SUPPLEMENTARY MATERIAL:

EVALUATION OF THE PATIENT WITH REPAIRED TETRALOGY OF FALLOT

Evaluation of patients with repaired TOF is a life-long process. Integration of all aspects of clinical assessment including history and physical examination findings, 12-lead electrocardiogram and Holter findings, laboratory results, exercise testing and multi-modality imaging is required to allow for comprehensive evaluation and to inform frequently complex decision making. Accurate information pertaining to previous medical and surgical history is of paramount importance as source documents often provide invaluable information relating to original anatomy as well as childhood surgical and interventional procedures. It must be remembered that young patients with TOF may require multiple surgical or catheter based interventions through their lifetime. Thoughtful consideration should be taken when discussing the risks and potential benefits of any intervention, acknowledging the limitations of our current understanding on the optimal timing of PVR, particularly in those with minimal or absent symptoms. Finally, it should be noted that symptoms or signs of cardiovascular compromise can be seen in the setting of minimal PR and normal RV size if mediated primarily by the presence of atrial or ventricular tachyarrhythmias.

Electrocardiography

The majority of patients post TOF repair will exhibit complete right bundle branch block (RBBB) on their resting 12-lead ECG. The duration of the QRS complex has been associated with the extent of RV dilatation. Gatzoulis and colleagues were the first to recognize that a QRS duration >180 msec was an independent risk factor for sustained VT and SCD.\(^1\) In a more recent study by Cuypers et al. a steady increase in QRS duration over time was evident however QRS duration was not a predictor of mortality.\(^2\)

Imaging Modalities

A multi-modality imaging approach is vital for evaluation of the adult with repaired TOF as no single modality has the ability to accurately determine every aspect of cardiac anatomy and physiology\(^3\) (Table 1). In the stable patient, echocardiography is typically performed every 1-2
years and CMR at 2-3 yearly intervals \(^4,5\) with the aim of delineating anatomical and functional abnormalities, ascertaining severity of residual lesion(s) and provision of information to aid in decision-making on intervention if necessary.\(^3\) Published guidelines for the use multi-modality imaging in patients with repaired TOF are available\(^3\) as well as cardiovascular magnetic resonance imaging (CMR) specific recommendations.\(^6\) These suggest that thorough assessment of both the left and right heart, extending to the branch PAs and aorta, be completed whenever possible.

**Echocardiography**

The advantages of two-dimensional echocardiography are its non-invasive and portable nature, wide availability and relative cost-effectiveness as a screening tool. Echocardiography is the primary modality used for the surveillance of RV size and function as well as qualitative assessment of valvular function. Doppler echocardiography is necessary to obtain quantitative assessment of RVOT and/or conduit gradients and therefore severity of stenosis as well as right heart pressure (Figure 2).

At our institution RV size is assessed in multiple acoustic windows but is measured in the apical 4-chamber view with cut-off values for RV dilatation of >42 mm at the base, and >35 mm at mid-ventricular level as per the American Society of Echocardiography (ASE) guidelines.\(^3\) We use qualitative assessment and select quantitative methods to assess RV function, including tricuspid annular plane systolic excursion (TAPSE), tricuspid annulus S’ and fractional area change (FAC) with the overall assessment based on these collective data.

As LV dysfunction occurs in approximately 20% of patients with repaired TOF, and is considered one of the strongest imaging predictors of adverse outcomes late after TOF repair,\(^7\) the LV also requires careful assessment.\(^8\) Adverse ventricular-ventricular interaction associated with RV dilatation (which impacts upon LV filling) has been suggested as a possible mechanism leading to deterioration in LV function. The potential causes of late LV dysfunction that may be prevented at the time of initial repair include long bypass time, insufficient myocardial protection and coronary artery injury. Repair at an early age may also protect the LV from a longstanding VSD and high output state due to a BT shunt. LV dysfunction is also more common in TOF
patients with SCD. Tzemos et al. found LV dysfunction and dyssynchrony in 75 adults with repaired TOF which was associated with QRS duration and therefore considered a marker of adverse RV-LV interactions. In our practice, cardiac resynchronization therapy is considered in the setting of at least moderate LV dysfunction and a QRS duration > 150 msec.

**Cardiovascular Magnetic Resonance Imaging**

CMR is the reference standard for assessment of the right heart. CMR provides comprehensive, reproducible and accurate information on biventricular size and function, cardiac anatomy, blood flows, severity of semi-lunar valve insufficiency and myocardial fibrosis, with unrestricted plane acquisition (Figure 3). It is well-suited for longitudinal follow-up of patients with repaired TOF, albeit with some limitations. CMR cannot be completed in those with recognized contraindications (such as an ICD or pacemaker, or those with significant claustrophobia or anxiety); while CMR can be completed in pregnant women or those with renal dysfunction, gadolinium should not be administered. It should be noted that pressure gradients and the anatomic evaluation of small shunts are not optimally achieved by CMR.

Despite the widespread use of CMR in repaired TOF there are topics of ongoing debate. Specifically, there is currently no universal agreement on the standards by which the RV should be assessed. Disparity in defining the distal aspect of the RVOT in the setting of a trans-annular patch, and the inclusion or exclusion of RV trabeculations in the assessment of RV mass are topics requiring further investigation. Test-retest reproducibility of RV measurements, within and between observers in short axis and axial planes have been published from our institution and our approach to contouring the RV in the setting of TOF has been described in detail. Blalock and colleagues demonstrated that, with the exception of RV mass, interstudy variability of RV volumes and function in adolescents and adults with TOF was similar to LV measurements. Late gadolinium enhancement (LGE) has been shown both within the LV and RV of patients with repaired TOF. Suggestive of focal areas of fibrosis and scarring, LGE has been associated with poor outcomes such as ventricular dysfunction, exercise intolerance, arrhythmias and neurohormonal activation. Using T1 measurements of extracellular volume fraction (ECV) as a marker of diffuse myocardial fibrosis, it has recently been shown that LV and RV ECV values are positively correlated, indicating an adverse ventricular-ventricular
interaction at tissue level. Increased LV ECV has been shown to be associated with arrhythmias and adverse outcomes.\textsuperscript{19, 20} The role of ECV in assisting with the risk stratification and timing of re-interventions is likely to be further scrutinized in future studies.

**Cardiac Computed Tomography**

Gated cardiac computed tomography (CT) is a very useful imaging technique for quantification of RV size in patients who are unable to undergo CMR.\textsuperscript{21} Although spatial resolution is superior, radiation exposure renders this modality inappropriate for serial imaging.\textsuperscript{5} In some TOF patients pre-operative CT imaging is important in determining coronary artery anatomy and in defining the spatial relationships between the sternum and anterior cardiac structures (RVOT, RV-PA conduit, coronary arteries and aorta). Temporal resolution of cardiac CT is inferior to other imaging modalities and evaluation of ventricular function may therefore be suboptimal.

**Invasive Testing**

When cardiac catheterization is required as part of the work-up for PVR it should be performed in centers with expertise in adult congenital heart disease (ACHD).\textsuperscript{5,22,23} The coronary artery anatomy in TOF is recognized to be variable and careful delineation of coronary anatomy is critical prior to RVOT-PA intervention to avoid coronary artery compression during stent expansion. It is also important to understand the coronary artery anatomy when planning surgical revision. This has often been established in childhood, so review of previous surgical and catheterization reports is helpful. Additionally, it is important to assess for coronary artery disease in older patients or those with risk factors such as smoking or a family history of premature ischemic heart disease. Hemodynamic data obtained from these studies may also contribute to the pre-operative assessment.\textsuperscript{5,23} In the setting of pulmonary artery stenosis, stenting for relief obstruction may result in attenuation of PR severity.\textsuperscript{24}

Anatomic characteristics often relating to previous surgical approach can provide the substrate for development of VT, and as such are desirable targets for electroanatomical mapping and ablation.\textsuperscript{25} Criteria for pre-operative electrophysiology (EP) study and intra-operative cryoablation for the management of ventricular arrhythmias are not standardized and may vary
between institutions based on the interpretation of risk.\textsuperscript{25,26} In our center an EP study will be performed (1) prior to PVR if there are symptoms/signs suggestive of VT (such as syncope), documented evidence of VT and/or significant ventricular dysfunction with QRS duration >180 msec and (2) following PVR with cryoablation to assess for arrhythmia inducibility and the need for an implantable defibrillator.

**Cardiopulmonary Exercise Testing**

Cardiopulmonary exercise testing (CPET) can be used to assess cardiovascular response to physiologic stress and assess for arrhythmias related to exercise. Serial data are often helpful to detect decline in functional capacity.\textsuperscript{5} Pre-operative CPET has been shown to predict surgical outcome in the TOF population\textsuperscript{27} although there is a lack of clearly defined exercise data for the stratification of asymptomatic patients. While oxygen consumption (peak VO2) is the most widely recognized parameter for risk stratification on CPET, the performance of this measure has been disappointing in the TOF population, given absence of a relationship to RV size, rate of RV deterioration or extent of RV remodelling post PVR. Ventilatory response to exercise (VE/VCO2 slope) is considered a more consistent measurement which can be derived from a submaximal exercise test and is independent of patient motivation; VE/VCO2 has been identified as the most powerful predictor of mortality in those with ACHD.\textsuperscript{28}

**Brain Natriuretic Peptide (BNP)**

The role of BNP and N-terminal pro-B-type natriuretic peptide (NTproBNP) in risk stratification for adults with repaired TOF remains unclear. It has been suggested that BNP may aid in determining the timing of PVR but larger studies are necessary to establish its true prognostic value.\textsuperscript{29} Several studies have shown a positive correlation between the severity of PR and RVEDV with BNP.\textsuperscript{30,31,32} Plasma BNP and exercise capacity including peak oxygen uptake have a negative correlation,\textsuperscript{33} and BNP has been shown to fall post PVR in keeping with the reduction in RVEDV.\textsuperscript{31,34}
REFERENCES


Supplementary Table 1: Summary of published consensus guidelines and position statements which address timing of surgical PVR in the asymptomatic patient with hemodynamically significant PR* (class of recommendation and grade of evidence appear in brackets)

<table>
<thead>
<tr>
<th></th>
<th>AHA/ACC, 2008 33</th>
<th>CCS, 2009 47</th>
<th>ESC, 2010 12</th>
<th>Geva, 2011 24</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PR</strong></td>
<td>Severe PR and at least one of the following:</td>
<td>Free PR</td>
<td>Severe PR and at least one of the following:</td>
<td>Moderate or severe PR (regurgitant fraction &gt;25%)</td>
</tr>
<tr>
<td><strong>RVEDVi</strong></td>
<td>Moderate to severe enlargement (IIa, B)</td>
<td>&gt;170mls/m2 or progressive enlargement (IIa, C)</td>
<td>&gt;160mls/m2 or progressive enlargement (IIa, C)</td>
<td>&gt;150 ml/m2 or Z-score &gt;4, or RV/LV end-diastolic volume ratio &gt;2</td>
</tr>
<tr>
<td><strong>RVESVi</strong></td>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
<td>&gt;80 ml/m2</td>
</tr>
<tr>
<td><strong>RV dysfunction</strong></td>
<td>Moderate or severe dysfunction (IIa, B)</td>
<td>Moderate or severe dysfunction (IIa, C)</td>
<td>Progressive RV systolic dysfunction (IIa, C)</td>
<td>RVEF&lt;47%</td>
</tr>
<tr>
<td><strong>Cardiopulmonary Exercise Test</strong></td>
<td>Not specified</td>
<td>Not specified</td>
<td>Decrease in objective exercise capacity (IIa, C)</td>
<td>Not specified</td>
</tr>
<tr>
<td><strong>Arrhythmias</strong></td>
<td>Symptomatic or sustained atrial and/or ventricular arrhythmias (IIa, B)</td>
<td>Atrial/ventricular arrhythmias (IIa, C)</td>
<td>Sustained atrial/ventricular (IIa, C)</td>
<td>Sustained tachyarrhythmia related to right heart volume load</td>
</tr>
<tr>
<td><strong>Tricuspid Regurgitation</strong></td>
<td>Moderate or severe (IIa, B)</td>
<td>“important TR” (IIa, C)</td>
<td>Progressive TR (≥moderate) (IIa, C)</td>
<td>≥ Moderate TR</td>
</tr>
</tbody>
</table>

PR, pulmonary regurgitation; RF, regurgitation fraction; RVEDVi, Right ventricular end diastolic volume indexed; RVESVi, right ventricular end systolic volume indexed; RV, right ventricle; RVEF, right ventricular ejection fraction; TR, tricuspid regurgitation.

*At the Toronto Congenital Cardiac Centre for Adults at the Toronto General Hospital we have employed the following algorithm since 2012 to guide surgical referral for the asymptomatic individual with severe PR, late after TOF repair:
1. Asymptomatic patients with no other risk factors – consider for PVR when RVEDVi exceeds 170 mL/m2
2. Asymptomatic individuals with one or more risk factors – consider for PVR when RVEDVi is 151-170 mL/m2. Risk factors include: QRSd > 180 msec, progressive increase in QRSd >2.5 msec/year, LVEF < 50%, RVEF < 30%, progressive RV enlargement or progressive ventricular dysfunction, objective evidence of decline in exercise capacity (no other cause found).