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ORIGINAL ARTICLE

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Midterm outcomes of right ventricular outflow tract reconstruction using the Freestyle xenograft

James A. Kuo MD[1] | Tyler Hamby PhD[2] | Maham N. Munawar MMS[3] | Eldad Erez MD[4] | Vincent K. H. Tam MD[5]

[1]Department of Cardiology, Cook Children's Medical Center, Fort Worth, Texas

[2]Department of Research, Cook Children's Healthcare System, Fort Worth, Texas

[3]School of Medicine, University of North Texas Health Sciences Center, Fort Worth, Texas

[4]Department of Cardiothoracic Surgery, Hadassah Medical Center, Jerusalem, Israel

[5]Department of Cardiothoracic Surgery, Cook Children's Medical Center, Fort Worth, Texas

Correspondence
James A. Kuo, MD, Department of Cardiology, Cook Children's Medical Center, 1500 Cooper Street, 3rd Floor, Fort Worth, TX 76104.
Email: James.Kuo@cookchildrens.org

Abstract

Objective: Various options exist for right ventricular outflow tract (RVOT) reconstruction in congenital heart disease. The Freestyle porcine aortic root may be used but its longevity is not well defined.

Design: We performed a retrospective review of all non-Ross RVOT reconstructions using the Freestyle root in our institution. Survival and reintervention, either by surgery, transcatheter valve implantation, balloon valvuloplasty, or bare metal stent placement, were recorded. Factors associated with reintervention were assessed using Cox regression.

Results: Between January 2002 and December 2015, there were 182 patients identified. Sixteen patients were lost to follow-up and 3 patients died, unrelated to cardiac surgery. Of the remaining 163 patients, the median age was 12.2 years (interquartile range 6.4-16.4), median weight was 39.0 kg (interquartile range 19.9-59.3), and the median body surface area was 1.23 m^2 (interquartile range 0.79-1.64). Ninety-three (57%) patients had tetralogy of Fallot. The median follow-up was 5.4 years (interquartile range 2.9-8 years). There were no operative or cardiac-related deaths. Thirty-eight patients (23%) required reintervention. The rate of freedom from reintervention was 93.2% (95% CI 86.7%-96.6%) at 5 years and 48.4% (95% CI 34.9%-60.6%) at 10 years. Age < 10 years, weight < 39 kg, and body surface area <1.2 m^2 at the time of valve placement, as well as valve size ≤25 mm were significantly associated with need for earlier reintervention.

Conclusions: The Freestyle root in the RVOT is associated with excellent survival and low midterm need for reintervention. Its longevity is comparable to published data on homografts and other bioprosthetic valves.

KEYWORDS

bioprosthetic valve, right ventricular outflow tract reconstruction

1 | INTRODUCTION

Right ventricular outflow tract (RVOT) reconstruction is required to repair various congenital heart diseases (CHD). Because many children with CHD are surviving into adulthood, there is a need for durable surgically placed valve as this can limit the number of sternotomies needed throughout a patient's lifetime. Options for RVOT reconstruction (RVOTR) include homografts (aortic and pulmonary), bioprosthetic valves, and mechanical valves. Bioprosthetic valves are commonly used due to their availability and they do not require chronic anticoagulation. However, they still need replacement due to structural valve deterioration and leaflet calcification. Children also undergo rapid somatic growth which results in outgrowing a previously placed surgical valve. While "oversized" valves are often placed in the pediatric population, they are especially susceptible to early reintervention. Younger age at the time of RVOTR has been demonstrated to be a dominant risk factor predictive of early bioprosthetic pulmonary valve failure.[1-3] Data on mid- and long-term durability of bioprosthetic pulmonary valves in children and young adults remain somewhat limited.

The Freestyle valve (Medtronic, Minneapolis, Minnesota) is a stentless porcine aortic root bioprosthesis that is decellularized using glutaraldehyde and treated with alpha-amino oleic acid to minimize xenograft calcification. This valve was initially introduced for aortic valve replacement.[4-6] However, it has been used for RVOTR worldwide. This xenograft has been primarily used at our institution for RVOTR. This has been surgeon preference due to its firmer structure than a pulmonary homograft and it tends to resist minor distortion, especially when used in a nonorthotopic position. Most previous reports have described short-term outcomes.[7-11] A recent study described midterm outcomes in a predominantly young adult population.[3] The aim of this study was to describe the longevity of the Freestyle valve in the pulmonary position in a primarily pediatric population.

2 | METHODS

This study was a retrospective review of patients who underwent non-Ross RVOTR with the Freestyle porcine root heterograft. After receiving Institutional Review Board approval, medical charts were reviewed for baseline characteristics, underlying diagnosis, operative details, perioperative course, follow-up status, need for reintervention, and echocardiographic data. Patients were excluded if they were lost to follow-up within one year of surgery. Orthotopic RVOTR was defined as any patient with an underlying diagnosis of tetralogy of Fallot, pulmonary atresia, absent pulmonary valve, or pulmonary stenosis. All other diagnoses were considered to have heterotopic RVOTR. Reintervention included transcatheter balloon valvuloplasty, RVOT stent placement, transcatheter valve implantation, or surgical valve replacement. Timing for intervention was at the discretion of the referring cardiologist.

The surgical technique for RVOTR at our institution has been previously reported[11]; however, there have been modifications. A gusset of bovine pericardium between the anterior aspect of the RVOT and the proximal conduit is now used on all patients. Interrupted sutures are utilized to avoid purse stringing with half of the posterior suture line at the native pulmonary valve annulus. The distal anastomosis of the conduit is performed in a similar fashion. This was felt to reduce the incidence of proximal stenosis below the sewing ring and reduce distortion of the root itself.

Continuous data are described using median and ranges. Categorical data are described using frequencies and percentages. Time-to-event analyses were performed using the Kaplan–Meier actuarial method. Cox regression analyses were used to examine the potential predictors of reintervention. All continuous variables were dichotomized into categorical variables. The optimal cutoff point was determined by stratifying the variables and comparing the Kaplan–Meier curves for numerous levels of predictor variables. For ordinal variables with a finite number of possible values (eg, age in years and valve size), every level was stratified as a distinct curve. For truly continuous variables, the Kaplan–Meier method was stratified by deciles. Cox regression models were used for univariate and multivariate analyses assessing the association between variables and time-to-event. Statistical significance was inferred at a probability value of <.05. All analyses were performed using SAS Enterprise version 6.1 (SAS Institute, Cary, North Carolina).

3 | RESULTS

3.1 | Baseline characteristics

Between January 2002 and December 2015, 188 patients underwent RVOTR using the Medtronic Freestyle valve. Six patients had Ross procedures (3.2%). There were three deaths in the cohort (1.6%), all

TABLE 1 Distribution of patient risk factors

Variable	*n*	%
Sex		
Male	92	56.4
Female	71	43.6
Age		
<10 years	65	39.9
≥10 years	98	60.1
Weight		
<39 kg	81	49.7
≥39 kg	82	50.3
Body surface area		
<1.2 m^2	77	47.2
≥1.2 m^2	86	52.8
Valve size		
≤ 25 mm	83	50.9
27, 29 mm	80	49.1
Type		
Orthotopic position	137	84.0
Heterotopic position	26	16.0
PA augmentation		
Yes	69	42.3
No	94	57.7
Previous procedures		
≤1 procedure	78	48.1
>1 procedure	84	51.9

Abbreviation: PA, pulmonary artery.

were unrelated to cardiac surgery. An 18-year-old male died from hemorrhagic complications from ruptured cerebral giant aneurysm 45 months after surgery. A six-year-old female with Treacher-Collins syndrome with tracheostomy died following respiratory arrest at home 13 months after surgery. A six-year-old male with a history of pancreatic agenesis, short bowel syndrome, and chronic lung disease died from septic shock occurring at home five months after surgery. These patients were omitted from reintervention analyses. Sixteen patients (8.9%) were lost to follow-up within one year. Current data were available for the remaining 163 patients.

The median age of the cohort was 12.2 years (interquartile range 6.4-16.4 years). The median weight was 39.0 kg (interquartile range 19.9-59.3 kg). The median body surface area (BSA) was 1.23 m^2 (interquartile range 0.79-1.64). Ninety-two (56.4%) patients were male. There were 93 (57.1%) patients with tetralogy of Fallot, 24 (14.7%) with pulmonary atresia with ventricular septal defect (PA/VSD), 17 (10.4%) with truncus arteriosus, and 29 (17.8%) with other diagnoses. One hundred sixty-one patients (98.8%) had undergone a previous sternotomy and 34 patients (20.9%) had previous RVOTR with a variety of homografts or bioprosthesis. Concomitant procedures were performed on 106 patients with 69 of them requiring pulmonary artery (PA) augmentation. Patient demographics are listed in Table 1. The number of each size valve placed and the size of the valve for patient's BSA are depicted in Figure 1. Valve size *z*-scores were calculated based on valve measurements published by Zilberman et al[12] The mean *z*-score for the 19 mm valve was 2.4, 21 mm valve was 2.5, 23 mm valve was 2.1, 25 mm valve was 1.4, 27 mm valve was 0.93, and 29 mm valve was 1.2.

3.2 | Reintervention

The median length of follow-up was 5.4 years (interquartile range 2.9-8 years). Thirty-eight patients from the cohort (23.3%) required reintervention: 11 patients underwent surgical RVOTR, 22 patients underwent transcatheter pulmonary valve implantation, 4 patients underwent transcatheter balloon valvuloplasty, and 1 patient underwent transcatheter bare metal stenting. The reason for reintervention was due to conduit stenosis in 32 patients, insufficiency in 2 patients, and mixed stenosis and insufficiency in 4 patients. The rate of freedom from reintervention at 5 years was 93.2% (95% CI 86.7%-96.6%) and at 10 years was 48.4% (95% CI 34.9%-60.6%) (Figure 2).

3.3 | Risk factors for reintervention

Univariate Cox regressions were run to determine the predictors of reintervention (Table 2). Younger age, lighter weight, smaller BSA, and smaller valve size were each significantly associated with poorer freedom from reintervention. The 5- and 10-year rates of freedom from reintervention are shown in Table 3. Patients who had one or no prior surgical procedures had marginally worse outcomes. Sex, valve position, diagnosis, and concomitant PA augmentation were not significantly associated with reintervention.

Using stepwise Cox regression analysis on significant variables, only age less than 10 years emerged as a significant predictor of early reintervention (Figure 3).

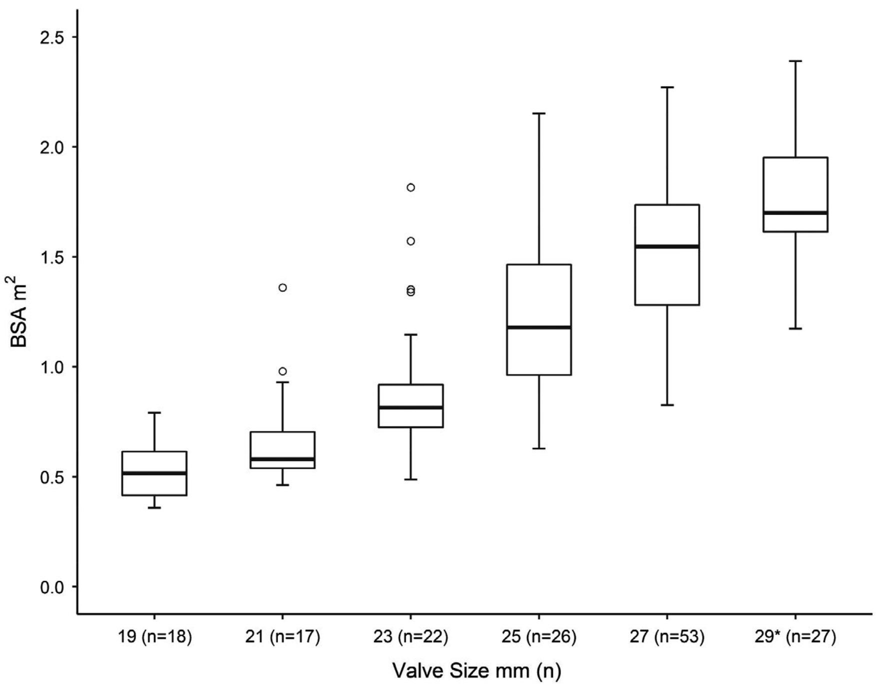

FIGURE 1 Freestyle valve size to body surface area. *1 value clipped with BSA 2.67 m^2. Abbreviation: BSA, body surface area

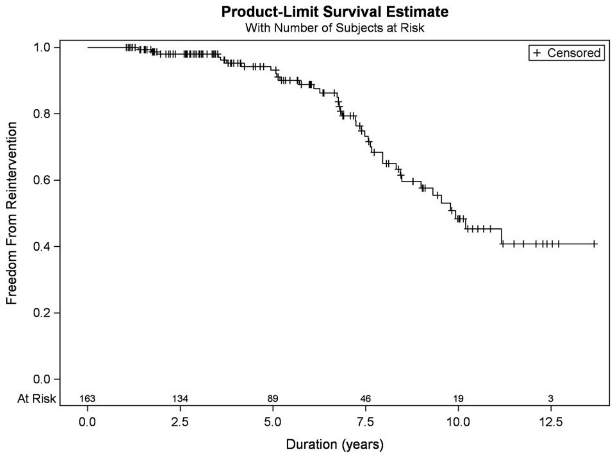

FIGURE 2 Kaplan–Meier survival curve of freedom from valve reintervention

4 | DISCUSSION

RVOTR beginning in childhood requires multiple interventions throughout a patient's lifetime. RVOTR can be performed with low operative mortality. Numerous choices exist for conduit placement, though superiority of one valve has not been demonstrated. To our knowledge, this is the largest cohort of primarily pediatric patients undergoing RVOTR using the Freestyle porcine aortic root heterograft and our findings demonstrate good outcomes. Previous studies have demonstrated that porcine aortic valves in the non-Ross population perform well in the short term[7-11] and intermediate term.[3,13] Dunne and colleagues[3] reported their experience with 114 patients with a median age of 21 years. Their freedom from reintervention rates at 5 years was 89% and at 10 years was 74%. While our overall 10-year freedom from reintervention was lower, our population was much younger. When comparing our patients who were over 10 years of age at the time of valve placement, our 10-year freedom from reintervention was comparable at 82.6%.

Our results are compatible with previous studies[1,2,14] demonstrating younger age is significantly associated with need for earlier reintervention. This is despite consistently oversizing the valve in younger children. The mechanism for valve dysfunction is not well understood with potential roles of active calcium metabolism or immune-mediated responses.[15-17] In our experience, the primary mode for conduit failure is valve stenosis, seen in 84.2% of patients requiring reintervention. It has been noted both by direct visualization

TABLE 2 Univariate analysis of risk factors for early reintervention

		Reintervention		
Variable	Reference group	HR	95% CI	*P* value
<10 years	≥10 years	5.50	2.49, 12.17	<.01
<39 kg	≥39 kg	3.73	1.69, 8.25	<.01
<1.2 BSA	≥1.2 BSA	3.83	1.79, 8.19	<.01
≤25 valve	27, 29 valve	3.75	1.61, 8.71	<.01
Male	Female	1.85	0.91, 3.76	.09
Orthotopic position	Heterotopic position	1.74	0.68, 4.46	.25
PA/VSD/MAPCAs	Other	0.95	0.29, 3.05	.93
PA augmentation	Other	1.11	0.58, 2.11	.76
≤1 previous procedure	>1 previous procedure	1.68	0.88, 3.21	.12

Abbreviations: BSA, body surface area; PA, pulmonary artery; PA/VSD/MAPCAs, pulmonary atresia with ventricular septal defect and multiple aortopulmonary collateral arteries.

TABLE 3 5- and 10-year rates of freedom from reintervention

		5-year freedom from reintervention		10-year freedom from reintervention	
		Rate (%)	95% CI	Rate (%)	95% CI
Age	<10 years	**92.5**	81.1%-97.1%	**18.0**	6.5%-34.1%
	≥10 years	**93.6**	83.4%-97.6%	**82.6**	67.0%-91.3%
Weight	<39 kg	**93.8**	84.3%-97.7%	**25.7**	11.8%-42.1%
	≥39 kg	**92.4**	80.5%-97.1%	**79.2**	61.2%-89.5%
BSA	<1.2 m^2	**95.2**	85.8%-98.4%	**24.1**	10.1%-41.3%
	≥1.2 m^2	**92.2**	80.1%-97.1%	**74.1**	54.0%-86.4%
Valve size	≤25 mm	**92.4**	82.7%-96.8%	**33.2**	18.4%-48.7%
	27, 29 mm	**93.9**	81.4%-98.1%	**76.3**	54.7%-88.6%

The bold numbers represent the actual percentage of patients who did not require reintervention.
Abbreviation: BSA, body surface area.

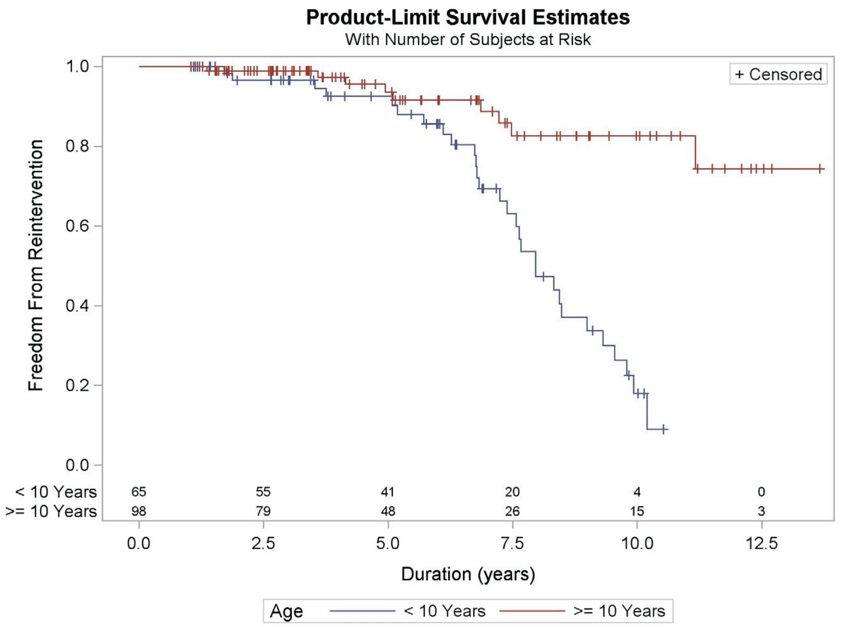

FIGURE 3 Kaplan–Meier survival curve of freedom from valve reintervention in patients < 10 years and ≥ 10 years of age

following Freestyle explantation and by cineangiography in patients who underwent transcatheter valve implantation that valve dysfunction occurs primarily by narrowing at the native annulus and occasionally just below the annulus in the sewing ring. We have not seen subvalvular pannus formation[9] or stenosis at the right ventricle suture line,[3] which have been reported in the past. It is unclear if this is entirely due to alteration in the surgical technique as mentioned above.

Stentless porcine aortic root heterografts appear to have a relatively low rate of developing significant insufficiency. In our patients requiring reintervention, pulmonary insufficiency was the primary indication in only 5.3%. Mixed stenosis and insufficiency was seen in 10.5%. This is lower than what was observed by Dunne and colleagues,[3] who reported pulmonary insufficiency in 12.5% of cases of structural valve dysfunction and mixed stenosis and insufficiency in an additional 16.7%. Hawkins et al[13] reported low reintervention rate at five years (4/150 patients, 2.6%) for a similar aortic root bioprosthesis and all were due to stenosis. Of their remaining patients at five-year follow-up, only five patients had moderate insufficiency with the remainder having none to mild insufficiency. We have hypothesized that the low rate of insufficiency may be protective against further right ventricular dilation and dysfunction in patients whose indication for RVOTR was chronic pulmonary insufficiency and right ventricular failure. However, this study did not have a matched cohort to test this hypothesis.

A recent systematic review was published on the longevity of the Freestyle valve compared to homografts.[18] In a mixed age population, five-year reintervention rates reported for homografts range from 10% to 51% compared to 6.8% in our series. Ten-year reintervention rates for homografts range from 25% to 67% compared to 51.6% in our cohort. Christenson et al reported reoperation of blood group–compatible and non-blood group–compatible homografts in a pediatric population of 14.3% and 37% with mean follow-up of 115 months. On shorter follow-up (64 months), they also demonstrated good durability of the Contegra valve with a reoperation rate of 11%.[19]

Lee et al[2] reported increased risk for early reintervention of the Freestyle valve compared to stented bioprosthetic models. Their 10-year freedom from reintervention was 31.2%. This was compared to 48.5% in stented porcine valves and 84.6% in stented bovine pericardial valves. However, they reported that patients who received the Freestyle valve were younger with smaller valves compared to the cohort with stented bioprosthetic valves. While our younger patients also had worse longevity of their Freestyle valves, older patients had improved durability similar to their reports of stented porcine valves.

Some cohorts report improved durability of bovine pericardial valves with five-year freedom from reintervention from 97% to 93%.[20-22] However, 10-year freedom from reintervention ranges from 50% to 84%. Two studies comparing the durability between bovine pericardial and porcine leaflets did not demonstrate any differences.[22,23]

This is study is limited by its retrospective single center design and its lack of direct comparison with other bioprosthetic valves.

The use of the Freestyle porcine aortic root in the RVOT is associated with excellent survival, low midterm need for reintervention, and comparable longevity to homografts and other bioprosthetic valves. Its use can be considered as an alternative to homografts and other bioprosthetic valves in RVOTR.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

Kuo JA conceived and designed the study; collected the data; analyzed and interpreted the data; drafted and critically reviewed the article.

Hamby T was responsible for the statistics, data analysis/interpretation, and drafting and critically revising the article.

Munawar MN collected the data and drafted the article.

Erez E conceived and designed the study and revised and approved the article.

Tam VKH conceived and designed the study and revised and approved the article.

ORCID

James A. Kuo https://orcid.org/0000-0002-7401-9551

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