Risk stratification in adults operated for tetralogy of Fallot

Thesis for the degree of Philosophiae doctor (Ph.D)

Alessia Quattrone, MD
Institute of Clinical Medicine
Faculty of Medicine
University of Oslo
Department of Cardiology
ProCardio Center for Innovation
Oslo University Hospital
Rikshospitalet

Oslo, Norway 2022
Contents

Acknowledgements 7

List of papers 9

1. Impact of pregnancy and risk factors for ventricular arrhythmias in women with tetralogy of Fallot
2. Long term follow-up and sex differences in adults operated for tetralogy of Fallot
3. Is experienced pregnancy in women with repaired tetralogy of Fallot related to diffuse myocardial fibrosis?

Abbreviation 10

Introduction 11

Definition 11

Incidence and etiology 12

Pathophysiology and clinical presentation 12

Diagnosis 13

Treatment 13

Prognosis and complications 14

Follow – up in adult with corrected TOF 16

Pregnancy 17

Aims 20

General aims of the thesis 20

Specific aims and hypotheses 20

Paper 1 20

Paper 2 20
<table>
<thead>
<tr>
<th>Section</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives</td>
<td>22</td>
</tr>
<tr>
<td>Specific objectives</td>
<td>22</td>
</tr>
<tr>
<td>Paper 1</td>
<td>22</td>
</tr>
<tr>
<td>Paper 2</td>
<td>22</td>
</tr>
<tr>
<td>Paper 3</td>
<td>22</td>
</tr>
<tr>
<td>Material and methods</td>
<td>23</td>
</tr>
<tr>
<td>Study population and design</td>
<td>23</td>
</tr>
<tr>
<td>Clinical data</td>
<td>25</td>
</tr>
<tr>
<td>Exercise capacity</td>
<td>25</td>
</tr>
<tr>
<td>Marker of heart failure</td>
<td>25</td>
</tr>
<tr>
<td>ECG parameters and cardiac arrhythmias</td>
<td>26</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>27</td>
</tr>
<tr>
<td>CMR protocol</td>
<td>29</td>
</tr>
<tr>
<td>Statistics</td>
<td>31</td>
</tr>
<tr>
<td>Summary of results</td>
<td>32</td>
</tr>
<tr>
<td>Paper 1</td>
<td>32</td>
</tr>
<tr>
<td>Paper 2</td>
<td>38</td>
</tr>
<tr>
<td>Paper 3</td>
<td>46</td>
</tr>
<tr>
<td>Discussion</td>
<td>52</td>
</tr>
<tr>
<td>TOF and VA</td>
<td>53</td>
</tr>
<tr>
<td>Pregnancy and its influence on the outcome</td>
<td>56</td>
</tr>
<tr>
<td>Deformation imaging parameters and myocardial fibrosis</td>
<td>57</td>
</tr>
<tr>
<td>Section</td>
<td>Page</td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Sex differences</td>
<td>58</td>
</tr>
<tr>
<td>Clinical implications and future perspectives</td>
<td>59</td>
</tr>
<tr>
<td>Limitations</td>
<td>60</td>
</tr>
<tr>
<td>General limitations</td>
<td>60</td>
</tr>
<tr>
<td>Specific limitations</td>
<td>60</td>
</tr>
<tr>
<td>Paper 1</td>
<td>60</td>
</tr>
<tr>
<td>Paper 2</td>
<td>60</td>
</tr>
<tr>
<td>Paper 3</td>
<td>61</td>
</tr>
<tr>
<td>Conclusions</td>
<td>62</td>
</tr>
<tr>
<td>General conclusions</td>
<td>62</td>
</tr>
<tr>
<td>Specific conclusions</td>
<td>62</td>
</tr>
<tr>
<td>Paper 1</td>
<td>62</td>
</tr>
<tr>
<td>Paper 2</td>
<td>62</td>
</tr>
<tr>
<td>Paper 3</td>
<td>63</td>
</tr>
<tr>
<td>References</td>
<td>64</td>
</tr>
</tbody>
</table>
Acknowledgements

This work was performed at the Center for Cardiological Innovation (CCI), Department of Cardiology at Oslo University Hospital, Rikshospitalet and the Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, from 2017 to 2021 with support of the South-Eastern Norway Health Region.

My first thanks go to Mette-Elise Estensen, the person who gave me the opportunity to start my career as cardiologist and researcher in Norway. Her trust and dedication turned an idea popped up during an ordinary conversation into a successful research project, and I will forever be grateful for her support and commitment.

I cannot express my respect and admiration enough to Thor Edvardsen and Kristina Haugaa, two world famous researchers and prominent cardiologists who gave their invaluable support throughout my entire PhD time. It has been an honor for me to be part of your research group.

I want to thank Charlotte de Lange and Kirsti Try, from the Pediatric Radiology Division. Working together to achieve our project goals was both challenging and exciting.

I have fond memories of the time I spent as intern in the GUCH outpatient clinic at Rikshospitalet. Gunnar Erikssen, Helge Skulstad, Ola Gjesdal, Anne Skeide, Katrine Eriksen, Aldiana Prnjavorac and Solvor Eliassen are not only top-level professionals in the field of congenital heart diseases, but also they are nice and humanly close to colleagues and patients.

And here is the best group of colleagues a person could wish for, the researchers of CCI, which later started to be called ProCardio. I want to mention first Marianne Forså and Anders Bjerring, who were my roommates for most of the time I spent as PhD student. We shared thoughts, laughter, challenges and experiences during life’s ups and downs. Jorun Tangen
joined the office later, and she has been a good office companion to me. We exchanged both personal and professional experiences and enjoyed those chats.

And then Christine Rootvelt, Isotta Castrini, Monica Chivulescu, Maria Ruud, Tove-Elizabeth Hunt, Esther Scheirlynck, the CCI girls, a group of friends who enjoyed spending time together and celebrating birthdays, bachelorette parties, baby showers; we also loved having dinner together in town and arranging summer parties.

I have to reach a big thank to Øyvind Haugen Lie and Lars Andreas Dejgaard, who were experienced PhD students when I started at CCI. I know I can count on them when in need for fun and laughter, scientific support and personal advice.

I would also like to mention Fedo Kirkels, our visiting PhD student from the Netherlands, an exquisite person. Eystein Skjølsvik, an excellent cardiologist and a loyal friend.

Malin Sæter, Lars Gunnar Klæbo, Pål Brekke, Stian Ross, Eyvind Aabel, Christoffer Andresen, Margaret Ribe have been nice people to share coffee and meetings with.

And there is my fantastic mother in law Marit Sagen, who gave her support to me all along the way, deserves the greatest thank you in the world.

It is challenging to find enough words to express my gratitude and love to my parents Carmelo Quattrone and Nadia Pizzichemi, who have followed and supported me 2000% every day in every aspect of my life. Without their tireless commitment all of this would have never been possible.

And last but not least my husband Marius Sagen, the love of my life and the person who made me literally pack my bags and move to Norway. With our daughter Astrid you are the reason I wake up every day.
List of papers

1. Impact of pregnancy and risk factors for ventricular arrhythmias in women with tetralogy of Fallot.

*Open Heart.* 2021 Jan;8 (1):e001400.

Alessia Quattrone, Øyvind H. Lie, Eirik Nestaas, Charlotte de Lange, Kirsti Try, Harald L. Lindberg, Helge Skulstad, Gunnar Erikssen, Thor Edvardsen, Kristina H. Haugaa, Mette-Elise Estensen

2. Long term follow-up and sex differences in adults operated for tetralogy of Fallot


Alessia Quattrone, Øyvind H. Lie, Eirik Nestaas, Charlotte de Lange, Kirsti Try, Harald L. Lindberg, Helge Skulstad, Gunnar Erikssen, Thor Edvardsen, Kristina H. Haugaa, Mette-Elise Estensen

3. Is experienced pregnancy in women with repaired tetralogy of Fallot related to diffuse myocardial fibrosis?


Charlotte de Lange, Alessia Quattrone, Kirsti Try, Anita Helset Bakke, Anette Borger Kvalserud, Kristina Hermann Haugaa, Mette-Elise Estensen
**Abbreviation**

CMR: cardiac magnetic resonance  
EF: ejection fraction  
GLS: global longitudinal strain  
LV: left ventricle  
NT-proBNP: N-terminal pro-brain natriuretic peptide  
NYHA: New York Heart Association  
RV: right ventricle  
TOF: tetralogy of Fallot  
VA: ventricular arrhythmias
**Introduction**

**Definition**

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease. It was described first in 1671 by the Danish physician/anatomist Niels Stenson, and William Hunter at St Georges Hospital Medical School in London provided a more precise anatomical illustration in 1784.

Etienne-Louis Fallot, a French physician, refined the description in 1888 in his work *L'anatomie pathologique de la maladie bleu*, illustrating a congenital heart disease occurring with relative frequency which consisted of a combination of four cardiac defects (*tetralogie* in French, from Greek tetralogia- a collection of four works): ventricular septal defect, right ventricular outflow obstruction, right ventricular hypertrophy and over-riding of the aorta¹.

The eponym in English language “tetralogy of Fallot” was first used by the Canadian pediatric cardiologist Maude Abbott in 1924, who contributed in popularizing the term².

---

**Figure 1. Tetralogy of Fallot** (from Mayo Clinic.org)

---
**Incidence and etiology**

TOF occurs in 1 of every 30,000-35,000 live births, and accounts for 7-10% of all congenital cardiac malformations. Most cases of TOF occur sporadically, although the risk for recurrence in a family is approximately 3\%\(^3\).

The etiology of TOF is multifactorial. About 25% of patients have chromosomal disorders, the most frequent being trisomy 21 and 22q11.2 microdeletions. Indeed, TOF is frequently diagnosed in children with Di George syndrome, which the most severe type of 22q11.2 microdeletion.

**Pathophysiology and clinical presentation**

During embryogenesis, the anterior deviation of the infundibular septum, which separates the outflow tract of the two ventricles, displace it under the pulmonary valve, creating the four anatomical features of TOF. The malalignment of infundibular septum results in the subpulmonary obstruction with consequently right ventricle (RV) hypertrophy, ventricular septal defect (VSD) and overriding of the aorta over both ventricles. The VSD is typically large and non-restrictive, ensuring that the pressure is quite balanced in the two ventricles.

The severity of the obstruction of the right ventricular outflow tract (RVOT) determines the direction of blood flow through the VSD. If the RVOT obstruction is severe, or if there is pulmonary atresia, the newborn baby presents with cyanosis due to the low pulmonary blood and consequent large right-to-left shunt. Most TOF patients have a low to moderate RVOT obstruction, resulting in adequate pulmonary blood flow at birth. However, those babies soon develop cyanosis during the first weeks and months of life.
Diagnosis

TOF has been mostly diagnosed during fetal life in the last three decades.

Before the extensive use of prenatal ultrasound, diagnosis was frequently made during the neonatal period or within the first months of life. Depending on the grade of pulmonary obstruction, babies developed a cyanosis which occurred earlier for those with severe obstruction of the RVOT.

Treatment

The treatment is solely surgical, permitting the correction of the anatomical defects of TOF and restoring an effective pulmonary circulation.

Alfred Blalock, a heart surgeon and the pediatrician Helen Taussig were the first in developing a palliative systemic-to-pulmonary shunt, which was named after them. The first operation was performed in 1944 at Johns Hopkins Hospital in Baltimore, Maryland (USA), on a 15-month-old girl. Originally, the subclavian artery was connected with the ipsilateral branch of the pulmonary artery with a distal ligation to an end to side anastomosis. This shunt permitted to increase pulmonary arterial blood flow which was severely compromised in patients with RVOT obstruction.

Nowadays, the use of synthetic graft, usually expanded polytetrafluoroethylene (Gore-Tex®), to connect subclavian artery and pulmonary artery, in the established method in the modified Blalock-Taussig shunt.

The first intracardiac complete repair of TOF is reported performed in 1954. Since this first operation, the age of patients receiving primary corrective surgery has gradually decreased.
In the present era, TOF repair consists of a transatrial-transpulmonary approach to close the VSD and to perform the resection of the obstructive infundibular muscle bundles. This is completed by a transpulmonary access to tackle the pulmonary valve component and eventually the hypoplasia of the pulmonary artery\(^7\).

The right bundle branch block is common after transatrial repair of TOF. This is usually produced by infundibular resection, resulting in damage to portions of the RV conduction system, and is associated with delayed activation of the pulmonary outflow tract and base of the RV\(^8\). A conservative infundibulectomy, consisting of a shorter ventriculotomy without touching the septal bundle, could reduce the incidence of post-operative right bundle branch block\(^9\).

There is currently no complete and uniform consensus on the optimal timing for corrective surgery in TOF patients. Many cardiac surgery centers promote neonatal primary intracardiac repair, even within the first few days of life. Some centers have concluded that early primary repair of TOF can be performed safely and effectively in infants under 4 months of age, and even in newborns younger than 28 days with severe hypoxemia or duct-dependent pulmonary circulation\(^10\). Although all those positive feedback on the safety of early repair, patients undergoing primary repair at <3 months of age were more likely to have a longer stay in intensive care unit, as well as a longer period of mechanical ventilation and increased need for inotropes.\(^11\)

**Prognosis and complications**

After the advent of the palliative and corrective surgery, life expectancy of children born with TOF has significantly improved to a survival of 94% twenty-five years\(^12\) and 72% forty
years\textsuperscript{13} following TOF repair. Another study showed that the 36-year survival rate was 85%, with mortality increasing particularly 25 years postoperatively from 0.24%/year to 0.94%/year\textsuperscript{14}. Early repair is also promoted in order to avoid polycythemia and excessive RV hypertrophy.

Despite development of corrective surgical treatment, TOF patients are still subject to higher mortality rate than in the general population, and a considerable high risk for severe malignant arrhythmias. In particular ventricular arrhythmias (VA) and sudden cardiac death (SCD) represent major concerns in adults operated for TOF.

One of the largest multicenter studies conducted on 793 patients provides a comprehensive risk assessment in patients operated for TOF. This study indicated that the absolute duration of QRS and the rate of change of duration (>3 ms per year over a 10-year period) were the most important predictors of death. Furthermore, pulmonary regurgitation was the most prominent hemodynamic risk factor of clinically relevant arrhythmia\textsuperscript{15}. The most common cause of death was SCD (49%), heart failure and coronary artery disease followed. Another study performed on the INDICATOR multicenter cohort showed that RV hypertrophy, left or right ventricular dysfunction and atrial tachyarrhythmias predict sudden cardiac death and sustained ventricular tachycardia in adults with repaired TOF\textsuperscript{16}.

Pulmonary valve regurgitation (PR) is the most common indication for reoperation later in life\textsuperscript{17}. Pulmonary valve replacement (PVR) in patients requiring intervention due to pulmonary insufficiency has showed several benefits, in term of improvements in the volume and function of right and left ventricle. Also QRS duration decreases\textsuperscript{18}. Pulmonary valve replacement should be performed before RV systolic and diastolic volumes increase importantly\textsuperscript{19}. 


Follow-up in adult with corrected TOF

Adult operated for TOF require lifelong surveillance, with periodical controls. For the long-term follow-up, current guidelines recommend an annual clinical and echocardiographic evaluation in postoperative TOF, even though it can be less frequent in patients with minimal residual lesions and stable hemodynamic disturbances\textsuperscript{20}. Imaging follow-up must always be accompanied by clinical evaluation and functional status and other tests like electrocardiogram, cardiopulmonary stress test and Holter monitoring.

Echocardiography, both classical and with new techniques, remains the cornerstone and first-line imaging diagnostic modality in TOF patients, as it is inexpensive, widely available and radiation-free. Although its unquestionable advantages, echocardiography does not permit to evaluate extensively the RV size and function, due to the complex geometry of the RV with its triangular shape; a poor acoustic window is often an additional limiting factor.

Other imaging modalities are available in order to integrate the information provided by echocardiography. Cardiac magnetic resonance (CMR) has gradually overcome echocardiography\textsuperscript{`s} limitations. CMR is now considered essential and it is recommended as imaging modality in adult with repaired TOF. It provides detailed information on cardiovascular morphology and hemodynamic, especially in case of associated congenital defects, with a precise quantification of RV size and function and of PR. However, it is more expensive and less available than echocardiography, and it has several contraindications, e.g. all cardiac implantable electronic device like pacemakers and implantable cardioverter defibrillators (ICD), which are not uncommon in adult corrected for TOF. Cardiac computer tomography (CT) is recommended as an alternative in patients with absolute contraindications to CMR or where CMR is not available\textsuperscript{21}. Each of these imaging modalities has its advantages...
and pitfalls in TOF patient follow-up. Therefore, they remain complementary tools in the thorough evaluation.

According to the current knowledge\textsuperscript{15,16}, risk of complications in adult life is similar in males and females for TOF operated patients. Although reports have previously indicated a slightly higher prevalence of atrial and ventricular arrhythmias in male patients, a different profile risk in sexes is not well outlined. Risk stratification is ultimately not comprehensive in present, and despite regular follow-up, it is not always possible to identify patients who are more prone to severe arrhythmic complications and/or SCD.

**Pregnancy**

*Physiology of normal pregnancy*

During normal pregnancy, the cardiovascular system of the mother adapts to the metabolic needs of both mother and fetus in order to maintain tissue perfusion with adequately oxygenated blood by increasing cardiac output (CO) by 30-50\%, increasing heart rate by 10-20 beats per minute and by decreasing peripheral vascular resistance by 30\%\textsuperscript{22}. Myocardial contractility in normal pregnancy has been found altered in some studies\textsuperscript{23,24}. 
Figure 2. Hemodynamic changes in the normal pregnancy.
CO = cardiac output; SV = stroke volume; HR = heart rate; MAP = mean arterial pressure; SVR = systemic vascular resistance. From Weinberg CR et al. US Cardiology Review 2020;14:e10

Pregnancy and TOF

Pregnancy is usually well tolerated in women with repaired TOF. Those patients are generally included in risk class II (small increased risk of maternal mortality or moderate increase in morbidity) according to the modified World Health Organization (WHO) classification of maternal cardiovascular risk described in the latest European Society of Cardiology (ESC) guidelines of pregnancy. Cardiac complications like arrhythmias and heart failure are the most common complications, which have been observed in 8% of repaired TOF patients, especially in those taking cardiac medications. Dysfunction of the RV and/or moderate to
severe PR and use of medication prior to pregnancy were risk factors. Previous pregnancy may be associated with a persisting increase in RV size and long-term cardiac events. Latest guidelines recommend moreover follow-up every trimester at local hospital for most patients, while women with severe PR, cardiac evaluation should take place monthly or bimonthly.

It is currently not clear whether the cardiovascular alterations related to pregnancy might have an influence on the long-term cardiovascular outcome. Importantly, no studies have previously explored the role of pregnancy in the general risk stratification, particularly on the occurrence of VA.
Aims

General aims of the thesis

The overall purpose of this thesis was to contribute to more comprehensive risk stratification in adults operated for TOF. We aimed to improve risk stratification in TOF patients and to provide a better identification of risk factors that exposes young adults operated with TOF to complications and unfavorable outcome.

Specific aims and hypotheses

Paper 1

We aimed to investigate the influence that one or more pregnancies might have on the long term outcome on women operated for TOF. We hypothesized that the prolonged, and in some cases reiterated, hemodynamic stress of pregnancy due to the considerable increase in both CO and heart rate is associated with adverse outcome in TOF women.

Paper 2

We aimed to investigate the general long term outcome in adults corrected for TOF. We hypothesized that sex might have an impact on the prevalence of complications and adverse cardiac events during adult life.

Paper 3

We aimed to investigate the long term effects of pregnancy on the ventricular and valve function in women operated for TOF using CMR derived parameters. The main hypothesis
was that the hemodynamic changes of pregnancy would lead to increased diffuse myocardial fibrosis.
Objectives

Specific objectives

Paper 1

To investigate the impact of pregnancy in women operated for TOF, by determining whether the prevalence of cardiovascular events such arrhythmias, cardiac arrest and heart failure, as well as functional capacity, RV and LV functioning and pulmonary valve status, is different in women with TOF who had experienced pregnancy compared to those who had not.

Paper 2

To explore cardiac function and the prevalence of complications like VA and heart failure in adult patients operated for TOF, in order to investigate a possible impact of sex on the long term outcome.

Paper 3

To evaluate the possible differences related to pregnancy in TOF women using CMR derived parameters. We aimed to show possible pregnancy induced differences in TOF women by assessing LV and RV myocardial fibrosis, function and volumes in addition to pulmonary valve status.
Material and methods

Study population and design

In all papers, patients over 18 years of age diagnosed for TOF and with history of complete surgical correction were selected from the GUCH (Grown-Up Congenital Heart disease) registry at Oslo University Hospital - Rikshospitalet. This database includes all patients with congenital heart diseases who have been followed and treated at the GUCH unit of Oslo University Hospital, Rikshospitalet, Norway in the period 1970-2020. Written informed consent was obtained from all participants. Patients incapable to express informed written consent were excluded.

In paper 3, a population of healthy individuals >18 years old and matched for age were recruited as control group from families and hospital employees’ social network.

All the studies presented in the papers included in this thesis complied with the Declaration of Helsinki and was approved by the Regional Committees for Medical Research Ethics.

Paper 1

Female patients corrected for TOF were selected from the GUCH registry for this observational cross-sectional study. Patients with history of pregnancy were recruited only if delivery had occurred at least one year prior to the inclusion. In all, 80 women with repaired TOF were eligible for the study, and were contacted with an information letter. Most patients agreed to the direct inclusion and underwent a structured study protocol, while the remaining subjects who chose not to participate to the active recruitment consented to the use of registry data and echocardiographic exams within three years (2015-2017).
Paper 2

In this retrospective cross-sectional study, all patients with TOF diagnosis and who had a history of surgical repair were selected from the GUCH registry. All medical records available were reviewed, and the most recent echocardiographic exam performed during the period 2015-2020 was analyzed.

Paper 3

Female patients who had undergone complete repair for TOF were invited to participate in the study and prospectively included from October 2015 through December 2017 in an observational cross-sectional study. Women who had experienced pregnancy were included only after at least one year since latest child birth. Patients unable to perform CMR due to contraindication as incompatible implants or claustrophobia, were excluded.

Demographic and clinical data were collected from all medical records available. A CMR examination was performed. Functional, volumetric data and velocity mapping of the pulmonary artery and ascending aorta as well as late gadolinium enhancement (LGE) and T1 mapping/ECV were analyzed.

A control group of healthy individuals >18 years without history of cardiac events matched for age were recruited from families and hospital employees’ social network and examined on the same CMR unit from August 2017 through February 2018.
Clinical data

In all three papers, demographic and clinical data were collected from all medical records available in the hospital electronic medical record system.

Exercise capacity

In paper 1, patients included the active recruitment group were tested with an exercise stress test. All other patients in paper 1 and paper 2 had in a similar way received assessment of exercise capacity during their annual or biennial follow up at the GUCH unit at Oslo University Hospital. Exercise stress test was performed on a bicycle ergometer following Bruce protocol and includes a continuous monitoring of 12-lead electrocardiogram, oxygen saturation and heart rate, while cuff blood pressure is measured every 2nd minute.

Marker of heart failure

Blood tests included N-terminal pro-brain natriuretic peptide (NT-proBNP) measurement as a marker of heart failure. In paper 1 and paper 3, normal reference values were <170 ng/L for all women. In paper 2, patient recruitment and data collection took place at least two years later than in paper 1 and paper 3, and cut-off in laboratory reference values had changed. Thus, in paper 2 the reference values for NT-proBNP were age and sex specific: <170 ng/L for women <49 years of age, <85 ng/L for men <49 years of age, <300 ng/L for women 50 - 69 years of age, <250 ng/L for men 50 - 69 years of age. For all patients, NT-proBNP concentration in plasma was assayed on a Modular platform (Elecsys - Roche Diagnostics, Basel, Switzerland),
ECG parameters and cardiac arrhythmias

In paper 1 and 2, patients’ most recent 12 leads- ECG was analyzed. Heart rhythm, heart rate, PQ - QRS - QTc interval, and bundle branch block were assessed.

VA considered clinically relevant for patients were: non-sustained ventricular tachycardia, defined as consecutive runs of ≥3 ventricular beats >100 beats/minute for <30 seconds; sustained ventricular tachycardia, defined as runs of consecutive ventricular beats >100 beats for >30 seconds; ventricular fibrillation; appropriate therapy from an ICD and aborted cardiac arrest.

The occurrence of clinically relevant VA was recorded in 12 leads- ECG, 24-hours Holter registration and implantable cardioverter-defibrillator (ICD) monitoring.
**Echocardiography**

All echocardiograms reviewed in paper 1 and 2 were performed using GE Healthcare ultrasound machines. Picture and data obtained were later analyzed off-line on EchoPAC® version 201(GE Healthcare).

*Conventional echocardiography*

Echocardiographic examination consisted of all measurement which are normally part of standard echocardiogram (M-mode, B-mode, color Doppler, pulsed-wave and continuous-wave Doppler), with a special focus on the RV dimensions. Proximal RVOT diameter was assessed in the parasternal short axis view, while RV basal diameter and RV fractional area change (RVFAC) was measured in the RV focused four-chamber view. Regional RV akinesia and/or dyskinesia were detected in parasternal long- or short-axis view and RV focused four-chamber view. LV ejection fraction (EF) was calculated by the modified Simpson’s biplane method. Pulmonary valve status assessment was also part of the examination, in particular pulmonary valve stenosis and regurgitation of moderate to severe grade were considered significant.
Deformation imaging

In addition to the conventional echocardiographic measurement, left and right ventricular function were assessed by global longitudinal strain (GLS) using speckle tracking technique at frame rates >50/s. LV global longitudinal strain (LVGLS) was defined as the average of peak systolic negative longitudinal deformation/strain from a 16 segments LV model\textsuperscript{31}. RV longitudinal strain was defined as an average peak negative systolic longitudinal strain from six RV segments\textsuperscript{32, 33}.

Mechanical dispersion, defined as the standard deviation of the time-interval from onset of the Q/R wave in the electrocardiogram to the peak negative longitudinal strain in six RV and sixteen LV segments, was calculated as a measure of contraction heterogeneity\textsuperscript{33}.

\textbf{Figure 3:} Two-dimensional speckle-tracking echocardiography. White dotted lines indicate GLS. White arrow indicates RV GLS (a), LV GLS (b). GLS = global longitudinal strain, LV = left ventricular, RV = right ventricular. From Miyake M, et al. Int J Cardiovasc Imaging. 2021 Feb;37(2):569-576, with permission.
CMR protocol

In paper 3, both TOF patients and healthy controls underwent the same scanning protocol on a 3T MR unit, (Philips Achieva, Erlangen, The Netherlands) without anesthesia or sedation.

The protocol included 2D steady-state-free precession sequences performed in an axial, coronal and sagittal plane. A modified Look Locker inversion recovery sequence (MOLLI) was performed in three short-axis views at the basal, mid and apical level to measure T1 times of the myocardium and blood.

The presence of LGE was assessed after injection of 0.2 mmol /kg bodyweight of gadoterate meglumine (Guerbet, Villepinte France) and scanning was performed in long and short-axis views using a standard 2-dimensional breath hold phase sensitive inversion recovery sequence. A repeated MOLLI sequences at least 15 minutes after contrast injection was performed to assure a steady state in contrast enhancement. Flow measurements were performed by velocity encoded phase contrast sequences. Evaluation of the LGE images was done in consensus between two CMR radiologists.

The ECV was calculated based on the pre- and post-contrast and blood pool T1 values, using hematocrit values sampled within 24 hours of the CMR examination.

Observer variation of the T1 measurements was assessed in randomly selected 10 patients and 10 controls. For intra and inter-observer variation, all measurements were performed blinded by two observers with fifteen years’ experience of performing CMR.

Volumetric measurements were performed on the short-axis cine images by manually tracing the contours in end-systole and end-diastole in the picture archiving and communication system. Cardiac volumes indexed to body surface area were compared to normal values. The indexed mass-volume ratio was calculated for both ventricles in patients.
Blood samples were retrieved the same day preceding the CMR. NT-proBNP concentration in plasma was assayed on a Modular platform (Roche Diagnostics, Basel, Switzerland).

Figure 4: Representative CMR images from patients with repaired TOF. A: demonstrates a 46-year-old female with repaired TOF, pulmonary regurgitation fraction of 65%, LV end-diastolic volume index of 70 mL/m², and RV end-diastolic volume index of 141 mL/m². B: demonstrates a 57-year-old male with repaired TOF, pulmonary regurgitation fraction of 57%, LV end-diastolic volume index of 65 mL/m², and RV end-diastolic volume index of 172 mL/m². From Pettit, K.A. et al. Pediatr Cardiol 40, 1530–1535 (2019), with permission.
Statistics

Statistical analysis was performed by using IBM SPSS v 25 in paper 1, IBM SPSS v 26 in paper 2 and IBM SPSS version 27 in paper 3. Data were presented as mean ± standard deviation for normally distributed variables or median with range for non-normally distributed variables. In paper 3, Shapiro Wilkes test was performed to assess normal distribution. In all papers, we performed the comparisons of continuous data by the unpaired Student’s t-test for normally distributed data, or by Mann-Whitney test for non-normally distributed data. When >two groups were compared, the analysis of variance (ANOVA) F-test was used, with the Bonferroni post hoc correction in paper 1 and 2 and with postHoc Tukey test in paper 3. Categorical variables were compared by the $\chi^2$ test or Fisher’s exact test as appropriate. P-values ≤0.05 were considered statistically significant.

In paper 1, odd of VA in patients with previous pregnancy versus those without pregnancy was assessed by logistic regression, and the effect of increasing number of pregnancies was analyzed separately. Multivariable logistical regression was performed retaining covariates of interest from univariable analyses, after controlling for multicollinearity. We adjusted for age using logistic regression, having pregnancy and age at arrhythmic event used as covariates in the logistic regression analysis. Akaike’s information criterion (AIC) were used to assess overfitting by the tradeoff of added complexity and precision in the regression models, and increasing values suggested inferior models. The optimal threshold of NT-proBNP to detect VA was assessed using a single threshold regression (STATA SE 15.1, StataCorp, Texas, USA). By Kaplan Meier curves, we showed the incidence of VA according to this.

In paper 3, intra- and inter-observer agreements were assessed with Bland-Altman analyses\textsuperscript{37}, and results were expressed as the % bias and coefficient of variation.
Summary of results

Paper 1

We recruited 80 female patients corrected for TOF; of them, 55 participated in active recruitment and 25 gave consent to the use of registry data.

In all, 55 (69%) women had experienced pregnancy (age 40 ± 9 years, median parity 1, range 1-4), while 25 (31%) were nulliparous. Nulliparous women were significantly younger compared to women with children (31 ± 9 years vs. 40 ± 9 years, p < 0.01) (Table 1).

Exercise capacity, NYHA class and QRS duration were comparable in both groups (Table 1).

The use of transannular RVOT reconstruction with patch as surgical correction method was reported to be similar in both nulliparous and women with previous pregnancy (11 vs 19, 44% vs 36%, p = 0.53, Table 1). Information on type of surgery was not available for 3 patients.

Echocardiographic parameters

No difference in RV end-diastolic and end-systolic volumes, RVFAC and the RV outflow tract dimensions were reported; in women who had experienced pregnancy, the grade of pulmonary valve stenosis and regurgitation and all LV parameters, included strain and mechanical dispersion, were similar to nulliparous women. The only difference emerging was the longitudinal diameter of the RV (D3), which was greater in women who had been pregnant (Table 1).
### Table 1: Clinical characteristics and echocardiographic parameters in TOF women grouped by parity (paper 1).

<table>
<thead>
<tr>
<th></th>
<th>TOF N = 80</th>
<th>TOF without children (n = 25)</th>
<th>TOF with children (n = 55)</th>
<th>P-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Transannular patch (%)</td>
<td>30 (37)</td>
<td>11 (44)</td>
<td>19 (36)</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Exercise capacity, watt</td>
<td>131 ± 27</td>
<td>127 ± 24</td>
<td>132 ± 28</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td>1 (1-3)</td>
<td>1 (1-3)</td>
<td>1 (1-3)</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>NT-ProBNP, ng/L</td>
<td>174 (30-836)</td>
<td>110 (30-372)</td>
<td>198 (49-836)</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>132 (82-174)</td>
<td>124 (86-162)</td>
<td>134 (82-174)</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>RV EDV, mL</td>
<td>21.7 ± 4.6</td>
<td>20.5 ± 4.8</td>
<td>21.9 ± 4.0</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>RV ESV, mL</td>
<td>11.3 ± 2.9</td>
<td>10.8 ± 2.9</td>
<td>11.3 ± 2.7</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>RV FAC, %</td>
<td>47.8 ± 7.2</td>
<td>47.1 ± 7.4</td>
<td>48.1 ± 7.3</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>RV D3, cm</td>
<td>7.3 ± 0.7</td>
<td>7.1 ± 0.7</td>
<td>7.4 ± 0.7</td>
<td>0.03</td>
<td>2.1 (1.1-4.3)</td>
</tr>
<tr>
<td>LV MD, ms</td>
<td>43.3 ± 14</td>
<td>41.4 ± 10</td>
<td>45.3 ± 10</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>LV GLS, %</td>
<td>-18.9 ± 3.3</td>
<td>-19.2 ± 3.1</td>
<td>-17.5 ± 3.6</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>RV MD, ms</td>
<td>42 ± 13</td>
<td>38 ± 12</td>
<td>43 ± 14</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>RV GLS, %</td>
<td>-19.1 ± 4.1</td>
<td>-19.7 ± 4.1</td>
<td>-18.3 ± 4.1</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>RVOT, cm</td>
<td>2.9 ± 0.5</td>
<td>2.9 ± 0.4</td>
<td>3.1 ± 0.6</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>LV EF, %</td>
<td>55 ± 8</td>
<td>56 ± 8</td>
<td>54 ± 8</td>
<td>0.39</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation or median with range; p-value from the Student’s t-test, Mann-Whitney or $\chi^2$-test, and multivariable logistic regression adjusted for age. EDV = end-diastolic volume; ESS = end-systolic strain; ESV = end-systolic volume; GLS = global longitudinal strain; LV = left ventricular; LVEF = left ventricular ejection fraction; MD = mechanical dispersion; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association classification; OR = odds ratio; RV = right ventricular; RVD3 = right ventricular longitudinal diameter; RVFAC = right ventricular fractional area change; RVOT = right ventricular outflow tract; TOF = Tetralogy of Fallot; VA = ventricular arrhythmias
Risk factors for VA

Occurrence of VA was registered in 17 women (21%). Mean age was comparable in patients with and without VA. Prevalence of VA was higher in women who had experienced pregnancy compared to nulliparous [n = 16 (94%) vs. n = 1 (6%), p = 0.02].

The result was adjusted for age in order to strengthen our findings. The prevalence of VA was confirmed higher in women with children also when adjusted for age at arrhythmic event [OR 12.9 (95% CI 1.5-113.2), p = 0.02]. All arrhythmic events occurred after pregnancy, except one case of symptomatic sustained ventricular tachycardia diagnosed in a nulliparous woman who received ICD implantation in her mid-twenties. The prevalence remained statistically significant also when this patient was excluded from the statistical analysis [p = 0.01, OR 11.3 (95% CI 1.3-99.5), p = 0.02 adjusted for age at the arrhythmic event] (Table 2, Figure 5).

NT-proBNP was significantly higher in patients with VA [211 ng/L (127-836) vs. 139 ng/L (30-465), p = 0.007], and remained as a significant marker of VA when adjusted for age [adjusted OR 1.4 (95% CI 1.1-1.7) by 50 unit increments, p = 0.009]. Threshold regression suggested an optimal differentiation level of NT-proBNP of 321 ng/L as cut-off value to discriminate those with higher risk of VA; this result was confirmed by Kaplan Meier survival analyses, which showed better freedom from VA in those with NT-proBNP below the value 321 ng/L (Table 2, Figure 6).

ECG QRS width was similar in both nulliparous and women with children and was not associated with VA (Table 2).
Table 2: Comparisons of female patients corrected for TOF without and with history of VA, and markers for VA

<table>
<thead>
<tr>
<th></th>
<th>TOF without VA</th>
<th>TOF with VA</th>
<th>P-value</th>
<th>OR</th>
<th>p-value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>36 ± 9</td>
<td>40 ± 9</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of pregnancy, no (%)</td>
<td>39 (61)</td>
<td>16 (94)</td>
<td>0.02</td>
<td>13 (1.5-113.2)</td>
<td>0.02a</td>
</tr>
<tr>
<td>Exercise capacity, watt</td>
<td>125 ± 25</td>
<td>140 ± 26</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td>1 (1-3)</td>
<td>1 (1-2)</td>
<td>0.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP, ng/L</td>
<td>139 (30-465)</td>
<td>211 (127-836)</td>
<td>0.007</td>
<td>1.4 (1.1-1.7)</td>
<td>0.017a</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>135 (82-174)</td>
<td>133 (86-152)</td>
<td>0.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV EDV, mL</td>
<td>21.1 ± 4.1</td>
<td>22.7 ± 3.6</td>
<td>0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV ESV, mL</td>
<td>11.1 ± 2.6</td>
<td>11.8 ± 2.5</td>
<td>0.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV FAC, %</td>
<td>47 ± 7</td>
<td>47 ± 8</td>
<td>0.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV D3, cm</td>
<td>7.3 ± 0.7</td>
<td>7.4 ± 0.7</td>
<td>0.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV MD, ms</td>
<td>43 ± 13</td>
<td>48 ± 16</td>
<td>0.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV GLS, %</td>
<td>-19.2 ± 3.1</td>
<td>-17.5 ± 3.6</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV MD, ms</td>
<td>39 ± 14</td>
<td>50 ± 8</td>
<td>0.009</td>
<td>2.1 (1.3-7.5)</td>
<td>0.01a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.016</td>
<td>5.7 (3.5-9.2)</td>
</tr>
<tr>
<td>RV GLS, %</td>
<td>-19.7 ± 4.1</td>
<td>-18.3 ± 4.1</td>
<td>0.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVOT, cm</td>
<td>2.9 ± 0.4</td>
<td>3.1 ± 0.6</td>
<td>0.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV EF, %</td>
<td>56 ± 9</td>
<td>54 ± 8</td>
<td>0.39</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean±standard deviation or median with range; p-value from the Student’s t-test or Mann-Whitney, and multivariable logistic regression.

a = adjusted for age at VA
b = adjusted for age at echocardiography

EDV = end-diastolic volume; ESS = end-systolic strain; ESV = end-systolic volume; GLS = global longitudinal strain; LV = left ventricular; LVEF = left ventricular ejection fraction; MD = mechanical dispersion; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association classification; RV = right ventricular; RVD3 = right ventricular longitudinal diameter; RVFAC = right ventricular fractional area change; RVOT = right ventricular outflow tract. TOF = Tetralogy of Fallot; VA = ventricular arrhythmias.
RV mechanical dispersion was significantly higher in patients with VA (0.050 ± 0.008 s vs. 0.039 ± 0.014 s, p = 0.009), also when adjusted for age at VA [OR 2.1 (95% CI 1.3-7.5), p = 0.01] and age at echocardiography [OR 5.7 (95% CI 3.5-9.2), p = 0.03], while no other parameter related to the LV and/or RV function or dimension differed between patients with and without VA (Table 2).

Prevalence of VA was higher in female patients corrected for TOF with history of pregnancy, also when adjusted for age at arrhythmic event (Figure 5).

![Figure 5: Pregnancy and risk of VA (paper 1).](image)

The red colored segments of two columns show that VA was significantly more represented in women who had experienced pregnancy compared to nulliparous.

OR = odds ratio; TOF = tetralogy of Fallot; VA = ventricular arrhythmias.
Figure 6: NT-proBNP and risk of VA (paper 1). Kaplan-Meier plot shows that NT-proBNP values >321 ng/L (normal values <170 ng/L) help with discrimination of female patients corrected for TOF with significantly higher risk of presenting VA, also when adjusted for age at arrhythmic event.

NT-proBNP = N-terminal pro-brain natriuretic peptide; OR = odds ratio; TOF = tetralogy of Fallot; VA = ventricular arrhythmias.
In all, we included 148 patients, of which 80 (54%) were females. Mean age at the time of follow-up was 37 ± 10 years (38 ± 10 years for males vs. 37 ± 10 years for females, p = 0.52) (Table 3). Mean time surgery-to-follow-up was 32 ± 9 years (33 ± 8 in males vs. 31 ± 10 in females, p = 0.25).

Age at surgical correction was 4 years (1-15) and number of operations was 1 (1-4), with no differences between sexes. All clinical characteristics were similar, except for larger body size and higher systolic blood pressure in men (Table 3).

**ECG, exercise capacity and heart failure**

Mean QRS duration was prolonged with 141 ± 30 ms, with significantly longer QRS duration in male patients (151 ± 30 ms vs. 128 ± 25 ms, p < 0.001) (Table 3).

The total population had mean exercise capacity of 155 ± 38 watt, with males having higher exercise capacity than females (174 ± 35 watt vs. 131 ± 27 watt, p < 0.001) (Table 1).

More than half of patients (53%) had NT-proBNP above normal values, with similar prevalence in males and females (p = 0.19). NYHA class was also equal between sexes (Table 3).
Table 3: Clinical characteristics in TOF patients (paper 2).

<table>
<thead>
<tr>
<th></th>
<th>TOTAL (n = 148)</th>
<th>MEN (n = 68)</th>
<th>WOMEN (n = 80)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>37 ± 10</td>
<td>38 ± 10</td>
<td>37 ± 10</td>
<td>0.52</td>
</tr>
<tr>
<td>Age at surgery, years</td>
<td>4 (1-15)</td>
<td>4 (1-14)</td>
<td>5 (1-15)</td>
<td>0.46</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172 ± 9</td>
<td>177 ± 5</td>
<td>165 ± 7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78 ± 18</td>
<td>85 ± 18</td>
<td>68 ± 13</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.9 ± 0.2</td>
<td>2.0 ± 0.2</td>
<td>1.7 ± 0.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Operation, no</td>
<td>1 (0-4)</td>
<td>1 (0-4)</td>
<td>1 (0-3)</td>
<td>0.57</td>
</tr>
<tr>
<td>NYHA class</td>
<td>1 (1-3)</td>
<td>1 (1-3)</td>
<td>1 (1-3)</td>
<td>0.49</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>123 ± 14</td>
<td>127 ± 14</td>
<td>116 ± 11</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>72 ± 11</td>
<td>72 ± 12</td>
<td>71 ± 10</td>
<td>0.45</td>
</tr>
<tr>
<td>Exercise capacity, watt</td>
<td>155 ± 38</td>
<td>174 ± 35</td>
<td>131 ± 27</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>High NT-proBNP, no (%)</td>
<td>79 (53)</td>
<td>34 (50)</td>
<td>45 (56)</td>
<td>0.19</td>
</tr>
<tr>
<td>QRS, ms</td>
<td>141 ± 30</td>
<td>151 ± 30</td>
<td>128 ± 25</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QTC, ms</td>
<td>457 ± 45</td>
<td>456 ± 53</td>
<td>460 ± 31</td>
<td>0.53</td>
</tr>
<tr>
<td>VA, no (%)</td>
<td>35 (23)</td>
<td>18 (26)</td>
<td>17 (21)</td>
<td>0.45</td>
</tr>
<tr>
<td>Age at VA, years</td>
<td>38 ± 9</td>
<td>39 ± 9</td>
<td>37 ± 9</td>
<td>0.39</td>
</tr>
<tr>
<td>ICD, no (%)</td>
<td>22 (14)</td>
<td>13 (19)</td>
<td>9 (11)</td>
<td>0.18</td>
</tr>
<tr>
<td>within ICD %</td>
<td>59</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>within SEX %</td>
<td>19</td>
<td>11</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BSA = Body Surface Area; DBP = diastolic blood pressure; HR = heart rate; ICD = implantable cardioverter-defibrillator; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association classification; SBP = systolic blood pressure; TOF = Tetralogy of Fallot; VA = ventricular arrhythmias.
Echocardiography

In the total population, RV dimensions were increased compared to normal values also when indexed for BSA. RV and LV global function were slightly impaired measured by EF and GLS (Table 4).

RV and LV function were significantly impaired in males compared to females, expressed by lower LV EF and both RV and LV global longitudinal strain (p = 0.001) (Table 4).
Table 4: Echocardiographic parameters in TOF patients (paper 2).

<table>
<thead>
<tr>
<th></th>
<th>TOTAL (n = 148)</th>
<th>MEN (n = 68)</th>
<th>WOMEN (n = 80)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV EDA, cm²/m²</td>
<td>12.1 ± 2.5</td>
<td>12.1 ± 2.6</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>RV ESA, cm²/m²</td>
<td>6.2 ± 1.6</td>
<td>6.5 ± 1.6</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>RV FAC, %</td>
<td>48.2 ± 7.1</td>
<td>48.7 ± 7.1</td>
<td>47.8 ± 7.1</td>
<td>0.44</td>
</tr>
<tr>
<td>RV D1, cm/m²</td>
<td>2.2 ± 0.3</td>
<td>2.5 ± 0.3</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>RV D2, cm/m²</td>
<td>1.7 ± 0.5</td>
<td>1.7 ± 0.3</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>RV D3, cm²/m²</td>
<td>3.8 ± 0.3</td>
<td>4.2 ± 0.3</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>LVOT cm</td>
<td>2.4 ± 0.2</td>
<td>2.4 ± 0.3</td>
<td>2.3 ± 0.2</td>
<td>0.26</td>
</tr>
<tr>
<td>RVOT cm</td>
<td>2.9 ± 0.4</td>
<td>3.1 ± 0.3</td>
<td>2.9 ± 0.4</td>
<td>0.45</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>53 ± 8</td>
<td>51 ± 8</td>
<td>55 ± 8</td>
<td>0.005</td>
</tr>
<tr>
<td>LV EDV, (mL/m²)</td>
<td>43 ± 12</td>
<td>45 ± 13</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>LV ESV, (mL/m²)</td>
<td>21 ± 7</td>
<td>20 ± 6</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>LV MD, ms</td>
<td>45.6 ± 15.2</td>
<td>48.4 ± 15.1</td>
<td>43.2 ± 14.9</td>
<td>0.05</td>
</tr>
<tr>
<td>LV GLS, %</td>
<td>-17.4 ± 3.5</td>
<td>-15.8 ± 3.1</td>
<td>-18.8 ± 3.2</td>
<td>0.001</td>
</tr>
<tr>
<td>RV MD, ms</td>
<td>38.6 ± 21.1</td>
<td>35.1 ± 27.3</td>
<td>41.4 ± 13.8</td>
<td>0.09</td>
</tr>
<tr>
<td>RV GLS, %</td>
<td>-17.6 ± 4.3</td>
<td>-15.8 ± 3.9</td>
<td>-19.1 ± 4.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

EDA = end-diastolic area; EDV = end-diastolic volume; ESA = end-systolic area; ESV = end-systolic volume; GLS = global longitudinal strain; LV = left ventricular; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; MD = mechanical dispersion; RV = right ventricular; RVD1 = right ventricular basal diameter; RVD2 = right ventricular mid cavity diameter; RVD3 = right ventricular longitudinal diameter; RVFAC = right ventricular fractional area change; RVOT = right ventricular outflow tract; TOF = Tetralogy of Fallot.
LV GLS and RV GLS were lower in male patients operated for TOF in all age groups (Figure 7 and 8).

Figure 7: LV GLS values in male and female TOF patients according to age (paper 2).

LV GLS = left ventricle global longitudinal strain
Incidence of arrhythmias

In all, VA occurred in 35 patients at a mean age of 38 ± 9 years, 32 ± 6 years after surgery. Sustained VA was the first registered VA in 19 patients, while 17 patients had NSVT as first presentation of VA.

In all, 22 (14%) patients were implanted with ICD (16 secondary preventive ICD and 6 primary preventive ICD).

Higher RV D1 (4.3 ± 0.5 vs 4.6 ± 0.6, p = 0.01), lower EF (55 ± 8 vs. 50 ± 9, p = 0.02) and lower RV GLS (-18.1 ± 4.0 vs. -16.1 ± 4.8, p = 0.04) in the entire cohort were associated with higher incidence of VA (table 5). RV D1 had strongest association to incidence of VA (Table 5).
Patients with VA had more frequently NT-proBNP over reference range [n = 27 (23%) vs. n = 8 (77%), p < 0.001].

We found no differences in the incidence of VA, nor at age at VA between males and females (Table 5). Male patients had mostly experienced sustained VT (77%) as first presentation of VA, while female patients frequently had NSVT (76%) at first VA presentation (p < 0.01). VA had occurred at median 7 years (range 1-18 years) prior to last follow-up.

QRS duration did not differ in those with and without VA (143 ± 32 ms vs 137 ± 28 ms, p = 0.2).

Of the 22 patients with ICD, 13 were men (59%). ICD had been implanted in 19% of the males compared to 11% of the females (Table 3).
Table 5: Risk factors and incidence of VA in TOF patients (paper 2).

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>NO VA (n = 113)</th>
<th>VA (n = 35)</th>
<th>p-value</th>
<th>OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at operation, years</td>
<td>4.6 ± 4.5</td>
<td>4.6 ± 0.2</td>
<td>0.94</td>
<td>2.4 (1.2-5.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>136 ± 27</td>
<td>147 ± 34</td>
<td>0.06</td>
<td>2.8 (1.1-6.9)</td>
<td>0.025</td>
</tr>
<tr>
<td>NYHA class</td>
<td>1 (1-3)</td>
<td>1 (1-3)</td>
<td>0.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise capacity, watt</td>
<td>151 ± 38</td>
<td>151 ± 33</td>
<td>0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operations, no</td>
<td>0.8 ± 0.9</td>
<td>1.0 ± 0.8</td>
<td>0.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV FAC, %</td>
<td>48.5 ± 6.9</td>
<td>47.3 ± 7.5</td>
<td>0.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV D1, cm</td>
<td>4.3 ± 0.5</td>
<td>4.6 ± 0.6</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVOT, cm</td>
<td>2.9 ± 0.4</td>
<td>2.9 ± 0.5</td>
<td>0.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV EF, %</td>
<td>55 ± 8</td>
<td>50 ± 9</td>
<td>0.02</td>
<td>0.94 (0.90-0.99)</td>
<td>0.02</td>
</tr>
<tr>
<td>LV MD, ms</td>
<td>44 ± 14</td>
<td>49 ± 16</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV GLS, %</td>
<td>-17.7 ± 3.3</td>
<td>-16.5 ± 3.9</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV MD, ms</td>
<td>37 ± 22</td>
<td>42 ± 17</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV GLS, %</td>
<td>-18.1 ± 4.0</td>
<td>-16.1 ± 4.8</td>
<td>0.04</td>
<td>1.1 (1.0-1.2)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

GLS = global longitudinal strain; LV = left ventricular; LVEF = left ventricular ejection fraction; MD = mechanical dispersion; RV = right ventricular; RVD1 = right ventricular basal diameter; RVFAC = right ventricular fractional area change; RVOT = right ventricular outflow tract; TOF = Tetralogy of Fallot.
**Paper 3**

Fifty out of 55 TOF women completed a CMR. Median age in the TOF group was 36 years (range 21-67). Forty women (73%) had experienced pregnancy with a median parity of 1 (range 1-4), while 15 women (27%) were nulliparous. The control group included thirty individuals, of which 16 were men, with a median age of 42 years (range 24-64).

The QRS duration in the TOF group was $128 \pm 25$ ms, significantly higher than in the control group ($84 \pm 8$ ms, $p<0.001$). The QRS duration did not present any difference between nulliparous and women having experienced pregnancy ($124 \pm 28$ ms vs. $129 \pm 24$ ms, $p = 0.3$).

S-hematocrit and NT-proBNP values were comparable in the groups (Table 6).
Table 6. Clinical characteristics in TOF patients and the healthy controls (paper 3).

<table>
<thead>
<tr>
<th></th>
<th>TOF (n = 50)</th>
<th>Controls (n = 30)</th>
<th>p-value</th>
<th>TOF no pregnancy (n = 15)</th>
<th>TOF pregnancy (n = 34)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>female (n = 14)</td>
<td>TOF vs controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at CMR (years, median (range))</td>
<td>36 (21-67)</td>
<td>42 (24-64)</td>
<td>0.07</td>
<td>29 ± 10</td>
<td>41 ± 9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>116 ± 11</td>
<td>113 ± 10</td>
<td>0.3</td>
<td>115 ± 9</td>
<td>117 ± 12</td>
<td>0.6</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>71 ± 10</td>
<td>64 ± 9</td>
<td>0.04</td>
<td>72 ± 8</td>
<td>70 ± 11</td>
<td>0.5</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>128 ± 25</td>
<td>84 ± 8</td>
<td>&lt; 0.001</td>
<td>124 ± 28</td>
<td>129 ± 24</td>
<td>0.3</td>
</tr>
<tr>
<td>Age at 1. operation, years</td>
<td>3 (1-19)</td>
<td>Na</td>
<td>Na</td>
<td>2 (1-5)</td>
<td>3 (1-19)</td>
<td>0.4</td>
</tr>
<tr>
<td>Number of operations</td>
<td>2 (1-4)</td>
<td>Na</td>
<td>Na</td>
<td>1 (1-3)</td>
<td>2 (1-4)</td>
<td>0.08</td>
</tr>
<tr>
<td>NYHA class</td>
<td>1 (1-3)</td>
<td>Na</td>
<td>Na</td>
<td>1 (1-3)</td>
<td>1 (1-3)</td>
<td>0.1</td>
</tr>
<tr>
<td>NT-ProBNP, ng/L</td>
<td>171 (30-770)</td>
<td>Na</td>
<td>Na</td>
<td>137 (30-372)</td>
<td>188 (49-770)</td>
<td>0.1</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.4 ± 0.3</td>
<td>0.4 ± 0.3</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR = heart rate; DBP = diastolic blood pressure; NYHA = New York Heart Association classification; NT-proBNP = N-terminal pro-brain natriuretic peptide; TOF = tetralogy of Fallot; SBP = systolic blood pressure.

Cardiac magnetic resonance data

Volumetric indexed values were measured in 49/50 patients. Indexed LV mass (LVmassi) was slightly higher in the pregnancy group (43 ± 10 vs. 38 ± 5 g/m², p = 0.03) while RV EF was lower (49 ± 7 % vs. 53 ± 6 %, p = 0.04). The indexed mass-volume ratio for LV revealed elevated values in the pregnancy group (0.54 ± 0.13 g/ml compared to the non-pregnancy group, (0.47 ± 0.05, p = 0.006) (Table 7).
Table 7. CMR volumetric measurements. Native T1 times and ECV in TOF women according to parity and compared to healthy controls.

<table>
<thead>
<tr>
<th>MR volumetry</th>
<th>TOF all N = 49</th>
<th>TOF no pregnancy (n = 15)</th>
<th>TOF pregnancy (n = 35)</th>
<th>Normal values (range)* female &lt; 35 years &gt; 35 years</th>
<th>P-value TOF with vs no pregnancy</th>
<th>P-value TOF vs controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV EDVi (mL/ m²)</td>
<td>82 ± 11</td>
<td>82 ± 9</td>
<td>81 ± 13</td>
<td>80 (62-98)</td>
<td>73 (51-95)</td>
<td>0.8</td>
</tr>
<tr>
<td>LV ESVi (mL/ m²)</td>
<td>37 ± 7</td>
<td>37 ± 5</td>
<td>37 ± 8</td>
<td>25 (13-37)</td>
<td>23 (11-35)</td>
<td>1.0</td>
</tr>
<tr>
<td>LV SVi (mL/ m²)</td>
<td>45 ± 7</td>
<td>45 ± 6</td>
<td>44 ± 7</td>
<td>55 (43-67)</td>
<td>51 (35-67)</td>
<td>0.6</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>55 ± 5</td>
<td>55 ± 4</td>
<td>55 ± 5</td>
<td>69 (57-81)</td>
<td>69 (57-81)</td>
<td>0.9</td>
</tr>
<tr>
<td>LV massi (g/ m³)</td>
<td>42 ± 9</td>
<td>38 ± 5</td>
<td>43 ± 10</td>
<td>53 (35-71)</td>
<td>52 (34-70)</td>
<td>0.03</td>
</tr>
<tr>
<td>RV EDVi (mL/ m²)</td>
<td>101 ± 26</td>
<td>96 ± 19</td>
<td>103 ± 28</td>
<td>89 (76-111)</td>
<td>80 (42-118)</td>
<td>0.4</td>
</tr>
<tr>
<td>RV ESVi (mL/ m²)</td>
<td>52 ± 16</td>
<td>46 ± 13</td>
<td>55 ± 17</td>
<td>35 (25-45)</td>
<td>30 (26-54)</td>
<td>0.07</td>
</tr>
<tr>
<td>RV SVi (mL/ m²)</td>
<td>51 ± 12</td>
<td>50 ± 9</td>
<td>52 ± 13</td>
<td>54 (40-68)</td>
<td>54 (32-68)</td>
<td>0.5</td>
</tr>
<tr>
<td>RV EF %</td>
<td>50 ± 7</td>
<td>53 ± 6</td>
<td>49 ± 7</td>
<td>61 (55-67)</td>
<td>64 (50-78)</td>
<td>0.04</td>
</tr>
<tr>
<td>RV massi g/ m²</td>
<td>19 ± 4</td>
<td>18 ± 3</td>
<td>20 ± 4</td>
<td>21 (15-27)</td>
<td>19 (13-25)</td>
<td>0.1</td>
</tr>
<tr>
<td>LV mass-volume ratio g/ml</td>
<td>0.52 ± 0.12</td>
<td>0.47 ± 0.10</td>
<td>0.54 ± 0.13</td>
<td>na</td>
<td>na</td>
<td>0.006</td>
</tr>
<tr>
<td>RV mass-volume ratio g/ml</td>
<td>0.44 ± 0.15</td>
<td>0.41 ± 0.10</td>
<td>0.45 ± 0.20</td>
<td>na</td>
<td>na</td>
<td>0.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MR relaxometry</th>
<th>Controls female n = 14</th>
<th>Controls all = 30</th>
<th>P value TOF vs controls Female/all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native T1 LV (ms)</td>
<td>1254 ± 61</td>
<td>1251 ± 37</td>
<td>1255 ± 49</td>
</tr>
<tr>
<td>Native T1 RV (ms)</td>
<td>1393 ± 108</td>
<td>1407 ± 99</td>
<td>1388 ± 112</td>
</tr>
<tr>
<td>LV ECV (%)</td>
<td>25.9 ± 2.7</td>
<td>25.4 ± 1.8</td>
<td>26.5 ± 3.5</td>
</tr>
<tr>
<td>RV ECV (%)</td>
<td>37.7 ± 5.4</td>
<td>37.0 ± 4.4</td>
<td>38.0 ± 5.8</td>
</tr>
</tbody>
</table>

*Normal values according to age < and > 35 years in Hudsmith et al, JCMR 2005

ECV = extra cellular volume fraction; EDVi = end-diastolic volume index; ESVi = end-systolic volume index; EF = ejection fraction; LV = left ventricle; RV = right ventricle; PSV = peak systolic velocity; SVi = stroke volume index; TOF = tetralogy of Fallot
Late Gadolinium enhancement, MR TI mapping and extracellular volume fraction (ECV)

LGE was present in 27 of the 46 patients (58%) and located in the inferior septal free wall junction part and in the RV outflow tract (RVOT) n=14 (Fig 9).

Figure 9. Focal scaring assessed by late inversion recovery sequence with Gd enhancement (LGE) (paper 3). To the left, triangular small LGE in the inferior septum in a TOF woman (arrow) and to the right, in another participant in the RVOT (arrows) and septum (thick arrow) (paper 3)
One patient had LGE in LV apex. There was no significant difference of the presence of LGE between the two TOF groups.

T1 times and ECV in the LV in TOF women were comparable to values in female controls (1254 ± 61 ms/ 25.9 ± 2.7% vs. 1254 ± 45 ms/ 26.8 ± 2.6%, p = 0.9 and p = 0.4 respectively).

RV T1 times in all TOF women were 1393 ± 108 ms and ECV 37.7 ± 5.4%. The RV wall in controls was too thin to permit reliable measurements for comparison.

LV T1 and LV ECV did not show any significant difference in TOF patients compared to healthy controls (p = 0.8 and p = 0.2 respectively).

Valvular patency

Pulmonary regurgitation was mean 13 ± 13% (range 1-42%), without difference between groups. A mild regurgitation fraction of 0-10% was present 25 of the patients. Six patients had regurgitation fraction of 11-20%, two patients presented with a fraction of 21-30%. Severe regurgitation of 31-42% was present 13 patients.

Correlations

Indexed LV end-diastolic and end-systolic volumes correlated with LVECV (R = 0.5 – p = 0.003 and R = 0.4 – p = 0.005 respectively), while RV stroke volume correlated with LV ECV (R = 0.3- p = 0.03).

LV and RV ECV were positively correlated (R = 0.4, p = 0.005), but without association with LV and RV mass-to-volume ratio for LV (R 0.15, p = 0.3) and for RV (R -0.15, p=0.6).
The number of pregnancies was neither associated with LV T1 or ECV, (p = 0.9 for both) nor with RV T1/ ECV (p = 0.4 and p = 0.6 respectively).

No correlation was found between the presence of LGE in RVOT/ septum, p = 0.3 or pulmonary regurgitation >10 m/s, p = 0.9.

The type of surgical repair did not relate to increased CMR markers of fibrosis.
Discussion

In this thesis, we investigated the cardiovascular outcome of adults patients operated for TOF by combining different imaging modalities, with a special focus on newer echocardiographic techniques such as speckle tracking and CMR. We quantified the arrhythmic burden showing that almost one out of four adults operated for TOF experience VA in their late thirties.

Incidence of VA did not show significant differences between sexes, however males had a slightly higher prevalence of sustained VT as first presentation of VA and slightly higher prevalence of ICD implantation compared to females. Male patients showed an impaired LV and RV dysfunction compared to female patients, expressed by both deformation imaging parameters with lower RV and LV GLS values and by standard echocardiography with lower LV EF values calculated by Simpson.

Analyzing the long term influence of pregnancy in women operated for TOF, we found that pregnancy was associated with higher prevalence of VA, registered at least one year after latest delivery, independently of age. The increased risk of VA appears expressed by both echocardiographic deformation imaging parameters with more pronounced RV mechanical dispersion and by biochemical analysis with higher values of NT-proBNP, independently of age as well. CMR parameters did not show any particular influence of pregnancy in RV and LV volumes and function, and pulmonary valve function seemed not to be affected as well. CMR markers of fibrosis showed that RV myocardial fibrosis was higher in women operated for TOF, expressed by increased native T1 and ECV. However fibrosis seemed to be independent from age and experienced pregnancy.
TOF and VA

In paper 1 and 2, we investigated the burden of VA in adults operated for TOF. Almost 25% of the entire patients population of 148 patients had been diagnosed with VA around 30 years after surgical correction, meaning one out of four adults TOF patients. Thus, the prevalence of VA was considerably high, showing an important arrhythmic burden, in spite of a satisfactory life quality, a good exercise capacity and the possibility for women to experience pregnancy without considerable complication in the short term. The risk assessment for VA has historically been challenging, and has been a major concern especially in the past 30 years, along with the improving life expectancy of patients operated for TOF.

Male patients had a numerically slightly higher prevalence of VA, which occurred at approximately the same age in men and women. This finding confirmed the similar arrhythmic risk in both sexes previously shown in large multicenter studies, which represents milestones in the field of congenital heart disease and are considered a reference point for all researchers and clinicians involved in the health care of GUCH patients. In one of those studies, actually the largest multicenter study of the past 30 years with breakthrough results published in The Lancet, the most common causes of death were sudden cardiac death, counting for almost half of the deaths occurred in adults TOF. In particular, the QRS duration of 180 milliseconds or more, a QRS rate of change of duration (>3 milliseconds per year over a 10-year period), older age at repair and pulmonary regurgitation stood out as the most important risk markers of VA and sudden cardiac death in adults with repaired TOF. In our cohort of patients, our attempt to explore risk stratification of VA in TOF patients included those previously internationally recognized risk factors. In our cohort, the longest QRS duration registered was 172 ms, that meaning none of the 148 patients included who had been diagnosed with severe VA presented a QRS duration >180 ms. That
made it not possible for us to evaluate the diagnostic value of this parameter in our group of patients, many of whom had showed several episodes of symptomatic VA as sustained ventricular tachycardia and in some cases had experienced cardiac arrest. Our finding might start to rise questions on the possibility of a widely use of QRS duration >180 ms as risk marker for VA and sudden cardiac death in TOF patients.

With a similar prevalence of VA, the use of device therapy was slightly more represented in men, with 59% of the 22 patients who had received ICD implantation, although not significant. This was again a confirmation of what had been discovered by Gatzoulis and Valente\textsuperscript{15, 16}. Coming to the VA prevalence in the specific sex group, almost one out of 5 men required device therapy, compared to one out of 10 women.

The finding of equally distributed arrhythmic burden between sexes, in agreement with previous studies focused on TOF population, differed from both previous knowledge in general population and in other cardiomyopathies. Indeed, men in all age groups\textsuperscript{38} are actually significantly more prone to sudden cardiac arrest, possible due to the higher incidence of coronary artery disease together with a higher prevalence of cardiac structural abnormalities\textsuperscript{39} compared to women. A similar pattern is met in some cardiomyopathies, as arrhythmogenic right ventricular cardiomyopathy (ARVC) and Brugada syndrome, where male sex is one of predictors for VF and ICD therapy\textsuperscript{40} and history of VF is more frequent in men, who have also a lower age at the onset of VF\textsuperscript{41}.

In paper 1, our focus was directed to assess the influence of pregnancy in risk of VA. The short term outcome of pregnancy is known to be related to higher incidence of cardiovascular events during pregnancies, including mainly (supra) VA in other studies\textsuperscript{26}. We aimed to possibly eliminate the bias related to pregnancy-induced hemodynamic changes, and we chose consequently to include women only at least one year after latest delivery. The prevalence of VA in our study was shown to be significantly higher in women who had
experienced pregnancy compared to nulliparous, independently of age at the onset of VA. This finding might help to explain the balanced arrhythmic burden between sexes in TOF patients compared to general population and to some cardiomyopathies which was showed in paper 2. A possible explanation is that pregnancy, with its prolonged and in some cases reiterated hemodynamic stress\textsuperscript{26}, might contribute to increase the risk of VA in women operated for TOF by influencing the hemodynamic state over quite long time.

In paper 1, NT-proBNP emerged as marker of VA in women operated for TOF, independently of age. Our study showed the relation between NT-proBNP levels and incidence of arrhythmias, particularly with values of NT-proBNP $>321$ ng/L being related to a higher odds of VA. Prior to that, a systematic review of 49 other studies had shown correlation between proBNP levels and RV end-diastolic dimensions and severity of pulmonary valve regurgitation in patients corrected for TOF\textsuperscript{42}. These findings reflect generally structural changes in the RV, as expected in this type of congenital heart disease, as consequence of both the anatomic features of the disease and of surgical repair. Also in paper 2, more than 50\% of TOF patients had NT-proBNP values over normal reference range, although NYHA class was preserved indicating a generally good exercise capacity in the entire cohort, revealing an asymptomatic stage of heart failure showed by decreased RV and LV function showed by EF and GLS, especially in male patients.

NT-proBNP levels had although never been previously related to VA, which represent the most common complication. This finding might open opportunities in the risk stratification, casting new light on the importance of NT-proBNP in predicting VA.
Pregnancy and its influence on the outcome

We had a special focus on the ventricular function and structural features in TOF which were investigated with 2 different techniques, by echocardiography in paper 1 and by CMR in paper 3. The influence of pregnancy on the outcome was also under examination, and both paper 1 and 3 were dedicated to that, using echocardiography and CMR respectively.

LV dysfunction, ventricular dimension and pulmonic valve stenosis/regurgitation were not associated with higher prevalence of arrhythmias. Some large studies showed association between ventricular dysfunction and poor outcome\textsuperscript{16,43}, while other studies\textsuperscript{17} did not observe any influence.

Previous pregnancy(ies) seemed not to have any influence on pulmonary valve function and ventricular dimensions, being results analyzed by echo in paper 1 matching the findings obtained with CMR in paper 3.

Echocardiography did not reveal any evident effect of pregnancy in the dimension of the RV. Initially, the longitudinal diameter of the RV (D3) was found significantly higher in women who had experienced pregnancy compared to women who had not. Further statistical analysis confuted this finding. A comparison between women with only one pregnancy and nulliparous, showed no differences in D3, indicating no clear remodeling of the RV occurring during pregnancy.

In our CMR focused study (paper 3), we did not observe any influence of pregnancy on pulmonary valve status and more in general on all the CMR derived dimension parameters. Only RV EF was slightly reduced in women who had experienced pregnancy. Previous CMR focused studies showed opposing results regarding the effects of pregnancy on the valve and ventricle dimensions. Our results, found by echo in paper 1 and with CMR in paper 3, are supporting the findings obtained in one recent study, which observed no effects of pregnancy
on RV volumes and aortic dimensions measured before and at least 6 months after delivery in women with repaired TOF using CMR 44.

Deformation imaging parameters and myocardial fibrosis

In paper 1 and 2, we aimed to investigate the deformation imaging parameters in adults operated for TOF. In paper 1, RV mechanical dispersion was associated with VA in our patient’s population of 80 women. The finding was confirmed also when adjusted for age at VA and age at echocardiography.

Higher values of RV mechanical dispersion have been previously reported in TOF patients after corrective surgery, reflecting a variable grade of electromechanical dyssynchrony as consequence of both the disease’s anatomic features and of surgical repair45. The same electromechanical dyssynchrony manifests generally also with prolonged QRS duration and right bundle branch block recognizable at EKG46. Thus our findings in paper 1, in accordance with previous studies, confirm post-surgical higher values of RV strain and mechanical dispersion as expression of severe electromechanical dyssynchrony, indicating higher risk of VA.

Higher values of RV mechanical dispersion seem to have a predictive value for VA in different RV diseases. Mechanical dispersion has previously been reported as a marker of VA also in other cardiac diseases primarily affecting the RV, like ARVC47. This might be expression of myocardial fibrosis, which has been detected in patients with ARVC48.

In a similar way, in paper 3 women repaired for TOF showed increased RV markers of fibrosis, expressed by native T1 and ECV.
In our TOF patient population, LV seems not to have any predictive value for VA or to express myocardial fibrosis. In paper 1 none of LV parameters were associated with VA, and in paper 3 all CMR markers of LV myocardial fibrosis were found to be normal. Those results differs from the knowledge in other cardiac disease, in which mechanical dispersion in the LV was a strong marker of VA\textsuperscript{49,50}.

Previous investigations conducted in TOF patients showed lower strain values compared to healthy subjects\textsuperscript{51,52}. This might not be surprisingly in itself considering the anatomy of the disease and the surgical correction performed, as also showed in paper 1.

Sex differences

When comparing the TOF subpopulations, as we did in paper 2, RV GLS, LV GLS and LV EF were shown to be reduced in men, while women presented GLS values within the reference range of normal population. This result matches findings in other studies, where male TOF patients had significantly lower LV GLS and RV free wall strain compared to female\textsuperscript{53}. This finding might indicate that male TOF patients develop a significantly impaired contractility, requiring a closer monitoring during follow up.
Clinical implications and future perspectives

This thesis provides an overview of the outcome of adult operated for TOF. The results might be of importance for risk stratification, especially regarding the role of pregnancy. Clinical implication must, however, accommodate that our consideration are derived from retrospective studies and with a limited number of participants.

Preconception counselling and follow up

Female TOF patients who are planning pregnancy should be referred for a preconception evaluation and counselling, considering the possible higher risk of VA related to the number of pregnancies experienced. Furthermore, women with previous pregnancies should be monitored for VA later in life. Other parameters as pulmonary valve status, chamber dimensions and myocardial fibrosis seem not to be influenced by pregnancy.

Risk stratification

Specific parameters could be useful for arrhythmic risk assessment during the lifelong follow-up that all TOF patients undergo. In addition to established markers of risk, NT-proBNP and RV mechanical dispersion might add useful information in risk stratification of VA. Male TOF patients seemed to have significantly impaired LV and RV function at all ages, and might require a slightly closer monitoring during clinical evaluation.
Limitations

General limitations

Our studies were of single center retrospective study design, it is not possible to derive causal inference. Although the number of patients included is well represented considering the incidence of TOF and in general all congenital heart diseases, the sample size of our patients population is limited compared to other multicenter studies previously conducted.

Specific limitations

Paper 1

Patient’s population consisted of relatively young and healthy group. Nulliparous women were significantly younger than mothers. Age and pregnancy are closely related to each other, as parity inevitably follows age, and it is therefore impossible to separate those two aspects completely. Only a low percentage of our patients had moderate to severe pulmonary regurgitation, and the longest QRS duration measured in our cohort was 172 ms, lower than previously showed cut-off value. Those aspects might explain the discrepancies with multicenter studies previously conducted that pulmonary regurgitation was directly related to higher risk of VA.

Paper 2

This study was a cross-sectional cohort study with retrospective event adjudication, with intrinsic limitations. It is not possible to draw a conclusion about causal connection, and it is not possible to measure incidence. The relatively limited sample size may not give power to detect subtle differences.
Paper 3

The study was performed at a 3T unit, which is known to create more artefacts due to inhomogeneity of the higher magnetic field as compared to 1.5 T scanners. Contraindications to CMR might have affected patient’s recruitment as selection bias, and together with the limited sample size could introduce distortion in the results. We were not able to perform CMR in patients with CMR incompatible devices or severe claustrophobia.

T1 measurements in RV were only possible in the TOF as the RV ventral wall in the control group was too thin to allow reliable measurements.
Conclusions

General conclusions

This thesis confirmed the increased risk for VA in TOF patients, with almost equal risk in both sexes. For VA risk stratification, our results indicated RV mechanical dispersion and increased NT-proBNP levels as age independent markers for VA in TOF patients.

Importantly, our results indicated an increased prevalence of VA in women after experienced pregnancy.

Specific conclusions

Paper 1

TOF women who had experienced pregnancy presented with a higher prevalence of VA compared to TOF women who had not experienced pregnancy. RV mechanical dispersion and NT-proBNP were associated to VA, independently of age. These findings should be considered in risk stratification and pregnancy counselling of women operated for TOF.

Paper 2

Almost one out of four adults operated for TOF had experienced VA in his/her late thirties.

Male patients operated for TOF showed a significantly impaired LV and RV dysfunction compared to females. Although the incidence of VA was similar in both sexes, men had a slightly higher prevalence of sustained VT as first presentation of VA and more often
implanted with ICD. QRS duration >180 ms was not shown to be related to higher prevalence of VA.

*Paper 3*

Women with surgically corrected TOF showed evidence of increased fibrosis markers as RV native T1 and ECV. Pregnancy seems not to influence on myocardial markers, volumetric measurements or pulmonary regurgitation.
References


Impact of pregnancy and risk factors for ventricular arrhythmias in women with tetralogy of Fallot

Alessia Quattrone, Oyvind H Lie, Eirik Nestaas, Charlotte de Lange, Kirsti Try, Harald L Lindberg, Helge Skulstad, Gunnar Eriksseen, Thor Edvardsen, Kristina Haugaa, Mette E Estensen


Open access

ABSTRACT

Objective Patients with tetralogy of Fallot (TOF) have high survival rates 30 years after surgical repair. Many patients experience pregnancy; however, the effects of pregnancy on the long-term cardiovascular outcome are not well known. We investigated the association of pregnancy and cardiac function with occurrence of ventricular arrhythmia (VA) in women with TOF.

Methods We recruited 80 women with repaired TOF from the national database. Holter monitoring or implanted devices detected VA, defined as non-sustained or sustained ventricular tachycardia or aborted cardiac arrest. All patients underwent echocardiography. Blood tests included NT-proBNP (N-terminal pro-brain natriuretic peptide).

Results 55 (69%) women had experienced pregnancy. Mean age was lower in nulliparous compared with those with children (30±9 vs 40±9, p<0.01). VA had occurred in 17 (21%) women. Prevalence of VA was higher in women who had experienced pregnancy (n=16, 94%) compared with nulliparous (n=1, 6%) (p=0.02), also when adjusted for age (OR 12.9 (95% CI 1.5 to 113.2), p=0.02).

Right ventricular mechanical dispersion was more pronounced in patients with VA (50±8 ms vs 39±14 ms, p=0.01, age-adjusted OR 2.1 (95% CI 1.3 to 7.5), p=0.01). NT-proBNP was also a marker of VA (211 ng/L (127 to 836) vs 139 ng/L (30 to 465), p=0.007). NT-proBNP >521 ng/L (normal values <170 ng/L) detected women with VA (p=0.019), also independent of age (OR 7.2 (95% CI 1.7 to 30.1), p=0.007).

Conclusion Pregnancy was associated with higher prevalence of VA among women with TOF. Right ventricular mechanical dispersion and NT-proBNP were age-independent risk markers of VA. These may have importance for pregnancy counselling and risk stratification.

INTRODUCTION

Tetralogy of Fallot (TOF) is one the most common cyanotic congenital heart diseases. In the present era of cardiac surgery, patients with TOF enjoy a satisfactory quality of life and a survival rate of about 93% 20 years after corrective surgery, 80% 30 years after repair and 72% after 40 years. The most common cause of death in patients with surgically corrected TOF is sudden cardiac death (49%), heart failure (27%) and coronary artery disease (6%).

The high risk of arrhythmias in patients with TOF is well known and documented in previous large studies. The risk stratification is currently mostly based on 12-lead ECG with QRS duration >180 ms and QRS rate.
change as risk markers of sudden cardiac death; pulmonary regurgitation and older age at repair are associated with adverse cardiac events. However, risk stratification is insufficient and better methods are warranted. Myocardial deformation indices have recently shown to be useful in risk stratification in patients with TOF.

Most of the patients with TOF reach adulthood, and consequently many female patients want to give childbirth. During normal pregnancy, the cardiovascular system adapts to the metabolic needs of mother and fetus in order to adequately perfuse tissues with oxygenated blood by increasing cardiac output by 30%–50%, increasing heart rate by 10–20 beats per minute and decreasing peripheral vascular resistance by 30%. Myocardial contractility in normal pregnancy has been found altered in some studies but not in other. The impact of these haemodynamic and myocardial changes during pregnancy in women operated on for TOF are still not well known.

Several studies have focused on short-term outcome of pregnancy in women with TOF and indicated a higher rate of cardiovascular events, including ventricular and supraventricular arrhythmias, heart failure and progressive right ventricular (RV) dilation. However, it is not known if the pregnancy-induced cardiovascular alterations influence long-term cardiovascular outcome. Importantly, no previous studies have investigated the association of pregnancy in the general risk stratification, in particular on the occurrence of ventricular arrhythmias (VAs).

The aim of our study was to investigate the influence of one or more pregnancies on cardiac function and occurrence of VA in women corrected for TOF. We hypothesised that the prolonged haemodynamic stress of pregnancy is associated with adverse outcome in patients with TOF, including VA and heart failure.

METHODS

Study population

We included patients diagnosed for TOF recruited from our centre’s patient GUCH registry. This database included all patients followed at Oslo University Hospital, Rikshospitalet, Norway from 1953 to 2017.

We selected female patients >18 years of age who had been previously corrected for TOF; 80 patients were contacted with an information letter. We recruited patients with all forms of surgical repair, including those who had undergone a palliative operation as Waterstone or Blalock-Taussig shunt some months or years prior to surgical correction. Patients with history of pregnancy were recruited only if delivery had occurred at least 1 year prior to inclusion. Patients unable to give informed consent and patients with delivery occurred <1 year of time were excluded.

All patients approached to be involved in the study agreed to participate. Most patients agreed to the direct inclusion and underwent a structured study protocol, while the remaining subjects who chose not to participate to the active recruitment consented to the use of registry data within 3 years (2015–2017). All participants gave written informed consent. Medical records and echocardiographic exams available in the hospital electronic medical record system were reviewed. The study complied with the Declaration of Helsinki and was approved by the Regional Committees for Medical Research Ethics (reference number 2017/383).

This research was conducted without patient involvement in the study design, interpretation of results and writing this manuscript. The research project was presented to the Norwegian Association of Adults with Congenital Heart Diseases (VMH, Voksne med medfødt hjertefeil) prior to the initiation.

Electrocardiography and arrhythmias

An ECG and 24-hour Holter monitoring was obtained in all participants at the same visit as the echocardiographic examination. The history of VA was assessed from ECG, 24-hour Holter registration and implantable cardioverter-defibrillator (ICD) monitoring.

We considered clinically relevant VA as non-sustained ventricular tachycardia (NSVT), defined as consecutive runs of ≥3 ventricular beats >100 beats/min for <30 s; sustained ventricular tachycardia (SVT), defined as runs of consecutive ventricular beats >100 beats for >30 s; ventricular fibrillation (VF), appropriate therapy from an ICD; and aborted cardiac arrest (CA). We recorded age at first documented arrhythmic event.

Cardiopulmonary exercise test

All patients included in the study had undergone a cardiopulmonary exercise test, either during the active recruitment or during their annual follow-up at GUCH outpatient clinic. The exercise stress test was performed on a bicycle ergometer using Bruce protocol. Oxygen saturation, heart rate and 12-lead ECG were continuously monitored and, cuff blood pressure was measured every second minute.

Echocardiographic study

The echocardiographic study was performed on a Vivid E95 (GE Healthcare, Horten, Norway) and data were analysed off-line (EchoPAC V.201; GE Healthcare).

From 2D echocardiography, we assessed proximal right ventricular outflow tract (RVOT) diameter in the parasternal short axis view, and right ventricular (RV) basal diameter and right ventricular fractional area change (RVFAC) in the RV focused four-chamber view. Regional RV akinesia and/or dyskinesia were detected in parasternal long-axis or short-axis view and RV focused four-chamber view.

Left ventricular (LV) ejection fraction was calculated by the modified Simpson’s biplane method. Myocardial function was further assessed by global longitudinal strain (GLS) using speckle tracking technique, at frame rates between 80 and 100/s. RV longitudinal strain was...
Congenital heart disease

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics and echocardiographic parameters in female patients corrected for TOF grouped by parity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TOF n=80</td>
</tr>
<tr>
<td>Age, years</td>
<td>37±10</td>
</tr>
<tr>
<td>Height, cm</td>
<td>165±7</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68±13</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>69±13</td>
</tr>
<tr>
<td>Transannular patch (%)</td>
<td>30 (37)</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>116±11</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>71±10</td>
</tr>
<tr>
<td>QTc duration, ms</td>
<td>460±31</td>
</tr>
<tr>
<td>Exercise capacity, W</td>
<td>131±27</td>
</tr>
<tr>
<td>NYHA class</td>
<td>1 (1–3)</td>
</tr>
<tr>
<td>NT-ProBNP, ng/L</td>
<td>174 (30–836)</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>132 (82–174)</td>
</tr>
<tr>
<td>RV EDV, mL</td>
<td>21.7±4.6</td>
</tr>
<tr>
<td>RV ESV, mL</td>
<td>11.3±2.9</td>
</tr>
<tr>
<td>RV FAC, %</td>
<td>47.8±7.2</td>
</tr>
<tr>
<td>RV D3, cm</td>
<td>7.3±0.7</td>
</tr>
<tr>
<td>PV vei, m/s</td>
<td>1.9±0.6</td>
</tr>
<tr>
<td>Mod-sev PV reg</td>
<td>14 (17%)</td>
</tr>
<tr>
<td>LV MD, ms</td>
<td>43.3±14</td>
</tr>
<tr>
<td>LV GLS, %</td>
<td>−18.9±3.3</td>
</tr>
<tr>
<td>RV MD, ms</td>
<td>42±13</td>
</tr>
<tr>
<td>RV GLS, %</td>
<td>−19.1±4.1</td>
</tr>
<tr>
<td>RVOT, cm</td>
<td>2.9±0.5</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>55±8</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or median with range, as appropriate; p value from Student’s t-test, Mann-Whitney U or χ² test as appropriate, and multivariable logistic regression adjusted for age, DBP, diastolic blood pressure; EDV, end-diastolic volume; ESS, end-systolic strain; ESV, end-systolic volume; GLS, global longitudinal strain; HR, heart rate; LV, left ventricular; LVEF, left ventricular ejection fraction; MD, mechanical dispersion; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association classification; PV, pulmonary valve; RV, right ventricular; RV D3, right ventricular longitudinal diameter; RV FAC, right ventricular fractional area change; RVOT, right ventricular outflow tract; SBP, systolic blood pressure; TOF, tetralogy of Fallot; VA, ventricular arrhythmia.

defined as an average peak negative systolic longitudinal strain from six RV segments.ⁱ⁵ LV global longitudinal strain was defined as the average of peak systolic negative longitudinal deformation/strain from a 16-segment LV model.¹⁵

Mechanical dispersion, which is defined as the SD of the time interval from onset of the Q/R wave in the ECG to the peak negative longitudinal strain in 6 RV and 16 LV segments, was calculated as a measure of contraction heterogeneity.¹⁵

Pulmonary valve stenosis and pulmonary valve regurgitation of moderate to severe grade were also assessed and considered.

Biochemistry

Blood tests included N-terminal pro-brain natriuretic peptide (NT-proBNP) measurement, with reference values <170 ng/L. NT-proBNP concentration in plasma were assayed on a Modular platform (Roche Diagnostics, Basel, Switzerland).

Statistical analysis

Statistical analysis was performed by using IBM SPSS V.25. Data are presented as mean±SD or median with range, as appropriate. Comparisons of continuous data were performed by the unpaired Student’s t-test or Mann-Whitney U test, or by the ANOVA F-test and the Bonferroni post hoc correction when more than two groups were compared. Categorical variables were compared by the χ² test or Fisher’s exact test as appropriate. The odd of VA in patients with previous pregnancy versus those without pregnancy was assessed by logistic regression, and the effect of increasing number of pregnancies was analysed separately. Multivariable logistical regression was performed retaining covariates of interest from univariable analyses, after controlling for multicollinearity. We
adjusted for age using logistic regression, having pregnancy and age at arrhythmic event used as covariates in the logistic regression analysis. We used Akaike’s information criterion (AIC) to assess overfitting by the tradeoff of added complexity and precision in the regression models, and increasing values suggested inferior models. The optimal threshold of NT-proBNP to detect VA was assessed using a single threshold regression (STATA SE V.15.1; StataCorp, Texas, USA). By Kaplan-Meier curves, we showed the incidence of VA according to this. P values ≤0.05 were considered statistically significant.

RESULTS
Clinical characteristics
We included 80 female patients corrected for TOF recruited from our centre’s patient GUCH registry, of which 55 participated in active recruitment and 25 gave consent to the use of registry data.

In all, 55 (69%) women had experienced pregnancy (age 40±9 years, median parity 1, range 1–4), while 25 (31%) were nulliparous. Mean age was lower in nulliparous women compared with those with children (31±9 vs 40±9 years, p<0.01). Nineteen mothers had 1 child, 28 had 2 children and 8 had ≥2 children.

Use of transannular RVOT reconstruction with patch as corrective surgery was recorded in 30 patients, of which 11 (44% of 25 patients) were nulliparous and 19 (36% of 55 patients) had experienced pregnancy (p=0.53, table 1). Information on type of surgery was not available for three patients.

Electrocardiography, exercise capacity and arrhythmias
VA had occurred in 17 (21%) women, and was more prevalent in women who had experienced pregnancy compared with nulliparous (n=16 (94%) vs n=1 (6%), p=0.02).

Of the 17 women with VA, 9 had NSVT detected at 24-hour Holter monitoring, while 8 had clinical events as consequence of VT or VF/CA. Among the nine patients with NSVT, in three of them the presence of inducible VT was confirmed by electrophysiological study; those patients underwent subsequently ICD implantation.

Due to suspected confounding, we adjusted for age at event using logistic regression. Importantly, VA was more prevalent in women with children also when adjusted for age at arrhythmic event (OR 12.9 (95% CI 1.5 to 113.2), p=0.02 (table 1, figure 1). All arrhythmic events occurred after pregnancy, with the exception of one patient who received ICD implantation in her mid-twenties due to symptomatic sustained ventricular tachycardia. About 5 years after ICD implantation, this patient became pregnant and delivered without any reported complications. The prevalence remained statistically significant also when this patient was excluded from the statistical analysis (p=0.01, OR 11.3 (95% CI 1.3 to 99.5), p=0.02 adjusted for age at the arrhythmic event).

There was a trend of increasing odds of VA for every additional pregnancy, but this model had signs of overfitting (OR 1.6 (95% CI 0.9 to 2.7), p=0.06, AIC increased from 79 to 83) (table 2).

Mean age was similar between patients with and without VA (40±9 years vs 36±9 years, p=0.08, table 3).

ECG QRS width did not differ between nulliparous and women with children (table 1) and was not associated with VA (table 3). There were no differences in exercise capacity (127±24 W in nulliparous vs 132±28 W in women with children, p=0.55).

RV and LV function and morphology
We did not observe any difference in RV end-diastolic and end-systolic volumes, fractional area change and the RV outflow tract dimension, as well as in pulmonary valve stenosis and regurgitation grade and in LV parameters, including strain and mechanical dispersion, in women who had experienced pregnancy (table 1) compared with nulliparous women. The longitudinal diameter of the RV (D3) was, however, greater in women who had been pregnant (p=0.03, table 1).

RV mechanical dispersion was significantly higher in patients with VA (0.050±0.008 vs 0.039±0.014 s, p=0.009), also when adjusted for age at VA (OR 2.1 (95% CI 1.3 to 7.5), p=0.01) and age at echocardiography (OR 5.7 (95% CI 3.5 to 9.2), p=0.03) (table 3). Other parameters of left and right ventricular function or diameters did not differ between women with and without VA.

NT-proBNP and RV mechanical dispersion had a very weak correlation (p=0.02, with R² 0.082). NT-proBNP was higher and above reference value in patients with VA (211 ng/L (127 to 836) vs 139 ng/L (30 to 465), p=0.007), and remained as a significant marker of VA when adjusted for age (adjusted OR 1.4 (95% CI 1.1 to 1.7) by 50-unit increments, p=0.009). Threshold regression suggested an optimal differentiation level of NT-proBNP of 321 ng/L. Kaplan-Meier survival analyses showed better freedom...
from VA in those with NT-proBNP below the value 321 ng/L (figure 2).

**DISCUSSION**

This is the first larger study exploring the relationship between pregnancy and outcome in women corrected for TOF. We showed that pregnancy was associated with adverse long-term outcome, with higher prevalence of VA in patients who had experienced pregnancy independently of age. Importantly, our study showed that also a heterogeneous RV contraction pattern and higher values of NT-proBNP were associated with VA.

**Pregnancy and ventricular arrhythmia**

Our findings indicated that pregnancy relate to a higher incidence of VA. One of the main concerns and complication that occurs during adult life of patients with TOF is the incidence of VA, which is often the main cause behind sudden cardiac death. Several previous studies investigate the short-term outcome of pregnancy in women with TOF, showing a higher incidence of cardiovascular events during pregnancies, including mainly (supra) VA, heart failure and progressive RV dilatation. Predictors of complications were the use of cardiac medication before pregnancy, LV dysfunction, severe pulmonary hypertension and severe pulmonic regurgitation with RV dysfunction. Occurrence of NSVT with hypertension and sinus bradycardia of pregnant woman with repaired TOF has also been described. LV dysfunction and pulmonic valve stenosis and/or regurgitation were not associated with higher prevalence of arrhythmias in our study.

---

**Table 2: Clinical characteristics and echocardiographic parameters in female patients corrected for TOF grouped by number of pregnancies**

| Age, years | Height, cm | Weight, kg | HR, bpm | SBP, mmHg | DBP, mmHg | QTc duration, ms | Exercise capacity, W | NYHA class | NT-ProBNP, ng/L | QRS duration, ms | TOF with VA (n=17) | RV EDV, mL | RV ESV, mL | RV FAC, % | RV D3, cm | PV vel, m/s | Mod-sev PV reg | LV MD, ms | LV GLS, % | RV MD, ms | RV GLS, % | RVOT, cm | LVEF, % |
|------------|-----------|------------|---------|-----------|-----------|------------------|---------------------|-----------|-----------------|------------------|-----------------|-------------|-------------|-----------|---------|----------|-------------|--------|----------|-----------|---------|---------|---------|-----------|---------|
| 29±10      | 165±7     | 67±11      | 73±10   | 115±9     | 71±7      | 460±30           | 127±24             | 1 (1–3)   | 109 (30–372)   | 124 (86–162)   | 20.5±4.8        | 10.8±2.9   | 47±7       | 7.0±0.7   | 1.9±0.7  | 5 (22%)  | 41±10     | −19.0±3.0 | 38±12    | −19.2±5.0 | 2.9±0.3   | 57±7    | 38±11    | 11±14     | 6±3          | 1±14     |
| 38±11      | 166±4     | 62±6       | 63±13   | 111±14    | 65±10     | 458±30           | 131±25             | 1 (1–2)   | 177 (110–836)  | 148 (94–174)   | 22.8±4.8        | 12.1±3.7   | 46±8       | 7.6±0.9   | 2.0±0.5  | 3 (15%)  | 45±11     | −18.8±3.6 | 43±16    | −18.1±3.8 | 3.2±0.5   | 56±9    | 40±7     | 117±10    | 69±15         | 71±11     |
| 40±7       | 165±7     | 63±6       | 67±13   | 117±10    | 71±11     | 462±33           | 133±29             | 1 (1–3)   | 126 (49–558)   | 134 (82–172)   | 21.7±4.1        | 11±2.1     | 49±6       | 7.3±0.6   | 1.8±0.5  | 9 (25%)  | 45±16     | −18.7±3.2 | 43±13    | −19.4±3.2 | 2.8±0.5   | 54±8    | 115±9    | 117±10    | 69±15         | 67±13     |

Data are presented as mean±SD or median with range, as appropriate; p value from Student’s t-test, Mann-Whitney U, χ² test or ANOVA as appropriate, and multivariable logistic regression adjusted for age. DBP, diastolic blood pressure; EDV, end-diastolic volume; ESS, end-systolic strain; ESV, end-systolic volume; GLS, global longitudinal strain; HR, heart rate; LV, left ventricular; LVEF, left ventricular ejection fraction; MD, mechanical dispersion; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association classification; PV, pulmonary valve; RV, right ventricular; RV D3, right ventricular longitudinal diameter; RV FAC, right ventricular fractional area change; RVOT, right ventricular outflow tract; SBP, systolic blood pressure; TOF, tetralogy of Fallot; VA, ventricular arrhythmia.
A recent study showed no deleterious effects of pregnancy on RV volumes and aortic dimensions using cardiovascular magnetic resonance (CMR) measured before and at least 6 months after pregnancy in women with repaired TOF.\textsuperscript{19} In contrast, another study observed an accelerated rate of RV remodelling with an increase in RV end-diastolic volume measured by CMR after pregnancy, without deterioration of the RV systolic function.\textsuperscript{20} Echocardiography in our study did not detect any clear change in the dimension of the RV after pregnancy; with all the limitations connected to the use of echocardiography compared with CMR, which is currently the gold standard for volumetric measurements, our findings suggest that pregnancy has no significant effects on RV function and dimensions that are easily detectable with echocardiography.

### Risk markers of VA

TOF is so far been perceived to be predominantly RV disease. In our study, none of the measures of LV were associated with VA. Mechanical dispersion in the LV has been shown to be a powerful marker of ventricular arrhythmias in previous studies.\textsuperscript{21 22}

In our study, a longer QRS duration did not relate to VA in patients corrected for TOF, as previously showed in other studies, where a QRS duration >180 ms was a risk marker of cardiac event.\textsuperscript{4} In a similar way, pulmonary regurgitation was not associated with VA. Only a low

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Comparisons of female patients corrected for TOF without and with history of VA, and markers for VA adjusted for age</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOF without VA n=63</td>
<td>TOF with VA n=17</td>
</tr>
<tr>
<td>79%</td>
<td>21%</td>
</tr>
<tr>
<td>Age, years</td>
<td>36±9</td>
</tr>
<tr>
<td>Height, cm</td>
<td>165±7</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68±13</td>
</tr>
<tr>
<td>History of pregnancy, n (%)</td>
<td>39 (61)</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>68±11</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>115±11</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>68±9</td>
</tr>
<tr>
<td>QTC duration, ms</td>
<td>458±31</td>
</tr>
<tr>
<td>Exercise capacity, W</td>
<td>125±25</td>
</tr>
<tr>
<td>NYHA class</td>
<td>1 (1–3)</td>
</tr>
<tr>
<td>NT-proBNP, ng/L</td>
<td>139 (30–465)</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>135 (82–174)</td>
</tr>
<tr>
<td>RV EDV, mL</td>
<td>21.1±4.1</td>
</tr>
<tr>
<td>RV ESV, mL</td>
<td>11.1±2.6</td>
</tr>
<tr>
<td>RV FAC, %</td>
<td>47±7</td>
</tr>
<tr>
<td>RV D3, cm</td>
<td>7.3±0.7</td>
</tr>
<tr>
<td>PV vel, m/s</td>
<td>1.9±0.6</td>
</tr>
<tr>
<td>Mod-sev PV reg</td>
<td>12 (19%)</td>
</tr>
<tr>
<td>LV MD, ms</td>
<td>43±13</td>
</tr>
<tr>
<td>LV GLS, %</td>
<td>−19.2±3.1</td>
</tr>
<tr>
<td>RV MD, ms</td>
<td>39±14</td>
</tr>
<tr>
<td>RV GLS, %</td>
<td>−19.7±4.1</td>
</tr>
<tr>
<td>RVOT, cm</td>
<td>2.9±0.4</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>56±9</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or median with range, as appropriate; p value from Student’s t-test or Mann–Whitney U test as appropriate, and multivariable logistic regression.

*Adjusted for age at VA.
†Adjusted for age at echocardiography.

DBP, diastolic blood pressure; EDV, end-diastolic volume; ESS, end-systolic strain; ESV, end-systolic volume; GLS, global longitudinal strain; HR, heart rate; LV, left ventricular; LVEF, left ventricular ejection fraction; MD, mechanical dispersion; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association classification; PV, pulmonary valve; RV, right ventricular; RV D3, right ventricular longitudinal diameter; RV FAC, right ventricular fractional area change; RVOT, right ventricular outflow tract; SBP, systolic blood pressure; TOF, tetralogy of Fallot; VA, ventricular arrhythmia.
The longest QRS duration associated with a significant deterioration in RV volume.

Mechanical dyssynchrony is expected after surgical repair in TOF, manifesting as prolonged QRS duration and right bundle branch block at EKG. Furthermore, higher RV mechanical dispersion values have been reported in TOF after surgical repair, reflecting electromechanical dysynchrony severity and the underlying pathophysiology.

Our study and the previous ones concur in showing that surgical repair is followed by a more severe grade of electromechanical dysynchrony, manifesting with higher RV strain and mechanical dispersion, and giving higher risk of VA. These findings are also in line with previous reports showing RV mechanical dispersion, possibly reflecting myocardial fibrosis as a marker of VA in patients with arrhythmogenic right ventricular cardiomyopathy.

NT-proBNP was a marker of VA independent of age. In particular, values of NT-proBNP >321 ng/L (upper limit of 170 ng/L) related to a higher odds of VA, and every 50-unit increment of NT-proBNP increased the odds of VA by 40%. A systematic review of 49 other studies showed that BNP levels were elevated and correlated significantly with RV end-diastolic dimensions and severity of pulmonary valve regurgitation in patients corrected for TOF.

Our study supports the relation between NT-proBNP levels and incidence of arrhythmias, which may indicate that this parameter can be helpful in future evaluation of patients corrected for TOF.

Clinical implications

Importantly, this study suggests that number of pregnancies was associated with risk of VA in patients corrected for TOF. This information should be validated in future studies since this is of uppermost importance in preconception counselling of these patients.

Assessment of NT-proBNP together with RV mechanical dispersion might become useful parameters to consider in the VA risk stratification of patients operated for TOF.

Study limitations

This was a cross-sectional study with retrospective adjudication of outcome with associated limitations. We cannot derive causal inference. The patient population included in our study consists of a limited number of cases at a relatively young age. Among all patients, only one of them had severe ventricular arrhythmias without previously experiencing pregnancy. For this reason, there was a wide CI for the OR. The effect size should be interpreted with caution, and the test merely suggests that the odds for adverse outcome increased. In the same way, assessment of the impact of number of pregnancies was less robust than analysis grouping all women with previous pregnancy. Nulliparous women were significantly younger than mothers. A possible cause for the lower prevalence of VA registered in nulliparous women operated for TOF could be that cardiac remodelling and consequently risk of arrhythmias is progressive and it might increases with age. Importantly, age and pregnancy are closely related to each other, as parity inevitably follows age. Although we adjusted our statistical analyses for the differences in age, it is impossible to separate those two characteristics completely. Patients with more pronounced cardiac disease in the present study were more likely to have implantable cardiac devices, and many of these were not eligible for cardiac MRI. Therefore, the subgroup eligible for MRI represented a non-representative selection that was not included in the present analysis. This study was not designed to include CMR data, as only a subset of patients had CMR data due to contraindications or to personal reasons. Future studies should include CMR providing the most robust RV data in patients with TOF.
CONCLUSIONS

History of pregnancy was associated with higher prevalence of VA among women with surgically corrected TOF. The higher prevalence of severe ventricular arrhythmias in women, particularly after experienced pregnancy, may be of clinical importance despite the limited number of patients in this study. RV mechanical dispersion and NT-proBNP were also age-independent markers of VA. Larger and prospective studies are needed before we can advise against pregnancy in these patients. However, these important findings should be considered in risk stratification and pregnancy counselling of women operated on for TOF.

Acknowledgements

We thank all the patients who participated in this study.

Contributors

AO: acquired data, analysed data, performed statistical analysis, writing. OHL: analysed data, performed statistical analysis, made critical revision of the manuscript. EN: designed the study, made critical revision of the manuscript for important intellectual content. CDL: conceived and designed the study, made critical revision of the manuscript for important intellectual content. KT: acquired data, made critical revision of the manuscript for important intellectual content. HLL: conceived and designed the research, made critical revision of the manuscript for important intellectual content. HS: acquired data, made critical revision of the manuscript. KHH: analysed data, performed statistical analysis, made critical revision of the manuscript. MEE: conceived and designed the research, made critical revision of the manuscript for important intellectual content, handling funding and supervision, writing.

Funding

This study was supported by the South-Eastern Norway Regional Health Authority (NR 2017:103).

Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

The study was carried out according to the principles of the Declaration of Helsinki. This protocol was approved by the Regional Committees for Medical Research Ethics South East D (HKE-ær-D, reference number 2017/383) and the Oslo University Hospital Information Security and Privacy Office (number 19/0949).

Data availability statement

All data relevant to the study are included in the article or uploaded as online supplemental information. Researchers interested in the data, methods or analysis can contact the corresponding author for more information.

Open access

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs

Alessia Quattrone http://orcid.org/0000-0001-8915-2630
Kristina Haugaa http://orcid.org/0000-0002-4900-0453

REFERENCES

Long-term follow-up and sex differences in adults operated for tetralogy of Fallot

Alessia Quattrone 1,2, Oyvind H Lie,1,2 Eirik Nestaas,3 Charlotte de Lange,4,5 Kirsti Try,4 Harald L Lindberg,6 Helge Skulstad,1,2 Gunnar Eriksen,1 Thor Edvardsen,1,2 Kristina Haugaa,1,2 Mette E Estensen1

ABSTRACT

Objective Adults operated for tetralogy of Fallot (TOF) have high risk of ventricular arrhythmias (VA), QRS duration >180 ms is an established risk factor for VA. We aimed to investigate heart function, prevalence of arrhythmias and sex differences in patients with TOF at long-term follow-up.

Methods We included TOF-operated patients: 18 years from our centre’s registry. We reviewed medical records and the most recent echocardiographic exam. VA was recorded on ECGs, 24-hour Holter registrations and from implantable cardioverter defibrillator.

Results We included 148 patients (age 37±10 years). Left ventricular global longitudinal strain (LV GLS, −15.8±3.1% vs −18.8±3.2%, p<0.001) and right ventricular (RV) GLS (−15.8±3.9% vs −19.1±4.1%, p=0.001) were lower in men at all ages compared with women. Higher RV D1 (4.3±0.5 cm vs 4.6±0.6 cm, p=0.01), lower ejection fraction (55%±6% vs 50%±9%, p=0.02), lower RV GLS (−18.1±4.0 ms vs −16.1±4.8 ms, p=0.04) and N-terminal pro-brain natriuretic peptide (NT-proBNP) over reference range (n=27 (23%) vs n=8 (77%), p<0.001) were associated with higher incidence of VA. QRS duration was longer in men (151±30 ms vs 128±25 ms, p<0.001). No patients had QRS duration >180 ms. QRS duration did not differ in those with and without VA (143±32 ms vs 137±28 ms, p=0.06).

Conclusions Our results confirmed reduced RV function in adults operated for TOF. Male patients had impaired LV and RV function expressed by lower LV and RV GLS values at all ages. Reduced cardiac function and elevated NT-proBNP were associated with higher incidence of VA and may be important in risk assessment.

INTRODUCTION

Tetralogy of Fallot (TOF) has an incidence of 0.34 per 1000 live births, and is the most common cyanotic congenital heart disease. Since the first surgical repair of TOF reported in 1954, the life expectancy of children born with TOF has dramatically improved to a survival of 94% at 25 years, and 72% at 40 years, following TOF repair. After surgical correction, patients generally enjoy a good quality of life that is almost similar to that of the general population. However, long-term survival is still significantly lower than in the general population. Despite significant advances in treatment and management, previous studies have documented a high risk of arrhythmias in patients with TOF. Especially ventricular arrhythmias (VA) and sudden cardiac death (SCD) remain major concerns in adults corrected for TOF late after surgical repair. Previous reports have indicated a slightly higher prevalence of atrial and VA in male...
patients; however, significant sex differences in cardiac function and outcome are not known.\textsuperscript{9,10}

We aimed to investigate cardiac function, prevalence of VA and heart failure in adult patients operated for TOF. Furthermore, we aimed to explore possible sex differences.

METHODS

Data collection

For this retrospective cohort study, we reviewed our centre’s Adult with Congenital Heart Disease (ACHD) patients’ registry which includes all adult patients with congenital heart diseases who have been diagnosed, treated, followed and/or operated at Oslo University Hospital, Rikshospitalet, Norway in the period 1970–2020.

Patient and public involvement statement

This research was conducted without patient involvement in the study design, interpretation of results and writing this manuscript. The research project was presented to the Norwegian Association of Adults with Congenital Heart Diseases (VMH, Voksne med medfødt hjertefeil) prior to the initiation.

Inclusion criteria

All patients diagnosed with TOF, who were ≥18 years of age at the time of follow-up and with a history of surgical correction, were recruited from the ACHD registry. All medical records available within the past 5 years (2015–2020) were reviewed. All forms of surgical repair were considered, including cases where Waterstone or Blalock-Tausig shunt was performed prior to surgical correction.

Patients were contacted with an information letter; all of them agreed to participate to the study and informed consent was obtained from each patient.

Exclusion criteria

We excluded patients who were incapable to give informed consent.

Clinical characteristics

Patients were classified according to the severity of symptoms of heart failure using New York Heart Association (NYHA) Functional Classification.

We included patients’ most recent ECG and assessed rhythm, heart rate, PQ-QRS-QTc interval\textsuperscript{11} and bundle branch block.

Exercise capacity was routinely assessed by exercise stress test in all patients during regular annual/biannual follow-up. Patients performed exercise stress test following Bruce protocol\textsuperscript{12} on a bicycle ergometer, and we used results from the most recent exercise test.

We recorded N-terminal pro-brain natriuretic peptide (NT-proBNP) as a marker of heart failure from the most recent clinical visit. The reference values for NT-proBNP were age and sex specific\textsuperscript{13} (Elecsys—Roche Diagnostics, Basel, Switzerland): <170 ng/L for women<49 years of age, <85 ng/L for men<49 years of age, <300 ng/L for women 50–69 years of age, <250 ng/L for men 50–69 years of age.

Echocardiography

The most recent echocardiographic exam for each patient, performed during the period 2015–2020, was analysed offline on EchoPAC V.201, GE Healthcare, Horten, Norway. Echocardiography included all measurement obtained during a standard echocardiogram performed (M-mode, B-mode, colour Doppler, pulsed-wave and continuous-wave Doppler), including left ventricular (LV) ejection fraction (EF) calculated by the modified Simpson’s biplane method. The right ventricular (RV) basal, mid and longitudinal diameter and the RV fractional area change (FAC) were obtained from the RV-focused view. In addition, we assessed cardiac function by global longitudinal strain (GLS) using a speckle tracking technique at frame rates>50/s. LV GLS was defined as the average of peak systolic negative longitudinal deformation/strain from the three apical views.\textsuperscript{14} RV GLS was defined as an average peak negative systolic longitudinal strain from RV-focused 4-chamber view.\textsuperscript{15,16}

Mechanical dispersion, a measure of RV and LV contraction heterogeneity,\textsuperscript{17} was defined as the SD of the time interval from onset of the Q/R wave in the ECG to the peak negative longitudinal strain in, respectively, 6 RV and 18 LV segments.

Ventricular arrhythmias

We recorded the occurrence of VA on ECGs, 24-hour Holter registrations and from implantable cardioverter defibrillator (ICD) monitoring.

We considered the following VA as clinically relevant: non-sustained ventricular tachycardia (NSVT), defined as consecutive runs of ≥3 ventricular beats>100 beats/min for <30s; sustained ventricular tachycardia (VT), defined as runs of consecutive ventricular beats>100 beats for ≥30s\textsuperscript{18}; ventricular fibrillation (VF) with appropriate therapy from an ICD; aborted cardiac arrest (CA).

Statistics

We performed statistical analysis by using IBM SPSS V.26. Data were presented as mean±SD or median with range, as appropriate. We performed the comparisons of continuous data by the unpaired Student’s t-test or Mann-Whitney U test and compared categorical variables by the $\chi^2$ test or Fisher’s exact test as appropriate. We showed the differences in the ventricular function in male and female patients by Kaplan-Meier curve. P values ≤0.05 were considered statistically significant.

RESULTS

Clinical characteristics

We included 148 patients, of which 80 (54%) were women. Mean age at the time of follow-up was 37±10 years (38±10 years for men vs 37±10 years for women, $p=0.52$; table 1).
Mean time surgery-to-follow-up was 32±9 years (33±8 in men vs 31±10 in women, p=0.25).

Age at surgical correction was 4 years (1–15) and number of operations was 1 (0–4), with no differences between sexes. All clinical characteristics were similar, except for larger body size and higher systolic blood pressure (SBP) in men (123±14 in men vs 115±13 in women, p=0.02). No sex differences were observed in RV and right ventricular mid cavity diameter (RV FAC) nor in LV longitudinal diameter (LV GLS) and RV GLS were lower in male patients operated for TOF in all age groups (figures 1 and 2).

No sex differences were observed in RV and right ventricular outflow tract diameters, RV FAC nor in LV and LVOT diameter (table 2).

Incidence of VA
In all, VA occurred in 35 patients at a mean age of 38±9 years, 32±6 years after surgery. Sustained VA was the first registered VA in 19 patients, while 17 patients had NSVT as first presentation of VA.

Cardiac function of RV and LV were significantly impaired in men compared with women, expressed by lower LV EF and both RV and LV GLS (p<0.001; table 2). LV GLS and RV GLS were lower in male patients operated for TOF in all age groups (figures 1 and 2).

### Table 1
Clinical characteristics in patients with tetralogy of Fallot

<table>
<thead>
<tr>
<th></th>
<th>Total (n=148)</th>
<th>Men (n=68)</th>
<th>Women (n=80)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>37±10</td>
<td>38±10</td>
<td>37±10</td>
<td>0.52</td>
</tr>
<tr>
<td>Age at surgery, years</td>
<td>4 (1–15)</td>
<td>4 (1–14)</td>
<td>5 (1–15)</td>
<td>0.46</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172±9</td>
<td>177±5</td>
<td>165±7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78±18</td>
<td>85±18</td>
<td>68±13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.9±0.2</td>
<td>2.0±0.2</td>
<td>1.7±0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA class</td>
<td>1 (0–3)</td>
<td>1 (0–3)</td>
<td>1 (0–3)</td>
<td>0.57</td>
</tr>
<tr>
<td>Operation, no</td>
<td>1 (0–4)</td>
<td>1 (0–4)</td>
<td>1 (0–3)</td>
<td>0.49</td>
</tr>
<tr>
<td>High NT-proBNP, no</td>
<td>79 (53)</td>
<td>34 (50)</td>
<td>45 (56)</td>
<td>0.19</td>
</tr>
<tr>
<td>QRS, ms</td>
<td>141±30</td>
<td>151±30</td>
<td>128±25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>70±13</td>
<td>70±13</td>
<td>69±13</td>
<td>0.55</td>
</tr>
<tr>
<td>Exercise capacity, W</td>
<td>155±38</td>
<td>174±35</td>
<td>131±27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exercise capacity, W</td>
<td>155±38</td>
<td>174±35</td>
<td>131±27</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 2**
Echocardiographic parameters in patients with tetralogy of Fallot

<table>
<thead>
<tr>
<th></th>
<th>Total (n=148)</th>
<th>Men (n=68)</th>
<th>Women (n=80)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV D1, cm²/m²</td>
<td>12.1±2.5</td>
<td>12.1±2.6</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>RV D2, cm²/m²</td>
<td>6.2±1.6</td>
<td>6.5±1.6</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>RV FAC, %</td>
<td>48.2±7.1</td>
<td>48.7±7.1</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>RV D1, cm²/m²</td>
<td>2.2±0.3</td>
<td>2.5±0.3</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>LV D2, cm²/m²</td>
<td>1.7±0.5</td>
<td>1.7±0.3</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>LV D3, cm²/m²</td>
<td>3.8±0.3</td>
<td>4.2±0.3</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>LV D4, cm²/m²</td>
<td>2.4±0.2</td>
<td>2.3±0.2</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>LV D5, cm²/m²</td>
<td>2.9±0.4</td>
<td>2.9±0.4</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>LV EF, %</td>
<td>53±8</td>
<td>51±8</td>
<td>55±8</td>
<td>0.005</td>
</tr>
<tr>
<td>LV EDV (mL/m²)</td>
<td>43±12</td>
<td>45±13</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>LV ESV (mL/m²)</td>
<td>21±7</td>
<td>20±6</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>LV MD, ms</td>
<td>45.6±15.2</td>
<td>48.4±15.1</td>
<td>43.2±14.9</td>
<td>0.05</td>
</tr>
<tr>
<td>LV GLS, %</td>
<td>−17.4±3.5</td>
<td>−18.8±3.3</td>
<td>−18.3±3.2</td>
<td>0.001</td>
</tr>
<tr>
<td>RV MD, ms</td>
<td>38.6±21.1</td>
<td>35.1±27.3</td>
<td>41.4±13.8</td>
<td>0.09</td>
</tr>
<tr>
<td>RV GLS, %</td>
<td>−17.6±4.3</td>
<td>−19.1±4.1</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

EDA, end-diastolic area; EDV, end-diastolic volume; ESA, end-systolic area; ESV, end-systolic volume; GLS, global longitudinal strain; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MD, mechanical dispersion; RV, right ventricular; RV FAC, right ventricular fractional area change; RVOT, right ventricular outflow tract.

### Cardiac Arrhythmias
Higher RV D1 (4.3±0.5 vs 4.6±0.6, p=0.01), lower EF (55±8 vs 50±9, p=0.02) and lower RV GLS (−18.1±4.0 vs −16.1±4.8, p=0.04) in the entire cohort were associated with higher incidence of VA (table 3). RV D1 had strongest association to incidence of VA (table 3).

### ECG, exercise capacity and heart failure
Mean heart rate was 70±13 beats/min and QTC duration was 457±45 ms, similar in both sexes.

Mean QRS duration was prolonged with 141±30 ms, with significantly longer QRS duration in male patients (151±30 ms vs 128±25 ms, p<0.001; table 1).

The total population had mean exercise capacity of 155±38 W, with men having higher exercise capacity than women (174±55 watt vs 131±27 watt, p<0.001; table 1). NYHA class was equal between sexes.

More than half of patients (53%) had NT-proBNP above normal values, with similar prevalence in men and women (p=0.19; table 1).

One patient required heart transplant at the age of 40 due to biventricular heart failure.
Patients with VA had more frequently NT-proBNP over reference range (n=27 (23%) vs n=8 (77%), p<0.001). NT-proBNP values were missing for five patients.

We found no differences in the incidence of VA, nor at age at VA between men and women (table 3). Male patients had mostly experienced sustained VT (77%) as first presentation of VA, while female patients frequently had NSVT (76%) at first VA presentation (p<0.01). VA had occurred at median 7 years (range 1–18 years) prior to last follow-up.

QRS duration did not differ in those with and without VA (143±32 ms vs 137±28 ms, p=0.2).

Of the 22 patients with ICD, 13 were men (59%). ICD had been implanted in 19% of the male cohort compared with 11% of the female cohort (table 1).

**DISCUSSION**

This study confirmed reduced RV and LV function in adult patients operated for TOF. Interestingly, we showed that male patients had more reduced cardiac function at follow-up at all ages, indicating a more severe heart failure outcome compared with female patients. The incidence of VA was similar in men and women and 1 out of 4 patients experienced VA at the age of 38±9 years, an average of 32 years after surgical repair.

**Heart failure outcome**

In our study, patients operated for TOF showed lower RV function and dilated RV at long term follow-up. Similar results were showed in other adult TOF populations, where RV GLS was reduced compared with normal controls, despite unchanged RV EF on cardiac magnetic resonance and only modest RV dilatation. The decrease in strain values compared with healthy subjects is not unexpected, as both the anatomical features of the congenital heart disease and the following surgical correction influence the ventricular contractility resulting in alteration of GLS.

Also, LV function was decreased in our patients with TOF. Several studies investigating ventricular function and contractility have been conducted on patients with TOF. One study showed that asymptomatic paediatric TOF population with a normal LV EF already exhibited abnormal segmental and global LV longitudinal and circumferential strains compared with a matched healthy control group.

Interestingly, our study showed that male patients with TOF had worse RV function compared with female patients at long-term follow-up. This finding supports previous findings of Menting et al as they showed that male patients with TOF had significantly lower LV GLS and RV free wall strain compared with female patients and speculated that RV dysfunction adversely affects LV function, probably by mechanical coupling of the ventricles.

**Cut-off values and possible explanations for sex differences in RV function**

In a healthy population, LV GLS <−16% and RV GLS <−23% are generally considered abnormal. 

Extremes of age and SBP may be related to lower LV GLS values. There are currently no reference values for RV GLS in patients after corrective surgery for TOF. However, in other cardiomyopathies affecting primarily the RV, as arrhythmogenic RV cardiomyopathy, the cut-off value for abnormal RV GLS proposed is −18%. In our cohort of patients with TOF, more than 30 years after surgery, RV and LV GLS and global LV EF was impaired in men with TOF at all ages, while women had GLS values within the reference range of normal population. Higher SBP values reported in our male patients with TOF might influence GLS values, although SBP was within normal range in our male patients (<130mm Hg). Lower RV and LV GLS values in male patients at all ages, together with lower EF, might reveal a subclinical myocardial dysfunction and consequently an early stage of heart failure ahead of the symptomatic phase which occur earlier than in female patients.
NYHA class level and the generally good exercise capacity in both men and women supported that myocardial dysfunction was mainly asymptomatic. However, more than 50% of patients with TOF had elevated NT-proBNP values, supporting the finding of subclinical heart failure confirmed by imaging parameters.

### Incidence of VA and device therapy

Our study confirmed a high incidence of VA of 25%–30 years after surgery in patients with TOF. A large multicentre study reported SCD as the most common causes of death in TOF with 49%, followed by heart failure (27%) and coronary artery disease (6%).9 Importantly, our study showed that in the entire TOF cohort reduced cardiac function expressed by reduced EF and RV GLS was associated with VA, highlighting the importance of follow-up cardiac imaging in risk assessment for VA in these patients. GLS has been shown to predict VA in certain patient populations, as after myocardial infarction and in arrhythmogenic RV cardiomyopathy.23 Similarly, use of strain echocardiography for arrhythmic risk assessment could be broadened to patients with congenital heart disease, in particular patients operated for TOF. The incidence of VA was equally represented in both sexes and VA occurred at approximately the same age for male and female patients. This finding confirmed that the arrhythmic burden is equally distributed in both sexes during adult life as showed in previous multicentre studies.9 10 In contrast, men in the general population have higher risk of sudden CA than women, in all age groups,24 and the higher incidence of coronary artery disease and a higher prevalence of cardiac structural abnormalities may explain these differences.25 Our patients were young and probably too young to include the full risk regarding coronary artery disease. Nevertheless, the equal VA incidence between sexes in our TOF population may indicate a relatively higher risk of SCD in female patients with TOF compared with the general population.

A similar pattern is observed in some cardiomyopathies, where male patients have generally higher risk of severe VA. In arrhythmogenic RV cardiomyopathy, male sex is one of predictors for VF and ICD therapy.26 In a similar way, a history of VF is more frequent in men with Brugada syndrome, being the age at the onset of VF also lower in men than in women.27

Our study confirmed prolonged QRS duration in long-term follow-up of patients with TOF as reported previously,28 with the novel finding of longer QRS duration in male patients. An increased QRS duration has previously been recognised as risk factor for VA and SCD in patients with TOF. QRS duration of 180 ms or more, QRS duration rate of change (>3 ms per year over a 10-year period), older age at repair and pulmonary regurgitation were the most important risk markers of VA and SCD in adults with repaired TOF. In contrast, we found no association between QRS duration and VA in our population. None of our patients diagnosed with severe VA presented QRS duration >180 ms. This finding highlights increased arrhythmic risk also at QRS duration below 180 ms.

In our cohort, 14% of patients had received ICD implantation during adult life. We found no sex differences in frequency of ICD implantation (19% of men, 11% of women). However, we cannot exclude that larger studies may show sex differences.

### Table 3  Risk factors and incidence of VA in patients with TOF

<table>
<thead>
<tr>
<th></th>
<th>No VA (n=113)</th>
<th>VA (n=35)</th>
<th>P value</th>
<th>OR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at operation, years</td>
<td>4.6±4.5</td>
<td>4.6±0.2</td>
<td>0.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>136±27</td>
<td>147±34</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td>1 (I–3)</td>
<td>1 (I–3)</td>
<td>0.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise capacity, W</td>
<td>151±38</td>
<td>151±33</td>
<td>0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operations, no</td>
<td>0.8±0.9</td>
<td>1.0±0.8</td>
<td>0.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV FAC, %</td>
<td>48.5±6.9</td>
<td>47.3±7.5</td>
<td>0.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV D1, cm</td>
<td>4.3±0.5</td>
<td>4.6±0.6</td>
<td>0.01</td>
<td>2.4 (1.2 to 5.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>RVOT, cm</td>
<td>2.9±0.4</td>
<td>2.9±0.5</td>
<td>0.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV EF, %</td>
<td>55±8</td>
<td>50±9</td>
<td>0.02</td>
<td>0.94 (0.90 to 0.99)</td>
<td>0.02</td>
</tr>
<tr>
<td>LV MD, ms</td>
<td>44±14</td>
<td>49±16</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV GLS, %</td>
<td>−17.7±3.3</td>
<td>−16.5±3.9</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV MD, ms</td>
<td>37±22</td>
<td>42±17</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV GLS, %</td>
<td>−18.1±4.0</td>
<td>−16.1±4.8</td>
<td>0.04</td>
<td>1.1 (1.0 to 1.2)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

GLS, global longitudinal strain; LV, left ventricular; LVEF, left ventricular ejection fraction; MD, mechanical dispersion; RV, right ventricular; RVD1, right ventricular basal diameter; RVFAC, right ventricular fractional area change; RVOT, right ventricular outflow tract; TOF, tetralogy of Fallot; VA, ventricular arrhythmias.
The reason of a more balanced distribution of severe VA between sexes in patient with TOF compared with the general population and to cardiomyopathies is currently not known. One might speculate that the prolonged and, in some cases, reiterated haemodynamic stress occurring in pregnancy, might outweigh females' benefit and increase the risk of VA in female patients with TOF, according to a previous report.

**Study limitations**

This was a cross-sectional cohort study with retrospective event adjudication, with intrinsic limitations. We cannot draw a conclusion about causal connection, and we cannot measure incidence. The relatively limited sample size may give rise to insufficient power to detect subtle differences.

**CONCLUSION**

This study confirmed reduced RV function in adult patients operated for TOF at long-term follow-up. Male patients had significantly impaired LV and RV function expressed by lower LV and RV GLS values at all ages. The incidence of VA was high, 25% at 30 years after surgery and was similar between sexes. Reduced cardiac function and elevated NT-proBNP were associated with higher incidence of VA and may be important in risk assessment.

**Acknowledgements**

We thank all the patients that participated in this study.

**Contributors**

AQ: acquired data, analysed data, performed statistical analysis, writing. OHL and KH: analysed data, performed statistical analysis, made critical revision of the manuscript. EN: designed the study, made critical revision of the manuscript for important intellectual content. CDL and HLL: conceived and designed the study, made critical revision of the manuscript for important intellectual content. KT: acquired data, made critical revision of the manuscript. MEE: conceived and designed the research, provided study tools and materials, performed statistical analysis, made critical revision of the manuscript. KH: performed statistical analysis, made critical revision of the manuscript.

**Funding**

This study was supported by the South-Eastern Norway Regional Health Authority (NR 201703). The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Regional Committees for Medical Research Ethics (reference number 2017/383).

**Provenance and peer review**

Not commissioned; internally peer reviewed.

**Data availability statement**

All data relevant to the study are included in the article or uploaded as supplementary information.

**Open access**

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

**ORCID iDs**

Aleksa Quattrone http://orcid.org/0000-0001-8915-2630
Thor Edvardsen http://orcid.org/0000-0002-3800-765X
Kristina Haugaa http://orcid.org/0000-0002-4900-0453

**REFERENCES**


---

**Open Heart**

First published as 10.1136/openhrt-2021-001738 on 18 October 2021. Downloaded from http://openheart.bmj.com/ on January 4, 2022 by Universitetet i Oslo. Protected by copyright.

---

**Open Heart**

First published as 10.1136/openhrt-2021-001738 on 18 October 2021. Downloaded from http://openheart.bmj.com/ on January 4, 2022 by Universitetet i Oslo. Protected by copyright.
congenital heart disease


Is experienced pregnancy in women with repaired tetralogy of Fallot related to diffuse myocardial fibrosis?

Charlotte de Lange a, b, *, Alessia Quattrone c, d, e, Kirsti Try a, Anita Helset Bakke a, Anette Borger Kvaslerud a, d, e, Kristina Haugaa c, d, e, Mette-Elise Estensen a, d, e

a Division of Radiology and Nuclear Medicine, Section of Pediatric Radiology, Oslo University Hospital, PO Box 4950, N-0424, Oslo, Norway
b Department of Radiology, Queen Silvia Children’s Hospital, Sahlgrenska University Hospital, Diagnos. 11, 41650 Göteborg, Sweden
c ProCardio Center for Innovation, Department of Cardiology, Oslo University Hospital Rikshospitalet, PO Box 4950, N-0424, Oslo, Norway
d Institute of Clinical Medicine, University of Oslo, PO Box 1171, Blindern 0318, Oslo, Norway
e Dept. of Cardiology, Oslo University Hospital Rikshospitalet, PO Box 4950, N-0424, Oslo, Norway

ARTICLE INFO

Keywords:
Magnetic resonance imaging
MR T1 mapping
Pregnancy
Tetralogy of Fallot

ABSTRACT

Objectives: To assess the impact of pregnancy on cardiac function and fibrosis by cardiovascular magnetic resonance (CMR) in patients with repaired Tetralogy of Fallot (rToF).

Background: CMR T1 mapping can assess diffuse myocardial fibrosis which is associated to adverse clinical outcomes. Right ventricular (RV) accelerated remodeling is reported in rToF women with experienced pregnancy.

Methods: We included rToF women from the national registry of congenital heart disease to perform CMR, assessing functional data, T1 mapping/ extracellular volume fraction (ECV). The results including clinical data were compared between women with experienced pregnancy vs non-experienced pregnancy and healthy individuals.

Results: Fifty rToF women performed CMR, median age 36 (range 21–67) years. Fifteen were nulliparous. T1 mapping was compared to 30 controls, (14 women) median age 42 (24–64) years. In the left ventricle (LV), T1 times and ECV in all rToF women vs female controls were 1248 ± 61 ms/ 25.8 ± 2.9% vs 1255 ± 40 ms/ 26.8 ± 3.1%, p = 0.7 and p = 0.3, respectively. In rToF, RV T1 times was 1385 ± 124 ms and ECV 37.7 ± 5.4%. There was no association to parity or age in rToF LV T1 / ECV, p = 0.9 for both, or RV T1/ECV, p = 0.4 and p = 0.6, respectively. Indexed LV mass was higher in the rToF pregnancy group, 43 ± 10 vs 38 ± 6 g/m², p = 0.03 while RV ejection fraction was lower, 49 ± 7% vs 53 ± 6%, p = 0.04. Conclusion: Women with rToF showed evidence of increased RV CMR markers suggestive of diffuse fibrosis while LV CMR markers were within normal values. Having experienced pregnancy might affect RV function, however without association to CMR biomarkers.

1. Introduction

Tetralogy of Fallot is the most common cyanotic congenital heart defect (CHD) occurring in approximately 0.1% of live births. The long-term survival after primary surgical repair is generally considered to be good (1). However, late complications such as pulmonary regurgitation, ventricular arrhythmia, progressive right ventricular (RV) and left ventricular (LV) remodeling have been reported to be related to cardiovascular morbidity and mortality (2–5).

Most women with repaired tetralogy of Fallot (rToF) can experience a successful pregnancy (1,2). The hemodynamic changes during normal pregnancy are mandatory with increased cardiac output and altered LV contractility (3,4). Women with rToF seem to have a more limited cardiac reserve to adapt to the physiological changes during pregnancy.

Abbreviations: ANOVA, analysis of variance; CMR, cardiovascular magnetic resonance imaging; COV, coefficient of variation; ECV, extracellular volume fraction; EDVI, end-diastolic volume indexed to body surface area; EF, ejection fraction; LGE, late Gadolinium (Gd) enhancement; LV, left ventricle; LVMass, left ventricle mass indexed to body surface area; MOLLI, modified Look Locker inversion recovery; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-brain natriuretic peptide; ROI, region of interest; RV, right ventricle; RVOT, right ventricular outflow tract; rToF, repaired tetralogy of Fallot.

* Corresponding author at: Dept. of Radiology, Queen Silvia Childrens’ Hospital, Sahlgrenska University Hospital, Diagnos. 11, S-41650 Göteborg, Sweden.
E-mail addresses: charlotte.de.lange@vgregion.se, charlotte.delange@medisin.uio.no (C. de Lange).

https://doi.org/10.1016/j.jicard.2021.09.033
Received 30 April 2021; Received in revised form 13 July 2021; Accepted 16 September 2021
Available online 20 September 2021
0167-5273/© 2021 Elsevier B.V. All rights reserved.
Furthermore, the long-term impact of pregnancy in rToF women and especially on RV function are less known (3). A few studies have reported an accelerated RV remodeling and dilatation at short term follow-up postpartum (1,6).

Myocardial fibrosis is linked to LV dysfunction and adverse clinical outcomes in many cardiac conditions, including rToF patients (7-9). Little is known about the possible long-term effect of the hemodynamic stress in pregnancy and the development of myocardial fibrosis. Cardiovascular magnetic resonance (CMR) can be used to visualize and quantify both focal myocardial scarring as well as diffuse generalized myocardial fibrosis. Using an established method of T1 mapping sequence, native T1 times with calculation of extracellular volume fraction (ECV) can evaluate diffuse myocardial fibrosis, while focal scarring is assessed by late gadolinium enhancement sequence (LGE). Focal scar and diffuse fibrosis seem to be independent markers in rToF patients related to decreased LV and RV systolic function and RV dilatation (10).

We hypothesized that the hemodynamic changes in pregnancy in rToF women have a long-term effect on myocardial function and are associated with increased diffuse myocardial fibrosis. The objective of this study was to quantify CMR derived markers of fibrosis, native T1 times and ECV, in women with rToF, as compared to healthy controls. Furthermore, we aimed to evaluate possible differences in ventricular function and valvular patency related to previous experienced pregnancy.

2. Methods

This cross-sectional study was approved by the Regional committee for Medical Research (Reference number 2017/383) and is compliant with the Health Insurance Portability and Accountability Act, Helsinki declaration. Written informed consent was obtained from all participants and controls.

2.1. Study participants

Patients were identified from the national registry of congenital heart disease which included all patients followed at Oslo University Hospital, Rikshospitalet in Norway from 1953 to 2017. Female patients >18 years of age who had undergone complete rToF were invited to participate in the study. Women who had experienced pregnancy, at least one year after latest child birth, and women without experienced pregnancy were prospectively included from October 2015–October 2017.

Demographic and clinical data were registered and collected from medical records available in the hospital electronic medical record system and a CMR examination was performed.

Patients with complex malformations (atrioventricular canal defect, double outflow right ventricle and genetic syndromes) and patients with contraindications to CMR, including CMR incompatible devices or psychological problems such as severe claustrophobia were excluded from the study.

A control group of healthy individuals >18 years, without established cardiovascular disease, were recruited from volunteers responding to an advertisement at Blood Bank of Oslo University Hospital. They were examined from August 2017–February 2018.

2.2. CMR protocol

All participants in the study underwent the same scanning protocol on the same 3 T MR unit, (Philips Achieva, Philips Healthcare, Best, The Netherlands) without anesthesia or sedation.

The protocol included standard 2D steady-state-free precession sequences performed in an axial, coronal and sagittal plane over the thorax for an anatomical overview. Standard cine steady-state-free precession sequences were performed during breath hold in ventricular two, three and four chamber and short-axis planes for functional evaluation. The cine short-axis plane provided a complete coverage from base to apex of both ventricles.

T1 mapping was performed by a modified Look-Locker inversion recovery sequence (MOLLI) (11) in three short-axis views at the basal, mid and apical level to measure T1 times of the myocardium and ventricular blood pool. The sequence consisted of two inversion recovery prepared ECG synchronized Look-Locker experiments with inversion pulses as well as five and three single shot images after these pulses. The pause between the two experiments was adjusted according to the patients’ heart rate, to avoid falsely low T1 times known to be influenced by a high heartrate.

The presence of LGE was assessed after injection of 0.2 mmol /kg bodyweight of gadoterate meglumine (Guerbet, Villepinte, France) and scanning was performed after 10 min in long and short-axis views using a standard two-dimensional breath hold phase sensitive inversion recovery sequence. A repeated MOLLI sequence at least 15 min after contrast injection was performed to assure a steady state in contrast enhancement with the same slice position as the pre-contrast series. In addition, standard flow measurements were performed by velocity encoded phase contrast sequences, through plane, just above the pulmonic and aortic valve.

2.3. MRI analysis

The evaluation of pre- and post-contrast MOLLI images as well as visual inspection of the presence of LGE was performed in the picture archive and communication system (PACS). Evaluation of the LGE images was made in consensus between two CMR radiologists (GdL, KT).

For T1 mapping, T1 parametric maps were generated on the scanner using motion corrected images of the midventricular short axis planes. Manually traced regions of interest (ROI) >22 mm² (~20 pixels) were drawn in the RV ventral wall (in patients referring to the ventral part of the RV myocardium towards the thoracic wall, while in the LV, one ROI in the septum and one ROI in the free LV wall. ROIs were traced avoiding the ventricular lumen and areas with focal scarring ie. LGE to avoid falsely high T1 times (11), (Fig.1). Post contrast T1 times were derived based on post-inversion recovery times and signal intensities. A circular ROI was placed in the ventricular lumen of the RV and LV. T1 times in the LV was reported as the mean value of the septal T1 and free ventricular wall (Fig. 2).

The ECV was calculated based on the pre- and post-contrast and blood pool T1 values, using hematocrit values sampled within 24 h of the MR examination, according to the formula (11):

\[
ECV = \left(1 - \frac{1}{\text{hematocrit}}\right) \frac{1}{\text{post contrast T1 myocardium}} - \frac{1}{\text{native T1 myocardium}} \frac{1}{\text{post contrast T1 blood}} - \frac{1}{\text{native T1 blood}}
\]

Observer variation of the T1 measurements and ECV was assessed in randomly selected 10 patients and 10 controls. For intra and inter-observer variation, all measurements were performed blinded by two
Fig. 1. Focal scarring assessed by late inversion recovery sequence with Gd enhancement (LGE). To the left, triangular small LGE in the inferior septum in a rToF woman (arrow) and to the right, in another participant in the right ventricular outflow tract (arrows) and septum (thick arrow).

Fig. 2. Native T1 map with regions of interest in the RV ventral wall, the LV septum and lateral wall as well as in the respective blood pool in a woman with rToF without experienced pregnancy. Increased T1 values of 1480 ms, in the RV wall.

CMR trained observers (CDL, KT).

Volumetric measurements were performed on the short-axis cine images by manually tracing the contours in end-systole and end-diastole in the picture archiving and communication system. Cardiac volumes indexed to body surface area were compared to normal values (12). The indexed mass-volume ratio was calculated for both ventricles in all participants (13).

Blood samples were retrieved the same day preceding the CMR, including S-Kreatinin S-hematocrit, N-terminal pro-brain natriuretic peptide (NT-proBNP, reference values <170 ng /L). NT-proBNP concentration in plasma was assayed on a Modular platform (Roche Diagnostics, Basel, Switzerland).

2.4. Statistical analysis

Data are presented as mean value ± standard deviation (SD) for normally distributed variables and as median (range) for the non-normally distributed. Shapiro Wilkes test was performed to assess normal distribution. Comparisons of continuous data were performed by the unpaired Student’s t-test or Mann-Whitney test, or by the analysis of variance (ANOVA) with postHoc Tukey test. Correlations between continuous and categorical parameters were assessed with Persons correlation test and Fischer exact test as appropriate. The level of significance for all tests was defined as p < 0.05 (two-sided). Intra- and interobserver agreement were assessed with Bland-Altman analyses (14): results are expressed as the % bias and coefficient of variation (COV). Statistical analyses were performed with SPSS version 27 (IBM, Armonk, NY, USA).

3. Results

3.1. Patient demographics

Fifty out of 55 women with rToF, median age 36 (range 21–67) years, completed a CMR. Five patients were unable to perform CMR due to incompatible implants (n = 3), severe claustrophobia (n = 1) and one patient had recently performed a clinically indicated CMR and a new examination was considered unnecessary.

Forty women had experienced pregnancy with a median parity of 1 (range 1–4), while 15 women (27%) were nulliparous. Tetralogy of Fallot with pulmonary artery stenosis was the initial diagnosis in 48 (96%) patients. Twenty-three (46%) patients were repaired with a transannular patch (Table 1).

Thirty individuals constituted the control group that performed CMR, with a median age of 42 years (range 24–64). There were 16 men and 14 women.

Electrocardiogram in the rToF group presented with a QRS duration of 128 ± 25 ms, significantly higher than in the control group (84 ± 8 ms, p < 0.001). The QRS duration did not differ between nulliparous (124 ± 28 ms), and women having experienced pregnancy (129 ± 24 ms, p = 0.3).

S-hematocrit and NT-proBNP values were within normal range and did not differ between the groups (Table 1).
Table 1
Clinical characteristics in rToF patients grouped by parity and the healthy controls.

<table>
<thead>
<tr>
<th>Variable</th>
<th>rToF all (n = 50)</th>
<th>Controls (n = 30)</th>
<th>p-value rToF vs controls</th>
<th>rToF no pregnancy (n = 15)</th>
<th>rToF pregnancy (n = 34)</th>
<th>p-value rToF pregnancy vs no pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>rToF subtype, n (%)</td>
<td>48 (96)</td>
<td>2 (4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary area</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at CMR (years, median (range))</td>
<td>36 (21-67)</td>
<td>42 (24-64)</td>
<td>0.07</td>
<td>29 ± 10</td>
<td>41 ± 9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165 ± 8</td>
<td>168 ± 4</td>
<td>0.1</td>
<td>165 ± 7</td>
<td>165 ± 7</td>
<td>0.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68 ± 13</td>
<td>64 ± 7</td>
<td>0.2</td>
<td>66 ± 11</td>
<td>69 ± 13</td>
<td>0.5</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.8 ± 0.2</td>
<td>1.8 ± 0.1</td>
<td>0.9</td>
<td>1.8 ± 0.2</td>
<td>1.7 ± 0.2</td>
<td>0.9</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>69 ± 12</td>
<td>66 ± 9</td>
<td>0.4</td>
<td>73 ± 10</td>
<td>67 ± 14</td>
<td>0.1</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>116 ± 11</td>
<td>113 ± 10</td>
<td>0.3</td>
<td>115 ± 9</td>
<td>117 ± 12</td>
<td>0.6</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>71 ± 10</td>
<td>64 ± 9</td>
<td>0.04</td>
<td>72 ± 8</td>
<td>70 ± 11</td>
<td>0.5</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>128 ± 25</td>
<td>84 ± 8</td>
<td>&lt;0.001</td>
<td>124 ± 28</td>
<td>129 ± 24</td>
<td>0.3</td>
</tr>
<tr>
<td>Type of rToF n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infundibular patch</td>
<td>18 (36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmural patch</td>
<td>23 (46)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV-PA conduit</td>
<td>2 (4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>7 (14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at 1. operation, years</td>
<td>3 (1-19)</td>
<td>na</td>
<td>na</td>
<td>2 (1-5)</td>
<td>3 (1-19)</td>
<td>0.4</td>
</tr>
<tr>
<td>Number of operations</td>
<td>2 (1-4)</td>
<td>na</td>
<td>na</td>
<td>1 (1-3)</td>
<td>2 (1-4)</td>
<td>0.08</td>
</tr>
<tr>
<td>NYHA class</td>
<td>1 (1-3)</td>
<td>na</td>
<td>na</td>
<td>1 (1-3)</td>
<td>1 (1-3)</td>
<td>0.1</td>
</tr>
<tr>
<td>NT-ProBNP, ng/L</td>
<td>171 (30-770)</td>
<td>na</td>
<td>na</td>
<td>137 (30-372)</td>
<td>188 (40-770)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

BRA body surface area; HR heart rate; DBP diastolic blood pressure; NYHA New York Heart Association classification; NT-proBNP N-terminal pro-brain natriuretic peptide; rToF repaired tetralogy of Fallot; SBP systolic blood pressure.

Table 2
CMR volumetric measurements, Native T1 times and ECV in rToF women according to parity and compared to healthy controls.

<table>
<thead>
<tr>
<th>MR volumetry n = 49</th>
<th>rToF all n = 49</th>
<th>rToF no pregnancy (n = 15)</th>
<th>rToF pregnancy (n = 35)</th>
<th>Normal values (range)</th>
<th>P-value rToF vs vs no pregnancy</th>
<th>P-value rToF vs controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV EDVI (mL/m²)</td>
<td>82 ± 11</td>
<td>82 ± 9</td>
<td>81 ± 13</td>
<td>80 (62-98)</td>
<td>73 (51-95)</td>
<td>0.8</td>
</tr>
<tr>
<td>LV ESVi (mL/m²)</td>
<td>37 ± 7</td>
<td>37 ± 5</td>
<td>37 ± 8</td>
<td>25 (13-37)</td>
<td>23 (11-35)</td>
<td>1.0</td>
</tr>
<tr>
<td>LV SVi (mL/m²)</td>
<td>45 ± 7</td>
<td>45 ± 6</td>
<td>44 ± 7</td>
<td>55 (43-67)</td>
<td>51 (35-87)</td>
<td>0.6</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>55 ± 5</td>
<td>55 ± 4</td>
<td>55 ± 5</td>
<td>69 (57-81)</td>
<td>69 (57-81)</td>
<td>0.9</td>
</tr>
<tr>
<td>LV mass (g/m²)</td>
<td>42 ± 9</td>
<td>38 ± 5</td>
<td>43 ± 10</td>
<td>53 (35-71)</td>
<td>52 (34-70)</td>
<td>0.03</td>
</tr>
<tr>
<td>RV EDVI (mL/m²)</td>
<td>101 ± 26</td>
<td>96 ± 19</td>
<td>103 ± 28</td>
<td>89 (76-111)</td>
<td>80 (42-118)</td>
<td>0.4</td>
</tr>
<tr>
<td>RV ESVi (mL/m²)</td>
<td>52 ± 16</td>
<td>46 ± 13</td>
<td>55 ± 17</td>
<td>35 (25-45)</td>
<td>30 (26-54)</td>
<td>0.07</td>
</tr>
<tr>
<td>RV SVi (mL/m²)</td>
<td>51 ± 12</td>
<td>50 ± 9</td>
<td>52 ± 13</td>
<td>54 (40-68)</td>
<td>54 (32-68)</td>
<td>0.5</td>
</tr>
<tr>
<td>RV EF (%)</td>
<td>50 ± 7</td>
<td>53 ± 6</td>
<td>49 ± 7</td>
<td>61 (55-67)</td>
<td>64 (50-78)</td>
<td>0.04</td>
</tr>
<tr>
<td>RV mass/g/m²</td>
<td>19 ± 4</td>
<td>18 ± 3</td>
<td>20 ± 4</td>
<td>21 (15-27)</td>
<td>19 (13-25)</td>
<td>0.1</td>
</tr>
<tr>
<td>LV mass-volume ratio</td>
<td>0.52 ± 0.12</td>
<td>0.47 ± 0.10</td>
<td>0.54 ± 0.13</td>
<td>na</td>
<td>na</td>
<td>0.006</td>
</tr>
<tr>
<td>RV mass-volume ratio</td>
<td>0.44 ± 0.15</td>
<td>0.41 ± 0.10</td>
<td>0.45 ± 0.20</td>
<td>na</td>
<td>na</td>
<td>0.2</td>
</tr>
<tr>
<td>Aortic valve PSV m/s</td>
<td>1.1 ± 0.2</td>
<td>1.1 ± 0.2 (0.9-1.6)</td>
<td>1.1 ± 0.2 (0.8-1.6)</td>
<td>na</td>
<td>na</td>
<td>1.0</td>
</tr>
<tr>
<td>Aortic regurgitation (%)</td>
<td>4 ± 0 (0-14)</td>
<td>4 ± 0 (0-14)</td>
<td>3 ± 0 (0-14)</td>
<td>na</td>
<td>na</td>
<td>0.4</td>
</tr>
<tr>
<td>Pulmonary valve PSV m/s</td>
<td>1.7 ± 0.6</td>
<td>1.8 ± 0.8 (1.0-3.8)</td>
<td>1.7 ± 0.5 (0.5-2.6)</td>
<td>na</td>
<td>na</td>
<td>0.4</td>
</tr>
<tr>
<td>Pulmonary regurgitation (%)</td>
<td>13 ± 0.4</td>
<td>13 ± 0.15 (0-42)</td>
<td>13 ± 12 (0-40)</td>
<td>na</td>
<td>na</td>
<td>1.0</td>
</tr>
</tbody>
</table>

ECV extra cellular volume fraction; EDVI end-diastolic volume index; ESVi end-systolic volume index; EF ejection fraction; LV left ventricle; RV right ventricle; PSV peak systolic velocity; SVi stroke volume index; rToF repaired tetralogy of Fallot.

<table>
<thead>
<tr>
<th>MR relaxometry</th>
<th>Controls n = 15</th>
<th>P value rToF vs controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native T1 LV (ms)</td>
<td>1254 ± 61</td>
<td>0.8</td>
</tr>
<tr>
<td>n = 48</td>
<td>n = 15</td>
<td>n = 32</td>
</tr>
<tr>
<td>Native T1 RV (ms)</td>
<td>1393 ± 108</td>
<td>0.6</td>
</tr>
<tr>
<td>n = 45</td>
<td>n = 13</td>
<td>n = 31</td>
</tr>
<tr>
<td>LV ECV (%)</td>
<td>25.0 ± 2.7</td>
<td>0.3</td>
</tr>
<tr>
<td>n = 46</td>
<td>n = 13</td>
<td>n = 30</td>
</tr>
<tr>
<td>RV ECV (%)</td>
<td>37.7 ± 5.4</td>
<td>0.8</td>
</tr>
<tr>
<td>n = 42</td>
<td>n = 12</td>
<td>n = 29</td>
</tr>
</tbody>
</table>

ECD extra cellular volume fraction; EDVI end-diastolic volume index; ESVi end-systolic volume index; EF ejection fraction; LV left ventricle; RV right ventricle; PSV peak systolic velocity; SVi stroke volume index; rToF repaired tetralogy of Fallot.

Normal values according to age < and > 35 years in Hudsmith et al, JCMR 2005.
3.2. CMR data

Volumetric indexed values were measured in 49/50 patients and presented in Table 2. The images of one patient were affected by severe breathing artefacts resulting in unreliable measurements. Indexed LV mass (Lvmassis) was slightly higher in the pregnancy group (43 ± 10 vs. 38 ± 5 g/m², p = 0.03) while RV ejection fraction (EF) was lower (49 ± 7% vs. 53 ± 6%, p = 0.04). The indexed mass-volume ratio for LV revealed elevated values in the pregnancy group, 0.54 ± 0.13 g/ml compared to the non-pregnancy group revealing 0.47 ± 0.05, p = 0.006 (Table 2). Other indexed volumetric measurements were within the normal range for gender and age (12) except for a slightly decreased LV EF and RV EF in the lower range of normal values when considering all patients (Table 2).

3.3. LGE, MR T1 mapping and ECV

Of the included 50 patients, only a few image sets were incomplete. Four patients did not receive Gd contrast agent due to refusal of intravenous injection and thus prolonged examination with postcontrast sequences. One patient had a clear outlier pre- and post T1- value due to image artefacts. These patients were excluded from the T1/ECV analysis. Thus, LGE and ECV were evaluated in 46 and 45 patients respectively. LGE was present in 27 of the 46 patients (58%) and located in the inferior septal free wall junction part and in the RV outflow tract (RVOT) n = 14 (Fig.1). None had LGE in the diaphragmatic RV wall. One patient had LGE in LV apex. There was no significant difference of the presence of LGE between the two rToF groups. T1 times and ECV were compared to 30 controls, of whom 14 were women. All patients and controls had a heart rate ≤ 100 beats per minute. In a few patients, artefacts precluded measurements. LV T1 times were eventually measured in 48 of 50 patients, LV ECV and RV T1 times in 45 patients and RV ECV in 42 patients.

T1 times and ECV in the LV in rToF women were comparable to female controls (1254 ± 61 ms/ 25.9 ± 2.7% vs. 1254 ± 45 ms/ 26.8 ± 2.6%, p = 0.9 and p = 0.4 respectively).

(Fig.3). RV T1 times in all rToF women were 1393 ± 108 ms and ECV 37.7 ± 5.4%. The RV wall in controls was too thin to permit reliable measurements for comparison.

No significant difference was found when comparing LV T1 and LV ECV in rToF women to the whole control group (men and women) with p = 0.8 and p = 0.2, respectively (Table 2). No significant difference was found for LV and RV T1 and ECV according to age grouped in tertiles, p = 0.2-0.9 (Fig. 4).

3.4. Valvular patency

Pulmonary valve patency was reliably measured in 46/50 patients, with a mean peak systolic velocity of 1.7 ± 0.6 m/s, median 1.6 m/s (range 0.5–3.8 m/s). Five patients displayed a peak systolic velocity ≥ 2.5 m/s (Table 2).

Pulmonary regurgitation was present in 46 patients. The mean regurgitation fraction was 13% ± 13 (range 1–42%) without difference between groups (Table 2). A mild regurgitation fraction of 0–10% was present in 25 patients. Six patients had regurgitation fraction of 11–20%, two patients presented with a fraction of 21–30%. Severe regurgitation of 31–42% was present 13 patients (Table 2).

3.5. Correlations

Considering rToF patients, indexed LV end-diastolic and end-systolic volumes correlated with LV ECV, (R = 0.5, p = 0.003, and R = 0.4 p = 0.005 respectively), while LV end-diastolic volume index correlated with LV ECV (R = 0.4 p = 0.02) but not to RV ECV (R = 0.1 p = 0.7) (Table 3).

LV and RV ECV were positively correlated (R = 0.4, p = 0.005), but without association with LV and RV mass-to-volume ratio, for LV (R 0.15, p = 0.3) and for RV (R – 0.12, p = 0.6) (Table 3). However, LV and RV mass to volume ratio were positively correlated (R 0.7, p < 0.001).

The number of pregnancies in rToF women was neither associated with LV T1 or ECV, (p = 0.9 for both) nor with RV T1 or ECV (p = 0.4 and p = 0.6, respectively).

For the rToF patients, no correlation was found between the presence of LGE in RVOT and septum, p = 0.3 or pulmonary regurgitation > 10 m/s, p = 0.9.

There was no association of increased CMR markers to the type of surgical repair.

3.6. Observer variation

Bland Altman plots for observer variation of the T1 and ECV measurements were performed in a subgroup of 10 patients and 10 controls (Appendix). For the rToF patients the native T1 times in the LV revealed moderate observer variation with an intra-observer bias 0.01% (COV 0.6); the interobserver bias was –0.1% (COV 0.3).

For T1 in controls the intra-observer bias was 0.3% (COV 1.7) and interobserver bias 0.9% (COV 1.6). In the RV T1 in patients revealed a lower repeatability with an intra-observer bias of 2.1% (COV 3.7) and for interobserver a bias of 3.3% (COV 5.5). Variability in ECV in the LV and RV are displayed in the Appendix.
4. Discussion

We performed a cross sectional single-center study with prospective inclusion of women with rToF. Our primary finding was that women with rToF express increased RV native T1 and ECV, while CMR markers of LV myocardial fibrosis were normal. Secondly, we found that RV EF was slightly reduced in women who had experienced pregnancy and in addition, that higher LV ECV was associated with larger LV and RV volumes. Furthermore, LV and RV ECV were correlated. Lastly, there was no association between CMR markers of fibrosis and age, type of surgical repair or number of pregnancies. Experienced pregnancy did not show any influence on pulmonary valve regurgitation or on other CMR derived parameters.

4.1. CMR data

RV remodeling has been described in rToF women following pregnancy and delivery (1.6). This has important clinical implications due to concerns about preserving the RV integrity in this patient group and might impact patient counseling for pregnancy (15). In our study, indexed RV end-diastolic volume (EDVI) values were in the upper normal range while RV EF were in the lower values. This can be interpreted as a tendency of RV remodeling (12). However, there was no significant difference in RV or LV values when considering the number of experienced pregnancies.

4.2. T1 mapping and LGE

Although being primarily a right heart condition, LV dysfunction is not uncommon in rToF.

This is considered as a risk factor for adverse outcome (16,17) as associated with the presence of LGE and diffuse myocardial fibrosis (13,18,19). In adults with rToF, evidence of increased markers of LV ECV as quantified by CMR T1 mapping has previously been shown (7,13,20). Pediatric studies have shown diverging results, reporting LV ECV associated with biventricular enlargement and reduced exercise tolerance in one study (18), while another revealed values comparable to normal subjects (21). The study by Tim et al., including 100 pediatric patients, demonstrate findings similar to our results, with normal LV markers. RV T1 and ECV were increased compared to controls and related to RV volume overload (21). In our study, including 50 adult female patients, the RV size and mass were not clearly dilated or hypertrophic with RV EDVI within the upper limits of normal values. Increased markers of RV T1 and ECV has been found in patients with diverse CHD (22).

Our results reveal similar findings with focal scarring in the RVOT and septum in a large part of the patients as reported by other studies (6,13). Cochet et al. report that scar size is related to RV systolic dysfunction (10). The possible mechanisms for RV diffuse fibrosis in rToF patients has been proposed as cellular remodeling with a loss of cardiomyocytes or adaptive atrophy (13). CMR derived ECV reflects the extracellular matrix volume to total myocardial volume (extracellular matrix volume plus cardiomyocytes volume) (23,24). Increased ECV indicates that the extracellular matrix exceeds the hypertrophy or atrophy of the cardiomyocytes, which makes the extracellular matrix proportionally larger. A decreased RV mass-volume ratio which is negatively associated with increased RV ECV could represent loss of or atrophied cardiomyocytes (13). In our study, we found a slightly decreased RV mass-volume ratio in combination with increased RV ECV, however without significant correlation.

On the other hand, the high values of RV T1 and ECV might also be due to the naturally higher collagen content in the RV as proposed by Kawai Boehm et al. They investigated T1 times in 20 normal subjects with T1 mapping at 1.5 T, showing slightly but significantly increased values in RV (25–27). However, they did not calculate ECV which is known to be a more stable and reproducible measurement than native T1 times (11). Normal reference values of RV T1 and ECV at 3 T MRI has not been reported to our knowledge.

As expected when performing T1 mapping on 3 T MR, we found relatively higher values of T1 due to the higher field strength with accompanying artefacts from magnetic inhomogeneity (11). Nevertheless, we found a more pronounced relative difference in LV and RV T1 times than in the mentioned study and with RV ECV equally increased (21).

More importantly, no difference was found in LV, RV T1 times and ECV depending on having experienced pregnancy or not.

4.3. Correlations

As previously showed by others, we observed several moderate associations between measures of fibrosis, ECV and LV systolic function. There was a positive correlation between LV and RV ECV indicating an adverse ventricular-ventricular interaction at the tissue level as also found in a study by Chen et al. (13).

The increased markers in RV for both groups were not associated with RV dilatation or the slightly decreased systolic function. In addition, the presence and severity of pulmonary regurgitation were comparable between the groups and was not associated to the number of experienced pregnancies.

This is opposed to previous studies showing RV dilatation, RV remodeling with decreased EF and exercise capacity (1,10,28). Haggerty et al. studied 40 rToF patients, finding LV T1 and ECV within normal range but associated with impaired mechanics and LV dysynchrony and index peak radial strain, suggesting that diffuse fibrosis could be a causal factor to LV dysfunction (19). However, they did not perform MR relaxometry. Previous studies have shown an association between increased T1 ECV and transannular patch compared to valve sparing.
techniques and RV conduits (18). Our material revealed no association of increased CMR markers to the type of surgical repair.

We interpret our findings of limited alterations in cardiac RV and LV functional parameters and biomarkers of fibrosis as an indication of a generally satisfactory cardiac function in female rToF patients. Having one or more pregnancies did not reveal detectable decreases measures even when considering older women compared to younger. At the time of our study, CMR strain analysis was not available, which could have added valuable information about regional LV and RV cardiac motion. Previous studies have reported impaired CMR LV strain in both pediatric patients (18) and in adult rToF patients (19). In the future, adding CMR tissue phase mapping could enable analysis of changes in myocardial velocities as shown in a pilot study in rToF patients of the feasibility to detect regionally abnormal LV and RV motion (29).

The clinical inference of our study results, is that young women with rToF have in general a good cardiac function. Even though, we acknowledge our study's small sample size and that a longitudinal follow up on the development of myocardial fibrosis related to cardiac function is needed to draw more concise conclusions and eventually recommendations for future family planning and counseling of fertile rToF woman. Our study shows that an otherwise healthy rToF woman with good RV function could be counselled to have children with little risk of decreased cardiac function. However, systematic monitoring pre-pregnancy, during and after a pregnancy to optimize cardiac function and treatment is mandatory.

4.4. Limitations

The sample size of the studied women was limited, with only 15 patients without previous experienced pregnancy, and this could introduce some skewness in the results. We were not able to perform CMR in a few patients with MR incompatible devices or severe claustrophobia. The study was performed at a 3 T MR unit, which is known to create more artefacts due to inhomogeneity of the higher magnetic field as compared to 1.5 T scanners. This could interfere with relaxometry and volumetric measurements. However, caution was taken to avoid artefacts during manual tracing of the ventricular wall and lumen as well as placement of ROIs inside the ventricular wall.

TI measurements were only possible in the RV in the patient group. Quantification of TI times and ECV in the RV is challenging due to the thin trabeculated wall (20). The RV ventral wall in the control group was too thin to allow for reliable measurements at 3 T MR. In the future TI mapping performed in end systole might be useful to obtain a thicker RV muscle enabling more reliable TI/ECV measurements.

Lastly, we acknowledge some differences between the rToF groups where several factors might have an impact on myocardial function later in life and notably on the RV EF and LV mass. The slightly older age of women in the pregnancy- versus non-pregnancy group, the number of interventional and surgical procedures as well as the difference in perioperative care during different time periods may introduce a skewness in the results which should therefore be interpreted with caution.

5. Conclusion

Women with rToF show evidence of increased RV native T1 and ECV which could represent diffuse fibrosis. LV and RV ECV were positively correlated and might indicate an adverse ventricular-ventricular interaction at the tissue level with slightly increased LV and RV volumetric measurements. Myocardial markers, volumetric measurements, and pulmonary regurgitation were not influenced by having experienced pregnancy in women with rToF, however the latter might affect RV systolic function in the long term.

Funding

Financial support was received from the South-Eastern Norway Health Authority to second author A. Quatrone (NR 2017103). The Authors have control of all the data and information submitted for publication.

Disclosure statement

The authors declare to have nothing to disclose.

Acknowledgement

We thank the MR radiographers at the Interventional center at Oslo University Hospital, Rikshospitalet for planning and performance of MRI scanning of all the participants.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcardio.2021.09.053.

References


