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The ongoing debate: Longevity of biological valves in pulmonary position

Marlene Müller, Daniel Biermann, Miriam Righa, Henning Carstens, Rainer G Kozlik-Feldmann, Michael Hübler, Jörg S Sachweh.

Affiliations below.

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Abstract:
Background
In patients with tetralogy of Fallot (ToF) or ToF-like anatomy, factors possibly impacting the longevity of biological valves in pulmonary position were investigated.

Method
Between 1997 and 2017, 79 consecutive hospital survivors with a median age of 8.7 years (range 0.2-56.1 years; IQR 14.8 years) with ToF or ToF-like anatomy underwent surgical implantation of Contegra™ (n=34), Hancock™ (n=23), Perimount™ (n=9), pulmonary homograft (n=9), and miscellaneous (n=4) conduits. The median internal graft diameter was 19mm (range 11-29mm; IQR 8mm) which refers to a median z-score of 0.6SD (range -1.8-4.0SD; IQR 2.1SD).

Results
The median time of follow-up was 9.4 years (range 1.1-18.8 years; IQR 6.0 years). Thirty-nine patients (49%) underwent surgical (n=32) or interventional (n=7) pulmonary valve re-replacement. Univariate cox regression revealed patient age (p=0.018), body surface area (p=0.004), internal valve diameter (p=0.005) and prosthesis z-score (p=0.018) to impact valve longevity. Multivariate cox regression analysis, however, did not show any significant effect (likely related to multicollinearity). Subgroup analysis showed that valve revised patients have a higher average z-score (p=0.003) and a younger average age (p=0.007).

Conclusion
A decreased longevity of biological valves in pulmonary position is related to younger age, lower valve diameter, and higher z-score. Because valve size (diameter and z-score) can be predicted by age, patient age is the crucial parameter influencing graft longevity.

Corresponding Author:
Marlene Müller, Universitätsklinikum Hamburg-Eppendorf Universitäres Herzzentrum Hamburg GmbH, Abteilung für Interdisziplinäres Kinderherzprogramm, Martinistraße 52, 20246 Hamburg, Germany, marlene.mueller99@web.de, marlene.mueller@stud.uke.uni-hamburg.de

Contributors‘ Statement: 1. Conception and design of the work: M. Müller, D. Biermann, M. Righa, H. Carstens, R.G. Kozlik-Feldmann, M. Hübler, J.S. Sachweh
2. Data collection: M. Müller, D. Biermann, M. Righa, H. Carstens, R.G. Kozlik-Feldmann, M. Hübler, J.S. Sachweh
3. Analysis and interpretation of the data: M. Müller, D. Biermann, M. Righa, H. Carstens, R.G. Kozlik-Feldmann, M. Hübler, J.S. Sachweh
4. Statistical analysis: M. Müller, D. Biermann, M. Righa, H. Carstens, R.G. Kozlik-Feldmann, M. Hübler, J.S. Sachweh

5. Drafting the manuscript: M. Müller, D. Biermann, M. Righa, H. Carstens, R.G. Kozlik-Feldmann, M. Hübler, J.S. Sachweh
6. Critical revision of the manuscript: M. Müller, D. Biermann, M. Righa, H. Carstens, R.G. Kozlik-Feldmann, M. Hübler, J.S. Sachweh

Affiliations:
Marlene Müller, Universitätsklinikum Hamburg-Eppendorf Universitäres Herzzentrum Hamburg GmbH, Abteilung für Interdisziplinäres Kinderherzprogramm, Hamburg, Germany
Daniel Biermann, Universitätsklinikum Hamburg-Eppendorf Universitäres Herzzentrum Hamburg GmbH, Abteilung für Interdisziplinä-res Kinderherzprogramm, Hamburg, Germany
Miriam Righa, Universitätsklinikum Hamburg-Eppendorf Universitäres Herzzentrum Hamburg GmbH, Abteilung für Interdisziplinäres Kinderherzprogramm, Hamburg, Germany
[...]
Jörg S Sachweh, Universitätsklinikum Hamburg-Eppendorf Universitäres Herzzentrum Hamburg GmbH, Abteilung für Interdisziplinäres Kinderherzprogramm, Hamburg, Germany

Table 1: Frequency of different valve types and mean graft sizes (SD) in 79 patients

Table 2: Hazard ratio of freedom from reoperation or reintervention with regard to certain covariates

Table 3: Reasons for graft revision in patients who received an oversized graft

Table 4: Reasons for graft revision in patients who did not receive an oversized graft

Figure 1: Biological valve size displayed as inner diameter (blue coloured) and z-score (orange coloured) in relation to patient age at time of follow-up

Figure 2: Z-score in relation to patient age differentiated according whether graft revision was performed (red) or not (green)

Table 1: Frequency of different valve types and mean graft sizes (SD) in 79 patients

Valve Type	
Homograft	9 (11%)
Contegra™	34 (43%)
Hancock™	23 (29%)
Perimount™	9 (11%)
Misc.	4 (6%)
Prosthesis inner diameter (mm)	19 (range 11 - 29; IQR 8)
Prosthesis z-score (SD)	0.6 (range -1.8 - 4.0; IQR 2.1)

Table 2: Hazard ratio of freedom from reoperation or reintervention with regard to certain covariates

	Univariate Analysis		Multivariate Analysis	
Covariate	**Hazard ratio (95% CI)**	**(P-value)**	**Hazard ratio (95% CI)**	**(P-value)**
Age	0.96 (0.93 - 0.99)	**0.018**	1.00 (0.94 - 1.06)	0.971
Gender				
Male (n = 42; 53%)	1			
Female (n = 37; 47%)	0.87 (0.63 - 1.21)	0.401		
BSA	0.40 (0.21 - 0.75)	**0.004**	0.30 (0.02 - 5.66)	0.421
Main cardiac diagnosis				
ToF/PS (n = 44; 56%)	1	0.147		
PA/VSD/PDA (n = 26; 29%)	1.47 (0.71 - 3.0)	0.298		
PA/VSD/MAPCA (n = 12; 15%)	2.32 (0.99 - 5.42)	0.053		
PA vs. PS				
PA (n = 35; 44%)	1			
PS (n = 44; 56%)	1.30 (0.94 - 1.80)	0.110		
MAPCAs in general				
No (n = 63; 80%)	1			
Yes (n = 16; 20%)	1.16 (0.80 - 1.68)	0.447		
Prev. cardiovascular surgery				
No (n = 6; 8%)	1			
Yes (n = 73; 92%)	0.77 (0.46 - 1.30)	0.328		
Systemic to pulmonary shunt				
No (n = 37; 47%)	1			
Yes (n = 42; 53%)	1.15 (0.83 - 1.58)	0.397		
Previous RVOT surgery				
No (n = 44; 56%)	1			
Yes (n = 35; 44%)	0.76 (0.54 - 1.07)	0.116		
Valve Substitute				
Homograft	1			
Contegra™	1.61 (0.86 - 3.04)	0.137		
Hancock™	1.02 (0.49 - 2.14)	0.952		
Perimount™	1.00 (0.30 - 3.42)	0.994		
Misc.	0.53 (0.11 - 2.64)	0.435		
Valve prosthesis inner diameter (see table 1)	0.89 (0.82 - 0.97)	**0.005**	1.01 (0.80 - 1.28)	0.937
Valve prosthesis z-score (see table 1)	1.33 (1.05 - 1.67)	**0.018**	0.89 (0.52 - 1.54)	0.678

Table 3: Reasons for graft revision in patients who received an oversized graft

Reasons for Graft Revision	Frequency	Percentage
Stenosis	8	61.5%
Regurgitation	1	7.7%
Both	2	15.4%
Endokarditis	2	15.4%
Total	13	100%

Table 4: Reasons for graft revision in patients who did not receive an oversized graft

Reasons for Graft Revision	Frequency	Percentage
Stenosis	11	45.8%
Regurgitation	1	4.2%
Both	7	29.2%
Unknown	5	20.8%
Total	34	100%

The ongoing debate: Longevity of biological valves in pulmonary position

Abstract

Background
In patients with tetralogy of Fallot (ToF) or ToF-like anatomy, factors possibly impacting the longevity of biological valves in pulmonary position were investigated.

Method
Between 1997 and 2017, 79 consecutive hospital survivors with a median age of 8.7 years (range 0.2-56.1 years; IQR 14.8 years) with ToF or ToF-like anatomy underwent surgical implantation of Contegra™ (n=34), Hancock™ (n=23), Perimount™ (n=9), pulmonary homograft (n=9), and miscellaneous (n=4) conduits. The median internal graft diameter was 19mm (range 11-29mm; IQR 8mm) which refers to a median z-score of 0.6SD (range -1.8-4.0SD; IQR 2.1SD).

Results
The median time of follow-up was 9.4 years (range 1.1-18.8 years; IQR 6.0 years). Thirty-nine patients (49%) underwent surgical (n=32) or interventional (n=7) pulmonary valve re-replacement. Univariate cox regression revealed patient age (p=0.018), body surface area (p=0.004), internal valve diameter (p=0.005) and prosthesis z-score (p=0.018) to impact valve longevity. Multivariate cox regression analysis, however, did not show any significant effect (likely related to multicollinearity). Subgroup analysis showed that valve revised patients have a higher average z-score (p=0.003) and a younger average age (p=0.007).

Conclusion
A decreased longevity of biological valves in pulmonary position is related to younger age, lower valve diameter, and higher z-score. Because valve size (diameter and z-score) can be predicted by age, patient age is the crucial parameter influencing graft longevity.

Introduction

In patients with congenital heart disease (CHD), structural malformations involving the right ventricular outflow tract (RVOT) are common. Among these, tetralogy of Fallot (ToF) often serves as an example of cyanotic CHD, which is associated with subpulmonary obstruction at one or more levels. When a patient's autologous pulmonary valve is not suitable for sustained repair, valve replacement becomes necessary to prevent the deleterious effects of right ventricular volume and/or pressure overload. Another frequent indication for pulmonary valve replacement is the Ross operation, where the pulmonary autograft serves as the aortic root. This situation is unique, as an initially healthy RVOT is transformed into a diseased one with the potential for lifelong necessity for reoperations and/or reinterventions [1].
In pulmonary position, biological prostheses are the valve substitutes of choice, as there is usually no need for long-term anticoagulation, and the hemodynamic load on the valve is typically lower than in the systemic circulation. However, despite being increasingly implanted since the 1970s, the longevity of biological valves of any type remains a matter of

concern. Recent literature reports freedom from re-replacement of biological valves in the pulmonary position to be between 68% and 95% at 5 years and between 0% and 59% at 10 years, as biological prostheses are subject to a process of degradation [2].
The size of the bioprosthetic valve has always been suspected to play a relevant role [3]. However, there is still the question of whether valve size is the decisive parameter in this context or if other factors play a more significant role.
Finding answers to this question holds more than just academic significance. This information not only has the potential to enhance surgical longevity but also to prolong the interval between surgical valve replacements, particularly in light of advancements in transcatheter techniques [4,5,6].

Patients and methods

This study included 79 consecutive hospital survivors with ToF or ToF-like anatomy, who had undergone first time biological pulmonary valve replacement (referred to as the "index surgery") between 1997 and 2014. The median age at that time was 8.7 years (range 0.2 - 56.1 years; IQR 14.8 years), and the median body surface area (BSA) was $0.9m^2$ (range 0.2 - $2.1m^2$; IQR $1.2m^2$). Forty-two patients (53%) were male. Table 1 displays parameters related to the protheses.

Comparability of prosthesis size

The actual measurable size (diameter) of xenografts at the annular level is up to 2mm smaller than the labeled size, depending on the particular conduit type [7]. To ensure close comparability among different valve prostheses, the "true" internal (stent) diameters were used to calculate z-scores. The calculated z-scores are related to the body surface area (BSA) and provide a more realistic estimation of conduit size. The valve size in relation to the body size takes the impact of somatic growth into account [8]. A z-score between -2 and +2 (within the second standard deviation) is referred to as "normal".

Investigated covariates

The following covariates were tested if they had a statistical impact on freedom from surgical or interventional valve re-replacement:

- age at index surgery
- gender
- body surface area (BSA)
- diagnosis (ToF, PA/VSD, DORV)
- multifocal pulmonary perfusion (MAPCA)
- previous RVOT procedures
- graft type
- graft size (absolute diameter in mm, diameter z-score)

Statistics

Patient data was extracted from the clinical information system, anonymized, and transferred to SPSS (IBM SPSS Statistics 29, USA).
Most of the variables were not normally distributed based on the outcome of the Shapiro-Wilk test (age $p < 0.001$; BSA $p < 0.001$; follow-up time p 0.013; prosthesis inner diameter p 0.001). Only for the z-score, a normal distribution was confirmed (p 0.389). To maintain a

consistent overview, measures of central tendency and dispersion are displayed as median and minimum/maximum range, as well as interquartile range (IQR). Freedom from surgical or interventional valve re-replacement of the implanted bioprostheses was set as the primary endpoint. A Cox regression model was applied for survival analysis, with a p-value < 0.05 considered significant. All covariates with a p-value < 0.10 in univariate analysis were subjected to a multivariate Cox regression model.

Results

The median follow-up time was 9.4 years (range 1.1 - 18.8 years; IQR 6.0 years), equivalent to 707 patient-years. Follow-up was defined as the time from the first biological pulmonary valve replacement to the last documented clinical or outpatient check-up. In case of surgical or interventional valve re-replacement, the time from the index surgery until the date of reoperation or reintervention served as the follow-up period. During the follow-up, valve prosthesis re-replacement was necessary in 39 out of 79 patients (32 surgical and 7 interventional; 49%). Indications were stenosis (53.8%), regurgitation (5.1%), combined (23.1%), endocarditis (5.1%), and unknown (12.8%).

The results of univariate and multivariate Cox regression performed on all investigated covariates are presented in table 2. Figure 1 shows the connection between patient age and valve size displayed as internal diameter and z-score. It reveals that at a younger age, grafts were “bigger” as compared to older patients.
The patient cohort was then subdivided into two groups based on whether or not surgical or interventional valve re-replacement was performed. In the following, the subgroup where no prosthesis exchange was deemed necessary will be referred to as the green group, whereas the red group comprises all patients for whom a valve revision was performed. Subsequently, the mean differences in z-score and patient age between the two subgroups were investigated, confirming that the average z-score was significantly higher in the red group (1.3 ± 1.3 > 0.5 ± 1.2, p 0.003) and the average patient age was significantly higher in the green group (17.0 ± 16.4 > 7.2 ± 11.0, p 0.007).
The distribution of z-scores in both subgroups depending on the time of revision or follow-up time suggests a higher z-score in the red group. Ultimately, it can be noted that patients who underwent valve revision not only had a relatively larger implant but were also younger at the time of their index surgery.
Figure 2 shows the age at index surgery as a function of the z-score of the prosthesis. For both groups, a connection between a younger age and a higher z-score and vice versa can be found. Age and z-score influence each other mutually in both subgroups and, therefore, the development of the green curve and the red curve is approximately similar. That means when both variables are considered together, no difference between green and red can be seen. This suggests that only the univariate approach proves that z-score and age significantly influence the necessity of graft revision.

Discussion

Many investigations sought to identify predictors of degradation of valved bioprostheses in pulmonary position in ToF patients. [3,9,10,11,12,14]. However, their results are visibly disparate. The present work identified patient age and graft size to be interrelated factors influencing the freedom from valve re-replacement. This raises the question: Which risk factors should mainly be considered when it comes to valve prosthesis revision in ToF patients?

Age

Data analysis indicated that patient age is the most important covariate in connection with this issue because of its direct relationship with valve size parameters. The findings of this study align with the results of literature research. Chen et al., 2011 concluded that younger age was significantly associated with earlier structural valve prosthesis deterioration and also demonstrated the correlation between patient age and valve size. In addition, they pointed out that the incidence of valve oversizing was higher among children, meaning that adult patients are more likely to have an “appropriate” valve size [3]. Baird et al., 2020 arrived at the same conclusion in a large multicenter study [9].

Graft size

As one of very few studies, it was differentiated between inner diameter and z-score as a measure of the valve’s accuracy of fit. This allowed for the identification of oversized conduits defined as a z-score > 2 SD. Interestingly, both variables not only had a significant influence on the probability of conduit failure but also correlated with each other and age at index surgery. Taken in isolation, a smaller diameter and a higher z-score are risk factors for an earlier need for graft revision, which was also confirmed by the study of Chen et al., 2011 [3].

A similar study by Kim et al., 2022 examined the impact of oversizing on the durability of Contegra™ conduits. The authors highlighted a direct relationship between a larger conduit size, indexed to the patient’s body weight, and earlier conduit failure and emphasized the clinical relevance of appropriately sized conduits to the patient’s individual body dimensions. The most negative effects of oversizing are observed in small babies. This not only urges surgeons to actively avoid intentional oversizing but also calls upon manufacturers of valve-containing RV-PA conduits to include even smaller sizes in their product inventory. Clear explanations for the adverse effects of oversizing have not been provided so far. Kim et al., 2022 state that the size mismatch between the conduit and the downstream pulmonary artery can lead to an aneurysmal dilation of the conduit, with subsequent annulus dilatation and valve regurgitation [10]. Although this would be an interesting approach, it could not be verified in this study. Tables 3 and 4 show that the most common cause of valve revision, regardless of the z-score, is graft stenosis. While isolated regurgitation occurs more frequently in patients with an oversized graft, a combination of regurgitation and stenosis is more common in patients without oversizing.

The discussion now focuses on whether the graft size parameters are independent or confounding variables considering their influence on graft longevity. The assumption of confounding is supported by the fact that the significance of the influence of age, diameter, and z-score on freedom from valve revision is missing in multivariate analysis because of multicollinearity. In conjunction with the finding that a tighter diameter, a bigger z-score, and a younger age are associated with earlier valve degeneration, it can be suspected that first, oversizing not only has no benefit with regard to graft longevity but can possibly shorten freedom from valve revision and, second, patient age might be more relevant than the graft size because the latter is a potential confounding factor. For a precise determination of the causes of earlier need for valve re-replacement in oversized conduits with a focus on age-related factors, the importance of additional multicenter studies in a larger patient cohort is emphasized.

Gender

The influence of gender on the longevity of bioprosthetic valves is evaluated differently. In this study, no evidence of gender-specific differences for graft longevity could be observed. This is also shown by Nomoto et al., 2016 [11]. On the other hand, Zubairi et al., 2011 suggest that male gender is a risk factor for pulmonary valve failure [12]. A landmark achievement in this subject was the study of Sarikouch et al., 2011 whereby 407 patients with repaired ToF underwent standardized cardiac magnetic resonance (CMR) ventricular volumetry and flow quantification. Although there was no gender-specific difference for the age at corrective surgery, female patients tended to have a relatively more severe right ventricular dilatation than male patients [13]. This suggests that more research is needed to understand the impact of gender on the outcome of patients with repaired ToF.

Graft Type

The choice of conduit type seemed not to play a role considering the hypothesis. However, it should be noted that in this study the majority of valve substitutes were Contegra™ and Hancock™. It seems that both achieved similar results in their durability. Though, Al Mosa et al., 2021 describe an increased risk for graft revision for Contegra™ compared to Perimount™ and pulmonary homograft [14].

Conclusion

Patient age rules: In nature, valve size is related to hemodynamical needs, which are related to the patients' body dimension, activity level, and, thus, age. Initially, valve size may appear to have the biggest impact on prosthesis longevity. However, valve size can be predicted by patient age. This multicollinearity implies that patient age at index surgery is far more relevant than graft size, which is determined mainly by age. Patients at risk for earlier reoperation or reintervention are those who were operated on at a younger age.

Limitations

This study is limited by its retrospective character. As a single-center study, it is also affected by the particularities of the institution. Additionally, the statistical methods only provide clear evidence of correlation, not of causality. The study is furthermore limited to ToF patients who underwent biological pulmonary valve replacement via open surgery. Consequently, the durability of transcatheter valves, which could become increasingly relevant even in the primary care of ToF patients, has not been investigated. Nonetheless, this study provides useful information about possible risk factors for decreased valve longevity in a specific group of patients. Further research is needed for the examination of more risk factors in a prospective and multicentric setting. Also, with the advancements in interventional cardiology, it seems reasonable to explore alternatives to conventional surgical approaches more extensively.

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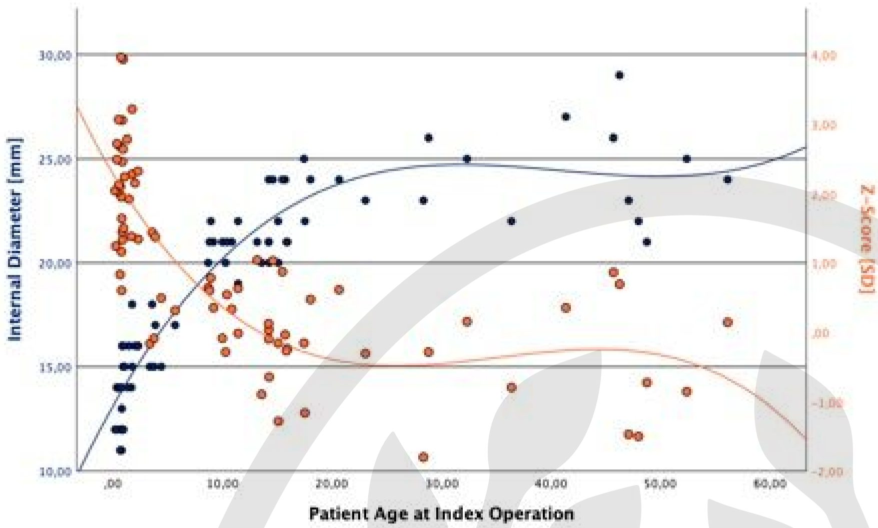
Internal Diameter [mm]
Z-Score [SD]
Patient Age at Index Operation


Graft Revision
No
Yes
Z-Score [SD]
Patient Age at Index Operation [years]