Neo-aortic growth rate and diameter as risk factors for neo-aortic valve regurgitation after arterial switch operation – data re-analysis (August 22, 2020)

INTRODUCTION

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 are common and require longitudinal monitoring on severity and progression. Although current reoperation rates for neo-aortic root dilatation or neo-aortic regurgitation (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 article[4] 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 of the 345 patients (9.6%) developed at least moderate AR (AR≥moderate) and mild or more AR (AR≥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. Univariable time-dependent Cox-regression (TD-Cox) analysis to assess the effect of changing aortic dimensions over time on the risk of AR≥moderate showed a clear relationship between neo-aortic annulus and root dimensions and AR≥moderate. However, with the multivariable TD-Cox analysis only neo-aortic root dimensions were independently associated with the development of AR≥moderate (HR 1.09 (1.01-1.17), p=0.040). No significant association could be established for the development of AR≥mild, neither in the univariable nor in the multivariable analysis.

However, TD-Cox analysis is an analysis method with several restrictive assumptions and recent developments in biostatistics allow a more comprehensive statistical analysis approach for the evaluation of the association between longitudinal markers and time-to-event outcomes by means of joint modeling.[5] A major disadvantage of TD-Cox analysis compared to joint modeling is the assumption that the aortic dimensions between two measurement points remain constant. This might have had an effect on the results and conclusions from our series. Therefore, a re-analysis of the data from the study was performed using the joint modeling.

METHODS

All data from the original article (i.e. neo-aortic dimensions and neo-aortic valve function of the entire population) were used for the re-analysis.[4]

Statistical analysis – joint modeling and its advantages

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 take place somewhere between the last two measurements, the exact time point of the event is unknown. A joint model can take the interval-censored nature of the data into account. 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≥mild or AR≥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]

RESULTS

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, 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 shown to be an independent risk factor for the development of AR≥mild (HR 1.15 (1.08-1.22), p<0.001), where previously no significant association was found. Moreover, the neo-aortic annulus dimension was an independent risk factor for the development of AR≥mild and AR≥moderate (AR≥mild: HR 1.18 (1.10-1.27), p<0.001; AR≥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≥mild. For AR≥moderate, growth rate of the neo-aortic annulus and 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≥moderate.

DISCUSSION

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 this patient’s aortic dimensions is available, the probabilities can be updated.

In conclusion, based on the joint model analysis, main independent drivers for AR are both annulus and root dimensions and additionally growth rate of the former native pulmonary valve annulus and adjacent root. 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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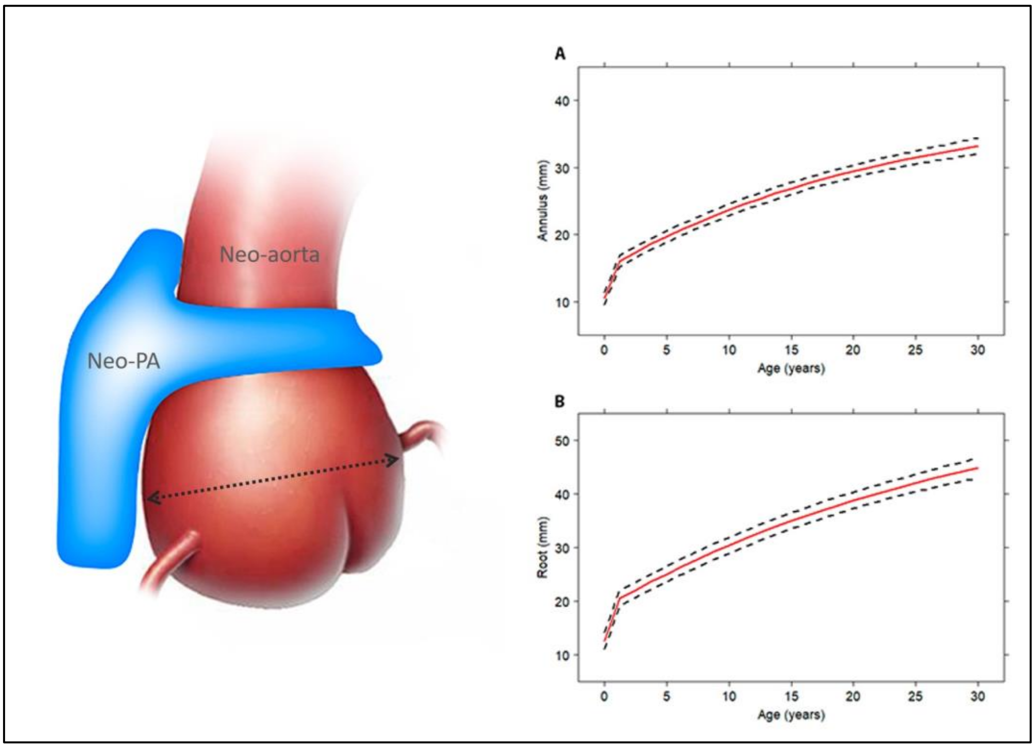
Figure The great arteries after arterial switch operation and mean progression of neo-aortic dimensions



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 time for all patients after arterial switch operation for transposition of the great arteries; panel A: neo-aortic annulus, panel B: neo-aortic root. Mean profiles are plotted with the described risk factors set to the reference level; dashed lines represent 95% confidence intervals.

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

TD Cox [$]		AR ≥ moderate*			AR ≥ mild**	
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**

Joint Model		AR ≥ moderate*			AR ≥ mild**	
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**	dimension	1.18 (1.10 – 1.27)	**<0.001**
Annulus (per mm) - *dimension and slope*	dimension	1.20 (1.07 – 1.37)	**0.006**	dimension	1.11 (1.03 – 1.20)	**0.008**
	slope	1.75 (0.44 – 6.24)	**0.376**	slope	3.06 (1.40 – 6.45)	**0.004**
Root (per mm) - *dimension*	dimension	1.25 (1.13 – 1.39)	**<0.001**	dimension	1.15 (1.08 – 1.22)	**<0.001**
Root (per mm) - *dimension and slope*	dimension	1.25 (1.13 – 1.38)	**<0.001**	dimension	1.10 (1.04 – 1.18)	**0.006**
	slope	1.26 (0.36 – 3.72)	**0.647**	slope	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).