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The aorta in transposition of the great arteries

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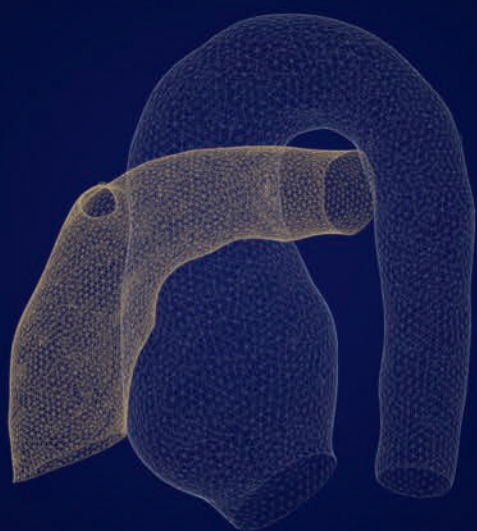


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CHAPTER 5

Neo-aortic growth rate and diameter as risk factors for neo-aortic valve regurgitation after arterial switch operation

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To the Editor

Patients after arterial switch operation (ASO) for transposition of the great arteries (TGA) usually have excellent late survival with good quality of life. However, residual sequelae may develop post-ASO of which neo-aortic root dilatation and neo-aortic valve regurgitation (AR) are common and require longitudinal monitoring on severity and progression. Although current reoperation rates for neo-aortic root dilatation or AR are relatively low,^{1,2} it is reported to be the second most common cause for reoperation in the long-term follow-up.³

In our recently published paper⁴ we reported on the ongoing progression of neo-aortic root dilatation beyond childhood (Figure, panels A and B) and identified TGA morphological subtype and male sex as risk factors for neo-aortic root dilatation. In that paper, neo-aortic dimensions and neo-aortic valve function derived from echocardiographic imaging were longitudinally assessed from birth till adulthood in 345 TGA patients after ASO. Thirty-three

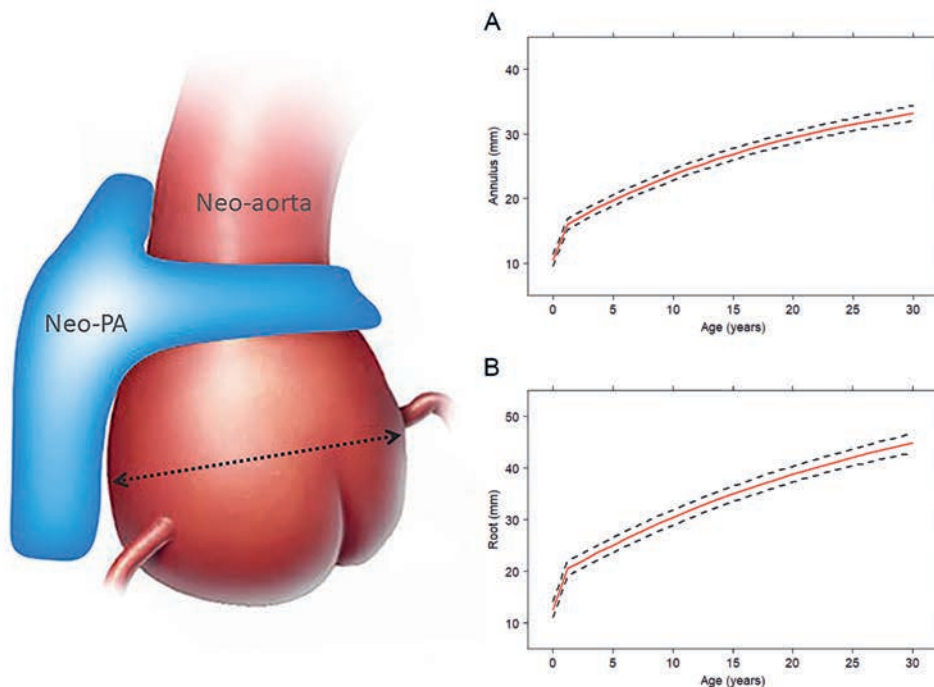


Figure. The great arteries after arterial switch operation and mean progression of neo-aortic dimensions. Neo-pulmonary artery and pulmonary artery branches (neo-PA) running in front and embracing the neo-aorta with its dilated neo-aortic root (dashed arrow). Panels A and B derived from van der Palen et al.⁴ represent mean progression of neo-aortic dimensions over time for all patients after arterial switch operation for transposition of the great arteries: neo-aortic annulus (A), neo-aortic root (B). Mean profiles are plotted with the described risk factors set to the reference level; dashed lines represent 95% confidence intervals.

of the 345 patients (9.6%) developed at least moderate AR ($AR \geq \text{moderate}$) and mild or more AR ($AR \geq \text{mild}$) was present in one hundred and eleven patients (32.2%). From these data, the mutual relationship between the neo-aortic root dilatation and the development of neo-aortic valve regurgitation was demonstrated. Univariate time-dependent Cox-regression (TD-Cox) analysis to assess the effect of changing aortic dimensions over time on the risk of $AR \geq \text{moderate}$ showed a clear relationship between neo-aortic annulus and root dimensions and $AR \geq \text{moderate}$. However, with the multivariate TD-Cox analysis only neo-aortic root dimensions were independently associated with the development of $AR \geq \text{moderate}$ (HR = 1.09 (1.01-1.17), $P = 0.040$). No significant association could be established for the development of $AR \geq \text{mild}$, neither in the univariate nor in the multivariate analysis.

Recent developments in biostatistics allow a more comprehensive statistical approach for the evaluation of the association between longitudinal markers and time-to-event outcomes by means of joint modeling.⁵ A major advantage of the joint model compared to the TD-Cox analysis is that the joint model reconstructs the complete trajectory of the longitudinal marker instead of assuming it to remain constant between two measurement points. This assumption of the TD-Cox model might have had an effect on the results and conclusions from our series. The joint model method combines a mixed effect submodel for the longitudinal marker with a time-to-event submodel for the risk of the event. The mixed effect submodel estimates the trajectory of a marker (i.e. neo-aortic diameter in our dataset), and the estimated marker value at the time of the event (i.e. reaching certain degree of neo-aortic valve regurgitation) is used to estimate the hazard of the event. Non-linear terms, such as quadratic terms or splines, can be included in the mixed effect submodel to obtain a modelled trajectory of the marker that follows the natural evolution over time. Since the event of neo-aortic regurgitation is only diagnosed at a visit, the exact time point of the event is unknown, but takes place somewhere between the last two measurements. This interval-censored nature of the data can be taken into account by the joint model. Another advantage of joint modeling over TD-Cox analysis is that it additionally easily allows for modeling of different associations between the marker and the event. For example, the slope of the marker can be additionally included. Therefore, analysis of the valve function over time in relation to neo-aortic dimensions with the joint modeling statistical approach is preferable to the TD-Cox model for the analysis of our dataset and the dataset was therefore re-analyzed.

In accordance with the previous analysis,⁴ cubic splines with knots at 2 and 10 years were used in the mixed effect model to capture non-linear evolutions over time. The mixed effect models were estimated for both neo-aortic annulus and root dimensions over time, and the event data were classified as either $AR \geq \text{mild}$ or $AR \geq \text{moderate}$. In addition to the estimated neo-aortic dimensions, the slope of this marker was added to the survival submodel, representing the estimated growth rate at each point in time. Additional risk factors measured at baseline were included in the risk submodel, which was estimated taking the interval censoring into account. Statistical analysis was performed with the JMbayes software package in R.^{6,7}

From the multivariable analysis using the joint modeling approach, it was confirmed that the neo-aortic root dimensions showed a positive significant association with AR \geq moderate, but the association was much stronger than was determined by the previous TD-Cox analysis (Joint modeling: HR = 1.25 (1.13-1.39), $P < 0.001$ vs TD-Cox: HR = 1.09 (1.01-1.17), $P = 0.040$ (Table). Furthermore, with joint modeling the neo-aortic root dimension was also shown to be an independent risk factor for the development of AR \geq mild (HR = 1.15 (1.08-1.22), $P < 0.001$), where previously no association was found. Moreover, the neo-aortic annulus dimension was an independent risk factor for the development of AR \geq mild and AR \geq moderate (AR \geq mild: HR = 1.18 (1.10-1.27), $P < 0.001$; AR \geq moderate: HR = 1.22 (1.08-1.38), $P < 0.001$). Apart from this, we identified that the neo-aortic annular growth rate as well as the neo-aortic root growth rate were independently associated with the development of at least mild neo-aortic regurgitation (Table). This means that a faster growth of the neo-aortic annulus and neo-aortic root, in addition to the neo-aortic dimensions itself, was associated with a higher risk of AR \geq mild. For AR \geq moderate, growth rate of the neo-aortic annulus and

Table. Time-dependent Cox models and Joint models for the risk on neo-aortic valve regurgitation

<i>TD Cox model</i> [§]		AR \geqmoderate*		AR \geqmild**	
Diameter increase		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Annulus (per mm)		1.09 (0.99 – 1.21)	0.09	1.03 (0.97– 1.09)	0.31
Root (per mm)		1.09 (1.01 – 1.17)	0.04	1.04 (0.99 – 1.09)	0.10
<i>Joint model</i>		AR \geqmoderate*		AR \geqmild**	
Diameter increase		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Annulus (per mm) - dimension	dimension	1.22 (1.08 – 1.38)	<0.001	1.18 (1.10 – 1.27)	<0.001
	dimension and slope	1.20 (1.07 – 1.37)	0.006	1.11 (1.03 – 1.20)	0.008
Annulus (per mm) - dimension and slope	slope	1.75 (0.44 – 6.24)	0.376	3.06 (1.40 – 6.45)	0.004
	dimension	1.25 (1.13 – 1.39)	<0.001	1.15 (1.08 – 1.22)	<0.001
Root (per mm) - dimension and slope	dimension	1.25 (1.13 – 1.38)	<0.001	1.10 (1.04 – 1.18)	0.006
	slope	1.26 (0.36 – 3.72)	0.647	2.28 (1.28 – 4.02)	0.008

[§] Results from time-dependent Cox model as reported by van der Palen et al.⁴

* Multivariable analysis adjusted for morphological subtype and gender. $n = 31/323$ (annulus); $n = 32/323$ (root).

** Multivariable analysis adjusted for morphological subtype, gender, pulmonary valve, previous pulmonary artery banding and age ASO ≥ 6 months of age. $n = 105/323$ (annulus and root).

AR, neo-aortic valve regurgitation.

root did not show such an association next to its absolute neo-aortic dimensions. This could be related to a lack of power as less than 10% of the patients developed AR \geq moderate.

Data on the evaluation of the neo-aortic growth rate next to neo-aortic dimensions is new in the clinical risk factor assessment on the development of neo-aortic valve regurgitation in patients after congenital heart surgery. This report is the first to show the effect of neo-aortic growth rate in addition to neo-aortic dimensions as critical factors for the impairment of neo-aortic valve function. These results, with stronger and additional effect measures compared to the previously reported outcomes by traditional TD-Cox regression analysis,⁴ support the knowledge and concept of AR mechanisms by root dilatation as presented previously by Grande et al. using computational modeling.⁸ From that study, progressive root dilatation has been shown to reveal a significant increase in stress and strain on the aortic valve leaflets, leading to significantly reduced leaflet coaptation and valve regurgitation.⁸

The advantages of multimarker analysis from joint modeling on large population data ultimately might help in tailoring surgical decision making for neo-aortic valve and/or root reinterventions after ASO. Furthermore, extensions to this joint model approach can also help for individual prediction of the occurrence of a defined event in future (i.e. reaching certain degree of AR), by the use of dynamic predictions of the repeated measures in the joint model. With this technique, for each individual patient the probability of a certain degree of valve regurgitation over time can be estimated. Each time new information on the patient's aortic dimensions is available, the probabilities can be updated.

In conclusion, based on the joint model analysis, both annulus and root dimensions are independently associated with AR and, additionally, growth rate of the former native pulmonary valve annulus and adjacent root is associated with AR as well. The fact that neo-aortic dilatation after ASO is progressive over time without stabilization in adulthood, predicts an increasing incidence of neo-aortic regurgitation in future with an expected growing need for surgical reinterventions on the neo-aortic valve and/or root.

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