Fallot and Its Variants: From Diagnosis to Pulmonary Valve Replacement

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Abstract

In this article, we summarize the most important issues and recommendations on the anatomy and physiology of tetralogy-like lesions, diagnosis prior to medical, interventional, or surgical intervention, timing and types of interventions, management of high-risk patients, and the need for future interventions in a subset of patients. The long versions of the original guidelines are reprinted in the supplement, providing a more comprehensive overview and enabling a more detailed approach to tetralogy and its variants.

Keywords

- congenital heart disease
- Tetralogy of Fallot
- Double outlet right ventricle
- Pulmonary atresia with ventricular septal defect
- Pulmonary valve replacement

The guideline committee of the German Society of Pediatric Cardiology and Congenital Heart Disease (DGPK) was commissioned to provide a framework on the most frequent forms of congenital heart disease and other topics of pediatric cardiology. Guidelines for diagnosis, treatment, and follow-up of tetralogy and its variants have been published between 2020 and 2023 and are also presented in a supplement of The Thoracic and Cardiovascular Surgeon [X].[1] For practical, formal, and historical reasons, there are separate guidelines on double outlet right ventricle (DORV) and pulmonary atresia with ventricular septal defect (PA/VSD), and an additional guideline focuses on pulmonary valve replacement (PVR), which is part of the lifelong treatment in many of the patients with tetralogy and its variants.

The guideline committee of the DGPK not only consists of pediatric cardiologists and cardiac surgeons from tertiary centers specialized in congenital heart disease but incorporates experience and expertise from general pediatricians and pediatric cardiologists working in non-specialized pediatric hospitals as well as in clinical practice. Furthermore, trainees in pediatric cardiology and patient representatives are members of the guideline committee. This composition might explain slightly more defensive real-world statements compared with recent original publications from high-volume tertiary surgical centers.

Morphology and Clinical Features

Tetralogy of Fallot (TOF) is the most frequent cyanotic heart defect characterized by a combination of pulmonary stenosis, right ventricular hypertrophy, a ventricular septal defect (VSD), and an overriding aorta. These anatomical arrangements are also found in varying degrees in the DORV* and PA/VSD.

These conotruncal anomalies embrace a displacement of the outlet septum (conus) to the anterior and superior direction resulting in a narrowed right ventricular outflow tract. Depending on the extent of this septal

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malalignment, the right ventricular outflow tract obstruction (RVOTO) ranges from infundibular muscular narrowing with or without pulmonary valve (PV) stenosis to complete occlusion or membranous atresia of the valve. The severity of RVOTO determines the degree of pulmonary blood flow. Whereas a "pink Fallot" or DORV* with only mild infundibular obstruction at rest might have normal systemic oxygen saturation and a tendency to pulmonary overcirculation, a severe RVOTO leads to the most important clinical finding of central cyanosis. These "blue" babies often need an additional source of pulmonary blood flow from the aorta, either unifocally via a persistent ductus arteriosus (PDA) or multifocally via so-called "major aortopulmonary collateral arteries" (MAPCAs). Key features in tetralogy of Fallot and its variants are presented in ►**Table 1.**

Pulmonary Stenosis/Atresia

The PV annulus is variably hypoplastic, and the valve itself is usually bicuspid with thick deformed leaflets. Right ventricular (RV) hypertrophy begins in fetal life and progresses postnatally. The pulmonary arterial tree may show any degree of hypoplasia.

Pulmonary atresia (PA) is highly variable but anatomically similar to TOF (biventricular aortic origin, Right ventricular outflow tract obstruction (RVOTO)). The PV and main pulmonary artery may be represented by a fused valve plate, or the connection may be absent. The central pulmonary arteries show a spectrum of hypoplasia, and in extreme cases, they may be diminutive or absent.

Right Ventricular Hypertrophy

Infundibular narrowing or atresia leads to a pressure load on the right ventricle resulting in myocardial hypertrophy. The more pronounced the RVOTO, the greater the muscular hypertrophy. Agitation and stress may lead to an increase in muscular RVOTO, dehydration, and a decrease in systemic vascular resistance may result in a markedly reduced pulmonary blood flow, both inducing severe cyanotic attacks ("hypercyanotic" or "tet-spells"). These spells have to be treated immediately to stabilize the infant, necessitating intensive care medicine in rare circumstances. They induce an urgent interdisciplinary discussion for subsequent palliative or curative treatment of the underlying lesion. Substances leading to an increase in pulmonary arterial blood pressure on one hand and those resulting in a reduced systemic vascular resistance on the other may aggravate the cyanosis and should therefore be avoided.

Ventricular Septal Defect

The interventricular septum growing from the apex toward the outflow tracts cannot fuse with the displaced conal septum, resulting in a so-called (anterior) malalignment VSD. The non-restrictive subaortic VSD leads to pressure equalization between the two ventricles (systemic pressure in the right ventricle). Rarely, a severe RVOTO in combination with a restrictive VSD, especially in elderly children with increasing right ventricular hypertrophy, may cause suprasystemic RV pressure.

Aortic Overriding

In accordance and reciprocally with the narrowing on the right side, the conal malalignment "to the right" leads to a widened left ventricular outflow tract with the downstream aortic structures. Consequently, the left ventricular outflow tract with the aortic valve "rides" over the VSD. Depending on the extent of the malalignment, both great arteries have a morphological connection to the right ventricle. In TOF, less than 50% of the aorta originate from the right ventricle, whereas in DORV* more than 50% of the aorta are supported by right ventricular structures. Its extreme variant in the case of two preserved outflow tracts in combination with membranous atresia of the PV is known as DORV* with PA. Furthermore, variations in the

	TOF	TOF-DORV	PA-VSD
Size of non-restrictive VSD	+	++	+++
Connection of both great arteries to the right ventricle	+	++	variable
Aorta from right ventricle	< 50%	> 50%	variable
Pulmonary stenosis	+	++	atresia
Infundibular stenosis	+	++	atresia
Right ventricular hypertrophy	+	++	+++

Anterior Malalignment of the Outlet Septum

Fig. 1 The degree of conal malalignment determines the severity of malformation. DORV, double outlet right ventricle; PA/VSD, pulmonary atresia with ventricular septal defect; TOF, tetralogy of Fallot; TOF-DORV, "Fallot type"-DORV.

position of the aortic root with reference to the pulmonary root are common, often being side-by-side in DORV*.[2] A substantial amount of systemic venous blood reaches the aorta (right-to-left shunt) in addition to the pulmonary venous blood. Therefore, the aorta in tetralogy and even more in PA/VSD may be twice as large as in a healthy person (►**Fig. 1**).

Diagnosis

Besides the leading symptom of cyanosis, the RVOTO in children with TOF or Fallot-type DORV* always causes a loud systolic murmur. Echocardiography is the primary diagnostic tool. It should be performed with special attention on the different level(s) of RVOTO (subvalvular, valvular, or supravalvular), PV function and morphology, size of the PV annulus and main and branch pulmonary arteries, and coronary artery anatomy as well. The more complex variants may benefit from cross-sectional imaging such as computed tomography angiography but this is not standard for typical TOF. It may be useful prior to surgical or interventional palliation to discern the need for any pulmonary arterioplasty. The cardiology and surgical team should always review the coronary artery anatomy before any intervention where an incision across the RVOT is anticipated. This includes interventional palliative treatment with RVOT stenting as the stent must be removed during corrective surgery often requiring an incision across the RVOT.

For neonatal and subsequent home monitoring, pulse oximetry should be used as a valuable tool easily applied by the parents. Transcutaneously measured oxygen saturations below 80% at rest indicate treatment to improve pulmonary perfusion.

Management

The variability of the morphologic features in TOF and its variants results in a broad spectrum of clinical features, from ductus-dependent severely symptomatic newborns to asymptomatic children awaiting elective surgical correction during the second half of their first year of life. Nevertheless, all should be followed closely by pediatric cardiologists, and most of them are treated medically or interventionally before corrective surgery.

Treatment algorithms for those with minor symptoms as well as highly symptomatic newborns are displayed in ►**Fig. 2A, B**, illustrating a mixture of medical, interventional, and surgical options. An individualized therapeutical approach should balance effectivity and specific risks according to the invasiveness of the different options.

Ductal stent or Shunt

Stent implantation in the PDA requires a high level of interventional expertise with regard to the typical anatomy of the tortuous and siphon-like ductus. An atypical vascular access (carotid or subclavian artery) may be required. Surgical palliation is usually achieved by creating an artificial systemic arterial–pulmonary arterial shunt to a central pulmonary artery, originating either from a proximal supra-aortic artery (modified Blalock–Taussig–Thomas shunt), from the ascending aorta (central shunt), or the right ventricle (Sano-shunt), respectively. Shunt circulation improves pulmonary perfusion at the expense of a reduction in systemic perfusion, as can be seen from the increased blood pressure amplitude at a low diastolic blood pressure level ("diastolic run-off"). Shunt surgery with its "specific" side effects resembling systemic low output is therefore associated with higher therapy-induced morbidity (catecholamine dependency, systemic circulatory insufficiency, and prolonged intensive care).

Comparing ductal stenting versus surgical shunt palliation, a recent meta-analysis summarizes that patent ductus arteriosus stent is associated with fewer complications and shorter length of stay. There is no significant difference in mortality or unplanned reinterventions to treat cyanosis after ductal stenting compared with aortopulmonary shunt.[3] Patent ductus arteriosus stent may therefore be favorable to surgical aortopulmonary shunt secondary to similar mortality and reintervention rates, but multiple benefits in post-intervention care. However, these results are still center-specific and dependent on institutional expertise and preference. Consensus-based guideline recommendations still cannot define a preferential treatment modality yet.[4]

RVOT stent or Transannular Patch

Primary catheter-based stent implantation in the hypoplastic right ventricular outflow tract—either subvalvular or transvalvular—has become an accepted option to establish antegrade pulmonary blood flow in a TOF-like RVOTO, which is hemodynamically better tolerated than shunt surgery. In PA/VSD, confluent genuine pulmonary arteries are a prerequisite for opening (by high-frequency perforation) of the atretic PV with subsequent balloon dilatation or transvalvular stent implantation in the RVOT. In most patients, minimally invasive interventional procedures to promote antegrade pulmonary blood flow can also be performed in the clinical setting with relevant concomitant diseases ("high-risk patients") with an irresponsibly extended risk for primary surgical treatment (►**Fig. 2B**).[4]

Palliative surgical enlargement of the RVOT consists of a longitudinal incision from the infundibulum into the main trunk of the pulmonary artery followed by the implantation of a transannular patch, leaving the VSD open. This procedure requires the use of cardiopulmonary bypass and may be considered in patients in whom complications of shunt palliation are feared (systemic "low output' or acute shunt thrombosis). Preterm or hypotrophic newborns with hypoplastic central pulmonary arteries might also be palliated using this approach.

* According to Lev's nomenclature, there are four different subtypes of DORV depending on the location of the VSD in relation to the great arteries, whereby this publication refers exclusively to DORV* with subaortic VSD and subpulmonary obstruction ("Fallot-type DORV").

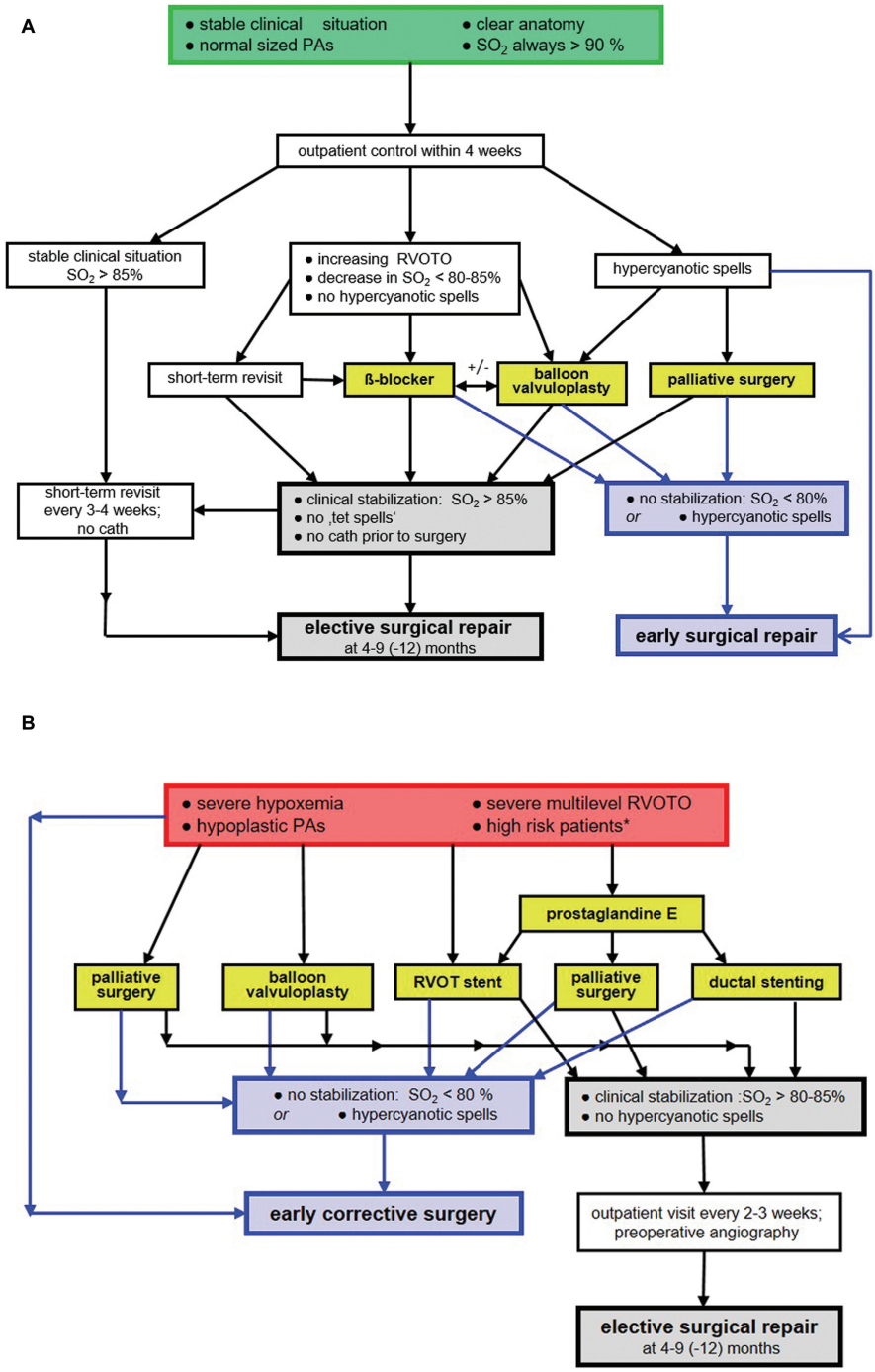

Fig. 2 (**A**, **B**) Management algorithms in patients with TOF depending on clinical status. (**A**) After a clinical and echocardiographic diagnosis of TOF, close monitoring by a pediatric cardiologist is established including monitoring of transcutaneously measured oxygen saturation (SO_2). Depending on the severity of subpulmonary obstruction, β-blockers are frequently used in newborns and young infants to alleviate infundibular RVOTO and are usually well tolerated. Most patients do not need any palliative intervention prior to corrective surgery. If SO_2 remains stable during subsequent visits, elective repair may be scheduled after 3 months of life, but can also be postponed into the second half of the first year of life. If SO_2 drops despite medical treatment, a balloon valvotomy may be considered to improve pulmonary blood flow. If clinical stabilization cannot be achieved or the infant suffers from hypercyanotic spells, shunt surgery or early surgical repair should be performed. (**B**) At the other end of the spectrum, highly symptomatic newborns with ductus-dependent pulmonary blood flow require a continuous prostaglandin infusion to bridge to further surgical or interventional palliation. If primary surgical correction is deemed too risky* or even not feasible in the individual patient, interventional or surgical palliation to improve pulmonary blood flow should be performed. Besides balloon valvotomy, ductal stenting, and RVOT stenting have been introduced into clinical practice as effective interventional alternatives to surgical palliation with proven benefit on subsequent growth of the pulmonary arteries. If clinical stabilization cannot be achieved, early corrective surgery is advised. *When evaluating symptomatic neonates with TOF, it is reasonable to consider those with low birth weight and/or prematurity, small or discontinuous pulmonary arteries, major genetic or extracardiac congenital anomalies or other comorbidities such as intracranial hemorrhage, sepsis, or other end-organ compromise as high-risk patients. PA, pulmonary atresia; RVOTO, right ventricular outflow tract obstruction; TOF, tetralogy of Fallot.

Table 1 Key features in tetralogy of Fallot and its variants

Fallot and its variants Guideline recommendations
Morphology
• The displacement of the outlet septum anteriorly and superiorly ("anterior malalignment") leads to overriding of the aorta over a non-restrictive ventricular septal defect, as well as to an obstruction in the right ventricular outflow tract
• The extent of the anterior malalignment determines the development of either subpulmonary stenosis in Tetralogy of Fallot (aorta <50% from RV) and DORV* (aorta >50% from RV), or pulmonary atresia
• The extent of cyanosis after postnatal adaptation reflects pulmonary perfusion in relation to systemic perfusion. The resulting systemic arterial oxygen saturation determines the urgency of an intervention in neonates or early infancy.
Differential diagnoses
Both in utero and postnatally, the following malformations must be differentiated on the basis of the key finding "VSD with overriding aorta":
▪ Common arterial trunk
▪ Malalignment VSD without RVOTO and "VSD-type" DORV, leading to pulmonary overperfusion
▪ Absent pulmonary valve syndrome with pulmonary valve agenesis, functionally severe pulmonary insufficiency, and often extremely dilated pulmonary arteries
Management
• The delivery of a newborn with a prenatally diagnosed VSD with an overriding aorta should take place in a maternity unit with access to specialized pediatric cardiology care
• Pulse oximetry should be used for neonatal and subsequent home monitoring. Transcutaneously measured oxygen saturations below 80% at rest indicate treatment to improve pulmonary perfusion
• Before interventional or surgical treatment of complex variants of TOF including those with atypical coronary arrangement, further diagnostic imaging (CT angiography, cardio-MRI, diagnostic catheterization, possibly with coronary angiography) should be performed in addition to echocardiography
• In symptomatic newborns (SO_2 permanently <80%), surgical or interventional corrective surgery should not be performed in the first 2 months of life due to increased perioperative morbidity and mortality

Abbreviations: DORV*, double outlet right ventricle; RVOTO, right ventricular outflow tract obstruction; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Unifocalization

In the presence of MAPCAs with multifocal pulmonary perfusion, unifocalization of the collateral vessels to the central pulmonary artery(ies) and their connection to the RV by means of a conduit is considered in addition to intracardiac corrective surgery. The management strategy (one-stage vs. staged repair) is always individualized, especially in the case of multifocal pulmonary perfusion, necessitating extensive imaging and hemodynamic evaluation with subsequent in-depth discussion of the treatment options in the interdisciplinary heart team. The aim of this joint strategy is to use all available forms of treatment synergistically to recruit as many lung segments as possible for exclusively antegrade perfusion from the RV with the goal of subsequent separation of the systemic and pulmonary circulation.

Biventricular Repair

Establishing non-restrictive antegrade pulmonary perfusion from the right ventricle and complete closure of the VSD is the primary goal of complete repair. A sufficient size of the pulmonary arteries is crucial and may preclude palliative treatment. Alleviating RVOT obstruction consists of both infundibular myectomy ("digging on the ground") and, if necessary, patch enlargement of the RVOT ("putting up the roof"). The latter should be limited to the subvalvular region or across the pulmonary annulus into the main pulmonary artery. Transannular patch surgery always results in PV insufficiency, which often leads to PVR in the long term. Therefore, valve-preserving surgery by a combined transatrial/ transpulmonary approach and neglecting or minimizing the size of the ventriculotomy, even if leaving minor residual stenosis, will likely have beneficial effects toward preserving RV function and possibly reduce long-term pulmonary regurgitation.[4–6]

The timing of corrective surgery is still a subject of controversy. In principle, it can be performed in the neonatal period, but there is significantly increased perioperative morbidity and mortality in the first 2 months of life. In addition, neonatal surgical repair nearly always requires the use of larger ventriculotomies while the preservation of the PV function might be easier achieved in infants beyond the first 6 months of life.

In "Fallot-type" DORV*, the variable extent of aortic overriding has implications for surgical repair, since in these circumstances a much larger patch will be required to baffle

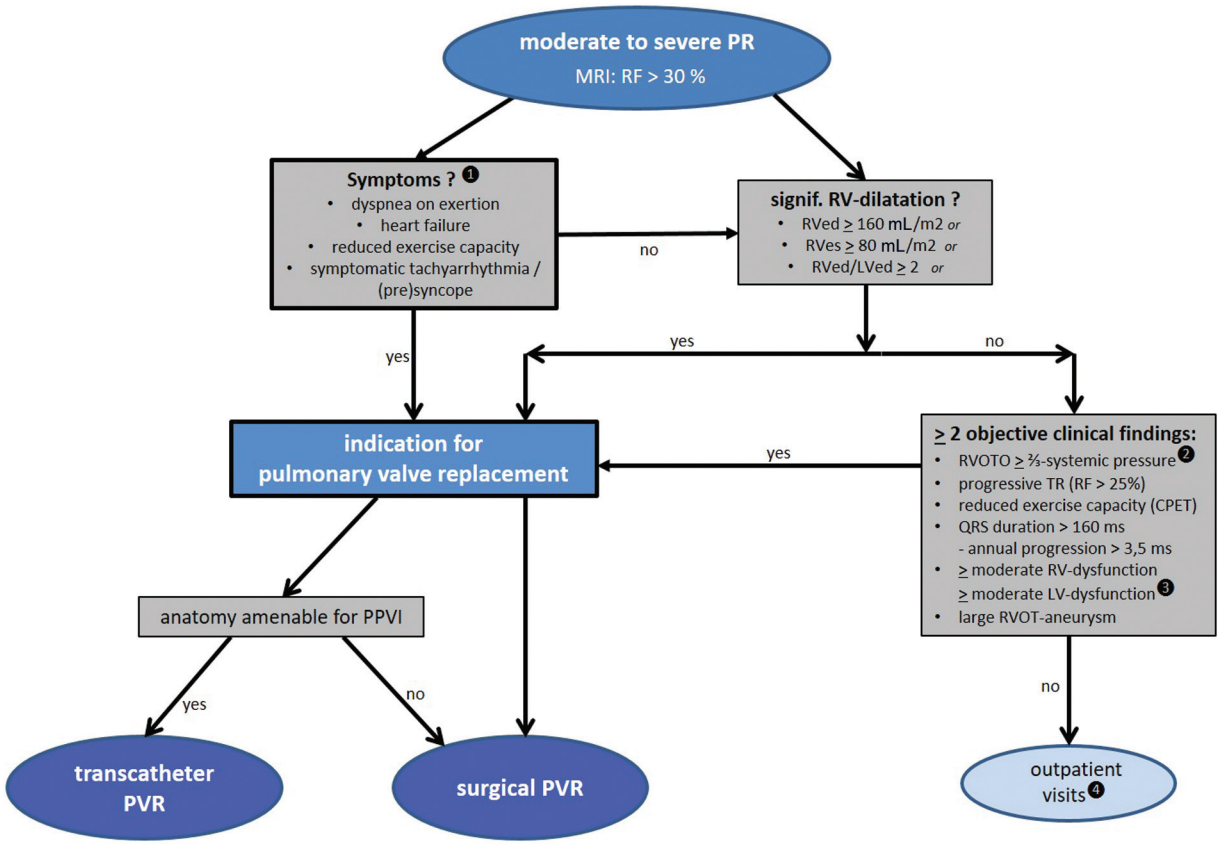

Fig. 3 Algorithm for pulmonary valve replacement in patients with repaired tetralogy of Fallot. [1] Severe clinical symptoms indicate PVR. In case of severe ventricular dysfunction, clinical stabilization should be achieved prior to PVR by medical or interventional procedures. This may include intensive care management and extracorporeal support. In asymptomatic patients, severe RV dilation indicates PVR. If there is no proof of severe RV dilation, the combination of objective clinical findings may indicate PVR. [2] Evaluation by diagnostic catheterization. [3] RV-EF <45% and LV-EF <45%. In case of an anatomical situation suitable for percutaneous pulmonary valve implantation (PPVI), transcatheter PVR should be considered in adolescents and adults as an alternative to surgical PVR. PVR, pulmonary valve replacement; LVed, left ventricular end-diastolic volume; RVed, right ventricular end-diastolic volume; RVes, right ventricular end-systolic volume; RVOTO, right ventricular outflow tract obstruction.

blood from the left ventricle and through the interventricular communication to the aortic root.[2]

If a conduit is needed during surgical repair in PA/VSD or because of significant coronary anomalies in TOF or DORV*, this is burdened by subsequent surgical revisions for conduit exchange. Its frequency is determined by somatic growth and degradation of the biological conduits used, often leading to two to three reoperations in childhood and adolescence.

Late Reintervention: Pulmonary Valve Replacement

Surgical PVR has been the most frequent reoperation in TOF, DORV*, and PA/VSD for decades. Indications for PVR have been defined to achieve restoration of RV size and function. Guideline indications for PVR include symptoms, exercise intolerance, the extent of RV dilation (RV end-diastolic volume index $>160\,ml/m^2$, RV end-systolic volume index $>80\,ml/m^2$), reduction of RV ejection fraction, and arrhythmia. ►**Figure 3** summarizes the current approach recommended in the guidelines.

The advent of transcatheter valves has changed the landscape for the management of pulmonary regurgitation, and utilization has increased steadily with expansion from the Melody valve (Medtronic, Minneapolis, MN) and Sapien XT to include Sapien 3 (Edwards Lifesciences, Irvine, CA), even though surgery remains the most common option. Infective endocarditis (IE) is a late complication after transcatheter PVR and remains a concern. It is more frequently compared with surgical PVR with rates of 7 to 8% at 10 years. Approximately half of the patients with IE will need another—presumably surgical—PVR. The optimal surgical strategy for TOF repair in the modern era should take these new technologies into account and consider creating an RVOT "landing zone" best suited to a future transcatheter PVR or valve implantation best suited to future transcatheter valve-in-valve technology.[6]

The timing of PVR for severe pulmonary regurgitation is typically in adolescence or early adulthood, and there has been a general trend to offer PVR earlier rather than later to preserve RV function and allow a better chance for remodelling. Long-term studies in the adult population after repair of tetralogy-like lesions have recently documented the clinical benefits of PVR.[7] Replacement by

either a transcatheter PVR or a surgically placed PV depends on anatomic considerations and concomitant lesions.

Conflict of Interest
None declared.

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