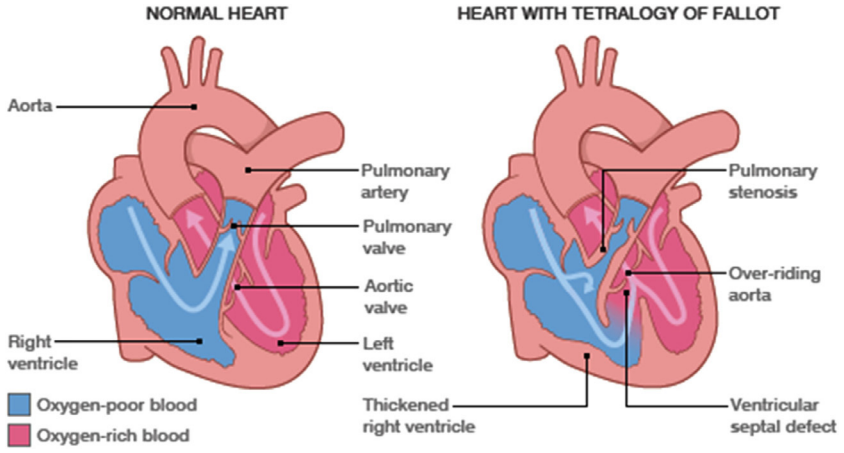

FIG. 1. Anatomical drawing of tetralogy of Fallot. (Color version of the figure available online.)

Several anatomical variants exist, including (1) TOF with pulmonary atresia with or without major aortopulmonary collaterals, (2) TOF with an absent, bicuspid or unicuspid pulmonary valve with or without pulmonary stenosis, (3) TOF with double outlet RV, and (4) TOF with an atrioventricular septal defect. TOF is also associated with congenital anomalies, such as an atrial septal defect, patent foramen ovale, anomalous left anterior descending artery from the right coronary sinus with course anterior to the RVOT, right-sided aortic arch, branch pulmonary vein stenosis, partial anomalous pulmonary venous return, and left superior vena cava draining into the coronary sinus.[4] When taking care of adults with TOF, it is important to know the anatomical variants and have the operative notes to help understand potential complications.

Surgical treatment for TOF has advanced over time. Early surgical techniques involved the initial creation of several palliative shunts with the goal of inducing enlargement and growth of the hypoplastic pulmonary vessels and allowing a future complete repair of the complex anatomy. In 1944, Drs Alfred Blalock and Helen Taussig along with surgical assistant Mr Vivian Thomas developed a palliative procedure that involved the creation of a systemic to pulmonary shunt by connecting the subclavian artery to the pulmonary artery.[5] This was known as the "Blalock-Taussig Thomas" (BTT) shunt, and it later became a palliative procedure for other cyanotic CHDs. In 1946, the creation of an anastomosis between the descending aorta and the left pulmonary artery was described, known as the Potts shunt; however, this was later abandoned due to difficulty in closing the shunt at the time of complete repair. In

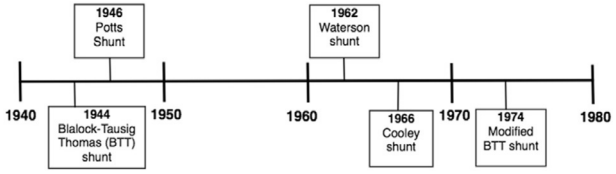

FIG. 2. Timeline of shunts.

1962, the Waterston shunt created an anastomosis between the ascending aorta and the pulmonary artery. In 1966, the creation of an intra-pericardial anastomosis from the ascending aorta to the right pulmonary artery was described, known as the Cooley shunt. The Potts, Waterston, and Cooley shunts were central shunts and less likely to thrombose when compared to the relatively peripherally placed BTT shunt. In 1974, the modified BTT shunt was designed using a prosthetic tube graft interposed between the systemic subclavian artery and the pulmonary artery, instead of the direct anastomosis previously described.[6] More recently, catheter-based balloon valvuloplasty with or without RVOT stenting has been used as the initial palliation in neonates with TOF to improve arterial oxygen saturation and pulmonary arterial growth[7] (Fig 2).

Complete surgical repair for TOF was first performed in 1954 by a surgical team led by C. Walton lillehei at the University of Minnesota.[5] In 1955, at the Mayo Clinic, John Kirklin and associates performed an open repair of complex congenital heart defects including ventricular septal defect and TOF. In the 1970s, Bonchek and Starr at the University of Oregon evaluated the use of surgical intervention in infancy and established the superiority of complete repair at an earlier age.[8]

The timing of surgical repair has been controversial and evolving over the years. Before the 1970s, most patients with TOF underwent palliative surgery that involved the creation of a systemic-pulmonary shunt followed by delayed intracardiac repair. After the 1970s, primary intracardiac repair became the treatment of choice in both symptomatic and asymptomatic patients. In the current era, palliative shunts are only performed in those who are poor candidates for intracardiac repair in infancy. Intracardiac surgical repair is usually performed electively in the first year of life.[9] Early operations provide the benefits of alleviation of cyanosis, normalizing the patient's cardiovascular physiology, and minimizing secondary damage to the heart and other organs. Elective surgeries are typically performed between 3 and 11 months due to an acceptable operative risk, low incidence of significant arrhythmias, and a long-term survival similar to that observed in the general population.

A complete surgical repair consists of patch closure of the ventricular septal defect as well as relief of the RVOT, pulmonary valve, and pulmonary artery obstruction. Closure of the ventricular septal defect is usually performed with continuous polypropylene suture, polyethylene terephthalate material, or Gore-Tex patch through either a transventricular or transatrial approach. To relieve the right-sided obstruction, resection of the infundibular stenosis, with possible muscle resection is the most widely used method. This relief of the high afterload caused by the RVOT obstruction reduces RV hypertrophy that can predispose to RV failure and ventricular arrhythmias. In children, RV augmentation can be performed by placing a transannular patch. Due to rapid growth in infancy and childhood, every attempt is made to preserve the native pulmonary valve when initial intracardiac repair is performed.[9] If the pulmonary valve is abnormal, a pulmonary valvotomy or pulmonary valve resection may be necessary. On occasion, a RV to pulmonary artery conduit is required when unfavorable anatomy, such as pulmonary atresia, or an anomalous left anterior descending artery off the right coronary cusp that courses the RVOT (5%-12% of cases), prevents safe surgical incision and complete repair.[5]

Over the years, materials used for surgical correction of RVOT obstruction have included placement of homografts, bovine jugular valved conduits, stentless valves, stented tissue valves, monocusp valves, mechanical valves, autologous pericardial valves, and transcatheter pulmonary valves. In 2010, the FDA approved the Medtronic Melody Transcatheter Pulmonary Valve. This device is used as an adjunct to surgery when managing pediatric and adult patients with (1) existence of a circumferential RVOT conduit that was equal to, or greater than 16 mm in diameter when implanted initially and (2) dysfunctional RVOT conduits associated with clinical symptoms and either greater than moderate regurgitation or stenosis with mean RVOT gradient >35 mmHg.[9]

The long-term complications of TOF correlate to the year and specific surgical repair performed. To achieve relief of the RVOT obstruction, disruption of pulmonary valve integrity is often necessary by valvotomy or a transannular patch, which leads to varying degrees of pulmonary regurgitation. While pulmonary regurgitation can be well tolerated in childhood, it can progressively lead to decreased exercise capacity, RV dilatation, and ventricular arrhythmias, which increase the risk of sudden cardiac death (SCD). Additionally, RVOT enlargement procedures result in scar formation and akinetic regions, which can lead to aneurysm formation. Other long-term complications include branch pulmonary stenosis, residual atrial septal defect or ventricular septal defect, tricuspid

regurgitation, RV dilatation and dysfunction, aortic dilatation, aortic regurgitation, and left ventricle (LV) dysfunction.[10] Aortic dilatation at the level of the sinotubular junction, although frequent in patients with repaired TOF, has a low rate of progression and does not warrant a more aggressive approach or frequent assessment with cardiac magnetic resonance imaging (CMR).[11] Evaluation of clinical status and potential complications must be periodically evaluated with imaging modalities.[10] Adults with repaired TOF should be followed at least annually and more frequently depending on symptoms and complications of the repair. These patients are monitored with imaging modalities, electrocardiograms, cardiopulmonary stress tests, and occasionally may need diagnostic or therapeutic cardiac catheterizations.[12] This review presents 3 clinical scenarios followed by evidence-based discussions of diagnostic imaging and strategies for managing complications of adults with TOF.

Case 1. A 49-year old woman with TOF presents with fatigue, malaise, and palpitations occurring with minimal exertion. She initially underwent a palliative left-sided BTT shunt within the first 2 years of life (1969). At the age of four (1971), she underwent a surgical ventricular septal defect repair with a pulmonary valvotomy and transannular patch.

Physical examination revealed blood pressures of 122/78, heart rate of 68 bpm and pulse oxygenation of 99% on room air. The patient had a harsh 2/6 systolic murmur with a 4/6 early diastolic murmur and single S2. Her electrocardiogram showed sinus rhythm with right bundle branch block with a QRS duration 188 ms. Her initial cardiac testing included an echocardiogram, cardiac magnetic resonance imaging (MRI) and cardiopulmonary stress test. Echocardiography revealed a severely dilated right atrium and RV, a large RVOT patch, no functional pulmonary valve with unrestricted pulmonary regurgitation, and normal left-heart size with low normal LV systolic function of 45%-50%. Cardiac MRI showed RV ejection fraction of 22%, RV end-diastolic volume of 248 cc/m^2, RV end-systolic volume of 192 cc/m^2 and LV ejection fraction (EF) of 49%. A cardiopulmonary exercise test showed normal breathing reserve with a peak VO_2 ($PkVO_2$) of 20.1 mL/kg/min indicating moderate functional impairment due to deconditioning.

Discussion

Given the findings of her testing, her nonspecific symptoms could be attributed to pulmonary valve insufficiency or RV enlargement. What diagnostic tests may be useful to help differentiate the etiology? What are the indications for intervention?

Despite the advances of early diagnosis, progression from a 2-stage correction to 1-stage repair in infancy and improved outcomes, most adult patients with repaired TOF continue to have residual anatomic and hemodynamic abnormalities resulting in increasing rates of morbidity and mortality. Initially, relief of the obstructions in the RVOT and pulmonary valve frequently results in pulmonary regurgitation, which initiates a cascade of pathophysiologic events leading to RV dilatation and subsequent dysfunction requiring pulmonary valve replacement (PVR).[13,14] In addition to the pulmonary regurgitation, an adult with TOF needs evaluation for pulmonary artery stenosis, RVOT aneurysm, tricuspid regurgitation, residual ventricular septal defect, LV dysfunction, aortic valve regurgitation, and aortic dilatation for which multimodality imaging is necessary to provide a comprehensive assessment.[13]

Interpretation of the effects of RV remodeling after PVR on CMR and echo require understanding of a few basic principles: (1) pulmonary regurgitation in adults with repaired TOF leads to progressive RV dilatation and progressive RV dysfunction, (2) RV dilatation is one of the leading risk factors for adverse cardiovascular events, and (3) timely prosthetic PVR with subsequent decrease in RV volumes decreases the risk of adverse events and improves long-term outcomes.[15] RV volumes measured by CMR is currently used to guide pulmonary valve intervention. Most recently, Bokma et al. reported the best preoperative threshold to achieve mid-to-late RV normalization was RV end-systolic volume $< 80\ mL/m^2$. Patients with preoperative RV end-systolic volume $>95\ mL/m^2$ were at an increased risk for suboptimal hemodynamic outcomes and adverse clinical events such as death, sustained ventricular arrhythmias, and worsening heart failure.[16] Some experts caution on timing PVR solely based on RV volumes, as doing so, may be an oversimplification of a complicated issue, especially in an asymptomatic patient.[17]

Cardiac imaging with ECHO, CMR, cardiac computed tomography (CT), and cardiopulmonary stress testing plays a pivotal role in the surveillance of patients, in identifying and measuring the anatomic and functional abnormalities, informing clinical decision-making, and aiding in risk stratification. Echocardiography is the primary noninvasive imaging modality in patients with CHD due to its wide availability, low cost, portability, lack of exposure to harmful ionizing radiation, and high level of experience with this modality by the clinicians caring for patients with CHD.[13] Two-dimensional (2D), tissue doppler, 3D, transesophageal, longitudinal strain, and stress echocardiography can all assist in the evaluation of these adults. 2D echocardiography allows qualitative and quantitative assessment of the right heart, RVOT, pulmonary arteries,

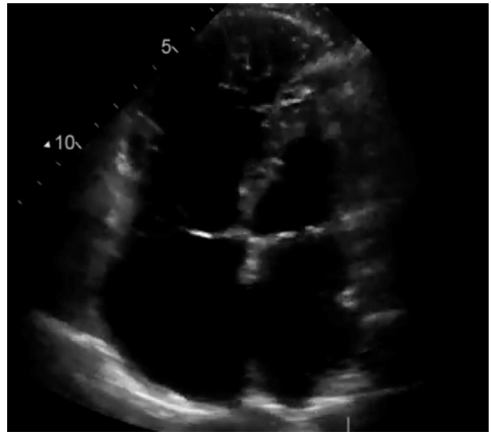

FIG. 3. Four chamber view on echocardiogram. (Color version of the figure available online.)

tricuspid valve, pulmonary valve, atrial and ventricular septa and aortic root (Fig 3). Doppler echocardiography is essential for assessment of hemodynamic assessment such as RV pressure, degree of pulmonary, and tricuspid regurgitation and diastolic dysfunction. 3D echocardiography can be used to quantitate RV volumes; however, the feasibility is low at 55% secondary to poor acoustic windows and challenges in defining the resolution between the endocardium and prominent trabeculations of the RV.[18] Despite an underestimation when reconstructing 3D images compared to CMR, it is promising that future developments may enable echocardiography to replace CMR for RV quantification.[19] Transesophageal echocardiography can be used to guide interventional procedures or evaluate anatomy when transthoracic imaging is challenging.[13] Preoperative strain echocardiography of the right and LVs has been shown to be predictive of postoperative ventricular function and New York Heart Association (NYHA) class after PVR and may be of assistance in identifying optimal timing of surgery. Interestingly, in the adult TOF patient population, both the LV and RV strain is reduced after PVR.[20]

Supine exercise echocardiography can also play in role in determining the time of surgery by assessing hemodynamics during stress. In a study of 128 patient with TOF, fractional area change, tricuspid annular plane systolic excursion (TAPSE), and RV pressures were measured at rest and stress. It was feasible to measure these parameters at stress in 96% of the patients. The study was able to identify patients whose TAPSE and RV fractional area change did not increase with stress testing. However, the prognostic value of this needs to be further determined as the peak VO_2 was the same in both the nonresponders and responders.[21]

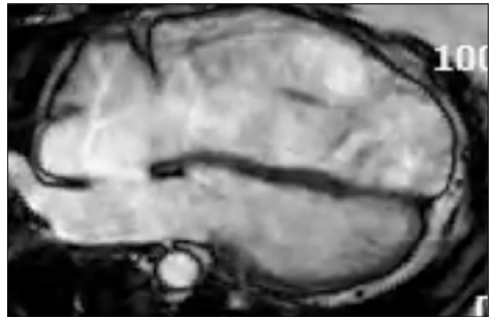

FIG. 4. Cardiac MRI image of RV.

The main limitation of echocardiography lies in its ability to adequately imaging the complex, crescentic shaped right heart and the poor acoustic windows once a patient reaches adulthood.[13] The importance of an accurate quantitative assessment of the RV size and function in adult patients with TOF requires the use of other imaging modalities such as CMR and CT.

CMR provides a comprehensive assessment of cardiovascular morphology and physiology independent of acoustic windows and without ionizing radiation, making it an ideal imaging modality for longitudinal follow-up. It is the gold standard for quantification of ventricular size and function in patients with TOF due to its ability to provide accurate and highly reproducible measurements (Fig 4). Additionally, this modality can detect scar tissue in the ventricular myocardium defined as late gadolinium enhancement.[13] Myocardial fibrosis is associated with adverse clinical outcomes such as ventricular dysfunction, exercise intolerance, neurohormonal activation, and clinical arrhythmia; its assessment is a key component of the evaluation by CMR.[22] Novel techniques allow measurement of the extracellular volume fraction, a marker of extracellular matrix remodeling. The limitations of CMR include the cost, lack of portability, limited availability, artifacts from implants containing stainless steel, and relative contraindication in patients with a pacemaker or implantable defibrillator.[13]

Although the focus of CMR in this patient population is often RV function, greater than 20% of adults with repaired TOF have concomitant LV dysfunction. A study by Geva et al. showed that moderate or severe RV or LV systolic dysfunction, but not pulmonary regurgitation fraction or RV diastolic dimension, is an important factor associated with poor clinical status of long-term survivors of TOF repair. The close relationship between LVEF and RVEF suggests unfavorable ventricular-ventricular

interaction.[14] Obviously, RV dilation and dysfunction results from pulmonary regurgitation. LV dilation and dysfunction results not only from tricuspid regurgitation, but also age at which palliative shunts were performed and aortic regurgitation. Measures to maintain or restore pulmonary valve function and to avoid RV aneurysm or akinesia are mandatory for preserving RV and LV function late after repair.[23] Thus, evaluation of LV dimensions and function is as critical in these patients as assessment of the RV.

Although RV volume load due to severe pulmonary regurgitation can be tolerated for many years, there is now evidence that the compensatory mechanisms of the RV myocardium ultimately fail. If the volume load is not eliminated or reduced by PVR, the dysfunction may be irreversible. As CMR is the gold standard for assessing the anatomical and functional sequelae in patients with repaired TOF, it has a role in the risk or benefit analysis that occurs as part of the decision related to timing for PVR. The decision to insert a pulmonary valve relies on clinical assessment of symptoms and signs attributable to the cardiovascular system and measurements of pulmonary regurgitation, biventricular volume and function, shunt ratio, and several morphological criteria including an RVOT aneurysm, branch pulmonary artery stenosis, and severe aortic dilatation. Although other imaging modalities can obtain some of this data, CMR is best suited to reliably provide most or all of the necessary information with one single noninvasive examination that does not require exposure to ionizing radiation.[14] As discussed above, cardiac MRI provides suggestions for times of PVR based on RV volumes.

Cardiac CT is most commonly used as an alternative imaging modality in patients with absolute contraindications to CMR or in locations where CMR is not available.[10] Electrocardiographically gated CT provides excellent, usually submillimeter, spatial resolution which allows a very clear depiction of cardiovascular anatomy, especially useful for evaluation of small blood vessels such as the coronary arteries or distal pulmonary artery branches. Other advantages include the ability to perform cardiac CT in patients with pacemakers and implantable defibrillators as well as imaging of structures that are obscured on CMR by stainless steel metallic artifacts. Cardiac CT has the inherent limitations of exposure to ionizing radiation, lower temporal resolution compared to echocardiography and CMR, and the inability to provide hemodynamic information on flow rate or velocity.[13]

In addition to the multiple imaging modalities, biomarkers such as brain-natriuretic peptide (BNP) and its precursor, N-terminal pro-B-type natriuretic peptide, may be useful in screening for late complications in

adult CHD. These biomarkers have firmly established diagnostic and prognostic value in acquired left-heart failure. Heng et al. investigated the role of BNP in adult patients with repaired TOF. They found that neurohormonal activation; as evident by elevated circulating levels of natriuretic peptides, ET-1, and renin; was present in even asymptomatic patients with repaired TOF. During their investigation, a BNP level of >15 pmol/L (equivalent to 126 pg/mL) was predictive of a 5-fold increase in mortality. The authors suggested that the attributes of BNP in left-sided chronic heart failure may be appropriately extended to chronic RV pathology in repaired TOF, as ventricular myocyte stretch in this patient population is most commonly due to chronic volume loading with pulmonary regurgitation. SCD in repaired TOF remains a poorly mitigated outcome, with a long-term estimated risk of 4%-6%. BNP measurements may have a role in the clinical risk assessment and decision-making process in the risk evaluation for SCD and sustained arrhythmia; however, additional investigation is needed to delineate its use in CHD.[24]

Cardiopulmonary exercise testing is a valuable tool in the assessment of patients with adult CHD. This noninvasive test allows for risk stratification with regards to morbidity and mortality as well as aids in the decision on the need and timing for therapeutic interventions. Peak VO_2 and VE/VCO_2 slope are well-established measures of exercise tolerance that have been shown to correlate with NYHA functional class, quality of life, and to be reliable independent predictors of morbidity and mortality, both in the setting of heart failure and CHD. Due to the inability to compare healthy volunteers to adults with CHD, who are known to have a reduced exercise capacity, Kempny et al[25] studied the distribution of exercise capacity across the spectrum of patients with adult CHD (Fig 5). They found exercise capacity differs significantly across the spectrum of adult CHD with the lowest peak oxygen uptake (VO_2) values and highest VE/VCO_2 slope values in patients with Eisenmenger syndrome and complex CHD. Patients with aortic coarctation and transposition of the great arteries after arterial switch operation were found to have the highest peak VO_2 values and lowest VE/VCO_2 slope values. Even in the patients with adult CHD with the highest peak VO_2 values, the average was significantly reduced when compared with healthy volunteers. In TOF, the reported average peak VO_2 was 27.2 ± 9.0 and 22.5 ± 6.8 mL/kg/min in males and females, respectively. The difference between genders was statistically significant. By comparing the disease-specific exercise capacity to that required for different physical activities and occupations, the authors provide information to guide therapy and assist in advising patients on physical activity and professional or career choices.[25]

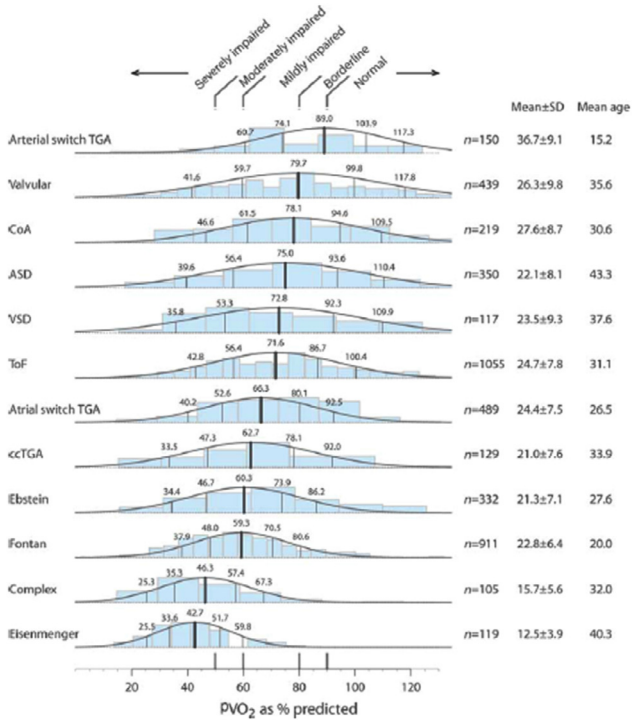

FIG. 5. Exercise capacity in adults with congenital heart disease. (Color version of the figure available online.)

Additionally, cardiopulmonary exercise testing has been proposed as an objective exercise tolerance test to determine the optimal timing of PVR because (1) symptoms are often volunteered late by patients but may be preceded by impairment in exercise testing and (2) impaired peak oxygen uptake on exercise testing is associated with a higher perioperative surgical risk.[26]

Diagnostic cardiac catheterization was once used universally in all patients with CHD but has been supplanted over the past 30 years by the multiple available noninvasive imaging modalities. Cardiac catheterization still retains a role when the noninvasive data is inconclusive or contradictory. In patients with right-sided congenital heart abnormalities, catheterization provides direct hemodynamic assessment and allows for accurate measurement of shunts and calculation of pulmonary arterial resistance.[27]

The cardiovascular testing discussed above is used to help guide the timing and need for PVR in patients with TOF and unrestricted pulmonary regurgitation. PVR can be performed using a transcatheter technique or surgically with one of many available bioprosthetic valves. The benefits of early

PVR are in resolution in pulmonary regurgitation, 30%-40% reduction in RV end-diastolic and end-systolic volumes, decrease in RV systolic pressure in those with preprocedural RVOT obstruction, and consistent improvement in NYHA functional class although without a consistent change in objective exercise parameters or arrhythmia burden. Additionally, an unchanged RV and LVEF and slightly increased LV size are expected.[14]

Despite investigations on timing, indications, techniques, and results for PVR, there is still considerable controversy on the best management strategy in asymptomatic patients.[14] In a study of over 1000 patients with TOF, the authors described the cardiac phenotype of patients defined as having good outcomes, as indicated by reaching age 35 years without a PVR, being asymptomatic, and having normal exercise tolerance. These patients were found to have nearly normal right heart structure and function, including at most mild RVOT obstruction, normal pulmonary valve annulus diameter, no more than mild-to-moderate pulmonary regurgitation, high-normal or minimally dilated RV, no RVOT aneurysm, and normal RV systolic function. Out of the 50 patients randomly selected for in-depth evaluation, only 14 met criteria for good outcome. However, the authors concluded that despite being in a high volume study, the ability to accurately prognosticate remains poor, due to 2 patients in their "good outcome" group requiring a subsequent PVR.[28] Additionally, studies on patients with repaired TOF often exclude those with more complex anatomical variants or associated anomalies; therefore, the burden of residual disease and mortality in the overall TOF population is difficult to assess. With the advent of transcatheter valve therapies, there has been a lowering of the threshold for PVR.

Preprocedural assessment, frequently with multiple imaging modalities such as ECHO and CMR, is essential for evaluation of the RVOT to determine gradients, diameters, and morphology, and to allow successful percutaneous pulmonary valve implantation (PPVI). Based on indications proposed by the American Heart Association European Society of Cardiology and Association for European Pediatric Cardiology and Geva et al, Figure 6 lists indications for surgical or transcatheter pulmonary valve intervention.[12,14,29] In symptomatic patients, the guidelines suggest intervention when the RV systolic pressure is above 60 mmHg (tricuspid regurgitation velocity $>$ 3.5 m/s) or when there is moderate or severe pulmonary regurgitation. In asymptomatic patients, PPVI is indicated with severe RVOT stenosis and severe pulmonary regurgitation in the presence of decreased exercise capacity, progressive RV dilation, progressive RV systolic dysfunction, progressive tricuspid regurgitation, RV systolic pressure $>$ 80 mmHg, or sustained atrial or ventricular arrhythmias. PPVI is

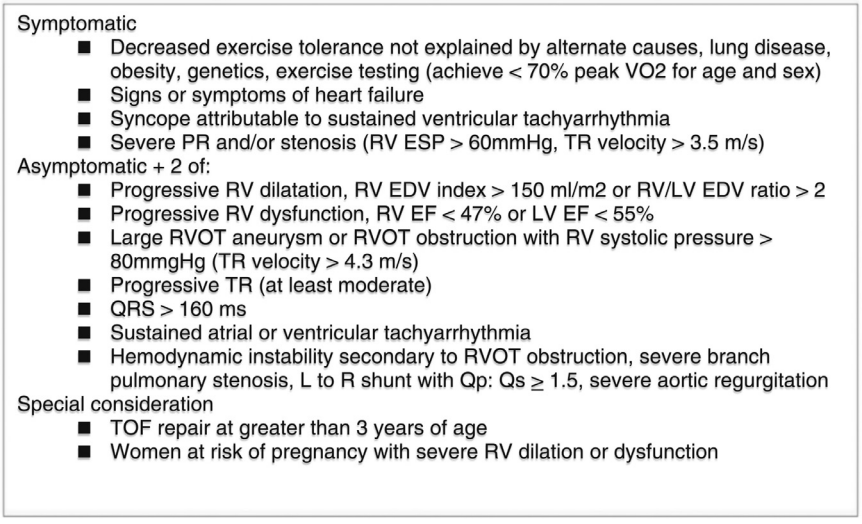

FIG. 6. Indications for pulmonary valve replacement.

indicated in dysfunctional surgical RVOT conduits with dilated diameters between 18-22 mm and 23-26 mm for the Melody and Sapien valves, respectively. PPVI is not currently recommended in native or patch-augmented RVOTs or in conduits less than 16 mm in diameter. Absolute contraindications include active infection, occluded central veins, and coronary compression observed with RVOT balloon dilatation. Aortic or coronary angiography is routinely performed with simultaneous high-pressure balloon inflation in the valvular landing zone to assess if coronary flow is impaired by this maneuver, to avoid this potentially fatal complication.[28] Future techniques and devices have the potential to expand routine PPVI eligibility to patients with native RVOTs, as well as those with RVOT diameters that are either smaller or larger than currently available devices, as patients presently having these features are requiring an open surgical approach.[27] In the subset of patients with CHD with native RVOT or RVOT patch repairs, there is a growing body of literature on the utility of commercially available valves used off-label. In one retrospective trial of 31 patients, Melody pulmonary valve implantation in the native RVOT due to either stenosis or regurgitation was safe and feasible; however, there was a high stent fracture rate of 32% despite prestenting[30] (Fig 7).

Currently, there are 3 percutaneous valve options on the market. The Melody transcatheter pulmonary valve by Medtronic Inc consists of a bare-metal platinum-iridium stent and a manually sewn valved segment of bovine jugular vein. The Melody valve is available in diameters of 16

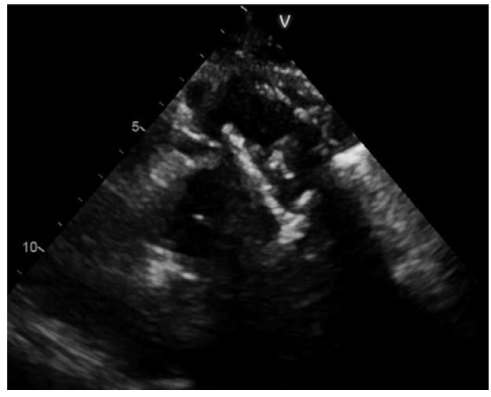

FIG. 7. Right-sided endocarditis on echocardiogram. (Color version of the figure available online.)

and 18 mm, which can be expanded to 18 or 20 mm or 18, 20, or 22 mm, respectively. This device is delivered by a balloon-in-balloon technique. The Edwards Sapien Pulmonic transcatheter heart valve by Edwards Lifesciences is a trileaflet bovine pericardial tissue valve hand-sutured in a balloon expandable, radiopaque, stainless steel stent. It is available in 23 or 26 mm diameters and is delivered with the use of a guiding catheter and a single-balloon catheter. The Venus P Valve by Venus Medtech is another novel self-expanding percutaneous pulmonary device composed of a trileaflet porcine pericardial valve mounted on a covered nitinol stent frame. This valve ranges in size from 20-32 mm in diameter.[27]

Data for the Edward Sapien valves are small but promising. A study was performed on 25 patients, mostly with TOF, to evaluate outcomes after PPVI. The authors demonstrated a high technical success rate of 96%, improvement in intraprocedural hemodynamics including a decrease in the mean RV to systemic pressure ratio from 0.64-0.36 and RV to pulmonary artery gradient from 39-9 mmHg following valve replacement, and no clinically significant pulmonary regurgitation. One patient required elective surgical PVR for a high residual gradient, and one patient required reintervention for severe pulmonary regurgitation at 1 year. At a mean follow-up of 3.5 years, there were no episodes of endocarditis and no stent fractures. There was preserved valve function during follow-up with no change in RV to pulmonary artery gradient nor pulmonary regurgitation severity. Based on the results, the authors concluded that the Edwards Sapien system is a viable and durable option for PPVI.[31]

Direct comparisons between surgical intervention and PPVI have not been performed. PPVI has the potential to avoid or delay open-heart

surgery and its associated morbidity. Freedom from reintervention after PPVI has been reported above 90%, 80%, and 70% in follow-up periods of 1, 2, and 4 years, respectively. Factors associated with reintervention include a high post-PPVI residual RVOT gradient and stent compression or recoil after valve deployment. The most frequent complication of PPVI is fracture of the stent frame, reported in up to 30% of cases. Stent fractures are classified as type I, no loss of stent integrity; type II, loss of stent integrity; and type III, separation or embolization of the fractured segment. Type I fractures are usually managed conservatively and followed regularly, as they can progress to more advanced fractures. Type II and III fractures can be successfully treated with valve-in-valve procedures, although type III stent fractures may require surgical management in the case of distal strut embolization.[27]

At present, the problem responsible for late mortality and reintervention or explantation in patients after PPVI is infective endocarditis. The risk of infective endocarditis in implanted homografts has been estimated at 2.4% per patient-year. Infective endocarditis occurs more frequently after PPVI than surgical PVR. Two large studies comparing the incidence and outcomes of right-sided endocarditis in patients after surgical or percutaneous PV intervention showed 4.5-fold high risk of infective endocarditis after a percutaneous procedure (Fig 8). Several factors explaining this difference have been proposed, include possible valvular damage before percutaneous implantation during crimping and balloon expansion, whereas surgical prostheses are placed directly into the RVOT without any manipulation.[32] Additionally, a high residual RVOT gradient, the resulting turbulence, and in situ thrombosis have been implicated in the pathophysiology of post-PPVI endocarditis.[27] Dijck et al reported that the Melody valve and Contegra had significantly higher incidence of infective endocarditis compared to the Sapien valve, 7.5% and 20.4% vs 2.4%, respectively. Infective endocarditis is also a significant threat for long-term conduit function.[33]

In addition to the pulmonary regurgitation, tricuspid regurgitation is a cause for concern in adults with repaired TOF; however, the management of functional tricuspid regurgitation is controversial. In a study by Woudstra et al,[34] severe tricuspid regurgitation, although present in only a minority of patients, was associated with an increase in the composite outcome of adverse clinical events including tachyarrhythmia, progression of heart failure, and death. In the study, patients with moderate tricuspid regurgitation and symptomatic (NYHA functional class > 2) heart failure, mainly attributed to RV dysfunction and significant tricuspid regurgitation, were at highest risk for progression to severe tricuspid

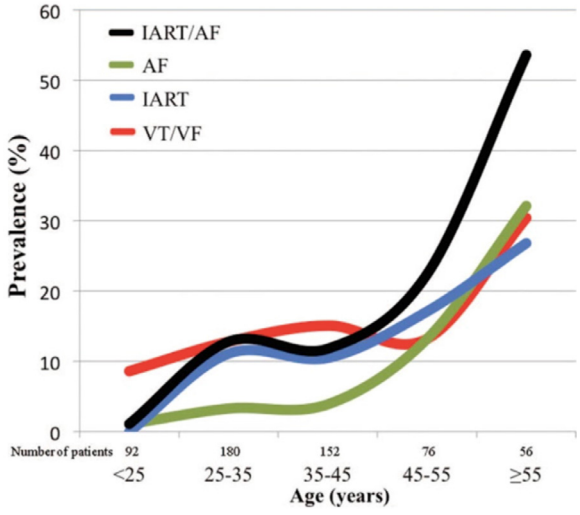

FIG. 8. Prevalence of arrhythmias with age. (Color version of the figure available online.)

regurgitation. Initially, surgeons tended to take a more aggressive approach to concomitant tricuspid valve annuloplasty at the time of PVR. Kogon et al[35] investigated the effect of tricuspid valve intervention during PVR surgery and noted that performing concomitant tricuspid annuloplasty not only requires several additional surgical steps, unnecessary for an isolated PVR, but also results in prolonged cardiopulmonary bypass time, which is associated with increased morbidity and prolonged lengths of stay in the setting of adult congenital heart surgeries. in a study of 65 patients undergoing PVR, there were no statistical differences between those patients undergoing concomitant tricuspid valve repair with PVR and those undergoing PVR alone in terms of the degree of tricuspid regurgitation and RV size six months after surgery.[36] Patients with moderate tricuspid valve regurgitation have also been observed to undergo significant improvement in tricuspid valve function and RV size following the first postoperative month after PVR, irrespective of concomitant tricuspid valve annuloplasty. Therefore, a conservative approach to tricuspid valve annuloplasty should be taken in patients who undergo subsequent PVR after surgical palliation of TOF and congenital pulmonary stenosis.

Case 1 Conclusion

In summary, this patient presented with atypical symptoms which can be attributed to long-term complications of TOF. Based on multimodality imaging she was noted to have severe pulmonary regurgitation on

echocardiography, a cardiac MRI with significant dilated RVEDV of 248 cc/m^2 and RVESV of 192 cc/m^2 and decreased Peak VO_2 all supporting RV dilatation secondary to severe pulmonary regurgitation, for which she underwent PVR. Following the procedure, the RV end-diastolic volume decreased to 168 cc/m^2 (33% reduction), and the RV end-systolic volume decreased to 131 cc/m^2 (32% reduction). This proportional decrease in volumes resulted in an unchanged RVEF of 22%. Use of various diagnostic modalities explained above helps cardiologists monitor for complications of TOF and determine indications for surgical or percutaneous intervention.

Case 2. A 46-year old man with known diagnosis of TOF, recurrent atrial flutter that required radiofrequency ablation, amiodarone-induced hypothyroidism complete heart block with permanent pacemakers and implantable cardioverter-defibrillators (ICD) in place. He presented with frequent episodes of palpitations and numerous shocks from his ICD. At age of 3, he underwent complete surgical repair of TOF, including pulmonary valvotomy. His condition was stable until age of 31 when he found to have progressive right heart enlargement from unrestricted pulmonary regurgitation, when he underwent a placement of a 29 mm Carpentier valve conduit in the pulmonary position and repair of the tricuspid valve. Twelve years later, at age of 42, he developed progressively worsening heart failure with pulmonary stenosis and insufficiency of the valve conduit resulting in implantation of a percutaneous Melody valve (Medtronic Inc) in the pulmonary position. His co-morbidities included hypertension, hyperlipidemia, and elevated calcium score found on cardiac CT scan. His presentation to emergency department was consistent with acute decompensated heart failure with frequent shock from ICD. He had also gained weight and started to smoke cigarettes to alleviate stress. His electrocardiography showed ventricular paced rhythm, and his ECHO showed increased RV size with low normal to mildly reduced RV systolic function. The peak velocity through the pulmonary valve conduit was 3 m/s and mild aortic insufficiency and mild tricuspid regurgitation. The LV was dilated with LVEF of 45% and mildly dilated aortic root.

Discussion

It is important to understand and assess the risk of atrial arrhythmias, ventricular arrhythmias, and SCD among patients with repaired TOF. What is the appropriate management of these arrhythmias? What are the indications for ICD implantation in such population?

Following surgical repair for TOF, most patients live well into their adult years; however, it is amongst the corrected congenital heart defects who are associated with the highest risk of ventricular arrhythmias and SCD.[37] The annual incidence of SCD among adult patients with TOF varies with age but is generally believed to be 1%-3% per year.[38] There are several traditional risk factors for the development of SCD, which can be placed into following 3 broad categories: patient history (older age at the time of repair), electrophysiologic markers (complete heart block, QRS duration of $\geq$180 ms, and premature ventricular contractions), and hemodynamic abnormalities resulting from chronic severe pulmonary regurgitation and other sequelae of surgical repair (ie, increased RV pressures following repair).[39] Although some of these predictors are more sensitive than others, most of them have a low positive predictive value.[40]

A large multicenter cross-sectional study evaluated the arrhythmia burden in adults with repaired TOF. Sustained tachyarrhythmias were present in 43% patients, with increasing burden in older age patients. Although atrial arrhythmias were more prevalent than ventricular arrhythmias, 20.1% vs 14.6%, respectively; the single most common arrhythmia subtype is ventricular tachycardia (VT) (14.2%) followed by intra-atrial re-entrant tachycardia (11.5%).[41] There is a 10-15 year period following corrective surgery in which tachyarrhythmias are less prevalent, followed by a steady decline in freedom from atrial and ventricular arrhythmias. It is important to note that while atrial fibrillation is uncommon and less prevalent than intra-atrial re-entrant tachycardia in patients <45 years of age, the prevalence of atrial fibrillation exceeds that of intra-atrial re-entrant tachycardia in patients more than 55 years of age[41] (Fig. 6).

Intra-atrial tachycardia in TOF is predominantly a right-sided atrial arrhythmia where the tricuspid regurgitation is the predominant hemodynamic lesion, presumably leading to right atrial dilation and creating the substrate for atrial arrhythmogenesis.[42] Atrial fibrillation, on the other hand, is associated with left atrial dilatation and LV dysfunction.[43] Older age is associated with higher prevalence of atrial fibrillation; there is a steep rise in prevalence of atrial fibrillation earlier in patients with TOF compared to general population, age > 45 years compared to >65 years, respectively.[41] In patients with TOF, treatment of atrial fibrillation with early radiofrequency ablation has shown high acute success rate, improvement in symptoms and lower chance for recurrence.[44] A retrospective chart review among patients with CHD, who planned to have a cardiac operation and had pre-existing atrial arrhythmia, concomitant cardiac procedures with Cox-maze procedure showed almost complete resolution of atrial arrhythmia postoperatively.[45]

Among TOF patients, VT accounts for the majority of ventricular arrhythmias likely due to hemodynamic and electrophysiological alterations that occurred in the congenital defect itself or due to the surgical correction of pre-existing lesion.[46] Contrary to tricuspid regurgitation being the primary hemodynamic lesion result in atrial arrhythmias, pulmonary regurgitation is the primary hemodynamic lesion that results in VT and sudden cardiac death.[42] Percutaneous pulmonary valve replacement has been shown to be protective against the development of recurrent arrhythmias. The use of catheter ablation for VT showed recurrence rate of 34% at 3.8 years.[47]

Additionally, prolonged QRS duration and the rate of prolongation are important predictors of VT and recurrent SVT; however, the threshold is QRS duration $>$ 160 and $>$ 180 ms for VT and SVT, respectively[43] in addition to being associated with an inducible VT, QRS duration $>$ 180 ms is also associated with adverse arrhythmic events such as sudden cardiac death (SCD).[43] Palliative shunts have also been independently associated with inducible ventricular arrhythmias and appropriate ICD shocks in patients with TOF. Despite the increase in RV pressure that occurs from RVOT, the multicentered study by Gatzoulis et al illustrated that isolated RVOT obstruction was not a predisposing factor for late clinical arrhythmias. Not surprisingly, there is an increased prevalence of atrial and ventricular arrhythmias with increasing number of cardiac surgeries performed.[41]

Approximately, 20%-25% of late deaths in adults with CHD occurs due to SCD. In TOF patients, the incidence is 2%-6% per year.[38] Prevention of SCD among TOF patients remains a major challenge, especially in reliably identifying the high-risk patients, and perhaps over-reliance on depressed LV function for primary prevention with ICD.[48] The combination of moderate-to-severe LV systolic dysfunction (EF $<$ 20%) and QRS $>$180 ms had a strong positive and negative predictive value, 66% and 93%, respectively for predicting SCD.[40] A multicenter observational cohort study of 870 patients identified RV hypertrophy, LV or RV systolic dysfunction (EF $<$ 44%) and atrial tachyarrhythmias were predictors of SCD or sustained VT in young adult patients with repaired TOF.[39] LV longitudinal dysfunction, measured by LV strain and mitral annular plane systolic excursion, were also identified as predictive of SCD suggesting use of routine echocardiographic measures to estimate prognosis.[49]

ICD therapy is reliable in sensing and terminating ventricular tachyarrhythmias as well as preventing SCD in high-risk patients. Among 121 patients with TOF, 31% had at least one appropriate ICD discharge, and 5.8% had inappropriate discharges yearly. The annual incidence of

appropriate ICD shocks in primary and secondary prevention was 7.7% and 9.8%, respectively. Based on patient outcomes, hemodynamic and functional characteristics, Khairy et al proposed a risk score of six clinical variables to predict appropriate ICD shocks in primary prevention: presence of prior palliative shunt, inducible sustained VT, QRS duration > 180 ms, ventriculotomy incision, nonsustained VT, and LV end-diastolic pressure > 12 mmHg.[50]

In addition to arrhythmogenic burden, it is well-known that the prevalence of heart failure among adults with CHD is higher compared to general population, and it is considered to be the leading cause of death among such population.[51] Diastolic dysfunction has been independently associated with ventricular arrhythmias and mortality in other disease states, such as postcoronary bypass surgery and chronic renal failure.[52] The value of LV diastolic dysfunction in risk stratification of patients with TOF remains to be demonstrated; however, the ratio of early transmitral flow velocity (E) to early diastolic mitral annular velocity (e′), more specifically, E/e ratio greater than 10 was a powerful predictor of ventricular arrhythmias. The association of diastolic dysfunction with increased RV afterload may contribute to the pathophysiology of RV failure, particularly in the setting of pulmonary regurgitation with chronic volume overload.[41]

Due to the advances in cardiothoracic surgery and medical management of patients with CHD, there are currently more adults living with adult CHD than children, and this number is expected to grow at a rate of approximately 5% per year.[53] As these patients age, they are prone to same diseases as the adult non-CHD populations, such as obesity, type 2 diabetes mellitus, and myocardial infarction. Because of the increased survival and an increasing effect of acquired heart disease, myocardial infarction is the leading cause of mortality in patients with noncyanotic adult CHD. In a prospective randomized trial aimed to investigated the safety of exercise among adult patients with repaired TOF. Results showed exercise was not proarrhythmic in patients with repaired TOF with no previous history of sustained ventricular arrhythmia determined by Holter monitor. Actually, exercise seemed to provide a beneficial effect on ventricular arrhythmias, as it showed a significant reduction in runs of nonsustained VT over the course of the 12 week exercise program. As exercise capacity in adults with CHD is lower than in the general population and is it has predictive power of morbidity and mortality, an overly restrictive approach to exercise training due to fears or misconceptions regarding exercise training might have an undesirable effect.[37]

Obesity is a prominent comorbidity in patients with adult CHD due a lack of physical activity and high caloric intake, and according to a study

evaluated patients with adult CHD, 54% of them were overweight.[54] Health care providers should evaluate anthropometry at every clinic encounter, assess diet and the level of physical activity, measure the blood pressure, fasting lipid panel, and glucose.[53] Although physical activity guidelines in adults with congenital heart disease is limited, dynamic rather than static exercises have been encouraged.[29] In patients with successfully repaired heart defects without residual sequelae, recommend performing 150 minutes of moderate physical activity or 75 minutes of vigorous physical activity, discuss restraints, if any, related to arrhythmias and how to incorporate physical activity into daily schedules.[55,56] High-risk patients such as those with advanced biventricular dysfunction and marked ascending aortopathy should participate in low-intensity activities.[57] In adults with CHD, physical activity not only increases the threshold for maximal oxygen consumption, peak oxygen consumption, peak oxygen pulse, exercise tolerance, total treadmill time, heart rate recovery, and walking distance, but also enhanced self-esteem, confidence, improved quality of life and reduction in psychological stress.[53] Encouraging dietary changes such as timely meals and lower-calorie nutrient dense foods will also be beneficial in weight loss and achieve normal body mass index.

As children with adult CHD grow into adulthood, they are also at risk for engaging in alcohol, tobacco, and other substance abuse. Approximately, 28% of adolescents and 54% of young adults with CHD reported substance abuse in the prior 30 days.[58] Health care providers should take the opportunity at every encounter to educate about the deleterious effects of alcohol, tobacco, and energy supplements on the patient's cardiovascular health.[53]

Our patient had been gaining weight, had a body mass index of 36 suggestive of obesity and had started to smoke. In addition, to address organic problems such as arrhythmias, it was also important for us as health care providers to discuss lifestyle choices and minimize risk factors for acquired heart disease.

In summary, adults with repaired TOF are at high risk of atrial and ventricular arrhythmias as well as complications of acquired heart disease and other co-morbidities. The patient in the case at age 46 had both atrial and ventricular arrhythmias. His atrial arrhythmias were most likely related to this enlarged right side and significant tricuspid regurgitation which was intervened on with a tricuspid ring in his 30 second. His atrial flutter was treated with radiofrequency ablation, and he started on amiodarone which was eventually stopped from amiodarone-induced hypothyroidism. In regards to his frequent episodes of ventricular arrhythmia, his native QRS was >180 ms and had depressed LV systolic function $< 50\%$

both of which, carries increased risk of having ventricular arrhythmias. This led to very frequent episodes of appropriate ICD shock to eliminate his arrhythmia. Unfortunately, these ICD shock significantly impaired the patient quality of life of our patient and created a substrate for post-traumatic stress disorder. Eventually, the patient decided to turned off his ICD with the understanding of risks associated with that. In addition to managing risk of arrhythmias, health care providers should also discuss risk of co-morbidities and discuss lifestyle modifications to minimize risk of obesity, coronary artery disease, and substance abuse.

Case 3. A 32-year-old woman with TOF who had complete surgical correction including pulmonary valvotomy at infancy presented for pre-pregnancy counseling. She has been unable to conceive with her husband for the past 12 months, and the couple considered in vitro fertilization. ECG showed normal sinus rhythm, right bundle branch block, and QRS duration of 132 ms. She underwent a cardiopulmonary exercise testing, which showed a peak oxygen uptake ($PkVO_2$) of 31 mL/kg/min. Her echocardiogram and cardiac MRI supporting the finding of normal LVEF of 64%; dilated RV with RVEDV of 177 cc/m^2 and RVESV of 95 cc/m^2; unrestricted severe pulmonary regurgitation and dilated sinus of Valsalva of 38 mm × 37 mm. Cardiac catheterization supported the above finding and additionally showed normal pulmonary pressures and no evidence of aortopulmonary collaterals.

Discussion

Among patients with TOF, what is the clinical effect of pregnancy on mother and fetal heart? What are the peripartum cardiac complications that could occur in the pregnant patient with TOF, specifically on the aorta and RV? What are the morbidity and mortality risk to the baby and the mother? What is the likelihood of transmission of CHD to the baby? Are there additional risks for pursuing infertility treatment?

Maternal organs undergo several significant physiological alterations during pregnancy. Maternal blood volume begins to increase with the early hormonal changes of conception and peaks around 32 weeks of gestation. The overall increase in blood volume during pregnancy is approximately 40% for a singleton and 67% for twin gestation. Both plasma volume and red blood cell mass contribute to the hypervolemia. Estrogen has a key role in plasma volume expansion and promotes sodium and water retention by upregulating the production of angiotensinogen, renin, and aldosterone. The disproportionate expansion of plasma volume relative to red blood cell mass contributes to the physiological anemia of pregnancy.[59] The average BNP in

a healthy pregnant woman is approximately twice that of nonpregnant control subjects, rising early in pregnancy and remaining elevated throughout gestation until 72 hours following delivery. Adverse maternal cardiac events have been associated with high BNP concentrations (>100 pg/mL), but its use as a negative predictive indicator appears to be of most value. In one series, the negative predictive value of NT-pro-BNP < 128 pg/mL at 20 weeks gestation exceeded 95%.[60]

The vasculature undergoes remodeling to accommodate the increased blood volume associated with pregnancy. Pulmonary vascular resistance declines by approximately 24% by eighth week of gestation and remains stable over the remainder of the pregnancy. The decrease in pulmonary vascular resistance accommodates the near 50% increase in pulmonary flow; thus, the mean pulmonary artery pressure remains unaltered in a normal pregnancy. The systemic vascular resistance also decreases during pregnancy, resulting in a decrease in preload and afterload. Within eight weeks after the last menstrual period, systemic vascular resistance is reduced by approximately 30%, reaching its lowest value around 24 weeks of gestation. Fall in systemic vascular resistance is associated with a 10-15 mmHg reduction in the diastolic pressure at 20-24 weeks gestation. After that point in time, systemic vascular resistance, and thus diastolic blood pressure, begins to increase again, approaching preconception levels by term. Cardiac output increases 30%-50% in a singleton pregnancy with an additional 10%-20% increment in a twin pregnancy. Maternal posture can significantly affect cardiac output, especially after 20 weeks of gestation when the gravid uterus compresses the inferior vena cava and pelvic veins.[60]

Tidal volume increases 40% with a proportional rise in minute ventilation. This physiological hyperventilation is greater than the increase in oxygen consumption and accounts for the breathlessness that begins in early pregnancy. Maternal heart rate progressively increases 10-20 beats per minute over pregestational rates, peaking in the late second or early third trimester. Pregnancy also lowers the threshold for isolated rhythm disturbances, including atrial and ventricular premature beats and re-entrant supra-VT. Moreover, during pregnancy, there is a fall in the oncotic pressure due to a 12%-18% decrease in circulating albumin concentrations with the lowest levels at approximately 24 weeks of gestation. This decline in oncotic pressure in addition to an increase in femoral venous pressure due to uterine compression of the inferior vena cava produces the edema of pregnancy. The lowered oncotic pressure can become hemodynamically significant, especially when combined with generous administration of crystalloid, making patients more susceptible to pulmonary edema.[60]

As pregnancy requires a complex set of adaptations of the cardiovascular system, which may be particularly demanding in the context of underlying heart disease, preconception care, and counseling is of fundamental importance. The woman and her partner should have a clear understanding of the potential risk of pregnancy for her and her offspring. For the woman contemplating an immediate pregnancy, a more focused discussion is required about pregnancy risk and the potential need to undergo diagnostic cardiovascular testing.[60] According to European Society of Cardiology Guidelines on the management of cardiovascular diseases during pregnancy, all patients should have a prepregnancy assessment including a medical history, echocardiography, and exercise testing.[61] An exercise test before pregnancy where a woman achieves <70% of expected workload, shows a drop in arterial pressure or a decrease in oxygen saturation will identify those at risk of developing symptoms or complications during pregnancy and further evaluation will be needed before conception.[61]

Overall, women with CHD during tolerated pregnancy well; however, they are at higher risk for potential cardiovascular complications during pregnancy, including heart failure, arrhythmias, stroke, death, thromboembolism, progressive aortic root dilation, RV dysfunction, and PV regurgitation.[60] These risk increases in the presence of underlying heart defect such as ventricular function, valvular function, functional class, and cyanosis.[61] The rate of miscarriages and maternal complications increases with more complex congenital heart diseases, and patients who experience complications during pregnancy may also be at higher risk of late cardiac events after pregnancy.[60] Historically, an emphasis was placed on quantifying and reducing maternal cardiac risk. A study by Ouyang et al assessed obstetrical outcomes in 112 pregnancies in 65 women with CHD, 33% of pregnancies were associated with adverse obstetrical events, such as preterm labor and delivery (21%), postpartum hemorrhage (14%), premature rupture of membranes (10%), pregnancy-induced hypertension and pre-eclampsia (3%), placental abruption (3%), and intrauterine fetal demise (2%).[62] Those who delivered vaginally but avoided Valsalva, as often recommended for high-risk patients, experienced a higher rate of postpartum hemorrhage and third- or fourth-degree lacerations. Adverse fetal and neonatal outcomes complicate 15%-39% of pregnancies. Frequent complications include premature birth, small-for-gestational-age birth weight, respiratory distress, and intraventricular hemorrhage. Reported independent risk factors for fetal and neonatal complications include NYHA functional class above II, or cyanosis during the baseline visit and left-heart obstruction. Additional risk factors

include older maternal age, multiple gestations, maternal smoking history, heparin/warfarin during pregnancy, history of premature delivery, antepartum bleeding after 12 weeks gestation, and febrile illness.[63]

There are several predictive scores when evaluating a TOF patient requesting counseling before pregnancy. In the CARPREG study, Siu and colleagues prospectively assessed predictors of adverse events in a cohort of 562 pregnant women with various forms of heart disease, including congenital, and determined 4 risk factors for a combined cardiovascular endpoint resulting in cardiac death, stroke, pulmonary edema, or arrhythmia. The risk factors identified with NYHA functional class III and IV were LVEF $< 40\%$, left-heart obstruction (mitral valve $< 2.0\ cm^2$, aortic area $< 1.5\ cm^2$, or peak LV outflow tract gradient >30 mmHg), and history of a cardiac event before pregnancy such as arrhythmia, stroke, transient ischemic attack or pulmonary edema. From this data, a risk index was generated. The rate of primary cardiac events was 4%, 27%, and 62% in women with zero, 1, and 2 or more risk factors, respectively.[64] The predictors of maternal cardiovascular events identified in CHD in the ZAHARA study includes a history of an arrhythmia event, baseline NYHA functional class $>$ II, left-heart obstruction (aortic valve peak gradient $>$ 50 mmHg), mechanical valve prosthesis, moderate or severe systemic atrioventricular valve regurgitation, moderate or severe subpulmonary atrioventricular valve regurgitation, use of cardiac medication prepregnancy, and repaired or unrepaired cyanotic heart disease.[65] A prospective study among pregnant women with CHD subsequently extended these findings by identifying a prior smoking history and decreased subpulmonary ventricular systolic function and severe pulmonary regurgitation as additional independent risk factors.[63] The ESC Guidelines place patients with severe systemic ventricular dysfunction, as defined by a LVEF $< 30\%$ or NYHA III-IV, into World Health Organization risk class IV, indicative of those in whom pregnancy is contraindicated.[61]

Women with repaired TOF usually tolerate pregnancy well with cardiac complications, commonly arrhythmias, and heart failure, occurring in up to 12% of patients. Other potential cardiac complications include thromboembolism, progressive aortic root dilatation, and endocarditis.[61] RV dysfunction and moderate-to-severe pulmonary regurgitation are risk factors for cardiovascular complications, and pregnancy may be associated with a persisting increase in RV size. In symptomatic women with marked dilatation of the RV due to severe pulmonary regurgitation, prepregnancy PVR using a homograft should be considered. In the majority of pregnant patients with repaired TOF, follow-up every trimester is sufficient; however, there are clinical situations that may necessitate more frequent evaluations. In women with severe pulmonary regurgitation,

monthly or bimonthly cardiac assessment with echocardiography is indicated. If RV failure occurs during pregnancy, treatment with diuretics should be started, and bed rest advised. Transcatheter valve implantation or early delivery may be considered in those who do not respond to conservative treatment.[61] Minimizing fetal radiation exposure can be accomplished by shortening fluoroscopic time, reducing the x-ray tube voltage, reducing the tube current, reducing the imaging frames per second to the lowest setting, using single-plane fluoroscopy, and avoiding cineangiography. Internal jugular or subclavian or radial approaches are preferable, avoiding femoral access if possible. Transcatheter interventional procedures are rarely performed during pregnancy, and if a procedure is considered, the patient should be referred to an adult CHD center with interventional expertise in the treatment of such conditions. Overall, patients with repaired TOF are classified as World Health Organization risk class II, which represents women who might have a small increase in maternal mortality or a moderate increase in morbidity with pregnancy.[60] Unrepaired TOF and the presence of morphologic pulmonary artery abnormality; including hypoplastic or disconnected pulmonary artery or ductal origin of the pulmonary artery; are independently predictive of low infant birth weight.[66]

Patients with surgically corrected TOF usually tolerate pregnancy well; however, an already compromised RV may be susceptible to further pregnancy-induced volume loading with right heart failure. Through ventricular-ventricular interactions, RV volume overload may impair LV diastolic compliance and contractility resulting in acute left-heart failure. Additional right-sided volume load may also predispose to arrhythmias. The goals in caring for a patient with surgically repaired TOF should include addressing the severe pulmonary regurgitation before pregnancy, avoid excessive fluid administration, avoid increases in pulmonary vascular resistance through the prevention of hypoxia and hypercarbia, and maintenance of sinus rhythm.[63] In some series, TOF is the single most common form of moderate CHD in pregnant women. Despite the absence of overt cardiac symptoms, patients remain at risk for maternal and fetal complications. Residual pulmonary regurgitation, although usually well tolerated in pregnant women with TOF, has been associated with an increased risk of fetal loss, symptomatic right heart failure, left heart failure, and arrhythmias. An increase in RV size may also persist after pregnancy.[63] There was no relationship between pregnancy and change in aortic root dilation.[67] Our patient had aortic root of 3.7 cm, which is considered to be dilated according to her age and body metrics.

Women with moderate CHD, which includes TOF, should be managed and delivered in specialized centers with multidisciplinary expertise and experience in CHD, obstetrics, anesthesiology, and neonatology. A coordinated care pathway for supervision of delivery and the postpartum period should be developed and in place by the third trimester and made available to all caregivers and the patients. The plan for delivery may change as the pregnancy evolves, but should include whether labor or cesarean delivery is indicated, and the recommended approach to labor analgesia or surgical anesthesia. In planning an obstetric anesthetic, it is important to understand the patient's cardiovascular anatomy and physiology, labor and delivery, hemodynamic alterations induced by different anesthetic techniques, and cardiac and obstetric complications for which the patient may be at risk. At the time of delivery, the preferred mode is vaginal.[61] Labor causes important hemodynamic changes, including elevations in heart rate, central venous pressure, and cardiac output. The maternal position has an effect on the degree of changes that are seen in these parameters. In the supine position, contractions are associated with a 15% rise in cardiac output, while cardiac output rises only 8%-11% in the lateral position. Additionally, uterine contractions augment maternal cardiac output as a result of enhanced sympathetic activity and expulsion of uterine blood into the central venous circulation. During a contraction, the uterus expels up to 400 mL of blood into the central venous circulation, leading to a rise in central venous pressure, right atrial pressure, cardiac output, and arterial pressure. The labor-induced augmentation of cardiac output is attenuated by effective epidural anesthesia. The increase in arterial pressure associated with labor can be attenuated by effective pain control and lateral tilting of the patient. Epidural anesthesia can reduce the return of blood to the heart due to venodilatation, so caution should be used in dosing.[60] Postpartum, maternal cardiac reserve is challenged by an increase in preload due to inferior vena cava decompression and extrusion of blood from the contracted uterus into the inferior vena cava. Augmented venous return increases maternal cardiac output by 60%-80% after vaginal delivery. This abrupt risk in cardiac output dissipates to prelabor values within one hour postpartum and falls further over the following 24 weeks. Mean arterial pressure can be elevated for 1 or 2 days postpartum before declining over the next 2 weeks.

One frequently asked question by potential mothers with CHD, is the estimated risk an offspring will be affected with a congenital abnormality. The role of genetic counseling has increased in relation to the growth of

available genetic information, noninvasive imaging to identify subtle defects, and the availability of targeted genetic testing. Advances in genetics now allow for accurate estimation of transmission risks for many forms of CHD, whether isolated, syndromic, or familial. Typically, the risk of transmission to the offspring of affected mothers is in the order of 2%-5%, which is a 10-fold increase in risk compared with the general population. Concordance rates may be higher in specific subtypes, including left-heart obstruction (8%) and deletion syndromes such as 22q11. Particularly high-risk groups include interrupted aortic arch, truncus arteriosus, and TOF, where the prevalence of 22q11 deletion may be as high as 50%, 14%, and 16%, respectively. Offspring of mothers with TOF, in general, have a reported incidence of CHD of approximately 3.1%.[66] In addition to genetic counseling, women with CHD should be offered fetal echocardiographic evaluation between 18 and 22 weeks of pregnancy.[63]

Before considering the possibility of assisted-reproductive technologies (ART), the first question to address is whether a pregnancy would be possible without having an inappropriate risk to the mother or the neonate. The specific risk of multiple gestations is associated with a further hemodynamic burden for the mother and must be taken into account. Multiple pregnancies are frequent in ART usage with the incidence of twins with in vitro fertilization-conceived pregnancies being approximately 27%. The extent to which women are able to cope with the hemodynamic challenges imposed by pregnancy, especially multiple pregnancies, depends on the nature, severity, and current status of the underlying heart condition. As stated previously, the overall increase in blood volume during pregnancy is approximately 40% for a singleton and 67% for twin gestation. The large increase in blood volume is a hemodynamic stressor, especially in a twin gestation, that must be considered when considering ART.[68] ART refers to all fertility treatments in which oocytes and sperm are handled with the goal of achieving pregnancy. For both in vitro fertilization and intracytoplasmic sperm injection, the woman's uterus and hormonal environment are primed for oocyte retrieval and endometrial implantation through the use of exogenous hormones. To control the menstrual cycle and ovarian maturation, oral contraceptives or gonadotrophin-releasing hormone analogs are given during the menstrual cycle before the ART attempt. Gonadotrophins, human menopausal gonadotrophins, human chorionic gonadotrophin, or clomiphene citrate are then delivered in order to achieve follicle stimulation over the first 1-1.5 weeks of the cycle. Once the target follicle size and estradiol level are reached, human gonadotrophin is administered to initiate ovulation, followed by oocyte retrieval. After in vitro fertilization and transfer

of the embryo into the uterus, estrogen, progesterone, human gonadotrophin may be given in the luteal phase and up to the end of the first trimester in order to encourage implantation and endometrial development. The estrogen levels resulting from ovarian stimulation lie well above normal physiological levels.[68] All ART results in pronounced changes in endogenous hormone levels, with potential effect on several components of the cardiovascular system. Estradiol suppression in response to gonadotrophin-releasing hormone agonists is associated with an increase in blood pressure and systemic vascular resistance. Conversely, an increase in estradiol levels during ovulation stimulation induces a decrease in mean arterial pressure and peripheral vascular resistance, as well as an increase in cardiac output. Changes in hormone levels also affect the coagulation cascade with a shift towards a coagulative state with increases in von Willebrand factor, Factor VIII, Factor V, and fibrinogen and increased activated protein C resistance which creates a prothrombotic state. There is also a reduction in important fibrinolytic agents such as tissue plasminogen activator. In addition, thrombin generation and fibrin formation are augmented in ART patients. In most patients without CHD, these hemodynamic and hemostatic changes have few clinical consequences; however, the statistics of consequence in CHD is unknown.[68]

Risk stratification and counseling are important for women with heart disease undergoing ART. ART, such as in vitro fertilization, in particular, are associated with an increased risk of gestational hypertension and preeclampsia. Moreover, multiple pregnancies and advanced maternal age further increase the risk of hypertensive complications. Rates of venous thromboembolism during pregnancy are also higher in women undergoing in vitro fertilization. The World Health Organization classification is a valuable tool for this purpose, and fertility treatments should not be performed in women who meet WHO class III and IV criteria. As stated previously, women with repaired TOF are considered World Health Organization class II and present only a small increased risk of maternal mortality or moderate increase in morbidity, and thus, are capable of undergoing ART.

Case 3 Conclusion

At the age of 32 years, with excellent exercise capacity despite severe pulmonary insufficiency and significantly increased right heart volumes, it was important to discuss our patient's and her baby's risk of morbidity and mortality especially if she was going to use ART. She was at risk of atrial arrhythmias secondary to right heart dilation and increased volume

during pregnancy and changes in hemodynamics with ART all discussed earlier. It was decided that patient undergo a PVR before pregnancy to decrease morbidity. She underwent PVR with a 25 mm bioprosthetic valve with arterioplasty of the main and left pulmonary arteries. In the following year, she used assisted-reproductive therapy to conceive and give birth to a healthy child. Peripartum and postpartum follow-up was arranged, no intervention was necessary during pregnancy.

Conclusion

Due to improvements in surgical technique and perioperative management, the number of patients with TOF surviving into adulthood continues to grow. The increasing prevalence necessitates the need for all cardiologists to understand that the long-term complications and risks in this particular patient population are dependent upon the congenital abnormalities present at birth and the surgical procedures performed in the repair of those abnormalities. In the long-term care of patients with TOF, a team approach should be used to address the complications of RV dilatation, arrhythmias, and assistance during reproductive years.

REFERENCES

1. Downing TE, Kim YY. Tetralogy of Fallot. General Principles of Management. *Cardiol Clin* 2015;33(4):531–41. https://doi.org/10.1016/j.ccl.2015.07.002.
2. van der Bom T, Bouma BJ, Meijboom FJ, Zwinderman AH, Mulder BJM. The prevalence of adult congenital heart disease, results from a systematic review and evidence based calculation. *Am Heart J* 2012;164(4):568–75. https://doi.org/10.1016/j.ahj.2012.07.023.
3. Apitz C, Webb GD, Redington AN. Tetralogy of Fallot. *Lancet* 2009;374 (9699):1462–71. https://doi.org/10.1016/S0140-6736(09)60657-7.
4. Sheikh A, Kazmi U, Syed N. Variations of pulmonary arteries and other associated defects in Tetralogy of Fallot. *Springerplus* 2014;3(1):467. https://doi.org/10.1186/2193-1801-3-467.
5. Kalra N, Klewer SE, Raasch H, Sorrell VL. Update on tetralogy of Fallot for the adult cardiologist including a brief historical and surgical perspective. *Congenit Heart Dis* 2010;5(3):208–19. https://doi.org/10.1111/j.1747-0803.2010.00402.x.
6. Karpawich PP, Bush CP, Antillon JR, Amato JJ, Marbey ML, Agarwal KC. Modified Blalock-Taussig shunt in infants and young children. Clinical and catheterization assessment. *J Thorac Cardiovasc Surg* 1985;89(2):275–9. http://www.ncbi.nlm.nih.gov/pubmed/3968910 Accessed February 22, 2018.
7. Quandt D, Penford G, Ramchandani B, Bhole V, Mehta C, Stumper O. Stenting of the right ventricular outflow tract as primary palliation for Fallot-type lesions. http://dx.doi.org/10.1186/s40949-017-0005-7.

8. Bonchek LI, Starr A, Sunderland CO, Menashe VD. Natural History of Tetralogy of Fallot in Infancy Clinical Classification and Therapeutic Implications. http://circ.ahajournals.org/content/circulationaha/48/2/392.full.pdf. Accessed February 22, 2018.
9. Swamy P, Bharadwaj A, Varadarajan P, Pai RG. Echocardiographic evaluation of tetralogy of Fallot. *Echocardiography* 2015;32:S148–56. https://doi.org/10.1111/echo.12437.
10. Daraban AM, Jurcuţ R, Bădilă E, Bartoş D, Dan GA. Following up adult patients with tetralogy of fallot: The role of echocardiography. *J Clin Ultrasound* 2017;45(2):79–95. https://doi.org/10.1002/jcu.22411.
11. Bonello B, Shore DF, Uebing A, et al. Aortic dilatation in repaired tetralogy of Fallot. *JACC Cardiovasc Imaging* 2018;11(1):150–2. https://doi.org/10.1016/j.jcmg.2017.01.021.
12. Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of a. *Circulation* 2008;118(23). https://doi.org/10.1161/CIRCULATIONAHA.108.190690.
13. Valente AM, Cook S, Festa P, et al. Multimodality imaging guidelines for patients with repaired Tetralogy of fallot: A report from the American society of echocardiography: Developed in collaboration with the society for cardiovascular magnetic resonance and the society for pediatric radiol. *J Am Soc Echocardiogr* 2014;27(2):111–41. https://doi.org/10.1016/j.echo.2013.11.009.
14. Geva T. Indications for pulmonary valve replacement in repaired tetralogy of fallot: The quest continues. *Circulation* 2013;128(17):1855–7. https://doi.org/10.1161/CIRCULATIONAHA.113.005878.
15. Greutmann M. Tetralogy of Fallot, pulmonary valve replacement, and right ventricular volumes: are we chasing the right target? *Eur Heart J* 2016;37(10):836–9. https://doi.org/10.1093/eurheartj/ehv634.
16. Bokma JP, Winter MM, Oosterhof T, et al. Preoperative thresholds for mid-to-late haemodynamic and clinical outcomes after pulmonary valve replacement in tetralogy of Fallot. *Eur Heart J* 2016;37(10):829–35. https://doi.org/10.1093/eurheartj/ehv550.
17. Greutmann M. Tetralogy of Fallot, pulmonary valve replacement, and right ventricular volumes: Are we chasing the right target? *Eur Heart J* 2016;37(10):836–9. https://doi.org/10.1093/eurheartj/ehv634.
18. Khoo NS, Young A, Occleshaw C, Cowan B, Zeng ISL, Gentles TL. Assessments of right ventricular volume and function using three-dimensional echocardiography in older children and adults with congenital heart disease: comparison with cardiac magnetic resonance imaging. *J Am Soc Echocardiogr* 2009;22(11):1279–88. https://doi.org/10.1016/j.echo.2009.08.011.
19. Senthilnathan S, Dragulescu A, Mertens L. Pulmonary regurgitation after tetralogy of Fallot repair: A diagnostic and therapeutic challenge. *J Cardiovasc Echogr* 2013;23(1):1–9. https://doi.org/10.4103/2211-4122.117975.
20. Sabate Rotes A, Eidem BW, Connolly HM, et al. Long-term follow-up after pulmonary valve replacement in repaired tetralogy of Fallot. *Am J Cardiol* 2014;114(6):901–8. https://doi.org/10.1016/j.amjcard.2014.06.023.

21. Ait-Ali L, Siciliano V, Passino C, et al. Role of stress echocardiography in operated Fallot: Feasibility and detection of right ventricular response. *J Am Soc Echocardiogr* 2014;27(12):1319–28. https://doi.org/10.1016/j.echo.2014.08.006.
22. Babu-Narayan SV, Kilner PJ, Li W, et al. Ventricular fibrosis suggested by cardiovascular magnetic resonance in adults with repaired tetralogy of Fallot and its relationship to adverse markers of clinical outcome. *Circulation* 2006;113(3):405–13. https://doi.org/10.1161/CIRCULATIONAHA.105.548727.
23. Davlouros PA, Kilner PJ, Hornung TS, et al. Right ventricular function in adults with repaired tetralogy of Fallot assessed with cardiovascular magnetic resonance imaging. *J Am Coll Cardiol* 2002;40(11):2044–52. https://doi.org/10.1016/S0735-1097(02)02566-4.
24. Heng EL, Bolger AP, Kempny A, et al. Neurohormonal activation and its relation to outcomes late after repair of tetralogy of Fallot. *Heart* 2015;101(6):447–54. https://doi.org/10.1136/heartjnl-2014-306398.
25. Kempny A, Dimopoulos K, Uebing A, et al. Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily lifesingle centre experience and review of published data. *Eur Heart J* 2012;33(11):1386–96. https://doi.org/10.1093/eurheartj/ehr461.
26. Babu-Narayan SV, Diller G-P, Gheta RR, et al. Clinical outcomes of surgical pulmonary valve replacement after repair of tetralogy of Fallot and potential prognostic value of preoperative cardiopulmonary exercise testing. *Circulation* 2014;129(1):18–27. https://doi.org/10.1161/CIRCULATIONAHA.113.001485.
27. Ansari MM, Cardoso R, Garcia D, et al. Percutaneous pulmonary valve implantation: Present status and evolving future. *J Am Coll Cardiol* 2015;66(20):2246–55. https://doi.org/10.1016/j.jacc.2015.09.055.
28. Frigiola A, Hughes M, Turner M, et al. Physiological and phenotypic characteristics of late survivors of tetralogy of fallot repair who are free from pulmonary valve replacement. *Circulation* 2013;128(17):1861–8. https://doi.org/10.1161/CIRCULATIONAHA.113.001600.
29. Baumgartner H, Bonhoeffer P, De Groot NMS, et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J* 2010;31(23):2915–57. https://doi.org/10.1093/eurheartj/ehq249.
30. Ghobrial J, Aboulhosn J. Impact of right-sided-catheter-based valve implantation on decision-making in congenital heart disease. *Curr Cardiol Rep* 2016;18(4):1–10. https://doi.org/10.1007/s11886-016-0712-2.
31. Wilson WM, Benson LN, Osten MD, Shah A, Horlick EM. Transcatheter pulmonary valve replacement with the Edwards sapien system: The Toronto experience. *JACC Cardiovasc Interv* 2015;8(14):1819–27. https://doi.org/10.1016/j.jcin.2015.08.016.
32. Biernacka EK, Ruzyllo W, Demkow M. Percutaneous pulmonary valve implantation-state of the art and Polish experience. *Postepy Kardiol Interwencyjnej* 2017;13(1):3–9. https://doi.org/10.5114/aic.2017.66180.
33. Van Dijck I, Budts W, Cools B, et al. Infective endocarditis of a transcatheter pulmonary valve in comparison with surgical implants. *Heart* 2014: 1–6. https://doi.org/10.1136/heartjnl-2014-306761.

34. Woudstra OI, Bokma JP, Winter MM, et al. Clinical course of tricuspid regurgitation in repaired tetralogy of Fallot. *Int J Cardiol* 2017;243:191–3. https://doi.org/10.1016/j.ijcard.2017.05.122.
35. Kogon B, Patel M, Leong T, McConnell M, Book W. Management of moderate functional tricuspid valve regurgitation at the time of pulmonary valve replacement: Is concomitant tricuspid valve repair necessary? *Pediatr Cardiol* 2010;31(6):843–8. https://doi.org/10.1007/s00246-010-9717-6.
36. Cramer JW, Ginde S, Hill GD, et al. Tricuspid repair at pulmonary valve replacement does not alter outcomes in tetralogy of fallot. *Ann Thorac Surg* 2015;99(3):899–904. https://doi.org/10.1016/j.athoracsur.2014.09.086.
37. Ávila P, Marcotte F, Dore A, et al. The impact of exercise on ventricular arrhythmias in adults with tetralogy of Fallot. *Int J Cardiol* 2016;219:218–24. https://doi.org/10.1016/j.ijcard.2016.06.011.
38. Khairy P, Van Hare GF, Balaji S, et al. PACES/HRS expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease. *Can J Cardiol* 2014;30(10):e1–e63. https://doi.org/10.1016/j.cjca.2014.09.002.
39. Valente AM, Gauvreau K, Assenza GE, et al. Contemporary predictors of death and sustained ventricular tachycardia in patients with repaired tetralogy of Fallot enrolled in the INDICATOR cohort. *Heart* 2014;100(3):247–53. https://doi.org/10.1136/heartjnl-2013-304958.
40. Ghai A, Silversides C, Harris L, Webb GD, Siu SC, Therrien J. Left ventricular dysfunction is a risk factor for sudden cardiac death in adults late after repair of tetralogy of Fallot. *J Am Coll Cardiol* 2002;40(9):1675–80. http://www.ncbi.nlm.nih.gov/pubmed/12427422 Accessed February 23, 2018.
41. Khairy P, Aboulhosn J, Gurvitz MZ, et al. Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: A multi-institutional study. *Circulation* 2010;122(9):868–75. https://doi.org/10.1161/CIRCULATIONAHA.109.928481.
42. Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: A multicentre study. *Lancet* 2000;356(9234):975–81. https://doi.org/10.1016/S0140-6736(00)02714-8.
43. Karamlou T, Silber I, Lao R, et al. Outcomes after late reoperation in patients with repaired tetralogy of Fallot: The impact of arrhythmia and arrhythmia surgery. *Ann Thorac Surg* 2006;81(5):1786–93. https://doi.org/10.1016/j.athoracsur.2005.12.039.
44. Refaat MM, Ballout J, Mansour M. Ablation of atrial fibrillation in patients with congenital heart disease. *Arrhythmia Electrophysiol Rev* 2017;6(4):191–4. https://doi.org/10.15420/2017.2017.15.1.
45. Gutierrez SD, Earing MG, Singh AK, Tweddell JS, Bartz PJ. Atrial tachyarrhythmias and the Cox-maze procedure in congenital heart disease. *Congenit Heart Dis* 2013;8(5). https://doi.org/10.1111/chd.12031.
46. Chiu S-N, Tsai C-T, Lin L-Y, et al. Repolarization alternans and ventricular arrhythmia in a repaired tetralogy of Fallot animal model. *J Am Heart Assoc* 2015;4(12). https://doi.org/10.1161/JAHA.115.002173.

47. Morwood JG, Triedman JK, Berul CI, et al. Radiofrequency catheter ablation of ventricular tachycardia in children and young adults with congenital heart disease. *Hear Rhythm* 2004;1(3):301–8. https://doi.org/10.1016/j.hrthm.2004.05.009.
48. Wu KC. Sudden cardiac death substrate imaged by magnetic resonance imaging. *Circ Cardiovasc Imaging* 2017;10(7):e005461. https://doi.org/10.1161/CIRCIMAGING.116.005461.
49. Diller G-P, Kempny A, Liodakis E, et al. Left ventricular longitudinal function predicts life-threatening ventricular arrhythmia and death in adults with repaired tetralogy of Fallot. *Circulation* 2012;125(20):2440–6. https://doi.org/10.1161/CIRCULATIONAHA.111.086983.
50. Khairy P, Harris L, Landzberg MJ, et al. Implantable cardioverter-defibrillators in tetralogy of Fallot. *Circulation* 2008;117(3):363–70. https://doi.org/10.1161/CIRCULATIONAHA.107.726372.
51. Van De Bruaene A, Meier L, Droogne W, et al. Management of acute heart failure in adult patients with congenital heart disease. *Heart Fail Rev* 2018;23(1):1–14. https://doi.org/10.1007/s10741-017-9664-x.
52. Jain A, Scott C, Chen HH. The renal-cardiac connection in subjects with preserved ejection fraction: a population based study. *ESC Heart Fail* 2017;4(3):266–73. https://doi.org/10.1002/ehf2.12143.
53. Rosenthal TM, Leung ST, Ahmad R, et al. Lifestyle modification for the prevention of morbidity and mortality in adult congenital heart disease. *Congenit Heart Dis* 2016;11(2):189–98. https://doi.org/10.1111/chd.12341.
54. Pemberton VL, McCrindle BW, Barkin S, et al. Report of the National Heart, Lung, and Blood Institute's Working Group on obesity and other cardiovascular risk factors in congenital heart disease. *Circulation* 2010;121(9):1153–9. https://doi.org/10.1161/CIRCULATIONAHA.109.921544.
55. Summary—2008 Physical Activity Guidelines—health.gov. https://health.gov/paguidelines/guidelines/summary.aspx. Accessed February 24, 2018.
56. Pemberton VL, McCrindle BW, Barkin S, et al. Report of the National Heart, Lung, and Blood Institute's Working Group on Obesity and Other Cardiovascular Risk Factors in Congenital Heart Disease. *Circulation* 2010;121(9):1153–9. https://doi.org/10.1161/CIRCULATIONAHA.109.921544.
57. Baumgartner H, Bonhoeffer P, De Groot NMS, et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010): The Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC). *Eur Heart J* 2010;31(23):2915–57. https://doi.org/10.1093/eurheartj/ehq249.
58. Reid GJ, Webb GD, McCrindle BW, Irvine MJ, Siu SC. Health behaviors among adolescents and young adults with congenital heart disease. *Congenit Heart Dis* 2008;3(1):16–25. https://doi.org/10.1111/j.1747-0803.2007.00161.x.
59. Chapman AB, Abraham WT, Zamudio S, et al. Temporal relationships between hormonal and hemodynamic changes in early human pregnancy. *Kidney Int* 1998;54(6):2056–63. https://doi.org/10.1046/j.1523-1755.1998.00217.x.

60. Canobbio MM, Warnes CA, Aboulhosn J, et al. Management of pregnancy in patients with complex congenital heart disease: A scientific statement for Healthcare Professionals from the American Heart Association. *Circulation* 2017;135(8):e50–87. https://doi.org/10.1161/CIR.0000000000000458.
61. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32(24):3147–97. https://doi.org/10.1093/eurheartj/ehr218.
62. Ouyang DW, Khairy P, Fernandes SM, Landzberg MJ, Economy KE. Obstetric outcomes in pregnant women with congenital heart disease. *Int J Cardiol* 2010;144(2):195–9. https://doi.org/10.1016/j.ijcard.2009.04.006.
63. Fernandes SM, Arendt KW, Landzberg MJ, Economy KE, Khairy P. Pregnant women with congenital heart disease: Cardiac, anesthetic and obstetrical implications. *Expert Rev Cardiovasc Ther* 2010;8(3):439–48. https://doi.org/10.1586/erc.09.179.
64. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* 2001;104(5):515–21. http://www.ncbi.nlm.nih.gov/pubmed/11479246 Accessed February 24, 2018.
65. Drenthen W, Boersma E, Balci A, et al. Predictors of pregnancy complications in women with congenital heart disease. *Eur Heart J* 2010;31(17):2124–32. https://doi.org/10.1093/eurheartj/ehq200.
66. Veldtman GR, Connolly HM, Grogan M, Ammash NM, Warnes CA. Outcomes of pregnancy in women with tetralogy of fallot. *J Am Coll Cardiol* 2004;44(1):174–80. https://doi.org/10.1016/j.jacc.2003.11.067.
67. Cauldwell M, Quail MA, Smith GS, et al. Effect of pregnancy on ventricular and aortic dimensions in repaired tetralogy of Fallot. *J Am Heart Assoc* 2017;6(7). https://doi.org/10.1161/JAHA.116.005420.
68. Rossberg N, Stangl K, Stangl V. Pregnancy and cardiovascular risk: A review focused on women with heart disease undergoing fertility treatment. *Eur J Prev Cardiol* 2016;23(18):1953–61. https://doi.org/10.1177/2047487316673143.

Due to improvements in surgical technique and perioperative management, the number of patients with Tetralogy of Fallot that survives to adulthood continues to grow. It is important for cardiologists to understand that the long-term complications and risks in this particular patient population.

Several perspectives can be taken from this excellent manuscript.

The first case, demonstrate the importance of multimodality imaging such as 2 D echocardiogram and more specifically cardiac MRI in the diagnosis of pulmonary regurgitation, a common complication of Tetralogy of Fallot. In addition, cardiac MRI helps to delineate also the right ventricular structure. The utilization of various diagnostic modalities will help cardiologists to monitor complications of Tetralogy of Fallot and decide the indications for surgical or percutaneous intervention.

The second case describe the management of other important complications of adult patients with repaired Tetralogy of Fallot such as atrial and ventricular arrhythmias, complications of acquired heart disease and other comorbidities. The authors state that besides the managing risk of arrhythmias, physicians should also discuss lifestyle modifications to minimize risk of obesity, coronary artery disease, and substance abuse in these patients.

The third case describe another important aspect of patients with tetralogy of Fallot, that is patients with complete surgical correction including pulmonary valvotomy at infancy that present for pre-pregnancy counseling. These patients can have full term pregnancies but several studies are needed prior pregnancy to determine the risk. This particular patient underwent a pulmonary valve replacement before pregnancy to decrease morbidity and with utilization of assisted-reproductive therapy to conceive gave birth to a healthy child without any complications peripartum and postpartum.

Finally, the authors stressed the importance pf a team in the management of the complications of RV dilatation, arrhythmias, and assistance during reproductive years in patients with tetralogy of Fallot.

I want to thank the authors for this excellent review on the challenges in the diagnosis and management of adult patients with tetralogy of Fallot.