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Short communication

The aortic root in repaired tetralogy of Fallot: Serial measurements and impact of losartan treatment☆

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ABSTRACT

Background: Aortic root dilatation is common in adults with repaired tetralogy of Fallot (rTOF) and might lead to aortic dissection. However, little is known on progression of aortic dilatation and the effect of pharmaceutical treatment. This study aims to determine factors associated with aortic growth and investigate effects of losartan.
Methods and results: We performed a prespecified analysis from the 1:1 randomized, double-blind REDEFINE trial. Aortic root diameters were measured at baseline and after 2.0 ± 0.3 years of follow-up using cardiovascular magnetic resonance (CMR) imaging. A total of 66 patients were included (68% men, age 40 ± 12 years, baseline aortic root 37 ± 6 mm, 32% aortic dilatation (>40 mm)). There was a trend towards slow aortic root growth (+0.6 ± 2.3 mm after two years, $p = 0.06$) ($n = 60$). LV stroke volume was the only factor associated with both a larger baseline aortic root (β: 0.09 mm/ml (95% C.I.:0.02, 0.15), $p = 0.010$) and with aortic growth during follow-up (β: 0.04 mm/ml (95% C.I.:0.005, 0.066), $p = 0.024$), after correction for age, sex, and body surface area using linear regression analysis. No treatment effect of losartan was found ($p = 0.17$).
Conclusions: Aortic root dilatation was present in about one-third of rTOF patients. A larger LV stroke volume was associated with both a larger baseline aortic root and ongoing growth. Our findings provide no arguments for lower aortic diameter thresholds for prophylactic surgery compared to the general population.

1. Introduction

Aortic root dilatation has been reported in 15–50% of adults with repaired tetralogy of Fallot (rTOF) [1–3]. Aortic root dissection, albeit very rare [4], is such a dramatic event, that prevention in the form of timely prophylactic aortic root surgery is considered good clinical practice. However, there are no clear data to guide us what "timely" is and guidelines lack specific cut-off values for rTOF patients [4–6]. Recent studies reported a considerable number of prophylactic aortic root surgeries while the rate of dissection was not higher than 0.1% per ten-years of follow-up [3,7]. Although this low dissection rate may implicate success of prophylactic surgery it also raises concerns for overtreatment.

We aimed to provide guidance in the follow-up intervals and clinical decision making for prophylactic aortic surgery. Therefore, we determined factors associated with aortic dilatation as assessed with cardiovascular magnetic resonance (CMR) imaging as well as progression during follow-up. In addition, we aimed to determine whether losartan might prevent progressive aortic root dilatation, as reported in patients with Marfan syndrome [8].

2. Methods

This was a prespecified substudy of the randomized (1:1, losartan/placebo target 150 mg) REDEFINE trial, of which the design and main paper have been published [9,10]. Briefly, adults with rTOF were eligible for inclusion if right ventricular (RV) ejection fraction (EF) was <50% and no severe valvular lesions were present. For the present substudy, we selected participating rTOF patients in which the aortic root

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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diameter could be assessed using CMR at baseline measurement. We assessed serial measurements in patients in whom the follow-up CMR was also of adequate quality. Informed consent was obtained from each patient and the study protocol was approved by the medical ethical board.

2.1. CMR imaging

CMR derived volume and function measurements were performed by a single observer (JPB), as previously described [9]. JiveX DICOM Viewer (VISUS, Bochum Germany), open source software for DICOM imaging analysis, was used to measure aortic root dimensions (measured by AG, blinded to patient and treatment allocation). The aortic root diameter was measured at end-diastole in the 3-chamber view at the level of the sinus of Valsalva (SoV) by drawing a line parallel to the aortic valve. Intra- and interobserver (AG and OIW) variability was assessed in random samples of 30 and 20 CMRs, respectively.

2.2. Statistical analysis

Statistical analysis was performed using SPSS software (version 26.0). Data were described as frequency with percentage, mean with standard deviation (±SD), or median with interquartile range (IQR). A p-value of <0.05 was considered statistically significant.

Intra- and interobserver agreement of SoV diameter measurements were assessed using the intraclass correlation coefficient (ICC). Paired t-test was used to analyze whether there was change of diameter over time in the entire cohort. To determine whether baseline characteristics or losartan treatment were associated with a larger aortic root diameter at baseline and/or increase of aortic root diameter (diameter 2-diameter 1), we performed linear regression analysis. All analyses for diameter changes were corrected for baseline diameter. Selected variables with $p < 0.05$ in univariable analysis were included in multivariable analysis, correcting for demographic factors such as age, sex, and body surface area.

3. Results

A total of 95 patients were included in the REDEFINE trial. Of these patients, 66 (69%) were included in the present analysis and had baseline aortic root diameter assessed. There were no significant differences between patients included in the present analysis compared to excluded REDEFINE patients (Supplementary Table 1). Intraobserver agreement and interobserver agreement of SoV diameter measurements were excellent (ICC = 0.978 (95% C.I.: 0.951, 0.989) and ICC = 0.976 (95% C.I.: 0.939, 0.990), respectively).

3.1. Baseline aortic root

Baseline aortic root diameter was 37 ± 6 mm. A total of 21 patients (32%) had an increased aortic root diameter (>40 mm). Factors associated with a larger baseline aortic root in univariable analysis are listed in Table 1. In multivariable analysis: male gender (β: 4.9 mm (95% C.I.: 2.4, 7.4), $p < 0.001$) and age at inclusion (β: 0.24 mm/year (95% C.I.: 0.14, 0.34), $p < 0.001$) remained associated with a larger aortic root at baseline (Fig. 1A). After adding LV stroke volume and body surface area to the model, larger LV stroke volume remained associated with a larger aortic root diameter at baseline (β: 0.09 mm/ml (95% C.I.: 0.02, 0.15), $p = 0.010$) while age and male gender also remained significantly associated with a larger aortic root ($p < 0.01$ for both).

3.2. Serial measurements

A total of 60 patients had adequate follow-up CMR for serial assessment of the aortic root, time between scans 2.0 ± 0.3 years. In general, there was a statistically non-significant trend towards a slow increase of aortic root diameter (+0.6 ± 2.3 mm after 2 years, $p = 0.06$). Factors associated with an increase in aortic root diameter during follow-up are listed in Table 1. Of note, older age and male gender were not associated with aortic root increase in diameter. Larger LV end-diastolic volume and LV stroke volume were associated with aortic root growth. There was a trend towards more growth in women, but not in

Table 1
Patient characteristics and factors associated with aortic root diameter and growth during follow-up.

Patient and surgical characteristics	All patients	Baseline aortic root		Serial growth ($n = 60$)	
	$N = 66$	β (95% C.I.)	P-value	β (95% C.I.)	P-value
Female gender	21 (32%)	−5.5 (−8.4, −2.6)	<0.001	1.3 (0.06, 2.6)	0.041
Age at inclusion (years)	39.9 ± 11.8	0.26 (0.15, 0.37)	<0.001	−0.001 (−0.06, 0.06)	0.97
Age at initial correction (years, IQR)	3.1 (1.5, 6.8)	0.57 (0.31, 0.82)	<0.001	0.09 (−0.03, 0.21)	0.13
Previous shunt procedure	27 (41%)	3.5 (0.6, 6.4)	0.020	0.45 (−0.72, 1.6)	0.45
Duration of shunt (years, IQR) ($n = 27$)	5.0 (2.6, 9.3)	0.7 (0.2, 1.1)	0.004	0.10 (−0.15, 0.34)	0.43
Previous PVR	42 (64%)	−3.5 (−6.4, −0.4)	0.026	−1.12 (−2.3, −0.02)	0.046
Body surface area (m^2)	1.98 ± 0.25	7.5 (1.8, 13)	0.010	−1.14 (−3.6, 0.88)	0.23
NYHA Class 2+	12 (18%)	−1.8 (−5.7, 2.0)	0.35	0.67 (−0.72, 2.1)	0.34
Beta blocker treatment	11 (17%)	−2.5 (−6.4, 1.5)	0.22	0.76 (−0.79, 2.3)	0.33
Heart rate (beats per minute)	69 ± 10	−0.02 (−0.16, 0.13)	0.80	−0.03 (−0.09, 0.02)	0.21
Systolic blood pressure (mmHg)	121 ± 13	0.05 (−0.06, 0.17)	0.36	0.008 (−0.03, 0.05)	0.69
Systolic blood pressure at exercise (mmHg)	181 ± 31	−0.01 (−0.06, 0.04)	0.65	0.002 (−0.02, 0.02)	0.83
Hemoglobin (mmol/L)	9.0 ± 0.8	2.2 (0.41, 4.1)	0.017	−0.64 (−1.4, 0.07)	0.08
Echocardiography					
Aortic regurgitation (none, mild, moderate)	48 (73%), 16, 2	2.6 (−0.17, 5.4)	0.065	0.77 (−0.27, 1.8)	0.14
CMR imaging					
RV EDV (ml/m^2)	109 ± 25	0.06 (−0.003, 0.12)	0.062	−0.003 (−0.03, 0.02)	0.80
LV EDV (ml/m^2)	93 ± 24	0.08 (0.02, 0.14)	0.006	0.03 (0.05, 0.51)	0.016
LV stroke volume ($ml/^2$)	47 ± 10	0.14 (−0.01, 0.29)	0.074	0.07 (0.02, 0.12)	0.011
LV stroke volume (ml)	92 ± 19	0.13 (0.06, 0.21)	0.001	0.03 (−0.001, 0.06)	0.054
RV EF (%)	43.4 ± 6.2	−0.27 (−0.50, −0.03)	0.026	0.01 (−0.08, 0.10)	0.83
LV EF (%)	51.3 ± 5.6	−0.37 (−0.63, −0.12)	0.005	−0.01 (−0.11, 0.09)	0.84
Pulmonary regurgitation (%, IQR)	2 (0,21)	0.09 (−0.03, 0.22)	0.14	−0.03 (−0.07, 0.02)	0.26
Aortic regurgitation (%, IQR)	0 (0, 4)	0.23 (−0.10, 0.56)	0.16	0.06 (−0.06, 0.18)	0.31

Data are described as frequency with percentage (%), mean ± SD, or median with IQR.
Abbreviations: IQR, interquartile range; NYHA, New York Heart Association; PVR, pulmonary valve replacement; CMR, cardiac magnetic resonance; RV, right ventricle; LV, left ventricle; EDV, end diastolic volume; ESV, end systolic volume; EF, ejection fraction.

multivariable analysis. In multivariable analysis, LV stroke volume remained associated with aortic root growth (β: 0.04 mm/ml (95% C.I.: 0.005, 0.066), $p = 0.024$) when corrected for age, gender, body surface area and baseline diameter.

3.3. Losartan treatment

Of 60 patients with serial CMR measurements, 30 were randomized to losartan treatment and 30 to placebo. Patients were treated for 1.8 ± 0.3 years with losartan, until the follow-up CMR. Losartan was not associated with reduced growth of the aortic root (β: −0.81 mm (95% C.I.: −1.9, 0.28), $p = 0.14$) (Fig. 1B).

4. Discussion

This is the first study to prospectively perform serial measurements of the aortic root using CMR imaging in rTOF patients. Other strengths of this study included CMR analysis by a single observer and uniform data acquisition during follow-up. We found that a larger aortic root was more likely in older males, although in these patients progressive growth of the aortic root was not likely. A large LV stroke volume was the only factor associated with both a larger root and ongoing growth.

Current guidelines suggest prophylactic aortic root or ascending aorta surgery at diameters above 55 mm in the general population without another indication for cardiac surgery [11]. None of the patients in our cohort had an aortic root >55 mm. Nonetheless, lower surgical thresholds are applied to patients undergoing cardiac surgery for another reason, which is common in rTOF. Based on both serial measurements and the association of age with baseline diameter, our findings suggest an average aortic root growth of 2-3 mm per 10 years. This is close to the general population [12] and less rapid compared to patients with bicuspid aortic valves [13] or Marfan syndrome [8]. We found no treatment effect of losartan, although our study is limited by sample size and follow-up duration. Considering the limited growth and low number of dissections in literature, we found no valid arguments for a different, more aggressive surgical approach in rTOF compared to the general population.

We found an independent association between the LV stroke volume and both a larger baseline root diameter and ongoing growth. Previous studies found reduced elastic properties of the aortic root in rTOF [14–17]. We hypothesize that a large stroke volume increases shear stress in the aortic root which could eventually lead to progressive dilatation. Cardiac factors that could contribute include aortic regurgitation or ongoing left-right shunting, for instance a (partly) residual palliative shunt or aortic-pulmonary collateral circulation. However, most shunts were operatively closed and data on aortic regurgitation was limited to echocardiography in most patients. Adding both RV and LV outflow tract flow measurements during CMR imaging could therefore be useful in this population. Non-cardiac factors such as hemoglobin level and sympathetic drive or heart rate could impact stroke volume, although these factors were not associated with aortic root dilatation. Previous childhood aortic volume overload may have impacted the aortic root size in adults, as late repair and presence and duration of a previous shunt were associated with a larger aortic root in univariable analysis. These factors were more common in older patients, which remained associated in multivariable analysis.

Limitations of this REDEFINE substudy include the limited sample size leading to wide 95% confidence intervals, in particular regarding the aortic root growth over time, and the limited follow-up duration. In addition, a subgroup of patients had no adequate images and could not be included in the present study and REDEFINE did not include patients with normal RV function or severe valvular dysfunction. We evaluated the aortic root in the three chamber view with good image quality. This was highly reproducible but could lead to underestimation if plane selection was inadequate, similar to echocardiography. Future studies may investigate a larger, general repaired TOF population to more accurately define aortic growth and implications for aortic root surgery.

In conclusion, in rTOF patients included in the REDEFINE trial, about one-third of patients had aortic root dilatation (>40 mm), more likely in older males. There was a trend towards limited aortic root growth during approximately 2 years of follow-up but there was no treatment effect of losartan. We found that LV stroke volume was the only factor independently associated with both a larger baseline diameter and ongoing aortic root growth.

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Declaration of Competing Interest

None.

Acknowledgements

None.

Appendix A

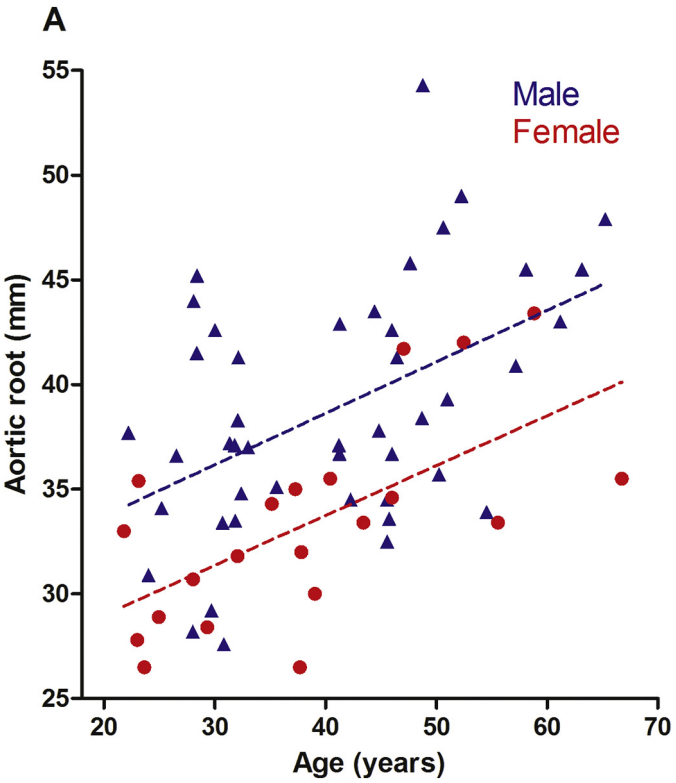

Fig. 1A. Aortic root diameter at baseline according to age and sex. Scatter plot for aortic root diameter and age at baseline, stratified by sex. Females are indicated with red dots (•) and males with blue triangles (Δ). Regression lines are added for males and females.

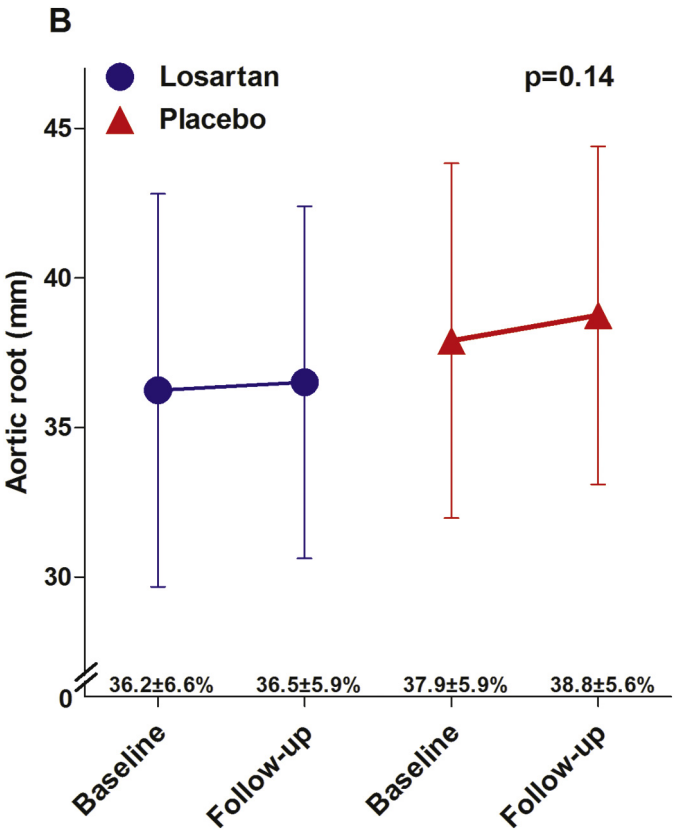

Fig. 1B. Aortic root diameter at baseline and follow-up scan, stratified by losartan treatment. Baseline aortic root diameter and follow-up aortic root diameter in patients allocated to losartan and placebo. Mean with standard deviation are displayed. *P*-value for treatment effect losartan.

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.10.037.

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