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Aortic angle is associated with neo-aortic root dilatation and regurgitation following arterial switch operation

Duarte Martins [a,b,*], Diala Khraiche [a], Antoine Legendre [a], Nathalie Boddaert [c], Olivier Raisky [a], Damien Bonnet [a], Francesca Raimondi [a,c]

[a] Unité Médico-Chirurgicale de Cardiologie Congénitale et Pédiatrique, Centre de référence Malformations Cardiaques Congénitales Complexes - M3C, Paris, France
[b] Pediatric Cardiology Department, Hospital de Santa Cruz, Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal
[c] Radiology Department, Hôpital Universitaire Necker Enfants Malades, Paris, France

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ABSTRACT

Introduction: Neo-aortic root dilatation and regurgitation are common progressive long-term complications of the arterial switch operation (ASO) for transposition of the great arteries (TGA) with increasing clinical burden. While several risk factors have been identified, most are constitutional. The acute aortic angle commonly seen after ASO might alter aortic dynamics and facilitate progression of the neo-aortic root dilatation and aortic regurgitation, but insufficient data is available. We intend to assess the effect of the aortic angle in the extent of neo-aortic root dilatation and presence of regurgitation.
Methods: Retrospective analysis of TGA patients undergoing CMR after ASO at a single tertiary centre from November 2010 to July 2017.
Results: 180 patients were analysed, 157 of which having adequate imaging of the aortic arch and root. Neo-aortic root Z score was normally distributed with 73% of patients having a Z score > 2. The aortic angle had a significant ($p < 0{,}001$) inverse relationship with the neo-aortic root Z score both in univariate and multivariate linear regression. Other significant associations were male gender and the concomitant presence of a VSD or a dysplastic neo-aortic valve. The presence of neo-aortic regurgitation was also inversely correlated with the aortic angle. The presence of a bicuspid neo-aortic valve was another significant association, further correlating with the more severe forms.
Conclusions: Acute aortic angles associate more extensive neo-aortic root dilatation and higher incidence of regurgitation. We believe a surgical technique promoting less acute aortic angles has potential for ameliorating the long-term outcomes of TGA.

1. Introduction

Transposition of the great arteries (TGA) is a common congenital heart disease, with a reported prevalence of 2,3–4,7/10 000 live births [1,2] and accounting for about 20% of all cyanotic congenital heart disease [1].

Neo-aortic root dilatation is a known late complication of the disease, both after palliative atrial surgery [3] or after arterial switch operation (ASO) [4], hinting that aortopathy is indeed a feature of the disease. The overall good results obtained with ASO translate into an increasing number of these patients coming to adult age. With the progressive nature of neo-aortic root dilatation affecting about ¾ of the patients and leading to neo-aortic regurgitation [5], the burden of this complication is likely to increase in the near future.

Several risk factors have been identified [4,6,7], such as the presence of a ventricular septal defect or aortic coarctation, size discrepancy of the great arteries, bicuspid pulmonary valve, previous pulmonary artery banding (PAB) and older age at repair. None of these risk factors are easily modifiable, as the first four are constitutional and the choice for PAB and postponed repair is usually dependent of significant comorbidities or late diagnosis.

Posterior dislocation of the ascending aorta with the Lecompte maneuver often results in a gothic configuration of the aortic arch. In 2008 Agnoletti and colleagues postulated that a more acute aortic angle would change aortic dynamics and predispose to neo-aortic root dilatation [8]. However, their study with catheterization data included normal (non-TGA) controls and failed to clearly demonstrate an effect of the aortic angle within the post-ASO population. More recently, other groups have assessed this post-ASO gothic configuration of the

Abbreviations: ASO, arterial switch operation; AUC, area under the curve; BSA, body surface area; CoAo, coarctation of the aorta; IVS, intact ventricular septum; cMRI, cardiac magnetic resonance imaging; VSD, ventricular septal defect; TGA, transposition of the great arteries.

* Corresponding author.
E-mail address: duartesaraivamartins@gmail.com (D. Martins).

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aortic arch. Computer modelling of aortic flow in typical post-ASO aortic geometries has demonstrated increased wall shear stress compared to normal controls [9]. A study of 105 patients using echocardiography data and classifying the aortic arch as either gothic or not established an association between a gothic aortic arch and neo-aortic root dilatation [10].

We intend to assess the role of the aortic angle as an independent risk factor for neo-aortic root dilatation, as it is a potentially modifiable risk factor. We based our study on cardiac magnetic resonance (cMRI) 3D anatomic data.

2. Methods

We retrospectively analysed all consecutive patients submitted to cMRI after ASO at a single tertiary centre from November 2010 to July 2017. Patients without adequate aortic arch imaging or poor anatomic definition of the neo-aortic root were excluded.

2.1. cMRI image acquisition

cMRI was performed using a 1.5 Tesla scanner (HdxT or MR450 GE Medical systems, Milwaukee, USA). Images were acquired with a 32-channel phased-array cardiac coil and a vector electrocardiogram for R wave triggering.

The complete imaging protocol included 3D respiratory-navigated balanced steady-state free procession sequence, first pass perfusion (FPP) before and after dipyridamole injection, unenhanced cine steady state free precession (cine SSFP) in short axis. Cine-MR echo-gradient images were first used to locate the anatomic axes of the heart.

The 3D respiratory-navigated balanced steady-state free procession sequence (3D FIESTA) was used to visualize cardiac and great vessels anatomy (T2 prepared, fat special, flip angle 65°, 4 RR intervals).

2.2. Image analysis

Neo-aortic root was analysed in multi-planar reformatted images from 3D sequences. A mean value of cusp to commissure and cusp to cusp diameters was obtained. Body surface area (BSA) was derived from weight and height according to the method described by Haycock and colleagues [11]. Z scores for cusp to commissure diameter were calculated using the method published by Kaiser and colleagues whenever applicable (i.e. BSA > 0,5 m^2) [12].

The aortic angle was defined as the angle between the centre of the ascending aorta at the level of pulmonary bifurcation, the highest point of the aortic arch and the centre of the descending aorta at the level of pulmonary bifurcation, similarly to previous publications [8]. This was done in multi-planar reformatted images from 3D sequences. Midpoints of the ascending and descending aorta were defined as the intersection between sagittal and coronal diameters in the strict axial projection at the level of the pulmonary bifurcation. A reformatted plane was then set between these two points and tilted to include the highest point of the aortic arch. Angle measurement was then made in this plane (Supplementary Fig. 1).

The presence of residual coarctaction was defined based solely on morphologic criteria as the presence of an isthmic stenosis of >50% of the diaphragmatic lumen size.

Aortopulmonary mismatch was based on intraoperative visual assessment as written on the surgical report. Neo-aortic regurgitation was evaluated by systematic echocardiography at the day of the cMRI, performed by experienced pediatric cardiologists and classified based on quantitative and qualitative data.

2.3. Statistical analysis

The statistical analysis was performed on Stata™ v12. Categorical variables were expressed as percentages. The continuous variables having a normal distribution were expressed as mean values, accompanied by their standard deviation. All continuous variables having a non-normal distribution were expressed as median values and 25th and 75th quartiles. Analysis of continuous variables was performed by use of an unpaired *t*-test. A value of $p < 0.05$ was accepted as significant. Categorical variables were analysed by a two-tailed Fischer's exact test. Both logistic and linear multivariate models were construed based on step down approach using significant univariate associations. Receiver operating characteristic (ROC) analysis was performed to assess significant predictors.

3. Results

180 patients were submitted to elective cMRI following ASO during the study period, most of which for systematic stress imaging during adolescence. Twenty tree patients met exclusion criteria. Characteristics of 157 patients included are summarised in Table 1. Despite some late surgeries offsetting the mean, the 75th centile of age at surgery is 12 days. There is equally a small percentage of PAB. One patient had aortic root and valve replacement (Bentall procedure) for severe dilatation and regurgitation.

Table 1
Demographic characteristics. TGA – Transposition of the Great Arteries; IVS – Intact Ventricular Septum; VSD – Ventricle Septal Defect; CoAo – Coarctation of the Aorta; PAB – Pulmonary Artery Banding; cMRI – Cardiac Magnetic Resonance Imaging; BSA – Body Surface Area.

n	157
Gender	69% male
Anatomy	
TGA IVS	59%
TGA VSD	26%
TGA VSD CoAo	13%
TGA subpulmonary stenosis	1%
Aortopulmonary mismatch	
None	18%
Mild	44%
Severe	38%
Age at surgery (days)	14,9 ± 30,9 (P75 12 days)
Previous PAB	1,28%
Neo-aortic valve anomaly	
Bicuspid	5%
Displastic	3%
Age at cMRI (years)	14,9 ± 4,6
Weight at cMRI (kg)	52,8 ± 17,7
Height at cMRI (cm)	159,2 ± 21,6
BSA at cMRI (m^2)	1,51 ± 0,36
Aortic root cusp to commissure (mm/$BSA^{0,5}$)	25,62 ± 6,02
Aortic root cusp to comissure Z score	2,94 ± 1,51
Aortic root cusp to cusp/$BSA^{0,5}$	27,15 ± 3,20
Aortic angle (°)	55,37 ± 10,51
Residual coarctation	5%

Seventy tree percent of patients had a dilated neo-aortic root (neo-aortic root Z score > 2, Z score values ranged from −0,34 to 7,01 following a normal distribution as proved by a non-significant Shapiro–Wilk test of normality (Supplementary Fig. 2)).

The measured aortic angle had a statistically significant inverse relationship with the neo-aortic root Z score ($p < 0{,}001$), with more acute angles being associated with greater dilatation (Fig. 1). Average Z score was found to be near-normal (2,2) when the aortic angle was 65° or higher. In fact, the aortic angle was a decent predictor of the neo-aortic dilatation upon ROC analysis, with an AUC of 0,72 for the prediction of important dilatation as defined by neo-aortic root Z score ≥ 3,5. The AUC obtained for the prediction of normal or near-normal neoartic root size (as defined by neo-aortic root Z score ≤ 2,5) was of 0,67. An aortic angle cutpoint of 52,5° was found to be the most accurate

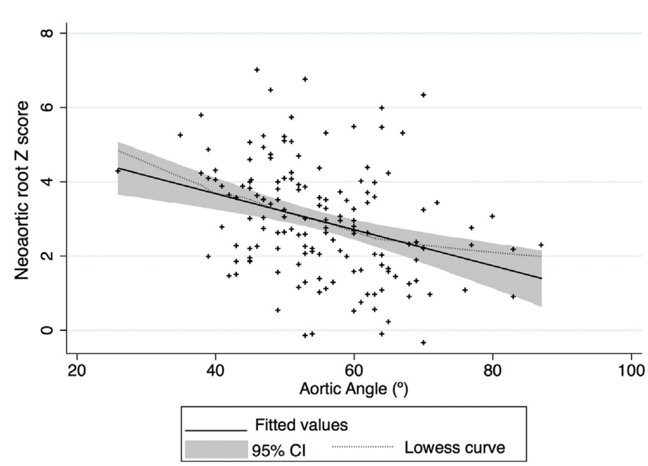

Fig. 1. Aortic angle vs Neo-aortic Z score scatter plot. Fitted linear regression in solid line with 95% CI in grey. The dotted line corresponds to the Lowess (Locally Weighted Scatterplot Smoothing) curve.

Table 2
Predictors of the extent of neo-aortic dilatation. Univariate and multivariate linear regression of Neo-aortic root Z score. TGA – Transposition of the Great Arteries; IVS – Intact Ventricular Septum; VSD – Ventricle Septal Defect; CoAo – Coarctation of the Aorta; PAB – Pulmonary Artery Banding; cMRI – Cardiac Magnetic Resonance Imaging.

	Univariate		Multivariate (adjusted R^2 0,365)	
	Coefficient	*p*	Coefficient	*p*
Gender (if female)	−0,74	0,004	−0,89	0,008
Anatomy (vs TGA IVS)				
TGA VSD	0,79	0,004	0,93	0,008
TGA VSD CoAo	1,44	<0,001	1,4	0,020
TGA subpulmonary stenosis	1,77	0,084	−1,68	0,378
Aortopulmonary mismatch				
Mild	0,34	0,481	0,16	0,693
Severe	1,05	0,033	0,1	0,816
Age at surgery	0,008	0,085		
Previous PAB	3,15	0,003	−1,56	0,628
Neo-aortic valve anomaly				
Bicuspid	0,88	0,106	0,38	0,528
Displastic	1,61	0,035	2,32	0,004
Age at cMRI	0,05	0,103		
Aortic angle	−0,05	<0,001	−0,05	0,001
Residual coarctation	0,89	0,104		

Table 3
Predictors of the presence of neo-aortic regurgitation. Univariate and multivariate logistic regression. TGA – Transposition of the Great Arteries; IVS – Intact Ventricular Septum; VSD – Ventricle Septal Defect; CoAo – Coarctation of the Aorta; PAB – Pulmonary Artery Banding; cMRI – Cardiac Magnetic Resonance imaging.

	Univariate		Multivariate (pseudo R^2 0,254)	
	OR	*p*	OR	*p*
Gender	0,5	0,136		
Anatomy (vs TGA IVS)				
TGA VSD	2,57	0,039	2,63	0,075
TGA VSD CoAo	3,23	0,035	1,91	0,370
Aortopulmonary mismatch				
Mild	1,92	0,446		
Severe	2,26	0,345		
Age at surgery	1,01	0,229		
Previous PAB	3,61	0,369		
Neo-aortic valve anomaly				
Bicuspid	13,8	0,002	24,65	0,002
Displastic	6,9	0,040	1,22	0,895
Age at cMRI	1,08	0,103		
Aortic angle	0,95	0,018	0,98	0,537
Residual coarctation	1,18	0,839		
Aortic root Z score	2,10	<0,001	1,98	0,001

in our series. Values over this cutpoint were found to associate with near-normal neo-aortic root sizes with 74% sensitivity and 60% specificity, while values under this cutpoint were found to be associated with important dilatation with 67% sensitivity and 73% specificity.

Inverse correlation was statistically significant both in univariate and multivariate linear regression. Other significant associations were male gender, the concomitant presence of a VSD or of a dysplastic neo-aortic valve (Table 2). Age at surgery was not found to be associated with neo-aortic root dilatation, losing statistical significance when corrected for anatomical subtype ($p = 0,353$). There was a non-significant increase of the average z score with age (2,5 in the 1st decade of life, 3,0 in the 2nd and 3,3 thereafter) with 77% of the study population in its 2nd decade of life.

Clinically significant neo-aortic regurgitation (mild to severe) was present in 22% of the patients, 20% of which (5% of the total) having a moderate to severe form. Trivial regurgitation was almost universal in the rest of the population. Neo-aortic root dilatation was associated with the presence of regurgitation, both in univariate and multivariate logistic regression. The aortic angle was inversely correlated to the presence of aortic regurgitation in univariate logistic regression, but not on multivariate regression (Table 3). Neither associated with the more severe forms, possibly due to the small number of cases.

Other important associations were the concomitant presence of a VSD, especially if associated with coarctation, and the presence of a bicuspid neo-aortic valve. The latter also correlated with severe forms, with an odds ratio of 69 and $p < 0,001$.

4. Discussion

Overall incidence of neo-aortic root dilatation in our series is coherent with the results previously shown by the Boston group [5]. Our population had a slightly lower overall incidence of neo-aortic regurgitation as compared with the results of this group. While mild regurgitation might have been underestimated due to lack of systematic aortic flow measurement, it is unlikely that moderate to severe regurgitation were overlooked.

The mean aortic angle in our population matches perfectly the mean angle of the post-ASO patients of previous catheterization data [8].

The normal distribution of the neo-aortic root Z score hints at the multitude of intervening factors at play. Even with four statistically significant associations, our regression model only had an adjusted R^2 of 0,36, with much individual variation not explained by current known risk factors. Moreover, gender differences were not accounted for in the development of the Z scores for the aortic dimensions used, as noted by Kaiser et al. [12]. Gender differences in our population might simply reflect normal differences not detected in the smaller population of the published reference values, rather than a true biological effect. This emphasizes the need for better reference values for children and adolescents. In addition to this, we believe that the lack of statistical significance of the presence of a previous PAB and the age at corrective surgery may be reflective of institutional policies, with small representation of the former and a tendency for early correction in our sample.

We demonstrated that the acute aortic angle is a risk factor for the extent of neo-aortic root dilatation following ASO. This measure is a surrogate of the complex aortic dynamics of flow and associated wall stress taking place [9] and a risk-assessment score with good individual prognostic value which can be used for tailored decision making should probably include a more direct measure of flow eccentricity and shear stress. Nevertheless, the aortic angle is a simple measurement with prognostic value that can be done quickly without the need for dedicated software.

The more acute aortic angle following ASO is also associated with neo-aortic regurgitation. We believe this happens through a mechanism of progressive neo-aortic dilatation, explaining the lack of statistical significance when corrected for the latter in multivariate regression. The other identified risk factors are compatible with those described in the literature [4]. It is interesting that the bicuspid neo-aortic valve is correlated to neo-aortic regurgitation while other forms of neo-aortic dysplasia associate with the extent of neo-aortic root dilatation. It is possible that the abnormal helical flow generated by bicuspid valve might in fact displace the point of maximum wall stress more distally [13], thus sparing the neo-aortic root. Further studies are needed looking into this.

We believe that the unique feature of the aortic angle as a risk factor is its potential for modification. We postulate that a modification of the current ASO surgical technique promoting a less acute aortic angle might have a positive long-term effect in preventing neo-aortic root and valve disease.

5. Limitations

This study is a retrospective, single centre study. Standardized cMRI protocols attenuate the retrospective nature of the study. Unfortunately, these did not include systematic aortic flow measurement, so aortic regurgitation presence and grading were based essentially on echocardiography data. Finally, as often is the case with congenital cardiac patients, sample size is not ideal even though this represents one of the largest series published to date.

6. Conclusions

Neo-aortic root dilatation is a common complication affecting 73% of TGA patients post-ASO. The neo-aortic root Z score is normally distributed in this population and is inversely correlated with the aortic angle, with more acute aortic angles associating with more important neo-aortic root dilatation. Neo-aortic root regurgitation is also inversely correlated with the aortic angle, with more acute angles associating with higher incidence of regurgitation. We believe a surgical modification of the ASO promoting a less acute aortic angle has the potential for ameliorating the long-term outcome of TGA.

6.1. Perspectives

Competency in medical knowledge: Aortic angulation following the arterial switch operation promotes late dilatation and subsequent regurgitation of the aortic root.

Competency in patient care: Measurement of the aortic angle is easily performed with basic image analysis software and has prognostic value for the development late dilatation and subsequent regurgitation of the aortic root.

Translational outlook: Although easy to measure, the aortic angle is a surrogate for a more complex interaction of altered anatomy and hemodynamics in the aortic arch following the arterial switch operation. Studies involving 4D phase contrast data associated with computer modelling may further elucidate the mechanism for neo-aortic root dilatation and regurgitation.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.01.042.

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