## Original Article

# *Midterm Longevity of Bioprosthetic Pulmonary Valves in Congenital Heart Disease Patients*

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## ABSTRACT

***Background:*** The durability of bioprosthetic valves in the pulmonary position is not well defined. In the present study, we aimed to examine the durability of bioprosthetic valves in the pulmonary position and the risk factors associated with bioprosthetic pulmonary valve dysfunction or valve failure.

***Methods:*** Records of 189 patients who underwent pulmonary valve replacement (PVR) with bioprosthetic valves between 2001 and 2012 were evaluated. The outcomes of PVR were defined as transvalvular leakage, gradient increase or stenosis, hospitalization, and redo PVR. The survival time for the occurrence of the consequences after replacement was depicted as Kaplan–Meier curves.

***Results:*** The most prevalent pathology leading to PVR was the tetralogy of Fallot (81.6%) either due to pulmonary insufficiency or pulmonary stenosis. The most prevalent valve used in our patients was the porcine type. During an average follow-up of 10 years, about 47% of the patients showed different degrees of valvular failure. There was at least moderate transvalvular leakage in the first 5 years in 20% of the patients.

***Conclusions:*** Bioprosthetic pulmonary valves are frequently used in patients with congenital heart disease. Although they avert the need for long-term anticoagulation, they have a degeneration process starting early in the first 5 years. ***(Iranian Heart Journal 2017; 18(3):21-27)***

**Keywords:** Pulmonary valve replacement, Bioprosthetic valves, Prosthetic valve failure

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Pulmonary valve replacement (PVR) is regularly performed during the repair of various congenital heart diseases. A typical circumstance that requires PVR is chronic pulmonary regurgitation after the repair of the tetralogy of Fallot. There are generally 2 surgical options for PVR: bioprosthetic and mechanical valves.[1-4] Bioprosthetic valves are undoubtedly very commonly used because they are readily available and they do not need permanent anticoagulation therapy. Nevertheless, most of these bioprosthetic valves will finally fail and require replacement mostly due to structural valve deterioration. As reported in the previous studies, a principal risk factor predictive of early bioprosthetic pulmonary valve failure is younger age at the time of the initial PVR. [1, 4] However, the long-term definite stability of bioprosthetic pulmonary valves implanted in young adults is not well defined mainly due to the small number of patients or the relatively short duration of follow-up. [1-3] A large number of studies recently conducted compared the long-term results between bioprosthetic and mechanical valves and found a significantly lower rate of complications caused by bioprosthetic valves, [5, 6] while patients younger than 65 years had significantly higher reoperation rates. [5-8] Additionally, many studies [2, 10, 11] are limited to a single valve type, and there are only a few reports [3, 11] dealing with the durability of the different types of bioprosthetic valves. In this study, we sought to assess multiple valve types in terms of their outcome and the risk factors associated with bioprosthetic pulmonary valve failure during a mean follow-up of 125 months in our center.

## METHODS

In this retrospective study, the records of patients who underwent PVR with bioprosthetic pulmonary valves between 2001 and 2012 were collected and evaluated. Age, sex, underlying diseases leading to valvular repair, and kinds of bioprosthetic pulmonary valves were determined. Patients who underwent valve conduit placement were excluded. Echocardiographic data including right ventricular size and function before and after surgery and bioprosthesis regurgitation and stenosis were also recorded. The outcome of PVR was defined as transvalvular leakage, increase in the gradient, thrombosis, hospitalization, and redo PVR. The survival time for the occurrence of each outcome after replacement was measured and depicted as Kaplan–Meier curves.

### Statistical Analysis

The continuous data were summarized as means ± standard deviations (SDs) or medians (ranges), as appropriate. Univariate comparisons were made using paired or unpaired *t* tests for the continuous data and the Fisher exact test or the $\chi^2$ test for the categorical data. All the data were analyzed using SPSS, version 18. With regard to adjusting or removing the effects of the confounding factor, multiple logistic regression tests were used to measure the outcome of PVR affected by the confounding variables. A *P* value less than 0.05 was considered statistically significant. The Kaplan–Meier curve was shown to measure the freedom from transvalvular leakage, redo PVR, increased gradient, and likelihood of having those consequences.

## RESULTS

In this study, 189 patients (85 [44.7%] male; mean age = 19.44 ± 5.8 y) were enrolled. The most prevalent anomaly leading to PVR was total correction of the tetralogy of Fallot, present in 155 (81.6%) of the patients. Pulmonary insufficiency and pulmonary stenosis were seen in 174 (91.6%) and 34 (17.9%) of the cases, respectively. (Some had a combination of pulmonary insufficiency and pulmonary stenosis.) All the demographic and clinical data are depicted in Table 1.

Among the 189 patients, the most prevalent valve used was porcine (142 [75%] cases), followed by pericardial (32 [17%] cases) and homograft (15 [7.9%] cases). Most of the valves (173 [91.5%]) were stented (Table 2). In all the cases, the choice of bioprosthetic valves was at the discretion of the surgeon.

Overall in the porcine valve group, the most prevalent subtypes were Epic (56 [39.5%]

cases), Carpentier–Edwards (44 [31%] cases), and Hancock II (32 [22.5%] cases) (Table 2).

The most prevalent rhythm abnormality in electrocardiography was right bundle branch block, which was present in 172 (90.5%) patients. The valve sizes used were 21 to 27 mm, with the 25-mm valve being the most common.

In 182 (95.8%) patients, no past medical history was found, and thyroid problems were seen in 5 (2.6%) patients. None of the cases had renal failure.

Of the 189 cases, 29 (15.3%) were hospitalized at least once during the follow-up for related causes including gastrointestinal bleeding (4 [2.1%] cases), arrhythmias (4 [2.1%] cases), and valve endocarditis (6 [3.2%] cases). Eight (4.2%) patients were found to have paravalvular leakage, 56 (29.5%) showed transvalvular leakage, 34 (17.9%) exhibited progressive increases in the gradient and stenosis, and 18 (9.5%) needed redo PVR in the defined follow-up due to valve failure (Table 1). In the majority of these patients, structural failure appeared in the first 5 years. There was at least moderate transvalvular leakage in the first 5 years in 20% of the patients.

The echocardiographic data regarding the right ventricular size and function before and after PVR are depicted in Table 2. The right ventricular size before PVR in most of the cases (62.6%) was severely enlarged since those patients were candidated for the replacement of the valve. After PVR, although the ventricular size showed a significant reduction in many, severe enlargement persisted in 38.9% of the cases postoperatively ($P < 0.001$).

With respect to the right ventricular function, various degrees of recovery were seen after PVR but the difference was not statistically significant ($P = 0.2$).

Following PVR, 167 (87.9%) patients took aspirin and 164 (86.8%) took warfarin in the initial 3 months (Table 2).

**Table 1.** Demographic and clinical data of the study population

| Variables | | |
|---|---|---|
| Sex | Male | 85 (44.7%) |
| | Female | 105 (53.3%) |
| Reason for PVR | PI | 174(91.6%) |
| | PS | 34(17.9%) |
| | TF | 155(81.6%) |
| | Post valvuloplasty | 9(4.7%) |
| Past medical history | None | 182(95.8%) |
| | Thyroid | 5(2.6%) |
| | Hematologic | 1(5%) |
| | Others | 2(1.1%) |
| | Renal disease | 0 |
| ECG | AF | 3(1.6%) |
| | RBBB | 172(90.5%) |
| Cause of hospitalization | No reason | 174(91.6%) |
| | Arrhythmia | 6(3.2%) |
| | Bleeding | 4(2.1%) |
| | Valve infection | 6(3.2%) |
| Taking ASA | | 167(88.4%) |
| Taking warfarin (first 3 mon) | | 164(86.8%) |
| Paravalvular leakage | | 8(4.2%) |
| Transvalvular leakage | | 56(29.5%) |
| Gradient increase | | 34(18%) |
| Redo PVR | | 18(9.5%) |

PVR, Pulmonary valve replacement; PS, Pulmonary stenosis; TR, Tricuspid regurgitation; PI, Pulmonary insufficiency;
ASA, Aspirin; RBBB, Right bundle branch block

**Table 2.** Clinical characteristics of the valves

| Variables | | N (%) |
|---|---|---|
| Types of valves | Porcine | 142(75.1%) |
| | Pericardial | 32(17%) |
| | Homograft | 15(7.9%) |
| Valves with stents | | 173(91.1%) |
| Stentless valves | | 16(8.4%) |
| Valve size | 17 | 1(5%) |
| | 19 | 1(5%) |
| | 21 | 13(6.8%) |
| | 23 | 51(26.8%) |
| | 25 | 95(59%) |
| | 27 | 27(14.2%) |
| Porcine valves | Epic | 56(39.5%) |
| | Carpentier–Edwards | 44(31%) |
| | Hancock II | 32(22.5%) |
| | Mosaic | 10(7%) |
| Pericardial valves | Mitroflow | 18(56.2%) |
| | PERIMOUNT | 9(28.1%) |
| | Magna | 4(12.5%) |
| | Trifecta | 1(3.1%) |

***Relationship between transvalvular leakage and the demographic or clinical data***

There was a significant relationship between the patients' age and transvalvular leakage (patients' mean age = 21.85 ± 7.19 y) (*P* < 0.05). Out of the 84 men, 24 (42.9%) cases and of the 104 women, 32 (57.1%) patients had transvalvular leakage (*P* = 0.7). Out of the 166 cases who took ASA, 45 (27%) had transvalvular leakage occurrence. There was a significant relationship between the type of the valve and transvalvular leakage. Out of the 56 patients with Epic valves, 7 (12.5%) cases and out of the 44 cases with Carpentier valves 18 (41%) showed transvalvular leakage. In the 32 cases with Hancock valves, 9 (28%) were found to have transvalvular leakage. Out of the 10 cases with Mosaic valves, transvalvular leakage was seen in 4 (40%). In the pericardial subgroup, 32.1% of the 18 cases with Mitroflow valves and 30% of the PERIMOUNT valves showed the occurrence of transvalvular leakage. Of the 4 cases with Magna valves, no patient had transvalvular leakage during the follow-up. Out of the 173 patients with stented valves, 49 (28.6%) had transvalvular leakage. Out of the 16 cases with stentless valve, 7 (44%) showed transvalvular leakage.

***Relationship between increased valvular gradients or stenosis and the clinical data***

Out of the 84 men, 20 (58.8%) and of the 105 women, 14 (41.2%) showed increased gradients and stenosis (*P* = 0.6) (mean age = 20.07 ± 7.02 y; *P* = 0.1). No significant association was found between ASA intake and the occurrence of increased valvular gradients and stenosis (*P* = 0.2). In the Porcine subgroup, 12 of the 44 (27.2%) patients with Carpentier valves, 4 of the 32 patients with Hancock valves, 6 of the 56 patients with Epic valves, and 2 of the 10 patients with Mosaic valves showed increased gradients and stenosis. In the pericardial valve group, 5 of the 18 (28%) patients with Mitroflow valves, 1 of the 9 patients with PERIMOUNT valves, and 1 of the 4 patients with Magna valves showed increased gradients or stenosis of the valve.

***Relationship between redo PVR and the clinical data***

Of the 84 men, 11 (13%) and of the 105 women (mean age = 21.13 + 6.34 y; *P* = 0.6), 7 (7%) needed redo PVR (*P* = 0.1). No significant association was seen between ASA intake and redo PVR occurrence. Most of the patients that needed redo PVR had used ASA. A significant relationship was found between the type of the valve and redo PVR (*P* = 0.02).

***After using the logistic regression test***

Regarding transvalvular leakage, the valve type (*P* = 0.04, CI: 1.02 to 3.59) had a significant relationship (*P* = 0.02, CI: 0.11 to 0.84) with the occurrence of valve failure or dysfunction. There was also a significant relationship between redo PVR and the valve kind (*P* = 0.004, CI: 1.6 to 14.28). With respect to increased gradients and stenosis, none of the clinical and demographic data showed a significant relationship (*P* > 0.05).

According to our Kaplan–Meier curve, the likelihood of having transvalvular leakage during the 125-month period increased and the freedom from events was decreased. In addition, the occurrence of a gradient rise during the 125-month period increased and the freedom from this event gradually decreased. With a slow drop, the likelihood of needing redo PVR increased and freedom from this event decreased. The mean time for the occurrence of an increased gradient, redo PVR, and transvalvular leakage was CI: 95.95 to 113.37 months, CI: 55.75 to 121.76 months, and CI: 72.98 to 88.25 months—respectively (Fig. 1 to 3).

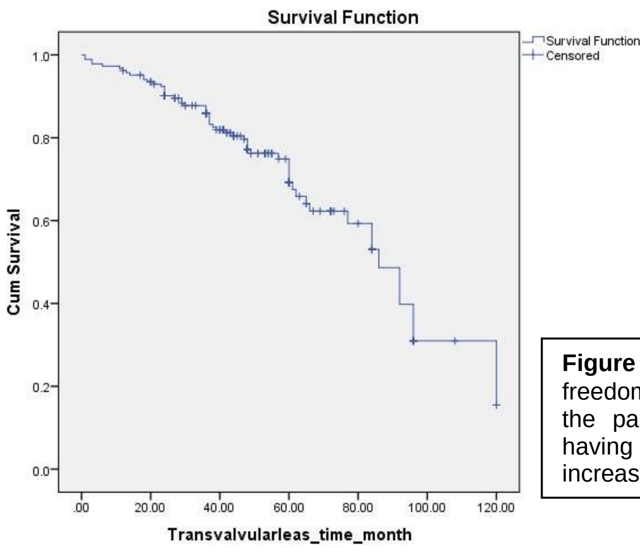


**Figure 1**. Kaplan–Meier curves and freedom from transvalvular leakage. With the passage of time, the likelihood of having transvalvular leakage was increased.

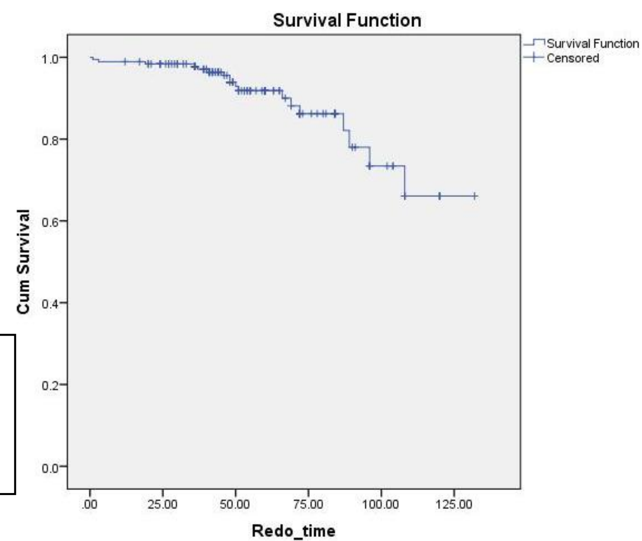


**Figure 2.** Kaplan–Meier curves and freedom from redo pulmonary valve replacement. With the passage of time, the likelihood of having redo pulmonary valve replacement was increased.

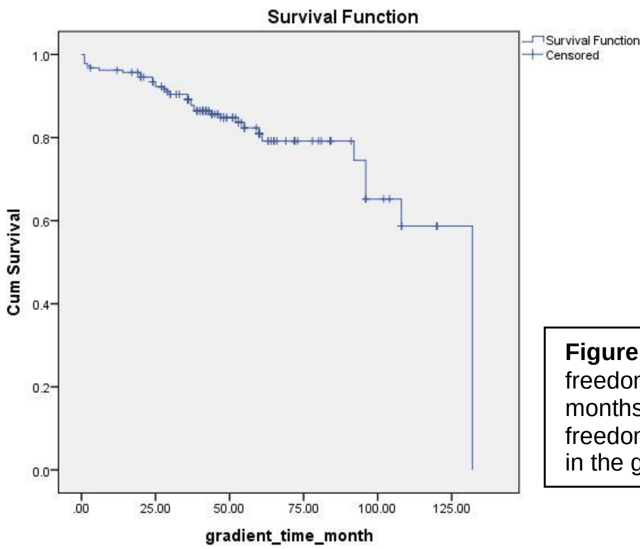


**Figure 3.** Kaplan–Meier curves and freedom from increased gradients. After 100 months, a sharp decrease was seen in freedom from gradient, which showed a rise in the gradient**.**

## DISCUSSION

Bioprosthetic heart valves are in homograft or xenograft types (made of human or animal tissues, respectively). The most common xenograft or heterograft valves are porcine or bovine pericardial valves. The porcine type is reported to last for 10 to 12 years. The pericardial type has also believed to have a durability of about 10 years.

Homografts have been reported to function better in the pulmonary position, especially in patients presenting with pulmonary regurgitation late after tetralogy of Fallot surgical repair. However, they have limited availability, making xenografts the alternative substitute. [9, 13]

Xenografts are usually treated with glutaraldehyde to maintain stability. Be that as it may, xenografts fixed with glutaraldehyde are vulnerable to calcific degeneration after implantation in human hearts.

Compatible with previous studies, [1, 8] our study showed that age and the type of the valve were significant factors affecting the occurrence of transvalvular leakage. The exact source and mechanism of an accelerated bioprosthetic valve failure in younger ages is not completely understood, but active calcium metabolism of rapidly growing children and leaflet calcification have been regarded as a culprit. Lately, however, some evidence has suggested that the greater immune system competence of children and young adults may contribute to an accelerated bioprosthetic valve failure. Some anticalcification protocols including immunologic modifications have been reported to delay the structural failure. [10] Nevertheless, almost all of these bioprostheses will eventually fail and require replacement due to structural deterioration, resulting in multiple surgeries and related morbidity and mortality.

Stentless valves are thought to have a better hemodynamic profile as stents lead to some degree of stenosis, but an inferior longevity of stentless porcine valves was seen in previous studies. [1-3] In our center, although a low number of stentless valves were used, a higher rate of reoperation was seen in the stentless valves. Over a 125-month period, the valvular gradient gradually increased. It was shown that after an average of 55 months, there would be a need for a second PVR: this denotes a more accelerated failure rate than that reported by other studies. Nonetheless, the reoperation rate for our biological valve recipients is consistent with that reported by other studies, which may be due to delay for referral for surgery on the side of treating physicians because of the higher risk of repeated sternotomies. [5, 7, 12]

In our study, the porcine, pericardial, and homograft valves all showed significant transvalvular leakage over time, but a rise in the gradient was seen to a lesser extent.

In summary, we examined freedom from transvalvular leakage and redo PVR using Kaplan–Meier curves and found that at the beginning of the study, almost all the patients were free from event. Additionally, after 125 months, the likelihood of the occurrence of the outcomes increased and freedom from events gradually decreased. After a mean of 55 months, there was a need for redo PVR.

## CONCLUSIONS

There was a significant relationship between the valve type used, structural failure presenting as transvalvular leakage, and the need for redo PVR in our study population. According to our study, the freedom from valve failure or dysfunction (transvalvular leakage, increased gradient, and redo PVR) was decreased based on a Kaplan–Meier curve and the likelihood of having those outcomes increased significantly over a follow-up period of 10 years.

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