Tetralogy of Fallot
Latest data in risk stratification and replacement of pulmonic valve

Alexandra A Frogoudaki
Adult Congenital Heart Clinic
Second Cardiology Department
ATTIKON University Hospital
• No conflicts of interest
Blue baby syndrome

Described in 1888
all four features of the condition
Late complications after surgical Tetralogy of Fallot repair

Pulmonary regurgitation: Severity of PR and its deleterious long-term effects are augmented by co-existing distal PA stenoses or PAH (the latter is uncommon).
Residual RVOTO
RV dilation and dysfunction
Residual VSD
Aortic root dilation with aortic regurgitation: Aortic root dilation (progressive) is seen in 15% of adults late after repair and relates to both intrinsic abnormalities of the aorta (cystic medial necrosis) and increased flow
LV dysfunction
Atrial/ventricular tachycardia and SCD (SCD is reported in 1–6% of cases)
Endocarditis: Endocarditis is rare.

ESC GUIDELINES, Eur Heart J, August 2010
Factors that contribute to development of heart failure in the adult late after tetralogy of Fallot repair

<table>
<thead>
<tr>
<th>Factors associated with development of heart failure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Damage to myocardium</td>
<td>Late age at tetralogy of Fallot repair</td>
</tr>
<tr>
<td></td>
<td>Long-standing palliative shunts</td>
</tr>
<tr>
<td></td>
<td>Insufficient myocardial protection at the time of cardiopulmonary bypass</td>
</tr>
<tr>
<td></td>
<td>Multiple cardiac surgeries</td>
</tr>
<tr>
<td>Sequelae from surgical repair strategies</td>
<td>Chronic volume overload (pulmonary valve insufficiency +/- tricuspid valve insufficiency)</td>
</tr>
<tr>
<td></td>
<td>Chronic pressure overload (insufficient relief of pulmonary stenosis at subvalvar/valvar/supravalvar levels or at the level of the pulmonary arteries)</td>
</tr>
<tr>
<td></td>
<td>Patch across the right ventricular outflow tract (confers wall motion abnormalities, typically akinisis/dyskinesis, of varying magnitudes)</td>
</tr>
<tr>
<td></td>
<td>Patch to close ventricular septal defect (may disrupt integrity of tricuspid valve resulting in chronic tricuspid valve insufficiency or may be incomplete, thereby allowing for ongoing volume overload due to residual left-to-right shunting)</td>
</tr>
<tr>
<td>Electrical conduction abnormalities</td>
<td></td>
</tr>
<tr>
<td>Adverse ventricular-ventricular interactions</td>
<td>Intraventricular/interventricular dyssynchrony</td>
</tr>
<tr>
<td>Coronary artery abnormalities</td>
<td>Alterations in right ventricular size and function can result in left ventricular dysfunction</td>
</tr>
<tr>
<td></td>
<td>Abnormal coronary arrangements (congenital)</td>
</tr>
<tr>
<td></td>
<td>Atherosclerotic disease (acquired)</td>
</tr>
</tbody>
</table>

RM Wald et al  Trends Cardiovasc Med 2015
Risk Stratification

- Imaging
- Biomarkers
- Exercise capacity
- Arrhythmia monitoring
<table>
<thead>
<tr>
<th>Complexity of CHD</th>
<th>Type of CHD</th>
<th>Prevalence (in CHD population)</th>
<th>Atrial Arrhythmia</th>
<th>Ventricular Arrhythmia</th>
<th>Other Pacing Needs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple</td>
<td>Patent ductus arteriosus</td>
<td>6-8%</td>
<td>AT</td>
<td>AF</td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>Pulmonary stenosis</td>
<td>6-8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ventricular septal defect</td>
<td>30-32%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Secundum atrial septal defect</td>
<td>8-10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Aortic coarctation</td>
<td>5-7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anomalous pulmonary venous return</td>
<td>0.5-2.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atrioventricular septal defect</td>
<td>3-5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aortic stenosis</td>
<td>3-5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ebstein’s anomaly</td>
<td>0.5-1.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tetralogy of Fallot</td>
<td>8-10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primum atrial septal defect</td>
<td>2-3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Truncus arteriosus</td>
<td>1.5-2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmonary stenosis</td>
<td>2-2.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Double outlet right ventricle</td>
<td>1.5-2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D-transposition of the great arteries</td>
<td>6-7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L-transposition of the great arteries</td>
<td>1-2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypoplastic left heart syndrome</td>
<td>3-4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other (heterotaxy, other single ventricles)</td>
<td>7-10%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Arrhythmia Burden in Adults With Surgically Repaired Tetralogy of Fallot
A Multi-Institutional Study

556 patients
Multicenter study conducted by the Alliance for Adult Research in Congenital Cardiology
The majority of patients with repaired ToF will present intraatrial reentrant tachycardia or atrial fibrillation
The prevalence of VT reaches 30% at 50 years of age or more

Khairy, P. et al. Circulation 2010
Risk factors for tachycardia

Number of surgeries

LV diastolic function

Khairy, P. et al. Circulation 2010
Risk score for sudden cardiac death in ToF patients

Contemporary predictors of death and sustained ventricular tachycardia in patients with repaired tetralogy of Fallot enrolled in the INDICATOR cohort

Valente AM et al. Heart 2014
The Usefulness of Brain Natriuretic Peptide in Complex Congenital Heart Disease

Tetralogy of Fallot, BNP elevated and correlated significantly with right ventricular end-diastolic dimensions and severity of pulmonary valve regurgitation.

Systemic right ventricle, elevated BNP levels, positive correlations between BNP and right ventricular function

Univentricular heart, elevated BNP levels before completion of the Fontan circulation or when patients were symptomatic

Einthoven et al. J Am Coll Cardiol Sep 2012
Neurohormonal activation and its relation to outcomes late after repair of tetralogy of Fallot

Neurohormonal activation is present in adults with rTOF including asymptomatic patients. BNP level ≥15 pmol/L is associated with a fivefold increased risk of death. 90 patients mean FU 10 years

Heng EL et al Heart 2015
B-type natriuretic peptide: another brick in the wall towards better risk stratification in repaired tetralogy of Fallot

• Clinical significance of serial BNP measurements?
• BNP concentrations could be used to guide therapy?
• Future studies will have to assess the incremental value of adding natriuretic peptides to the already studied parameters and risk prediction scores.

Giannakoulas et al Heart 2015
Peak oxygen uptake, ventilatory efficiency and QRS-duration predict event free survival in patients late after surgical repair of tetralogy of Fallot

875 patients
mean FU 4.1±2.6 y
30 patients (3.4%) death/VT
225 patients (25.7%) events (admissions, interventions)

J. Müller et al Int J Cardiol Oct 2015
Implantable defibrillator

Khairy et al Can J Cardiol 2014
Pulmonary valve regurgitation late after surgical repair
Impact of more than moderate pulmonary regurgitation in exercise capacity

Carvalho et al Br Heart J 1992
Impact of more than moderate pulmonary regurgitation in arrhythmia and sudden cardiac death prevalence

Gatzoulis et al Lancet 2000
The Rationale for Pulmonary Valve Replacement Summary

- To maintain RV function
- To improve functional capacity and quality of life and
- To reduce overall heart size, neurohormonal activation and improve objective exercise capacity and, thus, potentially improve survival.
- In parallel/risk stratification for VT and SCD is paramount. Non-invasive and invasive tools (EP) should be utilized and an individualized management approach needs to be discussed with the patient and action be taken
- A combination of surgical PVR, this point in time with percutaneous PVR next time round, in conjunction with arrhythmia targeting intervention is likely for a significant number of patients
- Planning pregnancy may bring forward this interventional cycle
Tetralogy of Fallot and Pulmonary Valve Replacement: Timing and Techniques in the Asymptomatic Patient

<table>
<thead>
<tr>
<th>Study</th>
<th>Indications for PVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frig iola</td>
<td>Presence of significant PR (PR fraction ≥ 35% on MRI) with evidence of progressive RV dilatation and dysfunction</td>
</tr>
<tr>
<td>et al</td>
<td>RV/LV end-diastolic ratio ≥ 1.5 in symptomatic patients</td>
</tr>
<tr>
<td></td>
<td>RV/LV end-diastolic ratio ≥ 2 in asymptomatic patients</td>
</tr>
<tr>
<td></td>
<td>Reduced exercise capacity with or without documented arrhythmias</td>
</tr>
<tr>
<td>Geva</td>
<td>Moderate or severe PR (PR fraction ≥ 25% on MRI) and two or more of the following criteria:</td>
</tr>
<tr>
<td></td>
<td>RV end-diastolic volume index ≥ 160 mL/m² (Z score &gt; 5)</td>
</tr>
<tr>
<td></td>
<td>RV end-systolic volume index ≥ 70 mL/m²</td>
</tr>
<tr>
<td></td>
<td>LV end-diastolic volume index ≥ 65 mL/m²</td>
</tr>
<tr>
<td></td>
<td>RV ejection fraction ≤ 45%</td>
</tr>
<tr>
<td></td>
<td>RV outflow tract aneurysm</td>
</tr>
<tr>
<td></td>
<td>Clinical criteria: exercise intolerance, symptoms and signs of heart failure, cardiac medications, syncope, sustained ventricular tachycardia</td>
</tr>
<tr>
<td></td>
<td>Presence of other haemodynamically significant lesions</td>
</tr>
<tr>
<td></td>
<td>Patients who underwent TOF repair at age ≥ 3 years, PVR may be indicated sooner and in the presence of less severe RV dilatation and dysfunction due to higher risk of adverse clinical outcomes</td>
</tr>
</tbody>
</table>
Preoperative thresholds for pulmonary valve replacement in patients with repaired tetralogy of Fallot using magnetic resonance imaging

- 71 TOF pts; prospective; multi-centre; MRI (baseline & 9 months post PVR)
- RV volumes decreased (mean of 28%)
- RVEF did no change (42 vs 43%)
- Concomitant RVOT aneurysm reduction > 25% greater RV reduction
- Higher pre-op RV volumes associated with higher post-op RV volumes; no thresholds were found above which RV volumes did not decrease after PVR
- Receiver operator characteristic analysis: cut off value of <160 ml/m² for normalization of RVEDV and <82 ml/m² for RVESV

Mulder et al Circulation 2007
Outcomes of pulmonary valve replacement in 170 patients with chronic pulmonary regurgitation after relief of right ventricular outflow tract obstruction: implications for optimal timing of pulmonary valve replacement.

- Median follow-up duration was 5.9 years
- Overall and event-free survival at 10 years was 98% and 70%
- Cutoff values for optimal outcome (normalized RV volumes and function) were 163 ml/m(2) for RV EDVI and 80 ml/m(2) for RV ESVI.
- Higher pre-operative RV ESVI was identified as a sole independent risk factor for suboptimal outcome.

Lee C et al J Am Coll Cardiol Sep 2012
Right Ventricular Remodeling After Pulmonary Valve Replacement: Early Gains, Late Losses

Palliative nature of PVR and the importance of continued surveillance

Individualised Prediction of Pulmonary Homograft durability in Tetralogy of Fallot

153 ToF patients

- PS ≥20 mm Hg
- postoperative PR ≥ grade 1
- age at PVR <18 years

Independently predicted homograft dysfunction

Bokma JP et al. Heart 2015
Risk Factors for Prosthetic Pulmonary Valve Failure in Patients With Congenital Heart Disease

146 interventions of PVR in 114 patients with CHD

102 in ToF

Oliver JM et al Am J Cardiol 2015
Transcatheter Valve Implantation

Fraisse A et al Clin Research 2014

<table>
<thead>
<tr>
<th></th>
<th>Pre-procedure (n = 64)</th>
<th>Post-procedure (n = 64)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV systolic pressure (mmHg)</td>
<td>74 (25–130)</td>
<td>42 (20–67)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Peak-to-peak systolic RV-PA gradient (mmHg)</td>
<td>50 (5–115)</td>
<td>14 (10–33)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RV/aorta pressure ratio</td>
<td>0.82 (0.19–1.44)</td>
<td>0.41 (0.17–0.72)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Data are mean (range). PA: pulmonary artery; RV: right ventricle.
Percutaneous pulmonary valve endocarditis: Incidence, prevention and management

485 right ventricle-to-pulmonary artery conduit implantations (surgical group)
93 percutaneous Melody valves implantations (PPVI group)
5.98 ± 2.11% (surgical group) and 8.6 ± 5.7% (PPVI group) ($P = 0.34$)
Male sex, previous IE, high number of stents and altered RVOT anatomy were identified as important risk factors
overall mortality rate of 13%

M. Patel et al Arch Cardiovasc Dis 2014
Is there a role for mechanical valve prostheses in pulmonary valve replacement late after tetralogy of Fallot repair?

- More research is required to accurately compare the haemodynamic properties of mechanical valves in the pulmonary position compared with other valves.
- Additionally, a more consistent follow-up of these patients in terms of echocardiographic, valve-related and warfarin-related complications is needed.

Meta analysis

145 patients with mechanical pulmonary valve prosthesis

Valve thrombosis 0%-33%

Bleeding 0%-5.6%

Reoperation 0% -55%

J.R. Abbas and J.A. Hoschtitzky
Interactive CardioVascular and Thoracic Surgery  2014
Recent development in pulmonary valve replacement after tetralogy of Fallot repair: the emergence of hybrid approaches

Minimizes procedure time, risks and complications and greatly improve the quality of recovery

Suleiman et al Front in Surg 2015
Ventricular Arrhythmia Risk Stratification in Patients With Tetralogy of Fallot at the Time of Pulmonary Valve Replacement

205 patients

Surgical right ventricular outflow tract cryoablation was performed in 22 patients (10.7%)

Surgical cryoablation does not seem to increase arrhythmic events and may be protective

Rotes et al Circ Arrhythm Electrophysiol 2015
Take Home Messages

• There should be close surveillance after tetralogy of Fallot repair
• <Classic> risk factors as QRS duration, left ventricular ejection fraction and arrhythmia as well as <new> risk factors as biomarkers and exercise capacity may predict outcome
• One or more reinterventions may be necessary in tetralogy of Fallot adult patients for pulmonary regurgitation and is matter of research type of valve and intervention