Are Bioprosthetic Valves Appropriate for Aortic Valve Replacement in Young Patients?

Aditya K. Kaza, and Frank A. Pigula

Selection of a prosthetic aortic valve for use in the young patient is complicated by a variety of important considerations. Age, growth potential, activity and life style expectations, child bearing, and social factors, in addition to anatomic considerations, are all important to the recommendation of a prosthetic valve choice. We review the clinical experience and expectations of currently available prosthetic aortic valves available for the young patient, and describe the advantages and disadvantages for each.
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Introduction

The choice of aortic prosthesis in a young patient is complex, with multiple factors often under consideration. Factors such as age, lifestyle, child bearing, and associated medical conditions must be reconciled with safety and durability of the chosen prosthetic valve. Traditionally, mechanical prostheses have been considered the most durable replacement option, owing to accelerated deterioration of bioprosthetic valves in the young patient. However, recent advances in both mechanical as well as bioprosthetic valve technologies further complicate an already complex decision-making process. We will review recent data on aortic valve replacement in the young patient, and discuss the role of contemporary options for aortic valve replacement in the young patient.

Biologic valve choices

1. Stented bioprosthesis
2. Stentless bioprostheis
3. Pulmonary autograft
4. Autologous stentless valve in-situ

The various choices of biological valves available for pediatric patients are shown here.

Central Message

We review important considerations affecting aortic valve replacements in young patients.

Preoperative Evaluation

The preoperative evaluation of patients with congenital heart disease includes a thorough history and physical exam. Comprehensive echocardiogram is performed to delineate the intracardiac anatomy and to determine the need for additional interventions. The various features examined include the diameter of aortic annulus, sinotubular junction, left ventricular outflow tract, and size and function of the pulmonary valve. The anatomy of the existing aortic valve leaflets is also determined.

Choices for Valve Replacement

Children and young adults with active lifestyles and women who intend to have children are candidates for bioprosthetic aortic valve replacement. There have been significant improvements in commercially available biological valves. Considerable effort has been given to the redesign of the valve cuff to help improve the effective orifice area and thus help reduce the incidence of patient-prosthesis mismatch. A newer generation of anti-calcific treatments has also helped reduce the acceleration of structural valve deterioration and thus help prolong the durability of these valves.

1. Stented bioprosthesis
2. Stentless bioprosthesis (xenograft and allograft)
3. Pulmonary autograft
4. Autologous stentless valve in-situ (Ozaki technique)

Department of Cardiac Surgery, Boston Children's Hospital, Harvard Medical School, Boston, MA.

Address correspondence to: Aditya K. Kaza, MD, Department of Cardiac Surgery, Boston Children's Hospital, Harvard Medical School, 300 Longwood Ave, Bader 273, Boston, MA 02115. E-mail: Aditya.kaza@cardio.chboston.org

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Stented Bioprosthesis

There are a variety of stented valves available for aortic valve replacement, such as porcine aortic, bovine, and equine pericardial valves. The valves differ in the types of anti-calcification process used and the configuration of the sewing cuff. The stented valves are usually available in outer diameter size 19 mm and up. There is variability in the inner diameter between valves made by different manufacturers, so it is important to understand the effective orifice area of different valves. This could potentially help avoid patient prosthesis mismatch by using appropriate sized valves. The important consideration when using the stented valves is the variable durability of these valves in the pediatric population. There have been several reports of accelerated deterioration of these valves. These concerns require regular surveillance of these patients with physical exam and echocardiographic evaluation. A recent paper[1] from our institution illustrated the rapid deterioration of stented bioprosthetic valves in young patients. The Mitroflow LXA (CarboMedics Inc, Arvada, CO) valve exhibited rapid progression of stenosis from mild to severe over a period of months, with freedom from valve failure at 3 years of 18%. Histologic and radiographic examination of the explanted valves revealed dense calcification of the leaflet center with thickening and immobility of the leaflet edges (Fig. 1). This resulted in essentially a "frozen" leaflet in the semi-closed position that contributed to the significant stenosis gradient. In comparison with the Mitroflow LXA valve, the freedom from failure of the Magna (Edwards Lifesciences Corp., Irvine, CA) valves was 100% at 3 years (Fig. 2). The authors speculate that the lack of anti-mineralization process for the Mitroflow LXA valves could have contributed to this rapid calcification and failure. This series illustrates the fact that biologic valves in younger patients are at a risk for accelerated deterioration and that routine surveillance and examination is mandatory. Other groups have examined failed Mitroflow (CarboMedics Inc., Arvada, CO) valves that have been explanted and postulate that, in addition to the lack of anticalcification treatment, valve design could have contributed to this early risk of failure.[2]

Figure 1 Gross appearance of the aortic surface of explanted Mitroflow LXA valve. (Adapted and reprinted with permission from Saleeb et al. Accelerated degeneration of a bovine pericardial bioprosthetic aortic valve in children and young adults. Circulation 2014;130:151-60.)

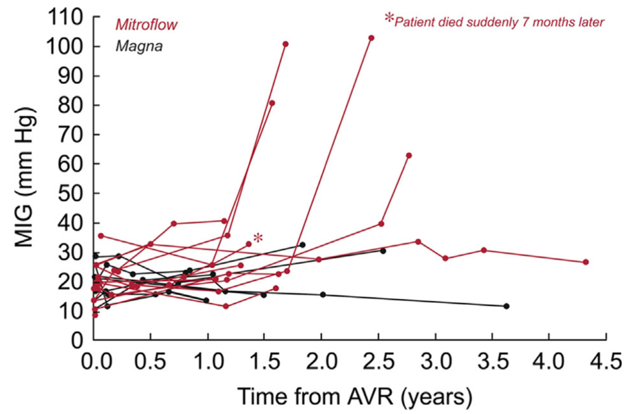

Figure 2 Plot illustrating the maximal instantaneous gradient with the two different types of aortic bioprosthetic valves. (Adapted and reprinted with permission from Saleeb et al. Accelerated degeneration of a bovine pericardial bioprosthetic aortic valve in children and young adults. Circulation 2014;130:151-60.)

Anti-mineralization treatment consists of treating biological tissues used for valve prosthesis with the intent of slowing structural valve deterioration secondary to calcification and mineralization. One study[3] examined the specific risk factors for structural valve deterioration and noted that lack of anti-mineralization therapy and patient prosthesis mismatch were the two most important predictors of valve failure (Fig. 3).

One large single-institution series examined the outcomes of pediatric biological valve replacement for both aortic and mitral valve replacement.[4] The series included 34 patients who underwent aortic valve replacement using either a homograft or stented bioprosthetic valve. They noted an aggregate freedom from valve reoperation at 5 years to be approximately 60% (Fig. 4). They also noted that the risk factor for requiring valve reoperation sooner was younger age of the patient at time of

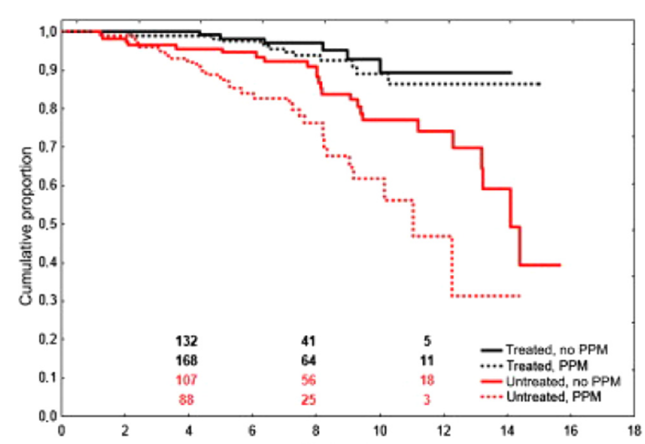

Figure 3 Effect of anti-mineralization treatment and patient prosthesis mismatch on valve durability. (Adapted and reprinted with permission from Flameng et al. Antimineralization treatment and patient-prosthesis mismatch are major determinants of the onset and incidence of structural valve degeneration in bioprosthetic heart valves. J Thorac Cardiovasc Surg 2014;147:1219-1224.)

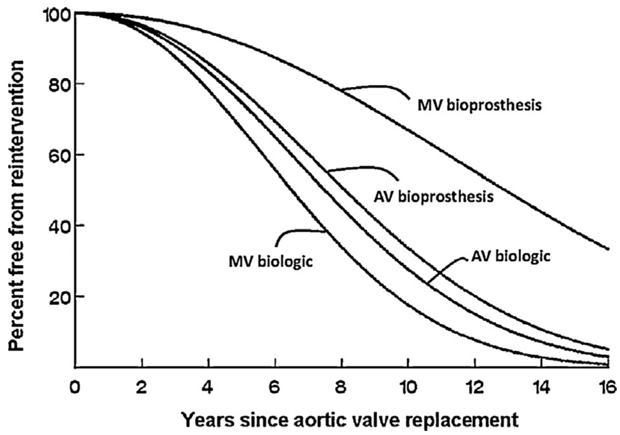

Figure 4 Risk of reoperation by valve type (biologic-homograft valves, bioprosthesis-stented biologic valves). (Adapted and reprinted with permission from Alsoufi et al. Aortic and mitral valve replacement in children: is there any role for biologic and bioprosthetic substitutes? Eur J Cardiothorac Surg 2009;36:84-90.)

valve implantation (Fig. 5). No bleeding or thromboembolic complications in patients who received a bioprosthetic aortic valve were reported.

Stentless Bioprosthesis (Xenograft and Homograft)

Stentless bioprostheses includes homografts and xenografts (porcine aortic root). These conduits can be used for either subcoronary implantation or full root replacement. The advantage of these valves is the lack of a rigid stent. The lack of rigid stent allows for implantation of a large-size valve conduit and having lower gradients across the left ventricular outflow tract. However, they are also plagued by the same structural valve deterioration concerns of other biological valves. There have been improvements in the anti-mineralization techniques that have positively impacted valve durability. The important consideration again is the avoidance of patient prosthesis mismatch.

One series[5] compared the outcomes of patients who received either homograft or xenograft (porcine) aortic root replacements over an 8-year period. The series included 166 adult patients who were randomized to one of the conduits. Freedom from reoperation at 8 years was significantly higher for the xenograft group when compared with the homograft group (100% *vs* 90%). Actuarial freedom from valve dysfunction (defined as $\geq$ than moderate regurgitation or stenosis gradient $>$ 20 mmHg) was 86% $\pm$ 5% for the xenograft group versus 37% $\pm$ 7% for the homograft group (Fig. 6). This series shows a significant durability advantage for the xenograft group. The caveat for the pediatric population is that the xenografts are not available in sizes smaller than 19 mm, whereas the homografts are available in a variety of smaller sizes.

Pulmonary Autograft

Utilizing autologous pulmonary valve for aortic valve replacement has several theoretical advantages. The main advantage of autograft replacement is the avoidance of stented prosthesis in the aortic position and avoidance of gradient in the left ventricular outflow tract. Numerous publications have illustrated the durability of this type of aortic valve replacement in the pediatric population.[6–8] However, there have also been reports about the potential for autografts to dilate and result in aortic insufficiency.[7,8] Incidences of autograft dilation have also led to a resurgence of the original subcoronary implantation technique. The contemporary indications for the use of autograft include patients with aortic stenosis and insufficiency without any evidence of ascending aorta dilatation or connective tissue disorders.

One single-institution series[6] examined 151 patients who underwent aortic valve replacement with autograft. Median age at surgery was 8.8 years and the 10-year freedom from reoperation on the autograft was 95%; 28% of the patients

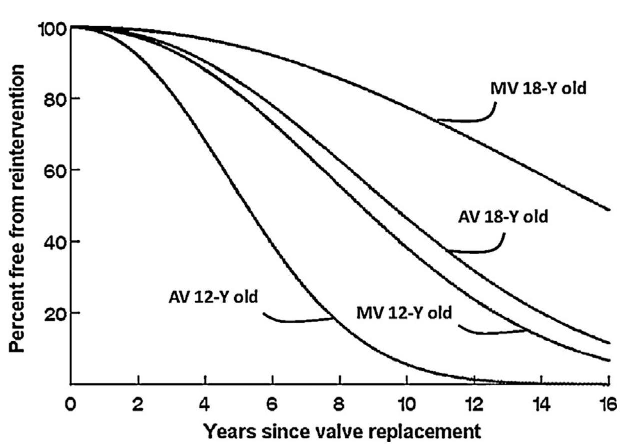

Figure 5 Reoperation risk by age of patient undergoing valve replacement. Younger age is a risk factor for needing reintervention sooner. (Adapted and reprinted with permission from Alsoufi et al. Aortic and mitral valve replacement in children: is there any role for biologic and bioprosthetic substitutes? Eur J Cardiothorac Surg 2009;36:84-90.)

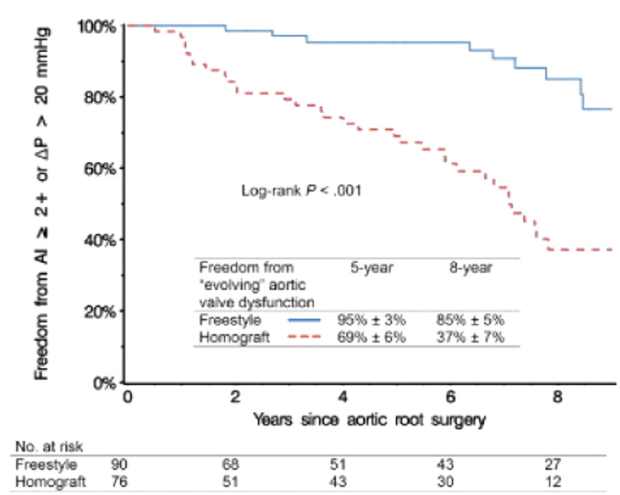

Figure 6 Actuarial freedom from aortic valve dysfunction after root replacement with either xenograft (freestyle) or homograft. (Adapted and reprinted with permission from El-Hamamsy et al. Late outcomes following freestyle versus homograft aortic root replacement: results from a prospective randomized trial. J Am Coll Cardiol 2010;55:368-376.)

in this series required enlargement of the aortic annulus to help autograft implantation (Ross-Konno). Risk factors for mortality in this series included age $<$ 1 year and no prior history of percutaneous or surgical intervention on the aortic valve. The authors noted the advantages of the autograft valve replacement to be the lack of bleeding or thromboembolic complications and 95% freedom form endocarditis at 15-year follow-up.

A large series of patients who had undergone the Ross procedures examined the concept of autograft reinforcement and subcoronary implantation technique.[7] The subcoronary implantation technique was evaluated in 347 patients and the freedom from valve-related interventions at 8 years follow-up was 95%; the maximum gradient across the autograft were $<$10 mmHg. A large multicenter study examined autograft function with the reinforcement technique.[8] This series included 1,335 adult patients, in whom 592 patients had autograft reinforcement at variable levels. Patients who did not have autograft reinforcement had 6-fold higher risk of developing valvar insufficiency and concomitant risk of requiring reoperation.

At Boston Children's Hospital we have performed 62 pulmonary autograft replacements of the aortic valve over a 14-year period (internal data, in press). Operative survival was 99% and 5-year survival was 96%. Freedom from reintervention on the autograft is 55% at 5 years.

Autologous Stentless Valve In Situ (Ozaki Technique)

There has been a growing interest in aortic valve repair in children using various biologic tissues. The most widely used materials are autologous pericardium and bovine pericardium. The durability of these repairs has been shown to depend on various patient factors, such as aortic valve anatomy and geometry and age. One of the newest pericardial reconstruction techniques is one proposed by Ozaki et al.[9] This technique involves resecting all the aortic valve leaflets in a dysfunctional valve and reconstruction based on recreating natural anatomy, which would minimize turbulence and resultant valve failure. This is a technique that essentially replaces the dysfunctional native aortic valve with a newly reconstructed stentless valve in situ (in essence, an autologous bioprosthetic valve). This technique has been used for aortic valve reconstruction in all types of valve morphology and in small aortic annulus requiring annular enlargement.[10,11] Recently published results of 404 aortic valve reconstructions have reported that this technique can achieve excellent results with minimal residual gradients (13.8 $\pm$ 3.7 mmHg at 3.5 years after surgery) and 96.2% freedom from reoperation at 53-month follow up (Fig. 7).[10] Theoretically, this technique is attractive for the pediatric population because of the avoidance of a stent in the left ventricular outflow tract and implantation of a fully autologous tissue valve. Long-term studies must be undertaken to determine valve function and durability in the pediatric population.

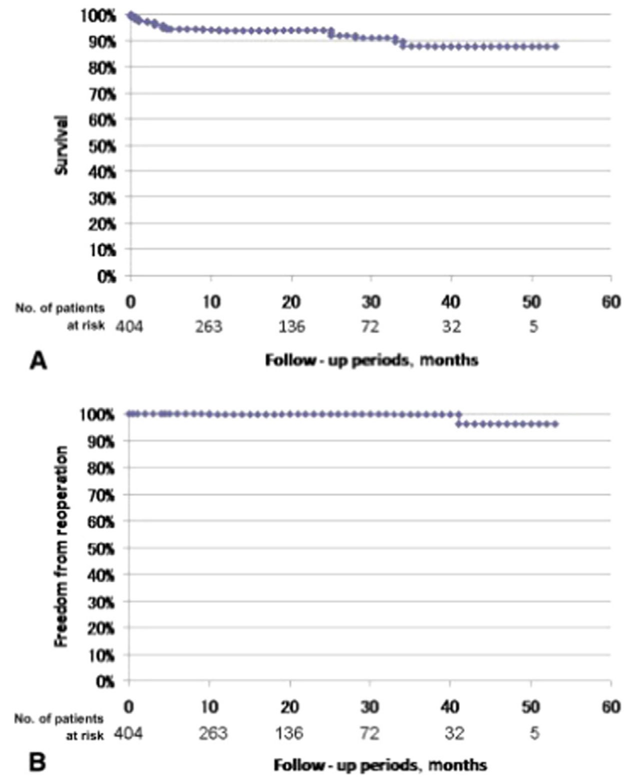

Figure 7 Curves illustrating survival and freedom from reoperation among patients who have had the autologous pericardial valve in-situ. (Adapted and reprinted with permission from Ozaki et al. A total of 404 cases of aortic valve reconstruction with glutaraldehyde-treated autologous pericardium. J Thorac Cardiovasc Surg 2014;147: 301-306.)

Mechanical Prosthesis

We briefly touch on this choice of valve prosthesis to highlight the risks and benefits of mechanical prosthesis. There have been significant improvements in the material and design of mechanical valves over the past few decades. There are mechanical prostheses available to size 15 mm, which makes them suitable for certain infant and pediatric patients. The advantage of this prosthesis is the potential for longer durability. One of the biggest drawbacks of mechanical valves is the need for anticoagulation and the annual risk of bleeding associated with this. In addition, there is also the risk of thromboembolism related to the mechanical prosthesis and lack of proper anticoagulation. Anticoagulation is a very important consideration when choosing valve types for pediatric patients because this can interfere with active lifestyles of children and young adults. With the advent of newer materials, there is considerable interest in these types of valves because they require lower anticoagulation levels. One such valve is the On-X valve (On-X Life Technologies, Inc, Austin, TX), which is approved by the US Food and Drug Administration for using lower anticoagulation target (INR 1.5 to 2.0).[12]

Conclusions

There are several choices for biological aortic valve replacement in children. However, this decision is something that takes several factors into consideration, such as patient and parent choice, patient lifestyle, anatomic characteristics of the aorta and aortic valve annulus, and the presence of other comorbidities. At our institution, there has been a renewed interest in the use of the autograft for aortic valve replacement. We also have been adopting the pericardial valve reconstruction in situ (Ozaki technique) because this technique may afford the favorable hemodynamic profile with early but encouraging durability profiles. As with any prosthetic valve technology, intermediate and long-term results are extremely important, but extremely difficult to obtain. Given the pace of change in valve technology, the moving target of the most "appropriate" aortic valve replacement in the young patient remains a customized decision, informed by the best available data.

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