Right Ventricular Outflow Tract Replacement With Xenografts in Ross Patients Older Than 60 Years

Alexander Karaskov, MD, Alexander Bogachev-Prokophiev, MD, Ravil Sharifulin, MD, Sergey Zheleznev, MD, Igor Demin, MD, Alexey Pivkin, MD, and Irina Zhuravleva, MD

Heart Valve Surgery Department and Bioprosthesis Laboratory, State Research Institute of Circulation Pathology, Novosibirsk, Russia

Background. **Because of the limited availability of pulmonary allografts, stentless pericardial xenografts have been proposed as an alternative for right ventricular outflow tract (RVOT) reconstruction during the Ross procedure. However, the durability of the bioprostheses for RVOT reconstruction in older patients is unknown. In the present study, we evaluated the use of pericardial xenografts for RVOT reconstruction during the Ross procedure in patients aged more than 60 years.**

Methods. **Between 1998 and 2014, 710 consecutive adult patients underwent the Ross procedure. We analyzed the results of the operation in 102 patients aged more than 60 years. The mean patient age was 63.4 ± 2.8 years (range, 60 to 68). The total root replacement technique was used in all patients. The RVOT reconstruction was performed with stentless pericardial xenografts. The mean size of the xenografts was 26.8 ± 1.3 mm. Xenograft calcification was assessed by computed tomography in 39 patients.**

Results. **At the time of discharge, the RVOT peak gradient was 10.3 ± 3.5 mm Hg. The mean follow-up duration was 52.3 ± 23.6 months. None of the cases required reoperation for xenograft dysfunction. At the final follow-up, the RVOT peak gradient was 17.9 ± 4.3 mm Hg. Computed tomography scan analyses showed that calcification was localized mainly at the graft wall, and that the valve was relatively free of calcium.**

Conclusions. **Stentless diepoxide-treated pericardial xenografts are an acceptable alternative to pulmonary allografts for RVOT reconstruction with the Ross procedure in patients aged more than 60 years, and yield good midterm results.**

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The use of a pulmonary autograft for aortic valve replacement was first proposed in 1967 by Donald Ross. Most surgeons consider the Ross procedure to be an attractive option for children and young adults [1–4]; however, its usefulness for older patients remains controversial. Although pulmonary allograft use is the gold standard for right ventricular outflow tract (RVOT) reconstruction in the Ross procedure, the availability of allografts is limited. Xenografts and expanded polytetrafluoroethylene conduits can be implanted in the RVOT location as an alternative to pulmonary allografts [5–8]. Some investigators have reported the possibility of using xenografts as an alternative to allografts in young patients; however, the follow-up duration in these studies has been short. Furthermore, the durability of the bioprostheses for RVOT reconstruction in older patients is unknown. In this observational study, we evaluated the use of diepoxide-treated pericardial xenoconduits for RVOT reconstruction during the Ross procedure in patients aged more than 60 years.

Patients and Methods

Between 1998 and 2014, 710 consecutive adult patients underwent the Ross procedure at our institution. A retrospective analysis of the results in 102 patients aged 60 years or more was performed. The study was approved by the Institutional Review Board.

The Ross procedure was offered as alternative surgical treatment for aortic valve disease to all patients with an active lifestyle and a desire to avoid lifelong anticoagulation therapy. The decision to perform the Ross procedure was made after discussion with the patient and obtaining informed consent. All operations were performed by a single surgeon. The presence of a primary aortic valve lesion was the main indication for surgery, in accordance with the American College of Cardiology/American Heart Association guidelines for the management of patients with valvular heart disease [9]. The contraindications for autograft implantation included coronary artery disease, other valve pathology requiring replacement, pulmonary valve anomaly, and severe concomitant diseases. The patients' mean age was 63.4 ± 2.8 years (range, 60 to 68). The preoperative patient characteristics are shown in Table 1.

Conduit Features

The RVOT was reconstructed with a stentless xenograft (Pilon; NeoCor, Kemerovo, Russia [Fig 1]). The conduit was manufactured from bovine pericardium that was treated with the diepoxy compound ethylene glycol diglycidyl ether of 97% purity (Research Institute of Organic Chemistry, Novosibirsk, Russia). The next stage

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Address correspondence to Dr Sharifulin, 15 Rechkunovskaya St, Novosibirsk 630055, Russia; email: ravil-sharifulin@rambler.ru.

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Table 1. Patient Preoperative Characteristics

Preoperative Characteristics	Values
Age, years	63.4 ± 2.8
Male	75 (73.5)
Aortic valve disease etiology	
Degenerative	52 (51)
Bicuspid	35 (34.3)
Endocarditis	15 (14.7)
Aortic valve hemodynamic lesions	
Stenosis	66 (64.7)
Insufficiency	25 (24.5)
Mixed lesion	11 (10.8)
Previous intervention	
Aortic balloon valvuloplasty	1 (0.98)
Percutaneous coronary intervention	2 (1.96)
NYHA functional class	
I	2 (1.96)
II	26 (25.5)
III	74 (72.5)
Mean left ventricular ejection fraction, %	62.2 ± 10.6

Values are mean ± SD or n (%).

NYHA = New York Heart Association; SD = standard deviation.

of treatment involved covalent immobilization with heparin, to enhance the prosthetic tissue biocompatibility.

Cutting out of the xenopericardium was performed using a computer-assisted laser system (Research Institute of Laser Physics, Novosibirsk, Russia). The biomaterial was mapped according to thickness by using the contact induction gauge built into this machine. The areas of uniform 0.9 mm to 1.0 mm thickness were selected for use as the proximal and distal tubular parts, and those of 0.40 mm to 0.45 mm thickness were selected for use as leaflets. Virtual templates were arranged on a computer "thickness map" and then used for laser cutting. The assembly of parts was performed manually using surgical sutures.

Operative Techniques

Cardiopulmonary bypass was established using the standard procedure with aortic and bicaval cannulation, followed by induction of moderate hypothermia (33°C to 34°C). Cold crystalloid (Custodiol; Kohler Pharma, Alsbach-Hahnlein, Germany) cardioplegic arrest was initiated with antegrade flow in all patients. The total root replacement technique was performed in all patients.

The mean xenograft size was 26.8 ± 1.3 mm (range, 25 to 29 mm). The conduit size was chosen based on the diameter of the distal portion of the pulmonary artery and was made as large as possible, depending on the patient. Consistency with the RVOT diameter was achieved through an oblique incision of the proximal tubular portion of the xenograft. Both the proximal and distal anastomoses were performed with 5-0 continuous polypropylene sutures. In most patients (78.4%), RVOT reconstruction was performed after cross-clamp removal to reduce myocardial ischemia time (Table 2).

Oral anticoagulants (Coumadin) were prescribed for 3 months postoperatively and were replaced with low-dose aspirin in patients who had sinus rhythm as documented by 24-hour Holter monitoring.

Postoperative Evaluation

In all patients, transesophageal echocardiography (Philips ie33; Philips Healthcare, Cleveland, OH) was performed to evaluate graft function after they were weaned off cardiopulmonary bypass, whereas transthoracic echocardiography (TTE) was performed before hospital discharge. The transvalvular aortic and pulmonary gradients were measured by continuous-wave Doppler ultrasound, using the Bernoulli equation. The severity of autograft and xenograft regurgitation was evaluated by color flow Doppler according to the guidelines of the European Association of Echocardiography [10], and was graded as none/trivial, mild, moderate, or severe.

The mean follow-up duration was 52.3 ± 23.6 months (range, 12 to 121), and examinations were scheduled annually. The follow-up results were evaluated in 90 patients (88.2%) who underwent TTE. Six patients were lost to follow-up as contact with these patients was lost. Thirty-nine patients (38.2%) also underwent computed tomography (CT [Toshiba Aquilion ONE 320-slice; Toshiba Medical Systems, Zoetermeer, Netherlands]) scanning. Among the patients who underwent CT scanning, the mean follow-up duration was 76.1 ± 13.1 months. The images were obtained using prospective electrocardiographically gated CT with 0.5-mm slice thickness. Conduit calcification was quantitatively analyzed with the VitrealFX workstation (Vital Images, Minnetonka, MN) by one experienced radiologist. Xenograft calcification was evaluated based on the Agatston score and calcium volume, as previously described for coronary arteries [11].

Statistical Analysis

Statistical analysis was performed with Statistica software, version 10.0 (StatSoft Inc, Tulsa, OK). Continuous data are presented as mean ± SD or median (25th to 75th percentile). Categoric data are described as absolute numbers and relative frequencies. The continuous variables were compared with the Student's t test or Mann-Whitney U test. The categoric variables were compared with the Wilcoxon matched pairs test. The Kaplan-Meier method was used to evaluate survival. Variables including age, sex, xenograft size, body surface area, and time since operation were evaluated to identify the predictors of a high RVOT peak gradient at follow-up. Correlation analysis was performed with Spearman's test. Multivariate analysis was performed by using linear regression models. Two-sided p values of less than 0.05 were considered statistically significant.

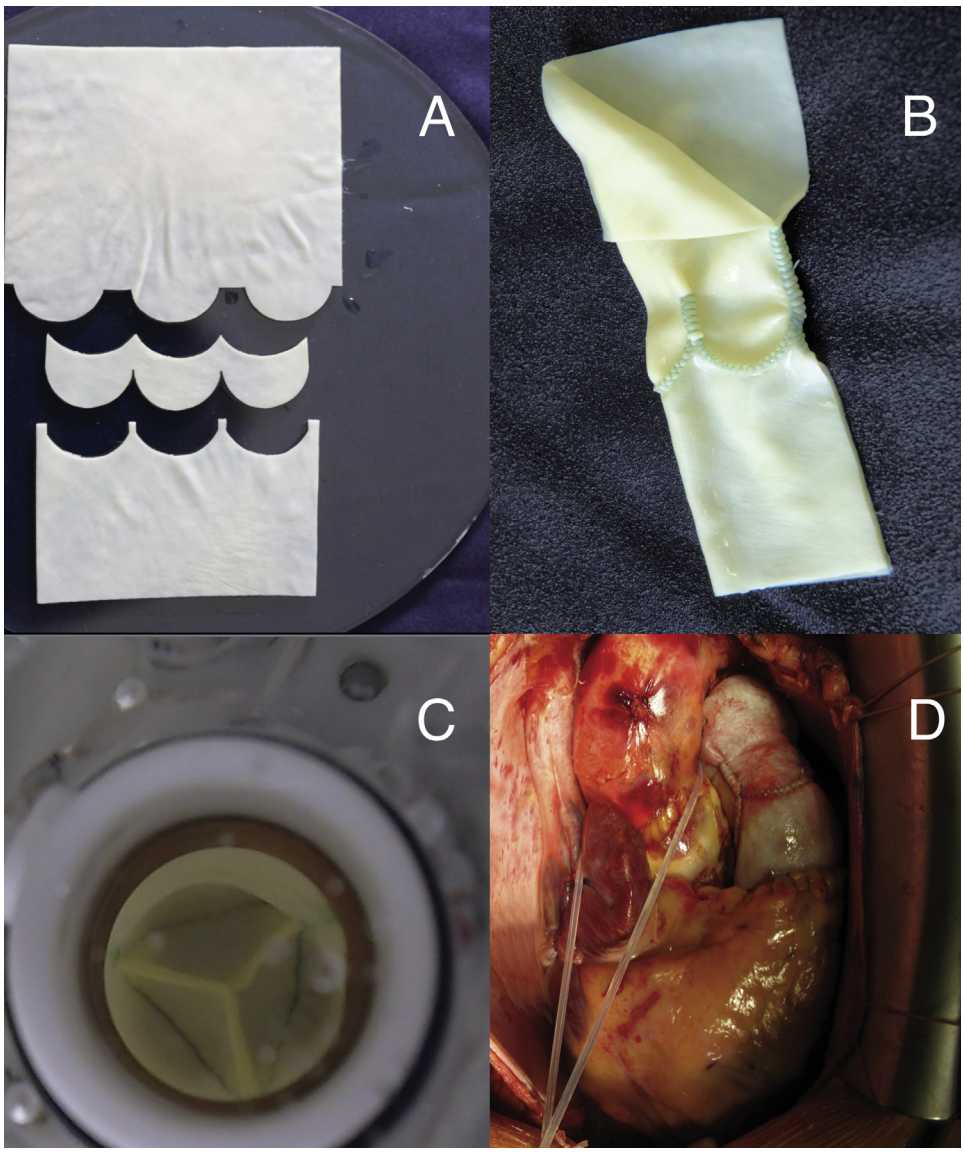

Fig 1. Diepoxide-treated bovine pericardial xenograft. (A) Pattern of the xenograft. (B) Conduit external view. (C) Bench-test of the conduit (cross-sectional view). (D) Right ventricular outflow tract reconstruction with the xenograft during the Ross procedure.

Results

Mortality and Morbidity

The inhospital mortality rate was 2.9% (3 patients). The cause of death was heart failure due to myocardial infarction in 2 patients and massive intraoperative bleeding in 1 patient. The details of postoperative complications are shown in Table 2. Three patients died during the follow-up period. The late deaths were sudden in 2 patients and were not cardiac-related in 1 patient. The survival rate at 5 years was 95.7% ± 2.1% (Fig 2).

Late Clinical Outcome

At the final follow-up, 80 patients (88.9%) were categorized as New York Heart Association functional class I to II, and 10 (11.1%) were categorized as functional class III. Moreover, 5 patients (5.6%) had atrial fibrillation at the final follow-up and continued warfarin treatment. There were no thromboembolisms or major hemorrhagic events during the follow-up period. One patient had infective endocarditis of the autograft and underwent surgical treatment.

Echocardiographic and CT Results

At discharge, the RVOT peak gradient was 10.3 ± 3.5 mm Hg. During the follow-up period, the peak gradient across the RVOT gradually increased, but remained within an acceptable range (Fig 3); it was significantly higher at the 12-month follow-up than at discharge. There was no correlation between graft size and RVOT peak gradient (Fig 4). Linear regression analyses identified the time since operation as the only factor associated with an increase in RVOT peak gradient at follow-up ($\beta = 1.1$, $p = 0.01$). None of the patients

Table 2. Operative and Postoperative Data

Operative and Postoperative Variables	Values
Cardiopulmonary bypass time, minutes	146.1 ± 19.1
Cross-clamp time, minutes	125.3 ± 17.8
Concomitant procedures	
Mitral valve repair	5 (4.9)
Tricuspid valve repair	3 (2.9)
Right ventricular outflow tract	
Mean graft size, mm	26.8 ± 1.3
25 mm	35 (34.3)
27 mm	63 (61.8)
29 mm	4 (3.9)
Postoperative complications	
Myocardial infarction	5 (4.9)
Reoperation for bleeding	4 (3.9)
Mediastinitis	2 (1.96)
Permanent pacemaker	2 (1.96)

Values are mean ± SD or n (%).

SD = standard deviation.

had significant calcification of the xenograft on TTE at the final follow-up. There were no patients with moderate/severe RVOT regurgitation (Table 3). None of the patients demonstrated right ventricular dysfunction or severe tricuspid regurgitation at follow-up. No cases of xenograft thrombosis or pulmonary embolism were recorded.

Among the 39 patients who underwent CT with calcium scoring, the mean calcium volume was 923 ± 154.3 mm^3, and the mean Agatston score was 534 ± 121.1. No calcification of conduit cusps was observed (Fig 5). Moreover, there were no differences in the degree of calcification of the hood or tubular portion of the conduit. Correlation analysis between the Agatston score and RVOT peak gradient revealed a weak but statistically significant correlation ($r = 0.33$, $p = 0.04$; Fig 6).

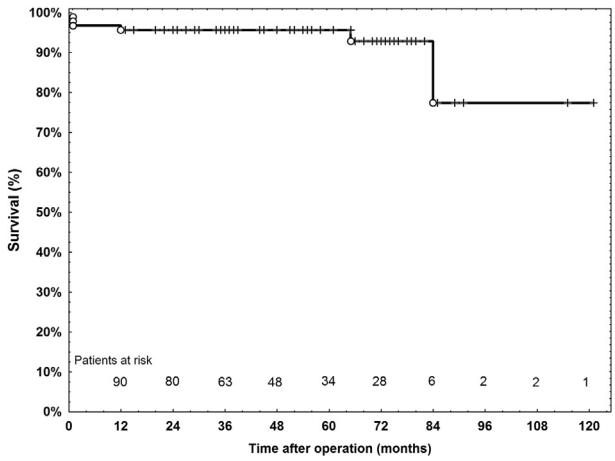

Fig 2. Survival after the Ross procedure.

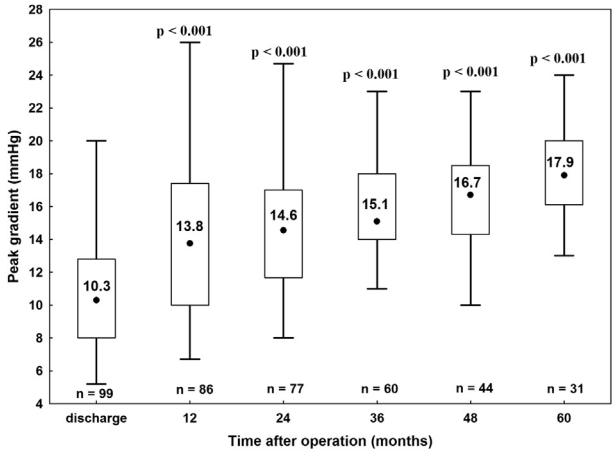

Fig 3. Dynamics of the pressure gradient between the right ventricle and pulmonary artery. Box plots depict median, interquartile range, and nonoutlier range. (p = comparison with the gradient at discharge; n = number of patients.)

Reoperations

There were no reoperations due to xenograft dysfunction among the patients. During the follow-up period, 2 patients (2.2%) underwent reoperations because of autograft failure. The reason for autograft dysfunction in 1 patient was the development of late infective endocarditis at 54 months postoperatively. The second patient underwent a reoperation for subvalvular false aneurysm (proximal anastomosis line) at 20 months after the Ross procedure, and closure with a xenopericardial patch was performed.

Comment

The pulmonary autograft provides excellent hemodynamics with minimal risk of thromboembolism, avoidance of anticoagulation therapy, and excellent long-term survival [1–3]. It is an attractive alternative to prosthetic aortic valve replacement in children and young adults. However, most researchers consider the Ross operation to be a complex surgical procedure that is not indicated for older patients [1, 3, 4]. Hence, experience with the Ross procedure in older patients is limited. Schmidtke and colleagues [12] demonstrated that the Ross procedure may be performed in patients aged over 60 years with mortality and complication rates similar to those observed in younger patients. The analysis of our data further demonstrated that the Ross procedure can be safely performed in patients aged 60 years or more. We consider this operation to be a potential alternative to prosthetic aortic valve replacement, but only for carefully selected patients. This procedure has the same advantages for older patients as for young patients: avoidance of anticoagulation therapy, high resistance to infection, low rate of thromboembolic events, and long-term autograft durability.

Despite all these advantages, the Ross procedure has a serious limitation—the need for double-valve intervention. The cryopreserved pulmonary allograft is the most

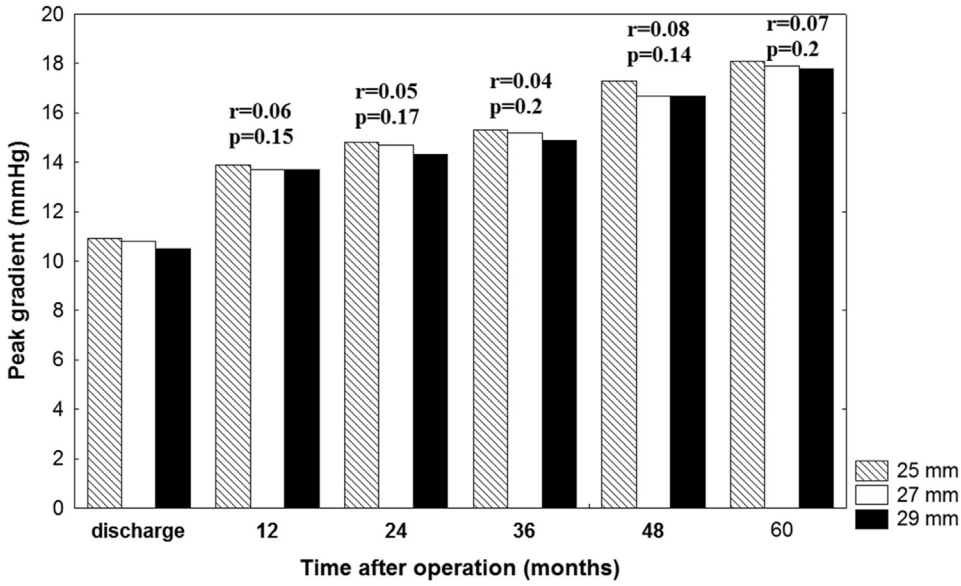

Fig 4. Correlation between graft size—25 mm (hatched bars), 27 mm (open bars), and 29 mm (solid bars)—and right ventricular outflow tract peak gradient. (r = Spearman's correlation coefficient.)

widely used conduit for RVOT reconstruction. Several reports have demonstrated excellent late results when using pulmonary allografts in the Ross procedure. In the German-Dutch Ross registry (1,775 adult patients), freedom from reoperation when using pulmonary allografts was 90.6% at 15 years [13]. In a meta-analysis of the Ross operation by Takkenberg and colleagues [2], the allograft deterioration rate in adults was 0.55% per patient-year. David and associates [3] also reported that the rate of freedom from allograft reoperation was 93.6% after 20 years. The most frequently reported risk factors for pulmonary allograft dysfunction are young patient age and donor age, small allograft diameter, and short duration of cryopreservation [1, 13–15]. It has been reported that allograft valve failure may be caused by immunologic factors. With regard to decreasing the

Table 3. Echocardiographic Results

Echocardiography Results	At Discharge (n = 99)	Last Follow-Up (n = 90)	*p* Value[a]
Left ventricular ejection fraction, %	58.2 ± 6.6	61.9 ± 4.2	0.1
RV fractional area change, %	42.1 ± 5.1	40.3 ± 6.8	0.23
Autograft regurgitation			
None/trivial	91 (91.9)	75 (83.3)	
Mild	6 (6.1)	11 (12.2)	0.3
Moderate	2 (2.0)	3 (3.3)	
Severe	0 (0)	1 (1.1)	
Autograft peak gradient, mm Hg	4.9 ± 2.3	5.7 ± 2.7	0.23
RVOT regurgitation			
None/trivial	90 (90.9)	76 (84.4)	
Mild	9 (9.1)	14 (15.6)	0.12
Moderate/severe	0 (0)	0 (0)	
RVOT gradient, mm Hg			
Mean	5.8 ± 3.2	10.1 ± 4.6	0.02
Peak	10.3 ± 3.5	17.9 ± 4.3	0.014
Tricuspid regurgitation			
None/trivial	83 (83.8)	70 (77.8)	
Mild	15 (16.7)	18 (20.0)	0.22
Moderate	1 (1.0)	2 (2.2)	

[a] Based on comparison with the findings at discharge.

Values are mean ± SD or n (%).

RV = right ventricular; RVOT = right ventricular outflow tract; SD = standard deviation.

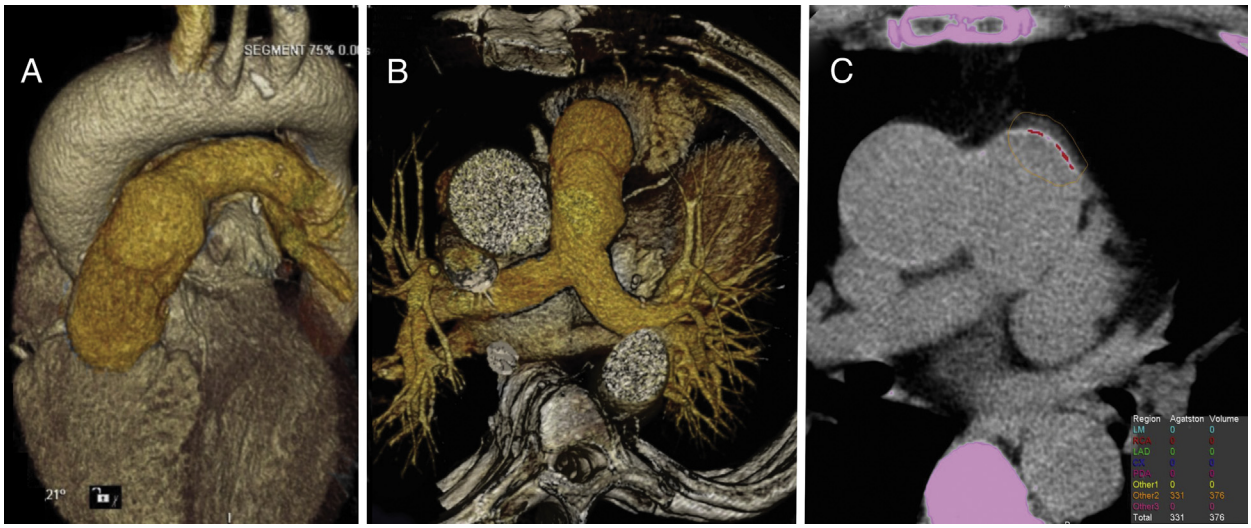

Fig 5. Computed tomography angiography 6 years after surgery. (A, B) Three-dimensional reconstruction of the xenograft. (C) Analysis of conduit calcification.

patient immune response and improving durability, several reports have demonstrated superior performance with decellularized pulmonary allografts compared with conventional cryopreserved pulmonary allografts [16, 17].

Although the allograft is the gold standard for RVOT reconstruction, its limited availability restricts its widespread use, and therefore, alternative grafts have been proposed. Konertz and colleagues [18] first applied a Medtronic Freestyle porcine aortic root for RVOT reconstruction with the Ross procedure in 1996. Since that time, some investigators have reported good early and midterm results with this conduit in children, similar to results with pulmonary allografts [19–22]. Hechadi and colleagues [6] compared long-term results between patients who received the Medronic Freestyle grafts (17 patients) and pulmonary allografts (37 patients). Over a mean follow-up period of 8.2 years, the researchers observed no differences in hemodynamics,

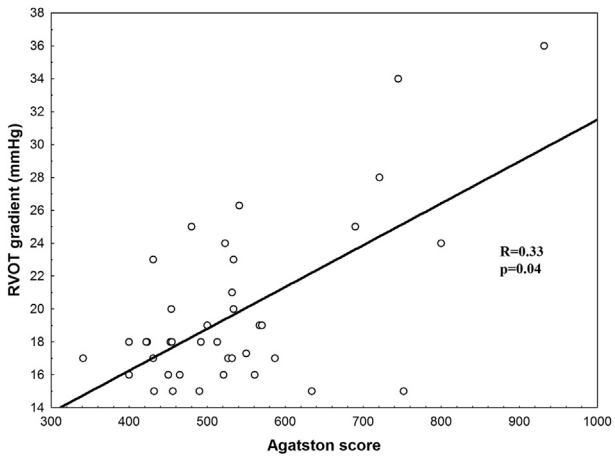

Fig 6. Correlation between the right ventricular outflow tract (RVOT) gradient and Agatston score. (r = Spearman's correlation coefficient.)

and concluded that the Freestyle grafts can be an acceptable alternative for RVOT reconstruction when a pulmonary homograft is not available. In a recent study, Juthier and associates [23] used different stentless porcine root models in 61 patients (median follow-up, 4 years). They reported a mean RVOT gradient of 13.5 ± 6.8 mm Hg at 5 years, and stated that a prosthesis diameter of less than 29 mm was a risk factor for a high postoperative RVOT gradient.

Niclauss and colleagues [24] reported acceptable hemodynamic results in 32 adults undergoing the Ross procedure using the Contegra bovine jugular vein conduit after medium-term follow-up. These researchers considered a conduit diameter of 22 mm to be adequate in adults. Several studies have also reported on the use of other xenografts during the Ross procedure in adults, with promising results [5, 7, 8].

However, contrary results using xenografts have also been reported by some investigators [25–28]. Miskovic and associates [25] and Weimar and colleagues [26] both reported that patients with bioprostheses in the RVOT position (Medtronic Freestyle) demonstrated a significantly higher risk of reintervention due to pulmonary conduit dysfunction after the Ross procedure; obstruction at the proximal part of the conduit was the main cause of reintervention in these cases. In the German-Dutch Ross registry, RVOT reconstruction with a bioprosthesis was associated with a significantly higher mean and peak gradient. The rates of freedom from reintervention or dysfunction for pulmonary allografts and xenografts were 90.6% and 79.5% at 15 years, respectively [13].

Patient age is known to be one of the primary predictors of conduit durability. In older patients, the immune response and calcium metabolism are decreased, leading to a reduced risk of bioprosthesis degeneration compared with younger patients. Schmidtke and colleagues [12] reported that the pressure gradient across the allograft was significantly lower in the patients

aged more than 60 years. Therefore, it may be reasonable to expect a longer durability of RVOT xenografts in older patients who undergo the Ross procedure.

We assessed the use of xenografts for RVOT reconstruction in 102 patients. Unlike previous studies, all patients in the present study were older than 60 years, and a different type of conduit was used—a pericardial xenograft treated with diepoxide. Our choice of conduit was determined by several factors. In particular, epoxy compound treatment has been experimentally shown to decrease biomaterial calcification [29–31]. We have extensive experience with different diepoxide-treated bioprostheses [32], with a maximum follow-up of 15 years. Approximately 20 clinics in our country currently use diepoxide-treated bioprostheses, and more than 1,000 implantations are performed annually. Cross-linked bovine pericardium is known to be more resistant to calcification as compared with porcine aortic valve leaflets and especially the aortic wall [33, 34]. The first-generation grafts used in our clinic for pulmonary artery positions consisted of xenoaortic tissues (porcine roots and composite grafts—a stentless xenoaortic valve in the xenopericardial tube). However, these prostheses demonstrated an unacceptable level of dysfunction due to the fast calcium-related degeneration of xenoaortic tissues. The freedom from reoperation for diepoxide-treated xenoaortic grafts in the pulmonary position (112 patients; mean age, 42.0 ± 13.5 years) was 93% and 80% at 5 and 10 years, respectively. Therefore, at present, we avoid conduits that included the porcine aorta. Moreover, we abandoned the use of xenografts in patients younger than 60 years.

At the midterm follow-up, xenografts in this study demonstrated acceptable hemodynamic characteristics. At the 5-year follow-up, the RVOT peak gradient was 17.8 ± 4.3 mm Hg. Our results are comparable to those from the reports of Hechadi and associates [6] and Juthier and associates [23]. In other adult series, xenografts had higher gradients as compared with our data [26, 27]. However, in contrast to the results of Juthier and associates [23], we did not observe a correlation between the transvalvular gradient and graft size, as prostheses with a diameter of 27 mm were primarily used in the present study.

Only one previous study has reported a calcification analysis of the RVOT conduit in patients who have undergone the Ross procedure. Hechadi and colleagues [6] compared calcification between Medtronic Freestyle grafts (11 patients) and pulmonary allograft recipients. The follow-up duration for the xenograft group was 7.8 ± 3.9 years. The degree of calcification was significantly higher in patients with Freestyle grafts (medium calcium volume, 2,782; medium Agatston score, 1,213). In the present study, we evaluated xenograft calcification in 39 patients over a mean follow-up period of 6.5 years. The quantitative data on conduit calcification were comparable to the allograft results reported by Hechadi and colleagues [6], which can be explained by all patients in our study being aged more than 60 years, and hence, would have been less likely to develop xenograft calcification. Moreover, we noted that calcification was localized primarily at the graft wall, whereas the valve remained completely free of calcium. These findings may be the reason for the lack of a strong correlation between the calcium score and RVOT peak gradient, which was observed in the study by Hechadi and colleagues [6]. There were no differences in the degree of calcification of the hood or tubular portion of the conduit. The logical explanation is that both conduit parts were made from the pericardium, with the same thickness and type of treatment. Moreover, TTE showed laminar blood flow throughout the xenograft, without any local turbulence.

Study Limitations

The present study has some limitations. It was a retrospective analysis, and no comparison group was included owing to the limited number of patients aged more than 60 years who undergo pulmonary allograft implantation. The xenografts used in this study are not available in other countries. Moreover, long-term follow-up results are needed.

Conclusion

The Ross procedure may be safely performed in older patients without an increased risk of mortality or complications. Stentless diepoxide-treated pericardial xenografts are an acceptable alternative to pulmonary allografts for RVOT reconstruction using the Ross procedure in patients aged 60 years or more, and yield good midterm results.

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