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Cardiovascular Surgery

Impact of Ross Operation on Outcome in Young Female Adult Patients Wanting to Have Children

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Background: The most appropriate valve substitute at aortic valve replacement (AVR) for young female adult patients wanting to have children is unclear.

Methods and Results: Between 1992 and 2013, 12 consecutive female patients aged >18 (median, 22.5 years; range, 18–34 years) underwent Ross operation (Ross group). Between 1984 and 2013, 9 consecutive female patients aged >18 (median, 30 years; range, 22–39 years) underwent AVR with bioprosthesis (bioprosthesis group). There was 1 late mortality in the bioprosthesis group, due to prosthetic valve endocarditis (PVE). Freedom from reoperation for aortic valve at 15 years was 90.0% in the Ross group, and 57.1% in the bioprosthesis group (log-rank, P=0.098). One in the Ross group underwent reoperation for aortic regurgitation (AR), whereas 4 in the bioprosthesis group did so for aortic stenosis (AS) in 2, combined AS and AR in 1, and PVE in 1. Five patients in the Ross group and 3 in the bioprosthesis group had 7 and 4 uneventful pregnancies, respectively. AR progressed during the perinatal period in a total of 7 of 11 pregnancies. No AS was seen at discharge, after 5 years, or during pregnancy in the Ross group.

Conclusions: The long-term outcome of Ross operation for female patients wanting to have children is excellent. Although subclinical pulmonary autograft valve regurgitation during pregnancy was often observed, pulmonary autograft stenosis did not occur, therefore it would be an ideal option for patients wanting to have children. (*Circ J* 2015; **79:** 1976–1983)

Key Words: Aortic valve replacement; Bioprosthesis; Pregnancy; Ross operation

The outcome of congenital heart surgery has greatly improved during the past 2 decades,[1,2] thus the indications for reoperation and/or choice of surgical procedure should be carefully decided so as to obtain better quality of life in adulthood.[3] For young women with congenital aortic valve disease, childbearing must be considered when deciding on surgical options.

When selecting a surgical option, the changes in ventricular stroke volume, both systemic and pulmonary vascular resistance, blood viscosity, and so on during the perinatal period must be taken into consideration.[4] Given that the efficacy of anticoagulation therapy for mechanical valves during pregnancy is still controversial,[5,6] mechanical valve implantation is still considered a non-optimal choice.[7,8] Pregnancy after biological aortic valve replacement (AVR), however, has a long history, with documented satisfactory outcome.[9,10] Although early degeneration of implanted prosthetic valve has been described, some reports did not find this, and recent development of the bioprosthesis itself is expected to overcome this issue.[11–13] Aortic valve repair or reconstruction is also a surgical option even for aortic stenosis or bicuspid valve,[14] but there are few data on long-term outcome and pregnancy.

Regarding pulmonary autograft implantation (Ross operation), superior outcome has been demonstrated, but it is still rare.[8,15,16] Moreover, there are no data on the function of the reconstructed right ventricular outflow tract (RVOT) during pregnancy.

Hence, this study compared surgical outcome and implanted valve function at the aortic position during the perinatal period between Ross operation and AVR using the bioprosthetic valve

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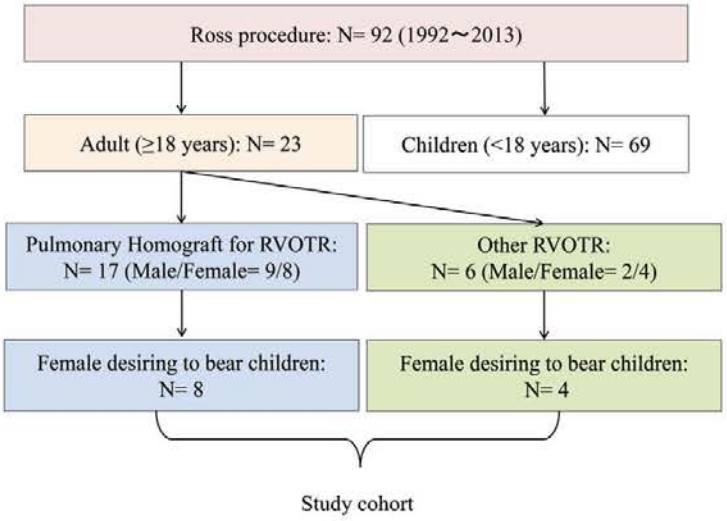

Figure 1. Flow chart for selection of study cohort. RVOTR, right ventricular outflow tract reconstruction.

Table 1. Patient Characteristics

	Ross group	Bioprosthesis group	P-value
No. patients (n)	12	9	
Age at operation (years)	22.5 (18–34)	30 (22–39)	0.027
Weight at operation (kg)	48.3 (36–59.5)	49.5 (38–61)	0.76
Indications for operation			
Stenosis	3 (25.0)	3 (33.3)	0.67
Regurgitation	6 (50.0)	5 (55.6)	0.80
Stenosis and regurgitation	3 (25.0)	1 (11.1)	0.42
Etiology of aortic valve			
Congenital	10 (83.3)	5 (55.6)	0.16
Acquired			
Infectious endocarditis	2 (16.7)	1 (11.1)	0.72
Rheumatic disease	0 (0.0)	3 (33.3)	0.030
Morphology			
Bicuspid	7 (58.3)	4 (44.4)	0.53
Tricuspid	5 (41.7)	5 (55.6)	0.53
Previous cardiac surgery	7 (58.3)	1 (11.1)	0.027
Previous procedures			
Balloon valvotomy	1 (8.3)	0 (0.0)	0.37
Surgical valvoplasty	4 (33.3)	0 (0.0)	0.054
AVR	1 (8.3)	0 (0.0)	0.37
ASD closure	0 (0.0)	1 (11.1)	0.24
VSD closure	1 (8.3)	0 (0.0)	0.37
CoA repair	2 (16.7)	1 (11.1)	0.72

Data given as median (range) or n (%). ASD, atrial septal defect; AVR, aortic valve replacement; CoA, coarctation of the aorta; VSD, ventricular septal defect.

in young female adult patients wanting to have children.

Methods

Patients

The National Cerebral and Cardiovascular Center Institutional Review Board approved this retrospective study and waived the need to obtain patient consent. From 1992 to 2013, 92 patients underwent Ross operation (Figure 1), of those, 12 consecutive female patients aged >18 selected this procedure because of their desire to bear children (Ross group). From 1984 to 2013, 9 consecutive female patients aged >18 underwent AVR using a bioprosthetic valve for the same reason (bioprosthesis group). Since 1984, AVR using Carpentier-Edwards Aortic Porcine Bioprosthesis has been used in young female adult patients at National Cerebral and Cardiovascular Center. During the decision-making process, the patients were carefully informed of the advantages and disadvantages of the Ross operation and

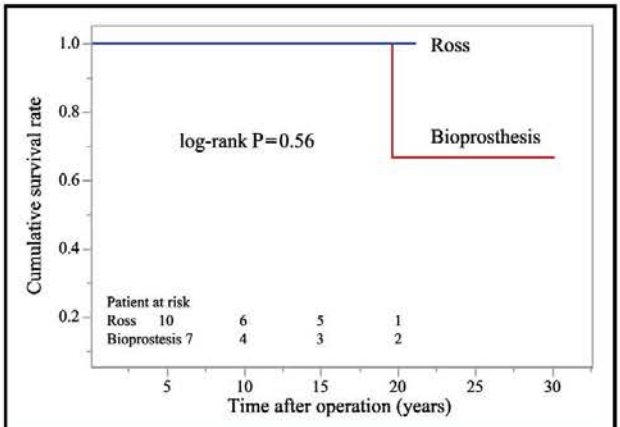

Figure 2. Kaplan-Meier Overall survival rate. Blue line, Ross group; red line, bioprosthesis group.

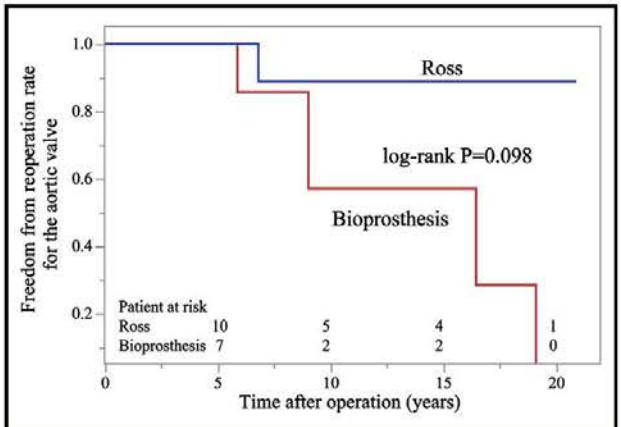

Figure 3. Kaplan-Meier rate of freedom from reoperation for the aortic valve. Blue line, Ross group; red line, bioprosthesis group.

bioprosthetic valve replacement.

Patient demographics are summarized in Table 1. Median age at operation was 22.5 years old (range, 18–34 years) in the Ross group and 30 years old (range, 22–39 years) in the bioprosthesis group. Age at operation in the Ross group was significantly younger than in the bioprosthesis group (P=0.027). The etiology of the aortic valve was congenital in 10 patients (83.3%) in the Ross group and in 5 patients (55.6%) in the bioprosthesis group (P=0.16). Seven patients (58.3%) in the Ross group and 1 patient (11.1%) in the bioprosthesis group had a history of previous cardiac surgery (P=0.027). Six patients (50.0%) in the Ross group had a previous surgical or catheter intervention for the aortic valve (P=0.019).

Surgical Procedures

At Ross operation, the neo-aortic root was reconstructed using a standard root replacement technique with coronary reimplantation. The Konno procedure for aortic annulus enlargement was concomitantly performed in 2 patients (16.7%). Pulmonary autograft inclusion in the polyester tube prosthesis to prevent neo-aortic enlargement was used in 1 patient (8.3%).

For the RVOT reconstruction at Ross operation, pulmonary homograft was used in 8 patients (66.7%), bovine pericardial roll with monocusp in 2 patients (16.7%), handmade valve conduit in 1 patient (8.3%), and excised native aortic root with aortic valve inserted into the autologous pericardial roll as a right ventricle-pulmonary artery conduit in 1 patient (8.3%).

In the bioprosthesis group, the implanted valves used were Carpentier-Edwards Aortic Porcine Bioprosthesis in 7 patients and Medtronic Mosaic Aortic Porcine Bioprosthesis in 2 patients. Nick's procedure for aortic annular enlargement was performed in 1 patient (11.1%). The median size of the implanted valve was 21 mm (range, 19–25 mm). The median effective orifice area index (EOAI) of the bioprosthesis was 1.02 cm^2/m^2 (range, 0.85–1.45 cm^2/m^2).

Statistical Analysis

Using data obtained from outpatient medical records, including echocardiography, the following variables were evaluated: (1) survival rate on Kaplan-Meier curve and log-rank test; (2) rate of freedom from reoperation for aortic valve on Kaplan-Meier curve and log-rank test; (3) postoperative trans-aortic blood flow and aortic insufficiency of pulmonary autograft and implanted bioprosthetic valve on echocardiography at time of discharge and at 5 years after operation; (4) change in valve function of pulmonary autograft and bioprosthetic valve during the perinatal period on echocardiography at the last outpatient clinic before pregnancy detection, during hospitalization and at the first outpatient clinic after childbirth; (5) function of pulmonary homograft as RVOT in Ross operation; and (6) New York Heart Association (NYHA) functional classification, current medication status, echocardiography findings, and biomarkers for heart failure. The grade of regurgitation was defined as follows: trivial, 1; mild, 2; moderate, 3; severe, 4.

Both the preoperative and postoperative data are expressed as median (range), except for blood flow velocity and valve regurgitation grade on echocardiography, which are expressed as mean±SD. Patient groups were compared using chi-squared test for categorical variables and Wilcoxon rank-sum test for continuous variables. Data were analyzed using JMP (SAS Institute, Cary, NC, USA), and differences were considered statistically significant for $P<0.05$.

Results

Overall Survival

Follow-up was completed in 100% of patients and the median follow-up period was 10.3 years (range, 1.0–20.8 years) in the Ross group and 7.8 years (range, 2.6–29.8 years) in the bioprosthesis group (P=0.34).

There was no mortality in the Ross group and 1 late mortality in the bioprosthesis group, due to prosthetic valve endocarditis (PVE) 19.6 years after the operation (Figure 2).

Postoperative Reoperation and Complications

Freedom from reoperation for the aortic valve at 5, 10, and 15 years was 100%, 90.0% and 90.0% in the Ross group, respectively, and 100%, 85.7% and 57.1% in the bioprosthesis group, respectively (log-rank, P=0.098; Figure 3). One patient in the Ross group required second valve replacement due to pulmonary autograft insufficiency 7 years after the operation, while 4 patients in the bioprosthesis group required second valve replacement because of PVE in 1 patient, combined stenosis and insufficiency in 1 patient and stenosis in 2 patients, 6, 9, 16 and 19 years after operation, respectively. One patient in the Ross group, who had a previous AVR with annular enlargement, underwent coronary arterial bypass grafting for

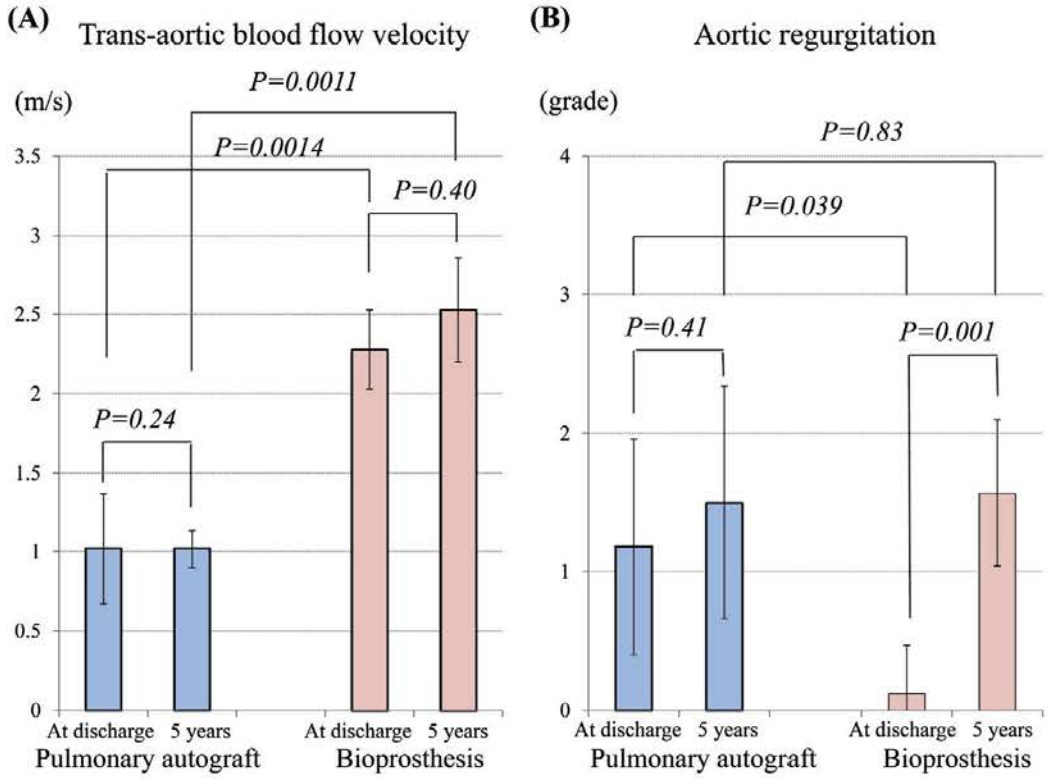

Figure 4. (A) Trans-aortic blood flow velocity and (B) grade of valve regurgitation at discharge and at 5 years.

Table 2. Outcome of Pregnancy

	Ross group	Bioprosthesis group	P-value
No. patients	12	9	
Patients giving birth	5	3	0.70
All births	6	5	
Once	4	1	
Twice	1	2	
Maternal complications			
Death	0	0	
Thromboembolism	0	0	
Arrhythmia	0	1	
Heart failure	0	0	
Fetal complications			
Death	0	0	
Preterm delivery	0	0	
Surgery-childbirth duration (years)	7.2 (2.1–17.3)	6.0 (2.4–8.3)	0.58
Surgery-first birth duration (years)	7.0 (2.1–17.3)	6.0 (2.4–6.0)	0.46

Data given as n or median (range).

stenosis of the left main trunk 1 year after Ross operation. There were no reoperations for RVOT in the Ross group and no surgical intervention for aortic root or ascending aorta dilatation in both groups, although 1 patient in the Ross group and 1 in the bioprosthesis group developed aortic root or ascending aorta dilatation (>40 mm) on contrast-enhanced computed tomography during the follow-up period.

No patients in either group developed postoperative atrioventricular block requiring pacemaker implantation, but 1 patient in the Ross group and 1 in the bioprosthesis group took medication for ventricular arrhythmia.

Pulmonary Autograft and Bioprosthetic Valve Function

Postoperative trans-aortic blood flow did not change in the Ross

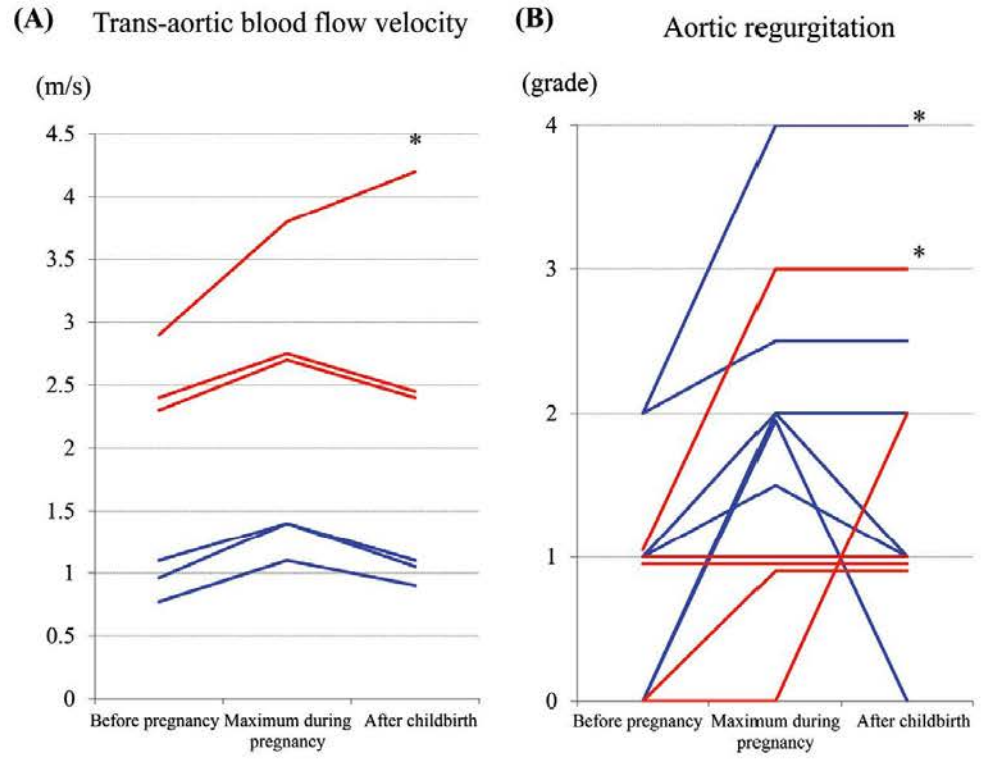

Figure 5. Individual serial changes in (**A**) trans-aortic blood flow velocity and (**B**) grade of valve regurgitation before, maximum during, and after pregnancy. Blue, Ross group; red, bioprosthesis group. *Redo aortic valve replacement after childbirth.

group between time of discharge and 5 years after operation (1.02±0.35 m/s vs. 1.02±0.12 m/s, P=0.24; **Figure 4A**). This was significantly lower compared with the bioprosthesis group, who had a slight increase from 2.28±0.25 m/s to 2.53±0.33 m/s after 5 years, but which was not statistically significant (P=0.40).

Regarding valve insufficiency, insufficiency grade at the time of discharge in the Ross group was significantly higher than that in the bioprosthesis group (grade 1.18±0.78 vs. 0.12±0.35, P=0.039), but at 5 years the difference was not significant (grade 1.50±0.84 vs. 1.57±0.53, P=0.83; **Figure 4B**).

Outcomes of Pregnancy

The outcomes of pregnancy are listed in **Table 2**. Five patients in the Ross group and 3 patients in the bioprosthesis group had 7 and 4 uneventful pregnancies, respectively. They all had full-term deliveries. There was no fetal death, nor any thromboembolic or hemorrhagic complications. Ventricular arrhythmia during pregnancy was seen in 1 patient in the bioprosthesis group, who had already had arrhythmia before AVR. The median interval from time of operation to childbirth was 7.2 years (range, 2.1–17.3 years) in the Ross group and 6.0 years (range, 2.4–8.3 years) in the bioprosthesis group (P=0.58). The median interval to the time of first childbirth was 7.0 years (range, 2.1–17.3 years) in the Ross group and 6.0 years (range, 2.4–6.0 years) in the bioprosthesis group.

Echocardiography during the perinatal period was carried out in all pregnancies in both groups. Trans-aortic blood flow velocity on echocardiography was documented in 6 of the 11 pregnancies (3 in the Ross group, 3 in the bioprosthesis group). Blood flow velocity increased from 0.96 m/s (range, 0.77–1.1 m/s) to a maximum of 1.4 m/s (range, 1.1–1.4 m/s) in the Ross group and from 2.4 m/s (range, 2.3–2.9 m/s) to 2.75 m/s (range, 2.7–3.8 m/s) in the bioprosthesis group. Blood flow velocity recovered to the pre-pregnancy level in all patients except in 1 patient in the bioprosthesis group, in whom the trans-aortic blood flow velocity increased from 2.9 m/s before pregnancy to 4.2 m/s after childbirth 8.3 years after operation (**Figure 5A**). In that patient, stenosis and regurgitation progressed during the second pregnancy, but not during the first pregnancy. That patient needed reoperation 8 months after the second birth. In 5 other pregnancies, no stenosis during pregnancy was noted on echocardiography.

Implanted valve regurgitation progressed during pregnancy in 7 (63.6%) of the total 11 pregnancies (**Figure 5B**). Of the 7 pregnancies, 1 patient in the Ross group and 1 patient in the bioprosthesis group needed reoperation at 2 years and at 8 months after childbirth, respectively. The interval from operation to childbirth in those 7 pregnancies with progression of aortic regurgitation during pregnancy tended to be longer than in the other 4 pregnancies (7.4 years, range, 4.8–17.3 years vs. 6.0 years, 2.1–7.1 years, P=0.10).

Pulmonary Homograft in Ross Operation

Pulmonary homograft was used for RVOT reconstruction at Ross operation in 8 out of 12 patients (67%). Blood flow velocity through pulmonary homograft did not change between discharge and 5 years after Ross operation (1.4±0.7 m/s vs. 1.9±0.6 m/s, P=0.22); the same was found for grade of regurgitation (1.5±0.9 vs. 0.8±0.8, P=0.17; **Figure 6**). And although blood flow velocity through the RVOT and pulmonary regur-

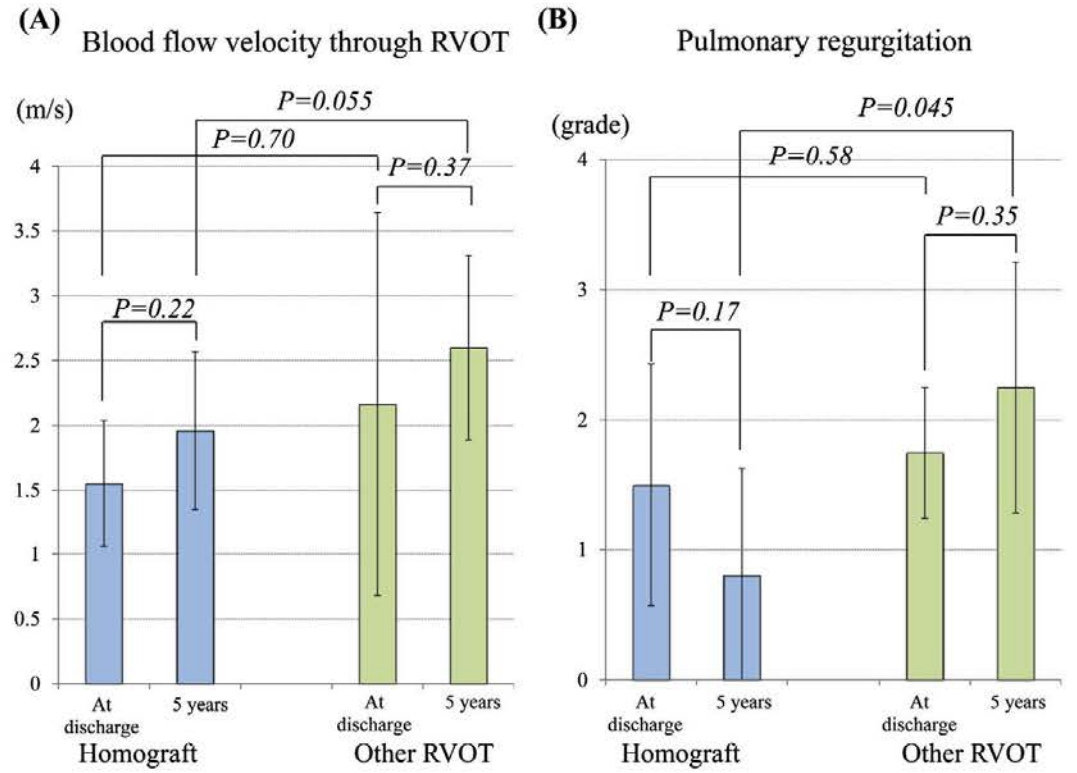

Figure 6. (A) Trans-pulmonary blood flow velocity and (B) grade of valve regurgitation at discharge and at 5 years in the Ross group. Blue, right ventricular outflow tract (RVOT) reconstructed with pulmonary homograft; green, RVOT reconstructed with other material.

gitation, for RVOT constructed from other materials, were similar to those for the pulmonary homograft at discharge, blood flow velocity through the RVOT tended to accelerate and regurgitation significantly progressed at 5 years for RVOT constructed from other materials, compared with the pulmonary homograft (blood flow velocity through RVOT, 1.9±0.6 m/s vs. 2.6±0.7 m/s, P=0.055; pulmonary regurgitation, 0.8±0.8 vs. 2.3±0.9, P=0.045; Figure 6).

Current Status

At the time of writing, NYHA functional classification was I in all patients in both groups except for 1 patient in the Ross group, who had NHYA II because of moderate aortic regurgitation, while 11 of the 12 patients in the Ross group and 5 of 8 patients in the bioprosthesis group were free from diuretic treatment or anti-arrhythmic agents. The latest echocardiography showed trans-aortic blood flow >2.0 m/s in all 8 of the bioprosthesis patients, but only in 1 of the 12 Ross patients, who developed mild stenosis (trans-aortic blood flow, 2.2 m/s) 20 years after Ross operation. One of the 12 patients in the Ross group and none of the 8 patients in the bioprosthesis group had moderate or greater aortic regurgitation. Median plasma brain natriuretic peptide in the Ross and bioprosthesis groups was 40.8 pg/ml (range, 23.3–158 pg/ml) and 39.6 pg/ml (range, 23.0–123 pg/ml), respectively. There was no difference between patients who became pregnant and those who did not, in either group (44.3 pg/ml, range, 23.3–52.9 pg/ml, and 40.2 pg/ml, range, 23.0–158 pg/ml, P=0.77).

Discussion

This study compared the long-term outcomes of Ross operation for young female adult patients of childbearing age with those of bioprosthetic valve replacement, and found that approximately half of patients safely gave birth after Ross operation. Although the direct impact on pregnancy of the implanted tissue valves was not clearly identified, the durability of bioprosthetic valve tended to be shorter than the pulmonary autograft. Implanted pulmonary homograft for the RVOT at Ross operation functioned well during the entire follow-up period, without a need for reoperation. Progression of implanted valve regurgitation over time, however, occurred only in the bioprosthesis group, and the trans-aortic blood flow velocity remained the same within each group, but was significantly faster in the bioprosthesis group at any time point. The acceleration of the trans-aortic blood flow velocity during pregnancy was common in both groups in response to the increase in maternal ventricular stroke volume, but it improved after childbirth, with the exception of 1 patient with bioprosthetic valve. In contrast, progressed implanted valve regurgitation during pregnancy was frequently observed in both groups, and did not improve in most cases.

Pregnancy After Ross Operation

There were 3 previous reports on pregnancy after Ross operation. Dore and Somerville reported 14 pregnancies in 8 patients after Ross operation between 1968 and 1993, with excellent

maternal and fetal outcomes.[15] The mean interval between Ross operation and first pregnancy was 5.6 years (range, 1–21 years). There was no significant progression of aortic regurgitation and right-sided lesions during or within 1 year after any of the pregnancies. There was no reoperation of pulmonary autograft during a mean follow-up period of 19.2 years, except for 1 reoperation on right-sided homograft 7 years after a second pregnancy (15 years after Ross operation). Yap et al reported 12 pregnancies in 5 patients after Ross operation between 2001 and 2005, which resulted in 10 successful live births.[16] The mean interval between Ross operation and pregnancy was 5.0±2.8 years (range, 1–9 years). Moderate aortic regurgitation was present in 3 women before pregnancy. During a mean follow-up period of 10.2 years, there was 1 reoperation 5 years after pregnancy for significant autograft regurgitation and pulmonary regurgitation. Heuvelman et al reported on 18 patients who became pregnant after Ross operation between 1987 and 2011.[8] The median interval from surgery to first pregnancy was 5.5 years (range, 1.8–9.4 years). Mean age at first, second and third pregnancy was 27.0±4.1 years, 30.0±3.9 years and 32.7±7.0 years, respectively. Trans-aortic blood flow before the first, second and third pregnancy was similar (1.36±0.42 m/s, 1.41±0.46 m/s and 1.41±0.48 m/s). There was no mortality or reoperation during any pregnancy.

In agreement with the 3 aforementioned reports, in the present study there was no clinically significant progression of autograft stenosis during pregnancy after Ross operation. Left heart obstruction is known to be a significant risk factor for cardiac events during pregnancy;[17,18] in this regard, Ross operation could be an optimal procedure for young female adult patients wanting to have children.

Worsening of autograft regurgitation was frequently observed during pregnancy, possibly because of increased ventricular stroke volume and cardiac output, and which then remained or further worsened after childbirth. Aortic valve regurgitation is said to be well tolerated during pregnancy, due to the afterload reduction and increased maternal heart rate.[17,18] A recently introduced autograft stabilization procedure that reinforces the annulus or sinotubular junction might prevent the progression of autograft regurgitation in the late term as well as during pregnancy.[19]

Bioprosthesis

Although statistically significant difference was not detected, the durability of the bioprosthesis tended to be short compared with pulmonary autograft. Whereas previous reports noted that bioprosthetic valve had a high rate of structural valve deterioration in young patients because of increased calcium turnover, fatigue-induced lesions and collagen degeneration and discrete immunologic reaction,[20–24] the impact of pregnancy on the structural valve deterioration of bioprosthetic valve is still controversial.[11,25–27] Indeed, stenosis of bioprosthetic valve progressed during pregnancy and required reoperation in 1 of the 5 of the present pregnancies, but that bioprosthetic valve had already showed moderate stenosis before pregnancy.

Another factor that had an effect in the present study was type of selected biological valve. A newly developed bioprosthetic valve has been shown to have excellent durability,[28] but none of the patients in the bioprosthesis group had the so-called "third-generation" Mosaic stented bioprosthetic valve. The use of such materials may improve the outcome of valve replacements for young women.

The bioprosthesis group had a significantly accelerated trans-aortic blood flow velocity at any time point, including during pregnancy. In the present study, median EOAI of the selected valve was 1.02 cm^2/m^2 (range, 0.85–1.45 cm^2/m^2) and a ≥23-mm bioprosthesis was implanted in only 3 of the 9 patients (33.3%) because of the relatively small-sized aortic annulus in young Japanese women. Minakata et al reported that a ≥23-mm Carpentier-Edwards Aortic Porcine bioprosthesis was used in 232 of 540 Japanese patients (43.0%) who underwent AVR with bioprosthesis.[29] Although transcatheter aortic valve-in-valve implantation has recently been reported for reoperation after AVR and is expected to improve outcome after the first bioprosthetic valve implantation,[30,31] the size of the previously implanted valve should be ≥23 mm, thereby making the majority of the present cohort ineligible for this procedure.

Tissue Bank and Pulmonary Homograft

The choice of material for RVOT reconstruction at Ross operation is also important for young women wanting to become pregnant. Satisfactory outcome of pulmonary homograft for RVOT reconstruction during pregnancy was described only by Dore and Somerville, otherwise, maintained function of pulmonary homograft during pregnancy for RVOT reconstruction in patients with tetralogy of Fallot has been demonstrated.[32] Patients undergoing Ross operation in adolescence or adulthood usually have completely normal, and therefore non-compensated, right ventricle, therefore mildly progressed stenosis or regurgitation at the pulmonary position during pregnancy might cause right ventricular function to deteriorate, which would adversely affect perinatal outcome. Pulmonary homograft was used in 8 of 12 patients (67%) in the present study, which functioned very well without significant stenosis or regurgitation during follow-up.

Because cryopreserved homograft was not commercially available in Japan, applied pulmonary homograft in this study was harvested from cardiac death patients by the institutional cardiovascular surgeons and preserved at the institutional tissue bank.[33] There is usually a shortage of donors because the presence and importance of cardiac homograft transplantation is not well recognized; thus, the improvement of such a situation and the expansion of human tissue transplantation are expected.

Conclusions

The long-term outcome of Ross operation in young female adult patients wanting to have children is excellent. Although the progress of pulmonary autograft valve regurgitation during pregnancy is a concern, pulmonary autograft showed good functionality and durability during the study period, and is therefore an ideal material.

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