STATE OF THE ART ARTICLES

Pulmonary Regurgitation after Tetralogy of Fallot Repair: Clinical Features, Sequelae, and Timing of Pulmonary Valve Replacement

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ABSTRACT

Pulmonary regurgitation following repair of tetralogy of Fallot is a common postoperative sequela associated with progressive right ventricular enlargement, dysfunction, and is an important determinant of late morbidity and mortality. Although pulmonary regurgitation may be well tolerated for many years following surgery, it can be associated with progressive exercise intolerance, heart failure, tachyarrhythmia, and late sudden death. It also often necessitates re-intervention. Identifying the appropriate timing of such intervention could be very challenging given the risk of prosthetic valve degeneration and the increased risk of reoperation. Comprehensive informed and regular assessment of the postoperative patient with tetralogy of Fallot, including evaluation of pulmonary regurgitation, right heart structure and function, is crucial to the optimal care of these patients. Pulmonary valve replacement performed in an experienced tertiary referral center is associated with low operative morbidity and mortality and very good long-term results. Early results of percutaneous pulmonary valve replacement are also promising.

Key Words. Tetralogy of Fallot; Pulmonary Regurgitation; Congenital Heart Disease

Introduction

Surgical repair of tetralogy of Fallot (TOF) has been successfully performed since 1955. Repair includes closure of the ventricular septal defect, and relief of right ventricular (RV) outflow tract obstruction that involves RV outflow tract infundibular muscle resection, pulmonary valvotomy or valvectomy, and commonly RV outflow augmentation with placement of a subvalvular or transannular patch. The long-term outcome reported following surgical repair of TOF is excellent with survival rate of 86% at 30 years.[1] Despite the profound impact of surgical intervention on functional status, survival, and quality of life,[2] postoperative residua and sequelae are expected in patients with repaired TOF and lifelong informed follow-up is required.[3]

Chronic pulmonary valve regurgitation (PR) is the most common cardiovascular sequela requiring reoperation in patients with repaired TOF. It is most commonly associated with extensive ventriculotomy, and infundibulectomy as well as generous transannular patching of the RV outflow tract; all of these techniques were routine surgical practice for TOF repair in the past.[4] It has detrimental long-term effects on RV size and function, and has a recognized impact on late outcome. It is anticipated that with increasing recognition of the detrimental impact of chronic PR, the rate of PV replacement will continue to increase and the timing of intervention will be refined.[5,6]

Determinants of PR

The degree of PR after TOF repair is determined by many anatomic and hemodynamic factors (Table 1).[7,8] In patients with TOF, the pulmonary valve (PV) is usually abnormal, often bicuspid, may be hypoplastic or absent (2%). Tetralogy of Fallot with absent PV presents early in life with massive enlargement of the pulmonary arteries due to severe PR, and is not included in this discussion.

Table 1. Determinant of Pulmonary Regurgitation

- Residual pulmonary valve abnormality
  - Hypoplastic
  - Absent valve
  - Postpulmonary valvotomy/valvectomy
- Transannular patch repair
- Right ventricular outflow tract aneurysm
- Right ventricular diastolic dysfunction
- Pulmonary annulus size
- Peripheral pulmonary artery stenosis
- Pulmonary vascular resistance
- Residual atrial and ventricular septal defects
- Acquired cardiovascular and pulmonary diseases
  - Pulmonary hypertension
  - Sleep apnea
  - Hypertension
  - Chronic lung disease
  - Kyphoscoliosis

Tetralogy of Fallot after repair is often associated with an altered geometric orientation of the branch pulmonary arteries, unequal pulmonary vascularity, and pulmonary perfusion abnormalities that contribute to PR.[9] The state of pulmonary arteriolar bed, pulmonary vascular resistance including compliance of the vessel wall, airway pressure, venous resistance, and left atrial pressure may also influence the pulmonary blood flow pattern and PR. Chaturvedi et al.[10] showed that a small increase in airway pressure led to increased total PR presumably because of subtle changes in pulmonary vascular resistance. Transannular patch enlargement and aggressive infundibulectomy are known to predispose to RV outflow tract aneurysm that adversely affects the RV and PR severity.[11–14]

Complications of PR

Chronic severe PR results in progressive RV enlargement, systolic and diastolic dysfunction, and eventually progressive tricuspid valve regurgitation. Patients may be asymptomatic for many years but may eventually present with fatigue, dyspnea, exercise limitation, atrial or ventricular tachyarrhythmia, and occasionally sudden death. Some patients tolerate severe PR better than others. This implies that the duration and severity of PR are not the only factors causing progressive clinical deterioration.

RV Enlargement and Dysfunction

The RV adaptive response to volume overload from PR depends on: (1) the duration and the degree of the PR; (2) the properties of the RV; (3) the status of the pulmonary arteries and the presence of pulmonary hypertension; (4) the presence and severity of tricuspid valve regurgitation; and (5) the presence of a residual shunt at atrial or ventricular level.

Reduced RV systolic function is common after repair of TOF and is related to: (1) the degree and duration of preoperative cyanosis; (2) the degree and duration of preoperative pressure overload with resultant RV hypertrophy; (3) tricuspid and PR; (4) residual RV outflow obstruction; (5) RV injury at the time of surgery from the right ventriculotomy and resection of RV muscle bundles; (6) placement of the a noncontractile RV outflow patch, and ventricular septal defect patch; and (7) potential interruption of coronary artery supply related to disruption of an anomalous coronary artery or inadequate myocardial preservation at the time of operation.[6] Histopathological studies have demonstrated irreversible RV myocardial damage leading to RV systolic and diastolic dysfunction after TOF repair.[6]

Davlouros et al.[11] demonstrated that RV hypertrophy, outflow tract aneurysm, and akinesis were all associated with lower RV ejection fraction in patients with repaired TOF. Contractile dysfunction was not found to be related to the use of an outflow patch, raising the concern that factors such as myectomy, infundibulectomy, and ischemic insult are in part responsible for the genesis of RV outflow tract akinesis in patients who did not have a patch.

Babu-Narayan et al.[15] demonstrated the presence of myocardial fibrosis using gadolinium enhancement during cardiac magnetic resonance (CMR). Areas of myocardial fibrosis were seen in regions of surgical resection, patch placement, suturing, or vent insertion, as well as areas remote from surgical instrumentation in trabecular and endocardial fibers of the RV that may be more vulnerable to ischemic insult. Patients with more severe fibrosis were older, had more RV dysfunction, exercise intolerance, and clinical arrhythmias.

Right ventricular diastolic dysfunction has been a concern in repaired TOF, and may be related to all the factors associated with RV systolic dysfunction. Diastolic dysfunction is particularly common in TOF patients after transannular patch placement. In a study by Munkhammar et al.,[16] 47 patients with repaired TOF were evaluated by echocardiography. Restrictive RV physiology was noted in 13 patients (28%). Ten percent of patients repaired before 6 months of age demonstrated restrictive features at the time of follow-up, increasing to 38% with repair after 9 months.

Approximately one third of patients with transannular patch repair demonstrated restrictive hemodynamics. The patients with restrictive hemodynamics had more severe preoperative pulmonary stenosis, were older at the time of TOF repair, and had less severe PR on follow-up. Right ventricular diastolic dysfunction with elevation in RV diastolic pressure limits the duration of PR and the degree of RV dilatation. As a result, patients with restrictive RV physiology have smaller RV volume.[5,8,13,16]

As the RV dilates in response to PR, its ejection fraction initially increases related to the volume overload. With time, the RV ejection fraction decreases as a reflection of a decrease in myocardial performance of the volume-loaded RV. Progressive deterioration of myocardial function finally results in decreased stroke volume and increased RV end systolic volume.

Left Ventricular Dysfunction

Although the left ventricle (LV) is not directly involved in the anatomic defects of TOF, patients who have had previous TOF repair are at risk of developing LV dysfunction. Factors that are known to contribute to the development of LV dysfunction include: (1) the duration of preoperative cyanosis; (2) volume overload from a previously placed systemic-to-pulmonary artery shunt; (3) suboptimal myocardial protection during cardiopulmonary bypass; (4) the duration of cardiopulmonary bypass itself; (5) patching of the ventricular septum; (6) myocardial fibrosis; and (7) aortic valve regurgitation secondary to aortic root enlargement.[15] Furthermore, Geva et al.[17] have suggested that LV dysfunction could be partly due to the abnormal septal motion and its detrimental effects of LV geometry and mechanical performance reflecting unfavorable ventricular/ventricular interaction.

Arrhythmias

Pulmonary valve regurgitation predisposes TOF patients to atrial and ventricular arrhythmias primarily because of the progressive enlargement of the right atrium and ventricle.

Malignant ventricular arrhythmias occur in approximately 0.5–6% of repaired TOF patients. However, the presence of premature ventricular beats and nonsustained ventricular tachycardia does not identify patients at high risk for sudden death. The predictive value of electrocardiographic changes, signal average electrocardiogram, Holter monitor, and electrophysiology testing for sustained ventricular tachycardia or sudden death is low.[7,8]

Right ventricular dilatation slows ventricular activation and intraventricular conduction and creates a mechanoelectrical substrate for re-entry circuits and may serve as an arrhythmogenic trigger. Gatzoulis et al.[18] demonstrated that PR was the most common cardiovascular hemodynamic abnormality noted in a group of patients who developed ventricular tachycardia, sudden death, or atrial arrhythmia. Helbing et al.[19] reported that the mean QRS duration correlated significantly with RV volume and mass, LV volume and mass, percent of PR, and age. This study suggests that QRS prolongation may be a surrogate risk factor for ventricular arrhythmia. A maximum QRS duration of $\geq$180 milliseconds or rate of change of >3.5 ms/y has been shown to be a sensitive and relatively specific marker for sustained ventricular tachycardia and sudden death in repaired TOF.[20] Perloff et al. have demonstrated that the presence of late potentials on the signal average electrocardiogram in repaired TOF patients also connotes an increased risk for ventricular arrhythmias.[21]

Atrial tachyarrhythmias, especially flutter and fibrillation, are relatively common following TOF repair, and have been reported in up to one third of adult patients.[5] Pulmonary valve regurgitation, RV outflow obstruction, tricuspid valve regurgitation, residual shunts, and surgical scars in the right atrium and septum are known predisposing factors that slow conduction promoting re-entry atrial tachyarrhythmias.

Assessment of Repaired TOF Patients with PR

Assessment of patients following repair of TOF should include a thorough medical history, and clinical examination. The surgical report is an important part of follow-up evaluation in all patients with repaired congenital heart disease and should be requested in all patients. Subsequent testing should include electrocardiogram, chest radiograph, transthoracic echocardiogram, exercise test for assessment of functional status, and a baseline CMR. Select patients require cardiac catheterization to delineate anatomy and hemodynamics.

Pulmonary regurgitation is usually tolerated for many years. Graham et al. reported that symptoms progressively increase after age 30 and that 50% of patients are symptomatic by age 49 years.[22]

Adverse effects of PR may be missed if the evaluation depends on history and physical examination alone. Marked RV enlargement and dysfunction can be present before the onset of symptoms. In our experience, dyspnea, fatigue, palpitations, clinical arrhythmias, and poor exercise tolerance are often the initial findings in patients with severe PR.

The cardiovascular examination in repaired TOF with severe PR may demonstrate prominent jugular venous pulsation with an increased jugular venous "a" wave suggesting elevation in the right atrial pressure, while a prominent "v" wave suggests associated tricuspid valve regurgitation. Right ventricular volume overload is suspected when an RV heave is present. The first heart sound is usually normal followed by a loud single second heart sound from the aortic valve. Typically, there is no pulmonary component of the second heart sound as pulmonary valvectomy or valvotomy is performed during surgical repair. The degree of PR can be difficult to ascertain by physical examination. A to-and-fro murmur in the pulmonary area reflects systolic and diastolic flow across the RV outflow tract. The diastolic murmur of PR is best heard with the bell of the stethoscope along the left sternal border and is low frequency. A pansystolic murmur noted along the left sternal border that increases with inspiration suggests tricuspid valve regurgitation. Signs of RV failure include elevated jugular venous pressure, edema, hepatomegaly (pulsatile when associated with tricuspid valve regurgitation), and ascites. These findings are uncommon unless severe tricuspid valve regurgitation or RV dysfunction coexists.

Right bundle branch block is almost universally present in patients who have had TOF repair via a right ventriculotomy, and is accompanied by left anterior hemiblock in up to 9–15% and less frequently left posterior hemiblock (Figure 1).

The chest radiograph in TOF patients with severe PR often demonstrates findings of RV volume overload with retrosternal fullness on the lateral view, and increased cardiothoracic ratio. A right-sided aortic arch is present in 20–30% (Figure 1). Patients with a cardiothoracic ratio of less than 0.5 are unlikely to have marked RV enlargement. The chest radiograph may also demonstrate a dilated RV outflow tract, and central pulmonary arteries, and may demonstrate dilatation of the ascending aorta.

Given the concerns about adaptability and the lack of reported symptoms in TOF with severe PR, exercise testing is routinely performed at our Center to document exercise capacity and identify changes in functional status over time in patients followed serially. There are no data demonstrating that PV replacement performed for decline in exercise tolerance improves patient outcome. In addition, comorbidities may affect results of exercise testing. Thus, results of exercise testing alone are not used as the primary indication for PV replacement in TOF patients with PR, but are used in conjunction with other data to help define optimal timing of operation. Wessel et al. showed that exercise performance was 82 ± 21% of predicted in male TOF patients in comparison with control and that the degree of dysfunction was related to cardiomegaly on chest X-ray.[23] Carvalho and coworkers showed significantly reduced duration of exercise and negative correlation between exercise time and the degree of PR.[24] Important contributors to exercise intolerance include comorbidities such as lung disease, and chronotropic incompetence.[8,25]

There is interest in the role of brain natriuretic peptide in the assessment of patients with PR after TOF repair. Brili et al.[26] reported on 25 adults with repaired TOF with PR and 25 healthy controls. Patients with repaired TOF had a significantly higher brain natriuretic peptide level than control, and the increased level correlated with RV to LV diameter ratio. Furthermore, Ishii et al.[27] examined the relation between brain natriuretic peptide and RV contractile reserve during exercise. Plasma brain natriuretic peptide levels were significantly higher in patients with TOF than in controls. Exercise was associated with increased plasma brain natriuretic peptide levels in both groups. However, a larger increment in brain natriuretic peptide was noted in patients with TOF than in normal subjects. Therefore, exercise-induced changes in plasma concentration of brain natriuretic peptide may reflect RV contractile reserve in patients with TOF, and could potentially be used in the assessment of asymptomatic patients with severe PR to determine the need for PV replacement.

Echocardiography

Transthoracic echocardiography is still the most commonly used primary noninvasive imaging modality in the assessment of patients with congenital heart disease. A comprehensive 2-dimensional (2-D) and Doppler transthoracic echocardiographic assessment following TOF repair is routinely performed and should include

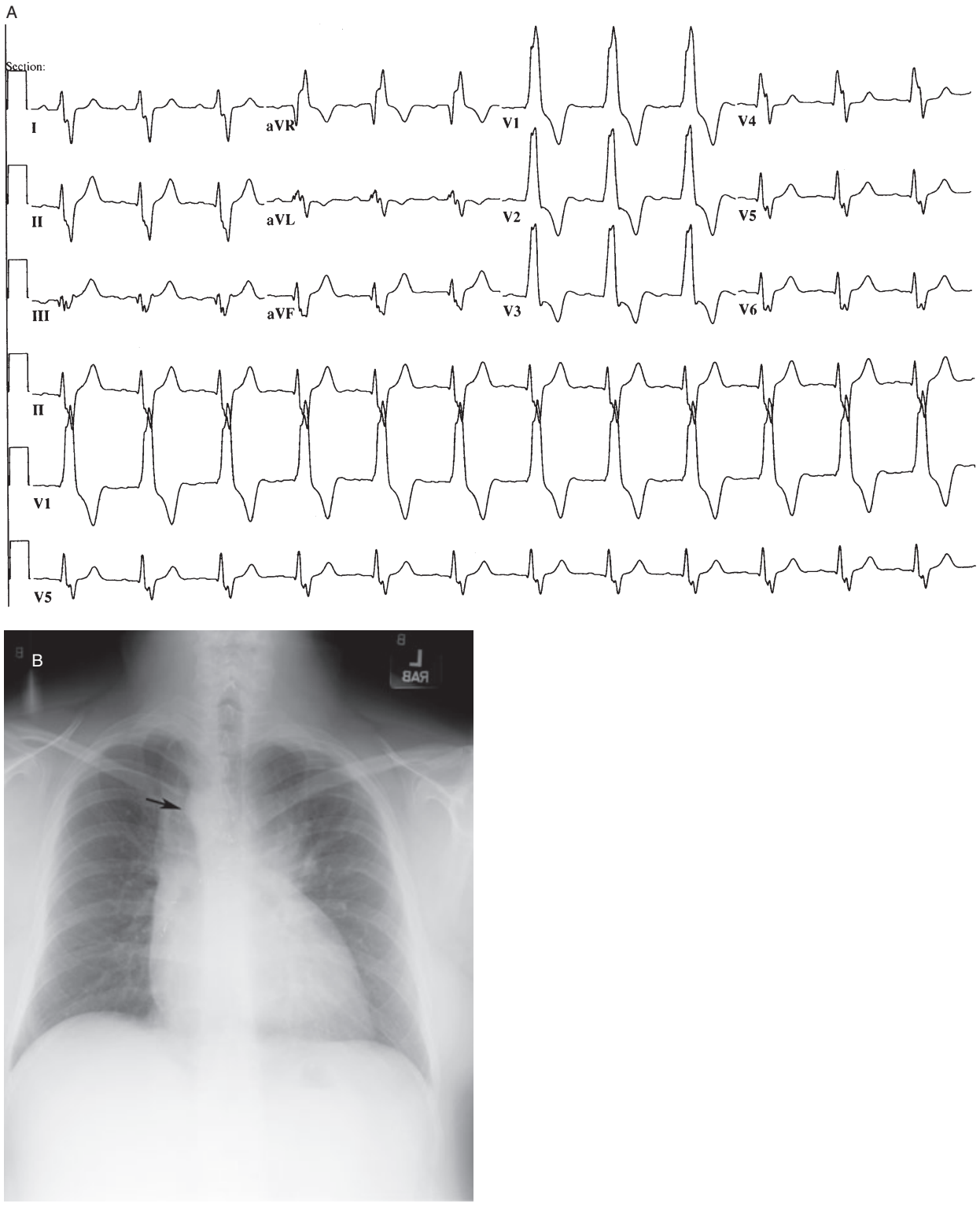

Figure 1. (A) Twelve lead electrocardiogram in a patient with severe pulmonary valve regurgitation following tetralogy of Fallot repair demonstrating right bundle branch block with QRS prolongation of 206 milliseconds and left posterior hemiblock. (B) The chest radiograph on the same patient demonstrates significant cardiomegaly with features of right heart enlargement and a right-sided aortic arch (arrow).

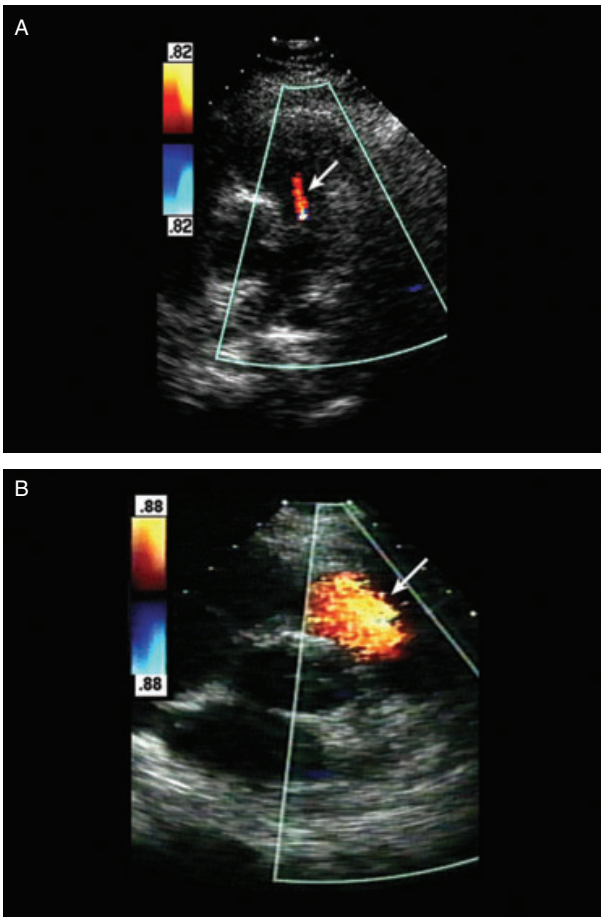

Figure 2. Parasternal short axis transthoracic echocardiographic images demonstrating diastolic color flow Doppler in the right ventricular outflow tract. The red jet represents the regurgitant pulmonary flow with (A) mild and (B) severe regurgitation (arrows). Notice the difference in the width of the color flow jet.

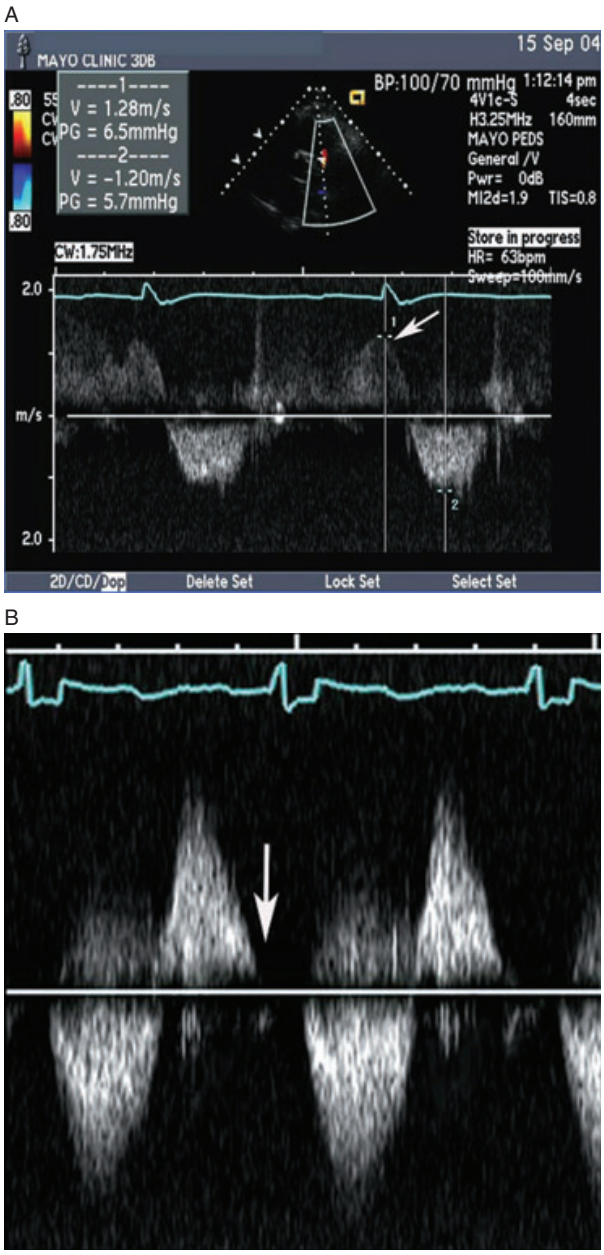

Figure 3. Continuous wave Doppler signal at the level of the pulmonary valve in a patient with mild pulmonary valve regurgitation demonstrates normal systolic forward flow and reversed flow that continues throughout diastole indicating mild pulmonary valve regurgitation. The low end diastolic velocity (A) suggests normal pulmonary artery diastolic pressure. In patients with (B) severe pulmonary regurgitation the regurgitant diastolic velocity (arrow) peaks early and decreases rapidly as the pulmonary artery to right ventricular pressures rapidly equilibrate, leading to early termination of the continuous wave Doppler signal.

assessment of (1) residual pulmonary stenosis, its level, cause, and severity; (2) possible cause(s) and severity of PR; (3) RV size and function; (4) presence and severity of tricuspid regurgitation; (5) RV systolic and pulmonary artery pressure; (6) presence of residual atrial or ventricular septal defect; and (7) LV size and function, and also should include the measurement of aortic root and ascending aorta diameter, and the determination of the presence and severity of aortic valve regurgitation.

Severe PR may cause pulsation in the pulmonary arteries that extend to the branches accompanied by abnormal color flow and spectral Doppler examination of the RV outflow tract (Figures 2 and 3). The degree of PR is classified according to the degree of retrograde diastolic flow into the main pulmonary artery and branch pulmonary arteries. Kobayashi et al.[28] reported that PR severity could be assessed using a PR area index defined as the maximum area of the PR color jet in the parasternal short axis imaging plane indexed to body surface area. This index was found

to correlate well with regurgitant fraction determined by angiogram. However, this technique is dependent on the direction of the PR jet, machine gain settings, transducer frequency, and other patient related issues. Williams et al.[29] suggested using linear measurements rather than area measurements. He demonstrated that the severity of PR can be determined by the ratio of PR color jet width to PV annulus in early diastole. A jet/annulus ratio of 0.7 separated patients with 2+ from those with 3+ angiographic PR.

Poor acoustic windows in patients with previous operation can limit the ability of accurate measurement of the jet/annulus ratio as well as the color flow Doppler assessment in the branch pulmonary arteries. As a result, other echocardiographic methods have been suggested for the assessment of the severity of PR using spectral and continuous wave Doppler. Spectral Doppler assessment at the level of the PV in patients with less than severe PR demonstrates normal forward flow in systole and reversed flow in diastole (Figure 3), the latter representing PR. The diastolic flow reversal is holodiastolic and its peak velocity is <1 m/s in the absence of pulmonary hypertension. In patients with severe PR (Figure 3), the regurgitant diastolic velocity peaks early and decreases rapidly as the pulmonary artery–RV pressure difference rapidly equilibrates, leading to early termination of the pulsed or continuous wave Doppler signal. This is a very common Doppler finding of severe PR but can also occur in patients with RV diastolic dysfunction due to an elevation in RV end diastolic pressure. In restrictive physiology there is early termination of the Doppler PR signal and presystolic forward flow (Figure 4), differentiating restrictive RV physiology from isolated severe PR.

Li et al.[30] suggested that the PR index, the ratios of the duration of the continuous wave Doppler PR signal to total diastole, could be measured and the ratio between the two correlated closely with CMR-derived regurgitant fraction. A PR index of <0.77 had a 100% sensitivity, and 85% specificity for identifying PR fraction of >24.5%, with a predictive accuracy of 95%. In a different study, using the PR velocity profile by continuous wave Doppler, the pressure half-time was measured and found to be inversely related to PR fraction.[31] A pressure half-time of less than 100 milliseconds was found to be a good indicator of severe PR.

Additional echocardiographic techniques for the assessment of severity of PR include: (1) measurement of regurgitant volume and effective regurgitant orifice by color Doppler technique such as proximal isovelocity surface area (PISA); (2) measurement of regurgitant volume and regurgitant fraction as well as effective regurgitant orifice by 2-D and Doppler echo such as continuity equation; and (3) measurement of the vena contracta. Finally, although the PISA method appears to be the most reliable method to assess regurgitant volume, this method has not gained widespread use in PR because the assumption of hemispheric shape is not valid in most cases of PR in which flow rates and trans-orifice pressure gradients are low.

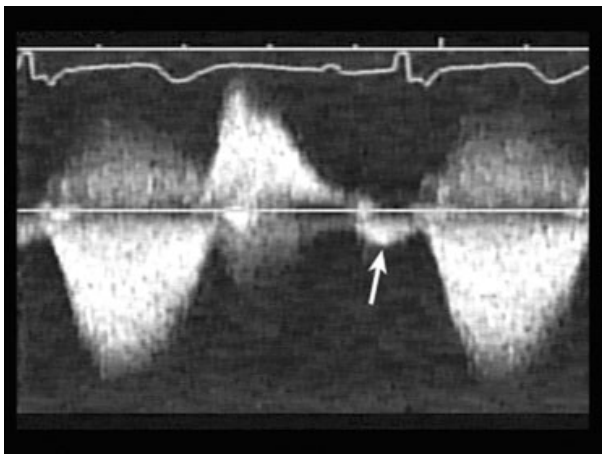

Figure 4. Assessment of right ventricular diastolic function in patients with pulmonary regurgitation following tetralogy of Fallot repair is an integral part of any comprehensive echocardiographic evaluation. Restrictive physiology leads to antegrade forward flow in the pulmonary artery (arrow) during atrial contraction. This should be noted during all phases of respiration and on 5 consecutive beats.

Patients with repaired TOF and PR can also have residual PV, infundibulum, or pulmonary artery branch stenosis. Obstruction can generally be assessed using continuous wave Doppler technique.

Assessment of the RV size and function is an integral part of any echocardiographic evaluation. Most quantitative 2-D echocardiographic measurements of ventricular size and performance are based on geometry assumptions that do not apply to the RV. The RV has a complex shape. It has a thinner wall and coarse trabeculations that make endocardial border delineation challenging. In our practice, we rely heavily on quantitative assessment and side-by-side comparison is used to assess RV size and function serially. Three-dimensional echocardiography promises accurate determination of RV volume and function; this technique is currently time-consuming and not widely used clinically.

Indirect information about RV systolic and diastolic function is available by conventional Doppler indices. The most commonly used echocardiographic parameters that have been suggested for the assessment of RV function include: (1) Doppler assessment of instantaneous rate of pressure increase (dP/dt); (2) right-sided index of myocardial performance (Tei index); (3) Doppler tissue imaging at the tricuspid annulus; and (4) strain and strain rate imaging.[26,32–38] All these methods have been used in assessing RV function in patients with PR following TOF repair. Changes in loading conditions may impact some of these measurements. Recently, a new easily reproducible Doppler measurement of systolic RV contractile function that is less dependent on loading conditions has been suggested. The isovolumic acceleration index is calculated by dividing myocardial velocity during isovolumic contraction by the time interval from the onset of the acceleration to the time at peak velocity.[39] Frigiola et al. reported that this index is useful in detecting early preclinical ventricular dysfunction before the onset of symptoms and thus determines appropriate timing of pulmonary valve replacement before significant RV dysfunction occurs.[39] Many of these echo-Doppler methods for assessment of RV function have been used predominantly as research tools; however, their clinical application in the future appears promising.

Assessment of RV diastolic function in patients with PR following TOF repair is an integral part of any comprehensive echocardiographic evaluation. Restrictive physiology leads to antegrade forward flow in the pulmonary artery during atrial contraction (Figure 4). This antegrade flow is related to abnormal RV compliance, but may be present in normal subjects during inspiration and therefore should be noted in at least 5 consecutive beats.[8]

CMR Imaging

Cardiac magnetic resonance has emerged as an accurate and reproducible technique for assessing RV volume, function, and PR severity.[40,41] Cardiac magnetic resonance has advantages over echocardiography; images are not compromised by air, bone, or surgical scar allowing unrestricted evaluation of RV outflow tract, and the pulmonary arteries. Multiplane CMR allows direct observation of RV cavity and its endocardial borders. Application of Simpson's rule for multiple tomographic slices acquired during ventricular systole and diastole permits direct and accurate measurement of RV volume and function. In addition, phase-contrast CMR provides a method of evaluation of velocity, volume, and the pattern of blood flow that would allow accurate mapping and measurement of both systolic and diastolic pulmonary artery flow and calculation of PV regurgitation fraction (Figure 5).[9,40–42]

Baseline CMR is recommended in many congenital heart centers for asymptomatic patients with repaired TOF in whom echocardiographic assessment of RV size and function, or other cardiac anatomy is suboptimal. In addition, periodic comparison CMR should be considered in select asymptomatic TOF patients to reassess RV size and function (Figure 5) in an effort to aid in determining the most appropriate timing of intervention for PR.

Right ventricular volume calculation using CMR correlates well with volume as measured by angiography.[43,44] The inter- and intraobserver variability is 5–15%. This is caused by the complex geometry of the RV, the difficulties in defining the correct tricuspid valve plane, difficulty with delineation of RV endocardial borders especially in the presence of an RV outflow aneurysm, increased trabeculation, and the presence of other structures such as the moderator band and patches. Using CMR, RV end diastolic and end systolic volumes are measured, indexed to body surface area, and compared with normal values (normal RV end diastolic volume = 91 ± 16 cc/m^2, RV end systolic = 69 ± 22 cc/m^2) to estimate the degree of RV enlargement. The RV ejection fraction is calculated using those measurements with normal being $61 \pm 6\%$.[45]

The main concern that had been raised using CMR is that it can underestimate the severity of PR when compared with echocardiography. In a study performed by Rebergen et al., only 15% of the cohorts had a PR regurgitant fraction of more than 40% whereas a larger proportion of patients, 61%, had severe PR by echocardiography.[40] It is the authors' opinion that the severity of PR is best assessed after a comprehensive evaluation of the surgical records to determine the type of operation performed in conjunction with echocardiographic examination as discussed earlier. The use of CMR to calculate regurgitant fraction is not routinely used as a clinical tool.

Gadolinium enhancement during CMR has been used to assess myocardial fibrosis related to areas of surgical resection, and patch placement or other surgical instrumentation may be detected.[15]

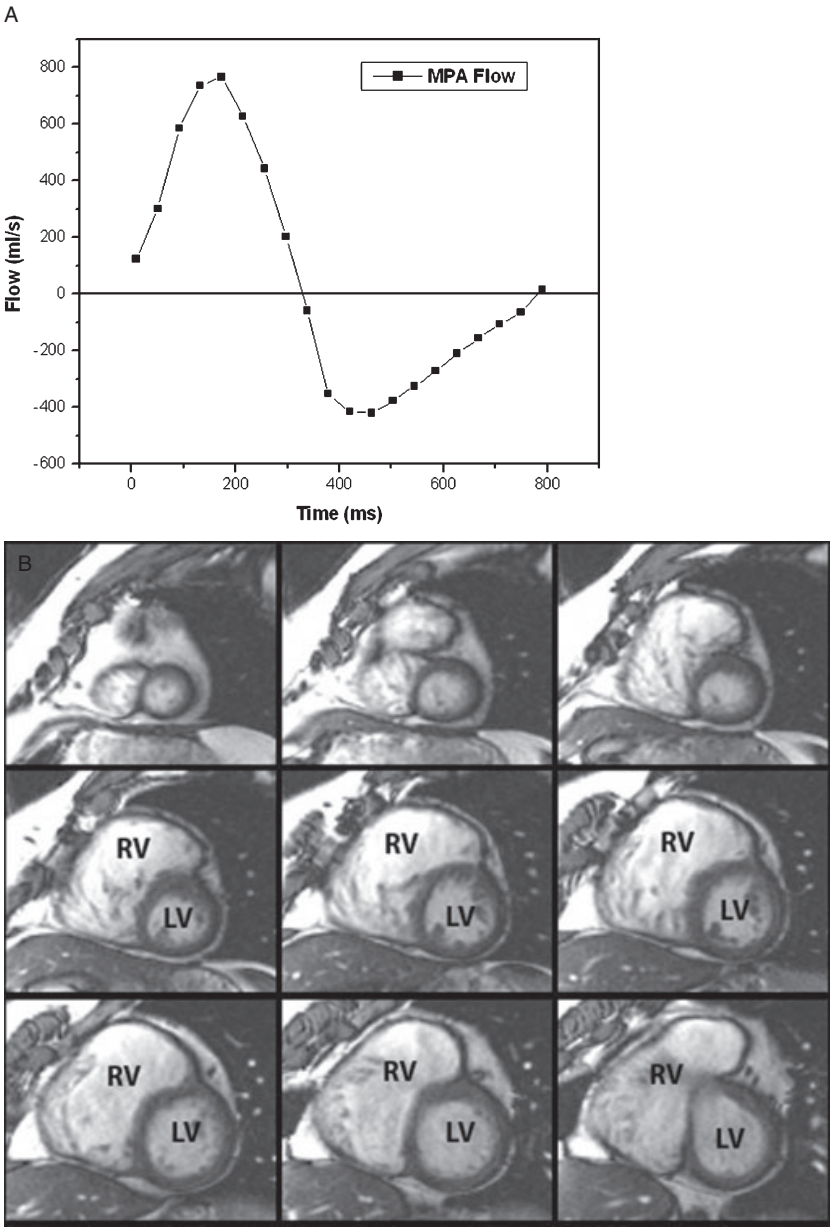

Figure 5. Phase contrast cardiac magnetic resonance imaging provides an accurate method of evaluation of (A) velocity, volume, and the pattern of blood flow that allow accurate measurement of both systolic and diastolic pulmonary artery flow and calculation of pulmonary valve regurgitation fraction. (B) Cardiac magnetic resonance imaging is also a reliable technique for assessing right ventricular size and function. MPA indicates main pulmonary artery; LV, left ventricle; RV, right ventricle.

The presence of myocardial fibrosis may have an impact on patient prognosis; however, additional data are required to determine the importance of this diagnostic tool.

Several studies have demonstrated the impact of CMR on the assessment of TOF patients with PR. Therrien et al.[46] noted that in order to improve RV size following PV replacement, operation should be performed before the RV end diastolic volume reaches 170 cc/m^2 or RV end systolic volume reaches 85 cc/m^2. Buechel et al.[47] reported on children with TOF, severe PR, and RV dilatation who underwent CMR. Pulmonary valve replacement was performed when RV end diastolic volume exceeded 150 cc/m^2. Postoperative RV remodeling with reduction in volume and mass was observed after PV replacement when preoperative RV end diastolic volume exceeds 150 cc/

m^2. Right ventricular ejection fraction did not change significantly. Based on these 2 studies, it appears that PV replacement should be performed when the RV end diastolic volume is great than 150 cc/m^2 and smaller than 170 cc/m^2.

Additional Imaging Techniques

Multislice computerized tomography (CT) scan is an emerging alternative imaging modality especially in TOF patients with implantable devices. However, CT imaging uses ionizing radiation and older-generation scanners require a low heart rate for optimal image acquisition. The modern CT scanners are less sensitive to heart rate for image acquisition. This technique can also be used to exclude anomalous coronary artery prior to reoperation.

Nuclear cardiac imaging at rest and during exercise could also be considered when CMR imaging is not available or feasible. Progressive RV enlargement and dysfunction and the failure of the RV ejection fraction to improve with exercise can be used in the evaluation of patients with repaired TOF and PR. This technique does, however, have some limitations. Radionuclide angiography requires the acquisition of views of the ventricles that exclude counts from other chambers, which can usually be achieved for the LV but often not satisfactory for the RV.[48] In addition, this modality requires an adequate bolus injection for the first-pass studies and regular rhythm with a minimal R–R variability. Its resolution is poor compared with other imaging methods and therefore has been of limited use recently.[43,48] On the other hand, ^{123}I metaiodobenzylguanidine (MIBG) with tomographic imaging has been suggested by Daliento et al. as a mean to analyze the adrenergic nervous system in repaired TOF.[49]

Cardiac catheterization is only performed in patients when alternative measures cannot accurately assess the RV and pulmonary artery anatomy or hemodynamics noninvasively. Cardiac catheterization is performed in patients with suspected pulmonary artery or branch stenosis, and in those suspected of having pulmonary hypertension. It is also performed when catheter-guided intervention such as relief of pulmonary artery stenosis is indicated. However, angiographic evaluation of PR severity is complicated by the fact that catheter position across the PV may influence the angiographic severity. Coronary angiography is performed routinely in adults prior to operative intervention, and in patients with suspected anomalous coronary artery to delineate the course of the coronary artery and outline operative management options (Figure 6).

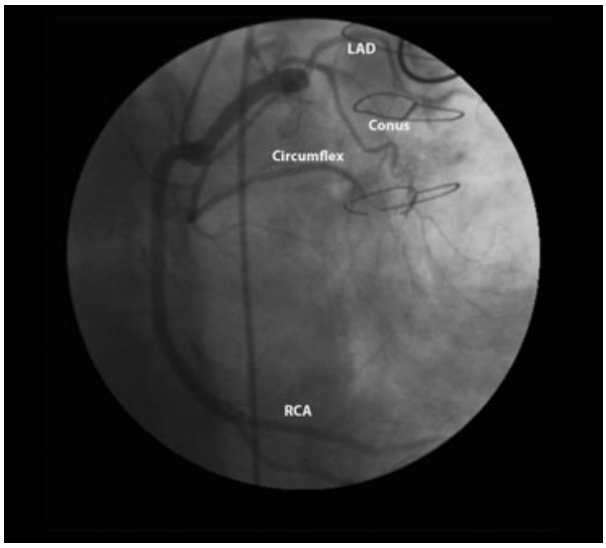

Figure 6. Coronary angiography in a 62-year-old woman with repaired tetralogy of Fallot demonstrates anomalous left anterior descending (LAD) and circumflex artery arising from the right coronary artery (RCA). The anomalous LAD courses anterior along the right ventricular outflow tract and demonstrates an important risk around the time of reoperation. Inadvertent transection of the anomalous coronary artery is potentially catastrophic.

Arrhythmia Assessment

Repaired TOF patients have the ideal substrate for ventricular arrhythmias. The aggressiveness of investigation and treatment of ventricular arrhythmias depends on symptoms, underlying structural derangement, and hemodynamic status. Evaluation typically includes electrocardiogram, 24-hour Holter monitoring, event monitoring, and at times signal averaged electrocardiogram, and electrophysiology study. The predictive value of programmed stimulation for sudden death is unclear in this population, in part because of relatively low event rates. A negative electrophysiological study may be helpful in the management of these patients, but a positive study should be interpreted with caution especially in the presence of hemodynamic abnormalities such as severe PR and RV enlargement.[50]

Treatment options include antiarrhythmic medication, radiofrequency ablation, implantable cardiac defibrillator, and arrhythmia surgery.

These usually should be performed in association with repair of the hemodynamic abnormalities such as PR.

Although correction of the hemodynamic abnormalities, such as PR, may be sufficient therapy to prevent ventricular tachycardia,[51] this cannot be reliably predicted. Patients with history of ventricular tachycardia or syncope prior to planned PV replacement should be considered for preoperative electrophysiological study to identify the mechanism of inducible ventricular tachycardia, and direct surgical approach to tachycardia intervention if feasible. Scars from prior transventricular incision and outflow patches are the ideal anatomic substrate facilitating a re-entrant rhythm.

Therrien et al.[52] reported that the freedom from preexisting clinical arrhythmia at 5 years with surgical cryoablation was 100% compared with 68% without concomitant cryoablation at the time of PV replacement in TOF patients. An aggressive approach for surgical treatment of atrial and ventricular arrhythmias is routinely followed in our practice. In addition, we would consider a repeat electrophysiological study after PV replacement and arrhythmia surgery in patients with preoperative ventricular arrhythmia to determine success of the operation or the need for implantation of automated defibrillator. However, the latter could be complicated by inappropriate defibrillator discharges due to atrial arrhythmias and therefore the benefits of an automated defibrillator should be weighed against potential complications.

Treatment of PR

Medical therapy for patients with severe PR following TOF repair is very limited. Diuretics are used in patients presenting with edema or symptoms of congestive heart failure. Afterload reduction with angiotensin converting enzyme inhibitor, angiotensin receptor blocker, or beta blocker has no proven benefit in TOF patients with PR.

Patients with PR demonstrate features of neurohormonal activation and impaired cardiac autonomic nervous system activity and therefore the use of medications may convey symptomatic benefits.[13] Elevated levels of brain natriuretic peptide at rest and with exercise have been demonstrated in patients with PR following TOF repair.[26,27] Although patients may demonstrate some symptomatic improvement with medical therapy, PV replacement is the only treatment modality with proven long-term benefit including reduction in RV size, and improvement or at least stabilization of RV function.

Table 2. Indications for Pulmonary Valve Replacement

Attributable symptoms and signs
- Exertional dyspnea
- Exercise intolerance
- Heart failure
- Symptomatic or sustained arrhythmias related to right heart enlargement

Asymptomatic patients with
- Decline in functional aerobic capacity (maximum V0 2) on exercise testing to <70% of gender-age predicted or a decline >20% compared with serial testing
- Progressive RVE and/or dysfunction noted on serial imaging studies
  - Cardiothoracic ratio on chest X-ray
  - Echocardiogram
  - CMR
  - RV EF <40%
  - Moderate or more tricuspid valve regurgitation related to long-standing PR
- TOF patients with severe PR and coexisting cardiac lesions themselves requiring surgical intervention such as
  - Significant residual shunt
  - RVOT obstruction (RVSP ≥2/3 systemic)
  - Clinical arrhythmias due to severe PR
  - Ventricular arrhythmia prevention
    - QRS ≥ 180 ms
    - QRS prolongation >3.5 ms/y

RVE indicates right ventricular enlargement; CMR, cardiac magnetic resonance; RV EF, right ventricular ejection fraction; PR, pulmonary valve regurgitation; TOF, tetralogy of Fallot; RVOT, right ventricular outflow tract; RVSP, right ventricular systolic pressure.

Timing of Pulmonary Valve Replacement

Pulmonary valve replacement carries a low operative risk when performed by experienced and skilled surgeons and leads to restoration of PV function, symptomatic improvement and improvement of RV size, and stabilization of function when performed at the optimal time.[1,14,25,46,52–54]

Indications for PV replacement are in evolution (Table 2). There is agreement that the presence of symptoms due to PR is an indication for PV replacement in TOF patients. However, determining timing of intervention in asymptomatic TOF patients with PR remains controversial. We recommend PV replacement for asymptomatic TOF patients with severe PR and the following: (1) progressive reduction in exercise tolerance or important reduction in exercise tolerance related to abnormal cardiac output response to exercise; (2) progressive RV enlargement (>150 cc/m^2 by CMR) or RV dysfunction;[1,13,22,25,46,52,55] (3) development of clinical arrhythmias, increased QRS duration on the electrocardiogram ≥180 millisec-

onds or QRS increase ≥3.5 ms/y; and (4) progressive tricuspid valve regurgitation.[46,47]

Pulmonary Valve Replacement

Despite advances in the development of bioprosthesis and homografts, progressive prosthetic valve deterioration requiring subsequent reoperation remains a problem following PV replacement. In addition, there is a small but important surgical risk. Therefore, appropriate surgical patient selection is important. Review of the risks and benefits of intervention vs. continued observation with its inherent risk must be carefully considered.

Isolated PV replacement continues to be a low-risk procedure with a perioperative mortality of 1–2% and excellent 10-year survival of 86–95% in experienced Adult Congenital Surgical centers, even in the presence of multiple reoperations.[5,12–14,55–58] The operative risk increases with the addition of concomitant surgical procedures that are performed in more than half of patients.[55] Additional procedures may include resection of RV aneurysm, reconstruction or remodeling of the RV outflow tract, repair of residual intracardiac shunts, intervention for tricuspid or aortic valve regurgitation, and maze or other antiarrhythmia intervention. It is imperative to determine the coronary anatomy prior to PV replacement from prior surgical records or angiography images or reports. Anomalous proximal coronary artery course is not uncommon in TOF patients and has an important impact on surgical approach. Inadvertent transection of an anomalous coronary artery during an operation can cause serious morbidity or even death.

Biological valves (porcine and pericardial heterografts, homografts) are usually used for PV replacement because of the good durability in this position and the lack of a need for warfarin anticoagulation. However, the use of biological valves carries an inherent risk of the need for reoperation. The cryopreserved pulmonary or aortic homograft is an option for orthotropic PV replacement. The pulmonary homograft functions optimally in the absence of pulmonary hypertension and distal pulmonary artery stenosis. Pulmonary homografts have been reported to last longer in the pulmonary position than the aortic homografts,[59] but they still carry the risk of calcification with resultant stenosis and/or regurgitation and the need for re-replacement. In general, both pulmonary and aortic homografts fail by a combination of regurgitation and stenosis. In our experience regurgitation is much more likely with the pulmonary homograft. Consequently, if a homograft is desired and pulmonary hypertension is present, an aortic homograft is preferred. In the current era, homograft prostheses, limited by the available size, are preferred when PV replacement is required during infancy and in patients undergoing the Ross procedure. The International Ross Registry report of 2610 documented Ross operations; freedom from reoperation on the RV outflow tract was 91% at 10 years and 84% at 25 years.[14]

In our practice, we favor porcine or pericardial bioprosthesis in children and adults when PV replacement is necessary. A pericardial patch is often used to enlarge the pulmonary annulus, and proximal pulmonary arteries as needed. This allows the prosthesis to be normal or slightly oversized, which may be especially important when there is significant RV dysfunction. In our experience, the durability of this type of reconstruction is superior to that of cryopreserved homograft or Dacron porcine-valved conduit.[60,61] Discigil et al.[55] reported the Mayo Clinic experience in 42 patients. Pulmonary valve heterograft prostheses were used in 33 patients and homografts in 9. Only 5 patients (12%) underwent isolated PV replacement with concomitant procedures in 37 patients. Functional class of patients improved significantly with 76% being in New York Heart Association Class III or IV before the operation, compared with 97% in Class I or II after operation ($P = .0001$). The freedom from reoperation in this group was $93 \pm 5\%$ and $70 \pm 11\%$ at 5 and 10 years, respectively. Eight patients underwent successful PV re-replacement without early mortality at the mean interval of 7.7 years after initial PV replacement. All patients who underwent repeat PV replacement had a heterograft prosthesis placed initially. The only significant risk factor for re-replacement by univariate analysis was younger age at the time of the initial PV replacement. In contrast, Lim et al.[62] demonstrated that earlier PV replacement prior to symptomatic deterioration showed beneficial effects. Patients in their series who were still symptomatic following PV replacement (n = 14) were older at the time of TOF repair, older at the time PV replacement, and had a longer interval between repair of TOF and PV replacement than asymptomatic patients (n = 43). Marked symptomatic improvement was noted in all patients. Therefore, this study as well as others suggested that early PV replacement prior to symptomatic manifestation may be

beneficial.[57,62,63] Yemets et al. reported a 10-year freedom form reoperation of 86 ± 7% in a group of 85 patients who had PV replacement at a mean age of 19 ± 6 years.[56]

To improve the chance of functional recovery, restoration of the outflow tract at the level of the ventricular arterial junction is important to prevent distortion of the geometry of the prosthetic valve, and avoid the risk of early prosthetic valve regurgitation. If this cannot be achieved, it may be prudent to use a stented prosthesis.[25] At the present time there is little evidence to support the use of a specific bioprosthetic valve in adults, in terms of long-term prosthetic valve function or patient survival. Many factors influence prothesis longevity such as size, and age of the patient at time of implantation. Whether or not medications such as statins or low-dose aspirin influence the outcome of valve prosthesis is yet to be determined. Preliminary data from our institution suggest that triglyceride levels may impact pulmonary prosthesis longevity.[64]

The use of mechanical valve prosthesis in the pulmonary position has been limited because of concerns of increased risk of thromboembolic complications. The St. Jude bileaflet mechanical valve prosthesis has a low profile, a large effective orifice area, and excellent hemodynamic profile. Unfortunately, 1 study suggested a failure rate of 35% predominantly from thrombotic complications.[65] However, these complications occurred primarily in patients who were suboptimally anticoagulated. In patients on therapeutic warfarin, the complication rate observed was 10%. Stulak et al.[66] reported the Mayo Clinic experience of mechanical PV prostheses in 10 patients. Nine were anticoagulated with warfarin. During a mean follow-up period of over 8 years, 1 patient required replacement for outgrowth of her mechanical prosthesis after 25 years. No case of clinically evident mechanical PV prosthesis thrombosis was noted. One late sudden death occurred 15 years after PV replacement.

In our practice, mechanical PV prostheses are considered in patients who need warfarin for another reason such as left-sided mechanical valve prosthesis, or in patients with documented accelerated deterioration of a previously placed PV bioprosthesis. In addition, there is the occasional patient with atrial fibrillation who will require long-term warfarin therapy, although this is increasingly uncommon because of the application of the maze procedure at the time of PV replacement. Other patients who might be considered for mechanical PV replacement are those patients who have had multiple previous operations in the past. When a mechanical PV is used, we aim for a target international nationalization ratio of 3.0 and also add aspirin (81 mg).

The use of the valved bovine jugular vein conduit (Contegra, Medtronic, Inc, Minneapolis, MN, USA) is soon to be commercially available and may provide a good alternative to the homograft. It is currently available in Europe and undergoing clinical trials in the United States. Advantages include greater availability of sizes, ease of handling, and price compared with pulmonary homografts. Brown et al.[67] reported early hemodynamics of the conduit to compare favorably with pulmonary homografts with regard to obstruction or regurgitation. Long-term results are lacking but the conduit may prove to be a good alternative to the pulmonary homograft for RV outflow tract reconstruction.

Percutaneous Intervention

Percutaneous balloon dilatation and stent placement for branch pulmonary artery stenosis has been used for many years and can decrease the hemodynamic effect of PR. Patients with free PR and branch pulmonary stenosis rarely tolerate PR well. Such patients should be considered for PV implantation with concomitant relief of pulmonary artery stenosis using pulmonary angioplasty performed either percutaneously or at the time of the operation with the pulmonary artery exposed. Pulmonary artery stent placement at the time of operation may be an attractive option in select patients.

Recent advances in the percutaneous intervention, and growing concerns about the risk of multiple reoperations, lead to an interest in percutaneous PV replacement using bovine valve of jugular vein mounted on a stent.[68] The first percutaneous PV implantation was reported by Bonhoeffer et al.[69] Since that original report, 2 large reports suggest that percutaneous PV implantation in the appropriately selected patient is a relatively safe, effective procedure with durable short-term results, and should be considered as a promising alternative to surgery.[65,68,70] Both approaches are safe with an acceptable level of morbidity and low mortality. The presence of favorable RV outflow tract morphology is based on echocardiographic and magnetic resonance imaging evaluation. Favorable features for percutaneous valve replacement include an RV outflow tract diameter of less than 24 mm, an RV outflow

gradient of greater than 30 mm Hg, the presence of discrete waist or calcification for implantation, and the absence of significant pulsatility. On the other hand, this procedure should not be considered in patients with limited access to the RV outflow tract due to occluded central vein or in those with aneurysmal RV outflow tract or in any patient with unfavorable shape, size (>24 mm), and elastic property of the RV outflow tract. Recent development of an infundibular reducing device may facilitate a percutaneous approach in these patients with larger outflow tract diameter. Evolving device design and experience with this technique will impact the future of re-intervention in patients with PR following TOF repair. Importantly percutaneous intervention will not address the need for resection of subvalvular hypertrophic muscle bundle, pulmonary infundibuloplasty in patients with severe RV dilatation and large akinetic or aneurysmal segment in the RV outflow tract, the need for tricuspid valve repair or intraoperative cryoablation to reduce the incidence of atrial and ventricular arrhythmias.

Outcome Following PV Replacement

Several studies reporting on patients who underwent PV replacement for PR in TOF have demonstrated improvement in the functional class, increased exercise tolerance, reduction in RV end diastolic diameter and volume, and at times, improvement in ejection fraction using echocardiography or CMR.[12,14,25,55,57,62,66,71,72] Bove et al.[71] were the first to demonstrate that RV dysfunction associated with PR is reversible and that PV replacement should be carried out before permanent RV dysfunction ensues. An increase of more than 5% in RV ejection fraction was noted in 7 patients. Warner et al. reported a 30% reduction in RV end diastolic diameter using echocardiography in 36 patients following PV replacement.[73]

Buechel et al.[47] reported significant beneficial remodeling in children with TOF who had CMR before and after PV replacement. A significant reduction in RV dimension, RV mass, and RV end diastolic volume was noted after PV replacement.

A recent study demonstrated improved RV diastolic function late after PV replacement.[12] Pulmonary valve replacement may also have a beneficial effect on the risk of ventricular arrhythmias. In a study by van Huysduynen et al.,[72] 26 patients were evaluated preoperatively and 6–12 months postoperatively by CMR and electrocardiogram. QRS duration decreased in the majority, and QRS duration changes correlated with improvement in RV end diastolic volume (P value = .001). In another study Doughan et al.[74] demonstrated a reduction in RV volume and QRS duration in patients with a preoperative QRS duration of >155 milliseconds compared with patients with QRS <155 milliseconds who had no decrease in QRS duration. However, it must be emphasized that although these 2 studies clearly demonstrate that QRS duration can improve after PV replacement, this may not correlate with reduced risk of arrhythmias.[52]

Despite the significant improvement noted in functional class, QRS duration, RV size, and function after PV replacement, significant residua and sequelae may persist. Conte et al.[57] examined the effect of PVR in 49 patients. The patients who did not benefit from PV replacement, in terms of exercise tolerance, had been exposed to PR for a considerably longer time (18 ± 7 vs. 12 ± 6 years). Patients who underwent PV replacement more than 15 years after TOF repair had only mild reduction in RV dilatation following surgery. Therrien et al.[75] noted subjective improvement in 25 adult patients with repaired TOF who underwent radionuclide angiography before and after PV replacement. However, exercise duration and maximal workload failed to increase significantly. In addition, there was no improvement in RV ejection fraction and dimension post PV replacement.

Strategies for Prevention of Late PR During Initial TOF Repair

Every effort is now made to maintain PV competence in order to avoid the recognized problems related to chronic PR in patients following repair of TOF. Current operative techniques often involve a combined transatrial and transpulmonary approach involving closure of ventricular septal defect and relief of the RV outflow tract obstruction. However, a limited RV incision is often required for patch augmentation of the RV outflow tract and/or the PV annulus. Under those circumstances, the use of a small stiff patch may provide a superior hemodynamic state than a large and expandable pericardial patch.[6] The patch should also be positioned to avoid producing severe PR. The latter could be at the expense of more residual RV outflow tract obstruction.[76]

Cheung et al.[77] reported the result of such pulmonary annulus preservation technique in 118 children undergoing TOF repair in Toronto. This

approach yielded a lesser need for transannular patch (20%), and a higher intraoperative RV outflow tract gradient (12 vs. 20 mm Hg). Follow-up echocardiogram, at the median of 16 months, showed equivalent RV pressure and degree of PR between the 2 groups. Preservation or restoration PV function is a desirable surgical strategy that could influence long-term outcome in patients with repaired TOF.

Conclusion

The adult patient with repaired TOF presents unique challenges. Advances in diagnosis, cardiac surgery, anesthesia, intensive care, and medical management have clearly transformed the outcome of these patients, and markedly improved prognosis. However, with increasing duration of follow-up, significant residua and sequelae are recognized. Pulmonary valve regurgitation is an important determinant of late morbidity, and the most common cause for re-intervention. Although tolerated well in childhood, it is associated with progressive exercise intolerance, RV enlargement and dysfunction, tachyarrhythmia, and even late sudden death.

Adult patients with repaired TOF should be monitored closely by trained adult congenital cardiac specialists for residual lesions and development of comorbidities. Appropriate timing of PV replacement is associated with improvement in exercise tolerance, RV size, and function and combined with arrhythmia surgery can lead to a decrease in the risk of arrhythmias and sudden death. The assessment and management of adult patients after TOF repair is best performed in centers with medical and surgical expertise in adult congenital heart disease. Although recent promising advances have been made including percutaneous PV replacement, and tissue engineering allowing growth of valves in vitro using biodegradable matrix,[78] in the United States, the percutaneous PV is not yet approved for routine clinical use by the US Food and Drug Administration, and there are several limitations to overcome before the clinical application of tissue engineering.

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