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Avaliação da Aorta Ascendente em Doentes Operados a Tetralogia de Fallot: Implicações no *Follow-up* Clínico e Imagiológico

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Aos meus pais

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Abreviaturas/Abbreviations

	Português	**English**
Ao	Aórtica/o	Aortic
AAo	Aorta ascendente	Ascending aorta
AoD	Diâmetro da raiz da aorta	Aortic root diameter
AoZ	z-*score* da raiz da aorta	Ao root z-score
AAoZ	z-*score* da aorta ascendente	Ascending aorta z-score
Ad	Diâmetro aórtico em diástole	Aortic diastolic diameter
AP	Aortopulmonar	Aortopulmonary
As	Diâmetro aórtico em sístole	Aortic systolic diameter
BP	Pressão arterial	Blood pressure
BSA	Superfície corporal	Body surface area
CHD	Cardiopatia congénita	Congenital heart disease
CI	Intervalo de confiança	Confidence interval
CMR	Ressonância magnética cardiovascular	Cardiovascular magnetic resonance
D	Distensibilidade	Distensibility
GUCH	Cardiopatia Congénita do Adulto	Grown Up Congenital Heart Disease
LV	Ventricular esquerda/o	Left ventricular
LVEDV	Volume telediastólico ventricular esquerdo	Left ventricular end diastolic volume
LVESV	Volume telesistólico ventricular esquerdo	Left ventricular end systolic volume
NS	Não significativo	Non-significant
OR	*Odds ratio*	Odds ratio

Pd	Pressão diastólica	Diastolic blood pressure
PP	Pressão de pulso	Pulse pressure
Ps	Pressão sistólica	Systolic blood pressure
Pts	Pacientes	Patients
RA	Auricular direita/o	Right atrial
RV	Ventricular direita/o	Right ventricular
SAC	Compliance arterial sistémica	Systemic arterial compliance
SD	Desvio padrão	Standard deviation
SoV	Seios de Valsalva	Sinuses of Valsalva
STJ	Junção sinotubular	Sinotubular junction
SV	Volume ejetivo	Stroke volume
SVI	Volume ejetivo indexado	Stroke volume index
TOF	Tetralogia de Fallot	Tetralogy of Fallot
TTE	Ecocardiografia transtorácica	Transthoracic echocardiography
2D	Bidimensional	Two-dimensional

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RESUMO/ABSTRACT 1

RESUMO

Introdução e objetivos

Uma possível aortopatia intrínseca poderá condicionar dilatação tardia da aorta na tetralogia de Fallot operada. A sua extensão e prevalência não estão bem definidas.

Pretendemos avaliar as dimensões e elasticidade de aorta, bem como encontrar preditores da dilatação da aorta, para elaborar um protocolo de *follow-up* clínico e imagiológico.

Métodos

Este é um estudo prospetivo com adultos operados a tetralogia de Fallot seguidos num centro de referência. Nestes doentes avaliamos a aorta torácica por ecocardiografia transtorácica e comparamos os resultados com os de controlos normais ajustados para o sexo e idade. Definimos dilatação da aorta para um z-*score* > +2. Parâmetros modo-M da aorta ascendente foram usados para calcular *strain*, distensibilidade e índice de rigidez.

Adicionalmente, avaliamos a aorta torácica por ressonância magnética cardiovascular e definimos dilatação da aorta ascendente para um rácio observado-esperado > 1,5.

Resultados

No estudo por ecocardiograma transtorácico incluímos 126 adultos operados a tetralogia de Fallot e 63 controlos. Os doentes (idade média 30±9 anos; 52% homens) foram operados com uma idade mediana de 5 (2-49) anos; tempo médio de seguimento desde a cirurgia 23±7 anos. A prevalência de dilatação dos seios de Valsalva e da aorta ascendente foi 29% e 24%, respetivamente. Comparativamente aos controlos, os doentes apresentavam maior z-*score* da aorta ascendente, menor *strain* (6,4 (0,0-61,5) vs 15,2 (0,0-45,0) %; p < 0,01) e maior índice de rigidez (7,3 (0,8-23,6) vs 3,1 (0,9-14,1); p < 0,01). Na análise multivariada o sexo masculino associou-se significativamente à dilatação dos seios de Valsalva (*odds ratio* 6,3, intervalo de confiança de 95% 1,5-26,3; p = 0,01).

No estudo por ressonância magnética cardiovascular incluímos 78 doentes adultos (idade média 31±10 anos; 56% mulheres); seguimento médio 23±7 anos desde a cirurgia. A prevalência de dilatação da aorta ascendente foi 11,5%. A aorta ascendente apresentava maior diâmetro do que os seios de Valsalva em 12,8% dos casos. Os doentes com dilatação da aorta ascendente eram mais velhos, maioritariamente homens, operados mais tarde, com massa e volumes ventriculares esquerdos maiores. Na análise multivariada a massa ventricular esquerda indexada foi a única variável independente associada a dilatação da aorta ascendente (*odds ratio* 1,1; intervalo de confiança de 95% 1,0-1,2; p = 0,03). A massa ventricular esquerda indexada

≥ 57,9 g/m2 apresentou uma sensibilidade de 89% e uma especificidade de 71% como preditor de dilatação da aorta ascendente.

Conclusões

Na tetralogia de Fallot operada há uma prevalência significativa de dilatação tardia da aorta, incluindo a raiz da aorta e a aorta ascendente, sublinhando a importância duma avaliação completa da aorta. A ecocardiografia transtorácica tem limitações no que respeita à janela acústica, especialmente em adultos com cardiopatias congénitas. A ressonância magnética cardiovascular tem um papel inquestionável neste contexto e a avaliação da aorta ascendente integrada no exame de rotina da tetralogia de Fallot operada está recomendada em particular nos homens, em doentes mais velhos, operados mais tarde, e com ventrículos esquerdos maiores.

Esta hipotética aortopatia associada à tetralogia de Fallot inclui não apenas dilatação, mas também uma elasticidade anormal da aorta, podendo condicionar uma remodelagem ventricular esquerda, e requer um *follow-up* clínico e imagiológico cuidado. A massa ventricular esquerda indexada tem potencial para ser usada no rastreio da dilatação da aorta ascendente com implicações clínicas no futuro.

ABSTRACT

Background and aims

A possible intrinsic aortopathy could lead to aortic dilatation late after tetralogy of Fallot repair. Its extension and prevalence are not clearly defined. We aimed to assess aortic dimensions and elasticity, and to find predictors of aortic dilatation, in order to set up a clinical and imaging follow-up protocol.

Methods

This is a prospective study including adult patients after tetralogy of Fallot repair followed at a referral centre. We assessed the thoracic aorta by transthoracic echocardiography in these patients and compared the results with those of sex- and age-matched normal controls. We defined aortic dilatation as a z-score > +2. M-mode parameters of the ascending aorta were used to calculated strain, distensibility and stiffness index.

Additionally, we assessed the thoracic aorta by cardiovascular magnetic resonance and defined ascending aorta dilatation as an observed-to-expected ratio > 1.5.

Results

In the transthoracic study we included 126 patients and 63 sex- and age-matched controls. Tetralogy of Fallot patients (mean age 30±9 years; 52% males) had a complete repair at a median age of 5 (2-49) years; mean follow-up time since repair 23±7 years. The prevalence of aortic dilatation at the sinuses of Valsalva and ascending aorta was 29% and 24%, respectively. Compared to controls tetralogy of Fallot patients had a bigger ascending aorta z-score, lower strain (6.4 (0.0-61.5) vs 15.2 (0.0-45.0) %, $p < 0.01$) and higher stiffness index (7.3 (0.8-23.6) vs 3.1 (0.9-14.1), $p < 0.01$). By multivariate analysis male gender was strongly associated with sinuses of Valsalva dilatation (odds ratio 6.3, 95% confidence interval 1.5-26.3, p=0.01).

In the cardiovascular magnetic resonance study, we included 78 patients (mean age 31±10 years; 56% females), mean follow-up 23±7 years since tetralogy of Fallot repair. The prevalence of ascending aorta dilatation was 11.5%. The ascending aorta was larger than the sinuses of Valsalva in 12.8% of cases. Patients with ascending aorta dilatation were older, predominantly males, with later repair and a bigger left ventricular mass and volumes. By multivariate analysis left ventricular mass index was the only independent factor associated with ascending aorta dilatation (odds ratio 1.1, 95% confidence interval 1.0-1.2, $p = 0.03$). A cut-off value for left ventricular mass index $\geq$ 57.9 g/m2 had an 89% sensitivity and 71% specificity as predictor of ascending aorta dilatation.

Conclusions

Tetralogy of Fallot has a significant prevalence of aortic dilatation late after repair, including the aortic root and the ascending aorta, outlining the importance of a complete aortic assessment. Transthoracic echocardiography has limitations concerning the acoustic window, especially in a GUCH population. Cardiovascular magnetic resonance role in this setting is unquestionable, and the ascending aorta assessment as part of a routine study after tetralogy of Fallot repair is recommended particularly in males, older patients, with later repair, and with bigger left ventricles.

This hypothetical tetralogy of Fallot's aortopathy includes not only aortic dilatation but also abnormal elastic properties of the aortic wall, possibly leading to left ventricular remodelling, requiring a careful clinical and imaging follow-up. Left ventricular mass index has the potential to become a screening tool for ascending aorta dilatation with future clinical implications.

INTRODUCTION 2

Introduction

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease with survival into adulthood and guidelines recommend regular, long-term follow-up in specialized Grown-up Congenital Heart Disease (GUCH) centres.(1)

An excelent late survival after tetralogy of Fallot repair is expected, with a 35-year survival around 85%.(2, 3) However, major residual lesions may remain at the level of the right ventricular outflow tract, including obstruction or aneurysm, and at the pulmonary valve due to either regurgitation or stenosis. Ventricular dysfunction and potentially fatal arrhythmias can also contribute to an adverse outcome leading to early death.(4)

In addition, as first described by Capelli et al.,(5) there is an increasing awareness that aortic (Ao) dilatation can occur late after TOF repair. Interestingly, Ao dilatation is a TOF's foetal feature that tends to disappear after early surgical repair,(6) preventing long-standing volume overload on the overriding aorta. Consequently, Ao dilatation may be a pathology of the past, not reflecting the current surgical era.(7) Nevertheless, for many reasons, including anatomical and surgical technical issues, not all patients (pts) can benefit from early repair. Moreover, aortic histological abnormalities present since infancy in TOF, mainly in the Ao root and ascending aorta (AAo) vascular wall, may contribute to Ao dilatation.(8, 9) Though less common, progressive aortic dilatation may lead to aortic regurgitation, and increase the risk of aortic aneurysm and dissection(10, 11) requiring surgery.(12)

The extension and prevalence of this possible TOF's aortopathy is not clearly defined. Transthoracic echocardiography (TTE) plays an important role in the follow-up of patients after TOF repair and should include an aortic assessment. Due to a deficient acoustic window, new imaging techniques are increasingly used in this setting, particularly computed tomography and cardiovascular magnetic resonance (CMR) imaging.(13-15) They are however expensive, have limitations, and should be used wisely.

AIMS 3

Aims

In our study we aimed to assess by TTE and CMR the prevalence, extension and relevance of aortic dilatation in adult patients after TOF repair.

Furthermore, we intended to determine demographic, clinical, surgical and imaging variables that may potentially predict aortic dilatation, in order to set up an imaging follow-up protocol.

Additionally, we aimed to assess noninvasively the ascending aorta elastic properties, and to contribute to a better understanding of the arterial-ventricular coupling in this setting.

POPULATION AND METHODS 4

Study population

Inclusion criteria

We included prospectively adult pts (age ≥ 18 years) more than 1 year after TOF repair, without pulmonary atresia or absent pulmonary valve, followed at Hospital São João GUCH Centre, between March 2011 and December 2013 for the TTE study, and we included sex- and age-matched healthy controls using a 2:1 matching criteria. In the CMR study the time interval for pts inclusion was from March 2011 till December 2015.

Exclusion criteria

In the TTE study we excluded pts due to:

- associated heart disease
- genetic syndromes
- pregnancy

Additionally, in the in CMR study we excluded pts without a CMR available for analysis due to the following reasons:

- claustrophobia
- contraindications for CMR
- technical reasons

Study protocol

- **Systemic arterial hemodynamics**

Arterial blood pressure (BP) [systolic (Ps) and diastolic (Pd)] was measured twice at a 2 min interval and averaged, in supine position, using an automated blood pressure monitor (SureSigns VS2 monitor, Philips Medical Systems). We chose to measure BP on the left brachial artery, due to the presence of a previous right Blalock-Taussig shunt in a significant number of cases (49 patients). If there was a left palliative shunt, BP was measured on the right arm (9 cases).

The ratio of stroke volume index (SVI) to pulse pressure (PP) was used as an indirect measure of total systemic arterial compliance (SAC = SVI/PP).(16)

The arterial stiffness was calculated according to 0.9xPs/SV (SV stand for stroke volume).(17)

- **Ascending aorta elastic properties**

AAo strain, distensibility (D) and TTE M-mode derived stiffness index (β1) were calculated as: AAo strain = (As– Ad)/Ad; D = 2(As– Ad)/[Ad(Ps– Pd)] $cm^2dyne^{-1}10^{-6}$, β1= ln(Ps/Pd)/(As–Ad)/Ad, where Ps and Pd are systolic and diastolic BP, respectively; As and Ad were obtained using the M-mode inner systolic and diastolic AAo diameters in short axis view, at the level of the pulmonary artery bifurcation, with Ad obtained at the peak of the R wave of the electrocardiogram simultaneously recorded, while As was measured at the maximal anterior AAo wall motion.(18)

Transthoracic echocardiographic protocol

TTE was performed immediately after BP evaluation using the ultrasound system Vivid E7 (GE Healthcare, Milwaukee, Wisconsin, USA) with a M4S sector array transducer (1.5-4.3 MHz) and digitally stored. All echocardiographic exams were performed and analyzed by an experienced cardiologist, certified by the European Association of Cardiovascular Imaging in Congenital Heart Disease Echocardiography, and blinded to patient data.

- **Aortic assessment**

Ao diameters were measured by 2D-TTE at the level of the sinuses of Valsalva (SoV), sinotubular junction (STJ) and at the proximal AAo, 2 to 3 cm above the STJ, in parasternal long-axis view, perpendicular to the Ao long-axis, using the maximal leading edge-to-leading edge diameter method at end-diastole, and were indexed to body surface area (BSA) according to Du Bois formula.(19)

We used the z-score as a standard score obtained by subtracting the population mean from an individual data value and then dividing the difference by the population standard deviation. It is represented by the number of standard deviations by which the value of an observation or data is above or below the mean value of what is being observed or measured. Ao sinuses z-score (AoZ) was obtained using the standard nomograms for Ao root size in healthy adults, adapted from Roman et al.(20) The AAo z-score (AAoZ) was based in reference values and equations from Campens et al.(21) We defined Ao dilatation as z-score > +2, both for the SoV and AAo.

- **Left ventricular assessment**

Left ventricular (LV) end-diastolic and end-systolic inner dimensions, posterior wall and septal thickness were measured by 2D-TTE in parasternal long-axis view.

The LV mass was calculated by the corrected formula of the American Society of Echocardiography.(22) The LV ejection fraction was calculated using the modified Simpson's rule.(22) The LV stroke volume was obtained by subtracting the end-systolic volume from end-diastolic volume, using 2D volumetric measurements for the ejection fraction calculation. LV measurements were indexed to BSA according to Du Bois formula.(19) Pulsed-wave tissue Doppler was used to estimate LV filling pressure by calculating the E/lateral e' ratio.(23) We did not use the septal e' because in TOF, following patch closure of the ventricular septal defect, the septal e' is underestimated and therefore not helpful in determining diastolic function.

Cardiovascular magnetic resonance protocol

CMR imaging was performed using a 3-T system (Siemens Magneton Trio, Washington D.C., USA). CMR image acquisitions and analysis were performed by two experienced investigators blinded to patient data. Electrocardiogram triggered balanced steady-state free precession cine acquisitions were acquired during all cardiac cycle in held expiration. Pulse sequence for a standard ventricular function examination was obtained with the following parameters: field of view 320 mm^2; matrix 153x208; voxel size 2.1x1.5x6.0 mm; repetition time: 52.9 msec; echo time: 1.4 msec; flip angle: 60°; slice thickness 6 mm; no gap; temporal resolution 41 msec. CMR measurements were indexed to BSA according to Du Bois formula.(19)

- **Aortic assessment**

Cine acquisitions aligned with the LV outflow tract in oblique sagittal and coronal orientations were also obtained. In the LV outflow tract sagittal and coronal planes, maximal end-diastolic external diameter of the aortic segment of interest was made perpendicular to longitudinal axis of the aorta, consistent with 2010 ACC/AHA Guidelines for thoracic aortic disease.(24) We calculated an Ao observed-to-expected ratio based on nomograms from Davis et al.(25) We defined two groups of patients: group 1 without AAo dilatation (observed-to-expected ratio ≤ 1.5) and group 2 with AAo dilatation (observed-to-expected ratio > 1.5).

- **Ventricular assessment**

Ventricular volumes were assessed using short-axis cine imaging at end-diastole and end-systole applying the Simpson's method. The right ventricular outflow tract was included in right ventricular volumes. For LV mass calculation a combination of semi-automated and manual correction of contours of the endocardial and epicardial borders were used, excluding

the papillary muscles. Contrast angiography and late gadolinium enhancement detection for both left and right ventricles were also performed.

Ethics

The study protocol complies with the Declaration of Helsinki. It was approved by the local institutional Ethics Committee and a written informed consent was obtained from all patients.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences, version 24.0 (SPSS Inc., Chicago, Illinois, USA). A two-tailed p value < 0.05 was considered statistically significant. Continuous data are expressed as mean ± standard deviation (SD) or as median (range), according to the normality distribution of the variable. Categorical variables are summarized as frequency and percentage. The normality of the data was verified with histograms and using the Kolmogorov-Smirnov or Shapiro-Wilk test as suited. To compare continuous variables in TTE study between patients and controls, a paired Student's t-test or a Mann-Whitney U test was performed as suited. In the CMR study differences between groups were compared with Fisher's exact test and unpaired Student's t-test for categorical and continuous variables, respectively. The intra-observer and inter-observer variability were evaluated in 15 and 18 randomly selected cases for TTE and CMR studies, respectively. A Bland–Altman analysis was used to determine the bias (mean of the difference) with 95% limits of agreement. The Pearson's correlation coefficient was estimated to analyse possible associations between continuous variables. Variables associated with predefined Ao dilatation were assessed in univariate and multivariate logistic regression models.

RESULTS 5

5.1. Characterization of the total cohort

5.1. Characterization of the total cohort

We included prospectively 126 pts and 63 sex- and age-matched healthy controls. From the initial cohort we excluded 21 pts: 3 pts had associated heart disease (1 Ao valve stenosis, 2 Ao mechanical prosthesis), 13 cases with genetic syndromes (11 Down and 2 DiGeorge syndrome), 5 pts due to pregnancy. Additionally, we excluded in our CMR study 26 patients without a CMR available for analysis, due either to technical reasons (11 cases) or to claustrophobia and contraindications (7 and 8 cases, respectively).

Study population demographic and echocardiographic data are listed in Table 1. The patient cohort (mean age 30±9 years; 52% males) had a mean follow-up since TOF repair of 23±7 years. The majority of TOF pts were asymptomatic (91%). A right Ao arch was present in 29 pts. A previous systemic-to-pulmonary shunt was done in 58 cases, with a median interval of 3 (1-22) years. The shunt-to-repair time interval was ≥ 5 years in 12 pts and 10 years in 2 pts. Surgical repair was done in adulthood (age ≥ 18 years) in 12 pts. A transannular patch was used for repair in 57 pts. TOF pts were normotensive, with normal pulse pressure, along with normal LV mass index, LV stroke volume index and a preserved LV ejection fraction. All aortic thoracic segments analysed were significantly bigger in TOF pts. The AAo diameter could be measured in 121 pts and it was larger compared to normal controls (33.8±4.8 vs 26.1±3.1 mm, $p < 0.01$), with effacement of the STJ in 53 cases. AAo was larger than the SoV in (48/121) 40% of TOF pts. The prevalence of Ao dilatation at the SoV and AAo (AoZ and AAoZ > +2) was 29% and 24%, respectively, with a maximal absolute SoV ≥ 45 mm in 5 cases and AAo ≥ 45 mm in 4 cases. Compared to controls TOF pts had a bigger AoZ and AAoZ, lower AAo strain (6.4 (0.0-61.5) vs 15.2 (0.0-45.0) %, $p < 0.01$) and higher AAo stiffness index (7.3 (0.8-23.6) vs 3.1 (0.9-14.1), $p < 0.01$).

Table 1 Demographic and echocardiographic data of the TTE study population.

	TOF (n = 126)	Controls (n = 63)	P value
Age (years)	30.2±9.2	31.4±10.1	0.42
Gender (male), n (%)	66 (52.4)	33 (52.4)	1.00
Body surface area (m^2)	1.7±0.2	1.7±0.2	0.22
Systemic arterial haemodynamics			
Systolic blood pressure (mmHg)	117.5±11.8	115.8±10.1	0.36
Diastolic blood pressure (mmHg)	70.7±8.8	70.0±8.7	0.65
Pulse pressure (mmHg)	46.8±8.0	45.8±6.3	0.38
Arterial stiffness (mmHg/mL)*	2.0±0.6	1.9±0.5	0.33
SAC (mL/m^2/mmHg)*	0.7±0.2	0.7±0.2	0.73
Aortic measurements			
Sinuses of Valsalva diameter (mm)	34.0±4.7	28.0±3.2	<0.01
Sinuses of Valsalva index (mm/m^2)	19.9±2.3	16.2±2.1	<0.01
Sinuses of Valsalva z-score	1.4±1.2	-0.6±1.2	<0.01
Sinotubular junction diameter (mm)	30.7±4.2	23.8±3.1	<0.01
Ascending aorta diameter (mm)‡	33.8±4.8	26.1±3.1	<0.01
Ascending aorta index (mm/m^2)‡	19.9±2.6	15.0±2.1	<0.01
Ascending aorta z-score‡	1.2±1.1	-0.7±0.7	<0.01
LV study			
LV mass index (g/m^2)	79.8±20.7	78.9±15.2	0.74
LV mass/volume ratio (g/mL)	1.6±0.5	1.5±0.4	0.14
LVEDV index (mL/m^2)	51.2±12.3	54.1±10.7	0.12
LVESV index (mL/m^2)*	18.9±6.3	18.9±6.2	0.99
LV stroke volume index (mL/m^2)*	33.4±8.6	33.8±7.8	0.79

LV ejection fraction (%)*	64.1±7.0	64.5±6.4	0.71
E/E' ratio	5.5±1.9	4.4±0.9	<0.01
Aortic elastic properties			
Aortic strain (%)*	6.4 (0.0-61.5)	15.2 (0.0-45.0)	<0.01
Aortic distensibility ($KPa^{-1}10^{-3}$)*	1.3 (0.0-14.0)	3.4 (0.0-12.5)	<0.01
Aortic stiffness index*	7.3 (0.8-23.6)	3.1 (0.9-14.1)	<0.01

Data are expressed as mean ± standard deviation (SD) or median (range). Categorical variables are summarized as frequency and percentage. Aortic diameters are measured in mm. LV left ventricular; LVEDV left ventricular end-diastolic volume; LVESV left ventricular end-systolic volume; SAC systemic arterial compliance; TOF tetralogy of Fallot; TTE transthoracic echocardiography. (*) calculated in 110 pts; (‡) measured in 121 pts.

Comparison between TOF pts according to AAo z-score are shown in Table 2. As expected, pts with AAo dilatation (AAo z-score > +2) had a significant higher BSA, but they had bigger LV mass and volumes even after indexing for BSA. Importantly, pts with AAo dilatation had a later TOF repair, with a similar median palliative shunt-to-repair time interval. Pts without AAo dilatation had an early repair but with a significantly higher percentage of transannular patch for surgical repair.

Table 2 Comparison between TOF patients according to AAo z-score.

	AAo z-score ≤ +2 (n = 92)	**AAo z-score > +2 (n = 29)**	**P value**
Age (years)	28.9±8.0	34.9±11.7	0.01
Gender (male), n (%)	45 (48.9)	19 (65.5)	0.12
Body surface area (m^2)	1.68±0.2	1.82±0.2	<0.01
Right aortic arch, n (%)	20 (21.7)	9 (31.0)	0.31
Transannular patch, n (%)	47 (51.1)	7 (24.1)	0.02

Previous palliative shunt, n (%)	46 (50.0)	9 (31.0)	0.07
Age at repair (years)	5 (2-39)	7 (2-49)	0.03
Shunt-to-repair time interval	3 (1-22)	3 (1-11)	NS
Follow-up since repair	23.3±5.4	23.6±10.0	0.87
Aortic regurgitation grade III-IV, n (%)	0 (0.0)	2 (6.9)	0.06
Systemic hypertension, n (%)	5 (5.4)	3 (10.3)	0.40
Systemic arterial haemodynamics			
Systolic blood pressure (mmHg)	117.0±12.0	119.6±11.3	0.32
Diastolic blood pressure (mmHg)	69.9±8.6	72.6±10.0	0.16
Pulse pressure (mmHg)	47.1±8.0	46.7±8.1	0.82
Arterial stiffness (mmHg/mL)*	2.0 (1.1-3.5)	1.7 (0.9-2.8)	NS
SAC (mL/m^2/mmHg)*	0.7 (0.3-1.4)	0.7 (0.4-1.5)	NS
Aortic measurements			
Sinuses of Valsalva diameter (mm)	32.6±4.0	38.6±4.1	<0.01
Sinuses of Valsalva index (mm/m^2)	19.6±2.4	21.3±1.6	<0.01
Sinuses of Valsalva z-score	1.2±1.2	2.2±0.7	<0.01
Sinotubular junction diameter (mm)	30.0±3.7	34.6±5.2	<0.01
Ascending aorta diameter (mm)	31.8±3.0	40.2±3.3	<0.01
Ascending aorta index (mm/m^2)	19.1±2.4	22.2±1.6	<0.01
Ascending aorta z-score	0.7±0.7	2.6±0.6	<0.01
LV study			
LV mass index (g/m^2)	76.9±18.6	90.4±23.7	<0.01
LV mass/volume ratio (g/mL)	1.6±0.5	1.6±0.4	0.92
LVEDV index (mL/m^2)	50.0±12.7	55.7±10.6	0.04
LVESV index (mL/m^2)*	18.3±6.1	21.3±6.5	0.04
LV stroke volume index (mL/m^2)*	32.9±8.3	35.0±9.6	0.29

LV ejection fraction (%)*	64.3±6.9	62.2±6.5	0.18
Aortic elastic properties			
Aortic strain (%)*	6.9 (0.0-40.0)	5.0 (0.0-61.5)	NS
Aortic distensibility ($KPa^{-1}10^{-3}$)*	1.4 (0.0-8.9)	1.0 (0.0-14.0)	NS
Aortic stiffness index*	7.2 (1.2-23.2)	9.9 (0.8-23.6)	NS

Data are expressed as mean ± standard deviation (SD) or median (range). Categorical variables are summarized as frequency and percentage. Aortic diameters are measured in mm. AAo ascending aorta; LV left ventricular; LVEDV left ventricular end-diastolic volume; LVESV left ventricular end-systolic volume; NS nonsignificant; SAC systemic arterial compliance; TOF tetralogy of Fallot. (*) calculated in 106 pts.

Although modest there was a significant positive correlation between AAoZ with SAC (Pearson's correlation (r) = 0.24, p = 0.01) and a negative correlation with arterial stiffness (r = -0.27, p = 0.008) but not with AAo strain or stiffness index. Also, there was a modest but significant correlation between AAoZ and LV mass index (r = 0.29, p = 0.001) and SVI (r = 0.28, p = 0.004) (Figure 1).

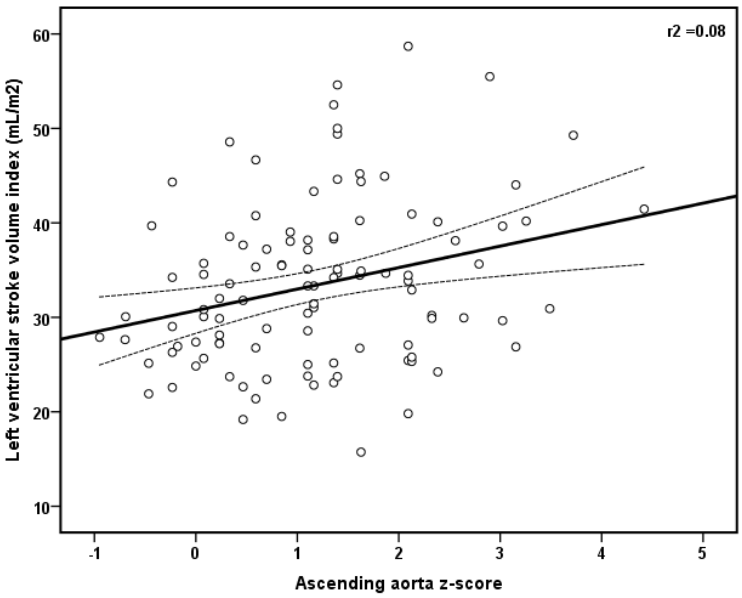


Figure 1. Grapfic representation of correlation between AAo z-score and left ventricular stroke volume index in TOF pts (Pearson's correlation = 0.28, p = 0. 004).

By multivariate analysis (Tables 3 and 4), male gender was strongly associated with SoV dilatation (odds ratio (OR) 6.3, 95% confidence interval (CI) 1.5-26.3, P=0.01), but not with AAo dilatation. Instead, AAo/SoV ratio > 1 showed the highest link with AAo dilatation (OR 5.3, 95% CI 1.3-20.9, P=0.02).

Table 3 Logistic regression by SoV dilatation (SoV z-score > +2).

	Univariate analysis		Multivariate analysis	
	OR	**P value**	**OR**	**P value**
Age (years)	1.03	0.18	0.98	0.57
Gender (male)	2.07	0.07	6.27	**0.01**
Right aortic arch	0.56	0.25		
Previous palliative shunt	0.53	0.12	0.71	0.62
Transannular patch	0.49	0.08	0.36	0.13
Time to surgical repair (years)	1.02	0.43		
Time since repair (years)	1.00	0.91		
AAo z-score	3.38	<0.01		
STJ effacement	1.14	0.75		
AAo/SoV ratio > 1	0.51	0.12	0.16	**0.01**
LV mass index (g/m^2)	1.03	0.01	1.05	**0.01**
LV mass/volume ratio (g/mL)	1.08	0.86		
LVEDV index (mL/m^2)	1.05	<0.01		
LVESV index (mL/m^2)	1.06	0.08		
LV stroke volume index (mL/m^2)	1.07	0.01	1.17	0.07
LV ejection fraction (%)	1.00	0.94		
Systolic arterial pressure (mmHg)	1.01	0.54		
Diastolic arterial pressure (mmHg)	1.03	0.22	1.04	0.30

Pulse pressure (mmHg)	1.00	0.58		
Arterial stiffness (mmHg/mL)	0.36	0.02	4.08	0.34
SAC (mL/m^2/mmHg)	9.62	0.02	0.55	0.83
Ao strain (%)	1.00	0.66		
Ao distensibility (KPa^{-1}10^{-3})	0.00	0.63		
Ao stiffness index	1.04	0.32		

Ao aortic; AAo ascending aorta; LV left ventricular; LVEDV left ventricular end-diastolic volume; LVESV left ventricular end-systolic volume; OR odds ratio; SAC systemic arterial compliance; SoV sinuses of Valsalva; STJ sinotubular junction; TOF tetralogy of Fallot.

Table 4 Logistic regression by AAo dilatation (AAo z-score > +2).

	Univariate analysis		**Multivariate analysis**	
	OR	**P value**	**OR**	**P value**
Age (years)	1.07	<0.01	1.00	0.98
Gender (male)	1.98	0.12	0.75	0.66
Right aortic arch	1.62	0.31		
Previous palliative shunt	0.45	0.08	1.02	0.98
Transannular patch	0.33	0.02	0.19	**0.03**
Time to surgical repair (years)	1.06	0.03	1.03	0.53
Time since repair (years)	1.01	0.82		
STJ effacement	3.24	<0.01	4.67	**0.03**
AAo/SoV ratio > 1	4.13	<0.01	5.28	**0.02**
LV mass index (g/m^2)	1.03	<0.01	1.03	0.14
LV mass/volume ratio (g/mL)	1.05	0.92		
LVEDV index (mL/m^2)	1.04	0.04	0.99	0.83

LVESV index (mL/m^2)	1.08	0.05	1.02	0.76
LV stroke volume index (mL/m^2)	1.03	0.28		
Systolic arterial pressure (mmHg)	1.02	0.31		
Diastolic arterial pressure (mmHg)	1.04	0.16	1.10	**0.03**
Pulse pressure (mmHg)	0.99	0.82		
Arterial stiffness (mmHg/mL)	0.54	0.16	0.89	0.91
SAC (mL/m^2/mmHg)	4.56	0.12	5.92	0.46
Ao strain (%)	1.00	0.90		
Ao distensibility (KPa^{-1}10^{-3})	7.65	0.82		
Ao stiffness index	1.02	0.56		

Ao aortic; AAo ascending aorta; LV left ventricular; LVEDV left ventricular end-diastolic volume; LVESV left ventricular end-systolic volume; OR odds ratio; SAC systemic arterial compliance; SoV sinuses of Valsalva; STJ sinotubular junction; TOF tetralogy of Fallot.

In 78 pts (mean age of 31±10 years; 56% females) a CMR study was available for analysis. The mean follow-up since TOF repair was 23±7 years. The majority (90%) of pts was asymptomatic, 7 were in functional class II and only 1 was in class III of the New York Heart Association. A right aortic arch was present in 22 patients. In 39 (50%) a systemic-to-pulmonary shunt was done prior to complete repair, with a median time interval of 3 (1-22) years. Thirty-eight pts had a transannular patch for TOF repair. Five pts had systemic hypertension (3 pts in group 2) but systolic blood pressure and pulse pressure were within normal range during study protocol and follow-up. Twenty-five pts were on medication: 6 on angiotensin converting enzyme inhibitor, 10 on beta blocker, and 9 on antiarrhythmics (4 on amiodarone, 2 on digoxin, 2 on propafenone and 1 on sotalol). The LV stroke volume index and LV ejection fraction were within normal range. The prevalence of AAo dilatation was 11.5%, with a maximal absolute AAo diameter ≥ 40 in 6 cases and ≥ 50 mm in 2 cases, but none above 55 mm. The AAo was larger than the sinuses of Valsalva (SoV) in 12.8%.

The study population demographic, haemodynamic and CMR data according to the presence or absence of AAo dilatation are listed in Tables 5 and 6. Pts with AAo dilatation were older,

predominantly males, with a later TOF repair and bigger LV mass and volumes. By multivariate analysis (Table 7) LV mass index was the only independent factor associated with AAo dilatation (odds ratio 1.10, 95% confidence interval 1.01-1.20, p = 0.03). A cut-off value for LV mass index ≥ 57.9 g/m^2 had 89% sensitivity and 71% specificity as predictor of AAo dilatation (Figure 2).

Table 5 Demographic and haemodynamic data of CMR study according to the presence or absence of AAo dilatation.

	Group 1 No AAo dilatation (n = 69)	**Group 2 AAo dilatation (n = 9)**	**P value**
Age (years)	29.8±8.8	39.7±12.9	<0.01
Gender (male), n (%)	26 (37.7)	8 (88.9)	<0.01
Right aortic arch, n (%)	21 (30.4)	1 (11.1)	0.23
Previous palliative shunt, n (%)	35 (50.7)	4 (44.4)	1.0
Transannular patch, n (%)	35 (50.7)	3 (33.3)	0.48
Time interval shunt to repair (years)	3 (1-22)	3 (2-11)	0.88
Age at TOF repair (years)	5 (2-49)	7 (4-21)	0.02
Follow-up time since TOF repair (years)	22.9±6.7	24.7±8.5	0.48
Systemic arterial haemodynamics			
Systolic blood pressure (mmHg)	115.8±12.2	117.7±11.5	0.65
Pulse pressure (mmHg)	46.6±7.6	47.4±9.4	0.77
SAC (mL/mmHg/m^2)	1.0±0.2	1.1±0.2	0.18

Data are expressed as mean ± standard deviation or median (range). Categorical variables are summarized as frequency and percentage. Aortic diameters are measured in mm. AAo ascending aorta; CMR cardiovascular magnetic resonance; SAC systemic arterial compliance; TOF tetralogy of Fallot.

Table 6 CMR data according to the presence or absence of AAo dilatation.

	Group 1 No AAo dilatation (n = 69)	Group 2 AAo dilatation (n = 9)	P value
Aortic measurements			
Sinuses of Valsalva diameter (mm)	33.6±4.6	43.1±6.5	<0.01
Sinuses of Valsalva index (mm/m^2)	20.1±2.6	23.1±1.9	<0.01
Sinotubular junction diameter (mm)	27.7±3.8	38.3±5.3	<0.01
Sinotubular junction index (mm/m^2)	16.6±2.3	20.7±2.0	<0.01
Ascending aorta diameter (mm)	28.6±4.0	43.2±5.5	<0.01
Ascending aorta index (mm/m^2)	17.1±2.2	23.4±3.4	<0.01
AAo observed-to-expected ratio	0.3±0.5	2.2±0.7	<0.01
AAo/SoV ratio > 1, n (%)	5 (7.2)	5 (55.6)	<0.01
AAo/Pulmonary trunk ratio	1.2±0.3	1.5±0.5	0.10
Left ventricular study			
LV mass index (g/m^2)	53.3±11.2	71.9±12.8	<0.01
LV mass/volume ratio (g/mL)	0.7±0.1	0.8±0.1	0.05
LVEDV index (mL/m^2)	76.8±14.8	92.1±15.9	<0.01
LVESV index (mL/m^2)	32.2±9.8	41.0±12.4	0.02
LV stroke volume index (mL/m^2)	44.6±8.1	51.1±10.0	0.03
LV ejection fraction (%)	58.5±6.7	56.1±8.9	0.10
Aortic regurgitation III or IV, n (%)	3 (4.3)	1 (11.1)	0.24
Right ventricular study			
RVEDV index (mL/m^2)	129.5±41.5	152.9±44.1	0.12
RVESV index (mL/m^2)	47.4±19.7	52.4±23.2	0.48

RV stroke volume index (mL/m^2)	61.0±17.0	63.0±10.4	0.74
RV ejection fraction (%)	47.9±5.9	42.8±7.8	0.02
RVEDV/LVEDV ratio	1.7±0.6	1.7±0.5	0.81
Pulmonary regurgitation fraction (%)	31.4±17.2	39.4±17.4	0.22

Data are expressed as mean ± standard deviation or median (range). Categorical variables are summarized as frequency and percentage. Aortic diameters are measured in mm. AAo ascending aorta; CMR cardiovascular magnetic resonance; LV left ventricular; LVEDV left ventricular end-diastolic volume; LVESV left ventricular end-systolic volume; RV right ventricular; RVEDV right ventricular end-diastolic volume; RVESV right ventricular end-systolic volume; SoV sinuses of Valsalva; TOF tetralogy of Fallot.

Table 7 Logistic regression by AAo dilatation.

	Univariate analysis		**Multivariate analysis**	
	OR	**P value**	**OR**	**P value**
Age (per year)	1.10	<0.01	1.07	0.09
Gender (male)	13.23	0.02	3.54	0.31
Right aortic arch	0.29	0.25		
Previous palliative shunt	0.78	0.72		
Transannular patch	0.55	0.44		
Time interval shunt to repair (per year)	1.05	0.67		
Age at TOF repair (per year)	1.03	0.34		
Time since TOF repair (per year)	1.04	0.48		
Systolic arterial pressure (mmHg)	1.01	0.65		
Diastolic arterial pressure (mmHg)	1.01	0.72		
Pulse pressure (mmHg)	1.01	0.77		

SAC (mL/mmHg/m^2)	7.00	0.19		
LV mass index (g/m^2)	**1.13**	**<0.01**	**1.10**	**0.03**
LV stroke volume index (mL/m^2)	1.09	0.04	0.98	0.80
RVEDV/LVEDV ratio	0.86	0.81		

AAo ascending aorta; LV left ventricular; LVEDV left ventricular end-diastolic volume; OR *odds ratio;* RVEDV right ventricular end-diastolic volume; SAC systemic arterial compliance; TOF tetralogy of Fallot.

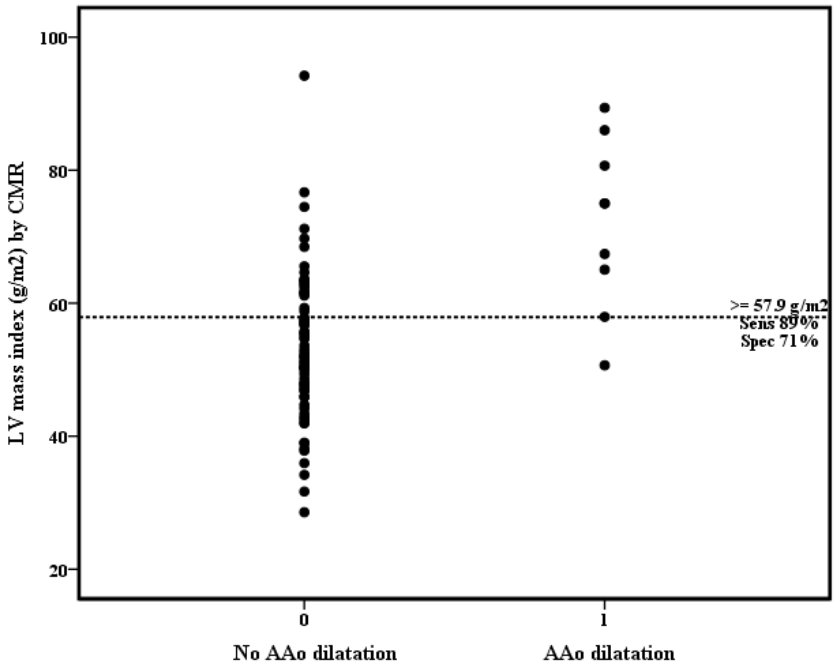


Figure 2. A dot diagram for LV mass index according to the presence or absence of AAo dilatation. The horizontal dotted line represents the cut-off point for the best diagnostic accuracy (cut-off ≥ 57.9 g/m^2 with a sensitivity of 88.9% and a specificity of 71.0%).

5.2. An important tool before tetralogy of Fallot reoperation

Case number 13-07: An important tool before tetralogy of Fallot reoperation

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We report a patient presenting with a massive aortic aneurysm, two decades after TOF repair, in whom the preoperative CMR assessed the risk of a conventional sternotomy for the planned Bentall operation. The two-step surgical approach, first with a right anterolateral thoracotomy and then a repeat-sternotomy, for the aortic root replacement contributed to the surgical success, minimizing the risk of a potentially fatal iatrogenic aortic rupture.

Clinical history

A 35-year-old male was followed at our Adult Congenital Heart Disease (ACHD) Clinic with the diagnosis of TOF.

In 1978, by the age of two, he had the diagnosis of TOF with a right aortic arch and underwent a palliative left Blalock-Taussig aortopulmonary shunt (1980). In 1984 a "TOF repair" was performed.

The patient had an uneventful development until adulthood except for a muscular weakness in the legs with abnormal gait which prompted a neurologic evaluation. The electromyography was normal and the screening of the repeat expansions on the DMPK gene excluded Steinert's disease. The patient was discharged from the Neurology Department without any further evaluation.

The EKG (Figure 1) showed regular sinus rhythm with a first-degree atrioventricular block and an incomplete right bundle branch block (maximal QRS duration 105 msec).

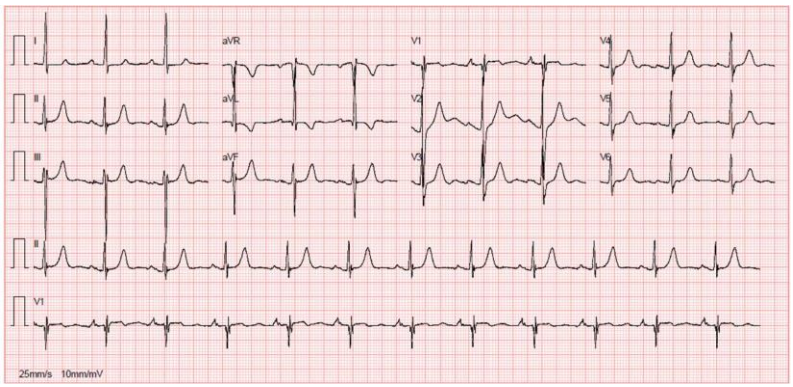


Figure 1: Patient's EKG showing sinus rhythm with a first degree atrioventricular block and an incomplete right bundle branch block.

The transthoracic echocardiogram (TTE) showed a right aortic arch; right sided cardiac chambers were moderately enlarged; dilated main pulmonary artery (pulmonary annulus 31 mm); pulmonary maximal instantaneous gradient

45 mmHg and a grade III-IV/IV pulmonary regurgitation. There was no residual intracardiac shunt. Normal bi-ventricular systolic function was present.

On serial echocardiographic evaluation, a progressive aortic root and ascending aorta dilatation along with aortic regurgitation was noted from 2002 to 2007 when a routine TTE reported an aortic root diameter of 69 mm and aortic regurgitation grade III/IV.

A magnetic resonance angiography (MRA) confirmed a massive aneurysm of the aortic root and ascending aorta (maximal diameter 67 mm) with effacement of the sinotubular ridge, extending for 7 cm longitudinally, with preserved dimensions of the aortic arch and descending aorta (Figure 2).

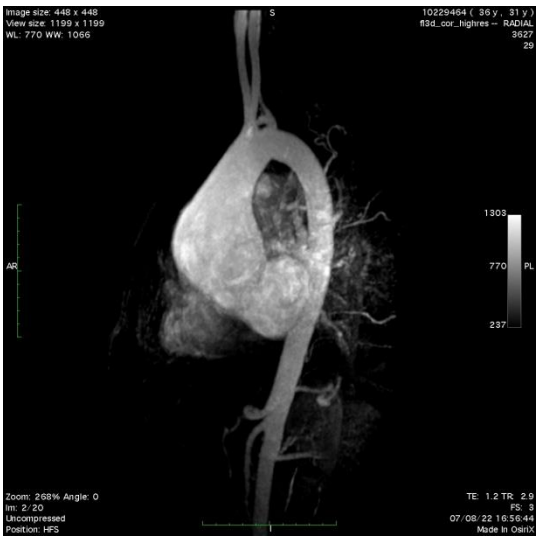


Figure 2: Preoperative 3D reconstruction MRA of the aorta showing the massive aortic root and ascending aorta aneurysm, in a patient with a previous tetralogy of Fallot repair.

No signs of dissection were found. Also, there was impressive adhesion of the anterior aortic wall just beneath the sternum, increasing the risk of a catastrophic bleeding at the time of the sternotomy for the aortic root replacement (Figures 3 and 4).

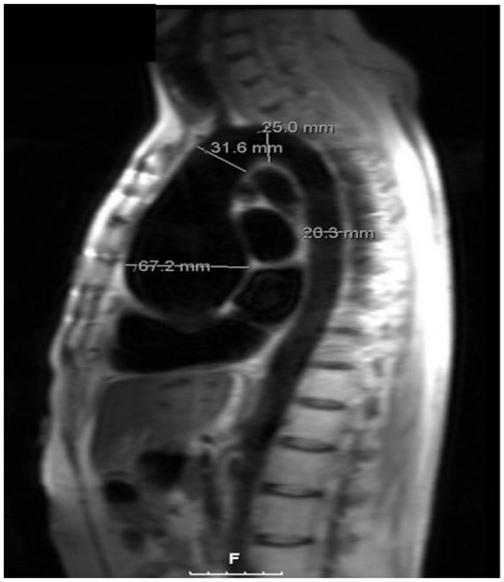


Figure 3: A turbo spin echo sequence of a preoperative magnetic resonance oblique sagittal aorta plane, showing the adhesion of the anterior aortic wall just beneath the sternum.

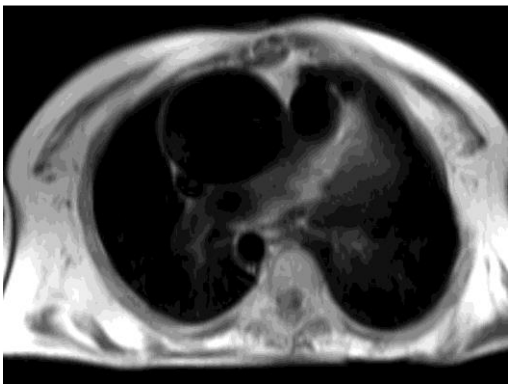


Figure 4: A transverse aorta plane showing the impressive adhesion of the anterior aortic wall to the sternum.

No history of thoracic trauma or chest pain were found. The patient's blood pressure was always within the normal range.

The patient was sent for cardiac surgery and a Bentall operation was planned. Due to the preoperative CMR findings the surgical approach changed to a two-step procedure, first an anterolateral thoracotomy was performed in order to dissect the scar tissue from the previous sternotomy and carefully separate the anterior wall of the ascending aorta from the sternum adhesions, than a conventional repeat-sternotomy was performed without any aortic wall damage. The aortic root was replaced, and a mechanical prosthesis was implanted in the aortic position. Also, the pulmonary valve was replaced by a St Jude 27 mechanical prosthesis and a De Vega tricuspid annuloplasty was done on aorto-bicaval cardiopulmonary bypass. The postoperative recovery was uneventful, and the patient was discharged on warfarin with an INR 3-3.5 and aspirin 100mg qd.

The postoperative CMR, performed 3 months after surgery, showed normal aortic dimensions, the ascending prosthetic conduit of 35 mm (Bentall operation), main pulmonary diameter 34 mm (Figure 4).

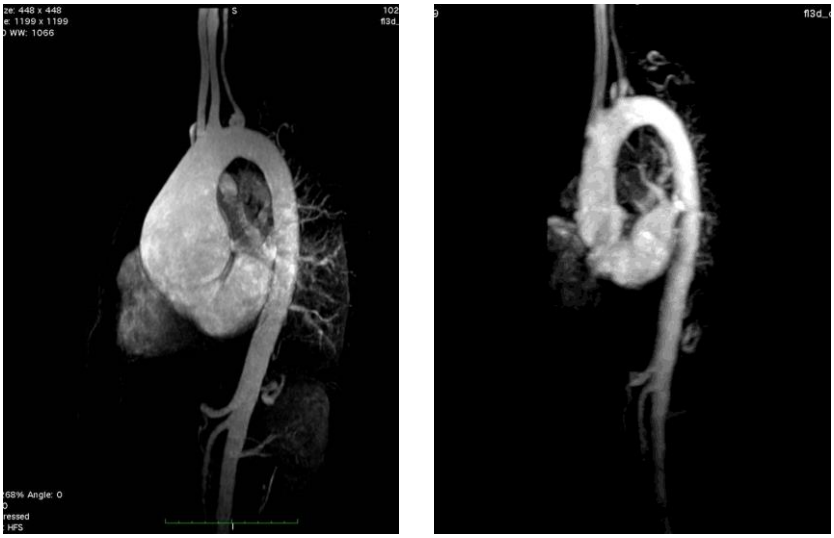


Figure 5: MRA, 3 months after a Bentall operation; preoperative MRA on the left for comparison.

The TTE evaluation, performed 4 months postoperatively, revealed normal diameters of the ascending aorta, aortic arch and descending aorta, mild dilation of the right atrium with normal dimensions of the right ventricle and left cardiac chambers; normal opening of mechanical aortic and pulmonary prosthesis with a maximal instantaneous gradient of 15 and 10 mmHg, respectively. No tricuspid regurgitation was found, and a normal bi-ventricular systolic function was present.

The patient is asymptomatic, working full time in a factory and is able to live an almost normal life nevertheless he needs a meticulous follow-up at an expert ACHD centre and a lifelong chronic oral anticoagulation.

Discussion and conclusion

Cardiac surgery improvements and the long-term good results of tetralogy of Fallot (TOF) repair allow adult survival [1] but residual lesions exist and evolve, demanding a meticulous clinical and imaging follow-up. Progressive dilatation of the aortic root after repaired TOF is a recognized complication first described by Capelli et al [2]. It has been postulated that the long-standing left-sided volume overload during fetal life and before complete repair, due to the association of right-outflow obstruction and right-to-left shunt, can be responsible for the progressive dilatation of the aorta. Niwa et al [3] reported that male sex, pulmonary atresia, right aortic arch, and longer time interval from palliative aortopulmonary shunts to repair are possible predisposing factors for aortic dilatation. Possibly intrinsic histological abnormalities in the aortic root and ascending aortic wall, present since infancy in TOF patients, can contribute to this progressive dilatation [4].

Imaging follow-up of TOF patients include chest X-ray, Doppler echocardiography, computerized tomography (CT) scan and cardiovascular magnetic resonance imaging (CMR). However, in patients with associated thoracic deformities and previous cardiac surgeries the ability to obtain an optimal acoustic window for Doppler echocardiography screening is far from perfect and the contribution of the CT scan and CMR in the setting of congenital heart disease imaging has increased rapidly in the past decade. CMR has been shown to be very accurate

in the diagnosis of thoracic aortic disease [5], including in TOF patients [6], assessing the entire aorta without exposing the patient to either radiation or iodinated contrast despite the relatively long scan duration. Three-dimensional reconstruction of the aorta by contrast enhanced magnetic resonance used as part of the examination of the aorta may, however, be a problem in patients with renal insufficiency or during pregnancy. Other potential difficulties in CMR are patients with claustrophobia or non-MRI compatible pacemaker or cardiac defibrillator.

Although patients with repaired TOF commonly have problems with residual pulmonary valve lesions and right ventricular dilatation and systolic dysfunction, the evaluation of the aorta in this subgroup of patients should not be neglected. This case report emphasizes the importance of the aortic root imaging in the follow-up of TOF patients and clearly shows the importance of CMR in the preoperative evaluation of repaired TOF. We report a patient presenting with a massive aortic aneurysm long-term after tetralogy of Fallot repair in whom the preoperative CMR showed impressive adhesion of the anterior aortic wall just beneath the sternum.

The preoperative CMR findings helped the cardiac surgeon in order to plan a different surgical approach, preventing a potential fatal iatrogenic aortic rupture while performing a conventional sternotomy, contributing to the surgical success and the patient survival.

Some case reports of aortic aneurysm and dissection late after repair of TOF [7-9] reinforce this concept and advise regular screening of the aorta in order to promptly diagnose and ultimately to prevent a potential cause of sudden death in this subset of TOF patients.

Perspective

CMR is an important tool for the assessment of congenital heart disease, including the imaging of the aorta in this subset of patients. Moreover, the preoperative evaluation of patients with previous cardiac surgeries requires a meticulous imaging follow-up. CMR provides important imaging findings that can help the cardiac surgeon while facing a reoperation scenario, in order to plan the best surgical approach, minimizing potential perioperative complications. This case report illustrates the role of CMR in this setting.

List of abbreviations

ACHD = adult congenital heart disease; CMR = cardiovascular magnetic resonance; CT = computerized tomography; MRA = magnetic resonance angiography; TOF = tetralogy of Fallot; TTE = transthoracic echocardiogram

Competing interests

None regarding the contents of this manuscript.

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5.3. Aortic dilatation after tetralogy of Fallot repair: a ghost from the past or a problem in the future?

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ORIGINAL ARTICLE

Aortic dilatation after tetralogy of Fallot repair: A ghost from the past or a problem in the future?

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KEYWORDS
Aortic dilatation;
Aortic elasticity;
Tetralogy of Fallot;
Transthoracic echocardiography

Abstract
Introduction and Aims: Intrinsic aortopathy can lead to dilatation late after tetralogy of Fallot (TOF) repair. Its extent and prevalence are not known. We aimed to assess aortic dimensions and elasticity and to find predictors of aortic dilatation.
Methods: A total of 126 adults were prospectively included after TOF repair and compared to 63 gender- and age-matched controls. Transthoracic echocardiography was used to assess aortic diameters at the level of the sinuses of Valsalva and ascending aorta and aortic dilatation was defined as z-score >+2. M-mode parameters of the ascending aorta were used to calculate strain, distensibility and stiffness index.
Results: TOF patients (mean age 30±9 years; 52% male) had a complete repair at a median age of five (2-49) years; mean follow-up time since repair was 23±7 years. The prevalence of aortic dilatation at the sinuses of Valsalva and ascending aorta was 29% and 24%, respectively. Compared to controls, TOF patients had a higher ascending aorta z-score, lower strain (6.4% [0.0-61.5] vs. 15.2% [0.0-45.0], p<0.01) and higher stiffness index (7.3 [0.8-23.6] vs. 3.1 [0.9-14.1], p<0.01). On multivariate analysis male gender was strongly associated with sinuses of Valsalva dilatation (odds ratio 6.3, 95% confidence interval 1.5-26.3, p=0.01).
Conclusions: The prevalence of aortic dilatation late after TOF repair is significant, with a larger and stiffer ascending aorta. Male gender appears to influence aortic root dilatation. This aortopathy requires careful follow-up in order to prevent future complications.
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PALAVRAS-CHAVE
Dilatação aórtica;
Elasticidade aórtica;
Tetralogia de Fallot;
Ecocardiografia transtorácica

Dilatação da aorta na tetralogia de Fallot operada: um fantasma do passado ou um problema no futuro?

Resumo
Introdução e objetivos: Uma possível aortopatia intrínseca poderá condicionar dilatação tardia da aorta na tetralogia de Fallot operada. A sua prevalência e extensão não estão definidas. Pretendemos avaliar as dimensões e a elasticidade da aorta e encontrar preditores da dilatação aórtica.
Métodos: Incluímos prospetivamente 126 adultos operados a tetralogia de Fallot e comparamos com 63 controlos. Avaliamos por ecocardiografia transtorácica os diâmetros dos seios de Valsalva e da aorta ascendente e definimos dilatação aórtica para z-score > +2. Parâmetros modo M da aorta ascendente foram usados para calcular *strain*, distensibilidade e índice de rigidez.
Resultados: Doentes com tetralogia de Fallot (idade média 30 ± 9 anos; 52% homens) foram operados com uma idade mediana de 5 (2-49) anos; tempo médio de seguimento desde a cirurgia 23 ± 7 anos. A prevalência de dilatação dos seios de Valsalva e da aorta ascendente foi 29% e 24%, respetivamente. Comparado aos controlos, os doentes com tetralogia de Fallot apresentaram maior z-score da aorta ascendente, menor *strain* (6,4 [0,0-61,5] *versus* 15,2 [0,0-45,0]%; p < 0,01) e maior índice de rigidez (7,3 [0,8-23,6] *versus* 3,1 [0,9-14,1]; p < 0,01). Na análise multivariada o sexo masculino associou-se significativamente à dilatação dos seios de Valsalva (*odds ratio* 6,3, intervalo de confiança de 95% 1,5-26,3; p = 0,01).
Conclusões: Na tetralogia de Fallot operada há uma prevalência significativa de dilatação tardia da aorta, com a aorta ascendente maior e mais rígida. O sexo masculino parece influenciar a dilatação da raiz da aorta. Esta aortopatia requer um seguimento cuidadoso para evitar complicações futuras.
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List of abbreviations

2D	two-dimensional
AAo	ascending aorta
AAoZ	ascending aorta z-score
Ad	aortic diastolic diameter
Ao	aortic
AoZ	Ao root z-score
As	aortic systolic diameter
BP	blood pressure
BSA	body surface area
CI	confidence interval
D	distensibility
DBP	diastolic blood pressure
GUCH	grown-up congenital heart
LV	left ventricular
LVEF	left ventricular ejection fraction
OR	odds ratio
PP	pulse pressure
SAC	systemic arterial compliance
SBP	systolic blood pressure
SD	standard deviation
SoV	sinuses of Valsalva
STJ	sinotubular junction
SV	stroke volume
SVI	stroke volume index
TOF	tetralogy of Fallot
TTE	transthoracic echocardiography

Introduction

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease in which survival into adulthood is common. The guidelines recommend regular long-term follow-up in specialized grown-up congenital heart (GUCH) centers.[1]

Major residual lesions after TOF repair occur at the level of the right ventricular outflow tract, including obstruction or aneurysm, and at the pulmonary valve due to regurgitation or stenosis. In addition, as first described by Capelli et al.,[2] there is an increasing awareness that aortic (Ao) dilatation can develop late after TOF repair. Interestingly, Ao dilatation is a fetal feature of TOF that tends to disappear after early surgical repair[3] without a palliative systemic-to-pulmonary shunt, thus preventing long-standing volume overload on the overriding aorta. Ao dilatation may be a disorder of the past, not reflecting the current surgical era.[4] Nevertheless, for many reasons, including anatomical and technical surgical issues, not all patients will benefit from early repair. Additionally, aortic histological abnormalities present since infancy in TOF, especially in the Ao root and ascending aorta (AAo) vascular wall, can contribute to Ao dilatation.[5,6] This intrinsic aortopathy can lead to Ao dilatation late after TOF repair, but its extent and prevalence are not known. We aimed to assess proximal thoracic aorta dimensions and elasticity by transthoracic echocardiography, in TOF patients and normal controls, and to find possible predictors of Ao dilatation.

Methods

Study population

Inclusion criteria

We prospectively included 126 adults (age ≥18 years) with repaired TOF, without pulmonary atresia or absent pulmonary valve, followed at our GUCH center between March 2011 and December 2013, and 63 gender- and age-matched healthy controls.

Exclusion criteria

We excluded 21 patients: three with associated heart disease (one Ao valve stenosis and two Ao mechanical prosthesis), 13 with genetic syndromes (11 Down syndrome and two DiGeorge syndrome), and five due to pregnancy.

Study protocol

Systemic arterial hemodynamics

Arterial blood pressure (BP) (systolic [SBP] and diastolic [DBP]) was measured twice with a 2-min interval in supine position and averaged, using an automated blood pressure monitor (SureSigns VS2, Philips Medical Systems). We chose to measure BP in the left brachial artery, due to the presence of a previous right Blalock-Taussig shunt in a significant number of cases (49 patients). If there was a palliative left shunt, BP was measured in the right arm (nine cases).

The ratio of stroke volume index (SVI) to pulse pressure (PP) was used as an indirect measure of total systemic arterial compliance (SAC=SVI/PP).[7]

Arterial stiffness was calculated as 0.9×SBP/stroke volume (SV).[8]

M-mode, two-dimensional and Doppler echocardiographic examination

Transthoracic echocardiography (TTE) was performed immediately after BP measurement using a Vivid E7 ultrasound system (GE Healthcare, Milwaukee, WI, USA) with an M4S sector array transducer (1.5-4.3 MHz) and digitally stored. All echocardiographic exams were performed and analyzed by an experienced cardiologist, certified in congenital heart disease echocardiography by the European Association of Cardiovascular Imaging and blinded to patient data.

Aortic assessment

Ao diameters were measured by two-dimensional (2D) TTE at the level of the sinuses of Valsalva (SoV) and sinotubular junction (STJ) and at the proximal AAo, 2-3 cm above the STJ, in parasternal long-axis view perpendicular to the Ao long axis, using the maximum leading edge-to-leading edge diameter method at end-diastole, and were indexed to body surface area (BSA) according to the DuBois formula.[9]

The Ao sinus z-score (AoZ) was obtained using the standard nomograms for Ao root size in healthy adults, adapted from Roman et al.[10] The AAo z-score (AAoZ) was based on reference values and equations from Campens et al.[11] Ao dilatation was defined as a z-score >+2, for both the SoV and AAo.

Elastic properties of the ascending aorta

AAo distensibility (D) was calculated as 2(As-Ad)/[Ad(SBP-DBP)] in $KPa^{-1} \times 10^3$, and M-mode derived stiffness index (β1) was calculated as ln(SBP/DBP)/(As-Ad)/Ad.

As and Ad were obtained using the M-mode inner systolic and diastolic AAo diameters in short-axis view, at the level of the pulmonary artery bifurcation, with Ad obtained at the peak of the R wave of the simultaneously recorded electrocardiogram, while As was measured at maximum anterior AAo wall motion.[12]

Left ventricular assessment

Left ventricular (LV) end-diastolic and end-systolic inner diameters, posterior wall and septal thickness were measured by 2D-TTE in parasternal long-axis view.

LV mass was calculated by the corrected formula of the American Society of Echocardiography. Left venricular ejection fraction (LVEF) was calculated using the modified Simpson's rule.[13] SV was obtained by subtracting end-systolic volume from end-diastolic volume, using 2D volumetric measurements for the LVEF calculation. LV measurements were indexed to BSA according to the DuBois formula.[9] Pulsed-wave tissue Doppler was used to estimate LV filling pressure by calculating the E/lateral e' ratio.[14] Septal e' was not used because in TOF, following patch closure of the ventricular septal defect, septal e' is underestimated and is therefore not helpful in determining diastolic function.

Ethics

The study protocol complies with the Declaration of Helsinki. It was approved by the local institutional ethics committee and written informed consent was obtained from all patients.

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics, version 24.0 (IBM SPSS Inc., Chicago, IL, USA). A two-tailed p-value <0.05 was considered statistically significant. Continuous data are expressed as mean ± standard deviation (SD) or as median (range), according to the normality of the variable's distribution. Categorical variables are summarized as frequency and percentage. The normality of the data was determined with histograms and using the Kolmogorov-Smirnov or Shapiro-Wilk test, as appropriate. A paired Student's t test or a Mann-Whitney U test, as appropriate, was performed to compare continuous variables between patients and controls. Intra- and interobserver variability were assessed in 18 randomly selected cases. Bland-Altman analysis was used to determine bias (mean of the difference) with 95% limits of agreement. Pearson's correlation coefficient was used to analyze possible associations between the AAo z-score and a number of continuous variables. Variables associated with Ao dilatation (SoV and AAo z-score >+2) were assessed in univariate and multivariate logistic regression models.

Table 1 Demographic and echocardiographic characteristics of the study population.

	TOF (n=126)	Controls (n=63)	p
Age, years	30.2±9.2	31.4±10.1	0.42
Male gender, n (%)	66 (52.4)	33 (52.4)	1.00
Body surface area, m^2	1.7±0.2	1.7±0.2	0.22
Systemic arterial hemodynamics			
Systolic blood pressure, mmHg	117.5±11.8	115.8±10.1	0.36
Diastolic blood pressure, mmHg	70.7±8.8	70.0±8.7	0.65
Pulse pressure, mmHg	46.8±8.0	45.8±6.3	0.38
Arterial stiffness, mmHg/ml[a]	2.0±0.6	1.9±0.5	0.33
SAC, $ml/m^2/mmHg$[a]	0.7±0.2	0.7±0.2	0.73
Aortic measurements			
SoV diameter, mm	34.0±4.7	28.0±3.2	<0.01
SoV index, mm/m^2	19.9±2.3	16.2±2.1	<0.01
SoV z-score	1.4±1.2	-0.6±1.2	<0.01
STJ diameter, mm	30.7±4.2	23.8±3.1	<0.01
AAo diameter, mm	33.8±4.8	26.1±3.1	<0.01
AAo index, mm/m^2	19.9±2.6	15.0±2.1	<0.01
AAoZ	1.2±1.1	-0.7±0.7	<0.01
LV study			
LV mass index, g/m^2	79.8±20.7	78.9±15.2	0.74
LV mass/volume ratio, g/ml	1.6±0.5	1.5±0.4	0.14
LVEDV index, ml/m^2	51.2±12.3	54.1±10.7	0.12
LVESV index, ml/m^2[a]	18.9±6.3	18.9±6.2	0.99
LV stroke volume index, ml/m^2[a]	33.4±8.6	33.8±7.8	0.79
LVEF, %[a]	64.1±7.0	64.5±6.4	0.71
E/E' ratio	5.5±1.9	4.4±0.9	<0.01
Aortic elastic properties			
Aortic strain, %[a]	6.4 (0.0-61.5)	15.2 (0.0-45.0)	<0.01
Aortic distensibility, $KPa^{-1}\times10^3$[a]	1.3 (0.0-14.0)	3.4 (0.0-12.5)	<0.01
Aortic stiffness index[a]	7.3 (0.8-23.6)	3.1 (0.9-14.1)	<0.01

Data are expressed as mean ± standard deviation (SD) or median (range). Categorical variables are summarized as frequency and percentage. Aortic diameters are measured in mm.
AAo: ascending aorta; AAoZ: ascending aorta z-score; LV: left ventricular; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; SAC: systemic arterial compliance; SoV: sinus of Valsalva; STJ: sinotubular junction; TOF: tetralogy of Fallot.
[a] calculated in 110 patients.
[b] measured in 121 patients.

Results

Demographic and echocardiographic characteristics of the study population are shown in Table 1. A total of 126 TOF patients were included (mean age 30±9 years; 52% male), with a mean follow-up since TOF repair of 23±7 years. Most were asymptomatic (91%). A right Ao arch was present in 29 patients. A previous systemic-to-pulmonary shunt had been performed in 58 cases, with a median interval of three (1-22) years. The shunt-to-repair time was ≥5 and ≥10 years in 12 and two patients, respectively. Surgical repair was performed in adulthood (age ≥18 years) in 12 patients. A transannular patch was used for repair in 57 patients. No differences were found between TOF patients and controls regarding pulse pressure, LV mass index or LV stroke volume index. AAo diameter could be measured in 121 patients; it was larger in TOF patients (33.8±4.8 vs. 26.1±3.1 mm, p<0.01), and the STJ was effaced in 53 cases. AAo was larger than SoV in 40% (48/121) of TOF patients. Compared to controls, TOF patients had higher AoZ and AAoZ, lower AAo strain (6.4% [0.0-61.5] vs. 15.2% [0.0-45.0], p<0.01) and higher AAo stiffness index (7.3 [0.8-23.6] vs. 3.1 [0.9-14.1], p<0.01). Comparison between TOF patients according to AAo z-score is shown in Table 2. The prevalence of Ao dilatation at the SoV and AAo (AoZ and AAoZ >+2) was 29% and 24%, respectively, with a maximum absolute SoV ≥45 mm in five cases and AAo ≥45 mm in four cases. As expected, patients with AAo dilatation (AAo z-score >+2) had a significantly higher BSA, but they had larger LV mass and volumes even after indexing for BSA. Importantly, patients with AAo dilatation had undergone later TOF repair, with a similar median palliative shunt-to-repair time. Patients without AAo dilatation had undergone early repair but the proportion receiving a transannular patch for surgical repair was significantly higher.

There was a significant, albeit modest, positive correlation between AAoZ and SAC (Pearson's correlation [r]=0.24, p=0.01) and a negative correlation with

Table 2 Comparison between tetralogy of Fallot patients according to z-score.

	AAo z-score ≤+2 (n=92)	AAo z-score >+2 (n=29)	p
Age, years	28.9±8.0	34.9±11.7	0.01
Male gender, n (%)	45 (48.9)	19 (65.5)	0.12
Body surface area, m^2	1.68±0.2	1.82±0.2	<0.01
Right aortic arch, n (%)	20 (21.7)	9 (31.0)	0.31
Transannular patch, n (%)	47 (51.1)	7 (24.1)	0.02
Previous palliative shunt, n (%)	46 (50.0)	9 (31.0)	0.07
Age at repair, years	5 (2-39)	7 (2-49)	0.03
Shunt-to-repair time	3 (1-22)	3 (1-11)	NS
Follow-up since repair	23.3±5.4	23.6±10.0	0.87
Aortic regurgitation grade III-IV, n (%)	0 (0.0)	2 (6.9)	0.06
Systemic hypertension, n (%)	5 (5.4)	3 (10.3)	0.40
Systemic arterial hemodynamics			
SBP, mmHg	117.0±12.0	119.6±11.3	0.32
DBP, mmHg	69.9±8.6	72.6±10.0	0.16
Pulse pressure, mmHg	47.1±8.0	46.7±8.1	0.82
Arterial stiffness, mmHg/ml[a]	2.0 (1.1-3.5)	1.7 (0.9-2.8)	NS
SAC, $ml/m^2/mmHg$[a]	0.7 (0.3-1.4)	0.7 (0.4-1.5)	NS
Aortic measurements			
SoV diameter, mm	32.6±4.0	38.6±4.1	<0.01
SoV index, mm/m^2	19.6±2.4	21.3±1.6	<0.01
SoV z-score	1.2±1.2	2.2±0.7	<0.01
STJ diameter, mm	30.0±3.7	34.6±5.2	<0.01
AAo diameter, mm	31.8±3.0	40.2±3.3	<0.01
AAo index, mm/m^2	19.1±2.4	22.2±1.6	<0.01
AAoZ	0.7±0.7	2.6±0.6	<0.01
LV study			
LV mass index, g/m^2	76.9±18.6	90.4±23.7	<0.01
LV mass/volume ratio, g/ml	1.6±0.5	1.6±0.4	0.92
LVEDV index, ml/m^2	50.0±12.7	55.7±10.6	0.04
LVESV index, ml/m^2[a]	18.3±6.1	21.3±6.5	0.04
LV stroke volume index, ml/m^2[a]	32.9±8.3	35.0±9.6	0.29
LVEF, %[a]	64.3±6.9	62.2±6.5	0.18
Aortic elastic properties			
Aortic strain, %[a]	6.9 (0.0-40.0)	5.0 (0.0-61.5)	NS
Aortic distensibility, $KPa^{-1}\times10^3$[a]	1.4 (0.0-8.9)	1.0 (0.0-14.0)	NS
Aortic stiffness index[a]	7.2 (1.2-23.2)	9.9 (0.8-23.6)	NS

Data are expressed as mean ± standard deviation (SD) or median (range). Categorical variables are summarized as frequency and percentage. Aortic diameters are measured in mm.
AAo: ascending aorta; AAoZ: ascending aorta z-score; DBP: diastolic blood pressure; LV: left ventricular; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; SAC: systemic arterial compliance; SBP: systolic blood pressure; SoV: sinus of Valsalva; STJ: sinotubular junction; TOF: tetralogy of Fallot.
[a] calculated in 106 patients.

arterial stiffness (r=-0.27, p=0.008), but not with AAo strain or stiffness index. There was also a modest but significant correlation between AAoZ and LV mass index (r=0.29, p=0.001) and SVI (r=0.28, p=0.004) (Figure 1). On multivariate analysis (Tables 3 and 4), male gender was strongly associated with SoV dilatation (odds ratio [OR] 6.3, 95% confidence interval [CI] 1.5-26.3, p=0.01), but not with AAo dilatation. Instead, AAo/SoV ratio >1 showed the strongest link with AAo dilatation (OR 5.3, 95% CI 1.3-20.9, P=0.02).

Intra- and interobserver variability

A sample of 15 randomly chosen cases were reanalyzed. Intraobserver variability was 0.93 mm (95% CI 0.22 to 1.64) (Figure 2a) for the SoV diameter and 1.53 mm (95% CI -0.68 to 3.74) (Figure 2b) for AAo diameter. Interobserver variability was -1.40 mm (95% CI -2.46 to -0.34) (Figure 2c) for the SoV and -1.27 mm (95% CI -4.19 to 1.65) for Aao diameters, respectively (Figure 2d).

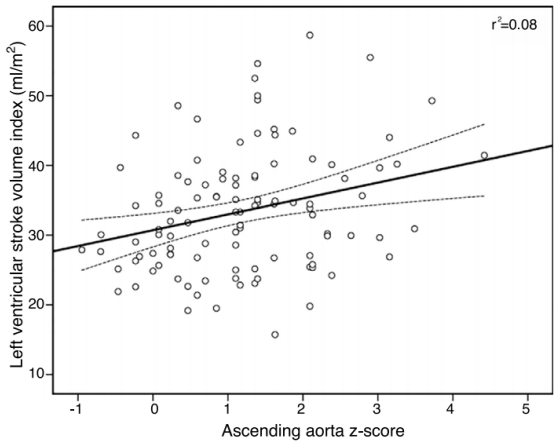


Figure 1 Correlation between ascending aorta z-score and left ventricular stroke volume index in tetralogy of Fallot patients (Pearson's correlation=0.28, p=0.004).

Discussion

Ao dilatation can occur in adults after TOF repair but its prevalence varies according to the study population, the Ao segment analyzed and the cut-off value used for definition. Niwa et al. reported 15% Ao root dilatation using an observed-to-expected cut-off >1.5 at the STJ.[15] A multicenter cross-sectional study found a prevalence of 7% using an observed-to-expected ratio >1.5 at the SoV,[16] while Nagy et al. found a prevalence of 51% using an SoV z-score >+2.[17] In contrast to previous studies, we decided to exclude pulmonary atresia and TOF with absent pulmonary valve in order to avoid a population bias, since in both anatomical variants Ao regurgitation and Ao root dilatation are more common after repair. Moreover, pulmonary atresia is frequently associated with a complex pulmonary vascular pattern and variable major aortopulmonary collaterals, with consequent LV volume overload and a higher prevalence of Ao dilatation.[18] A single-center study[19] also excluded pulmonary atresia and found Ao root dilatation (≥40 mm) in 24% of patients, similar to our results. In our study there was no association of right Ao arch and Ao dilatation in TOF, probably due to the exclusion of pulmonary atresia.[20] As stated above, this suggests that it is Ao volume overload that predisposes to Ao dilation and not the sidedness of the Ao arch.[4]

We decided to exclude genetic syndromes, including Down and DiGeorge syndromes, due to their frequent association with developmental delay, especially growth retardation, in order to avoid influencing study results when comparing TOF patients with normal controls (e.g. indexed Ao dimension or Ao z-score). Unfortunately, we cannot

Table 3 Logistic regression analysis according to sinus of Valsalva dilatation (z-score >+2).

	Univariate analysis		Multivariate analysis	
	OR	p	OR	p
Age	1.03	0.18	0.98	0.57
Gender (male)	2.07	0.07	6.27	0.01
Right aortic arch	0.56	0.25		
Previous palliative shunt	0.53	0.12	0.71	0.62
Transannular patch	0.49	0.08	0.36	0.13
Time to surgical repair	1.02	0.43		
Time since repair	1.00	0.91		
AAoZ	3.38	<0.01		
STJ effacement	1.14	0.75		
AAo/SoV ratio >1	0.51	0.12	0.16	0.01
LV mass index	1.03	0.01	1.05	0.01
LV mass/volume ratio	1.08	0.86		
LVEDV index	1.05	<0.01		
LVESV index	1.06	0.08		
LV stroke volume index	1.07	0.01	1.17	0.07
LVEF	1.00	0.94		
SBP	1.01	0.54		
DBP	1.03	0.22	1.04	0.30
Pulse pressure	1.00	0.58		
Arterial stiffness	0.36	0.02	4.08	0.34
SAC	9.62	0.02	0.55	0.83
Ao strain	1.00	0.66		
Ao distensibility	0.00	0.63		
Ao stiffness index	1.04	0.32		

AAo: ascending aorta; AAoZ: ascending aorta z-score; Ao: aortic; DBP: diastolic blood pressure; LV: left ventricular; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; OR: odds ratio; SAC: systemic arterial compliance; SBP: systolic blood pressure; SoV: sinus of Valsalva; STJ: sinotubular junction.

Table 4 Logistic regression analysis according to ascending aorta dilatation (z-score >+2).

	Univariate analysis		Multivariate analysis	
	OR	p	OR	p
Age	1.07	<0.01	1.00	0.98
Gender (male)	1.98	0.12	0.75	0.66
Right aortic arch	1.62	0.31		
Previous palliative shunt	0.45	0.08	1.02	0.98
Transannular patch	0.33	0.02	0.19	0.03
Time to surgical repair	1.06	0.03	1.03	0.53
Time since repair	1.01	0.82		
STJ effacement	3.24	<0.01	4.67	0.03
AAo/SoV ratio >1	4.13	<0.01	5.28	0.02
LV mass index	1.03	<0.01	1.03	0.14
LV mass/volume ratio	1.05	0.92		
LVEDV index	1.04	0.04	0.99	0.83
LVESV index	1.08	0.05	1.02	0.76
LV stroke volume index	1.03	0.28		
SBP	1.02	0.31		
DBP	1.04	0.16	1.10	0.03
Pulse pressure	0.99	0.82		
Arterial stiffness	0.54	0.16	0.89	0.91
SAC	4.56	0.12	5.92	0.46
Ao strain	1.00	0.90		
Ao distensibility	7.65	0.82		
Ao stiffness index	1.02	0.56		

AAo: ascending aorta; AAoZ: ascending aorta z-score; Ao: aortic; DBP: diastolic blood pressure; LV: left ventricular; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; OR: odds ratio; SAC: systemic arterial compliance; SBP: systolic blood pressure; SoV: sinus of Valsalva; STJ: sinotubular junction.

exclude the possible existence of partial 22q11 deletion in non-syndromic patients, as genetic testing was not performed systematically in all patients.

Although absolute Ao diameters are used for surgical decisions,[21,22] z-scores that adjust Ao dimensions for age and BSA appear to be more accurate for definition and longitudinal follow-up in congenital heart disease. Of note, the fact that Ao dilatation included not only the Ao root but also the AAo highlights the importance of complete Ao assessment late after TOF repair. We found a significant prevalence of Ao dilatation, partially explained by a referral bias to a GUCH center, but this was a real-world adult TOF population, reflecting the patients' historical medical, surgical and social background. Although this is rare, some patients are only diagnosed in adulthood. In our cohort 10% of patients had undergone surgical repair at age 18 or older. As previously reported, later TOF repair leads to longer Ao volume overload, which has an effect on late Ao dilatation. In our study, patients with AAo dilatation had also undergone later TOF repair, but with a similar median palliative shunt-to-repair time, compared to patients without AAo dilatation. More advanced age at surgical shunt or repair was found mostly in our historical older patients, with late referral for both medical and surgical care, which is not seen in contemporary TOF patient populations. In addition, only a small number of patients with AAo dilatation had a palliative shunt prior to repair, and this could have influenced the statistical analysis.

Similarly to Chong et al.,[23] who used M-mode strain in a pediatric population, we found abnormal AAo elasticity in adults. Reduced AAo strain in TOF patients could be an expression of abnormal AAo elasticity, a consequence of histological changes, and not simply a reflection of Ao dilatation, which would explain the absence of a significant correlation with AAoZ. We found no correlation between M-mode AAo strain and SAC or arterial stiffness. This lack of association may be explained by the patients' young age (<30 years in 54%), and by the fact that M-mode AAo strain is a local elastic measurement, and may not reflect overall systemic arterial elasticity. Applanation tonometry, as the gold standard method for assessing arterial stiffness, could help clarify whether aortopathy in TOF has a real impact on systemic arterial stiffness. Nevertheless, in TOF patients with AAo dilatation we found increased LV mass and volumes and a small correlation between AAoZ and LV mass index. It could be speculated that Ao dilatation with reduced Ao strain could increase afterload and influence LV remodeling. Further studies are needed to test this hypothesis.

Male gender appears to be the most consistent predisposing factor for Ao dilatation. As in previous studies,[15,16,24] male gender had a strong association with SoV dilatation. Even though predictors of Ao dilatation found in the literature, such as prior palliative shunt, late TOF repair and longer shunt-to-surgical repair time,[3,15] suggest that long-standing Ao volume overload prior to repair can lead to dilatation, in our study shunt-to-repair time and age

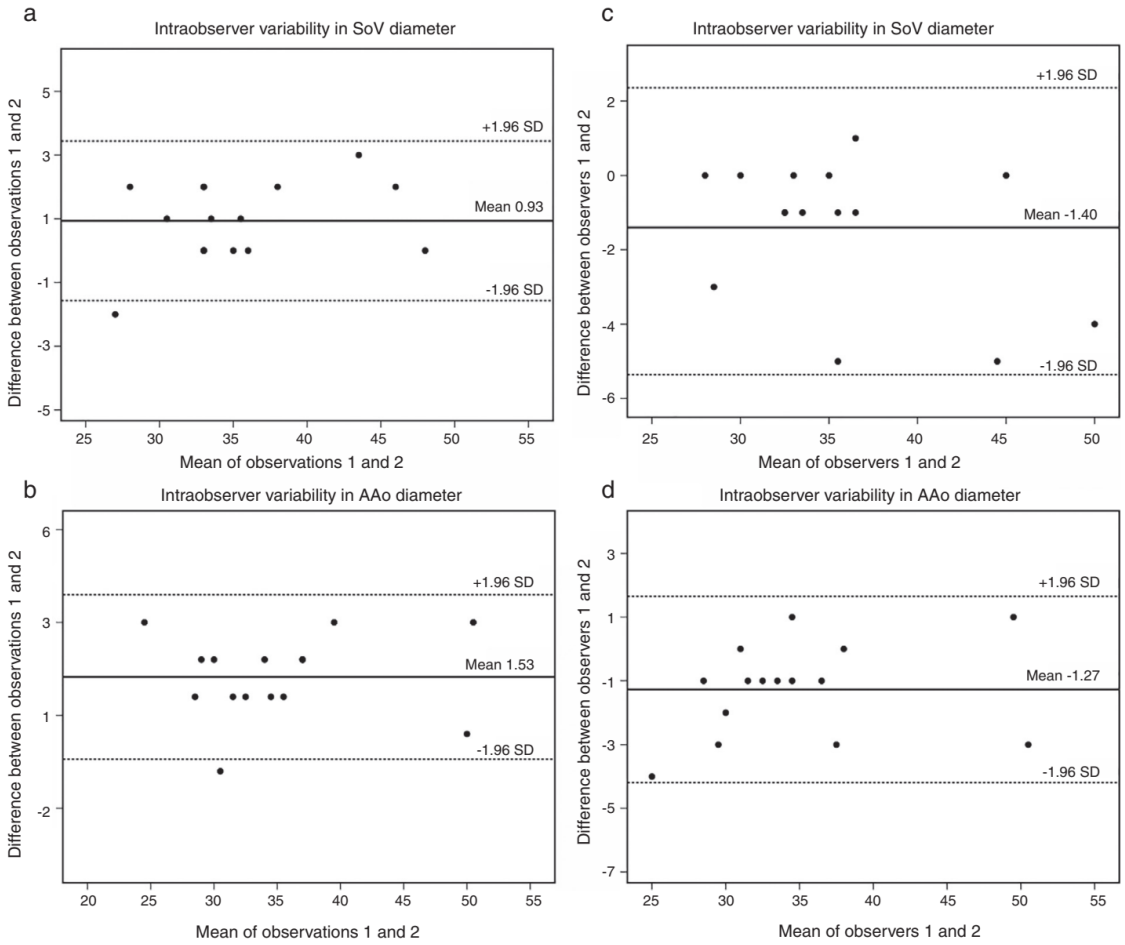


Figure 2 (a) Bland-Altman plot of intraobserver variability in SoV diameter measurements (in mm). Estimated bias: 0.93% (95% confidence interval 0.22 to 1.64); (b) Bland-Altman plot of intraobserver variability in AAo diameter (in mm). Estimated bias 1.53% (95% confidence interval -0.68 to 3.74); (c) Bland-Altman plot of interobserver variability in SoV diameter (in mm). Estimated bias -1.40 mm (95% confidence interval -2.46 to -0.34); (d) Bland-Altman plot of interobserver variability in AAo diameter (in mm). Estimated bias -1.27% (95% confidence interval -4.19 to 1.65 mm). AAo: ascending aorta; SD: standard deviation; SoV: sinuses of Valsalva.

at surgery were not predictors of Ao dilatation. This discrepancy could be partly attributed to the exclusion of pulmonary atresia, the sample size and the advanced age at repair of a significant number of patients, with and without Ao dilatation. We should emphasize that, apart from the Ao volume overload trigger, other underlying etiologies such as intrinsic histological and elastic changes may contribute to abnormal Ao deformation.

Ao dissection late after TOF repair has been reported, the longest interval being 46 years,[25] and in one case dissection was diagnosed at the age of 18 years, even though TOF repair had been performed in infancy at the age of two months.[26] Additionally, some patients need Ao root replacement during follow-up, most due to Ao regurgitation.[27] In our center, since the beginning of the study in 2011 to date two patients have been scheduled for a Bentall operation in addition to pulmonary valve replacement (unpublished data). These findings highlight the need for careful long-term follow-up in order to prevent Ao complications in the future. It remains to be seen whether early TOF repair in infancy will prevent late Ao dilatation.

Study limitations

The first limitation relates to the sample size and selection of patients referred to a single tertiary care center, which may have led to selection bias. However, the healthy control group was age- and gender-matched.

Secondly, TTE can be challenging in GUCH patients, due to a poor acoustic window. Nevertheless, SoV and AAo could be assessed in the vast majority of patients, but SV or LVEF using Simpson's rule was assessed in 110 cases. A multimodality imaging approach could perhaps increase the accuracy of LV volumetric variables. Echocardiographic data were assessed offline and the reviewer only had access to short-axis views of the AAo for M-mode and 2D reanalysis,

but we cannot exclude the possibility that the reviewer was able to identify cases of TOF.

Thirdly, we used brachial artery BP instead of central Ao pressure, and since this could have overestimated DBP, the assessment of Ao distensibility may also have been overestimated. However, the distensibility of the AAo measured by non-invasive methods is close to that obtained by direct measurements.[12] Also, PP amplification, especially in young individuals, may have led to overestimation of Ao stiffness when using brachial PP,[28] but this applies to the entire cohort and did not change the results when comparing TOF patients to controls.

Longitudinal imaging studies of the thoracic aorta in a larger population late after TOF repair are needed to find predictors that could be used to screen for and prevent adverse Ao outcomes, including dissection.

Conclusions

Tetralogy of Fallot patients have a significant prevalence of Ao dilatation late after repair, with a larger and stiffer ascending aorta. This aortopathy requires careful follow-up in order to prevent future complications.

Conflicts of interest

The authors have no conflicts of interest to declare.

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5.4. Is it important to assess the ascending aorta after tetralogy of Fallot repair?

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ORIGINAL ARTICLE

Is it important to assess the ascending aorta after tetralogy of Fallot repair?

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KEYWORDS
Aortic dilatation;
Ascending aorta;
Cardiovascular magnetic resonance;
Tetralogy of Fallot

Abstract
Introduction and Objectives: Aortic dilatation can develop late after tetralogy of Fallot repair. Its extension beyond the aortic root is not clearly understood. We aimed to assess the prevalence and predictors of ascending aorta dilatation to set up an imaging protocol.
Methods: In this prospective study including adult patients after tetralogy of Fallot repair followed at a referral center, we assessed the aorta by cardiovascular magnetic resonance and defined ascending aorta dilatation as an observed-to-expected ratio >1.5.
Results: We included 78 adults (mean age 31±10 years; 56% female), with a mean follow-up of 23±7 years since tetralogy of Fallot repair. The prevalence of ascending aorta dilatation was 11.5%. The ascending aorta was larger than the sinuses of Valsalva in 12.8% of cases. Patients with ascending aorta dilatation were older, predominantly male, with later repair and larger left ventricular mass and volumes. By multivariate analysis left ventricular mass index (LVMI) was the only factor independently associated with ascending aorta dilatation (odds ratio 1.10, 95% confidence interval 1.01-1.20, p=0.03). A cut-off value of ≥57.9 g/m^2 for LVMI had 89% sensitivity and 71% specificity for ascending aorta dilatation.
Conclusions: Ascending aorta assessment as part of a routine cardiovascular magnetic resonance study after tetralogy of Fallot repair is recommended to screen for future aortic complications, particularly in males and older patients, and those with later repair and larger left ventricles. LVMI assessment has potential as a screening tool for ascending aorta dilatation with future clinical implications.
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PALAVRAS-CHAVE
Dilatação da aorta;
Aorta ascendente;
Ressonância magnética cardiovascular;
Tetralogia de Fallot

É importante avaliar a aorta ascendente na tetralogia de Fallot operada?

Resumo
Introdução e objetivos: A dilatação da aorta é uma complicação tardia após correção da tetralogia de Fallot. A sua extensão além da raiz da aorta não está bem definida. Pretendemos avaliar a prevalência e os preditores de dilatação da aorta ascendente para elaborar um protocolo imagiológico.
Métodos: Estudo prospetivo com adultos operados a tetralogia de Fallot seguidos num centro de referência. Estudamos a aorta por ressonância magnética cardiovascular e definimos dilatação da aorta ascendente pelo rácio observado-esperado > 1,5.
Resultados: Incluímos 78 adultos (idade média 31 ± 10 anos; 56% mulheres); seguimento médio de 23 ± 7 anos desde a cirurgia. A prevalência de dilatação da aorta ascendente foi 11,5%. A aorta ascendente era maior do que os seios de Valsalva em 12,8% dos casos. Os doentes com dilatação da aorta ascendente eram mais velhos, maioritariamente homens, operados mais tarde, com massa e volumes ventriculares esquerdos maiores. Na análise multivariada a massa ventricular esquerda indexada foi a única variável independente associada a dilatação da aorta ascendente (*odds ratio* 1,10; intervalo de confiança de 95% 1,01-1,20; p = 0,03). A massa ventricular esquerda indexada ≥ 57,9 g/m^2 apresentou uma sensibilidade de 89% e uma especificidade de 71% para dilatação da aorta ascendente.
Conclusões: Recomendamos a inclusão da aorta ascendente na avaliação por ressonância magnética da tetralogia de Fallot operada, para prevenir complicações aórticas futuras, em particular em homens, doentes mais velhos, operados mais tarde e com ventrículos esquerdos maiores. A massa ventricular esquerda indexada tem potencial para ser usada no rastreio da dilatação da aorta ascendente com implicações clínicas futuras.
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Introduction

Imaging follow-up of tetralogy of Fallot (TOF) patients can be challenging, due to associated thoracic deformities and previous cardiac surgeries. Cardiovascular magnetic resonance (CMR) has an important role in identifying right ventricular outflow tract obstruction, aneurysms, or residual shunts, quantifying pulmonary valve regurgitation or stenosis, and assessing biventricular systolic function. In addition, as first reported by Capelli et al.,[1] there is an increasing awareness that aortic dilatation can develop late after TOF repair. Intrinsic histological abnormalities in the aortic root and ascending aortic wall, present since infancy, can contribute to progressive dilatation.[2] This possible aortopathy led us to focus our study beyond the aortic root and reinforces the importance of a complete aortic assessment. The accuracy of CMR in the diagnosis of thoracic aortic disease,[3] including TOF,[4] is unquestionable. Although CMR is expensive, requires long scan duration and has contraindications, it can provide a complete anatomical and functional assessment.[5] We sought to assess the ascending aorta (AAo) late after TOF repair and to find possible predictors of AAo dilatation in order to set up an imaging protocol.

Methods

A total of 127 adults after TOF repair, not including those with pulmonary atresia, are currently followed as regular outpatients at our tertiary care center. This study prospectively included 78 adults after TOF repair, from March 2011 to December 2015. Inclusion criteria were age ≥18 years, with a time interval since TOF repair of>1 year, and ability to undergo a CMR study. Forty-nine patients were excluded from the study (Figure 1). Exclusion criteria were association with other congenital or acquired heart disease, genetic

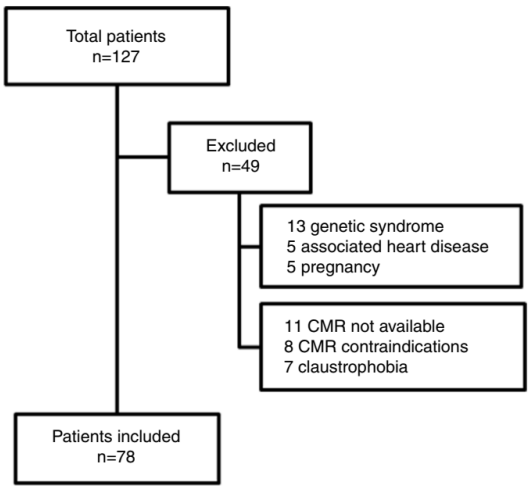


Figure 1 Graphic representation of the study population and exclusion criteria. CMR: cardiovascular magnetic resonance.

syndromes, pregnancy, and contraindications for CMR. The aorta was assessed by CMR and an observed-to-expected ratio was calculated based on nomograms from Davis et al.[6] The population was divided into two groups: group 1, without AAo dilatation (observed-to-expected ratio $\leq$1.5); and group 2, with AAo dilatation (observed-to-expected ratio >1.5). CMR measurements were indexed to body surface area according to the Du Bois formula.[7]

Systemic arterial hemodynamics

Arterial blood pressure was measured twice in supine position at 2-min intervals using an automated blood pressure monitor (SureSigns VS2, Philips Medical Systems) and averaged. It was decided to measure blood pressure in the left brachial artery, due to the presence of a previous right Blalock-Taussig shunt in a significant number (30) of cases. If there was a left palliative shunt, blood pressure was measured on the right arm.

The ratio of stroke volume index to pulse pressure was used as an indirect measure of total systemic arterial compliance.[8]

Cardiovascular magnetic resonance

CMR imaging was performed using a 3-T system (Siemens Magnetom Trio, Washington DC, USA). CMR image acquisitions and analysis were performed by two experienced investigators blinded to patient data. Electrocardiogram-triggered balanced steady-state free precession cine images were acquired throughout the cardiac cycle in breath-hold. Pulse sequences for a standard ventricular function examination were obtained with the following parameters: field of view 320 mm^2; matrix 153$\times$208; voxel size 2.1$\times$1.5$\times$6.0 mm; repetition time 52.9 ms; echo time 1.4 ms; flip angle 60°; slice thickness 6 mm; no gap; temporal resolution 41 ms. Ventricular volumes were assessed using short-axis cine imaging at end-diastole and end-systole applying Simpson's method. The right ventricular outflow tract was included in right ventricular volumes. For left ventricular (LV) mass calculation a combination of semi-automated and manual correction of contours of the endocardial and epicardial borders was used, excluding the papillary muscles. Cine acquisitions aligned with the LV outflow tract in oblique sagittal and coronal orientations were also obtained. In the LV outflow tract sagittal and coronal planes, the maximum end-diastolic external diameter of the aortic segment of interest was measured perpendicular to the longitudinal axis of the aorta, in accordance with the 2010 ACC/AHA guidelines for thoracic aortic disease.[3] Contrast angiography and late gadolinium enhancement detection were also performed for both left and right ventricles.

Ethics

The study protocol complies with the Declaration of Helsinki and was approved by the local institutional ethics committee. Written informed consent was obtained from all patients.

Statistical analysis

The statistical analysis was performed using IBM SPSS, version 24.0 (IBM SPSS Inc., Chicago, Illinois, USA). A two-tailed p value <0.05 was considered statistically significant. Continuous data are expressed as mean$\pm$standard deviation or as median (range), according to the normality of the variable's distribution. Categorical variables are summarized as frequency and percentage. The normality of the data was verified using histograms and the Kolmogorov-Smirnov or Shapiro-Wilk test as appropriate. Differences between groups were compared with Fisher's exact test and the unpaired Student's t test for categorical and continuous variables, respectively. Intra- and interobserver variability were assessed in 18 randomly selected cases. Bland-Altman analysis was used to determine bias (mean of the difference) with 95% limits of agreement. Pearson's correlation coefficient was estimated to analyze possible associations between AAo dilatation and a number of continuous variables. Receiver operating characteristic curve analysis was used to compute the discriminatory power of AAo dilatation predictors. Multivariate logistic regression was performed to test independent associations with AAo dilatation. Variables associated with probability values <0.1 in univariate analysis were included in the multivariate model.

Results

The demographic and hemodynamic characteristics of the study population are listed in Table 1 and CMR data in Table 2, according to the presence or absence of AAo dilatation. Seventy-eight patients (56% female) were included, with a mean age of 31$\pm$10 years. The mean follow-up since TOF repair was 23$\pm$7 years. Forty-nine patients were excluded (Figure 1). Of note, 15 patients were excluded due to CMR contraindications or claustrophobia.

The majority (90%) of patients were asymptomatic, seven were in NYHA functional class II and only one was in class III. A right aortic arch was present in 22 patients. In 39 (50%) a systemic-to-pulmonary shunt was performed prior to complete repair, with a median interval of three years. Thirty-eight patients underwent TOF repair with a transannular patch. Surgical repair was performed in adulthood (age $\geq$18 years) in nine patients (five male and four female). Five patients had systemic hypertension (three in group 2) but systolic blood pressure and pulse pressure were within normal ranges during the study protocol and follow-up. Twenty-five patients were on medication: six on angiotensin-converting enzyme inhibitors, 10 on beta-blockers, and nine on antiarrhythmics (four on amiodarone, two on digoxin, two on propafenone and one on sotalol). LV stroke volume index and LV ejection fraction were within normal ranges. The prevalence of AAo dilatation was 11.5%, with a maximum absolute AAo diameter $\geq$40 mm in six cases and $\geq$50 mm in two, but none above 55 mm. The AAo was larger than the sinuses of Valsalva (SoV) in 12.8%. Patients with AAo dilatation were older, predominantly male, with later TOF repair and larger left ventricular mass and volumes. By multivariate analysis (Table 3) LV mass index (LVMI) was the only independent factor associated with AAo dilatation (odds ratio 1.10, 95% confidence interval [CI] 1.01-1.20,

Table 1 Demographic and hemodynamic characteristics of the study population according to the presence or absence of ascending aorta dilatation.

	Group 1: no AAo dilatation (n=69)	Group 2: AAo dilatation (n=9)	p
Age, years	29.8±8.8	39.7±12.9	<0.01
Male gender, n (%)	26 (37.7)	8 (88.9)	<0.01
Right aortic arch, n (%)	21 (30.4)	1 (11.1)	0.23
Previous palliative shunt, n (%)	35 (50.7)	4 (44.4)	1.0
Transannular patch, n (%)	35 (50.7)	3 (33.3)	0.48
Time shunt to repair, years	3 (1-22)	3 (2-11)	0.88
Age at TOF repair, years	5 (2-49)	7 (4-21)	0.02
Follow-up since TOF repair, years	22.9±6.7	24.7±8.5	0.48
Systemic arterial hemodynamics			
Systolic blood pressure, mmHg	115.8±12.2	117.7±11.5	0.65
Pulse pressure, mmHg	46.6±7.6	47.4±9.4	0.77
SAC, ml/mmHg/m^2	1.0±0.2	1.1±0.2	0.18

Data are expressed as mean ± standard deviation or median (range). Categorical variables are summarized as frequency and percentage. Aortic diameters are measured in mm. AAo: ascending aorta; SAC: systemic arterial compliance; TOF: tetralogy of Fallot.

Table 2 Cardiovascular magnetic resonance data of the study population according to the presence or absence of AAo dilatation.

	Group 1: no AAo dilatation (n=69)	Group 2: AAo dilatation (n=9)	p
Aortic measurements			
SoV diameter, mm	33.6±4.6	43.1±6.5	<0.01
SoV index, mm/m^2	20.1±2.6	23.1±1.9	<0.01
STJ diameter, mm	27.7±3.8	38.3±5.3	<0.01
STJ index, mm/m^2	16.6±2.3	20.7±2.0	<0.01
AAo diameter, mm	28.6±4.0	43.2±5.5	<0.01
AAo index, mm/m^2	17.1±2.2	23.4±3.4	<0.01
AAo observed-to-expected ratio	0.3±0.5	2.2±0.7	<0.01
AAo/SoV ratio >1, n (%)	5 (7.2)	5 (55.6)	<0.01
AAo/pulmonary trunk ratio	1.2±0.3	1.5±0.5	0.10
Left ventricular study			
LV mass index, g/m^2	53.3±11.2	71.9±12.8	<0.01
LV mass/volume ratio, g/ml	0.7±0.1	0.8±0.1	0.05
LVEDV index, ml/m^2	76.8±14.8	92.1±15.9	<0.01
LVESV index, ml/m^2	32.2±9.8	41.0±12.4	0.02
LV stroke volume index, ml/m^2	44.6±8.1	51.1±10.0	0.03
LV ejection fraction, %	58.5±6.7	56.1±8.9	0.10
Aortic regurgitation grade III or IV, n (%)	3 (4.3)	1 (11.1)	0.24
Right ventricular study			
RVEDV index, ml/m^2	129.5±41.5	152.9±44.1	0.12
RVESV index, ml/m^2	47.4±19.7	52.4±23.2	0.48
RV stroke volume index, ml/m^2	61.0±17.0	63.0±10.4	0.74
RV ejection fraction, %	47.9±5.9	42.8±7.8	0.02
RVEDV/LVEDV ratio	1.7±0.6	1.7±0.5	0.81
Pulmonary regurgitation fraction, %	31.4±17.2	39.4±17.4	0.22

Data are expressed as mean ± standard deviation or median (range). Categorical variables are summarized as frequency and percentage. Aortic diameters are measured in mm.
AAo: ascending aorta; LV: left ventricular; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; RV: right ventricular; RVEDV: right ventricular end-diastolic volume; RVESV: right ventricular end-systolic volume; SoV: sinuses of Valsalva; STJ: sinotubular junction; TOF: tetralogy of Fallot.

Table 3 Variables associated with ascending aorta dilatation by univariate and multivariate logistic regression analysis.

	Univariate analysis		Multivariate analysis	
	OR	p	OR	p
Age (per year)	1.10	<0.01	1.07	0.09
Male gender	13.23	0.02	3.54	0.31
Right aortic arch	0.29	0.25		
Previous palliative shunt	0.78	0.72		
Transannular patch	0.55	0.44		
Time from shunt to repair (per year)	1.05	0.67		
Age at TOF repair (per year)	1.03	0.34		
Time since TOF repair (per year)	1.04	0.48		
Systolic arterial pressure	1.01	0.65		
Diastolic arterial pressure	1.01	0.72		
Pulse pressure	1.01	0.77		
SAC	7.00	0.19		
LV mass index	1.13	<0.01	1.10	0.03
LVESV index	1.09	0.04	0.98	0.80
RVEDV/LVEDV ratio	0.86	0.81		

AAo: ascending aorta; LV: left ventricular; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; OR: odds ratio; RVEDV: right ventricular end-diastolic volume; SAC: systemic arterial compliance; TOF: tetralogy of Fallot.

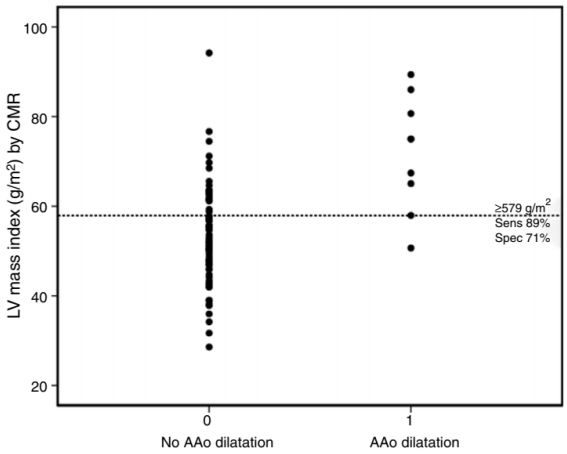


Figure 2 Dot diagram for left ventricular mass index according to the presence or absence of AAo dilatation. The horizontal dotted line represents the cut-off point for the best diagnostic accuracy (cut-off ≥57.9 g/m^2, with sensitivity of 88.9% and specificity of 71.0%). AAo: ascending aorta; CMR: cardiovascular magnetic resonance; LV: left ventricular; Sens: sensitivity; Spec: specificity.

p=0.03). A cut-off value of ≥57.9 g/m^2 for LVMI had 89% sensitivity and 71% specificity for AAo dilatation (Figure 2).

Intra- and interobserver variability in cardiovascular magnetic resonance

A sample of 18 randomly chosen cases was reanalyzed. Intraobserver variability of the AAo diameter measurement was 0.42 mm (95% CI: -3.97 to 4.81) (Figure 3a) and interobserver variability was -0.58 mm (95% CI: -4.40 to 3.24) (Figure 3b).

Discussion

To our knowledge this is the largest prospective CMR study to include only TOF patients without pulmonary atresia. With this exclusion condition we aimed to avoid a potential bias, as in this patient subgroup it is more common to find aortic regurgitation and aortic root dilatation after repair.[9] Additionally, we analyzed demographic and anatomical parameters that could be used as predictors of aortic dilation in future research.

A wide range of prevalence of aortic dilatation in TOF has been published. This is probably due to differences in patient selection and definition criteria. Similarly to a previous retrospective study by Kay et al.,[10] we defined AAo dilatation as an observed-to-expected ratio >1.5. They found a 6% prevalence of AAo dilatation, but used regression equations developed for computed tomography. In a multicenter study using transthoracic echocardiography,[11] the authors reported a 6.6% prevalence of aortic root dilation using the same cut-off ratio for the SoV. In a subgroup of patients the authors had access to the AAo diastolic diameter and reported an estimated prevalence of 18.7% for AAo dilatation, using an absolute diameter cut-off value of ≥40 mm. Although absolute aortic diameters are used for surgical decision,[12] adjusting for a gender-specific nomogram derived from a normal CMR reference range appears to be more precise for definition and long-term follow-up in congenital heart diseases, especially in a young population with expected long-term survival. Similarly to previous CMR retrospective studies,[10,13] in our cohort eight out of nine patients with AAo dilatation were male. Male gender appears to be the most consistent predisposing factor for AAo dilatation by univariate analysis. However, in our multivariate logistic regression model only LVMI was independently associated with AAo dilatation.

It has been postulated that long-standing volume overload of the aorta before complete TOF repair may be

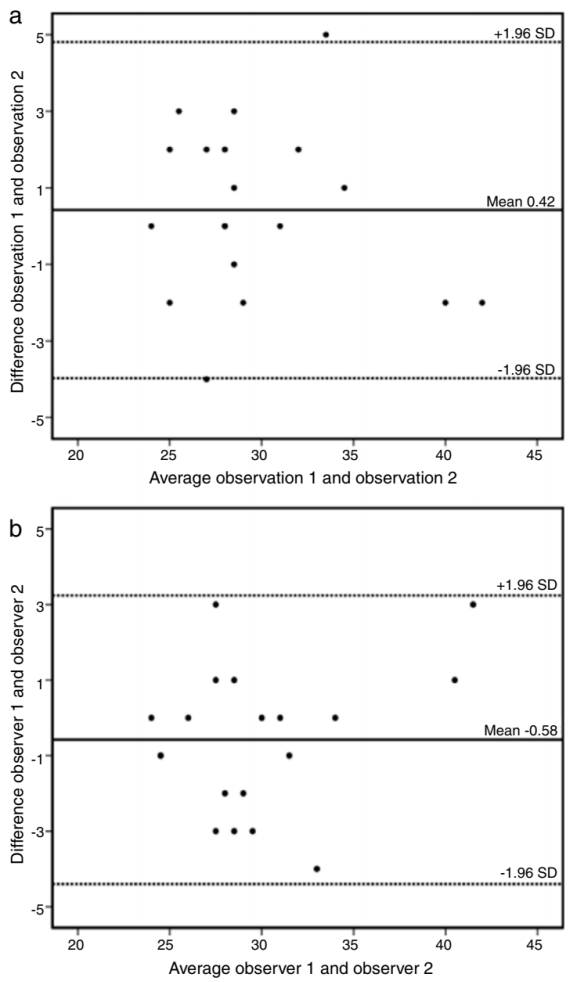


Figure 3 (a) Bland-Altman plot of intraobserver variability of ascending aorta data by cardiovascular magnetic resonance. Estimated bias 0.42 mm (95% confidence interval -3.97 to 4.81mm). SD: standard deviation. (b) Bland-Altman plot of interobserver variability of ascending aorta data by cardiovascular magnetic resonance. Estimated bias -0.58 mm (95% confidence interval -4.40 to 3.24mm). SD: standard deviation.

responsible for progressive aortic dilatation. In our cohort, patients with AAo dilatation had higher LV stroke volume index and longer time to TOF repair. Interestingly, nine patients underwent TOF repair in adulthood, due to late diagnosis in four cases (the oldest at age 49 years), and late referral or loss to follow-up during pediatric age in five cases. None showed Ao dilatation at the time of TOF repair. In addition, histopathological abnormalities, mainly in the aortic root and ascending aortic wall, can contribute to aortic dilatation and stiffness in TOF.[2,14] Grotenhuis et al.[15] and Rutz et al.[16] reported aortic dilatation and reduced aortic distensibility as a marker of an intrinsic aortopathy in TOF, compared with normal controls. Alterations in elastic properties were especially found in the proximal aorta,[17] and were thought to precede aortic dilation and to increase LV afterload.[18,19] Consequently, TOF aortopathy can lead to LV remodeling as a result of ventricular-arterial coupling. Increased LV end-diastolic pressure due to increased LV volumes and afterload could explain why in our study patients with AAo dilatation had a higher LVMI. Moreover, systemic hypertension was more prevalent in the dilated group, although pulse pressure and systemic arterial compliance were similar in the two groups, possibly reflecting good blood pressure control under medication. These findings highlight the need for regular clinical follow-up along with careful imaging follow-up of the aorta and LV parameters, including LV size and function, after TOF repair. We found a larger aortic diameter at the level of the AAo in 13% of patients, demonstrating the importance of complete aortic screening. Although echocardiography is relatively inexpensive, portable and widely available, it has limitations concerning AAo imaging. CMR and computed tomography are the current gold standard for a complete aortic assessment, however CMR imaging has the advantage of avoiding exposure to either radiation or iodinated contrast, compared to computed tomography, in young patients in need of long-term follow-up. The role of CMR for TOF follow-up is unquestionable due to its accuracy and reproducibility. A comprehensive CMR acquisition after TOF repair enables not only screening for residual RV outflow tract and pulmonary valve lesions, but also assessment of right and left ventricular parameters, including LV mass and volumes, and can accurately provide serial aortic diameters. A slow rate of aortic diameter progression in TOF has been reported,[10,13] but with a higher rate of progression in the AAo.[13] It has been proposed that CMR imaging of the aorta should be repeated every three years if the aorta is not dilated at baseline.[10] Although aortic dissection is rare, it can occur long after TOF repair. In the first such case, aortic dissection was reported beginning in the AAo in a 30-year-old man who had undergone TOF repair nine years before.[20] To prevent this complication, a complete assessment of the thoracic aorta should be included in a CMR imaging protocol for TOF. Based on our findings, we suggest a careful imaging follow-up of the AAo after TOF repair, especially in males, older patients, and those with later TOF repair and larger left ventricles.

Study limitations

This was a single-center study and data may have been influenced by selection and survivor bias. We excluded patients with genetic syndromes including DiGeorge syndrome but 22q11 mutations were not screened in all patients. Finally, 15 patients did not undergo CMR due to contraindications or claustrophobia, which represents a limitation of the CMR studies.

Further longitudinal studies with larger population and the use of a consensus definition for aortic dilatation may help to identify patients at risk of aortic events and may clarify the timing for aortic surgery in TOF patients after repair.

Conclusions

AAo assessment as part of a routine CMR study after TOF repair is recommended to prevent future aortic

complications, particularly in males, older patients, and those with later repair and larger left ventricles. LVMI assessment has potential as a screening tool for AAo dilatation with future clinical implications.

Conflicts of interest

The authors have no conflicts of interest to declare.

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6 DISCUSSION

Discussion

At present surgical repair of tetralogy of Fallot is performed at an early age and these patients are likely to survive into adulthood with a good quality of life and long life-expectancy. However, major right-sided cardiac residual lesions may remain after surgery. In addition, there is a growing evidence that also left-sided lesions can occur after tetralogy of Fallot repair, namely aortic dilatation. The present thesis addresses this complication.

When selecting our study population, we excluded patients with Down and DiGeorge syndromes since the association with growth retardation would introduce a bias when comparing patients with normal controls.

Although absolute aortic diameters are used for surgical decisions, z-scores that adjust aortic dimensions for age and body surface area appear to be more accurate for definition and longitudinal follow-up in congenital heart disease.

Of note, the fact that aortic dilatation included not only the aortic root but also the ascending aorta highlights the importance of a complete aortic assessment late after tetralogy of Fallot repair.

We found a significant prevalence of aortic dilatation, partially explained by a referral bias to a GUCH center, but this was a real-world adult tetralogy of Fallot population, reflecting the patients historical medical, surgical and social background. Although rare, some patients are only diagnosed in adulthood. In our cohort 10% of patients had surgical repair at age of 18 years or older. Older age at surgical shunt or repair was found mostly in our historical patients, with late referral for both medical and surgical care, which is an exception in contemporary tetralogy of Fallot patients.

1. Prevalence of aortic dilatation after tetralogy of Fallot repair

Aortic dilatation can occur among adults after tetralogy of Fallot repair, but the reported prevalence varies according to the study population, the imaging technique used, the aortic segment analysed, and the cut-off value used for definition.

Using transthoracic echocardiography and an observed-to-expected sinotubular junction diameter cut-off > 1.5, Niwa et al. reported 15% aortic root dilatation.(26) A multicenter cross-sectional study evaluated the sinuses of Valsalva diameter and used an observed-to-expected

ratio > 1.5 cut-off for dilatation. The authors found aortic dilation in 7% of patients. The same authors reported a 18.7% prevalence of ascending aorta dilatation, using an absolute diameter cut-off value ≥ 40 mm.(27) Nagy et al. using a sinuses of Valsalva z-score > +2 as cut-off, reported a 51% prevalence of aortic dilatation.(28) In contrast to previous studies, we decided to exclude pulmonary atresia and tetralogy of Fallot with absent pulmonary valve in order to avoid a population bias because in both anatomical variants aortic regurgitation and aortic root dilatation after repair are more common. Moreover, pulmonary atresia is frequently associated with variable major aortopulmonary collaterals, with a consequent left ventricular volume overload and higher prevalence of aortic dilatation.(12) More recently, a single centre study(29) also excluded pulmonary atresia and found aortic root dilatation (diameter ≥ 40 mm), in 24% of patients, similar to our results.

Similar to transthoracic echocardiographic studies, also in cardiovascular magnetic resonance studies a wide range of prevalence of aortic dilatation in tetralogy of Fallot has been reported. Kay et al.(30), defined ascending aorta dilatation as an observed-to-expected ratio > 1.5 and reported 6% prevalence of ascending aorta dilatation, but they used regression equations developed for computed tomography. More recently, Bonello et al.(31) reported a prevalence of 22% of ascending aorta dilatation (defined as a diameter > 2 standard deviations above the mean). Both studies included patients with pulmonary atresia. Similarly to Kay et al.(30), we defined ascending aorta dilatation as an observed-to-expected ratio > 1.5 using cardiovascular magnetic resonance nomograms. We found a 11.5% prevalence of ascending aorta dilatation.

In contrast with our transthoracic echocardiographic study, most patients included in our cardiovascular magnetic resonance study were females (48 vs 56%). This could be one explanation for the lower prevalence of ascending aorta dilatation (24 vs 12%) reported in our cardiovascular magnetic resonance study.

2. Aortic dilatation after tetralogy of Fallot repair: characteristics and predictive factors

When assessed by transthoracic echocardiography aortic diameter was larger at the ascending aorta than at the sinuses of Valsalva in 40% of our patients. However. this was the case in only 13% of our patients assessed by cardiovascular magnetic resonance. This discrepancy may reflect a possible overestimation, or an inaccurate measurement of the ascending aorta by

transthoracic echocardiography, due to a more difficult image acquisition, and emphasizes the need of a multimodality imaging approach.

Male gender seems to be the most consistent predisposing factor for aortic dilatation in this patient population. This is relevant since there is no difference in gender distribution in tetralogy of Fallot.

Using a left ventricular mass index cut-off ≥ 57.9 g/m2 may help to predict ascending aorta dilatation, since in our cardiovascular magnetic resonance study it showed an 89% sensitivity and a 71% specificity.

3. Clinical relevance

The complete understanding of the clinical relevance of aortic dilatation after tetralogy of Fallot repair remains unclear.

The fact that in many of our patients the aortic dilatation included not only the aortic root but also the ascending aorta, reinforces the need for a complete aortic assessment late after tetralogy of Fallot repair.

The expected long survival of these patients and the progressive nature of this lesion creates the opportunity for massive dilatation. A slow rate of progressive aortic dilatation has been reported,(30, 31) with a higher rate of progression at the ascending aorta.(31)

Over time aortic dilatation may lead to aortic regurgitation, and increase the risk of aortic aneurysm and dissection(10, 11) requiring surgery.(12) The clinical case included in this thesis is an example of this, and highlights the need for a longitudinal follow-up of these patients.

Aortic dissection is rare, but it can occur long time after tetralogy of Fallot repair. Fourty-six years is the longest time interval reported between tetralogy of Fallot repair and the occurrence of aortic dissection.(32)

4. Pathogenetic hypothesis

4.1. Aortic volume overload

Aortic dilatation is a foetal feature of tetralogy of Fallot. It tends to disappear after early surgical repair,(6) preventing long-standing volume overload on the overriding aorta, and potentially

decreasing the risk of developing aortic dilatation. Despite this, there is at least one published clinical case reporting an aortic dissection by the age of 18 years in a patient with a tetralogy of Fallot repair performed at 2 months old.(33) So it seems that additional factors than simply aortic volume overload could be implicated in aortic dilatation. Nevertheless, volume overload is certainly important in the pathogenesis of this complication. Consequently, one could assume that aortic dilatation may be a pathology of the past, not reflecting the current early surgical approach.(7) However, for many reasons, including anatomical and surgical technical issues, not all patients can benefit from early repair. In our cohort 10% of patients had surgical repair in adulthood. It represents a "real world" historical adult tetralogy of Fallot patient population, reflecting historical medical, surgical, economical and even social constraints. Older age at surgical palliative shunt or repair occurred mostly in previous decades, consequence of a late referral both for medical and surgical care, not reflecting a contemporary national and worldwide practice. As mentioned above, a later tetralogy of Fallot repair imposes longer aortic volume overload and potentially plays a role in late aortic dilatation. This may in part explain the high prevalence of aortic dilatation in our cohort.

In our study there was no association between right aortic arch and aortic dilatation, possibly due to exclusion of pulmonary atresia.(34) This suggests that it is the aortic volume overload that predisposes to aortic dilation and not the sidedness of the aortic arch.(7)

Other predictors of aortic dilatation reported in the literature, such as prior palliative shunt, longer shunt-to-surgical repair interval, late tetralogy of Fallot repair,(6, 26) reinforce the possible relevance of long-standing aortic volume overload prior to repair in the development of aortic dilatation.

4.2. Intrinsic aortopathy

Aortic root and ascending aorta histological abnormalities, present since infancy in tetralogy of Fallot, may contribute to aortic dilatation.(8, 9). This possible aortopathy involves not only aortic dilatation but also abnormal aortic elastic properties.

Compared to normal controls, our patient population (23±7 years after tetralogy of Fallot repair) showed decreased aortic strain and distensibility and increased aortic stiffness. Similarly to Chong et al.,(35) using M mode strain in a paediatric population, we found signs of abnormal ascending aorta elasticity in adults.

Reduced ascending aorta strain in tetralogy of Fallot patients may be an expression of an abnormal ascending aorta elasticity, due to histological changes, and not simply consequence of aortic dilatation. This could explain the absence of a significant correlation with the ascending aorta z-score.

Grotenhuis et al.(36) and Rutz et al.(37), when comparing tetralogy of Fallot patients with normal controls using cardiovascular magnetic resonance, reported aortic dilatation and reduced aortic distensibility in tetralogy of Fallot patients and interpreted these findings as markers of an intrinsic aortopathy. Elastic properties changes were especially found at the proximal aorta,(38) and were thought to precede aortic dilation and to increase left ventricular afterload.(39, 40) Consequently, tetralogy of Fallot's aortopathy could lead to left ventricular remodelling as a result of an arterial-ventricular coupling. Increased left ventricular end-diastolic pressure due to increased left ventricular volumes and afterload, could explain why our patients with ascending aorta dilatation have a higher left ventricular mass index.

4.3. Male gender

Male gender seems to be a strong and consistent predictor of aortic dilatation. This is relevant since there is no gender predominance in tetralogy of Fallot. As in previous transthoracic echocardiographic studies,(26, 27, 41) in our study male gender had a strong association with sinuses of Valsalva dilatation. Similarly to previous cardiovascular magnetic resonance studies,(30, 31) most of our patients with ascending aorta dilatation were males.

The explanation for this gender-based difference is unclear. Gender may influence arterial distensibility and stiffness, with females being reported to have higher aortic stiffness pre-puberty and post-menopause. Sex steroid differences between genders have been postulated to be one explanation for these findings.(42) We speculate on the possible hormonal influence on the phenotypical expression of this aortopathy.

4.4. Systemic hypertension

In our echocardiographic study, diastolic arterial pressure was an independent predictor of ascending aorta dilatation, although systemic blood pressure and pulse pressure were within normal range during study protocol and follow-up.

Additionaly, in our cardiovascular magnetic resonance study, even though tetralogy of Fallot patients were normotensive, a previous history of systemic hypertension was more prevalent in the group with a dilated ascending aorta. One should interprete this data with caution as the hypertensive patients's sample was very small, with systemic blood pressure and pulse pressure within normal range during study follow-up, may be reflecting a good blood pressure control under medication.

Systemic hypertension may be another predisposing pathogenetic factor for aortic dilatation over time and a careful blood pressure monitoring is a goal, also in this young patient population.

5. Implications for clinical practice

Although absolute aortic diameters are used as reference for surgical decision,(43, 44) adjusting aortic dimension for age and body surface area seems to be a more precise method for definition of aortic dilatation and for longitudinal follow-up, especially in a young population with an expected long-term survival and important changes in body surface area over the years.

The frequent occurrence of aortic dilatation, including the ascending aorta, in patients after tetralogy of Fallot repair, even if they are asymptomatic, highlights the importance of a systematic multimodality imaging follow-up.

Although echocardiography is relatively inexpensive, portable and widely available, it has limitations concerning ascending aorta imaging. Cardiovascular magnetic resonance and computed tomography are the current gold standards for a complete aortic evaluation. Since cardiovascular magnetic resonance imaging avoids exposure to either radiation or iodinated contrast, it seems more advantageous in young patients in need of a longitudinal screening. The role of cardiovascular magnetic resonance in tetralogy of Fallot follow-up is unquestionable due to its accuracy and reproducibility. A comprehensive cardiovascular magnetic resonance acquisition after tetralogy of Fallot repair allows not only to screen the right ventricular outflow tract and pulmonary valve residual lesions, but also to assess right and left ventricular parameters, including left ventricular mass, and volumes, and can accurately provide serial aortic diameter measurements.

It has been proposed to repeat cardiovascular magnetic resonance imaging of the aorta every 3 years if the aorta is not dilated at baseline.(30) To screen thoracic aorta dilatation and ultimately

to prevent aortic dissection, a complete assessment of the thoracic aorta should be included in a tetralogy of Fallot's cardiovascular magnetic resonance imaging protocol. According to our findings, we suggest a careful imaging follow-up of the ascending aorta after tetralogy of Fallot repair, especially in males, older patients, with a later surgical repair and bigger left ventricles. We report a left ventricular mass index cut-off ≥ 58 g/m2, determined by cardiovascular magnetic resonance, with a good sensibility but a fair specificity to predict the occurrence of ascending aorta dilatation. This results in a significant number of false positives, with an increased left ventricular mass index but no aortic dilatation. Although this is not an ideal accuracy for predicting this complication, in this context, it seems better to screen some false positives than miss false negatives. In our opinion this deserves further studies with a larger sample size.

7 LIMITATIONS

Limitations

This is a single-centre study and data may have been influenced by a referral selection and survivor bias.

We excluded patients with genetic syndromes including DiGeorge syndrome, but we cannot exclude the possibility of 22q11 partial deletion in non-syndromic patients has a systematic genetic test was not performed in all patients.

Transthoracic echocardiography can be very challenging in adult congenital patients due to a poor acoustic window, and contraindications or claustrophobia represent a limitation for cardiovascular magnetic resonance studies.

M-mode strain is a very limited tool for estimating aortic strain and stiffness. Echocardiography can be used to assess noninvasively tissue mechanical properties by tissue Doppler or speckle tracking technique, but there is no dedicated software to assess aortic strain. Aortic pulse wave velocity is the gold standard method for noninvasive evaluation of arterial stiffness in humans. Although this technique is easy to use, there are different available methods and algorithms for calculating the pulse propagation time, preventing its widespread use in clinical practice.

We used brachial artery blood pressure instead of central aortic pressure and due to a special overestimation of the diastolic blood pressure we could have increased aortic distensibility. However, the distensibility of the ascending aorta measured by noninvasive methods is closely related to that obtained by direct measurements.(18) Also, due to pulse pressure amplification phenomenon using brachial arterial measurements, especially in young individuals, could overestimate the aortic stiffness,(39) but that applies to the entire cohort and did not change the results while comparing tetralogy of Fallot patients to normal controls.

Further longitudinal studies with a large population sample and a consensus definition for aortic dilatation may help to identify patients at risk of aortic events and may clarify the timing for aortic surgery after tetralogy of Fallot repair, if needed.

CONCLUSIONS 8

Conclusions

Aortic dilatation has a significant prevalence late after tetralogy of Fallot repair. It involves the aortic root and ascending aorta, outlining the importance of a complete aortic assessment as part of an imaging follow-up protocol.

Transthoracic echocardiography is usually the first-line imaging tool. However, it has limitations concerning the acoustic window, especially in adult congenital patients. Thus, a multimodality imaging approach is warranted.

Cardiovascular magnetic resonance imaging role in this setting is unquestionable and seems more advantageous for a longitudinal screening. Thoracic aorta assessment as part of a routine cardiovascular magnetic resonance study after tetralogy of Fallot repair is recommended, particularly in males, older patients, with later repair, and bigger left ventricles. It requires a careful and long-term clinical and imaging follow-up.

Aortic dilatation in this context is probably due to multiple causes, including aortic volume overload and an intrinsic aortopathy. It is associated not only with aortic dilatation but also with abnormal elastic properties, with possible implications in left ventricular remodelling.
Left ventricular mass index has potential to be a predictor tool for the occurrence of ascending aorta dilatation with future clinical implications.

9 FUTURE RESEARCH

Future research

This thesis outlines the importance of a complete thoracic aortic assessment late after tetralogy of Fallot repair, using a multimodality imaging protocol. This strategy has the potential to increase the accuracy of aortic assessment but is expensive and financial resources are scarce. A prospective study using both transthoracic echocardiography and cardiovascular magnetic resonance to assess the grade of concordance of aortic measurements between both imaging methods in this setting is feasible. It could help to determine if indeed a multimodality imaging protocol represents an optimal management strategy and justifies the increased costs.

A multicentre longitudinal study to assess the rate of aortic diameter progression, comparing patients with early and late tetralogy of Fallot repair, could help to better define the timing for aortic imaging and could help to clarify the timing for aortic surgery, if needed.

The possible tetralogy of Fallot's aortopathy involves abnormal aortic elastic properties. Applanation tonometry, as the gold standard method for assessing arterial stiffness, could help to clarify if tetralogy of Fallot's aortopathy has a relevant impact in systemic arterial stiffness.

In tetralogy of Fallot aortic dilatation with reduced aortic strain may increase afterload and influence left ventricular remodelling. Increased aortic stiffness by increasing afterload may promote left ventricular hypertrophy. Further long-term studies are necessary to ellucidate this hypothesis.

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