Physiologic and Phenotypic Characteristics of Late Survivors of Tetralogy of Fallot Repair Who are Free from Pulmonary Valve Replacement

Running title: Frigiola et al.; Freedom from valve replacement post Fallot repair

Alessandra Frigiola, MD, MDres\textsuperscript{1,2}; Marina Hughes, DPhil, FRACP\textsuperscript{1}; Mark Turner, ACoRN\textsuperscript{3}; Andrew Taylor, MD, MRCP, FRCR\textsuperscript{1,2}; Jan Marek, MD, PhD, FESC\textsuperscript{1}; Alessandro Giardini, MD\textsuperscript{1}; Tain-Yen Hsia, MD\textsuperscript{1}; Kate Bull, MRCP\textsuperscript{1}

\textsuperscript{1}Great Ormond Street Hospital for Children, NHS Trust, London; \textsuperscript{2}University College of London, Institute of Cardiovascular Sciences, London; \textsuperscript{3}Adult Congenital Heart Disease Research Network, United Kingdom

Address for Correspondence:
Alessandra Frigiola, MD, MDres
Great Ormond Street Hospital for Children, NHS Trust
Great Ormond Street
WC1N 3JH, London, United Kingdom
Tel: +44 7747082265
Fax: +44 2078138262
E-mail: alessandra.frigiola@gmail.com

Journal Subject Code: Cardiovascular (CV) surgery:[41] Pediatric and congenital heart disease, including cardiovascular surgery
Abstract:

Background—Pulmonary valve replacement (PVR) after repair of tetralogy of Fallot (ToF) is commonly required and is burdensome. Detailed anatomic and physiologic characteristics of survivors free from late PVR and with good exercise capacity are not well described in a literature focusing on the indications for PVR.

Methods and Results—In 1085 consecutive patients receiving standard ToF repair in a single institution 1964-2009, survival and freedom from PVR were tracked. Of 152 total deaths, 100 occurred within the first postoperative year. Surviving patients between 10-50 years of age had an annual risk of death 4 (CL 2.8-5.4) times that of normal contemporaries. 189 patients have undergone secondary PVR to date, at mean age of 20±13 years (36% of those alive age 40). A random sample of 50 survivors (aged 4-57 years) free from PVR, underwent cardiovascular magnetic resonance, echocardiography and exercise testing. These patients had mildly dilated right ventricles (RVEDV=101±26 ml/m²) with good systolic function (RVEF=59±7%). Most had exercise capacity within normal range (z peak VO₂=-0.91±1.3; z VE/VCO₂ =0.20±1.5). In patients who are > 35 years with normal exercise capacity, there was mild residual RV outflow tract obstruction (mean gradient 24±13mmHg), pulmonary annulus diameters <+0.5z and unobstructed branch pulmonary arteries.

Conclusions—An important proportion of patients require PVR late after ToF repair. Patients surviving to age 35 without PVR and with a normal exercise capacity may have had a “definitive” primary repair; their RV outflow tracts are characterized by mild residual obstruction and pulmonary annulus diameter <0.5z.

Key words: tetralogy of Fallot, cardiac surgery, magnetic resonance imaging, exercise capacity
Introduction

Tetralogy of Fallot (ToF) was one of the first complex congenital heart diseases for which surgical treatment offered a major impact on the natural history of the disease\textsuperscript{1,2}. Early mortality was initially high but fell; partly with the work of Kirklin and others\textsuperscript{3}, who documented that severe residual right ventricular hypertension was poorly tolerated, while transannular enlargement of the hypoplastic pulmonary annulus and its resultant obligatory pulmonary regurgitation seemed to have little short or medium term disadvantage. Optimal strategies for ToF repair in childhood are still debated but many surgeons continue to use nomograms of pulmonary annulus diameter to support decisions about the timing of surgery and the need for transannular patching\textsuperscript{4}.

While the valve-sparing transatrial/transpulmonary surgical approach has gained popularity, an important proportion of patients continue to undergo transannular repair. Also, some with very poor native valves are necessarily left with severely defective pulmonary valvulation after repair despite an intact annulus. Thus many patients are committed to a new modified history of chronic pulmonary regurgitation and right ventricular volume overload\textsuperscript{5}. As a consequence, pulmonary valve replacement (PVR) has become the most common operation undertaken for adults with congenital heart disease\textsuperscript{6} and the optimal management of patients who may have clinical or physiological indications for PVR is widely researched and debated.

By contrast, in this paper we focus on characterising survivors of ToF repair who are stable without PVR in the hope of contributing to questions that still remain about the outcomes of the primary repair.

With the resource of a complete consecutive cohort of 1085 patients from a single institution, that dates from 1964, our primary aim was to describe the decreasing proportion over
time, of survivors who were free from secondary pulmonary valve implantation. Secondly, we closely examined 50 patients, aged 4-57 years, chosen at random from those who were stable without PVR, to provide balance to the literature on late Fallot physiology, which is largely derived from patients who are being actively considered for PVR. Finally we focused on patients aged over 35 years who were free from secondary PVR, and whose exercise capacity was within the normal range, in the hope of defining the postoperative morphology and physiology that suggests the primary repair was “definitive”.

**Methods**

We created a complete consecutive list of all patients undergoing repair of uncomplicated ToF at Great Ormond Street Hospital (GOSH) from February 1964 to January 2009. We excluded patients with absent pulmonary valve, pulmonary atresia or atrio-ventricular septal defect, those receiving an extra-cardiac conduit at their first repair and patients from outside the UK whose follow-up we do not manage. Early postoperative deaths and the dates of any childhood PVRs were documented from operation notes. Consistently since 1996, all UK patients have a unique identifier, their National Health Service (NHS) number, whose functionality links to national death certification records; dates of death are registered in the NHS record when death occurs. Using batch tracing and manual searches and the known dates of birth and childhood surnames of patients discharged or ‘lost’ before 1996, we attempted to establish the NHS numbers for the whole cohort. At age 16, patients are currently discharged from our paediatric centre to the care of their nearest Adult Congenital Heart Disease (ACHD) service. The Adult Congenital heart disease Research Network (ACoRN) represents each UK specialist ACHD center. Collaborators from ACoRN scanned their local databases for the listed patients to ascertain whether they were
under active review, or had died under their care, or had undergone PVR. Patients who were recorded as relocating abroad or whose NHS numbers we could not match were censored on the date last seen alive, to avoid any assumptions about their current status. The common closing date for data retrieval was January 2011. Patients who had corresponding NHS numbers but were not seen by ACHD centres were recorded as alive but assumed not to have had PVR, because this operation is only undertaken in specialist hospitals. The local Research Ethics Committee approved the project; this included the use of retrospective patient data and NHS number information without patient consent. For the 50 patients recruited prospectively into the physiological studies, informed consent was obtained.

Statement of Responsibility

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Survival and proportions free from PVR

Kaplan-Meier methodology was used to describe the survival. To establish the excess hazard in the age-frame 10-50 related to having survived Fallot repair for at least 1 year, we compared the risk of death in 5-year intervals for the Fallot cohort compared to deaths in the normal population sourced from the UK interim life tables for 1996, weighting the life table to correspond to the gender proportion in Fallot births. A proportional hazards model was used to explore the effect of operative era (decade of surgery) on late death; only patients alive one year postoperatively entered the analysis, and subsequent survival duration originated on that date. We used Life Table methodology to generate a graphic showing the changing proportions over time of patients in 3 mutually exclusive states: ‘dead without PVR’, ‘alive with no PVR’, ‘had PVR’. SPSS version 18 was used.
Physiology of patients free from PVR

Using a random number generator, 10 patients were chosen from each surgical decade (1960s to 2000s) from the list of those who were at least one year from surgery and had not had subsequent PVR. These patients were invited to return as volunteers to ‘represent’ patients without PVR. This sample size was based on our previous study; 10 patients in each of 5 decade-groups would be sufficient to detect a gradient of 0.14/decade in RV/LV volume ratio or 1.68/decade in VE/VCO₂ with 80% power (2-sided with 5% level of significance). We established from their operation notes whether or not the patients had received a transannular patch. Each patient underwent detailed cardiac MRI, echocardiography, ECG and cardiopulmonary exercise testing, and measurement of serum BNP levels as follows.

Cardiovascular Magnetic Resonance Imaging

Cardiovascular magnetic resonance (CMR) was performed using a 1.5 T MR scanner (Avanto, Siemens Medical Systems), using techniques previously described. All volume and flow measurements were indexed to body surface area (BSA) and compared with published normal values. For the 5 children aged less than 8, the regression equations generated using normal subjects aged 8-17 were used. Gadolinium contrast-enhanced MR angiography and 3D steady-state free precession imaging was used to obtain isotropic 3D images and delineate the pulmonary artery anatomy. The diameters of the hinge-points of the pulmonary valve were measured in diastole, using two 2D outflow tract cine images, acquired in the RV outflow tract in orthogonal planes. The two cross-sectional diameters were averaged.

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) was performed by patients older than 9 years, on an electronically-braked bicycle ergometer (Ergoline 900) with respiratory gas exchange analysis.
We used a ramp protocol as previously described\(^\text{10}\). Peak oxygen uptake (peak VO\(_2\)), VO\(_2\) at the anaerobic threshold and ventilatory response to carbon dioxide production (VE/VCO\(_2\)) were derived from respiratory gas analysis during maximal exercise testing; VE/VCO\(_2\) was measured as slope for the whole exercise.

**Echocardiography**

Standard Doppler echocardiography (ECHO) was performed using a VIVID 7 machine (GE Medical Systems, Milwaukee, USA) equipped with a multi-frequency transducer (3.5 and 5 MHz) as previously described\(^\text{10}\). From the same apical view, right and left atrial areas and tricuspid annulus diameters were measured and indexed for BSA\(^\text{14}\). Tricuspid annular plane systolic excursion (TAPSE) was obtained from M-mode interrogation of the lateral aspect of the tricuspid valve. Right and left atrial filling pressures were obtained from the ratio of the trans-tricuspid and trans-mitral early diastolic velocities and early myocardial velocities measured at the lateral atrio-ventricular valve annulus\(^\text{15, 16}\). Doppler tracing was taken during the patient’s breath hold. Peak velocity gradient across the RVOT was calculated from the maximum velocity obtained from the continuous wave Doppler signal\(^\text{17}\). The percentage collapse of the inferior vena cava diameter was measured from sagittal subcostal views during forced inspiration\(^\text{18}\).

Images were digitally stored for offline analysis with Echopac software (GE Vingmed, Horthen, Norway). All measurements were averaged from 3 consecutive cardiac cycles.

The CMR\(^\text{11, 12}\), CPET\(^\text{19-21}\) and Echo\(^\text{22-26}\) parameters were rendered, where applicable, as z-scores so that data could be summarized across the wide age range. Comparisons between groups are made with t-tests and hypotheses are rejected at \(p<0.05\).

**‘Definitive repairs’**

Finally we hypothesized that patients who have reached age 35 without PVR, and who have
objectively measured exercise tolerance within the normal range (peak VO2 better than -2z) may
never need surgical RVOT revision. However, they may yet experience myocardial or
electrophysiological complications of their underlying condition or its treatment. To characterise
the phenotype of repaired hearts that meet these stringent criteria of late function, we prepared
volume-rendered CMR images of the 14/48 patients who fulfilled these criteria and underwent
MRI scan.

Results

From February 1964 to January 2009, 1085 UK patients (58% males) had repair of ToF at
GOSH, at a mean age of 3.5±3.6 years (range 3 days to 18 years). Of 1085, we have either a
known date of death or an NHS number indicating current survival status in all but 35; females
represent 60% of the 35 patients we have failed to track suggesting that marital name changes
may undermine tracing. Figure 1 summarizes the current status of the whole cohort.

One hundred and fifty two patients are known to have died to date. One hundred died
within one year of repair (24 of 106 patients (23%) operated in the 1960s, compared to 6 of 246
(2%) operated in the 2000s). Given one-year postoperative survival, subsequent survival was not
demonstrably related to era (decade of surgery, p=0.57) or to age at repair (p=0.84). Twenty-six
of the 52 (50%) of the deaths that have occurred beyond the first postoperative year appear not to
have happened while the patient was under specialist care, making any summary of the causes of
late death for this cohort unreliable. Across the age range 10 – 50 years, patients face an
estimated 4-fold (C.L 2.8 - 5.4) increased annual probability of death compared to
contemporaries of the same age, drawn from the normal population.

Pulmonary valve replacement has been performed to date in 189 patients, mean age
20±13 years, all of whom are under specialist care. There were 7 deaths within 3 months of these operations though only 2 occurred when the operations had been done in an elective rather than an urgent context. 140 patients underwent their first PVR at age over 10 years and thus received ‘adult sized’ valve at the time of reoperation. To date, 10 of these have needed re-replacement at a median interval of 9 years after first PVR. Figure 2 shows the changing proportion over time of patients in 3 mutually exclusive states: ‘dead, no PVR’, ‘alive, no PVR’ and ‘had PVR’.

**Physiology of patients without PVR**

Characteristics of the 50 patients (10 from each decade) selected at random from the list of patients who had not received PVR is shown in Table 1. Two patients aged 27 and 50 years underwent elective PVR within 6 months of these investigations.

**CMR results**

CMR was performed in all but 2 volunteers; one patient had a pacemaker (male age 53), and another scan was terminated because the patient felt claustrophobic (female age 36). Findings are summarized in Table 2, which displays mean values, indexed where appropriate and Figure 3 shows individual results as z scores to summarize findings over the wide range of current ages. Overall, RV end-diastolic (EDV) and end-systolic (ESV) volumes were mildly larger than normal (z=1.8±2.3 and 1.8±3.0 respectively, p<0.0001), whereas LV volumes and biventricular systolic function were predominantly within normal range. A moderate degree of pulmonary regurgitation was common. For the group as a whole, the degree of pulmonary regurgitation was positively associated with pulmonary annulus diameter estimated at CMR (p<0.001, r=0.48) and those repaired using a transannular patch had significantly more pulmonary regurgitation than those without (31±14%, vs. 16 ± 13% p< 0.005).

**Exercise testing**
Of the volunteers tested (all older than age 8), only 8/44 had reduced objectively measured exercise capacity, when compared to normal subjects (Table 2, Figure 3).

Echocardiographic results

Throughout the age range, there was significant dilatation (>2z compared to normal values) of right atrial (RA) areas and correspondingly of the indexed tricuspid valve (TV) annulus diameters. Older patients exhibit the highest values for these indices but because the patients documented by this ‘cross sectional’ process represent a smaller proportion of the whole group as time from surgery increases, we cannot infer that these parameters increase longitudinally with age.

For the group as a whole, velocity across the RV out-flow tract was slightly increased (mean 2.2±0.6 m/s). RV tricuspid annular plane systolic excursion (TAPSE), a simple measure of RV ejection fraction was globally reduced, although the mean for the group is still within 2SD (z=-1.8±1.4). Tricuspid valve regurgitation was absent or mild in most patients, moderate in 1, severe in 2. The indicators of right and left ventricular filling pressures were within normal limits (TV E/e’= 0.9±0.5; MV E/e’= 0.9±0.4). IVC collapse was reduced compared to normal (mean 81±23%).

Phenotype of primary “definitive” repair

Of the 17 patients aged over 35 who were free from late PVR, 14 exercised within the normal range. Figure 4 shows 3D volume-rendered models from MR angiography, illustrating the morphology of the RV out-flow tracts of 12 of these 14 (2 patients did not undergo MRI). Three of the 14 had undergone transannular patching at the time of their primary repair and 6 others had valvotomy or valvectomy. All 14 were free from either significant outflow tract aneurysm or significant branch pulmonary artery stenosis. All patients but one had some residual RVOT
obstruction (group mean Doppler-estimated gradient 24mmHg (range 6-50mmHg (SD 13)). All patients but one had pulmonary regurgitation, but the degree of regurgitation was mild or moderate (regurgitant fraction group mean 18%, range 3-39% (SD 12). Only one of the patients aged over 35 who exercised normally had an estimated pulmonary valve diameter > +0.5z; this patient was the individual with the worst pulmonary regurgitation 39%) Figure 5.

Discussion

This study confirms that patients following tetralogy of Fallot repair have good long-term survival. However after 40 years, 36% of survivors have undergone PVR, and the proportion is even higher (58%) in those under active specialist follow up27. To date there is no ideal substitute pulmonary valve therefore many patients having PVR can expect to be burdened by further procedures28-30. Each re-intervention carries a risk comparable to the mortality we would currently quote for the primary repair, so aggregated over a lifetime the consequences of committing a patient at the time of their initial operation to later PVR is significant. Minimizing the burden of late PVR for patients requires addressing two uncertainties. Firstly how late-adult outcomes should impact decisions made at the time of primary repair and secondly resolving issues about the indications for late PVR.

A rigorous answer to either question is constrained by the enormous problems for any study-design that are presented by the interval – often of decades - between the intervention (here Tetralogy repair) and an outcome (perhaps PVR). Our unusual study design contributes to the common surgical decision about how best to leave an imperfect RV outflow tract at the end of a primary repair. In essence, morbidity related to early right ventricular hypertension is associated with leaving “too small” a pulmonary annulus3,4, and late problems of right
ventricular dilatation may be related to leaving one that is “too large”. By adding the perspective of data from late outcomes that have been exceptionally successful to what is already known about how to avoid early problems, we hoped to offer some tentative guidance about the size of annulus with or without transannular patch that may be optimal from a whole-life perspective.

That an element of residual RV outflow obstruction may protect against late RV dilatation is suggested by Yoo et colleagues who used CMR to assess 190 patients with repaired ToF and found that patients with residual RVOT obstruction (mean gradient 34.2±10.0 mmHg) had less RV volume overload and no medium term deterioration of RV function compared to those with predominant pulmonary regurgitation. Van der Hulst and colleagues also demonstrated that mild residual pulmonary stenosis reduced the need for PVR in 171 patients with ToF repair over a follow-up of 24 years. None of the patients in our own institution who required PVR for RVOT dysfunction 2004-2007 had any residual RVOTO (mean gradient 16±1.4mmHg) and all had dilated RV outflow tracts.

However, the surgical judgement is difficult. Right ventricular outflow tract gradients can be measured after discontinuation of bypass but are known to shift postoperatively and the degree of late pulmonary regurgitation is hard to gauge unless the valve is unusually excellent. In practice, surgeons commonly use nomograms intra-operatively to guide decisions about when to insert a transannular patch; the absolute values charted in these nomograms describe pulmonary annulus diameters of normal hearts guarded by competent pulmonary valves. Guidelines vary, but one recent series documents that leaving an annulus smaller than -1.3z is associated with a 25% chance of a late gradient of more than 30mmHg and the authors suggest that a transannular patch be used to enlarge these outflow tracts if the annulus is “significantly” smaller than this. But how large should the patch be? Given what is known about the protective
value of some residual obstruction when the valve is also regurgitant, it seems likely that the ideal pulmonary annulus after Fallot repair will be smaller than +2.0z. If we could be confident that the pulmonary valve annulus did not grow or shrink disproportionately with somatic growth, it would be tempting to note that virtually all of our patients aged over 35 with normal exercise capacity and no PVR have some degree of residual RVOTO (no more than mild), and have current pulmonary valve z scores <+0.5, suggesting that pulmonary annulus with or without transannular patching should be no bigger than this at the end of the repair. Unfortunately, the trajectory of pulmonary annulus growth under the various permutations of primary repair is poorly documented at present and our data about pulmonary valve annulus at the time of our patients’ repairs is patchy, so these recommendations are necessarily provisional.

The debate about indications for secondary PVR requires longitudinal data and our cross sectional study cannot contribute directly to this. However, much of the available literature on the postoperative physiology of ToF focuses on patients investigated in the context of consideration of PVR. Patients in our dataset were formally selected, at random, to ‘represent’ those who remain free from PVR. Our review confirms that most have only mildly dilated right ventricles, with good systolic function. These results are mirrored by a general clinical wellbeing, (median NYHA class I), and normal exercise capacity for the majority of patients. On echocardiography however, RV TAPSE was globally reduced, although still within 2SD (z=-1.8±1.4), suggesting that this echocardiographic parameter might be a sensitive marker of mild, sub-clinical cardiac dysfunction. Our data could help to power further the formal observational or randomised studies that will be needed to clarify the indications for PVR.

Limitations

Data linkage has been possible for all but 35 of our 1085 patients; the proportions of these 35
patients who may have died, moved abroad, changed their names or whose original data was incorrect is unknown and we have censored them when last seen alive to avoid introducing bias in estimates we provide. The cardiac status of the patients not under ACHD follow up may be better, worse or similar to those who are, though we have no particular indication that their original loss to follow up was informative in this respect. The reasons for loss to follow up and its impact are addressed elsewhere. Also, patients with the worst anatomy may be under-represented in the earliest surgical era as some may not have survived to or through open-heart repair, despite palliation. Further, Awori et al have reflected on the pitfalls related to the variety of benchmarks for estimating pulmonary valve z scores; we have chosen to use echo derived parameters though others have argued for using normal ranges derived from autopsy or transplant normal ranges.

Conclusions
Though patients with repaired ToF have good long-term survival, a high proportion of patients require re-interventions (PVR) at a relatively young age. A significant number of patients are free from re-interventions, have preserved systolic function and normal exercise capacity up to 45 years following their initial repair. These patients, whose initial repair has proved long lasting, have specific anatomical and functional characteristics that may reflect both an ideal anatomical substrate and optimal surgical therapy.

Our focus on patients who have avoided late PVR after ToF repair aimed to contribute late outcome data that might influence decisions made early in a current patient’s management. As is common in paediatric cardiac surgical practice, important clinical decisions may have to be made using a combination of data, inference and conjecture that is less than ideal. However, until
we know more about annulus growth, it may be prudent to suggest that the ideal pulmonary
annulus diameter, with or without a transannular patch after Fallot repair should be between -1.3
and +0.5z.

**Funding Sources:** This project was funded by the Great Ormond Street Hospital Children’s’
Charity.

**Conflict of Interest Disclosures:** None.

**References:**

1. Lillehei CW, Cohen M, Warden HE, Read RC, Aust JB, Dewall RA, Varco RL. Direct vision
intracardiac surgical correction of the tetralogy of Fallot, pentalogy of Fallot, and pulmonary

2. Castaneda AR, Freed MD, Williams RG, Norwood WI. Repair of tetralogy of Fallot in infancy.


Sluymans T, Robert A, Rubay J. Tetralogy of Fallot: transannular and right ventricular patching

6. NICOR: National Institute for Cardiovascular Outcomes Research – Congenital Heart Disease
Website. 2012.
Document?Benchmark

7. Kaplan, E L; Meier, P: Nonparametric estimation from incomplete observations. *J Amer Statist


Table 1. Clinical characteristics of 50 patients divided by surgical decade.

<table>
<thead>
<tr>
<th>Decade of operation</th>
<th>1960s n=10</th>
<th>1970s n=10</th>
<th>1980s n=10</th>
<th>1990s n=10</th>
<th>2000s n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>6/4</td>
<td>4/6</td>
<td>5/5</td>
<td>7/3</td>
<td>5/5</td>
</tr>
<tr>
<td>Age at operation (years)</td>
<td>9.7 ± 2.3</td>
<td>4.5 ± 3.4</td>
<td>2.0 ± 1.2</td>
<td>1.5 ± 1.1</td>
<td>0.7 ± 0.3</td>
</tr>
<tr>
<td>Age at Study (years)</td>
<td>52.5 ± 3.3</td>
<td>38.6 ± 5.2</td>
<td>27.9 ± 4.0</td>
<td>17.3 ± 4.1</td>
<td>7.7 ± 2.2</td>
</tr>
<tr>
<td>Trans-atrial-transpulmonary approach</td>
<td>0/10</td>
<td>0/10</td>
<td>0/10</td>
<td>6/4</td>
<td>7/3</td>
</tr>
<tr>
<td>Transannular patch (yes/no)</td>
<td>1/9</td>
<td>3/7</td>
<td>3/7</td>
<td>2/8</td>
<td>7/3</td>
</tr>
<tr>
<td>Previous palliation</td>
<td>L and/or R BT shunt</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Waterston shunt</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NYHA class</td>
<td>I (9), II (1) *</td>
<td>I (6), II (2), III (2)</td>
<td>I (9), III (1) *</td>
<td>I (8), II (2)</td>
<td>I (10)</td>
</tr>
</tbody>
</table>

* One 50 year old and one 27 year old underwent a PVR within 6 months of the study.

Table 2. For patients (age 4-58 years) selected at random from those without PVR. MRI (N=48), exercise parameters (N=44) and echocardiographic parameters (N=50).

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>78±14</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>132±24</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>171±130</td>
</tr>
<tr>
<td>RV EDV (mL/BSA)</td>
<td>101±26</td>
</tr>
<tr>
<td>RV ESV (mL/BSA)</td>
<td>42±16</td>
</tr>
<tr>
<td>RV EF (%)</td>
<td>59±7</td>
</tr>
<tr>
<td>LV EDV (mL/BSA)</td>
<td>73±16</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>64±6</td>
</tr>
<tr>
<td>PR (%)</td>
<td>21±15</td>
</tr>
<tr>
<td>Peak VO₂ (ml/kg/min)</td>
<td>27±8</td>
</tr>
<tr>
<td>VE/VCO₂ slope</td>
<td>28±5</td>
</tr>
<tr>
<td>IVC collapse (%)</td>
<td>81±23</td>
</tr>
<tr>
<td>RVOT velocity (m/s)</td>
<td>2.2±0.6</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>16.9±2.8</td>
</tr>
<tr>
<td>TV E/e’</td>
<td>0.9±0.5</td>
</tr>
<tr>
<td>MV E/e’</td>
<td>0.9±0.4</td>
</tr>
</tbody>
</table>

EDV= end-diastolic volume; ESV= end-systolic volume; EF= ejection fraction; PR= pulmonary regurgitant fraction; IVC= inferior vena cava; RVOT= right ventricular out-flow tract; TAPSE= tricuspid annular plane systolic excursion; TV= tricuspid valve; MV= mitral valve.
Figure Legends:

Figure 1. Flow chart describing outcomes for whole cohort.

Figure 2. This illustrates the changing proportion over time between 0 and 40 years after repair in which patients from the whole cohort are in 3 exhaustive and mutually exclusive states: ‘dead without PVR’, ‘alive without PVR’ and ‘had PVR’. The area above the upper line reflects those patients who died postoperatively without ever having PVR; there are early deaths but some continuing attrition. The area below the lower line reflects the increasing proportion of patients over time since surgery that have had PVR. The area between the lines reflects the decreasing proportion over time of patients alive without PVR. It is from this middle group that the random 10 patients from each decade were sampled.

Figure 3. Summary of parameters for randomly selected patients free of secondary PVR. Shaded areas correspond to normal range by age, displayed as $z \pm 2$. Two patients aged 28 and 51 subsequently underwent PVR. RVEDVz: right ventricular end-diastolic volume z-score; LVEF: left ventricular ejection fraction (%); PR: pulmonary regurgitant fraction (%); RVOTvel: right ventricular out-flow tract velocity (m/s); RA areaz: right atrial area z-score; TV diaz: tricuspid valve diameter z-score; PV diaz: pulmonary valve diameter z-score.

Figure 4. This graphic shows 3D volume-rendered images, generated from MR angiographic data, of the repaired RV outflow tract for 12 of the 14 patients who are aged 35 years, with normal exercise capacity. (2 patients in this category did not undergo MRI). These outflow
tracts share morphological traits, including mild-moderate obstruction, minimal RV outflow tract aneurysm, mild or moderate pulmonary valve regurgitation and unobstructed branch pulmonary arteries. The labelled flags indicate the level of RV outflow tract obstruction, if present (S-I = subinfundibular, I = infundibular, V = valvar, SV = supravalvar.) The grey arrows indicate the four patients with more than mild pulmonary valve regurgitation.

Figure 5 shows the relationship of pulmonary regurgitation (%) to pulmonary valve (pv) diameter-z. Highlighted are the individuals who are over 35 and whose CPET are within normal limits.
Figure 1
Figure 2

Proportion

Dead no PVR

Alive no PVR

Had PVR

Years since repair
Figure 3
Figure 5
Physiologic and Phenotypic Characteristics of Late Survivors of Tetralogy of Fallot Repair Who Are Free From Pulmonary Valve Replacement
Alessandra Frigiola, Marina Hughes, Mark S. Turner, Andrew M. Taylor, Jan Marek, Alessandro Giardini, Tain-Yen Hsia and Kate Bull

Circulation. published online September 24, 2013;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2013/09/26/CIRCULATIONAHA.113.001600

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/