

University of Groningen

## Right ventricular adaptation to chronic abnormal loading

Hagdorn, Quint

DOI:  
[10.33612/diss.135804654](https://doi.org/10.33612/diss.135804654)

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2020

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*  
Hagdorn, Q. (2020). *Right ventricular adaptation to chronic abnormal loading: and implications for patients with tetralogy of Fallot*. <https://doi.org/10.33612/diss.135804654>

### Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

### Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

# 1a

---

General introduction

## THE RIGHT VENTRICLE

The heart is a complex muscular organ that generates blood pressure and therewith blood flow in the circulatory system, in order to accommodate transportation of gases, nutrients and waste products. The mammalian heart consists of two separate, yet fused pumping systems: the right ventricle (RV) and the left ventricle (LV). These pumps are in-series connected by the pulmonary vascular bed distally from the RV, and the systemic vascular bed distally from the LV. Because of the serial connection, the output in terms of blood volume is equal for both ventricles in the absence of shunting. However, in terms of blood pressure, there are marked differences between the two ventricles in normal conditions. The resistance of the pulmonary vascular bed is far lower than the systemic vascular bed, resulting in a relatively low-pressure system in the RV, and a relatively high-pressure system in the LV. The RV was, since an often-cited study from the 1940's, for decades long considered to be relatively unimportant for maintaining adequate cardiac function.<sup>1</sup> Acknowledgement for its clinical relevance increased from the 1980's, until naming the RV "the forgotten chamber" in 1995 removed all doubts on its importance.<sup>2</sup> Since, our understanding of clinical RV pathophysiology has substantially increased. With regards to molecular and cellular mechanisms contributing to failure and targeted therapy, however, knowledge about the RV still lags behind that of the LV.<sup>3-5</sup> This is of particular importance for congenital heart diseases, such as tetralogy of Fallot, in which RV failure appears to be a key determinant of clinical status and outcome.

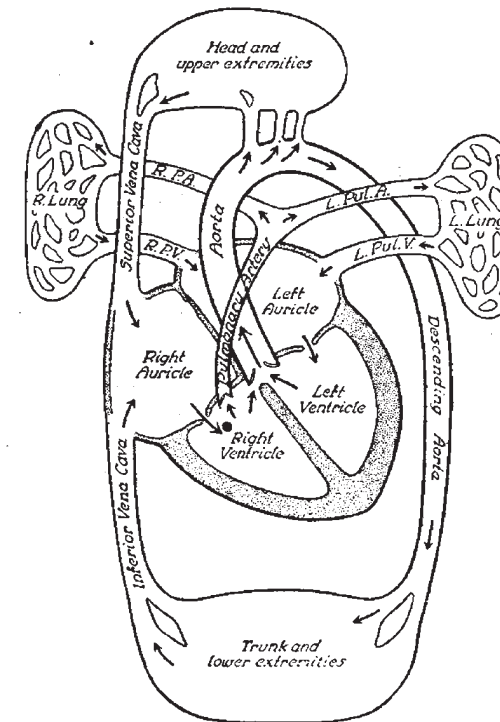
## TETRALOGY OF FALLOT

Tetralogy of Fallot is a cyanotic congenital heart disease, named after Étienne Fallot, a French physician who described this syndrome in 1888 as "maladie bleue".<sup>6</sup> Dr. Fallot acknowledged in his report that he was not the first to describe this syndrome, as multiple descriptions preceded that of Fallot. To date, the first known report of TOF was described by Niels Stensen in 1671.<sup>7</sup> This syndrome, schematically displayed in Figure , consists of the following tetralogy:

1. Stenosis of the pulmonary artery (PA)
2. Overriding aorta
3. Ventricular septal defect (VSD)
4. RV hypertrophy

Despite that dr. Fallot was not the first to describe this syndrome, he was the first to describe that these four features are not a coincidental gathering of distinct features. As he unequivocally showed, all these features result from anterior displacement of the aortopulmonary septum. Resulting from this displacement, the pulmonary trunk is narrower than in normal hearts, and

thus stenotic (feature 1). Furthermore, the aorta is wider and displaced towards the RV. This causes both overriding of the aorta (feature 2), and a VSD (feature 3). The fourth feature of TOF, the RV hypertrophy, is generally regarded as a secondary anomaly, as it results from the increased pressure that the RV has to withstand, because of the pulmonary stenosis and VSD.



**Figure 1** | Diagram of tetralogy of Fallot. Reproduced from Blalock A, Taussig HB. JAMA. 1945 May 19;128(3):189-202 with permission.

The aforementioned defects are not always present in the same degree when comparing patients.<sup>8</sup> Therefore, TOF can be seen as a disease-spectrum, with accompanying variability in clinical presentation and required management. The symptomology is mainly dependent on the degree of RV outflow tract (RVOT) obstruction and the resulting balance between pulmonary and systemic blood flow. This balance is determined by the direction of the blood flow through the VSD, which is in turn dependent on the pressure difference between the RV and the left ventricle (LV). This is because blood will always flow from the ventricle with the highest pressure, towards the ventricle with the lowest pressure. In normal hearts, the pressure in the LV is far higher than the RV. Therefore, when the RVOT and PA obstruction in TOF patients is not very severe, the RV pressure will not exceed LV pressure, so there will be a left-right shunt through the VSD. However, in the case of severe RVOT/PA obstruction, RV pressure would have

exceeded LV pressure, if there would not have been a VSD. Therefore, in such cases, there will be a right-left shunt through the VSD. This leads to hypo-perfusion of the pulmonary vasculature and cyanosis, which often requires early intervention. This is in contrast with infants who have balanced pulmonary and systemic flow, as those infants are usually asymptomatic in early life.

## CORRECTIVE SURGERY

Since the early '50s, TOF can be corrected surgically, by closing the VSD with a patch, relieving the RVOT obstruction, and widening the pulmonary artery.<sup>9,10</sup> The result of surgery is that the pressure load that burdened the RV in early life, due to RVOT obstruction, PA stenosis, and VSD, has at least for the most part been resolved. Pressure-loading conditions are therefore normal, and there is no more risk of cyanosis. However, the price of widening the stenotic PA is that the pulmonary valve (PV) mostly becomes incompetent, resulting in pulmonary regurgitation. Thus, the RV that has been exposed to increased pressure load in early life, is now exposed to increased volume load. Surgeons attempt to minimize the degree of regurgitation by using as little patching over the pulmonary valve annulus (trans-annular patch, TAP) as possible, or even without patching (annulus sparing). However, depending on the anatomy and the degree of PA stenosis, some degree of regurgitation often remains inevitable. Surgery is nowadays preferably performed in early childhood, before the age one year, since repair beyond this age has been associated with increased risk of morbidity and mortality.<sup>11,12</sup> However, primary repair prior to the age of three months has also been described as a risk factor for complicated operation or postoperative management in the intensive care unit.<sup>12</sup> Therefore, if an infant becomes symptomatic and requires early intervention, palliative procedures, such as for example aorto-pulmonary shunt palliation, RVOT stenting or enlargement, ductus arteriosus stenting or balloon pulmonary valvuloplasty may be needed before surgical repair.<sup>13-15</sup>

## LIFE AFTER SURGICAL 'REPAIR'

Post-surgical patients are usually referred to by 'repaired tetralogy of Fallot' patients, suggesting that they now have fixed and normal hearts. And indeed, after surgical correction, survival into adulthood is excellent, and most children and adolescents experience no or little functional impairment.<sup>16-18</sup> Even patients with residual lesions, such as pulmonary regurgitations, usually do not experience limitations for many years. However, at long term, patients remain at increased risk of RV failure and hazardous arrhythmias, both of which often lead to substantial morbidity and mortality. Also at long term, patients experience impaired physical functioning and quality of life compared to healthy individuals.<sup>19-22</sup> Despite surgical repair, their hearts have namely been exposed to increased pressure load of the RV in the

neonatal period prior to surgery, have been exposed to hypoxemia and have been scarred during surgery. After surgery, their RV's are often exposed to abnormal loading conditions due to residual lesions as pulmonary valve incompetence, leading to increased RV volume load, or RV outflow tract or pulmonary artery obstruction, leading to increased RV pressure load. The long term increased risk of RV failure can mostly be attributed to chronic pulmonary regurgitation, as prolonged RV volume loading is known to cause progressive RV dilatation, dysfunction and also LV dysfunction.<sup>23-27</sup> Monitoring RV dilatation and biventricular function is therefore reason for periodic cardiac follow-up in these patients.<sup>28,29</sup> For assessing RV morphology and function, cardiac magnetic resonance (CMR) imaging is the golden standard.<sup>30</sup>

Pulmonary regurgitation can be treated by either surgical or transcatheter pulmonary valve replacement (PVR), which relieves the RV of the increased volume load. This reverses RV dilatation and hypertrophy at least partially, and improves biventricular systolic function and functional status.<sup>31-36</sup> However, treating these patients with PVR also comes at a cost: perioperative mortality is low, but not zero, implanted valves are at increased risk of endocarditis, and implanted valves deteriorate over time, eventually requiring re-do PVR.<sup>34,37,38</sup> Therefore, performing PVR too early would unnecessarily expose patients to perioperative risks and stress and makes future re-do PVR or other interventions more complex. On the other hand, when PVR is being performed beyond a certain stage of remodeling, the RV will remain dilated and functionally impaired, and patients are at increased risk of death and arrhythmia.<sup>39,40</sup> Adequate timing of PVR is therefore key. Currently, timing is heavily based on the presence of symptoms, QRS duration on electrocardiography, and measures of RV dilatation and biventricular function on CMR imaging.<sup>28,29,41</sup>

As mentioned previously, the occurrence of arrhythmia's is, besides decreasing ventricular function, a common complication in the long-term follow-up of patients with TOF. Atrial arrhythmia's, such as atrial fibrillation or atrial flutter, are frequently seen in these patients and are associated with increased hospitalization and mortality.<sup>42,43</sup> Furthermore, patients are at risk of ventricular tachycardia (VT), ventricular fibrillation (VF) and sudden cardiac death (SCD), comprising a significant part of late morbidity and mortality.<sup>40,42,44-46</sup> To prevent mortality from ventricular arrhythmia, timely interventions are needed, such as PVR in the case of pulmonary regurgitation, to prevent progressive adverse remodeling. In some selected cases with a high risk of VT in which other treatment options were unsuccessful or insufficient, or after the occurrence of VT/VF, an implantable cardioverter-defibrillator (ICD) can be implanted. However, just like PVR, ICD implantation comes at a cost, as many patients experience distress, decreased quality of life, and anxiety after implantation.<sup>47</sup> Therefore, only a subset of patients, who are believed to be at substantially increased risk, are considered for ICD implantation. Identifying patients who are at high risk is therefore of great importance.

For secondary prevention, the treatment algorithm for implanting an ICD is clear, namely that in every patient who has experienced cardiac arrest, VT, or unexplained syncope, without reversible causes, ICD implantation is indicated.<sup>28,29</sup> However, for primary prevention, there is no clear treatment algorithm, and therefore ICD implantation for primary prevention can still be regarded as ‘controversial’.<sup>28</sup> Both the American and European guidelines classify ICD implantation for primary prevention as ‘reasonable’, when multiple risk factors are present. These risk factors include RV and/or LV dysfunction, non-sustained VT, QRS duration > 180ms, extensive RV fibrosis on CMR and inducible VT during electrophysiological (EP) testing.<sup>28,29</sup>

## SEX DIFFERENCES

In the last decades, evidence has been increasing that, in all fields of cardiovascular medicine, sex differences exist. These differences include different prevalence and incidence, different disease presentation and severity, different mortality, and subsequent differences in optimal treatment. This also applies to patients with congenital heart disease.<sup>48</sup> Female patients experience more symptoms, and are at increased risk to develop pulmonary hypertension, compared to male patients.<sup>49-51</sup> On the other hand, male patients are at higher risk of arrhythmia and mortality, compared to female patients.<sup>42,52</sup> In patients with repaired tetralogy of Fallot, male patients have lower biventricular ejection fraction, and both heavier and larger hearts, even when indexed for body surface area.<sup>53,54</sup> Furthermore, the RV of female patients with PAH demonstrated better recovery after initiation of treatment, compared to male PAH patients, under similar loading conditions and with similar pulmonary vascular resistance.<sup>55</sup> However, despite apparent differences between sexes, guidelines barely provide sex-tailored recommendations.<sup>28,29</sup>

The demonstrated differences between sexes raise the question of whether they arise from either beneficial or deleterious effects of sex hormones, or other factors, such as genetic differences. Data from a large cardiovascular disease-free cohort have demonstrated that sex hormones are at least partially accountable for cardiac sex differences, as increased levels of estradiol, or estradiol metabolism, are associated with better RV systolic function.<sup>56,57</sup> This is confirmed in experimental studies of RV dysfunction, in which estrogen exerts positive effects on RV function and testosterone decreases RV function.<sup>58-60</sup> However, it remains unknown whether these effects of sex-hormones on the RV could lead to new treatment options.

## MOLECULAR RIGHT VENTRICULAR REMODELING

While the need for heart failure therapy in congenital heart disease is growing, there is no pharmacological treatment available that has been proven to directly and effectively target

myocardial function.<sup>61</sup> Understanding the underlying mechanisms of cardiac adaptation, dysfunction and failure is of great importance to be able to develop targeted therapy for (right) heart failure. For such studies, cardiac tissue from patients in different stages of disease would be the ideal study material. However, for obvious reasons, these tissues are scarce as they can only be collected by biopsy, during surgery or post mortem. Furthermore, tissues are never collected at standardized stages of disease. Therefore, animal studies have greatly contributed to basic cardiology over the past decades. At first, experimental studies were mostly focused on the LV, and it was presumed that the knowledge obtained would be easily translatable to the RV. However, as we have come to increasingly understand, the RV and LV are not identical twins.<sup>5</sup> The RV and LV namely have a different embryological origin, as the RV originates from the secondary (or anterior) heart field and the LV from the primary heart field.<sup>62</sup> Furthermore, the RV and LV are designed for different pressure demands, and are therefore morphologically different and have specific motion and fiber orientation patterns. The LV cardiomyocytes are predominantly oriented in the circumferential direction, whereas the RV cardiomyocytes are mostly oriented in the longitudinal direction. Likewise, the LV contracts mostly circumferential, whereas longitudinal motion comprises the largest part of RV motion. With the increased appreciation of the differences between the RV and the LV, experimental research has now increasingly been focusing on the RV. However, within the field of experimental RV studies, there is a clear predominance of models of increased RV pressure load, such as pulmonary artery banding (PAB) or models of pulmonary hypertension (PH).<sup>3,63</sup> However, RV volume load is known to induce a different pattern of RV adaptation, compared to RV pressure load.<sup>64-66</sup> Pressure load induces concentric hypertrophy, fibrosis accompanied by diastolic dysfunction, alterations in cardiac lipid composition, compensatory enhancement of systolic function and eventually also loss of ventricular capillarisation and systolic failure, while volume load induces eccentric hypertrophy with initially stable diastolic and systolic function.<sup>65,67,68</sup> However, most studies compare pressure load and volume load of equal durations, while it is known that volume load causes RV failure not before long-term exposure. Considering that patients experience no or little functional impairment within the first years of exposure to volume load, while it may induce progressive, severe dysfunction on the longer term, it may thus be more appropriate to study volume load of a longer duration to better mimic the actual human clinical problem.

An often named mechanistic factor in heart failure is myocardial fibrosis: being excessive deposition of extracellular matrix in the myocardium.<sup>69,70</sup> Generally, fibrosis is regarded as detrimental for both systolic and diastolic function, and is thus considered to be a treatment target in various cardiovascular diseases.<sup>69,71</sup> In patients with repaired tetralogy of Fallot, indirect imaging markers of fibrosis indeed may be elevated.<sup>72-75</sup> However, its significance in RV failure is by no means clear yet<sup>76</sup>, as successfully targeting fibrosis in experimental RV

pressure load has not necessarily resulted in improved RV function.<sup>77</sup> Furthermore, it remains unclear what has caused fibrosis, as suggested by imaging markers, in patients with tetralogy of Fallot. A causal factor could be increased RV volume load due to pulmonary regurgitation, but also surgery at young age and pre-operative RV pressure load could be factors that induce fibrosis. To establish the role of fibrosis in the RV's of patients with tetralogy of Fallot, it is therefore of paramount importance to dissect the relative contribution of each potential cause of fibrosis, to determine what underlies the temporal development of fibrosis. To do so, animal experiments are necessary. Furthermore, it is highly relevant to determine whether novel anti-fibrotic therapies might benefit the dysfunctional RV.

### AIMS OF THIS THESIS

To address the challenges outlined above in the long-term follow-up of patients with repaired tetralogy of Fallot, understanding RV adaptation to chronic abnormal loading is of the essence. Therefore, the aims of this thesis were:

- To characterize RV adaptation to chronic abnormal loading. By studying functional and molecular characteristics of RV adaptation in animal models, we aim to identify molecular pathways involved in the decline towards RV failure, to aid the development of future targets of treatment.
- To identify prognostic factors on cardiac magnetic resonance imaging. Prognostic factors are essential for the development of risk stratification schemes, to allow a tailored and preventive approach for patients with repaired tetralogy of Fallot in long-term follow-up. Therefore, we aim to assess the predictive value of cardiac magnetic resonance, a cornerstone of long-term follow up, in patients with repaired tetralogy of Fallot.
- To study sex differences in RV adaptation to chronic abnormal loading. Currently, it remains unknown whether differences between sexes emerge not before puberty or already prior to pubertal development, and whether such differences merit a tailored approach with regards to cardiac imaging. Therefore, we aim to describe sex differences both an imaging-based study in patients with repaired tetralogy of Fallot and an animal model of childhood RV pressure load.

### OUTLINE OF THIS THESIS

In **chapter 2**, we first establish what the current state of knowledge is on experimental volume load-induced RV dysfunction. By systematic review, we provide an overview of what is known, expose gaps in our knowledge and understanding, and delineate where we should be headed.

In clinical practice, research with humans and in experimental studies, measures of cardiac morphology and function are often indexed for subject size, to allow comparison of subjects of different sizes. However, there has been little attention to the efficacy of current methods of indexing. In **chapter 3**, the current common practice of normalizing cardiac parameters in small animal models is evaluated and optimized. This novel methodology allows better temporal assessment of cardiac measures in growing animals as performed in some of the following chapters.

As described previously, imaging-based studies suggest that patients with tetralogy of Fallot demonstrate fibrosis. However, what has caused these processes remains unclear. Our systematic review in chapter 2 also raises the suggestion that fibrosis might be involved in volume load-induced RV dysfunction, but deals with a low amount of evidence with high heterogeneity. To assess whether myocardial fibrosis is truly associated with long-term volume load, **chapter 4** assesses the temporal development of ventricular fibrosis and pro-fibrotic signaling in a rat model of long-term cardiac volume load.

In both the development of myocardial fibrosis and pulmonary vascular remodeling in the case of pulmonary arterial hypertension, disturbed TGF $\beta$ /BMP signaling is a hallmark pathological process. Therefore, we aim to target remodeling and fibrosis in the pulmonary vasculature and myocardium with juglone, a pharmacological agent that in part inhibits disturbed TGF $\beta$ /BMP signaling, in models of pulmonary arterial hypertension and right ventricular pressure load in **chapter 5**.

While it is clear from literature that sex differences in RV adaptation to abnormal loading conditions exist, this has not been investigated nor described in children or young animal models. Such models of young animals provide the opportunity to study RV adaptation during pubertal development, before exposure to sex hormones begin to differ between sexes. Therefore, in **chapter 6**, pre- and post-pubertal sex differences in RV adaptation are investigated in a juvenile rat model of RV pressure load.

To aid future refinement of risk stratification for arrhythmia, **chapter 7** describes the prognostic value of conventional measures on cardiac magnetic resonance imaging for the development of both atrial and ventricular tachyarrhythmia is investigated in a combined Dutch and American cohort of patients with repaired tetralogy of Fallot.

In **chapter 8**, feature-tracking analyses are used to assess patterns of cardiac motion on cardiac magnetic resonance imaging. The prognostic value of such measures for the development of ventricular tachyarrhythmia and deterioration of ventricular function is investigated in a Dutch cohort of patients with repaired tetralogy of Fallot.

Currently, in both clinical practice and research, little attention is paid to differences between sexes, and a tailored approach for males and females is currently lacking. Therefore, differences between sexes on cardiac magnetic resonance are investigated in a combined American and Dutch cohort of children and adults with repaired tetralogy of Fallot in **chapter 9**.

In **chapter 10**, the findings of this thesis are summarized and discussed.

## REFERENCES

1. Starr I, Jeffers WA, Meade RH. The absence of conspicuous increments of venous pressure after severe damage to the right ventricle of the dog, with a discussion of the relation between clinical congestive failure and heart disease. *Am Heart J* [Internet]. 1943;26(3):291-301. Available from: <http://www.sciencedirect.com/science/article/pii/S0002870343903254>
2. Rigolin VH, Robiolio PA, Wilson JS, Harrison JK, Bashore TM. The forgotten chamber: the importance of the right ventricle. *Cathet Cardiovasc Diagn*. 1995 May;35(1):18-28.
3. Voelkel NF, Quaife RA, Leinwand LA, Barst RJ, McGoon MD, Meldrum DR, et al. Right ventricular function and failure: Report of a National Heart, Lung, and Blood Institute working group on cellular and molecular mechanisms of right heart failure. *Circulation*. 2006;114(17):1883-91.
4. Altamira LA, Redington AN. Right ventricular failure in congenital heart disease. *Hear Fail Congenit Hear Dis From Fetus to Adult*. 2019;31(5):109-22.
5. Friedberg MK, Redington AN. Right versus left ventricular failure: Differences, similarities, and interactions. *Circulation*. 2014;129(9):1033-44.
6. Fallot ELA. Contribution à l'anatomie pathologique de la maladie bleue (cyanose cardiaque). In: *Marseille médical*. 1888. p. 77-93, 138-58, 207-23, 341-54, 370-86, 403-20.
7. Stensen N. Embryo monsto affinis Parisiis dissectur. In: *Acta Medica & Philosophica Hafniensia*. 1671. p. 202-3.
8. Anderson RH, Weinberg PM. The clinical anatomy of tetralogy of fallot. *Cardiol Young*. 2005 Feb;15 Suppl 1:38-47.
9. Woodson RD, Burnell RH, Herr RH, Lees MH, Starr A. Surgical Management of Tetralogy of Fallot in Children under Age Four. *Ann Surg*. 1969;169(2):257-64.
10. Lillehei CW, Cohen M, Warden HE, Read RC, Aust JB, Dewall RA, et al. Direct vision intracardiac surgical correction of the tetralogy of Fallot, pentalogy of Fallot, and pulmonary atresia defects; report of first ten cases. *Ann Surg*. 1955 Sep;142(3):418-42.
11. Al Habib HF, Jacobs JP, Mavroudis C, Tchervenkov CI, O'Brien SM, Mohammadi S, et al. Contemporary patterns of management of tetralogy of Fallot: data from the Society of Thoracic Surgeons Database. *Ann Thorac Surg*. 2010 Sep;90(3):813-20.
12. Van Arsdell GS, Maharaj GS, Tom J, Rao VK, Coles JG, Freedom RM, et al. What is the optimal age for repair of tetralogy of Fallot? *Circulation*. 2000 Nov;102(19 Suppl 3):III123-9.
13. Blalock A, Taussig HB. The surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia. *JAMA* [Internet]. 1945 May 19;128(3):189-202. Available from: <https://doi.org/10.1001/jama.1945.02860200029009>
14. Dohlen G, Chaturvedi RR, Benson LN, Ozawa A, Van Arsdell GS, Fruitman DS, et al. Stenting of the right ventricular outflow tract in the symptomatic infant with tetralogy of Fallot. *Heart*. 2009 Feb;95(2):142-7.
15. Qureshi SA, Kirk CR, Lamb RK, Arnold R, Wilkinson JL. Balloon dilatation of the pulmonary valve in the first year of life in patients with tetralogy of Fallot: a preliminary study. *Br Heart J*. 1988 Sep;60(3):232-5.
16. Apitz C, Webb GD, Redington AN. Tetralogy of Fallot. *Lancet* (London, England). 2009 Oct;374(9699):1462-71.
17. Chiu SN, Wang JK, Chen HC, Lin MT, Wu ET, Chen CA, et al. Long-Term survival and unnatural deaths of patients with repaired tetralogy of fallot in an asian cohort. *Circ Cardiovasc Qual Outcomes*. 2012;5(1):120-5.
18. Geva T, Sandweiss BM, Gauvreau K, Lock JE, Powell AJ. Factors associated with impaired clinical status in long-term survivors of tetralogy of Fallot repair evaluated by magnetic resonance imaging. *J Am Coll Cardiol* [Internet]. 2004;43(6):1068-74. Available from: <http://dx.doi.org/10.1016/j.jacc.2003.10.045>



19. Bokma JP, De Wilde KC, Vliegen HW, Van Dijk AP, Van Melle JP, Meijboom FJ, et al. Value of cardiovascular magnetic resonance imaging in noninvasive risk stratification in tetralogy of Fallot. *JAMA Cardiol*. 2017;2(6):678–83.
20. Wald RM, Valente AM, Gauvreau K, Babu-Narayan S V., Assenza GE, Schreier J, et al. Cardiac magnetic resonance markers of progressive RV dilation and dysfunction after tetralogy of Fallot repair. *Heart*. 2015;101(21):1724–30.
21. Kahr PC, Radke RM, Orwat S, Baumgartner H, Diller GP. Analysis of associations between congenital heart defect complexity and health-related quality of life using a meta-analytic strategy. *Int J Cardiol* [Internet]. 2015;199:197–203. Available from: <http://dx.doi.org/10.1016/j.ijcard.2015.07.045>
22. Yu C, Moore BM, Kotchetkova I, Cordina RL, Celermajer DS. Causes of death in a contemporary adult congenital heart disease cohort. *Heart*. 2018;104(20):1678–82.
23. Frigiola A, Redington AN, Cullen S, Vogel M. Pulmonary regurgitation is an important determinant of right ventricular contractile dysfunction in patients with surgically repaired tetralogy of Fallot. *Circulation*. 2004 Sep;110(11 Suppl 1):II153–7.
24. Davlouros PA, Kilner PJ, Hornung TS, Li W, Francis JM, Moon JCC, et al. Right ventricular function in adults with repaired tetralogy of Fallot assessed with cardiovascular magnetic resonance imaging. *J Am Coll Cardiol* [Internet]. 2002;40(11):2044–52. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0735109702025664>
25. Kuehne T, Saeed M, Gleason K, Turner D, Teitel D, Higgins CB, et al. Effects of Pulmonary Insufficiency on Biventricular Function in the Developing Heart of Growing Swine. *Circulation*. 2003;108(16):2007–13.
26. Ylitalo P, Jokinen E, Lauerma K, Holmström M, Pitkänen-Argillander OM. Additional mechanism for left ventricular dysfunction: Chronic pulmonary regurgitation decreases left ventricular preload in patients with tetralogy of Fallot. *Cardiol Young*. 2018;28(2):208–13.
27. Bouzas B, Kilner PJ, Gatzoulis MA. Pulmonary regurgitation: Not a benign lesion. *Eur Heart J*. 2005;26(5):433–9.
28. Baumgartner H, Bonhoeffer P, De Groot NMS, De Haan F, Deanfield JE, Galie N, et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J*. 2010;31(23):2915–57.
29. Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM, et al. 2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Vol. 139, *Circulation*. 2019. 637–697 p.
30. Kilner PJ, Geva T, Kaemmerer H, Trindade PT, Schwittler J, Webb GD. Recommendations for cardiovascular magnetic resonance in adults with congenital heart disease from the respective working groups of the European Society of Cardiology. *Eur Heart J*. 2010;31(7):794–805.
31. Oosterhof T, Van Straten A, Vliegen HW, Meijboom FJ, Van Dijk APJ, Spijkerboer AM, et al. Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of Fallot using cardiovascular magnetic resonance. *Circulation*. 2007;116(5):545–51.
32. Lee C, Kim YM, Lee CH, Kwak JG, Park CS, Song JY, et al. Outcomes of pulmonary valve replacement in 170 patients with chronic pulmonary regurgitation after relief of right ventricular outflow tract obstruction: Implications for optimal timing of pulmonary valve replacement. *J Am Coll Cardiol* [Internet]. 2012;60(11):1005–14. Available from: <http://dx.doi.org/10.1016/j.jacc.2012.03.077>
33. Gorter TM, Van Melle JP, Hillege HL, Pieper PG, Ebels T, Hoendermis ES, et al. Ventricular remodelling after pulmonary valve replacement: Comparison between pressure-loaded and volume-loaded right ventricles. *Interact Cardiovasc Thorac Surg*. 2014;19(1):95–101.
34. Ferraz Cavalcanti PE, Sá MPBO, Santos CA, Esmeraldo IM, Escobar RR De, Menezes AM De, et al. Pulmonary valve replacement after operative repair of Tetralogy of Fallot: Meta-analysis and meta-regression of 3,118 patients from 48 studies. *J Am Coll Cardiol*. 2013;62(23):2227–43.
35. Frigiola A, Tsang V, Bull C, Coats L, Khambadkone S, Derrick G, et al. Biventricular response after pulmonary valve replacement for right ventricular outflow tract dysfunction: is age a predictor of outcome? *Circulation*. 2008;118(14 Suppl):182–90.
36. Heng EL, Gatzoulis MA, Uebing A, Sethia B, Uemura H, Smith GC, et al. Immediate and midterm cardiac remodeling after surgical pulmonary valve replacement in adults with repaired tetralogy of fallot: A prospective cardiovascular magnetic resonance and clinical study. *Circulation*. 2017;136(18):1703–13.
37. Lee C, Park CS, Lee CH, Kwak JG, Kim SJ, Shim WS, et al. Durability of bioprosthetic valves in the pulmonary position: Long-term follow-up of 181 implants in patients with congenital heart disease. *J Thorac Cardiovasc Surg* [Internet]. 2011;142(2):351–8. Available from: <http://dx.doi.org/10.1016/j.jtcvs.2010.12.020>
38. Robichaud B, Hill G, Cohen S, Woods R, Earing M, Frommelt P, et al. Bioprosthetic pulmonary valve endocarditis: Incidence, risk factors, and clinical outcomes. *Congenit Heart Dis*. 2018;13(5):734–9.
39. Bokma JP, Winter MM, Oosterhof T, Vliegen HW, van Dijk AP, Hazekamp MG, et al. Preoperative thresholds for mid-to-late haemodynamic and clinical outcomes after pulmonary valve replacement in tetralogy of Fallot. *Eur Heart J*. 2015;37(10):829–35.
40. Geva T, Mulder B, Gauvreau K, Babu-Narayan SV, Wald RM, Hickey K, et al. Preoperative Predictors of Death and Sustained Ventricular Tachycardia After Pulmonary Valve Replacement in Patients With Repaired Tetralogy of Fallot Enrolled in the INDICATOR Cohort. *Circulation*. 2018;138:2106–15.
41. Geva T. Indications for pulmonary valve replacement in repaired tetralogy of fallot: The quest continues. *Circulation*. 2013;128(17):1855–7.
42. Khairy P, Aboulhosn J, Gurvitz MZ, Opatowsky AR, Mongeon FP, Kay J, et al. Arrhythmia burden in adults with surgically repaired tetralogy of fallot: A multi-institutional study. *Circulation*. 2010;122(9):868–75.
43. Egbe AC, Miranda WR, Ammash NM, Ananthaneni S, Sandhyavenu H, Farouk Abdelsamid M, et al. Atrial Fibrillation Therapy and Heart Failure Hospitalization in Adults With Tetralogy of Fallot. *JACC Clin Electrophysiol*. 2019;5(5):618–25.
44. Valente AM, Gauvreau K, Assenza GE, Babu-Narayan S V., Schreier J, Gatzoulis MA, et al. Contemporary predictors of death and sustained ventricular tachycardia in patients with repaired tetralogy of Fallot enrolled in the INDICATOR cohort. *Heart*. 2014;100(3):247–53.
45. Bokma JP, Winter MM, Kuijpers JM, Jongbloed MR, Duijnhouwer AL, Hoendermis ES, et al. Role of Acquired Cardiovascular Disease in Tetralogy of Fallot Patients >50 Years of Age. *J Am Coll Cardiol* [Internet]. 2017;69(19):2465–6. Available from: <http://dx.doi.org/10.1016/j.jacc.2017.03.529>
46. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: A multicentre study. *Lancet*. 2000;356(9234):975–81.
47. Jackson AC, Murphy B. ICD surgery: highlighting the psychological consequences. *Br J Card Nurs*. 2017;12(10):482–6.
48. D'Alto M, Budts W, Diller GP, Mulder B, Egidy Assenza G, Oreto L, et al. Does gender affect the prognosis and risk of complications in patients with congenital heart disease in the modern era? *Int J Cardiol* [Internet]. 2019; Available from: <https://doi.org/10.1016/j.ijcard.2019.05.010>
49. Engelfriet P, Mulder BJM. Gender differences in adult congenital heart disease. *Netherlands Hear J*. 2009;17(11):414–7.
50. Verheugt CL, Uiterwaal CSPM, Van Der Velde ET, Meijboom FJ, Pieper PG, Vliegen HW, et al. Gender and outcome in adult congenital heart disease. *Circulation*. 2008;118(1):26–32.
51. Oliver JM, Gallego P, Gonzalez AE, Garcia-Hamilton D, Avila P, Alonso A, et al. Impact of age and sex on survival and causes of death in adults with congenital heart disease. *Int J Cardiol* [Internet]. 2017;245(June 2017):119–24. Available from: <http://dx.doi.org/10.1016/j.ijcard.2017.06.060>
52. Verheugt CL, Uiterwaal CSPM, Van Der Velde ET, Meijboom FJ, Pieper PG, Van Dijk APJ, et al. Mortality in adult congenital heart disease. *Eur Heart J*. 2010;31(10):1220–9.
53. Sarikouch S, Boethig D, Peters B, Kropf S, Dubowy KO, Lange P, et al. Poorer right ventricular systolic function and exercise capacity in women after repair of tetralogy of fallot a sex comparison of standard deviation scores based on sex-specific reference values in healthy control subjects. *Circ Cardiovasc Imaging*. 2013;6(6):924–33.



54. Pettit KA, Francois CJ, Aggarwal NR, Hess TM, Bartlett HL. Sex-Specific Differences in Ventricular Dimensions in Repaired Tetralogy of Fallot: A Retrospective Study. *Pediatr Cardiol* [Internet]. 2019;40(7):1530–5. Available from: <https://doi.org/10.1007/s00246-019-02181-5>
55. Jacobs W, Van De Veerdonk MC, Trip P, De Man F, Heymans MW, Marcus JT, et al. The Right Ventricle Explains Sex Differences in Survival in Idiopathic Pulmonary Arterial Hypertension. *Chest*. 2014;145(6):1230–6.
56. Ventetuolo CE, Ouyang P, Bluemke DA, Tandri H, Barr RG, Bagiella E, et al. Sex hormones are associated with right ventricular structure and function: The MESA-right ventricle study. *Am J Respir Crit Care Med*. 2011;183(5):659–67.
57. Ventetuolo CE, Mitra N, Wan F, Manichaikul A, Barr RG, Johnson C, et al. Oestradiol metabolism and androgen receptor genotypes are associated with right ventricular function. *Eur Respir J* [Internet]. 2016;47(2):553–63. Available from: <http://dx.doi.org/10.1183/13993003.01083-2015>
58. Liu A, Schreier D, Tian L, Eickhoff JC, Wang Z, Hacker TA, et al. Direct and indirect protection of right ventricular function by estrogen in an experimental model of pulmonary arterial hypertension. *Am J Physiol Circ Physiol*. 2014;307(3):H273–83.
59. Lahm T, Albrecht M, Fisher AJ, Selej M, Patel NG, Brown JA, et al. 17 $\beta$ -Estradiol attenuates hypoxic pulmonary hypertension via estrogen receptor-mediated effects. *Am J Respir Crit Care Med*. 2012;185(9):965–80.
60. Hemnes AR, Maynard KB, Champion HC, Gleaves L, Penner N, West J, et al. Testosterone negatively regulates right ventricular load stress responses in mice. *Pulm Circ*. 2012;2(3):352–8.
61. Brida M, Diller GP, Nashat H, Strozzi M, Milicic D, Baumgartner H, et al. Pharmacological therapy in adult congenital heart disease: Growing need, yet limited evidence. *Eur Heart J*. 2019;40(13):1049–56.
62. Zaffran S, Kelly RG, Meilhac SM, Buckingham ME, Brown NA. Right ventricular myocardium derives from the anterior heart field. *Circ Res*. 2004 Aug;95(3):261–8.
63. Lahm T, Douglas IS, Archer SL, Bogaard HJ, Chesler NC, Haddad F, et al. Assessment of right ventricular function in the research setting: Knowledge gaps and pathways forward an official American thoracic society research statement. *Am J Respir Crit Care Med*. 2018;198(4):e15–43.
64. Bartelds B, Borgdorff MA, Smit-Van Oosten A, Takens J, Boersma B, Nederhoff MG, et al. Differential responses of the right ventricle to abnormal loading conditions in mice: Pressure vs. volume load. *Eur J Heart Fail*. 2011;13(12):1275–82.
65. Borgdorff MAJ, Bartelds B, Dickinson MG, Steendijk P, de Vroomen M, Berger RMF. Distinct loading conditions reveal various patterns of right ventricular adaptation. *Am J Physiol Heart Circ Physiol*. 2013;305(3):H354–64.
66. Borgdorff MAJ. The elusive heart: the right ventricle in chronic abnormal loading conditions. University of Groningen; 2014.
67. van Albada ME, Berger RMF, Niggebrugge M, van Veghel R, Cromme-Dijkhuis AH, Schoemaker RG. Prostacyclin therapy increases right ventricular capillarisation in a model for flow-associated pulmonary hypertension. *Eur J Pharmacol*. 2006 Nov;549(1–3):107–16.
68. Koop AMC, Hagdorn QAJ, Bossers GPL, van Leusden T, Gerding A, van Weeghel M, et al. Right ventricular pressure overload alters cardiac lipid composition. *Int J Cardiol* [Internet]. 2019;(xxxx). Available from: <https://doi.org/10.1016/j.ijcard.2019.04.004>
69. de Boer RA, De Keulenaer G, Bauersachs J, Brutsaert D, Cleland JG, Diez J, et al. Towards better definition, quantification and treatment of fibrosis in heart failure: a scientific roadmap by the Committee of Translational Research of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* [Internet]. 2018; Available from: <http://eprints.gla.ac.uk/174967/>
70. Suthahar N, Meijers WC, Silljé HHW, de Boer RA. From Inflammation to Fibrosis—Molecular and Cellular Mechanisms of Myocardial Tissue Remodelling and Perspectives on Differential Treatment Opportunities. *Curr Heart Fail Rep*. 2017;14(4):235–50.
71. Graziani F, Varone F, Crea F, Richeldi L. Treating heart failure with preserved ejection fraction: learning from pulmonary fibrosis. *Eur J Heart Fail*. 2018;
72. Hanneman K, Crean AM, Wintersperger BJ, Thavendiranathan P, Nguyen ET, Kayedpour C, et al. The relationship between cardiovascular magnetic resonance imaging measurement of extracellular volume fraction and clinical outcomes in adults with repaired tetralogy of Fallot. *Eur Hear J - Cardiovasc Imaging* [Internet]. 2017;1(July):777–84. Available from: <http://academic.oup.com/ehjcard/article/doi/10.1093/ehjci/jex248/4555486/The-relationship-between-cardiovascular-magnetic>
73. Haggerty CM, Suever JD, Pulenthiran A, Mejia-Spiegeler A, Wehner GJ, Jing L, et al. Association between left ventricular mechanics and diffuse myocardial fibrosis in patients with repaired Tetralogy of Fallot: A cross-sectional study. *J Cardiovasc Magn Reson*. 2017;19(1):1–10.
74. Cochet H, Iriart X, Allain-Nicolaï A, Camaioni C, Sridi S, Nivet H, et al. Focal scar and diffuse myocardial fibrosis are independent imaging markers in repaired tetralogy of Fallot. *Eur Hear J - Cardiovasc Imaging*. 2019;33:1–14.
75. Yim D, Riesenkampff E, Caro-Dominguez P, Yoo S-J, Seed M, Grosse-Wortmann L. Assessment of Diffuse Ventricular Myocardial Fibrosis Using Native T1 in Children With Repaired Tetralogy of Fallot. *Circ Cardiovasc Imaging* [Internet]. 2017;10(3):e005695. Available from: <http://circimaging.ahajournals.org/lookup/doi/10.1161/CIRCIMAGING.116.005695>
76. Borgdorff MAJ, Dickinson MG, Berger RMF, Bartelds B. Right ventricular failure due to chronic pressure load: What have we learned in animal models since the NIH working group statement? *Heart Fail Rev* [Internet]. 2015;20(4):475–91. Available from: <http://dx.doi.org/10.1007/s10741-015-9479-6>
77. Crnkovic S, Egemnazarov B, Damico R, Marsh LM, Nagy BM, Douschan P, et al. Disconnect between Fibrotic Response and Right Ventricular Dysfunction. *Am J Respir Crit Care Med*. 2018;1–48.