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## Indications for Pulmonary Valve Replacement in Repaired Tetralogy of Fallot: The Quest Continues

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Until Blalock and Taussig developed the first palliative systemic-to-pulmonary shunt operation in 1945,<sup>1</sup> tetralogy of Fallot (TOF) was a nearly uniformly lethal congenital cardiac anomaly. In the five decades since Lillehei and his colleagues at the University of Minnesota reported the first successful intracardiac repair in 1955, early mortality has decreased markedly from 50% to less than 2%.<sup>2–4</sup> In the modern surgical era, most infants with TOF survive the initial surgical repair and reach adulthood. More recently, the excellent results in the pediatric age group have led the field to shift its attention to late sequelae of repaired TOF in the rapidly growing population of adult patients, including the increasing rates of morbidity and mortality.

Despite many advances in surgical repair during the past 6 decades, the majority of TOF patients continue to suffer from residual hemodynamic and electrophysiologic abnormalities.<sup>5, 6</sup> To effectively relieve the obstructed right ventricular outflow tract (RVOT), the surgeon must often disrupt the integrity of the pulmonary valve, resulting in pulmonary regurgitation (PR). The ensuing chronic right ventricular (RV) volume overload and akinesis or dyskinesis of the RVOT wall, along with conduction delay from the nearly universal right bundle branch block, initiate a cascade of pathophysiologic abnormalities that lead to RV dilatation and, ultimately, dysfunction.<sup>7</sup> Left ventricular (LV) dysfunction, arrhythmias, exercise intolerance, heart failure symptoms, and death may follow.<sup>8</sup> Residual intracardiac shunts, tricuspid regurgitation, RVOT and/or pulmonary artery stenosis, impaired diastolic properties, atrial enlargement, RV hypertension, intra- and interventricular dyssynchrony, and diffuse myocardial fibrosis are some of the factors that might accelerate the adverse cardiac remodeling and lead to worse clinical outcomes. Indeed, the adverse remodeling that leads to electromechanical cardiomyopathy manifests in increasing rates of morbidity and mortality beginning during the 3<sup>rd</sup> decade of life.<sup>9</sup>

Pulmonary valve replacement (PVR) is increasingly utilized to treat the chronic volume overload from PR. The procedure can be performed using a transcatheter technique or surgically, utilizing one of the many available bioprosthetic valves. The procedural mortality is low, usually under 1%, but not negligible.<sup>7</sup> Importantly, the functional integrity of all

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available bioprosthetic valves deteriorates over time, typically requiring repeat valve replacement within 10 years. The early results of PVR have been well described by several groups, painting a consistent picture characterized by resolution or marked reduction of PR, 30 – 40% reduction in RV end-diastolic and end-systolic volumes, unchanged RV ejection fraction, slightly increased LV size with unchanged ejection fraction, decrease in RV systolic pressure in those with pre-procedural RVOT obstruction, and consistent improvement in New York Heart Association functional class without a clear change in objective exercise parameters or arrhythmia burden.<sup>10–13</sup> However, despite numerous investigations on timing, indications, techniques, and results of PVR, large gaps in knowledge persist on how best to manage these patients. To date, it remains unknown whether PVR reduces arrhythmia burden or improves survival in this population.

In this issue of *Circulation*, Frigiola *et al.* describe the outcomes of 1085 consecutive patients with TOF managed at the Great Ormond Street Hospital for Children from 1964 to 2009.<sup>14</sup> In addition to confirming that the mortality rate in this population is 4-fold higher than that of the general population and that the burden of morbidity is substantial, the investigators shed light on a long-neglected segment of this population, those with good late clinical outcomes. The study adds an important piece to the puzzle by characterizing the cardiac phenotype of patients defined by the authors as having “good outcomes” — reached age 35 years without PVR, were asymptomatic, and had normal exercise tolerance. From a sample of 50 randomly selected patients without PVR who were invited to undergo detailed evaluation by echocardiography, cardiovascular magnetic resonance, and exercise testing, 14 fulfilled the above criteria for good late outcomes. Not surprisingly, these patients had a nearly normal right heart structure and function, including at most mild right ventricular outflow tract obstruction, normal pulmonary valve annulus diameter, no more than mild-moderate PR, high-normal or minimally dilated RV, no RVOT aneurysm, and normal RV systolic function. The authors speculate that patients with this cardiac phenotype may not require additional interventions such as PVR and, hence, their primary repair can be considered “definitive.”

These results and inferences must be viewed cautiously. It is important to note that the cohort studied by Frigiola *et al.* comprises only patients with “simple” TOF — i.e., those with patent RVOT. Patients with more complex forms such as those with pulmonary atresia and other anatomic variants or associated anomalies were excluded. Therefore, the burden of residual disease and excess mortality reported in this paper depicts a best-case scenario, with higher rates of morbidity and mortality expected when high-risk groups are included. Furthermore, among the small random sample of “ideal” TOF patients who were invited for further evaluation, we do not know how many declined participation and whether those who underwent further testing represent the broader cohort of patients who are asymptomatic and did not require cardiac interventions during follow-up. Moreover, we do not know whether these patients are at risk for developing late cardiac complications such as atrial flutter/fibrillation, ventricular tachycardia, or ventricular dysfunction. It is, therefore, prudent to continue to view repaired TOF as a life-long disease that requires careful monitoring.

Despite these limitations, the study of Frigiola *et al.* provides useful information that highlights both ends of the disease spectrum and stimulates the ongoing discussion on timing and indications for PVR. Their findings confirm that a substantial proportion of adolescents and adults with repaired TOF receive PVR and that the frequency of the procedure increases as patient age rises. Notably, even among the small selected group of patients free of PVR, less than one third fulfilled the authors’ criteria for good outcome. This raises the question whether the remaining patients should have undergone earlier PVR and whether such a management strategy would have resulted in better outcomes. The authors correctly note the lack of consensus regarding optimal timing of PVR and comment that

their study does not directly address this question. However, coupled with the observation that PVR is the most frequently performed surgical procedure in adults with congenital heart disease in the UK, their findings underscore the importance of fine-tuning the indications for PVR in this population.

Despite the lack of consensus and the many persisting gaps in knowledge, the question when to recommend PVR is a dilemma that confronts clinicians with increasing frequency. Table 1 provides a set of possible recommendations based on the author's interpretation of the current literature. These recommendations, which do not represent the opinion of any institution or professional society, are based on the available evidence gleaned from studies that analyzed pre-PVR markers of post-PVR normalization of ventricular size and/or function. Little or no information is currently available to inform us about ventricular performance late after PVR, pre-PVR risk factors for post-PVR arrhythmias, exercise intolerance, or mortality. Furthermore, we have no information on how to apply pre-PVR risk factors to different anatomic and/or surgical phenotypes. We also do not know whether therapeutic interventions designed to modify these risk factors will, in fact, translate into a clinical benefit. With these limitations in mind, the guidelines outlined in Table 1 are meant to serve as a starting point for a discussion within our field and as a stimulus for future investigations designed to shed new light on areas where data are lacking<sup>15–20</sup>.

The study of Frigiola et al. raises intriguing questions about our ability to identify patients with good outcomes late after TOF repair and, conversely, those at risk of poor outcomes. Simultaneously, though, the authors illustrate that even in a center with a large patient volume, our current ability to prognosticate remains poor as highlighted by the 2 patients who were included in the good outcome group only to require subsequent PVR. Furthermore, as illustrated above, many controversies about optimal management of this growing population remain contentious. Thus, further progress in resolving these disagreements will only be achieved through large multicenter collaborative studies. Ideally, this will be performed with standardized prospectively acquired clinical, imaging, exercise, electrocardiographic, and laboratory data. Such a large multicenter investigation would allow us to create an evidence-based consensus on the optimal timing and indications for PVR as well as for refinement of surgical techniques. A collaborative endeavor like that will help to overcome the relatively short duration of time that the procedure has been performed routinely (less than a decade in many institutions), the low rate of hard outcomes (e.g. death, resuscitated cardiac arrest, sustained ventricular tachycardia), the reliance on surrogate outcomes of unclear clinical importance, and the ongoing evolution in treatment options. Such a prospective multicenter study would help generate hypotheses on optimal management that can then be tested in future randomized clinical trials.

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**Table 1**

Proposed indications for pulmonary valve replacement in patients with repaired TOF or similar physiology with moderate or severe pulmonary regurgitation (regurgitation fraction  $\geq 25\%$ ).

Indications	Supporting references
I. Asymptomatic patients with 2 or more of the following criteria:	
a. RV end-diastolic volume index $>150 \text{ ml/m}^2$ or Z-score $>4$ . In patients whose body surface area falls outside published normal data: RV/LV end-diastolic volume ratio $>2$	10, 12
b. RV end-systolic volume index $>80 \text{ ml/m}^2$	11, 13
c. RV ejection fraction $<47\%$	11, 15, 16
d. LV ejection fraction $<55\%$	11, 15, 16
e. Large RVOT aneurysm	17, 18
f. QRS duration $>160 \text{ ms}$	11
g. Sustained tachyarrhythmia related to right heart volume load	6
h. Other hemodynamically significant abnormalities:	
<input type="checkbox"/> RVOT obstruction with RV systolic pressure $\geq 0.7$ systemic	19
<input type="checkbox"/> Severe branch pulmonary artery stenosis ( $<30\%$ flow to affected lung) not amenable to transcatheter therapy	
<input type="checkbox"/> moderate tricuspid regurgitation	19
<input type="checkbox"/> Left-to-right shunt from residual atrial or ventricular septal defects with pulmonary-to-systemic flow ratio $\geq 1.5$	19
<input type="checkbox"/> Severe aortic regurgitation	19
II. Symptomatic patients fulfilling $\geq 1$ of the quantitative criteria detailed above. Examples of symptoms and signs include:	
a. Exercise intolerance not explained by extra-cardiac causes (e.g., lung disease, musculoskeletal anomalies, genetic anomalies, obesity), with documentation by exercise testing with metabolic cart ( $\geq 70\%$ predicted peak $\text{VO}_2$ for age and gender not explained by chronotropic incompetence)	
b. Signs and symptoms of heart failure (e.g., dyspnea with mild effort or at rest not explained by extra-cardiac causes, peripheral edema)	19
c. Syncope attributable to arrhythmia	
III. Special considerations:	
a. Due to higher risk of adverse clinical outcomes in patients who underwent TOF repair at age $\geq 3$ years, PVR may be considered if they fulfill $\geq 1$ of the quantitative criteria in section I	16
b. Women with severe PR and RV dilatation and/or dysfunction may be at risk for pregnancy-related complications. Although no evidence is available to support benefit from pre-pregnancy PVR, the procedure may be considered if fulfilling $\geq 1$ of the quantitative criteria in section I	20