



Chapter 4

Born with a Failing Right Heart

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Case Presentation

A 37-year-old woman with repaired Tetralogy of Fallot (ToF) was admitted for increased dyspnea on exertion. At age 22 months, she underwent ventricular septal defect (VSD) patch closure and right ventricular outflow tract (RVOT) transannular patch repair and felt well until age 18 years when she noted increased dyspnea on exertion and early fatigue with daily activities. Evaluation at the time revealed severe pulmonary regurgitation (PR), leading to recommendation to undergo surgical pulmonary valve replacement (PVR). This was pursued with successful valve implantation that was complicated by complete atrioventricular (AV)

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node block requiring placement of permanent pacemaker with atrial and ventricular epicardial leads. Her pacemaker was changed to a transvenous dual-chamber pacemaker at age 24 years.

4.1 What Are the Initial Thoughts?

The potential for lifelong heart failure (HF) for patients with congenital heart disease begins at birth. Symptoms and signs of HF depend on the complexity of the anatomic and physiologic disease—with more severe cases presenting at birth or shortly thereafter, necessitating urgent intervention. For those born with a failing right heart, all procedures, regardless of timing and type, should be considered palliative and not curative; despite repeated procedures, cumulative myocardial damage often occurs due to congenital pathophysiology, deranged hemodynamics, and the therapeutic procedures themselves.

4.2 What Is TOF?

Tetralogy of Fallot (ToF) is the most frequent cyanotic congenital heart disease with almost 33 cases per 100,000 live births [1]. The four fundamental features of ToF, first described in detail by Fallot in 1888, comprise of unrestricted malalignment VSD, pulmonary outflow tract obstruction (which may vary and contribute to relative direction and degree of intra-cardiac shunting), overriding aorta, and right ventricular (RV) hypertrophy [2] (Fig. 4.1). Given the advancements in surgical techniques since Lillehei first began operating on patients in 1955, there more patients are surviving, and even thriving, well into adulthood [3, 4]. Because of these advancements, physicians of all fields will encounter these patients.

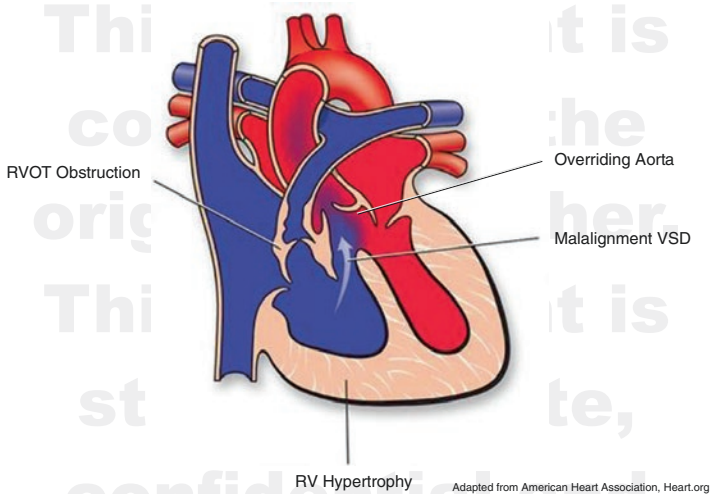


FIGURE 4.1 The four fundamental features of Tetralogy of Fallot (ToF). Tetralogy of Fallot is comprised of malalignment ventricular septal defect (VSD), right ventricle outflow tract (RVOT) obstruction, overriding aorta, and right ventricular (RV) hypertrophy. Adapted from American Heart Association, Heart.org

4.2.1 Anatomy and Physiology

Van Praagh et al. describes ToF as one basic abnormality—the inadequate development of the subpulmonary infundibulum (which may or may not involve the pulmonary valve itself) from which all pathophysiology results [2, 5]. The key to understanding the features of ToF is knowledge of RV anatomy: the inlet portion, the apical trabecular component, and the outflow. The embryology and anatomy of the RV is discussed in Chap. 1.

The hypoplastic infundibulum itself creates the obstruction within the pulmonary outflow tract. The VSD results because the displaced infundibulum no longer fills the area above the septal band and ventricular septum. The hypoplas-

tic infundibulum, which contains the infundibular septum as its floor, does not develop normally in a rightward, posterior, and inferior direction. Consequently, the aortic valve, which attaches to the infundibular septum, is malaligned anteriorly and superiorly, and thus overrides the aorta. In this case, the pulmonary valve (if developed) is often thickened and stenotic. RV hypertrophy occurs in the postnatal period if the RV is exposed to both a significant pulmonary outflow tract obstruction and a large non-restrictive VSD as pulmonary vascular resistance begins to fall [2].

Also in the postnatal period, the ductus arteriosus closes, and infants are solely reliant on the blood exiting the RV and flowing throughout the pulmonary vascular bed for systemic oxygenation. Thus, the degree of RVOT obstruction dictates the postnatal pathophysiology—the greater the obstruction, the less flow into the more distal pulmonary artery (PA). In infants born with significant obstruction (and/or if the pulmonary vascular resistance does not fall), there will be a net right-to-left shunt with flow of deoxygenated (blue) blood across the VSD, especially if it is large and unrestricted, into the systemic circulation, resulting in cyanosis [6].

4.3 What Are the Expected Physical Examination Findings in ToF?

In the post-operative adult, the physical exam directly correlates with the residual sequelae of the surgical intervention. A single S2 is due to the absence of functional pulmonary valve leaflets. A loud P2 may be due to a replaced pulmonic valve and/or pulmonary hypertension. A systolic ejection murmur can be heard if there is a residual outflow tract obstruction or abundant flow due to a regurgitant pulmonary valve. An early diastolic murmur denotes pulmonary regurgitation (PR) while flow due to tricuspid regurgitation (TR) or residual VSD can be heard throughout systole. A diminished or absent unilateral radial pulse and ipsilateral thoracotomy scar are key to the exam for patients who underwent subcla-

vian artery-to-pulmonary artery anastomosis (classic Blalock-Taussig-Thomas {BTT} shunt) in early childhood [7].

4.3.1 Case Continued

On physical examination, the patient's vital signs were normal, and she appeared comfortable. Well-healed sternotomy, abdominal, and deltopectoral scars were noted. The jugular venous pressure was elevated at 10 cm H₂O, and her lungs were clear. Cardiovascular examination revealed an RV heave, normal S1, split S2 with loud P2, a grade II/VI systolic murmur at the left upper sternal border, and a grade II/IV diastolic murmur at the left lower sternal border. Peripheral pulses were normal.

4.4 What Is the Approach to ToF?

The goal for all surgical repair of ToF involves relief of RVOT muscular bundles and/or pulmonary valve annular obstruction, VSD closure, and main PA augmentation (and branches as needed).

Early surgical repair involved an anastomosis of the subclavian artery to the ipsilateral PA in order to augment pulmonary blood flow in those with severe RVOT obstruction (BTT shunt) [8]. The procedure then evolved into the modern approach using a modified BTT shunt with a polytetrafluoroethylene interposition graft between the subclavian and pulmonary arteries, which may be taken down surgically later at the time of repair of the infundibulum and relief of the subpulmonary obstruction [8].

Earlier generations of patients may have undergone central shunt placement with anastomosis of the aorta to one of the branch pulmonary arteries in order to augment flow. Use of these shunts such as the Waterston (right PA to ascending thoracic aorta connection) and Potts (left PA to descending thoracic aorta anastomosis) has fallen out of favor as sys-

temic to pulmonary flow is difficult to control, potentially leading to pulmonary overcirculation, iatrogenic ligation of nearby branch upper PA segments, or early shunt closure [9].

For those undergoing neonatal surgical repair with a narrowed infundibulum, the transannular approach to repair involves a full thickness incision along the infundibulum, effectively splaying it open to relieve the obstruction, followed by patch augmentation at the level of the pulmonic annulus, which fundamentally disrupts the valve architecture in order to provide this relief—sometimes with extension of the patch into the main PA—and VSD patch closure [6, 7, 10].

A valve-sparing technique has been advocated but still involves infundibulotomy or ventriculotomy to access the right ventricular outflow tract and resect obstructive muscle bundles [11]. Full relief of the infundibular obstruction may not result, cumulating in RV hypertrophy, fibrosis, recurrent RVOT obstruction, and a higher chance of reoperation [6, 10, 12].

The use of RV to PA conduit (cadaveric homograft or xenograft) may be necessary if the pulmonary arteries are diffusely small or if the location of the coronary arteries preclude infundibular repair [6]. PA reconstruction may also be required [12].

Non-surgical approaches including transcatheter balloon valvuloplasty and stenting of the infundibulum have been used; the associated sequelae include residual RVOT obstruction, pulmonary regurgitation, tear within the infundibulum/main PA, and aneurysms and pseudoaneurysms within the outflow tract [13].

4.5 What Is the Pathophysiology of Right Heart Failure (RHF) in TOF?

ToF is an excellent model for RHF as the pathology begins before birth and has ramifications throughout life. In utero, the RV undergoes abnormal volume and pressure loading [14]. Concomitant poor development of pulmonary vascula-

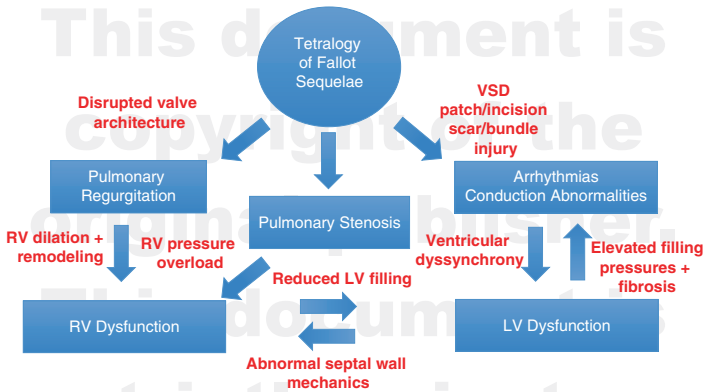


FIGURE 4.2 Pathophysiology of ToF sequelae. *RV* right ventricle, *LV* left ventricle, *VSD* ventricular septal defect

ture capacitance has significant long-term effects, and measurement of this value as a surrogate for RV afterload has noted implications for ventricular failure later on in life [15].

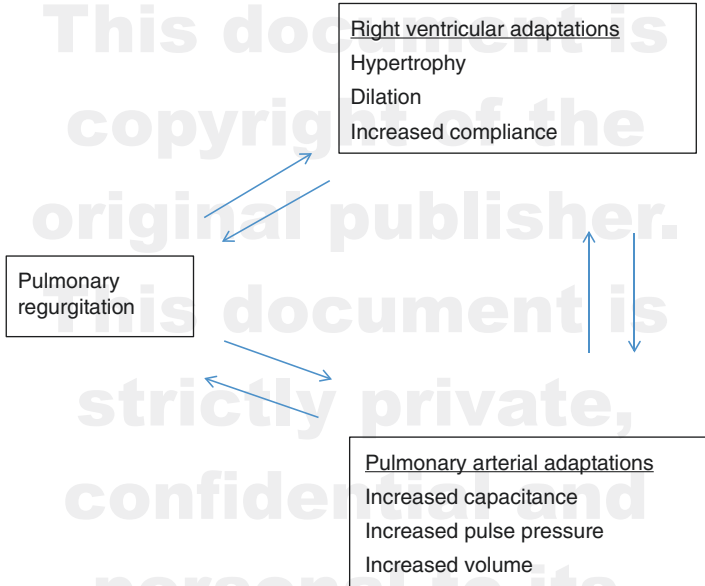
The six key sequelae of repaired ToF include pulmonary regurgitation, pulmonary stenosis, impaired RV function, LV dysfunction, arrhythmias, and conduction abnormalities; these contribute to the increasing morbidity and mortality seen in adulthood [16] (Fig. 4.2 and Table 4.1).

4.5.1 Pulmonary Regurgitation and Biventricular Dysfunction

Relief of RVOT obstruction often comes at the price of PR, resulting in adverse remodeling—as a compensatory measure to preserve stroke volume—due to volume, pressure, or mixed pressure/volume overload [1] (Fig. 4.3). Influential factors include: the duration of diastole, size of the orifice of regurgitation, the capacitance of the PAs, RV diastolic afterload, compliance of the RV, and the diastolic pressure gradient between the main PA and the RV [17, 18]. Alterations in pulmonary vascular resistance affect differential branch PA

TABLE 4.1 The six key sequelae of repaired ToF

Sequelae of ToF repair	Mechanism	Effect
Pulmonary regurgitation	Patch augmentation of the infundibulum → distortion of the annular architecture	Right ventricle dilation + decreased compliance + increased diastolic afterload → decreased global function
Pulmonary stenosis	Residual obstruction in the RVOT, at or above the level of the pulmonary valve, or within the pulmonary vascular bed	RV pressure load → eccentric and concentric hypertrophy → ventricular failure
Impaired RV function	Dilation + remodeling due to increased preload and afterload	Septal bulge → impaired contraction and decreased LV filling
Left ventricle dysfunction	Abnormal septal mechanics	Arrhythmias + symptoms of HF + SCD
Arrhythmias	Elevated filling pressures + scar at surgical site + ventricular fibrosis	HF symptoms, worsening ventricular function, SCD
Conduction abnormalities	Bundle branch injury due to VSD patch or suture placement + scar/fibrosis	Impaired ventricular synchrony → decreased RV + LV function
<i>RVOT</i> right ventricle outflow obstruction, <i>RV</i> right ventricle, <i>HF</i> heart failure, <i>SCD</i> sudden cardiac death, <i>VSD</i> ventricular septal defect, <i>LV</i> left ventricle		



Adapted from Geva, JCMR 2011, 13:9

FIGURE 4.3 Effects of pulmonary regurgitation on right ventricular failure. Adapted from Geva, JCMR 2011, 13:9

regurgitation with etiologies ranging from prior unilateral central shunt placement to external compression of the left lung by an enlarging heart [19].

Similar to LV adaptation to chronic volume loading in the setting of aortic valve regurgitation, the RV undergoes a pathophysiologic response to PR after ToF repair. First, there is a compensated stage during which end diastolic volume (EDV) increases, and eccentric and concentric hypertrophy occurs with maintenance of global systolic function and mass-to-volume ratio [20]. These mechanisms eventually fail (often years to decades later), leading to further ventricular dilation but with decreased mass-to-volume ratio (insufficient hypertrophy) and increased afterload with an associated decrease in global systolic function [17]. Eventually, these sequelae culminate in irreversible myocardial injury, characterized by

increased wall stress, interstitial fibrosis, and dyssynchrony both within the RV and between the ventricles [1, 20]. This remodeling influences ventricular-ventricular interaction on the basis of mechanical and hemodynamic factors through septal geometry changes and chronically reduced left ventricular filling, respectively [21].

4.5.2 *Pulmonary Stenosis*

Residual obstruction in the RVOT, at or above the level of the pulmonary valve, or within the pulmonary vascular bed, can all result after ToF repair as a consequence of surgical intervention itself and/or be inherent within the patient's anatomy. Pulmonary stenosis will result in additional RV pressure load. Animal models with surgically induced pressure overload demonstrate increases in contractile indices, systolic and diastolic reserves, and enhanced contractility via the Anrep effect [22]. This compensation may provide patients with an early protective effect on remodeling by preserving circumferential and radial myocardial strain while also negatively affecting LV intraventricular synchrony [23].

4.5.3 *Arrhythmias and Conduction Abnormalities*

In ToF, the His-Purkinje conduction pathway moves along the inferior aspect of the malalignment VSD, and therefore is often vulnerable to damage during surgery, resulting in classic postoperative right bundle branch block [24]. Atrial and ventricular arrhythmias late after repair are prevalent and correlated with a time-dependent risk of sudden cardiac death (SCD) [7]. Typical atrial flutter is the most common type of atrial arrhythmia in patients with repaired ToF [24]. SCD is the most common mode of death in ToF patients; the overall incidence ranges from 0.15% to 1.2% [25–28]. Risk scoring has been proposed for appropriate ICD shocks in primary prevention for patients with these variables: prior palliative

shunt, inducible sustained ventricular tachycardia (VT), QRS duration ≥ 180 ms, ventriculotomy incision, nonsustained VT, and LV end-diastolic pressure ≥ 12 mmHg; a lower risk score confers a lower risk of annualized rate of appropriate shocks [29, 30].

4.6 What Diagnostic Work Up Would You Recommend?

As shown in Chap. 3, serial imaging studies are required to assess RV size and function. Color Doppler echocardiography provides visualization of regurgitation jets, and pulsed wave Doppler demonstration of diastolic flow reversal in the main or branch PAs, regurgitant fraction $>40\%$, and jet pressure half-time of <100 ms are all indicative of severe regurgitation [31].

Data suggest ventricular size and function predict major cardiac outcomes. Increases in RV volumes and reductions in biventricular ejection fraction by cardiac magnetic resonance imaging (MRI) correlate well with decreases in tricuspid and mitral annular plane systolic excursion (TAPSE and MAPSE respectively). Right and left ventricular peak longitudinal 2-dimensional strain imaging on echocardiography is suggestive of adverse ventricular-ventricular interaction and interrelation of biventricular function [32, 33]. Similarly, myocardial deformation parameters of ventricular longitudinal and circumferential strain as measured by cardiac MRI feature tracking—a technique that assesses strain function—are predictors of outcome of a combined endpoint of death, successful resuscitation, or ventricular tachycardia [34, 35].

RV end-diastolic volume (EDV) dilation (with Z-scores based on published normal values ≥ 7) along with right and/or left ventricular dysfunction as measured on cardiac MRI are predictive of death, sustained ventricular tachycardia, and worsening functional status [36]. A pre-operative indexed RV end-systolic volume (ESV) of >95 mL/m², older age, lower RV ejection fraction, and lower LV ejection fraction are all

associated with adverse outcomes, including death, HF, and sustained VT; an indexed RV ESV $< 80 \text{ mL/m}^2$ is predictive of RV volume and function normalization after PVR [37].

Echocardiography is useful to identify the level of stenosis as well as severity. Moderate stenosis of a native valve is associated with a peak velocity of 3–4 m/s (or 36–64 mmHg) while velocities above 4 m/s (or 64 mmHg) indicate severe stenosis [38]. If an RV-PA conduit is used as part of the original repair, leaflet fibrosis and calcification of the conduit can degrade valve function and/or obstruct blood flow at any location along the entire conduit length [39].

ECG and Holter monitoring can be utilized for surveillance of arrhythmias and have been useful for clinical decision-making, such as referral for electrophysiology study and/or placement of ICD [40]. For patients undergoing programmed ventricular stimulation following ToF repair, inducible monomorphic VT and polymorphic VT predict future clinical VT and SCD [27]. Lengthening of the QRS interval on ECG reflects mechanical asynchrony present within the RVOT (and not within the RV body itself) resulting from prior surgical repair and fibrosis at the surgical site [41].

4.6.1 Case Continued

Our patient's electrocardiogram revealed sinus rhythm with a first-degree AV block, right bundle branch block, and left posterior fascicular block. Interrogation of the pacemaker device showed no arrhythmias. An echocardiogram showed normal LV size and systolic function, grade 1 diastolic dysfunction, moderately enlarged RV with moderately reduced systolic function, flattening of the interventricular septum, and a maximum instantaneous Doppler gradient of 53 mmHg across the RVOT, severe PR, and moderate TR with an estimated RV systolic pressure of 55 mmHg. Cardiac computerized tomography demonstrated unobstructed RVOT, no coaptation of pulmonary valve leaflets, a dilated RV with indexed RV EDV of 140 mL/m^2 ($53.6 \pm 10.5 \text{ mL/m}^2$)

and indexed RV ESV of 80 mL/m² (22 ± 7 mL/m²), a reduced RV ejection fraction of 42%, normal LV size with ejection fraction of 51%, normal sized main and branch PAs, and normal coronary artery course without stenosis.

4.7 What Are the Management Strategies for this Patient?

Patients often enjoy an asymptomatic period that lasts for several decades before manifesting signs of HF similar to their counterparts with acquired heart disease [42]. Archetypal HF symptoms such as exercise intolerance, dyspnea on exertion, volume overload, and fatigue may not be as overt in ToF patients [43].

Medical therapy often includes the same drug classes within the acquired LV HF armamentarium: diuretics; beta-blockers for myocardial preservation and arrhythmia management; and angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), aldosterone antagonists, and angiotensin receptor-neprilysin inhibitor (ARNi) for afterload reduction and prevention of adverse ventricular remodeling [44]. However, the evidence for HF drugs in ToF is lacking in randomized, double-blind placebo-controlled trials [45]. For ToF patients who develop pulmonary vascular disease, disease-targeting drug therapies have been used to decrease pulmonary vascular resistance and improve functional class [46]. Cardiac resynchronization therapy (CRT) has been shown to improve LV ejection fraction with favorable trends in LV volumes in repaired ToF patients who met clinical criteria for upgrade or implantation of CRT pacemaker [47]. Electrophysiological studies and ablative therapies are also employed for arrhythmia management as needed [43]. Additionally, any modifiable HF risk factors, such as tobacco use, obesity, diabetes, or hypertension, should also be addressed [16].

Residual obstructive or regurgitant lesions may require catheter-based or surgical interventions. PVR often improves symptoms in those with combined pulmonary stenosis and regurgitation rather than regurgitation alone and is reasonable in patients with symptoms and/or evidence of RV and/or LV dysfunction [48] (Fig. 4.4). PVR can be performed surgically or percutaneously; transcatheter PVR (TPVR) can be placed valve-in-valve (Medtronic Melody or Edwards SAPIEN valves) within existing RVOT conduits or previously placed surgical valves [49, 50]. Branch PA balloon dilation and stenting may be used for relief of stenosis while collaterals causing pulmonary vascular overcirculation or hemoptysis may require catheter-based coiling or vascular plug deployment [49]. Residual VSD(s), RVOT obstruction(s), PA stenosis, significant aortic regurgitation, RVOT aneurysm, and enlarged aortic root with diameter ≥ 55 mm also may require surgical intervention [51].

Referral for Pulmonary Valve Replacement after ToF Repair

- Symptoms attributed to moderate or more pulmonary regurgitation
 - Chest pain
 - Dyspnea
 - Decreased exercise tolerance
- Any 2 of the following (if symptoms not present)
 - Mild or moderate RV or LV dysfunction
 - Severe RV dilation (indexed RVEDV ≥ 160 mL/m² or RVESV ≥ 80 mL/m² or RVEDV $\geq 2 \times$ LVEDV)
 - RVSP due to RVOT obstruction $\geq 2/3$ systemic pressure
 - Progressive reduction in objective exercise tolerance via CPET or 6 minute walk test
- Sustained tachyarrhythmias
- Residual lesions requiring surgical interventions

Adapted from Stout et al, JACC 2019;73:e81-e192

FIGURE 4.4 Referral for pulmonary valve replacement after ToF repair. *ToF* tetralogy of fallot, *RV* right ventricular, *LV* left ventricular, *RVEDV* right ventricular end diastolic volume, *RVESV* right ventricular end systolic volume, *RVSP* right ventricular systolic pressure, *RVOT* right ventricle outflow tract, *CPET* cardiopulmonary exercise testing. Adapted from Stout et al., JACC 2019;73:e81-e192

4.8 What Are the Options for Advanced Therapies?

Advanced HF therapies have been employed in repaired ToF patients, including inotrope and vasopressor therapy, ventricular assist device (VAD), and heart transplantation [52, 53].

VAD placement for a subpulmonic RV is technically challenging given the anterior position of the RV, and its use is limited [54]. Data for the use of a subaortic LV VAD is also limited, though mortality is similar to those without congenital heart disease [55–57]. RV dysfunction often precludes LV VAD therapy. Cardiac transplantation may also be used in severe HF, but patients often have longer wait-list times and congenital heart disease-specific factors that may affect transplant candidacy, such as allo-sensitization, pulmonary hypertension, surgical challenges (e.g. adhesions, collateral vessels, PA reconstruction), and liver dysfunction [52, 58, 59]. Palliative care may be appropriate for those who are not candidates for advanced HF therapies [52] as discussed in Chap. 12.

4.9 What Is the Prognosis?

The utility of cardiopulmonary exercise testing (CPET) has been highlighted as a tool in the management of patients with HF. CPET provides insight into cardiac physiology as well as the response of pulmonary and musculoskeletal systems to the metabolic demands of exercise; use of peak VO_2 (peak oxygen consumption) and V_E/VCO_2 slope (minute ventilation-carbon dioxide output relationship, a measurement of ventilation-perfusion matching) has been described in risk stratification for patients with repaired ToF [60]. Multiple factors associated with repaired ToF influence myocardial reserve, including pulmonary and tricuspid valve regurgitation, RV-LV interactions, wall motion abnormalities due to surgical patches within the RVOT and ventricular septum, conduction abnormalities, neurohormonal imbalances, and myocardial architectural damage.

In turn, these factors affect the hemodynamic disturbances seen during exercise as noted by changes in submaximal and maximal CPET measurements [61].

Use of HF tools, such as the Seattle Heart Failure Model, for risk stratification in adults with congenital heart disease can help identify populations at high-risk for death and cardiovascular hospitalization [62]. Biomarker measurements may also be helpful as elevated levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin T, and growth-differentiation factor 15 have been associated with cardiovascular events [63, 64].

4.9.1 Case Conclusion

On the basis of the findings above, the patient underwent TPVR with a bovine pericardium bioprosthetic valve with a valve-in-valve approach. Her post-procedural course was uncomplicated, and on clinic follow up, her symptoms had resolved.

Clinical Pearls

- Heart failure in repaired ToF manifests as volume overload, atrial and ventricular arrhythmias, and decreased exercise tolerance.
- ToF results from infundibular septum hypoplasia, and surgical repair focuses on relieving RVOT obstruction, often at the expense of pulmonary regurgitation.
- Exam findings directly correspond to the sequelae of surgical repair, including single S2, murmurs of pulmonary stenosis and/or regurgitation, diminished or absent radial pulse due to prior BTT shunt, and residual VSD murmur.
- Electrocardiogram and echocardiogram are important diagnostic tools in patients with acute HF symptoms. Cross-sectional imaging, such as CT and MRI, is utilized for interventional planning. CPET can be used for prognostication. Invasive assessment of hemodynamics may be of particular utility when RHF is longstanding or concomi-

tant liver impairment is suspected, given the propensity towards low systemic vascular resistance in these cases.

- Diuretics and antiarrhythmics may be given in the acute presentation of HF. Standard HF guideline-directed medical therapy is often used for afterload reduction and prevention of adverse remodeling, though compelling data supporting long-term use are lacking. Pulmonary vasodilators are utilized in concomitant pulmonary hypertension management. Ablative therapies may be beneficial in specific instances of tachyarrhythmia; pacemakers and ICDs may be useful to treat bradyarrhythmias and to reduce incidence of sudden cardiac death.
- Advanced therapies, including inotrope infusion, mechanical circulatory support, and heart transplantation are generally offered for refractory heart failure.
- Diagnostic evaluation and therapeutic strategies for patients with RHF associated with congenital heart disease should be reviewed in conjunction with expert clinicians in the management of congenital heart disease.

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