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Review

Tetralogy of Fallot Across the Lifespan: A Focus on the Right Ventricle

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ABSTRACT

Tetralogy of Fallot is a cyanotic congenital heart disease, for which various surgical techniques allow patients to survive to adulthood. Currently, the natural history of corrected tetralogy of Fallot is underlined by progressive right ventricular (RV) failure due to pulmonic regurgitation and other residual lesions. The underlying cellular mechanisms that lead to RV failure from chronic volume overload are characterized by microvascular and mitochondrial dysfunction through various regulatory molecules. On a clinical level, these cardiac alterations are commonly manifested as exercise intolerance. The degree

RÉSUMÉ

De nombreuses techniques chirurgicales permettent aux patients présentant une tétralogie de Fallot (TF), une forme de cardiopathie congénitale, de survivre jusqu'à l'âge adulte. À l'heure actuelle, l'évolution naturelle de la TF corrigée est caractérisée par une insuffisance ventriculaire droite (VD) progressive attribuable à une régurgitation pulmonaire et à d'autres lésions résiduelles. Les mécanismes cellulaires sous-jacents qui mènent à l'insuffisance VD due à une surcharge volumique chronique sont caractérisés par une dysfonction microvasculaire et mitochondriale faisant intervenir

Although the advances in surgical and clinical management of patients with congenital heart disease (CHD) have led to most of the patients born with tetralogy of Fallot (ToF) reaching adulthood, these patients are often left with residual lesions that increase their risk of developing heart failure. Understanding the complex interplay between the anatomic defects, the contribution of residual lesions to right ventricular (RV) failure as well as the mechanisms of RV remodelling is paramount to improve the management of these patients. This paper aims to review ToF across the lifespan with a focus on the RV.

Anatomy of the Right Ventricle

From the anatomic viewpoint, during childhood, the RV remains the primary focus of attention in ToF, owing to the presence of aortic override across a ventricular septal defect (VSD) and subpulmonary outflow obstruction. The RV cavity is lined by trabeculations that are characteristically coarser than those seen in the left ventricle (LV). These trabeculations are crisscrossing muscle bundles that mostly occupy the apical third to one half of the ventricle but can also be found in the

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of exercise intolerance can be objectified and aid in prognostication through cardiopulmonary exercise testing. The timing for reintervention on residual lesions contributing to RV volume overload remains controversial; however, interval assessment of cardiac function and volumes by echocardiography and magnetic resonance imaging may be helpful. In patients who develop clinically important RV failure, clinicians should aim to maintain a euvolemic state through the use of diuretics while paying particular attention to preload and kidney function. In patients who develop signs of cardiogenic shock from right heart failure, stabilization through the use of inotropes and pressor is indicated. In special circumstances, the use of mechanical support may be appropriate. However, cardiologists should pay particular attention to residual lesions that may impact the efficacy of the selected device.

diverses molécules régulatrices. Sur le plan clinique, ces atteintes cardiaques se manifestent par une intolérance à l'effort qui peut être évaluée au moyen d'une épreuve d'effort cardiorespiratoire, ce qui permet de faciliter l'établissement d'un pronostic. Le moment propice pour une réintervention en cas de lésions résiduelles contribuant à la surcharge volumique du ventricule droit demeure controversé; toutefois, il peut être utile d'évaluer régulièrement la fonction et les volumes cardiaques au moyen d'une échocardiographie et de tests d'imagerie par résonance magnétique. En présence d'une insuffisance VD cliniquement importante, les cliniciens doivent tenter de maintenir les patients dans un état euvolémique en utilisant des diurétiques, tout en accordant une attention particulière à la précharge et à la fonction rénale. Si les patients manifestent des signes de choc cardiogénique associé à une insuffisance cardiaque droite, il convient de leur administrer des inotropes et des vasopresseurs pour stabiliser leur état. Dans certains cas, l'utilisation d'un dispositif d'assistance mécanique peut être appropriée. Cependant, les cardiologues doivent être attentifs aux lésions résiduelles, car elles peuvent influencer l'efficacité de ce dispositif.

RV basal segments. Apart from the trabeculations and the papillary muscles that support the tricuspid valve, there are several muscular structures on the endocardial aspect of the RV that are pertinent in ToF.

The septomarginal trabeculation, also known as the septal band, is a flat muscle band that adheres to the ventricular septum. It has a broad "body" with 2 short arms, one pointing cephalad towards the pulmonary valve and the other pointing posteriorly towards the tricuspid valve (Fig. 1). The VSD that the aortic valve overrides is situated between the arms of the septomarginal trabeculation. The outlet septum, also known as the infundibular or conal septum, is a muscular structure that arises from the septum at the cephalad arm of the septomarginal trabeculation and runs continuously with the subpulmonary infundibulum that supports the pulmonary valve. It is the anterior cephalad deviation of the outlet septum towards the RV free wall (Fig. 1B) that is considered by many to be the fundamental anatomic hallmark of ToF and is the root cause for its varying degrees of RV outflow obstruction.[1] At the posterior arm of the septomarginal trabeculation where it tapers towards the tricuspid valve, there is a flange of muscle that is continuous with the parietal part of the outlet septum. This flange of muscle is termed the supraventricular crest or ventriculo-infundibular fold, or parietal band. This muscular fold separates the tricuspid from the pulmonary valve and continues into the parietal wall of the ventricle.

In the outflow tract, there are bundles termed septoparietal trabeculations that arise from the septum to line the anterior wall of the outflow tract. These can add to subpulmonary obstruction, especially when hypertrophied. The septomarginal trabeculation carries the cord-like right bundle branch in its subendocardium. The portion of body of the septomarginal trabeculation that runs towards the ventricular apex usually has a muscle bundle of varying thickness that crosses the cavity and inserts into the free wall at a site close to where the anterior papillary muscle of the tricuspid valve arises. This muscular bundle is termed the moderator band and carries a fascicle from the right bundle branch of the conduction system.

Although each muscle structure is given a different name, they are by no means structurally independent; rather, these muscular structures form a continuum. The outlet septum continues into the subpulmonary infundibulum and the ventriculo-infundibular fold into the free wall, whereas the septomarginal trabeculation on the septum continues into the free wall through the moderator band. Resections or divisions of any of these structures could impact ventricular function.[2]

Myoarchitecture of the right ventricle

The free wall, septum, and the muscle structures within both ventricles mainly comprise myocytes. These cells are longer than wide. They branch at their ends joining with adjacent myocytes to form a complex 3-dimensional (3D) syncytium within a framework of connective tissue. The RV in ToF has thicker walls, with myocyte hypertrophy and increased fibrosis reported in both the RV and LV after the first decade of life in unrepaired hearts and in patients who underwent complete repair after the age of 5 years.[3] Myoarchitecture, as revealed by gross dissection, provides a guide to the overall arrangement of longitudinally arranged strands of myocytes across the thickness of the wall. Despite obvious limitations, dissections reveal changes in the direction of these strands from the subepicardium to the subendocardium. These perceptible changes in orientation are described as layers but are not separated by fibrous tissue sheaths. Instead, the myocardial strands are all interconnected when traced through the thickness of the wall.[4,5]

The normal RV is relatively thin and comprises 2 layers. The superficial or subepicardial layer comprises circumferentially arranged strands approximately parallel to the atrioventricular groove that continue into the superficial strands of the LV. In the subendocardium lining the RV cavity, the strands run longitudinally from base to apex.[5] There is an additional middle layer in hearts with ToF, the mesocardium. As revealed in a study on the hearts of 9 patients aged 8 hours to 59 years, in ToF, the strands in the subepicardial layer are more obliquely orientated on the sternocostal aspect as well as the diaphragmatic aspect of

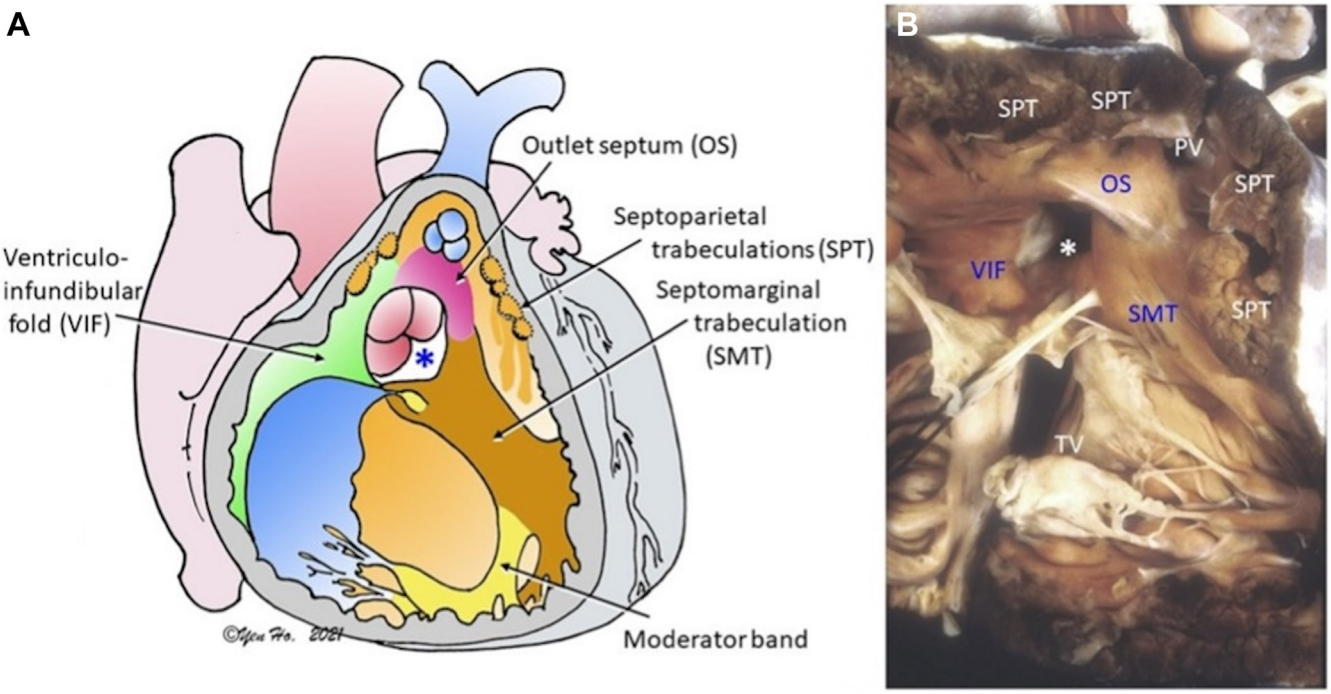

Figure 1. Diagram and gross dissection of the right ventricle in tetralogy of Fallot. (**A**) Diagram showing the characteristic features of the right ventricle in tetralogy of Fallot and the names of various muscle structures (with their abbreviations), and (**B**) a heart specimen opened through the right ventricular outflow tract. The overriding aortic valve is visible through the ventricular septal defect (**asterisk**). PV, pulmonary valve; TV, tricuspid valve.

the RV (Fig. 2).[6] However, at the more basal third adjacent to the acute margin, there is a mix of longitudinal and transverse strands. Underneath this thin superficial layer lies the thick middle layer with circumferentially orientated strands that is interrupted in the septum by the VSD (Fig. 2D). Beneath the mesocardium lie predominantly longitudinal strands making up the subendocardial layer, except for the outlet septum where strands run transversely.

At the septal end of the outlet septum, the transverse strands continue directly into the longitudinal strands of the septomarginal trabeculation, whereas parietally they continue into the free wall and the ventriculo-infundibular fold (Fig. 2D). Although the outlet septum is situated exclusively in the RV, its transverse strands continue into the anterior wall of the LV, as shown in a more contemporary study using polarized light imaging on perinatal heart specimens.[7] This imaging study also corroborated the findings made by gross dissections.[6]

Right Ventricular Failure and Mechanisms of Adaptation

RV failure is an important determinant of clinical status and outcomes in children and adults with various types of CHD, especially those with right-sided lesions, such as ToF.[8] After initial surgical repair, degeneration or calcification of the reconstructed RV outflow tract (RVOT) can lead to chronic RV volume and/or pressure overload. Although the RV can handle this load for many decades, there is a 30% probability of developing right heart failure by the third decade of life. This chronic RV volume and/or pressure overload is further compounded by a ventriculotomy, repeated surgical interventions, arrhythmias, electromechanical dyssynchrony, ischemia and fibrosis contributing to RV failure, and predisposing patients to premature or sudden death.[9–12] Pulmonary valve replacement (PVR) is the current therapeutic strategy to address chronic RV volume and/or pressure overload in repaired ToF and prevent RV failure. However, in some patients, RV function remains impaired after PVR despite removing the haemodynamic load, suggesting that irreversible cellular remodelling has set in, or that other mechanisms make important contributions to RV failure.[13,14] This raises the question whether avoiding excessive adverse RV remodelling could preserve long-term RV function and emphasizes the need to understand the mechanisms by which the RV adapts to chronic volume and/or pressure overload.

Intrinsic differences between the left ventricle and right ventricle

Differences in ventricular structure and loading conditions are thought to represent the main differences between the RV and LV. Cellular divergence begins early in fetal development, with the primary and secondary heart fields leading to the differentiation of LV and RV cardiomyocytes, respectively, and continues with chamber-specific differences in cell signalling and calcium ion handling. There are, therefore, fundamental differences between the 2 ventricles at the cellular level.[15–17] The divergence in the response of the 2 ventricles to heart failure therapies further highlights the

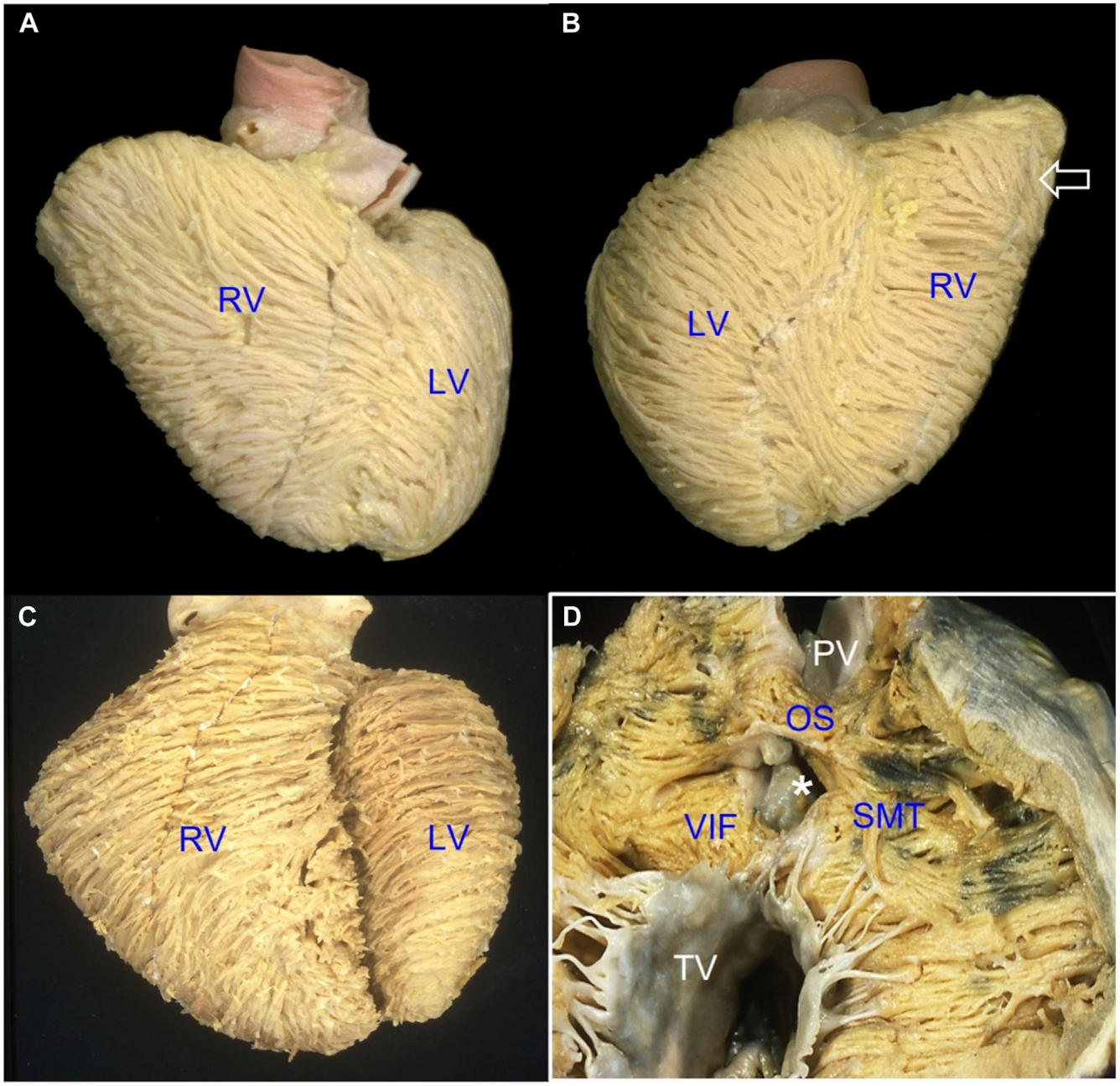

Figure 2. Dissections of a heart with tetralogy of Fallot. Dissections showing the myoarchitecture in tetralogy of Fallot. (**A**) The subepicardium with obliquely oriented strands on the sternocostal surface of the right ventricle (RV). (**B**) They continue onto the diaphragmatic surface apart from an area near the base (**open arrow**). (**C**) Deeper in, the oblique strands become more circumferential forming a thick middle layer like in the left ventricle (LV). (**D**) The strands in the right ventricular outflow tract displayed. OS, outlet septum; PV, pulmonary valve; SMT, septomarginal trabeculation; TV, tricuspid valve; VIF, ventriculo-infundibular fold.

fundamental differences in the mechanisms of RV vs LV failure. Multiple clinical trials have shown that standard heart failure drugs (β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers [ARBs], and sodium-glucose cotransporter-2 inhibitors), developed and tested in patients with LV failure, do not improve RV function or survival in patients with ToF.[8,18,19]

Right ventricle molecular response to stress and right ventricular fibrosis

Despite the differences in ventricular development and cell signalling, the cellular and molecular responses to stress are mostly similar between the RV and LV. However, fundamental differences exist in the mechanisms of RV vs LV

failure.[20–22] Data from animal models of RV stress mimicking residual lesions after the repair of ToF have shown extracellular matrix and cytoskeletal remodelling, heightened reactive oxygen species production and downregulation of antioxidant protection, angiogenesis, energy production, and mitochondrial function. This is more than what is seen in the LV under stress and is more prominent in RV pressure overload than in isolated RV volume overload or combined RV pressure and volume overload.[17,22] Indeed, heart failure drug therapy effectiveness could potentially be impacted by these differences.

In response to various stressors, the development of myocardial fibrosis is thought to predispose to RV dysfunction. Using late gadolinium enhancement, myocardial fibrosis is seen in patients with ToF.[23] The clinical implications of myocardial fibrosis in repaired ToF were demonstrated by Yamamura et al.,[24] who found that the severity of fibrosis was associated with increased RV end-systolic volume, RV mass, right atrial area after PVR, and a trend towards increased heart failure events. These parameters are thought to be risk factors for adverse outcomes in this population. Cochet et al.[23] noted that scar size relates to systolic dysfunction and diffuse fibrosis to RV dilatation. Both scar size and diffuse fibrosis are related to the occurrence of ventricular arrhythmias.[23] Therefore, RV myocardial fibrosis is emerging as a potential therapeutic target. Interestingly, treatment with losartan led to an improvement in fibrosis and cardiac hypertrophy in preclinical models of RV pressure overload.[25] However, renin-angiotensin-aldosterone inhibition using losartan has not been shown to be beneficial for patients with mild RV failure based on the REDEFINE (**R**ight v**E**ntricular **D**ysfunction in t**E**tralogy of **F**allot: **IN**hibition of the r**E**nin-angiotensin-aldosterone system) trial in adults with ToF.[19] The findings from this study may suggest that once RV fibrosis has developed, it cannot be reversed with ARBs. Whether the institution of ARBs before the development of fibrosis may be beneficial requires further investigation.

Right ventricle microvascular and mitochondrial dysfunction

Dysregulated angiogenesis and failure of neovascularization, like that seen in pulmonary hypertension, have been demonstrated in the RV in patients with ToF. This dysregulated response is a potential contributing mechanism to the increased susceptibility of the pressure-loaded RV to progress to failure.[26–28] RV capillary rarefaction due to an intriguing dysregulation of the hypoxia-inducible factor 1α—vascular endothelial growth factor axis was seen both in a murine model of RV pressure overload and in children with RV failure. The mechanism of this dysregulation in angiogenesis was shown to be due to microRNA-34a—mediated inhibition of angiogenic pathways in both cardiomyocytes and endothelial cells, raising the potential for microRNA-34a—targeted therapy in patients with an at-risk RV as in ToF. In addition, Hwang et al.[29,30] found evidence of lipid peroxidation—mediated damage, leading to dysregulated myocardial metabolism and bioenergetics in RV failure both in a preclinical model of RV pressure overload and in children with ToF.[31] Metabolic, mitochondrial, sarcomeric, and cytoskeletal proteins were all noted to be adversely affected by oxidative damage in patients with RV failure. While carvedilol treatment of oxidatively damaged cardiomyocytes did not improve bioenergetics, alternative strategies to decrease oxidative damage and improve mitochondrial energy generation could be potential targets in ToF for promoting cardiomyocyte survival.

In summary, there are multiple mechanisms whereby chronic RV volume and/or pressure overload in repaired ToF predisposes to RV failure. The molecular events underlying RV failure are characterized by fibrosis, cellular energetic failure, and oxidative damage. A better understanding of these adaptive processes may pave the way for the development of novel therapies to improve the RV adaptation to stress.

Residual Lesions and Their Implications for the Right Ventricle

In the late 1970s and early 1980s, initial corrective surgery in the first year of life in the form of transannular patch (TAP) repair became the procedure of choice.[32] More recently, we have seen the development of a surgical approach characterized by a pulmonary valve sparing technique,[33] and it is hoped that this will improve the late trajectory of children undergoing repair today. However, in current adult practice, only the minority of patients do not have a residual haemodynamic or electrical abnormalities after ToF repair; most are left with or develop pulmonary regurgitation (PR) or pulmonary stenosis, and patients with ToF and pulmonary atresia, who were repaired with the use of a RV to pulmonary artery conduit, are almost guaranteed to require further interventions during their lifespan.

Pulmonary regurgitation

PR is the most common residual lesion after ToF repair, mainly in those with TAP repair, and leads to progressive RV dilatation,[34,35] which may produce tricuspid regurgitation.[36] Progressive RV dilatation, fibrosis, and dysfunction induce diminished cardiac output, exercise intolerance, and the risk of congestive heart failure, as well as ventricular arrhythmias that can cause sudden cardiac death (SCD).[37]

The timing for PVR in these patients remains controversial owing to the lack of an ideal treatment option. The longevity of a bioprosthetic valve in the pulmonary position is on average 10-15 years and, as such, commits these, often young, patients to a procedure every 10-15 years after their initial PVR. Alternatively, waiting too long to operate may lead to irreversible RV dilatation and dysfunction with the associated risk of persistent exercise intolerance and the risk of ventricular tachycardia (VT) and SCD.[38] Criteria for the timing of PVR are provided in clinical guidelines and are based on RV size and function, LV function, and the presence of symptoms or exercise intolerance.[39–41] Patients with progressive reduction in exercise tolerance and an RV end-diastolic volume index of $\geq$160 mL/m^2 and/or an RV end-systolic volume index (RVESVi) of $\geq$80 mL/m^2, or an RV ejection fraction (RVEF) of <45% or an LV ejection fraction (LVEF) of <55% or progressive tricuspid regurgitation should be considered for PVR.[42] One study looking

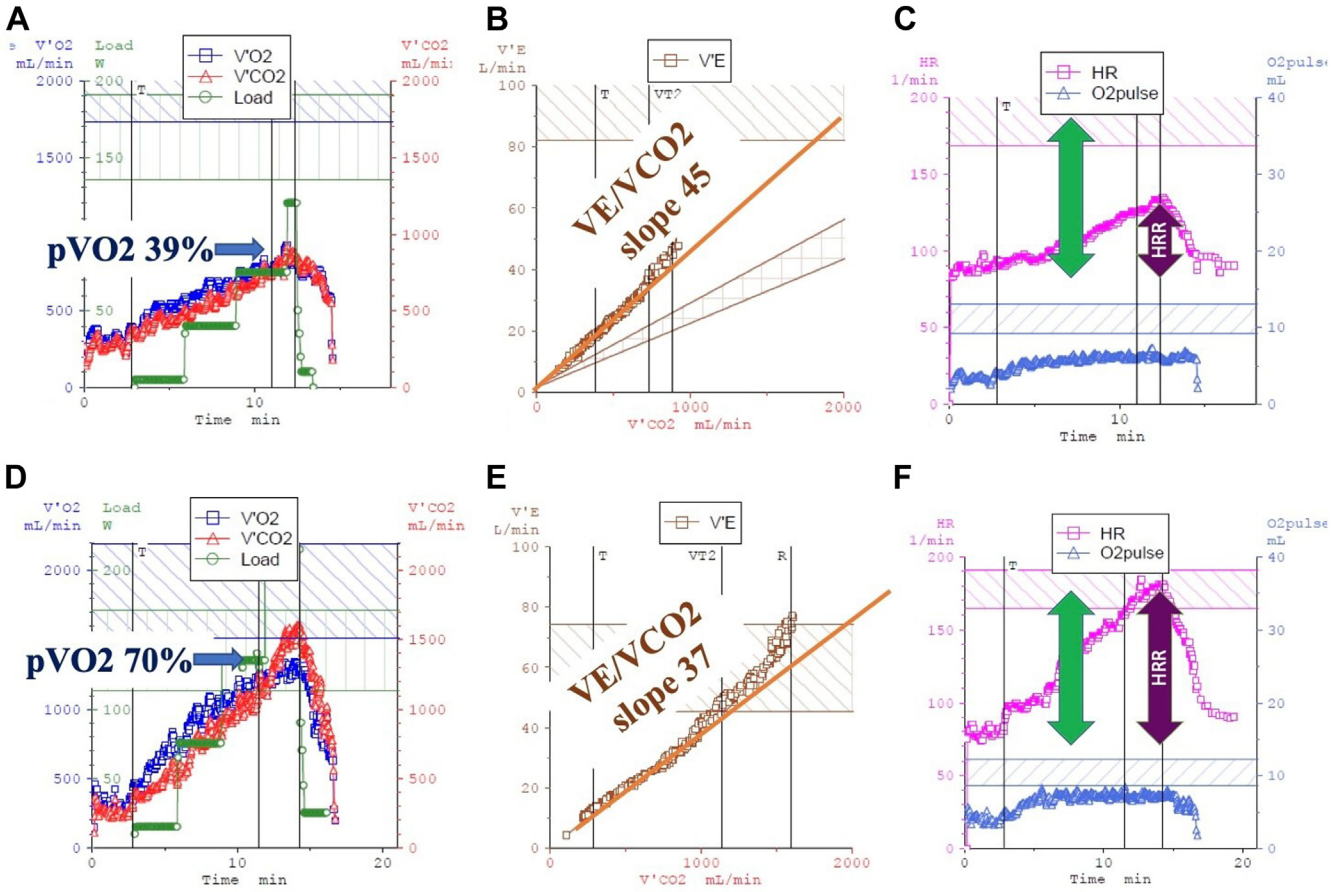

Figure 3. Cardiopulmonary exercise stress test highlighting the physiology limitations in unrepaired and repaired tetralogy of Fallot (ToF). (**A-C**) Cardiopulmonary stress testing of a 30-year-old patient with unrepaired ToF, severe right ventricular outflow tract obstruction, and a bicuspid aortic valve with severe stenosis. The patient stops exercising soon after reaching anaerobic threshold (17 mL/kg/min), with a severely reduced peak oxygen consumption (peak VO_2) (19 mL/kg/min, 39% of predicted as noted in (**A**)) and a raised VE/VCO_2 slope. There is a reduced heart rate reserve (HRR) with a reduced chronotropic index (ratio of **purple to green arrow** in (**C**)) and a low O_2 pulse (**flat blue line** in (**C**)). This patient desaturated from 90% to 80% at peak exercise, with a blunted blood pressure response (systolic blood pressure 96-106 mm Hg at peak exercise). The above cardiopulmonary exercise testing findings are a combination of the severe bilateral obstructive lesions, reduced pulmonary blood flow, and right-left shunting (translating into inefficient ventilation). (**D-F**) Cardiopulmonary stress testing of a patient with repaired ToF and moderate residual pulmonary stenosis. This patient exercised beyond the anaerobic threshold but reached a peak VO_2 of only 70% of predicted (mildly impaired as noted in (**D**)), with a raised VE/VCO_2 slope as shown in (**E**), attributable to the pulmonary stenosis and reduced pulmonary blood flow. (**F**) There is a good HRR and mildly reduced O_2 pulse. VE/VCO_2, minute ventilation to carbon dioxide production.

at cardiac output suggests that a cardiac index of <2.4 L/min/m^2 is predictive of clinical deterioration and could be used as another marker to time PVR and that undergoing PVR in a timely fashion provides survival benefits for these patients.[43]

Although surgical PVR remains the standard of care in patients with severe PR and native outflow tract, transcatheter PVR is usually considered in patients with a previous surgically implanted pulmonary valve or RV to pulmonary artery conduit.[44,45] This is often in the context of progressive valve dysfunction due to its intrinsic lifespan, with the exception of those with significant tricuspid regurgitation in which surgical PVR with concomitant tricuspid valve repair should be considered. In recent years, several self-expanding transcatheter valves have been developed for native outflow tracts, broadening the population of patients eligible for transcatheter PVR.[46]

Patients with ToF are at risk of developing VT with an annual incidence of 0.2% per year. Risk factors for developing VT include older age at surgery, extensive right ventriculotomy, ventricular dysfunction, QRS prolongation or fragmentation, and extensive fibrosis. Patients with symptomatic VT or SCD require an electrophysiologic study (EPS) with ablation of the VT pathway and automated implantable cardioverter defibrillator implantation as secondary prevention.[47] EPS may also be considered in patients with high-risk features of SCD as part of their risk stratification. The role of systematic EPS before PVR is still a matter of debate, with some groups recommending it in all patients with ToF to identify a VT pathway and perform an ablation at the time of EPS or intraoperatively at the time of PVR.[48]

Pulmonary stenosis and right ventricular outflow tract obstruction

In the late 1990s, after 20 years of the TAP technique and its aftermath in terms of PR and RVOT scarring, a new surgical approach was developed, with the aim to preserve the pulmonary valve annulus and valve integrity, sometimes at the cost of residual RVOT obstruction. Indeed, approximately 10% of patients after pulmonary valve sparing surgical correction require reintervention due to residual RVOT obstruction at 10 years of follow-up.[49] While patients with moderate RVOT obstruction can remain asymptomatic or minimally symptomatic, those with severe obstruction often develop exercise intolerance, chest pain, and, less commonly, syncope. Long-standing severe RVOT obstruction can lead to atrial arrhythmias and congestive heart failure. Intervention should be considered for patients with ToF with symptomatic moderate RVOT obstruction or severe RVOT obstruction regardless of symptoms.[42]

Residual shunts

Residual VSDs are uncommon after ToF repair and, when present, are unlikely to be haemodynamically significant. Reintervention for a residual VSD may be considered in symptomatic patients with a ratio of pulmonary (Qp) to systemic flow (Qs) of >1.5 and concomitant dilatation of the left chambers.[50] Careful attention should be given to counselling these patients on the need for infective endocarditis prophylaxis.[51]

Patients with ToF plus an atrial septal defect (ASD) in whom the ASD has not been repaired may present with RV dilation and a haemodynamically significant ASD. In this setting, the decision regarding indication and mode of ASD closure is similar to that of non-ToF patients, though expertise is needed to discern the contribution on RV dilatation of the ASD vs residual pulmonary or tricuspid regurgitation.

Restrictive right ventricle physiology

The mechanism through which some patients with ToF develop restrictive RV physiology is multifactorial and remains unclear. It occurs in approximately 10%-30% of patients after repair. The existing preoperative RV hypertrophy due to the RVOT obstruction renders the tissue susceptible to ischemic injury. Moreover, in the intraoperative period, inadequate RV protection during cardiopulmonary bypass (especially in the early surgical era) can result in myocardial necrosis with subsequent RV fibrosis.[52,53] These pathologic changes can produce a "restrictive" RV, which is characterized by elevated filling pressure and, if severe, decreased preload. Restrictive RV physiology can be diagnosed by echocardiography when a forward presystolic "a" wave is observed in the pulmonary valve pulsed Doppler flow throughout the respiratory cycle.[54] The impact of RV restriction and its associated prognosis are still debated. There are studies that suggest that it may confer long-term advantages in patients with residual PR owing to a decreased predisposition of the RV to dilate and fewer arrhythmias.[55,56] In patients with ToF with restrictive RV physiology, deciding on the timing of PVR in the presence of severe PR becomes complicated, as RV size cannot be relied upon; in such circumstances, evaluation of symptoms and markers of reduced exercise capacity can be of assistance.

Cardiopulmonary Exercise Test in ToF

Cardiopulmonary exercise testing (CPET) has become a fundamental part of the routine assessment of all adults with CHD. Objective assessment of exercise capacity is important in making decisions with regards to the impact of haemodynamic lesions and the need for intervention in patients with ToF. Changes in exercise capacity over time are also important in assessing the effect of chronic residual haemodynamic lesions or the impact of interventions. CPET provides valuable information with regards to the mechanisms contributing to exercise tolerance, which are numerous in CHD, including ventricular dysfunction, chronotropic incompetence, ventilatory inefficiency, and reduced breathing reserve (often related to scoliosis and previous thoracotomies).

The multitude of information and parameters provided by the CPET should all be routinely reported and interpreted (Fig. 3). Peak oxygen consumption (peak VO_2) is the parameter most often reported and used; it is a reliable estimate of maximal exercise capacity and correlates with biventricular function. Moreover, it is a good prognostic marker and often used for referral to transplantation.[57,58] The minute ventilation to carbon dioxide production slope can also provide valuable information on ventilatory efficiency during exercise and reflects physiological dead space. Concomitant evaluation of more standard parameters, such as blood pressure and heart rate response, oxygen pulse (VO_2/HR), oxygen uptake efficiency slope, and oxygen saturation at peak exercise, is also useful.

Mechanisms of exercise intolerance in ToF

The natural history of ToF has been revolutionized by early repair, yet residual lesions are common and exercise intolerance is present in a significant proportion of patients. Inuzuka et al.[59] showed in a large tertiary adult CHD centre that the median peak VO_2 in patients with ToF was reduced at just over 70% of predicted, suggesting that, in this cohort, a significant proportion had a less than normal exercise capacity (Fig. 4).[60] Chronotropic incompetence is also common in ToF, affecting approximately one-half of patients, as is a rise in the minute ventilation to carbon dioxide production slope, all parameters pointing towards a multitude of mechanistic contributors to exercise intolerance in this population.[61,62] Indeed, the routine assessment of patients with repaired ToF is geared towards recognizing, monitoring, and treating/repairing residual lesions and long-term sequelae, most of which can affect exercise capacity.

Role of the CPET in setting the indication for intervention and exercise prescription

Reintervention is common after repair of ToF and is typically aimed at relieving RVOT obstruction or replacing the pulmonary valve, percutaneously or surgically. A reduction in objective exercise capacity is integral in current adult CHD guidelines for recommending PVR or relief of RVOT

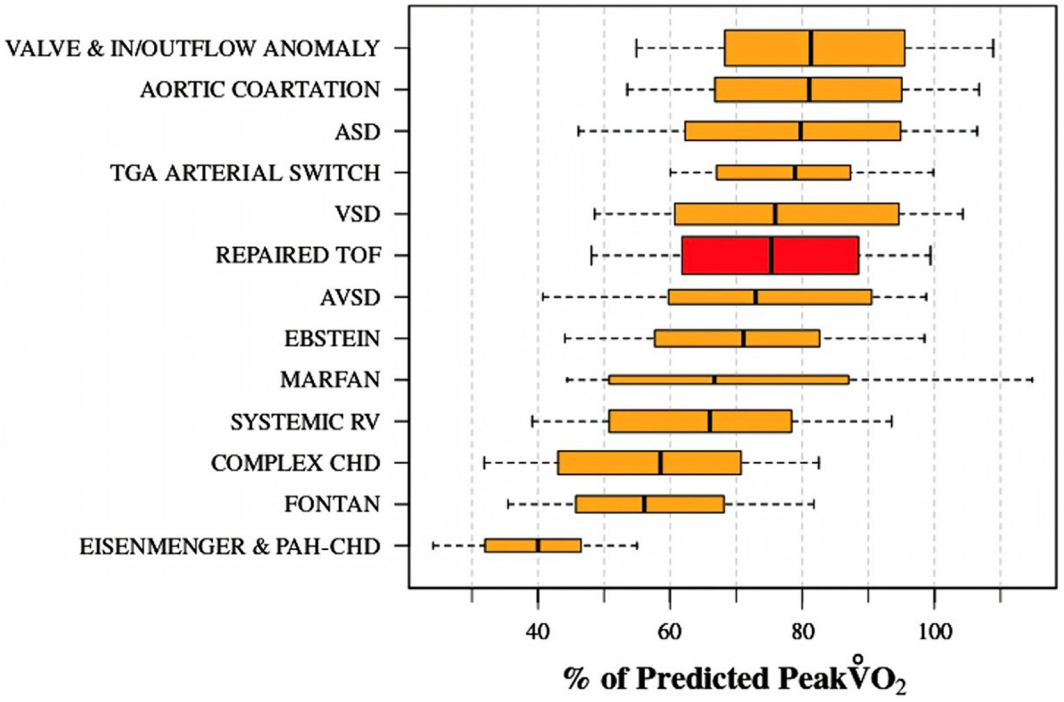

Figure 4. Diagram delineating predicted peak oxygen consumption (peak VO_2) in various congenital heart diseases. Patients with repaired tetralogy of Fallot (ToF) (**in red**) have a median peak VO_2 in the mildly impaired region, suggesting that the majority of patients have at least mild exercise intolerance due to a combination of the congenital defect, residual lesions, and detraining. The box size proportionate to the sample size. ASD, atrial septal defect; AVSD, atrioventricular septal defect; CHD, congenital heart disease; PAH-CHD, pulmonary arterial hypertension related to CHD; systemic RV, systemic right ventricle; TGA, transposition of great arteries.

obstruction in repaired ToF.[63,64] Although the presence of symptoms is important and should be considered, CPET provides an objective means of assessing exercise tolerance and may unmask exercise limitation, even in asymptomatic patients. CPET also provides valuable information on perioperative risk and offers an objective assessment of the impact of surgery or intervention. The relief of pulmonary stenosis appears to translate in a greater improvement in peak VO_2 than intervention for PR.[65]

Deconditioning is common in the adult CHD population and should be avoided through regular exercise prescription, individualized to each patient. Exercise prescription should take into account several parameters, including exercise capacity.[66] CPET provides information regarding not only exercise tolerance but also the type and intensity of exercise that can be safely prescribed for each individual. Finally, CPET is also useful in prepregnancy counselling in adult CHD patients. Heart rate reserve and peak VO_2 are strong predictors of maternal and fetal events in adult CHD patients.[67,68]

Advanced Imaging in ToF

Imaging the RV is crucial in the follow-up of patients after ToF repair, and a multimodality approach has been proposed in recently updated guidelines published by the American Society of Echocardiography.[69] Deciding on optimal timing for PVR remains controversial and has been largely based on imaging data. Both the American College of Cardiology/American Heart Association and the European Society of Cardiology adult CHD guidelines suggest that PVR is indicated in the presence of severe RV dilation, and recent data suggest a benefit of PVR on death or sustained VT, specifically in patients with severely dilated RV defined as RVESVi >80 mL/m^2.[70] These criteria for PVR set the stage for the importance of cardiac magnetic resonance imaging (MRI) in the adult patient cohort but should be applied cautiously to children as there are even less data supporting the use of these criteria for a paediatric population. For children <10 years of age, echocardiography remains the main imaging technique for monitoring RV size and function as cardiac MRI is difficult to perform without sedation or general anaesthesia, especially in younger children. Cardiac MRI in this age group should only be performed for specific indications, such as for assessing pulmonary artery stenosis or in selected patients with severe RV dilatation on echocardiography, especially when associated with RV dysfunction.

When ToF correction is performed around 6 months of life and severe PR is created, significant RV remodelling typically occurs within the first 5 years after surgical repair with RV dilatation generally stabilizing beyond 5-10 years after repair. RV remodelling affects 2 main areas of the RV, basal bulging occurring in the RV lateral inflow portion and dilation of the trabecular apical area, with loss of the typical crescentic shape of the RV.[71] Recent data suggest that basal bulging may be a more unfavourable form of RV remodelling compared with apical dilatation and could be related to

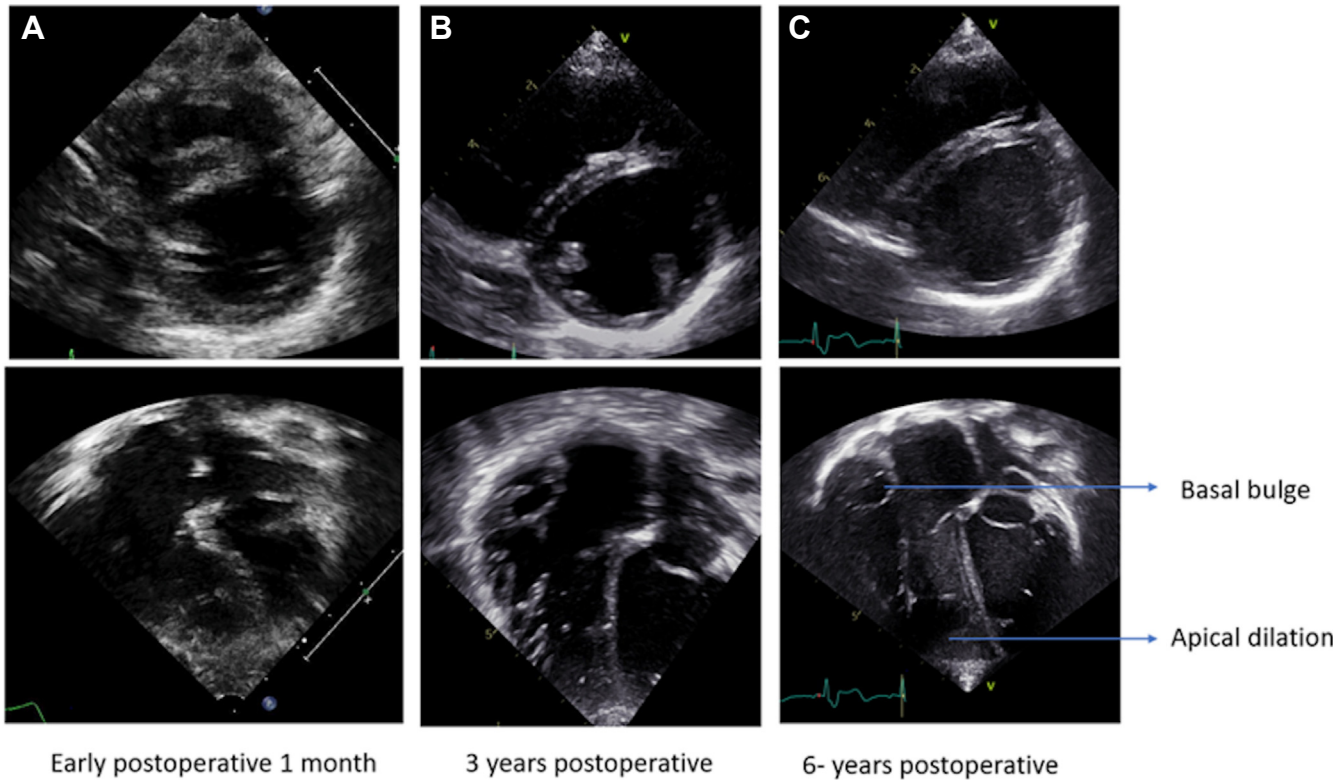

Figure 5. Echocardiographic images of right ventricle (RV) dilatation across the lifespan in repaired tetralogy of Fallot (ToF). Figure delineating progressive changes of the RV anatomy on echocardiography in the same patient after ToF repair. (**A**) The RV is highlighted within 1 month after repair, (**B**) the RV is shown 3 years after repair, and (**C**) the RV is shown 6 years postoperatively. This figure emphasizes that most of the RV remodelling occurs within the first 3 years with significant basal bulging. After 6 years from repair, there was some additional apical dilatation. RV function remained stable with a fractional area change of 43%, RV free wall strain −20%, and RV ejection fraction estimated by 3-dimensional echocardiography at 43%.

abnormal inflow dynamics.[72,73] Progressive RV dilatation beyond adolescence should be considered as a sign of early RV dysfunction as pulmonary regurgitant fraction or regurgitant volume should not significantly increase over time (Fig. 5). Thus, after 10 years of life, intercurrent monitoring of RV size and function by cardiac MRI is recommended every 3 years. In the authors' opinion, as for decision-making in aortic regurgitation, the use of RVESVi may be more sensitive as a combined parameter for RV dilatation and RV contraction. There is less consensus on the current clinical role of late gadolinium enhancement and RV T1 mapping techniques in the routine follow-up.

At all ages, echocardiographic assessment should include RV and LV size and function. In children, an RV end-diastolic area of <20 cm^2/m^2 has been associated with an RV end-diastolic volume index of <170 mL/m^2 measured by MRI.[74] 3D echocardiography with assessment of RV volumes may be a good alternative in selected patients, especially because recent improvements in automated postprocessing of RV volumetric datasets make it more feasible. However, feasibility remains limited as it can be difficult to include the entire RV in a 3D volume, especially if significant dilation is present. Alternatively, a 2D-based 3D reconstruction method relying on magnetic tracking has demonstrated to have high accuracy but requires special hardware and software, limiting clinical introduction.[75]

Strain echocardiography has revealed that RV electromechanical dyssynchrony (EMD) could contribute to the development of RV dysfunction in patients with severe PR, but the role of resynchronization therapy in patients with significant RV dysfunction remains uncertain.[76] The progression of tricuspid regurgitation can also indicate progressive RV dysfunction, and a combination of moderate-to-severe tricuspid regurgitation with severe PR should be monitored closely. Finally, reduced LV function, characterized by decreased LVEF or impaired LV strain, has been associated with a poor outcome in this population.[77,78] Although patients with ToF may develop LV dysfunction, in adult patients with cardiovascular risk factors and LV dysfunction, other causes should be ruled out.

Medical Management of Heart Failure in ToF

The development of chronic heart failure in ToF occurs through multiple mechanisms including myocardial damage, surgical sequelae, conduction abnormalities, adverse interventricular interactions, and coronary artery anomalies.[79] After surgical repair, most of the patients are left with significant PR, leading to RV dilatation and ultimately RV dysfunction. Initially, the end-diastolic volume increases to maintain stroke volume and ventricular mass augments to match wall stress.[80] Eventually, these compensatory mechanisms fail, and heart

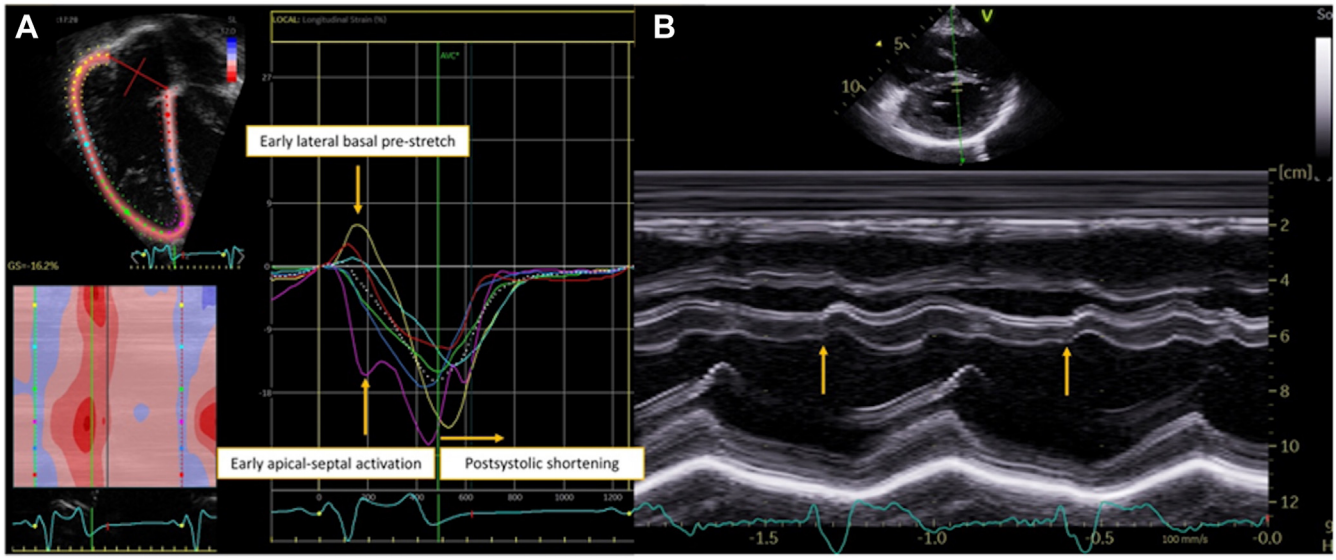

Figure 6. Myocardial strain imaging of the right ventricle in repaired tetralogy of Fallot. (**A**) 2-dimensional myocardial strain imaging. The pattern of activation includes an early septal-apical activation alongside basal-lateral prestretch and postsystolic shortening. (**B**) M-mode image showing a "septal flash" (**arrows**).

failure develops. The phase before the development of right heart failure can be long, and predicting decompensation is challenging.

The principles of managing acute RV failure in patients with ToF are similar to those with predominant RV failure of other etiologies. In patients with RV dysfunction, there is a narrow window for the optimization of cardiac output by modulating RV filling pressure. In this setting, significant volume unloading may be necessary before improvement in RV function is achieved. However, this needs to be performed gradually as the failing RV needs sufficient preload to maintain cardiac output. In parallel, optimizing RV contractility and afterload with inotropes, vasopressors, and/or pulmonary vasodilators, where appropriate, may be required to improve cardiac output and renal perfusion. When inotropes are required, dobutamine, a synthetic β1- and β2-receptor agonist that improves inotropism, and milrinone, a phosphodiesterase-3 inhibitor that increases cardiac inotropy, lusitropy, and peripheral vasodilation, are commonly used. In the context where improved coronary perfusion and maintenance of an adequate mean arterial pressure are required, norepinephrine, a predominately α1- and α2-receptor agonist, or a low dose of vasopressin, is usually preferred to epinephrine or dopamine. Vasopressin reduces pulmonary vascular resistance and increases systemic blood pressure, making it a desirable agent in patients with pulmonary hypertension or severe RV dysfunction. However, at doses >1.16 units/kg/h, it causes pulmonary vasoconstriction potentially resulting in higher afterload on the right heart.[81] Phenylephrine should be avoided because it increases pulmonary vascular resistance and subsequently RV afterload.

The standard guideline–directed medical therapy with β-blockers, angiotensin-converting enzyme inhibitors, ARBs, angiotensin receptor/neprilysin inhibitors, or sodium-glucose cotransporter-2 inhibitors is appropriate in patients with RV failure and concomitant LV systolic dysfunction. However, there is a lack of evidence to support its use in isolated right heart failure.

In patients with ToF, there have been 2 important studies that evaluated the use of some of these pharmacologic agents in isolated RV failure. In the APPROPRIATE (**A**ce inhibitors for **P**otential **PR**evention **O**f the deleterious effects of **P**ulmonary **R**egurgitation **I**n **A**dults with repaired **TE**tralogy of Fallot) trial, which included patients with repaired ToF with moderate-to-severe PR who underwent 6 months of therapy with ramipril or placebo,[18] there was no difference in the primary endpoint of RVEF. In this study, a subset of patients with restrictive RV physiology showed an improvement in indexed LV end-systolic volume and LVEF. A *post hoc* analysis of this cohort showed that treatment with ramipril appears to limit the progression of both diastolic and systolic LV function in this population.[82] The REDEFINE trial included patients with repaired ToF and RV dysfunction (RVEF <50%) but without severe valvular dysfunction. Patients were randomly assigned to losartan or placebo with target treatment duration between 18 and 24 months, and losartan did not show any significant effect of losartan on RV dysfunction.[19]

Despite the lack of randomized controlled trials supporting the use of mineralocorticoid receptor antagonist and loop diuretics in patients with failing RV, these remain the backbone of the medical management of chronic RV failure. The titration of diuretics to maintain optimal preload, and, therefore, cardiac output, needs to be gradual and should be monitored by weight, urine output, urine electrolytes, and serum creatinine.

Cardiorenal syndrome and the failing right ventricle

In patients with ToF, the progression from RV dysfunction to chronic RV failure develops insidiously, often without overt congestive heart failure for long periods, but with a fragile haemodynamic balance and increased vulnerability

towards decompensation as a complication of arrhythmia, infection, and so on. In such circumstances, acute kidney injury is not uncommon as the kidneys are especially susceptible to injury in chronic right heart failure through multiple mechanisms. Renal venous congestion and central venous hypertension can cause renal deterioration in patients with RV failure through altered intraglomerular haemodynamics, sympathetic and baroreceptor stimulation, neural reflexes, renin-angiotensin-aldosterone system activation, and proinflammatory enhancement. The presence of ascites may further compromise renal blood flow and impact kidney function. Finally, altered hepatosplanchnic haemodynamics and hepatorenal syndrome may also contribute to renal dysfunction.

The management of kidney injury in patients with ToF with a failing RV includes close monitoring of urine output and renal function using serum biomarkers. Creatinine often increases with the initiation of diuresis and remains high until cardiac output improves with off-loading. Although creatinine clearance is frequently impaired in these patients, the ability of the kidneys to manage volume, quantified by urine output and sodium excretion, is often maintained. In the case where urine output decreases, inotropes may be used to augment cardiac output. An ideal cardiac output is usually achieved when urine output increases and renal function improves. At this point, it is important to maintain the same dose of diuretics that was used for volume reduction and continue to monitor renal function daily. A gradual trend of renal function improvement should continue until it worsens again, indicating that the patient has reached a euvolemic state.

Electromechanical Dyssynchrony in Patients With ToF: Significance, Assessment, and Treatment

After initial repair, patients with ToF commonly develop a right bundle branch block (RBBB) thought to be caused by surgical injury to the right conducting bundle or its branches.[83] The conduction delay in the activation of the RV free wall manifests as prolongation of the QRS duration (QRSd), which in turn results in dyssynchronous activation and contraction between the early activated apex and septum and the late activated RV free wall causing EMD. The specific and typical pattern of RV EMD in repaired ToF includes early activation of the apex and septum, which causes prestretch of the RV lateral wall, followed by late activation and contraction of the RV mid, and especially basal, lateral free wall.[84–86] In the LV, a mirror-image pattern from the left bundle branch block has been termed "classic pattern dyssynchrony."[87] The delayed activation of the RV basal lateral free wall stems predominantly from the RBBB, although regional conduction delays, related in part to surgical scarring and RV dilatation, may also contribute to QRSd prolongation.[37,86]

RV EMD is associated with decreased exercise tolerance and RV dilatation and dysfunction.[76,88–90] Furthermore, QRSd prolongation is associated with increased incidence of ventricular arrhythmias and mortality.[37,77,91–93] Using patient data and computer modelling, it has been shown that the effect of EMD on exercise capacity is independent of, and perhaps more important than, the effect of chronic PR.[76,89]

As the impact of the electrical conduction delay on cardiac mechanics, function, and remodelling is heterogeneous, there is still a need to characterize the mechanical component of EMD in addition to the RBBB morphology and QRSd on electrocardiogram. The mechanics of RBBB-related EMD can be most readily visualized as an abrupt early systolic rightward motion of the apex-septum during the QRS complex termed as "rightward septal flash."[90] Echocardiography is the most readily available tool to observe the septal flash using visual inspection of the moving image, M-mode, tissue Doppler, or myocardial strain imaging. The use of tissue Doppler has decreased as it is angle-dependent and intrinsically noisy, which can complicate accurate interpretation and measurement.

2D strain imaging captures multiple RV and septal segments simultaneously, at a sufficiently high frame rate, during the same cardiac cycle. Strain imaging can, thus, capture the rightward septal flash and prestretch of the RV basal lateral wall, followed by its late contraction, which define the classic pattern dyssynchrony (Fig. 6). An apical 4-chamber or parasternal short-axis view can be used for the strain assessment of EMD. We prefer the 4-chamber view as it captures the length of the septum, the apex, and the RV basal lateral wall. Nonetheless, beyond characterizing EMD as present or absent based on the observation of a rightward septal flash and the specific pattern of mechanics described above, quantification of EMD, and hence categorization of its severity, remains a challenge.

In practice, QRSd is measured to quantify the electrical component of EMD, although QRS fragmentation and dispersion may also be important.[94] Several indices have been proposed to quantify the mechanical component of EMD. These include analysis of the time to peak strain in the RV basal lateral wall, the delay between apical/septal to lateral onset or peak strain, and mechanical dispersion, defined as the standard deviation of time to peak strain in the third septal and third lateral wall segments (Fig. 6).[84] However, it is important to note that mechanical dispersion is a nonspecific index of incoordinate contraction, which can stem from various causes, not only from EMD. Thus, increased mechanical dispersion can be present without EMD and, in this situation, will not predict response to cardiac resynchronization therapy (CRT). Consequently, only the specific mechanical activation pattern described above and the corresponding QRSd prolongation should be used to define EMD.

The role of CRT in ToF

Although there is extensive literature on CRT to treat left bundle branch block–induced LV EMD, there is a paucity of literature on RV-CRT in patients with repaired ToF, and the data show mixed results.[95–100] Studies in animal models with repaired ToF suggested a favourable effect of CRT, and human studies showed favorable acute haemodynamic effects with increased RV filling time, pressure generation, and ventricular efficiency.[97,98,100–102] These effects coincided with a decrease in QRSd and RV mechanical delay.[96,99] Evidence from noninvasive electrophysiological mapping showed improvement and even abrogation of abnormal activation propagation with CRT. However, there are scant data on the

Table 1. Characteristic, advantages, and disadvantages of different mechanical circulatory support devices

	Device characteristics				Haemodynamics					
	Inflow	Outflow	Flow range (L/min)	Duration of use	RAP	mPAP	CO	Deployment	Advantages	Disadvantages
Protek Duo RVAD	RA/RV	PA	4-5	<24 h	↓	↑	↑	Percutaneous	Single access site with percutaneous deployment	Potential for SVC syndrome
Impella RP	RA/IVC	PA	4-5	14 d	↓	↑	↑	Percutaneous	Single access site with percutaneous deployment	Risk of thrombosis contraindicated in right valvar dysfunction
Surgical CentriMag RVAD	RA/IVC/SVC/RV	PA	Up to 7	30 d	↓	↑	↑	Surgical	Low rate of red blood cell destruction	Surgical implantation
Venoarterial ECMO	RA/IVC/SVC	FA	2-6	Indefinite	↓	↓	↓	Percutaneous or surgical	Percutaneous and emergent bedside deployment	Increased risk of limb ischemia/thrombosis
HeartMate 3	RA/RV	PA	4-6	Indefinite	↓	↑	↑	Surgical	Patient dischargeable to home with a device	Surgical implantation

CO, cardiac output; ECMO, extracorporeal membrane oxygenation; FA, femoral artery; IVC, inferior vena cava; mPAP, mean pulmonary artery pressure; PA, pulmonary artery; RA, right atrium; RAP, right atrial pressure; RV, right ventricle; RVAD, right ventricular assist device; SVC, superior vena cava.

long-term outcomes after RV-CRT with only a few studies reporting medium-term outcomes.[96,103] The patients included in these studies were heterogeneous in terms of their CHD and RV morphology. For example, these studies included patients with a systemic RV, which may have a different prognosis and RV-CRT response rates.[104,105] Lastly, there are significant challenges in patient selection and in the definition and assessment of what constitutes a positive response. Selection of patients based on EMD rather than on nonspecific mechanical dispersion alone is important. As for LV-CRT, refinement of indications and selection criteria can improve CRT response rates. When nonspecific mechanical dispersion was used to assess for RV-CRT eligibility and effect, there was little to no impact on RV function and, at times, QRSd.[95] This lack of granularity in assessment and appropriate candidate selection, together with a heterogeneous patient cohort, may have contributed to some of the negative outcomes observed in studies to date. In the context of the paucity of evidence, the most recent Heart Rhythm Society guidelines support fusion-based pacing in the failing subpulmonary RV with an RBBB pattern (2b, level of evidence C-LD).[106]

In conclusion, EMD is common in repaired ToF and has an adverse independent effect on outcomes. Potential treatment with RV-CRT holds promise and has been shown to be useful in several patient groups with favourable acute and medium-term effects. However, the assessment of EMD, and especially its quantification beyond QRSd, remains challenging. Consequently, there is a lack of adequate granularity in candidate selection and assessment of response to RV-CRT. Together with the heterogeneity in patient cohorts, current evidence should be interpreted cautiously with a pressing need for further research to address these gaps so that RV-CRT can be applied appropriately.

Advanced Therapies in Righ Ventricular Failure

As discussed above, progressive RV failure in ToF can be caused by multiple mechanisms including volume and/or pressure overload, EMD, and/or progressive RV fibrosis.[107] Although RV failure portends poor clinical outcomes, strategies for management of the RV failure depend on etiology.

Progressive RV failure in repaired ToF should be halted by addressing the underlying causes, including replacing dysfunctional valves and evaluating for RV resynchronization therapy. Resynchronization therapy with RV pacing has been effective in improving haemodynamics acutely in patients with RBBB.[108] Similarly, long-term RV-CRT, accomplished by atrial-synchronized single-site RV free wall pacing at sites of late RV activation, demonstrated both an acute and chronic improvement in RV function and synchrony at a medial follow-up of 14.3 months.[100] Postsurgical RV failure in ToF requires a careful evaluation of causal factors to determine medical management.

Acute RV failure caused by pulmonary embolism and myocardial infarction needs judicious management of preload with the use of inotropes and occasionally mechanical circulatory devices. Concomitantly, the use of pulmonary vasodilators is the mainstay of treatment in RV failure in inpatient cardiac care units. However, the utility of these medications in the absence of pulmonary vascular disease is limited. When pulmonary arterial hypertension is present, frank RV failure can be acutely reverted to normal haemodynamics with appropriate medical management. Unlike the LV, the RV pumps in a low-pressure system primarily due to the low resistance of the pulmonary vascular bed. Furthermore, the RV is resilient in maintaining its contractility at high end-diastolic volumes and reverting to normal RV volumes after causal lesions are corrected. Hence, pulmonary vasodilators for RV failure that are directed towards increasing pulmonary compliance have limited applicability in CHD where RV failure can be attributed to nonpulmonary vascular causes such as valve or conduit abnormalities, RV myocardial disease due to fibrosis, and/or EMD.

Mechanical circulatory support in right ventricular failure

In progressive RV failure that fails to respond to medical therapy, mechanical circulatory support (MCS) is

occasionally required as a bridge. Table 1 summarizes various MCS devices, their characteristic, advantages, and disadvantages. These devices include microaxial flow pumps (Impella RP, Abiomed, Danvers, MA), extracorporeal centrifugal flow RV assist devices (extracorporeal membrane oxygenation), and surgically implanted RV assist devices (VAD).

The goal of mechanical support is to facilitate forward flow and support end-organ perfusion while unloading the RV.[109] Unlike the LV, the RV often only requires short-term support to reverse failure because it has lower oxygen demands and increased adaptability to high end-diastolic volumes. This makes microaxial flow controllers feasible without the need to escalate to longer-term support devices. In the case of intra-aortic balloon pumps that are commonly employed in LV failure, they have not been found to be effective in decompressing the RV. On the other hand, the Impella RP has found increased use after the COVID-19 pandemic, when the Food and Drug Administration allowed an emergency use of RV support for COVID-19 infections. However, Impella and other devices with outflow cannula in the pulmonary artery are often problematic in patients with ToF because PR is often present and represents a major contraindication. In these cases, percutaneous PVR in tandem with MCS deployment can be considered.

Finally, clinical experience for the use of extracorporeal membrane oxygenation and VAD to support the RV is primarily derived from non-CHD patients experiencing myocarditis, infarction, postoperative complications, orthotopic heart transplant, and left VAD implantation in one known case with arrhythmogenic RV cardiomyopathy.[110] Despite the optimal use of MCS, in-hospital mortality rates are estimated as high as 70%-75%.[109]

Emerging therapies for right ventricular failure

As RV failure in patients with ToF predominantly results from intracardiac causes, the benefit of pulmonary vasodilators, which primarily targets the pulmonary vasculature, is unclear. There is evidence of myocardial benefit from these drugs, but this is derived from preclinical studies where drugs were tested concomitantly or before injury (such as pulmonary artery banding in mice) and demonstrated prevention of RV dysfunction and fibrosis rather than reversal of long-term disease. The use of pulmonary vasodilators after the implantation of left VAD to prevent RV failure has shown no significant benefit and instead uncovered an increased risk of bleeding, demonstrating that there may be diverse mechanisms in RV modelling.[111] Drugs influencing metabolic, inflammatory, and oxidative stress have also been tested in preclinical and clinical studies and have shown inconsistent results.[112] However, these studies have helped with the identification of serum-based biomarkers that should be tracked to evaluate disease severity and progression. Inflammatory markers such as tumour necrosis factor-α, interleukin (IL)-1β, IL-6, and IL-1, and myeloperoxidase are unequivocally elevated in patients with RV dysfunction.[113–116] However, it is unclear if elevation of these markers is primarily from pulmonary endothelial vs myocardial dysfunction. Hence, clinical benefit of directly inhibiting serum markers with drugs such as anakinra (IL-1β inhibitor), etanercept (tumour necrosis factor-α receptor blocker), tocilizumab (IL-6 inhibitor) as well as modulators or metabolism (eg, rosiglitazone), or oxidative stress (eg, dimethyl fumarate and bardoxolone methyl, both Nerf-1 agonists) is being investigated with clinical trials.[117–121] Early initiation of therapy, use of combination therapy, and targeting markers that have broader anti-inflammatory effects may prove beneficial in achieving the desired clinical benefit. In addition, targeting epigenetic changes associated with chronic RV failure may intervene on the upstream pathways driving chronic RV remodelling in ToF.[122,123] However, epigenetic targets can have antagonistic effects at a tissue or cellular level. For example, histone deacetylase inhibitors with antiangiogenic or proapoptotic effects may be detrimental to the RV myocardium.[124] Hence, careful insight into the mechanism of action is essential for selecting agents for clinical testing.

Emerging Research Directions

Patients with ToF constitute one of the largest cohorts in CHD. Despite this, several research questions remain largely related to the long-term outcomes of heart failure, arrhythmia, and residual pulmonary valve dysfunction. The impact of redo PVR surgically or percutaneously remains controversial. The decision to follow numerical values of RV size and function in patients with subclinical disease who maybe asymptomatic remains problematic when redo surgical interventions are considered in the absence of lifespan long-term data. Trajectories of heart failure measured over decades of life will help measure outcomes that are more meaningful to patients.[125,126] The fundamental question we ask is: how early should we intervene to prevent deterioration of RV function decades later? Large data sources linked to carefully curated clinical data will help map the long-term outcomes with and without interventions that will provide optimal timing of interventions. Linking genetic data to phenotype will also shed light on personalized responses to interventions.

Conclusions

The natural history of repaired ToF is characterized by residual lesions that lead to progressive RV remodelling and insidious onset of right heart failure. Regular monitoring of the RV size and function, as well as exercise capacity, is paramount, and timely PVR should be considered to prevent developing chronic right heart failure. In patients with ToF who do develop chronic RV failure, evidence on medical therapy is lacking; diuretic therapy to maintain an euvolemic state, with careful attention to preload to maintain cardiac output, is critical. Guideline-directed medical therapy is only likely to be useful in those patients with repaired ToF and concomitant LV dysfunction. Some patients might benefit from resynchronization therapy, and an automated implantable cardioverter defibrillator should be considered in patients with sustained ventricular arrhythmias or those with high-risk features of SCD. In patients with acute heart failure, inotropes and vasopressors might be needed, and MCS should be considered in refractory cases. Beyond the short-term benefit, long-term data on the impact of interventions decades later will inform more personalized approaches to management.

Ethics Statement

The research reported has adhered to the relevant ethical guidelines.

Patient Consent

Because this article does not include patient data, the authors confirm that patient consent is not applicable to this article.

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