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# The right ventricle in tetralogy of Fallot: adaptation to sequential loading

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Right ventricular dysfunction is a major determinant of outcome in patients with complex congenital heart disease, as in tetralogy of Fallot. In these patients, right ventricular dysfunction emerges after initial pressure overload and hypoxemia, which is followed by chronic volume overload due to pulmonary regurgitation after corrective surgery. Myocardial adaptation and the transition to right ventricular failure remain poorly understood. Combining insights from clinical and experimental physiology and myocardial (tissue) data has identified a disease phenotype with important distinctions from other types of heart failure. This phenotype of the right ventricle in tetralogy of Fallot can be described as a syndrome of dysfunctional characteristics affecting both contraction and filling. These characteristics are the end result of several adaptation pathways of the cardiomyocytes, myocardial vasculature and extracellular matrix. As long as the long-term outcome of surgical correction of tetralogy of Fallot remains suboptimal, other treatment strategies need to be explored. Novel insights in failure of adaptation and the role of cardiomyocyte proliferation might provide targets for treatment of the (dysfunctional) right ventricle under stress.

## KEYWORDS

tetralogy of Fallot, right ventricular dysfunction (RV dysfunction), myocardial adaptation, pulmonary regurgitation, congenital heart disease, ventricular hypertrophy, animal models

## 1. Introduction

Tetralogy of Fallot (TOF) is the most prevalent diagnosis in most follow up cohorts of complex congenital heart disease (CHD) (1, 2). Present day practice of direct early surgical correction significantly reduced mortality and the average life expectancy has risen to well above 60 years of age (3, 4). Unfortunately, the growing cohort of survivors with TOF exhibits a number of late sequelae, e.g., development of heart failure, necessity of re-interventions and arrhythmogenic vulnerability (5).

Heart failure is the most common cause of death in survivors with CHD and its prevention in TOF is one the three major focus areas in research (3, 6). Heart failure in TOF is mostly right ventricular (RV) failure and in many cases associated with chronic pulmonary regurgitation (PR), a common complication following the surgical intervention aimed to relieve pulmonary stenosis (7). The development of the RV failure has been studied extensively in the last decades, albeit mostly in models of acquired RV pressure

overload and pulmonary hypertension, a disease phenotype with several major dissimilarities from TOF and chronic PR.

Currently, medical treatment options for RV failure are lacking (8, 9). The most common treatment for patients with PR is pulmonary valve replacement. Timing of pulmonary valve replacement is highly debated, as repeat interventions due to child growth and valve graft degeneration are major limiting factors in its application. Furthermore, re-intervention for pulmonary valve replacement also fails to reduce incidence of RV failure or death, despite improvement of RV volumes and symptoms (10, 11).

Identification of novel targets for treatment of RV failure is necessary, which requires a deeper understanding of the shift from adaptive remodeling to failure. To be able to develop strategies to predict, detect, treat, or prevent heart failure and other late sequelae in TOF, a thorough understanding of the myriad of drivers of disease progression is needed. The drivers of other late sequelae, e.g., malignant arrhythmia, might overlap with those of RV dysfunction but will not be specifically discussed.

This narrative review will focus on what is known of the mechanisms of RV dysfunction in TOF, chronic PR and present knowledge-gaps. We aim to integrate information from functional, cellular and molecular studies with clinical data and explore potential targets for therapy.

## 2. Sequential loading: abnormal loading during growth and development

Patients with TOF experience a unique sequence of abnormal loading conditions, which affects myocardial adaptation and ultimately cardiac function. Unlike in the normal heart, there is no unloading of the RV at birth when separation of the systemic and pulmonary circulation occurs. Due to right ventricular outflow tract (RVOT) obstruction, the postnatal RV remains subjected to pressure overload, as in the fetal circulation, and the myocardium retains some of its fetal characteristics after birth (12). In addition, most infants with unrepaired TOF develop hypoxemia due to ventricular right-left shunting. This combination of pressure overload and hypoxemia persists and requires corrective surgery to prevent imminent RV failure (13). After corrective surgery, repaired TOF (rTOF) patients experience different degrees of PR inducing volume overload (Figure 1). This volume overload is introduced in an already pressure overloaded RV and will affect RV function differently opposed to introducing isolated PR in an otherwise healthy RV (14). RVOT structure and function may be altered due to patch repair and right bundle branch block may eventually predispose to dyssynchrony. In some cases, residual RVOT obstruction remains present after corrective surgery. Unloading of volume and/or pressure overload can occur after pulmonary valve replacement. For isolated pressure overload, other invasive treatment options may be required. Limited valve graft durability, however, often results in recurrence of PR, RVOT obstruction or a combination of both (15). This might require repetitive

pulmonary valve replacements, posing a heavy burden on patients without the guarantee of freedom from adverse events (10, 11).

Thus, this pattern of sequential loading and hypoxemia gives rise to a complex physiology. In understanding this response, the separate mechanisms, their interactions and the time-relationship should be taken into account.

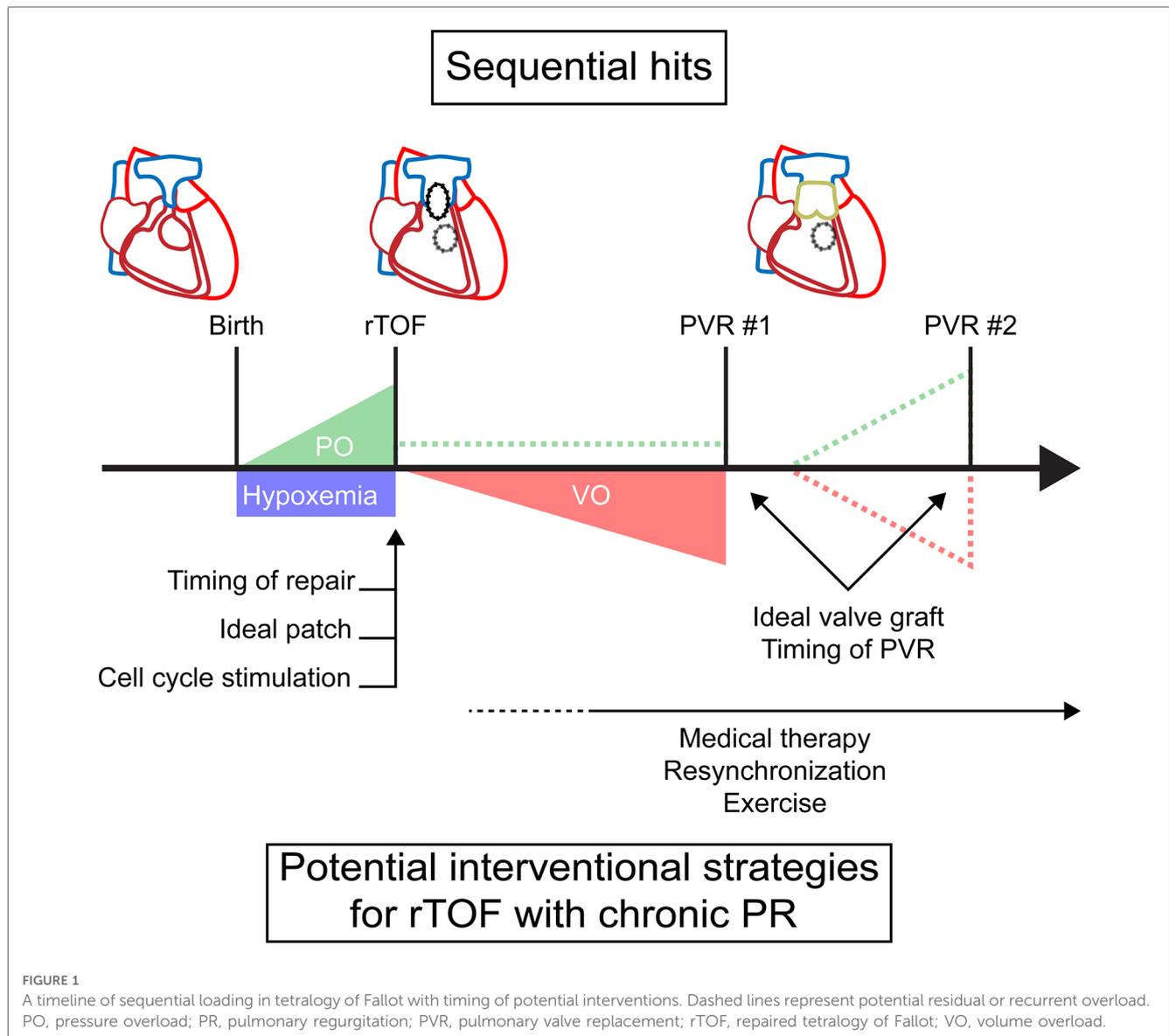
## 3. The phenotype of right ventricular dysfunction

The temporal profile of RV adaptation to RV failure has multiple features, of which the causality is difficult to define. RV dilatation and prolonged QRS duration have been first recognized as hallmarks. Features of (mal)adaptation of the RV may be categorized into three groups: factors affecting ventriculo-arterial interactions (systolic function, PR), factors affecting atrio-ventricular interactions (e.g., impaired relaxation, atrial dysfunction), and factors affecting interventricular interactions (e.g., dyssynchrony, septal shift) (Figure 2).

### 3.1. Systolic dysfunction and ventriculo-arterial interactions

RV dilatation has been recognized as hallmark of RV dysfunction in pulmonary hypertension (16). In patients with rTOF with PR, progressive RV dilatation is a response to the PR-induced volume overload. Although (progressive) RV dilatation is widely used in guidelines for timing of pulmonary valve replacement, this strategy does not always ensure a favorable long-term outcome (11, 17, 18). In addition, longitudinal follow-up has demonstrated that RV dilatation is an unreliable marker of adverse events (19–22). Dilatation can contribute to development of secondary tricuspid regurgitation and the majority of TOF patients present with at least mild tricuspid regurgitation when referred for pulmonary valve replacement (23). Especially in the basal and mid-ventricular portions of the RV, geometrical changes of the tricuspid valve apparatus cause leaflet malcoaptation due to annular dilatation and papillary muscle displacement (24). Tricuspid regurgitation will lead to additional RV volume overload and might not necessarily regress after pulmonary valve replacement without concomitant tricuspid valve intervention (25).

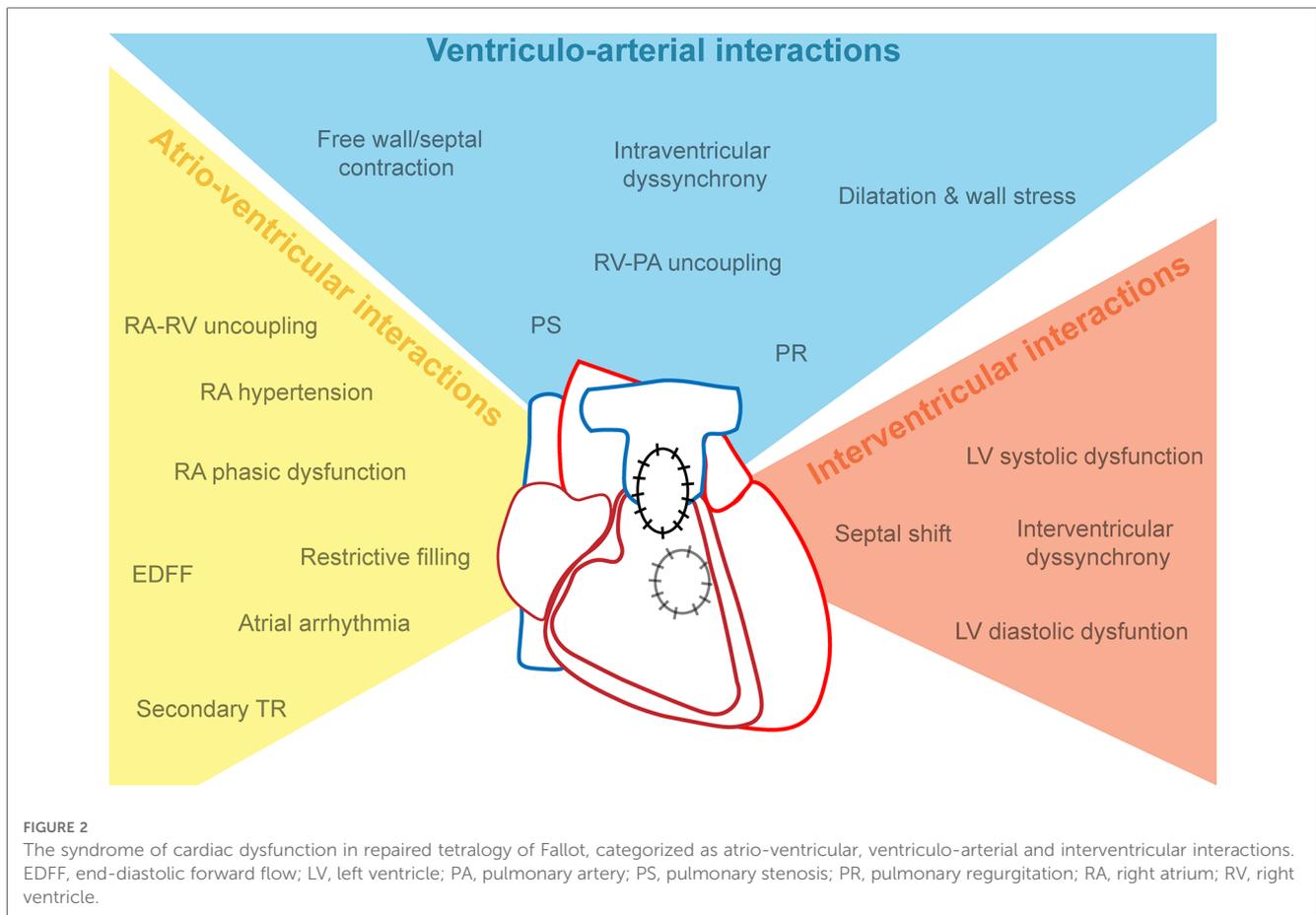
RV dilatation in response to pressure overload, e.g., in pulmonary hypertension, is a hallmark of decompensation due to failure of homeometric adaptation (26). According to the law of Laplace, the larger inner diameter will increase wall stress (and thus afterload) if wall thickness and transmural pressure remain constant. In rTOF, RV dilatation can be accompanied by reduced ejection fraction signaling RV systolic dysfunction (27–29). However, decreases in RV ejection fraction over time are small and occur slowly, making it not an ideal marker for disease progression (19, 21). Maximal elastance, the load-independent assessment of contractility, remains the gold standard for systolic



function, but data from invasive studies in rTOF are scarce and none of those studies compared rTOF patients to healthy controls (30, 31). Experimental models of chronic PR show a decrease in load-independent measures of contractility, such as maximal elastance and preload recruitable stroke work, which is an important distinction from the increased contractility observed in response to pressure overload (32, 33). Additionally, surgical RVOT scarring due to transannular patching significantly impairs RV contractility even further, due to RVOT aneurysm and akinesia (27, 34). Regional dysfunction might also be attributed to electromechanical dyssynchrony resulting in mechanical inefficiency of myocardial contraction (35).

Non-invasive markers of systolic function, e.g., RV ejection fraction, tricuspid annular plane systolic excursion and strain, are heavily load-dependent and a reflection of ventriculo-arterial coupling rather than contractility (36). Ventriculo-arterial coupling is the relation of contractility to pulmonary arterial

afterload, an increasingly popular concept for assessment of RV systolic function. In pulmonary hypertension, deterioration of ventriculo-arterial coupling is a prelude to RV failure (37). As of date, its role in TOF remains unclear. Invasive assessment of ventriculo-arterial coupling and contractility has been performed only by Latus et al. (30). When comparing data of pulmonary hypertension patients with the study of Latus et al., shown in **Figure 3**, it appears that both contractility and afterload are much lower in rTOF, but the coupling ratio is decreased too (30, 38, 39). Of note, these different studies use different methods, so direct comparison is impossible. A recent study has published on ventriculo-arterial coupling in rTOF, non-invasively assessed by using cardiac magnetic resonance (CMR) derived RV volumes only (40). The need for pressures in the equation is supposedly eliminated by forcing the linear regression of the end-systolic pressure volume relation through the origin. Thereby, this method is nothing more than a variation on RV ejection fraction.

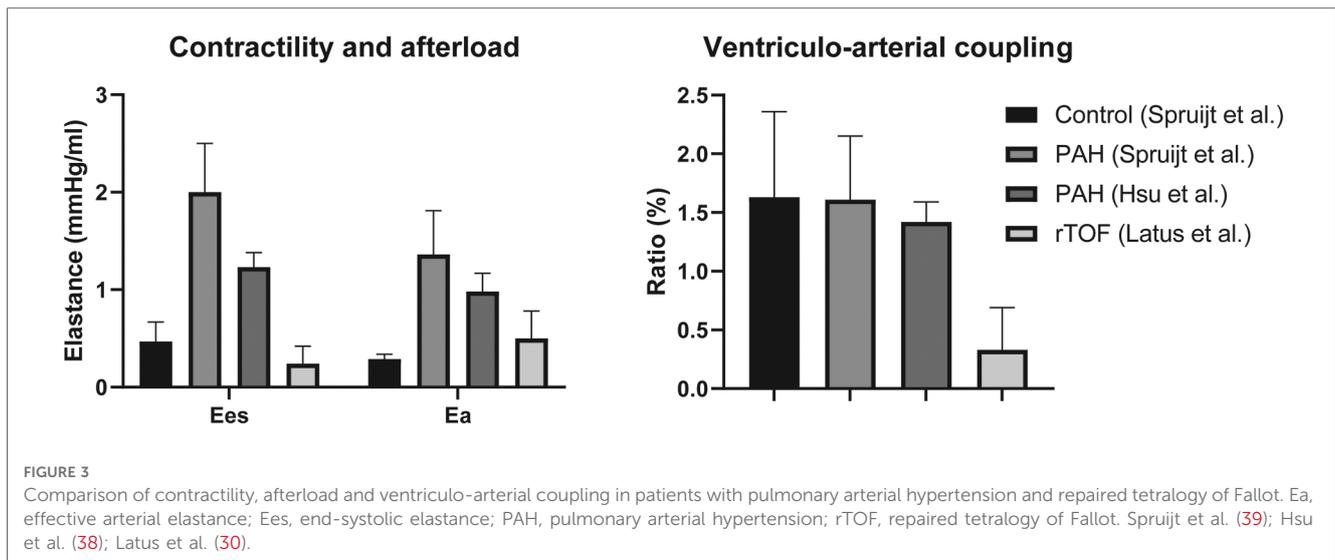


### 3.2. Diastolic dysfunction and atrio-ventricular interactions

Diastolic dysfunction might be an earlier, more prominent feature of maladaptation than systolic dysfunction. PR, the main hemodynamic lesion after corrective surgery, occurs during diastole (Figure 4). In the healthy RV, 4-dimensional flow measurements using CMR suggest that the inflow pattern allows an efficient outflow to the pulmonary artery during subsequent contraction. In rTOF patients with PR, however, abnormal diastolic flow patterns were consistently present, whereas systolic flow remained preserved in the large majority (41). From these studies it appears that PR flow interferes with normal diastolic vorticity enhancing RV filling from inflow to outflow, as is illustrated in Figure 4 (41, 42).

The purpose of diastole is to fill the ventricular cavity. Signs and symptoms associated with diastolic dysfunction include increased filling pressures, right atrial (RA) enlargement and peripheral edema. A general definition is lacking as several mechanisms may cause of diastolic dysfunction, such as impaired relaxation, increased stiffness or interventricular interactions. For this manuscript, diastolic dysfunction will be defined as the inability of the RV to fill in an energetically efficient manner. Normal diastolic function requires sufficient preload and low myocardial stiffness. Whereas preload in rTOF patients is generally maintained because of PR, it is not clear to

what extent myocardial stiffness is affected. Invasive measurements in rTOF patients demonstrate increased RV end-diastolic pressures in half of the patients (43, 44). One study grouped pediatric and adult rTOF patients according to their indexed end-systolic volumes (cut-off 34.7 ml/m<sup>2</sup>) and found that patients with lower indexed end-systolic volumes also had higher myocardial stiffness, measured as load-independent end-diastolic elastance (31). In animal models of chronic PR, however, findings on end-diastolic elastance are conflicting, although a significantly higher stiffness was found in animals with pressure load-induced RV hypertrophy preceding the induction of PR (14, 45–47). In pressure overload, this increased stiffness as a result of reactive interstitial fibrosis is found only in more severe RV dysfunction (48). In isolated volume overload, however, interstitial fibrosis is not as commonly found (14, 46, 47, 49–51). Apart from fibrosis, myocardial stiffness is also determined by intrinsic stiffness of the cardiomyocytes, which mainly includes titin expression, its isoforms and phosphorylation, but also other sarcomeric and cytoskeletal proteins (52). Ex vivo studies on RV myocardium of rTOF patients demonstrated that myocardial and passive myofilament stiffness was not affected when compared to control samples (49, 53), which is in accordance with the observation that titin expression, isoforms and phosphorylation were unchanged in TOF patients (53–55). Other proteins have been associated with RV stiffness in TOF, mainly those involved in sarcomeric



structure and calcium signaling, such as Z-disc proteins, tropomyosin-1 and phospholamban (54).

Unfortunately, demonstrating presence of diastolic dysfunction is complicated by the lack of reliable markers. Common measures of RV filling based on tricuspid inflow/annular velocity ( $E/A$ ,  $E/e'$ ) do not correlate with RV end-diastolic pressure, and do not take the contribution of PR filling and increased diastolic vorticity into account (44, 56). Presence of end-diastolic forward flow during atrial contraction has been suggested to indicate reduced myocardial compliance during diastole, also referred to as “restrictive physiology”. Its role as a marker of dysfunction or poor prognosis is contested however (57–63).

Atrial function relates closely to diastolic ventricular function. Atrial functional measurements may therefore provide insights in the mechanisms of diastolic dysfunction and may serve as a disease marker, since robust alternatives are lacking. Increased RA pressures predict adverse cardiovascular events (64). RA phasic function has found to be altered in rTOF, with abnormalities in reservoir, conduit and pump function (Figure 4) (62, 65, 66). Load-independent atrio-ventricular coupling has not yet been investigated in TOF, but was found to be impaired in a model of early LV diastolic dysfunction and could serve as an early disease marker (67).

### 3.3. Interventricular interactions

In the assessment of RV systolic function, the role of the interventricular septum (IVS) is often underexplored relative to the RV free wall. The presence of the ventricular septal defect (VSD) divides the deep myocardial layer of the IVS, resulting in a reduction of longitudinally oriented myofibers (68, 69). Since 80% of the RV function is derived from longitudinal shortening, VSD-induced IVS dysfunction could add to global RV dysfunction. This type of dysfunction has received little attention (70). Interestingly, patients with isolated VSD show signs of

impaired RV function late after VSD closure, but to what extent the IVS contributes to this dysfunction has yet to be determined (71, 72).

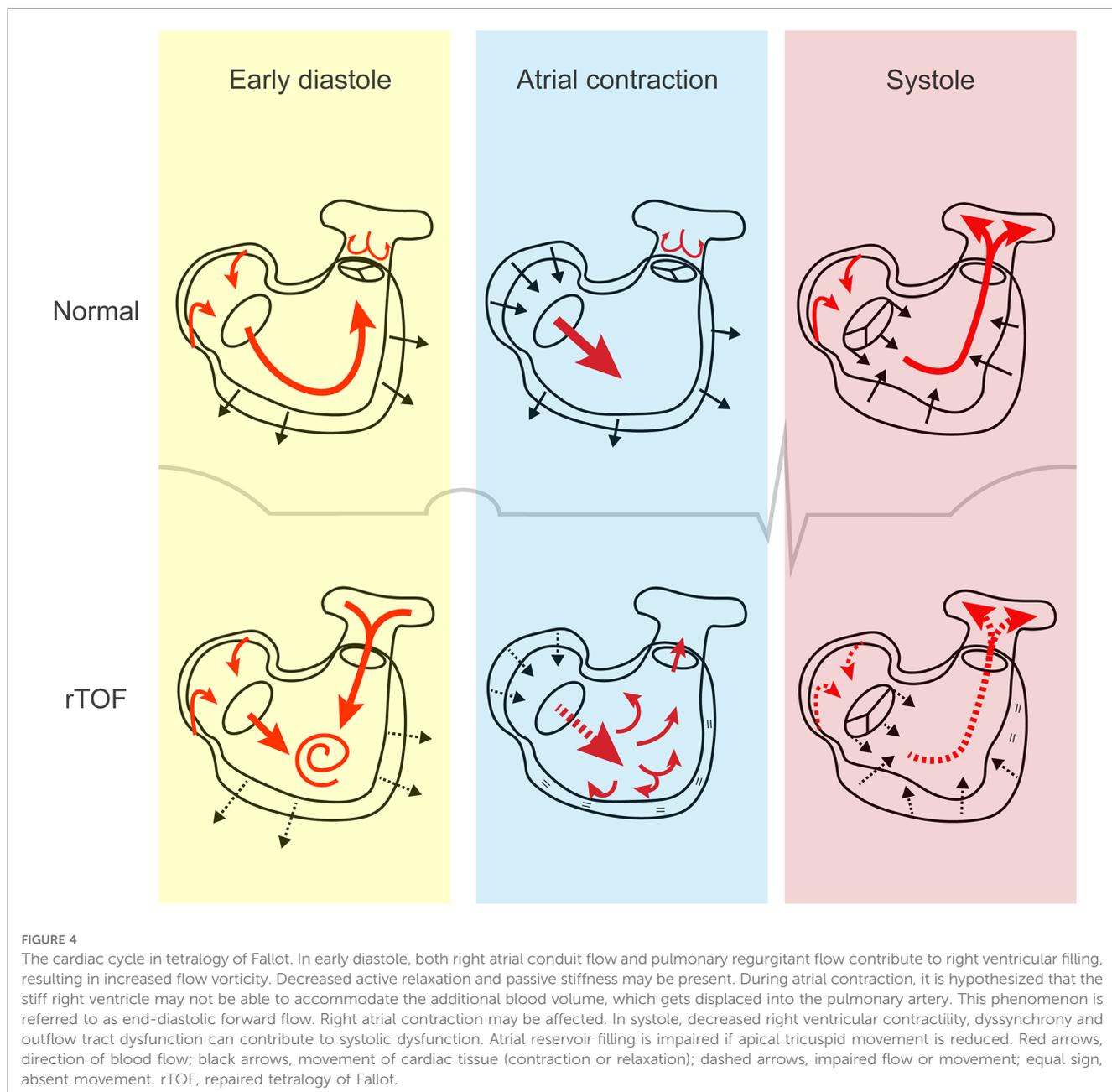
In recent years, it has become apparent that LV function is also affected in rTOF. LV diastolic dysfunction is commonly the result of geometrical changes and increased RV diastolic pressure, causing a leftward shift of the IVS hindering LV filling (46, 62, 73, 74). LV systolic dysfunction is found in 20% of rTOF patients and is independently associated with adverse outcomes (75, 76). Isolated PR does not seem to affect LV contractility *per se*, but electromechanical and interventricular dyssynchrony have been demonstrated as potential relevant mechanisms of biventricular dysfunction (77–79).

In summary, the phenotype of RV dysfunction can be regarded as a syndrome encompassing disturbed filling, dyssynchrony, and perhaps disturbed ventriculo-arterial coupling (Figure 2). The combination of abnormal diastolic flow patterns and reduced myocardial relaxation may lead to significant kinetic energy loss in diastole. In systole, lower contractility and dyssynchrony impairs efficient flow from the RV inlet into the pulmonary artery (41, 80, 81). A deeper understanding of the temporal relation and interactions between all these mechanisms is necessary to design specific treatments and preventive strategies.

## 4. Histopathology: what do we know?

Studies on histopathology of TOF are scarce. Consequently, much of what is known is derived from historical observations, mostly from patients corrected at what is presently regarded as “later stages”, e.g., more than 6 months of age or at death after uncorrected survival into adulthood (82–86). Hence, results may be affected by survival and selection bias, particularly in the group of patients studied during re-do surgery.

Most commonly described histopathological features are myocyte hypertrophy, fibrosis and altered capillary density. The



degree of hypertrophy increases with age, likely initially as an adaptive response until a point of no return is reached with onset of maladaptive features (87–89). In a single-center study comparing biopsies obtained at primary repair between 4 months and 168 months of age, the degree of hypertrophy correlated with RV function, assessed as global strain. The recovery of RV strain after corrective surgery was reduced in the group of patients corrected after 1 year of age, suggesting irreversible remodeling if repair surgery is postponed (89). The hypertrophy is not homogenous; a postmortem study identified larger endocardial cardiomyocytes in the infundibulum as compared with other regions of the RV (90). In biopsies taken at a younger age less cardiomyocyte hypertrophy was found, which might be explained by the shorter exposure to overload (87–89). Alternatively, cardiomyocyte proliferation may be increased,

enhancing RV adaptation. After birth, cardiomyocyte proliferation capacity is lost in mammals as a result of several postnatal processes, such as changes in oxygen levels and the transition from placental to enteral nutrition (91). However, recent studies have shown that cardiomyocytes retain the potential to proliferate after birth when under stress (12, 92).

Cardiomyocyte proliferation promotes adaptation to pressure overload better than cellular hypertrophy (92–95). Stimulating proliferation in mature cardiomyocytes or prolonging proliferative capacity after birth is therefore an attractive treatment target to preserve function of the overloaded RV. From cultured cardiomyocytes, isolated from biopsies of TOF patients, Liu et al. reported a high proportion of binucleated cardiomyocytes. This indicated that proliferation was initiated under adverse loading, but arrested in the cytokinesis stage. The

authors demonstrated that failure of cytokinesis is mediated by beta-adrenergic signaling and that beta-adrenergic blockade can increase cell division by rescuing cardiomyocytes from cytokinesis failure. Additionally, this was confirmed in a neonatal mouse model of myocardial infarction (96). Although a previous randomized controlled trial (RCT) of beta-blockade in adult rTOF patients could not demonstrate a clinical benefit, a new RCT is being conducted to investigate its effects on cardiomyocyte proliferation in infants before repair surgery (ClinicalTrials.gov Identifier: NCT04713657) (9). Cell cycle activity can also be stimulated by administration of neuregulin-1. In both mature and weaning rats with RV pressure overload, neuregulin-1 attenuated maladaptive remodeling, with improved systolic and diastolic RV function (92, 94, 95). It is important to note that postnatal cardiomyocyte proliferation requires high oxidative energy metabolism (97). If proliferation was to be stimulated in an already metabolically demanding environment, this could exacerbate the energy deficit.

Myocardial fibrosis in rTOF has been associated with the risk of RV dysfunction, ventricular arrhythmia and sudden death (98–100). Recently, CMR studies in TOF have shown that increased late gadolinium enhancement, suggesting increased fibrosis, is a risk factor for late mortality (22). In this study, a composite fibrosis score was used, irrespective of location or type of fibrosis. Interstitial fibrosis, reactive to adverse loading, should be distinguished from replacement fibrosis following scarring, patch material and myocardial ischemia. Interstitial fibrosis has been shown in RV biopsies taken at the time of correction and appears to increase with the age of patients (83, 85, 87–89). Yet, according to RV samples of TOF patients younger than 9 months of age, collagen content is not significantly different from controls (101). These results suggest that neonatal RV pressure overload does not necessarily cause appreciable fibrosis in the first months of life, i.e., collagen production is still part of a beneficial adaptation process. Excessive collagen production being a feature mainly in patients older than 12 months at biopsy in the study of Xie et al. further supports this (89). Additionally, a greater amount of fibrosis was seen in patients with more functioning hypoxia inducible factor 1 $\alpha$  (HIF1 $\alpha$ ) alleles, a mediator of the response to hypoxemia (102). Intriguingly, not all tissue biopsy studies of rTOF patients identified increased fibrosis (49, 87, 103). Assessing fibrosis in rTOF patients late after repair should be done in the context of sequential loading. Irrespective of the duration and degree of PR or residual RVOT obstruction, every rTOF patient was subjected to a period of neonatal pressure overload and underwent corrective surgery with aortic-cross clamping. Prolonged exposure to pressure overload can result in increased reactive fibrosis (48). Prolonged aortic-cross clamping time carries the risk of myocardial injury which will also result in fibrosis, but of the replacement type (104). Unlike in pressure overload, reactive interstitial fibrosis in response to isolated volume overload is much less pronounced or even absent (14, 34, 46, 47, 51, 105). In an older rTOF population with larger RV volumes, Yamamura et al. found that median collagen content of patients undergoing pulmonary valve replacement was 7.1%, which is

comparable to the reference value of 7.4% found in healthy RV myocardium (103, 106). A subpopulation in the uppermost quartile of fibrosis in Yamamura's study had a median collagen content of 17.9%. In this small sample, the increased amount of fibrosis was associated with longer cross-clamp time as well as post-operative retention of larger RV end-systolic volumes, RV mass and RA area (103). In a younger, more contemporary managed rTOF population, fibrosis was not significantly different from control tissue samples (49). From these observations, it may be hypothesized that interstitial fibrosis presented in rTOF patients with PR is predominantly the remnant of pre-repair pressure overload and perhaps ischemic remodeling due to hypoxemia and aortic-cross clamping. The association between fibrosis and outcome may suggest a causal relationship, yet, inhibition of reactive fibrosis to either pressure or volume overload did not improve RV dysfunction (107, 108). In addition, interfering with fibrosis in cardiac tissue may have detrimental effects as fibrosis also has a cardioprotective effect (109). In line with this protective function, patients with more functional HIF1 $\alpha$  alleles and more fibrosis benefited with less progression of PR, preservation of RV volumes and systolic function and greater freedom from re-interventions (102). These findings suggest that aforementioned adverse outcomes in rTOF patients could be related more to maladaptive fibrosis induced by triggers other than adverse loading. Reactive fibrosis, resulting from pressure and/or volume overload, appears to be merely a marker and not a targetable substrate. Further studies are necessary to identify the nature and optimal balance of adaptive and maladaptive fibrotic remodeling. At present, prevention of fibrosis by early repair and limiting formation of replacement fibrosis, e.g., by optimizing surgical technique and myocardial protection, seem superior to the use of anti-fibrotic treatments.

In addition to hypertrophy and fibrosis, increased capillary density has been demonstrated, both in tissue obtained during initial repair and in human heart specimens (86–88). The increased capillary density measured was attributed to an increased smaller number of vessels, with upregulation of pro-angiogenic factors. These findings indicate angiogenic sprouting to preserve the aerobic metabolic demand, although these vessels have been suggested to be immature and may not be conducting blood (87, 88). In contrast, in many (but not all) experimental models, RV pressure overload is associated with capillary rarefaction and a decrease in angiogenesis has been found to mark the transition from compensated to decompensated RV hypertrophy (110, 111). Based upon these observations, the increased angiogenic response in TOF is different from what is seen in acquired pulmonary hypertension, where cardiomyocyte hypertrophy exceeds the capacity for new capillary formation. Although the vasculature in TOF may not be completely functional, increased angiogenesis seems to be an adaptive feature. A role of hypoxemia and HIF1 $\alpha$  in this process is likely, which is supported by the cardioprotective effects of the amount of functioning HIF1 $\alpha$  alleles (102, 112). Several studies found increased mRNA expression of angiogenic factors, e.g., vascular endothelial growth factor (VEGF), in TOF patients at the time of repair when compared to healthy and VSD controls (87, 88,

102). However, cyanosis in TOF patients was associated with reduced VEGF expression when compared to those without cyanosis, complicating the interpretation of these angiogenic signals (55). Furthermore, a transcriptomic study demonstrated higher levels of apoptosis associated genes and decreased expression of genes associated with contractility and calcium handling in cyanotic patients (113). In order to preserve adequate oxygen delivery, myocardial vessel formation could be stimulated by targeting angiogenesis. Therapeutic options for promoting angiogenesis in the RV have recently been reviewed elsewhere (114).

In short, the main histopathological findings are cardiomyocyte hypertrophy and increased fibrosis, the severity increasing with older age at repair. Although cardiomyocyte proliferation is temporarily sustained in neonatal models of pressure overload, there is no concrete evidence of increased proliferation in TOF patients. This might suggest that by the time of repair, the adaptive response favors cardiomyocyte hypertrophy rather than proliferation. Late after repair, increased reactive fibrosis due to adverse loading is not necessarily a sign of maladaptation and may not be a suitable target for treatment. A remarkable distinction from pulmonary hypertension and isolated pressure overload is the increased, but potentially incomplete angiogenesis, which requires further investigation.

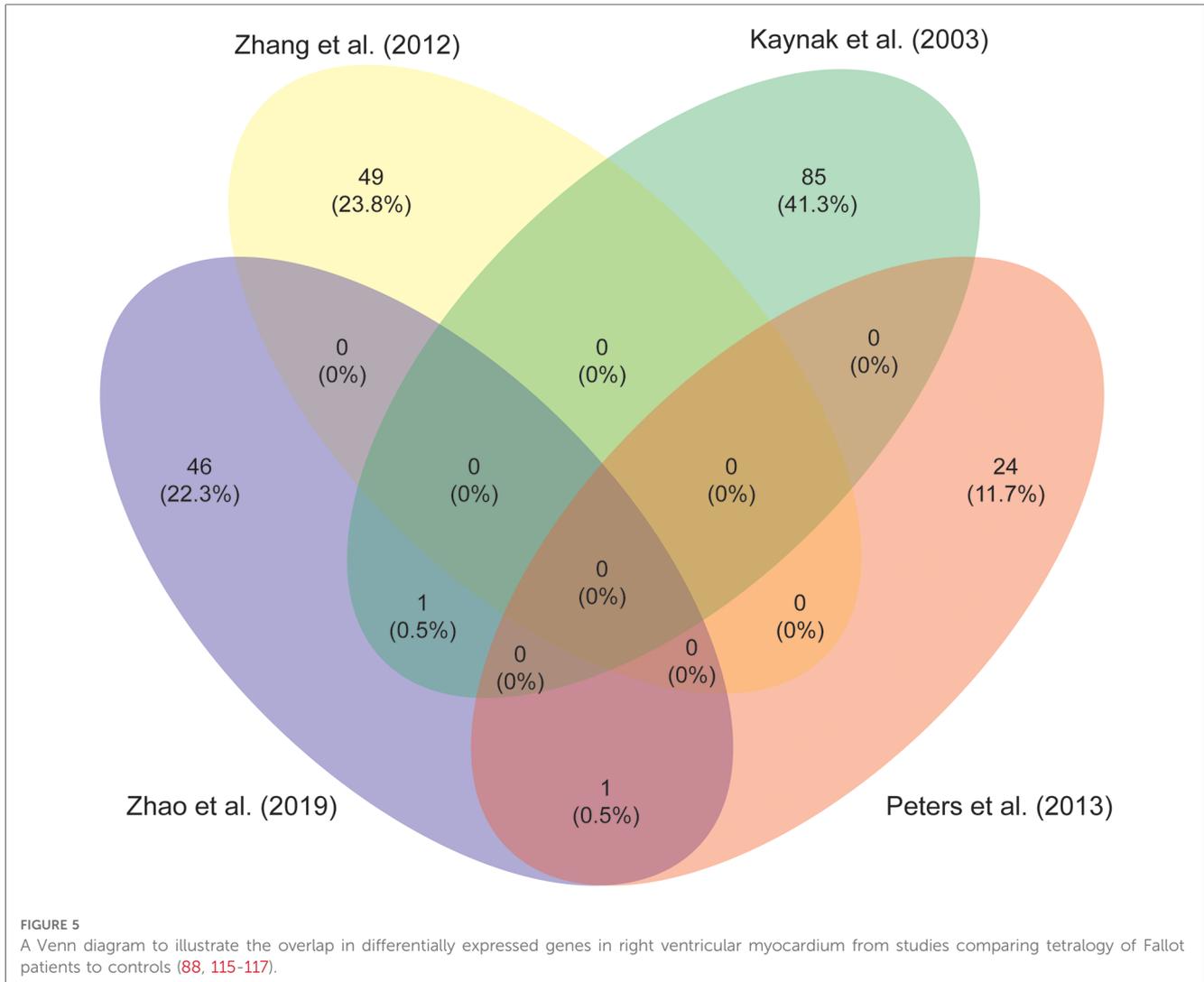
## 5. Is there a molecular signature in the right ventricle of tetralogy of Fallot?

Identification of pathways involved in RV remodeling is perhaps one of the most important steps in the search for specific treatments. Stimulation of adaptive features and inhibiting maladaptive remodeling might be key in preventing or delaying progression to RV failure. Unfortunately, a comprehensive analysis of patients tissue characteristics is complicated, as tissues may generally only be harvested at initial repair or at pulmonary valve replacement and are compared with different control groups. Intriguingly, there is little overlap in responses described in the studies aiming to elucidate adaptive pathways, as is illustrated in **Figure 5**, which shows a comparison of the studies investigating differential expression of mRNA between RV tissue samples of TOF patients and healthy controls (88, 115–117). Functional protein association network analysis of all the genes reported in these studies reveals several clusters, the largest encompassing extracellular matrix (ECM) proteins, fibroblasts and angiogenesis (118). Other clusters comprise protein synthesis, mitochondrial metabolism, second messengers, contractile apparatus and cell cycle associated proteins (see **Supplementary Figure S1 and Table S1**). There is ongoing debate on the contribution of inflammation in the development of heart failure (119). The majority of studies report changes in ECM proteins, which is linked to inflammatory pathways, yet, specific evidence of increased inflammation in the RV of TOF patients is lacking (49, 55, 87, 88, 113, 115–117, 120, 121).

Expression levels of ECM proteins vary between studies in tissue samples taken at the time of repair (54, 121). At the time of pulmonary valve replacement, however, no changes in ECM protein levels were found when comparing to healthy age-matched controls, although mRNA expression of several proteins involved in ECM are increased (49). Similarly, protein and mRNA expression of the ECM proteoglycan lumican was decreased at initial repair, but at the time of pulmonary valve replacement protein levels were unaltered despite increased mRNA expression (49, 121). Interestingly, in an animal model of PR, expression of ECM components also undergo a change in expression, from being initially downregulated to becoming upregulated in the chronic phase (105).

Proteins associated with calcium handling and the contractile machinery of the sarcomere have been found to be affected in uncorrected TOF patients when compared to isolated VSD patients (54). This is also evident from experimental PR models, with myosin heavy chain isoform switch as part of the fetal gene reactivation and altered expression of cardiac muscle actin and Xin actin binding protein for example (105, 122). Whether protein changes in the contractile apparatus are relevant in chronic volume overload late after TOF repair is questioned by the study of Brayson et al. (49). They found that in RV tissue taken at the time of pulmonary valve replacement, myofilament contractility and calcium sensitivity was comparable to non-diseased RV tissue. Enhancement of contractility could be managed by administration of myosin modulators. Omecamtiv mecarbil increases the amount of time in contraction and is investigated extensively in LV failure (123). Studies on its effects in the RV are still scarce however (124, 125). Interestingly, a rat model of chronic aortic regurgitation demonstrated that treatment with omecamtiv mecarbil significantly reduced wall stress in the LV (126). If this also applies to the RV, omecamtiv mecarbil could counteract adverse remodeling in TOF patients with PR. Although controversial, it is important to keep in mind potential side effects of these inotropic treatments. A metabolic burden could be imposed on the myocardium by increasing its oxygen consumption, while reducing myocardial perfusion by decreasing the time spent in diastole (127–130).

Cardiac metabolic inflexibility is the reliance on glycolysis alone for energy production instead of utilizing several different substrates. It has been suggested as a maladaptive phenomenon in a protein analysis study of RV tissue of TOF patients compared to other CHD diagnoses (121). This metabolic shift, with downregulation of beta-oxidation in favor of less efficient glycolysis, is already known from experimental RV pressure overload studies, but has also been observed in a model of chronic PR (105, 131, 132). Accommodating a higher metabolic demand requires optimizing myocardial energetics in the dysfunctional RV to prevent progression to failure. The metabolic shift towards inefficient glycolysis can be (partially) reversed. As an example, dichloroacetate enhances glucose oxidation, thereby restoring mitochondrial function and reducing myocardial apoptosis. Treatment in experimental models of pulmonary hypertension resulted in improved RV systolic function and reverse remodeling (133–135). Similar beneficial



effects were observed during treatments to either increase or partially inhibit fatty acid beta oxidation, the latter in order to favor glucose oxidation (136, 137).

A recent study aimed to generate a circRNA-miRNA-mRNA network in TOF. They analyzed three datasets available in GEO databases comparing profiles and identified 29 miRNA, 13 circRNAs and 88 mRNAs (138). Interestingly, a comparison between overlapping miRNA profiles in four other studies yielded two miRNAs that were identified in all 4 studies and 5 miRNAs that were identified in at least 3 of the 4 studies (Table 1) (139-142). MiR-222, also identified in the network by Kan et al. has

been associated with exercise-induced myocardial adaptation, atrial fibrillation, is involved in function of L-type calcium channels and is a target of angiogenesis and proliferation via ERBB4 and HIF1α (138, 143-146). MiR-194 has been linked to the p53 pathway and may be involved in pulmonary angiogenesis (147). For disease markers as well as therapeutic targets, these pathways may be worthwhile to explore, albeit that these have not been described in experimental models mimicking TOF.

Generally, experimental studies show that many molecular mechanisms of RV adaptation are similar in pressure and volume overload, albeit that the latter exhibits a milder

TABLE 1 Heat map of overlapping differentially expressed microRNA in tetralogy of Fallot patients, as fold change compared to controls.

Hsa-miR nr.	Abu Halima et al. (139)	Liang et al. (140)	O'Brien et al. (141)	Zhang et al. (142)
222	-2.16	2.05	3.49	2.14
194	-2.49	1.24	2.16	1.84
93		1.23	1.65	2.55
155		2.02	1.68	2.37
381		-1.28	-0.16	2.32
30	-2.15	-1.32	1.65	
151	-2.20	1.11	1.14	

phenotype with slower disease progression (50, 148). In addition, most clinical studies are too heterogeneous to compare in order to derive a disease-specific molecular signature. Also, the relation between tissue expression patterns and serum biomarkers is difficult to determine. A comprehensive analysis of serum biomarkers associated with adverse outcomes could provide additional insights in adaptation of the overloaded RV, but is beyond the scope of this review (149).

## 6. Current and future strategies

### 6.1. Treatment of right ventricular dysfunction

Currently, attempts for medical support of the failing RV in rTOF have been futile (3, 150). A widely accepted treatment regimen, including cornerstone medication, resynchronization and exercise for cardiac rehabilitation, as described in patients with heart failure due to LV dysfunction, is therefore absent. Guidelines on medical therapy are limited to diuretics, merely for relieving symptoms of RV decompensation (151). Furthermore, the lack of robust clinical markers to assess RV dysfunction and outcomes in rTOF patients complicates the decision regarding the initiation of treatment.

As a cornerstone of heart failure therapy, renin-angiotensin-aldosterone system (RAAS) inhibition lowers systemic afterload and blood volume status, whilst having antifibrotic and antihypertrophic effects in the myocardium itself (152). Several RCTs on RAAS inhibition have been conducted in TOF, but none could demonstrate a beneficial effect on RV function (8, 153). Although there is evidence of RAAS activation in the setting of RV pressure overload, its mechanisms in TOF have yet to be elucidated (108, 154, 155). The novel valsartan-sacubitril combination drug inhibits the angiotensin receptor-nepriylisin pathway and might be promising in the treatment of RV dysfunction (156). Currently only a case report of the use of valsartan-sacubitril in TOF is available, but in a small cohort of patients with a systemic RV improvement of echocardiographic markers and reduction of NT-pro-BNP was observed over six month follow-up (157, 158).

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are increasingly used in the treatment of LV failure. Even though the mechanism of action is still unclear and there are no myocardial SGLT2 receptors, they lower cardiovascular mortality independent of patient diabetic status (159). From experimental studies in rats with monocrotalin induced pulmonary hypertension, it appears that SGLT2 inhibitors lower pulmonary pressure by attenuating pulmonary vascular remodeling (160, 161). When regarding effects on the RV itself, however, dapagliflozin treatment did not result in any improvements in myocardial function or remodeling (162). Clinical data on primary RV dysfunction is lacking except for a case report in systemic RV (163).

Rather than ameliorating adverse loading, enhancing myocardial contractility is another potential treatment path.

Phosphodiesterase 5 (PDE5) inhibitors are known for their pulmonary vasodilatory effects in the treatment of pulmonary hypertension. Recently, they have been found to also increase RV contractility (133, 164). In RV pressure overload models, PDE5 becomes upregulated in remodeled RV myocardium and PDE5 inhibition has resulted in a multitude of effects, independent of afterload (165). Besides its RV specific inotropic effects, improvement of diastolic dysfunction and dilatation have been observed in sildenafil-treated rats with pulmonary artery banding (166). The improvement in diastolic function might be explained by the increased phosphorylation of titin to its more distensible form (167). As discussed earlier, however, the involvement of titin in diastolic dysfunction in rTOF has yet to be demonstrated.

Important gain of function can be achieved by improving the efficiency of RV contraction in TOF. Electromechanical dyssynchrony and right bundle branch physiology hinder a properly coordinated contraction, which makes rTOF a “synchronopathy” (35). The studies of Janousek et al. on cardiac resynchronization therapy of the RV in CHD demonstrated improved mechanics of contraction in both acute and chronic phases (78, 168). Patch material and scarring in the RVOT and VSD, however, remain akinetic regions where loss of energy and efficiency are bound to occur. Removal of dysfunctional RVOT tissue at the time of pulmonary valve replacement did not seem to have benefits over isolated pulmonary valve replacement (169). Tissue engineering might be able to overcome the problems arising from the electromechanical disconnection of patch material and the surrounding scar formation. Patches could be biological scaffolds incorporating cardiomyocytes or endothelial cells to become functional myocardium or vessel respectively (170). With tissue engineering, other opportunities may arise, like implantation of contractile bands to enhance RV biomechanics (171).

### 6.2. Preventing right ventricular deterioration

Patients with CHD are usually in follow-up from birth. This provides a major opportunity for implementing preventive strategies early on in the disease process, in contrast to acquired heart failure which is only diagnosed and treated in a symptomatic stage.

The obvious solution to prevent RV dysfunction would be the relief of adverse loading as soon as possible. Neonatal correction minimizes the duration of pressure overload and hypoxemia, but at the cost of a higher risk of more severe residual lesions (i.e., PR and RVOT obstruction) and worse event-free survival (172). Furthermore, the impact on RV function and histological changes is limited if correction is performed before the first year of age (87, 89). This justifies an early, but not neonatal, repair strategy to address the repercussions of loading on remodeling. Chronic PR will probably remain a culprit for as long as it takes for growing tissue valves to become available. Until then, treatment strategies could/should focus on reinforcing adaptive

processes of RV remodeling in order to better accommodate adverse loading (92, 96).

In addition, exercise training could aid in strengthening the RV. Exercise training has already proven to be useful in the treatment of left-sided heart failure (173, 174). Intriguingly, recent experimental studies have shown that exercise also induces cardiomyocyte proliferation (175, 176). In the treatment of RV dysfunction in CHD, studies have demonstrated the safety of exercise therapy and applicability even in young children (177–182). Although significant improvements in cardiac function have not yet been confirmed in rTOF cohorts, several investigations are ongoing and looking into optimal training regimens (177, 178, 181, 182).

## 7. Summary

TOF is characterized by a unique sequential loading pattern. Histopathology reflects these different stages of loading, but at present does not provide a targetable substrate for therapy. There is little to no consensus regarding specific adaptation mechanisms due to the wide variation in studies, but it seems likely there is no unifying molecular pathway leading to dysfunction. Knowledge of the distinctive physiology in TOF explains the lack of success of current treatment strategies. Cardiac dysfunction can be described as a combination of impaired ventricular kinetic energy and a disturbed filling pattern. The potential for future strategies is in optimizing RV biomechanics, kinetic energy and treatments to improve myocardial relaxation. In addition to novel drug targets, other promising options include resynchronization therapy, tissue engineered grafts and strategies aimed to strengthen the RV.

## Author contributions

RSAS and BB conceptualized, designed and drafted the manuscript. All other authors edited and revised the manuscript. All authors approved the final version of the manuscript.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fped.2023.1098248/full#supplementary-material>.

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