Long-term outcome of cryopreserved allograft for aortic valve replacement

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ABSTRACT

Objective: The most efficient surgical approach to severe aortic valve disease in the young adult is still debated: cryopreserved aortic allograft offers excellent hemodynamic and avoid anticoagulation, but long-term durability is influenced by structural valve deterioration (SVD). This study aimed to describe long-term results of aortic allografts and to identify factors influencing long-term durability.

Methods: From January 1993 to August 2010, 210 patients underwent aortic allograft replacement via the free-hand subcoronary implantation technique (N = 55) or root replacement with coronary reimplantation (N = 155). Clinic and echocardiographic follow-up was updated to April 2016.

Results: Overall mortality and cardiac mortality occurred in 80 (38.1%) and 64 (30.5%) patients, respectively. Reoperation was required in 69 cases (32.8%), whereas SVD required reoperation in 57 cases (27.1%). No early endocarditis occurred, whereas late endocarditis occurred in 4 patients. The free-hand technique seems to be associated with improved left ventricular remodeling compared with the root-replacement technique, and smaller allograft size represents a predictor of reoperation independently on the surgical technique used. In the overall population, there were 44 women of childbearing age, and 37 patients remained pregnant during the follow-up of the study. No differences were found in the clinical outcomes among women who had children and who did not.

Conclusions: Cryopreserved allograft is a valid option, especially in complex infective endocarditis and in women of childbearing age. A careful choice of allograft size and implantation technique can reduce the risk of SVD. (J Thorac Cardiovasc Surg 2018;156:1357-65)

Allograft replacement for recurrent endocarditic pseudoaneurysm after Bentall procedure.

Central Message

Cryopreserved allograft is a valid option, especially in infective endocarditis and during childbearing age. A careful choice of allograft size and implantation technique can reduce the risk of reoperation.

Perspective

Cryopreserved allograft (CA) showed good outcomes, acceptable durability, and low reinfection rate, representing a valid option, especially in cases of complex endocarditic destruction and during childbearing age. These aspects should be considered when weighing the procedural risks of CA implantation against its long-term benefits and when these are compared with prosthetic valves.

See Editorial Commentary page 1366.

See Editorial page 1351.

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Diseases of the aortic valve raise difficult therapeutic problems in the young population.¹ Currently there is no unanimous consensus on the most efficient surgical approach to severe aortic valve disease in the young adult. Moreover, even the accepted surgical dogma concerning the preference in the use of autologous or allogeneic tissues

Scanning this QR code will take you to the supplemental video, appendix, and tables for the article.

Abbreviations and Acronyms

CA	= cryopreserved aortic allograft
NYHA	= New York Heart Association
SVD	= structural valve deterioration

in infective conditions has been recently lively debated.²⁻⁴ Some experts have advocated the use of allograft for the lack of complications related to oral anticoagulation and the excellent quality of life permitted by the enhanced hemodynamic performance of the valves.⁵⁻⁹

Consensus on the use of cryopreserved aortic allograft (CA) remains firm in women with future plans of pregnancy and in pediatric cardiac surgery. Recently, initial steps in the use of decellularized allografts for aortic root replacement have been taken, with promising results.^{10,11} However, the actual obstacle that affects long durability of the CA is structural valve degeneration (SVD). Failure of allograft conduit and valve is approximately 30%, leading frequently to reoperation.^{12,13} Hence, disadvantages related to the complexity of the technique of implantation, which is not normally mastered in all the centers, the restricted the availability of CA, and the increased complexity of reoperations have limited its use.

Here, we present our series of 210 patients who have undergone aortic allograft implantation and were followed up for 20 years. We aim to describe the long-term results of this procedure in our cohort and eventually to identify factors influencing long-term durability of aortic allograft (Video 1).

PATIENTS AND METHODS

Study Population and Operative Data

The records of 210 patients (150 males) with severe aortic disease who underwent aortic allograft replacement from January 1993 to August 2010 were reviewed and all events until April 31, 2016, were analyzed. The mean

age was 40.1 ± 17.9 years (range 10-77 years) with 10 patients younger than 18 years. Four surgeons in 2 centers were involved in these cases. Details of the clinical and operative characteristics are listed in Tables 1 and 2. Surgical strategy was based on the extent of valve lesions. The technical details of aortic allograft insertion have been widely described (APPENDIX E1), and 2 techniques have been used: the free-hand subcoronary implantation technique and the allograft root replacement with coronary reimplantation.

Valve-associated events such as SVD, cardiac death, valve-related mortality, and other outcomes are defined by Valve Academic Research Consortium-2 (VARC-2) criteria. Standard 2-dimensional and Doppler echocardiographic examinations with color-flow mapping were performed on all patients 1 week before operation. Baseline echocardiography for clinical follow-up was performed immediately after the operation at the time of discharge. Follow-up echocardiography was obtained during periodical outpatient clinics or immediately before redo surgery. All echocardiographic data were analyzed in random order by 2 independent expert cardiologists blinded with regard to the clinical data and timing of the echocardiogram (APPENDIX E1).

Statistical Analysis

Categorical variables, presented as frequencies and percentages, were compared with χ^2 analysis or the Fisher exact test. Normality criteria were checked and met for each continuous variable, which was expressed as mean and standard deviation and compared with the Student *t* test. Kaplan–Meier analyses were used to assess the probability of survival or other survival-related outcomes. For death and composite endpoints including death, a multivariable Cox regression model was used, including age, sex, etiology, type of implantation, size of the valve, and preoperative ejection fraction. For competing risk endpoint (such as SVD) with death, a competing risk framework was used and data reported as cumulative incidence.

Graphical presentation includes Kaplan–Meier curves to present crude survival probabilities in the overall population and cumulative incidence for competing risk endpoints. Longitudinal analysis was performed with a mixed-effect statistical package with random effects. Continuous (left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left ventricular ejection fraction, etc) and ordinal (aortic valve regurgitation grade, New York Heart Association [NYHA] class) data were analyzed with the “meglm” package when evaluating echocardiographic parameters in the overall population (with specific tests for continuous and ordinal data), and “xtreg” or “xtlogit” packages when evaluating the effect of the surgical treatment. As for Cox regression, proportional hazard assumption was tested with Schoenfeld residuals (“estat phtest” command) and was not violated in any described outcome. As for competing risk analysis, the proportionality assumption was checked with the option “tvc” after the command “sterreg.” Statistical analysis was performed with STATA Version 13 for Windows (StataCorp, College Station, Tex). A *P* < .05 was considered statistically significant.

RESULTS

Baseline characteristics and operative data of the patients are shown in Tables 1 and 2. Mean follow up was 13.0 ± 5.6 years, median follow-up was 13.6 (interquartile range, 9.2-17.3 years), and maximum follow up was 22.1 years. All the explants were performed at hospitals. In total, 154 patients (73.3%) were followed up more than 10 years and 82 patients (39.0%) more than 15 years. A total of 80 deaths (38.1%), 64 cardiac deaths (30.5%), and 69 reoperations (32.8%) occurred. Echocardiographic results and details about clinical outcomes are shown in Tables E1 and E2.

VIDEO 1. Summary of design and main findings of the study. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)31020-1/fulltext](https://www.jtcvs.org/article/S0022-5223(18)31020-1/fulltext).

TABLE 1. Baseline characteristics

Patients	N = 210	Percentage
Male sex	150	71.4
Age at implantation		
Mean $\pm$ SD	40.8 $\pm$ 18.9	
Median [IQR]	33 [26-62]	
Range	10-77	
Age <40 y	125	59.5
Hypertension	85	40.5
Smoking habit	68	32.4
COPD	29	13.8
Dyslipidemia	35	16.7
Diabetes mellitus	19	9.0
NYHA class		
1	0	0.0
2	64	30.5
3	83	39.5
4	63	30.0
Etiology		
Endocarditis	118	56.2
Complex	75	63.6
Noncomplex	43	36.4
Aortomitral junction, abscess	22	18.6
Circumferential abscess	21	17.8
NVE	77	65.2
PVE	41	34.7
<i>Staphylococcus methicillin</i> -susceptible	20	16.9
<i>Staphylococcus methicillin</i> -resistant	23	19.49
<i>Streptococcus viridans</i>	25	21.18
Other <i>Streptococcus</i>	10	8.47
Enterococcus	19	16.10
Other	9	7.6
Negative culture	12	10.66
Embolic events	32	27.11
Cerebral	25	21.18
Vegetation diameter >10 mm	57	48.30
Rheumatic	40	19.0
Congenital	31	14.7
Degenerative	21	10.0
Bicuspid aortic valve	38	18.1
Surgical indication		
Isolated severe aortic stenosis	46	21.9
Isolated severe aortic regurgitation	85	40.5
Mixed aortic stenosis and regurgitation	79	37.6
Rationale for allograft implantation		
Age <40 y	125	59.5
Woman of childbearing age	44	20.9
Contraindication to oral anticoagulation	86	40.9
Poor compliance to treatment	15	7.1
Personal preference	17	8.1
Childbearing age	44	20.9
Bleeding disorders	10	4.7
Endocarditis	118	56.2

(Continued)

TABLE 1. Continued

Patients	N = 210	Percentage
Previous cardiac surgery	41	19.5
Redux	35	16.7
Tridux	5	2.4
Quadridux	1	0.5
Previous cardiac surgery	41	19.5
Aortic valve replacement	33	15.7
Allograft	6	2.8
Other	2	1.0
Urgent surgery	68	32.4

SD, Standard deviation; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis.

Survival

All-cause early (<30 days) mortality was 5.7% (n = 12). Ten of 12 patients underwent urgent surgery, and 11 of 12 patients underwent surgery due to endocarditis. Five patients died of heart failure, 4 patients died of multiorgan

TABLE 2. Operative characteristics

Patients	N = 210	Percentage
Surgical technique		
Miniroot	155	73.8
Freehand	55	26.2
Allograft size, mm		
17	4	
19	6	1.9
21	68	2.8
23	96	32.4
25	33	45.7
27	3	15.7
Mean size	22.5 $\pm$ 1.7	1.4
Concomitant procedures	49	23.3
Myocardial revascularization	19	9.0
Mitral valve homograft	10	4.8
Tricuspid valve repair	9	4.3
Mitral homograft valve repair	8	3.8
Tricuspid valve replacement	3	1.4
Severe aortic annular calcification	23	10.9
Cardiopulmonary bypass, min	230 $\pm$ 82	
Aortic crossclamp time, min	185 $\pm$ 71	
Donor		
Age, mean $\pm$ SD	44.1 $\pm$ 7.1	
Age, range	5-61	
Age >50 y	68	
Annulus, mean $\pm$ SD	25.2 $\pm$ 3.6	32.3
Sex mismatch	92	43.8
Annular size mismatch (>5 mm)	11	5.2
Blood group mismatch	109	51.9
Rh antigen mismatch	34	16.2

SD, Standard deviation.

TABLE 3. Summary of adverse outcomes

	No. patients
Patients	210
Overall mortality	80
Early mortality (<30 d or in-hospital death)	12
Urgent surgery	10
Endocarditis (n = 118/210)	11
Miniroot technique	11
Late mortality	68
Valve-related mortality and morbidity	
Reoperation	12
Urgent surgery*	9
Structural valve degeneration†	14
Reinfection	4
Thromboembolism	3
Anticoagulant-related hemorrhage	3
Composite valve-related mortality and morbidity (valve-related events)	36
Nonvalve-related events	22
Heart failure	16
Sudden cardiac death	6
Noncardiac mortality	10
Malignancies	6
Respiratory failure	3
Renal failure	1

Follow-up duration: max: 22.1 years; mean: 13.0 ± 5.6 years; time at risk: 2731.7 allograft-years. *Nine of 12 patients underwent urgent surgery. †Twelve patients were not reoperated, 6 died before intervention, and 6 refused surgical treatment.

failure, and 3 patients died of acute respiratory distress syndrome, respectively (Table 3, Figure 1, A). All-cause late (>30 days) mortality occurred in 80 patients, with 64 cardiac deaths, 16 noncardiac deaths, and valve-related mortality in 18 patients (Table 4). Survival from cardiac related events is shown in Figure 1, B, and Table 4.

Reoperation

Eighty-one patients had aortic allograft failure, and 69 of these revealed SVD (Table 4). Table 5 summarizes the specifics of the explanted allografts and the details of the 69 reoperations. Freedom from reoperation on the allograft conduit is displayed in Figure 1, C. Reoperation-related mortality was 15% for both first-time and multiple-time redo-procedure, and 9 of 12 patients underwent urgent surgery. This high rate of mortality was related to hostile calcification of the root and endocarditis recurrence (4 patients) after multiple repeat surgery. Nine SVD-reoperations had late mortality, and 48 SVD reoperations are still in follow up. Expected valve durability (median survival time without reoperation) is 17.7 years.

Major Adverse Cardiac and Cerebrovascular Events

Overall freedom from major adverse cardiac and cerebrovascular events (all valve-related mortality; valve-

related morbidity: structural and nonstructural valve dysfunction with the need of reoperation, thrombosis, bleeding, embolism, neurologic events, endocarditis, rehospitalization for heart failure, and worsening NYHA class) is shown in Table 4 and Figure 1, D.

Infective Endocarditis

No early endocarditis occurred. Late endocarditis occurred in 4 patients (freedom from endocarditis at 20 years: $98.1\% \pm 1.5\%$). Overall, 4 allograft reoperations referable to endocarditis were performed.

Thrombosis and Bleeding

Allograft-related thrombotic and thromboembolic events occurred in 3 patients. Major internal or external bleeding was revealed in 1 patient. A total of 3 patients skilled the composite end point of thrombosis, embolism, or bleeding (freedom from thrombosis and bleeding at 20 years: $98.6\% \pm 1.4\%$).

Structural Valve Degeneration

SVD required reoperation in 57 patients (Table 4). Twelve patients did not undergo reoperation, 6 died before intervention, and 6 refused surgical treatment. Twelve interventions were performed for nonstructural valve deterioration, of these 4 patients required reoperation for late endocarditis. Cumulative incidence of SVD at 10, 15, and 20 years was $0.6\% \pm 0.6\%$, $3.2\% \pm 1.6\%$, and $57.0\% \pm 6.6\%$, respectively (Figure 2).

SVD was revealed with leaflet tear of the right cusp in 26 patients and of the left cusp in 24 patients. In total 19 patients experienced a tear of both cusps. All patients had severe clinical presentation of severe dyspnea related to severe regurgitation. In 23 patients, aortic stenosis was associated. Usually, the time between SVD and the appearance of symptoms ranged from less than 1 months to 3 months, and reoperation was required within the same period. Fifty-six patients manifested chronic symptoms and required reoperation after 3 months. No significant difference was found in the position of tear with regard to the surgical procedure ($P = .264$, Table E3). Generally, the location of tears was at the base of allograft or in the proximity of the commissures. Macroscopic calcifications were observed in younger patients who developed an early structural valve degeneration with severe aortic regurgitation caused by leaflet tear. In patients with severe stenosis allograft leaflet were severely calcified.

Quality of Life

Functional status as evaluated by NYHA class showed a statistical significant improvement both postoperatively and in the long-term in comparison with the baseline conditions. This improvement was stable over the course of the study, and very few patients experienced a worsening of

FIGURE 1. Kaplan–Meier analysis. A, Overall survival; B, survival from cardiac-related events; C, freedom from reoperation; D, and freedom from MACCEs. MACCEs, Major adverse cardiac and cerebrovascular events.

NYHA class or rehospitalization for heart failure during follow-up ([Supplementary Materials](#)).

Outcomes in Childbearing Age

In the overall population, there were 44 (21%) women of childbearing age. Among those, 37 (84.1%) patients remained pregnant during the follow-up of the study and gave birth to at least 1 or more healthy children. We found no statistical significant difference in the clinical outcomes among women who had children and who did not ([Table E4](#)).

Regression Analysis

Cox regression showed that overall mortality and cardiac mortality were not influenced by allograft implantation technique or valve size. Notably, a greater valve size was associated with a reduced risk of reoperation (hazard ratio 0.79, $P = .012$) ([Table E5](#)).

The longitudinal analysis of echocardiographic data showed that freehand technique might turn into a better remodeling of the left ventricle (with decreased left ventricular end-diastolic diameter, decreased left

ventricular end-systolic diameter, and improved left ventricular ejection fraction) with reduced NYHA class compared with the miniroot technique. However, the freehand technique tends to increase gradients through the aortic valve ([Table E6](#)).

DISCUSSION

The main findings of this study are that (1) CA is still a valid option in aortic valve replacement, especially in cases of annular and periannular tissue destruction, providing acceptable durability and clinical outcomes with optimal hemodynamic performance; (2) reoperation is rare in the first years after implantation and tends to be required for SVD after more than 15 years after surgery; (3) the long-term incidence of endocarditis after allograft implantation is low; (4) the miniroot technique seems to be associated with detrimental left ventricular remodeling compared with the freehand technique; (5) small allograft size represents a predictor of reoperation independently on the surgical technique used; and (6) women with future plans of pregnancy might benefit from allograft

TABLE 4. Clinical outcomes

	Event, n (%)	Freedom from event at 1 y	Freedom from event at 5 y	Freedom from event at 10 y	Freedom from event at 15 y	Freedom from event at 20 y	MST, y	AUC, y
Overall mortality	80 (38.1)	94.3 ± 1.6 (90.2-96.7)	93.3 ± 1.7 (88.9-95.9)	85.5 ± 2.5 (79.7-89.7)	61.3 ± 40.4 (52.9-68.7)	41.8 ± 5.1 (31.7-51.5)	18.9	16.7
Cardiac mortality	64 (30.5)	94.3 ± 1.6 (90.2-96.7)	93.3 ± 1.7 (88.9-95.9)	87.9 ± 2.3 (82.5-91.7)	97.6 ± 3.5 (66.9-80.8)	48.4 ± 5.5 (37.4-58.6)	19.8	17.5
MACCEs	115 (54.7)	94.3 ± 1.6 (90.2-96.7)	91.8 ± 1.9 (87.2-94.9)	78.1 ± 3.0 (71.6-83.3)	50.6 ± 4.1 (42.3-58.4)	4.6 ± 2.7 (1.1-12.0)	15.0	13.4
Reoperation	69 (32.8)	100.0 ± 0.0	100.0 ± 0.0	95.7 ± 1.6 (91.3-97.9)	84.3 ± 3.3 (76.4-89.8)	15.5 ± 4.8 (7.5-26.3)	17.7	17.2
Reoperation, SVD-related only	57 (27.1)	100.0 ± 0.0	100.0 ± 0.0	96.9 ± 1.3	89.4 ± 2.9	19.1 ± 5.8	19.0	17.8
	Event, n (%)	Cumulative incidence at 1 y	Cumulative incidence at 5 y	Cumulative incidence at 10 y	Cumulative incidence at 15 y	Cumulative incidence at 20 y		
SVD	57 (27.1)	0	0	0.6 ± 0.6 (0.1-4.1)	3.2 ± 1.6 (1.2-8.4)	57.0 ± 6.6 (44.7-70.1)		

Survival probability was calculated via Kaplan–Meier estimates. Results are shown as mean ± standard error of the mean (95% confidence interval). When the survival curve does not cross the 50% line, the MST is not applicable. *MST*, Median survival time, in years; *AUC*, area under the Kaplan–Meier curve, in years; *MACCEs*, major adverse cardiac and cerebrovascular events: all valve-related mortality; valve-related morbidity: structural and nonstructural valve dysfunction with the need of reoperation, thrombosis, bleeding, embolism, neurologic events, endocarditis, rehospitalization for heart failure, and worsening New York Heart Association class; *SVD*, structural valve degeneration.

implantation, as the long-term clinical outcomes are not different from the rest of the population.

Survival in the Overall Population

In the majority of case-series studies addressing the survival of CA, encouraging results have been published. In the series reported by Fukushima and colleagues,⁸ median survival was 11 years if age was 0 to 19 years at implantation, 24 years for those aged 20 to 39 years, 22 years for those aged 40 to 59 years, and 14 years for those aged 60 to 81 years. Arabkhani and colleagues⁵ showed an 8-year

actuarial survival of 77.6%, and in a recent large series followed-up to 20 years cumulative survival was 41%. We reported similar data to the actuarial survival, with 93.3% ± 1.7% at 5 years and 67.6% ± 3.7% at 15 years and 41.8 ± 5.1 at 20 years. After we excluded the early mortality, mainly attributable to intraoperative complications or difficulties related to the endocarditis indication usually characterizing CA use, the overall survival was not significantly different than mechanical valves, as testified by a large study by Chiang and colleagues¹⁴ in *JAMA* (actuarial 15-year survival was 60.6%) and biological valves (actuarial 15-year survival 62.1%). These results are in line with the reports on long-term follow-up of Carpentier-

TABLE 5. Details of explanted allografts

Overall explanted	N = 81
SVD	69
SVD, nonreoperations	12
SVD, reoperations	57
NSVD	12
Endocarditis	4
Cusp retraction	3
Pseudoaneurysm	2
Fibrosis	2
Right coronary ostia malposition*	1

A total of 44 of 81 patients (54.3%) had miniroot technique at the first surgery. Nine SVD reoperations had late mortality: 48 SVD reoperations are still in follow-up. Of the 69 reoperations: AVR mechanical 34 (49.3%), AVR biological 7 (10.1%), homograft 10 (14.5%), Bentall 16 (23.2%), ascending aorta 2 (2.9%). *SVD*, Structural valve degeneration; *NSVD*, nonstructural valve disease. *Patient was reoperated and underwent a Cabrol-type coronary ostia reimplantation.

FIGURE 2. Cumulative incidence of structural valve generation.

Edwards bioprosthesis (15 years survival 65.6%),¹⁵ with particular benefit in patients aged older than 60 years.^{15,16} In contrast, stentless valves implanted in subcoronary position have shown poorer results at 15 years' follow-up (survival 35%).¹⁷

These outcomes are particularly interesting, considering the need to weigh the results against the indications and the type of bioprosthesis used. Indeed, in contrast with bioprosthesis, the vast majority of allografts are used in critical conditions after failure of previous valve interventions with a significant increase in the surgical risk. Furthermore, differences among the type of prosthesis used (ie, mechanical vs biological)¹⁸ or the composition of bioprostheses¹⁹ might have a profound influence in determining the long-term outcomes of these patients. In this context, patients implanted with prosthetic valves are also more prone to reinfection, with aggressive prostheses lesions and need for reintervention.

The high reoperation-related mortality in this series was dictated by reinfection, which implies wide destructive surgery, and extensive calcification of the allograft. Also, these figures might be explained by the fact that study has been conducted in the presutureless technology era, which is a viable option to circumvent this issue, particularly in the younger population^{20,21} and also in case of homograft reinfection,²² whereas transcatheter aortic valve replacement might be safely applied in noninfected calcified SVD with reduced mortality and morbidity.^{4,23}

However daunting the procedural aspects of CA implantation, reoperation and reinfection rates are lower than prosthetic valve replacement, and this aspect needs to be considered when weighting the procedural risks of CA implantation against its long-term benefits^{24,25} and when comparing those with the natural history of a biological or mechanical valve and the mortality associated to reoperation for prosthetic valve endocarditis.^{4,26} Lastly, CA provides an enormous advantage in annular and periannular tissue destruction, for which allograft should be the primary indication.⁴ This is not related to the reinfection burden but rather to the fact that the CA has a curtain of perivalvular tissue that can be used to reconstruct the periannular structures.

Allograft Valve Replacement in Endocarditis

The estimates of aortic valve endocarditis with the need for operation are reported in 0.15%/patient-years. We advocate the use of autologous allogenic tissue in cases involving prosthetic valves and in complex and aggressive lesions, such as circumferential abscess formation or mitro-aortic junction extension. Indeed, despite in the past few years the use of stented xenograft and mechanical prostheses has greatly exceeded the use of allogenic tissues due to ease of implantation and scarce availability of CA, several reports have established the superiority of

autologous allogenic tissues in these circumstances.^{4,27-29}

In our study, we showed low risk of reinfection independent of the implant technique used. Interestingly, there was no significant difference in 30-day mortality or during the follow-up among the endocarditis versus nonendocarditis group. The observed 30-day rate of death (1.9% in the endocarditis group and 3.8% in nonendocarditis group) was greater in urgent conditions, in elderly patients, and in prosthetic valve endocarditis. These data are comparable with the national rates reported by the American College of Cardiology/American Heart Association and the Society of Thoracic Surgeons for mechanical or biological valves.³⁰

However, our findings are in contrast with the recently reported outcomes by Kim and colleagues² in a propensity-matched analysis comparing allografts, xenografts, and mechanical prostheses in the setting of infective endocarditis, which showed no demonstrable benefit in terms of mortality and resistance to reinfection in the allograft group. Our study confirmed a low rate of recurrent endocarditis among patients undergoing aortic allograft valve replacement, which is in contrast with the results by Kim and colleagues.² Conversely, our findings are similar to those reported in previous systematic reviews,³¹ and the evidence that the risk of recurrence of endocarditis is also related to predisposing factors unrelated to the valve type, such as diabetes mellitus, corticosteroid therapy, poor dental care, and blood product usage, might additionally support the use of the allogenic tissues in patients with infective endocarditis.³²

Reoperations on Allograft for Structural and Nonstructural Valve Deterioration

The estimates of structural and nonstructural allograft deterioration with the need for reoperation in young patients is reported to range between 2.47% and 3.83% per patient-year, with a pooled mean of 3.08% per patient-year.⁸ In contrast, in the present series reoperations on the allograft are common between 10 and 20 years from surgery with a freedom from reoperation of $95.7\% \pm 1.6\%$ at 10 years, $84.3\% \pm 3.3\%$ at 15 years, and $15.5\% \pm 4.8\%$ at 20 years, respectively. This is in accordance with the data of the series reported by Takkenberg and colleagues⁶ at 15 years. Aortic regurgitation was the leading cause of reoperation based on structural valve failure with root calcification; other indications were related to nonstructural valve deterioration or infective endocarditis. In population older than 40 years, the linearized estimates of structural and nonstructural allograft conduit deterioration with the need for reoperation have been shown to range between 0.7% and 1.7% and 0.05% and 0.32% per patient-year, respectively.⁵

In our series, SVD was related to leaflet tear in all cases, with consequent valve failure. The wear-and-tear

phenomenon has been attributed to a combination of hemodynamic and rheological disturbances and biomechanical stress on the leaflets, which lead to the formation and accumulation of calcium aggregates, as reported by several studies analyzing the mechanisms of failure of stentless valves.^{17,33,34} Although the relative contribution of these factors remains debated, the implant technique might play an important role in this context as imparting different degrees of mechanical stress at the level of the root complex dependently on the subcoronary or miniroot insertion.^{35,36} The wear-and-tear phenomenon was prevalently noticed in right and left cusp exposed to overpressure, whereas the noncoronary sinus appeared more protected. It might be speculated that the difficult geometric adjustment of the allograft during the implantation may determine an inhomogeneous mechanical stress on right and left suture line, which favors premature degeneration of the respective cusps, leading to leaflet dysfunction. The preferential localization of the tears in over pressurized areas might also allow us to hypothesize that reduced elastomechanical compliance of the degenerated and calcified allograft roots play a role in this context. From the clinical perspective, the short interval between the clinical presentation and the need for reoperation reinforce the idea of a rapid transition from a normally functioning valve to severe valve regurgitation induced by leaflet tear.

SVD and Pregnancy

To our knowledge, no other study has reported outcomes of allograft in childbearing age. In this series, 84% of the women of childbearing age gave birth to 1 or more babies, and we found no differences in the clinical outcomes in these women with respect to the rest of the women who underwent surgery. Interestingly, there was no association between the number of subsequent pregnancies and the risk of allograft degeneration, supporting the idea that elevated endogenous estro-progestinic levels do not play a significant role in SVD. Aortic allograft, avoiding anticoagulation, might constitute an additional advantage for this subcategory as allowing the patient to conduct a normal life after the operation.³⁷ These findings might be useful in patient counseling and during the heart team discussion regarding the best treatment option in this subset of patients with severe aortic valve disease.

Limitations

The authors acknowledge that one of the main limitations of this study is its retrospective inner nature, which might still carry a significant bias. However, common limitations might be mitigated by the fact that no missing data were present in our database and both echocardiographic evaluations and reoperations were performed in our centers.

CONCLUSIONS

This study reported the very long-term outcomes of CA in aortic position in 2 high-volume centers. CA represents a valid option, especially in the context of infective endocarditis and in a specific subset of patients, such as women of childbearing age. Long-term SVD is a considerable concern, but careful choice of allograft size and implantation technique might minimize this risk.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: cryopreserved aortic allograft, aortic valve replacement, endocarditis, long-term, allograft, structural valve degeneration

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APPENDIX E1. METHODS

Surgical Details

Patients who underwent aortic valve replacement with cryopreserved aortic allograft had at least 1 among the following inclusion criteria: age younger than 40 years ($n = 125$), woman of childbearing age ($n = 44$), contraindication to oral anticoagulation ($n = 86$) related to poor compliance to treatment, personal preference, childbearing age or bleeding disorders, and endocarditis ($n = 118$). The technical details of aortic allograft insertion have been widely described.^{E1} In the free-hand subcoronary implantation technique, the allograft was scalloped, and only the valve tissue and the annulus were grafted with a proximal interrupted suture line on the annulus and a distal running suture line on the ascending aorta. In the root replacement with coronary reimplantation, also known as the miniroot technique, the entire complex constituted by the aortic valve, and sinuses of Valsalva were transplanted. The proximal anastomosis on the annulus was initially achieved with interrupted sutures, then the allograft was positioned at the level of coronary ostia and secured with knots. Subsequently, the coronary arteries were reimplanted in situ and the distal anastomosis with the ascending aorta completed with running sutures.

Details on Clinical Follow-up

Periodical data collection was performed at discharge, at 6 months, and on a yearly basis. In addition, because of the different regional provenances of the patients, cross-sectional analysis in a retrospective manner was carried out over the first semester of the year 2016. Clinical examination in outpatient clinic or phone interview were used to obtain data for the

clinical follow-up. Complete clinical examinations from the referring cardiologists or general practitioners were also accepted. Systematic follow-up information was obtained at 1 years, 5 years, and 5-year intervals for 20 years, with patient consent at each contact. Noninvasive imaging was associated with outpatient visit, or a telephonic interview with 1 of the patient's relatives in case of adverse events. All indications for aortic allograft reoperation were in conformity with the American College of Cardiology/American Heart Association guidelines.

Echocardiographic Follow-up

Echocardiograms were obtained routinely before discharge and then every year to measure postoperative aortic valve (AV) configuration and hemodynamic stability. (AV mean and peak gradients [mm Hg], AV regurgitation grade, transvalvular gradients and effective valve orifice areas [EOAs], left ventricular end-diastolic diameter, aortic annular diameter, left ventricular outflow tract diameter, ascending aorta dimension, and left ventricular function). The EOA was indexed to the patient's body surface area. Homograft-patient mismatch was defined as an indexed EOA $\leq 0.73 \text{ cm}^2/\text{m}^2$.

E-Reference

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TABLE E1. Echocardiographic results and NYHA class changes

	Preoperative, N = 210	After 1 y, N = 198	After 5 y, N = 193	After 10 y, N = 154	After 15 y, N = 82	Preoperative term, coefficient (95% CI)*	Time term (mo), coefficient (95% CI)*
LVEDD	52.9 ± 6.4	46.6 ± 4.8	45.7 ± 4.6	45.8 ± 4.7	46.3 ± 4.7	0.911	0.001
Difference†		−5.6 ± 1.7	−0.9 ± 1.2	0.1 ± 0.3	0.3 ± 1.0	(0.90-0.92)	(−0.002 to 0.004)
P value		<.001	<.001	.032	.001	.001	.514
LVESD	38.0 ± 6.9	35.5 ± 6.4	34.7 ± 6.4	34.8 ± 6.4	35.7 ± 6.1	0.955	0.005
Difference†		−2.0 ± 1.2	−0.7 ± 1.1	0.1 ± 0.2	0.2 ± 0.9	(0.949-0.960)	(0.003-0.007)
P value		<.001	<.001	.052	.005	.001	.001
EF	51.8 ± 8.1	57.8 ± 5.7	58.8 ± 5.5	58.8 ± 5.5	58.0 ± 5.8	1.075	−0.002
Difference†		5.1 ± 2.9	1.0 ± 1.7	0.1 ± 0.2	−0.3 ± 1.3	(1.067-1.083)	(−0.005 to 0.002)
P value		<.001	<.001	.565	.007	.001	.326
AV regurgitation grade	2.6 ± 1.4	0.4 ± 0.5	0.4 ± 0.5	0.4 ± 0.5	0.8 ± 0.7	−0.072	0.008
Difference†		−2.1 ± 1.3	0.1 ± 0.1	0.1 ± 0.2	0.4 ± 0.7	(−0.158 to 0.014)	(0.006-0.011)
P value		<.001	.318	.416	<.001	.104	.001
AV gradient	25.3 ± 8.9	9.1 ± 1.6	9.1 ± 1.6	9.2 ± 1.6	9.9 ± 2.0	0.452	0.035
Difference†		−16.4 ± 9.2	0.1 ± 0.1	0.1 ± 0.2	0.8 ± 1.8	(0.428-0.476)	(0.027-0.043)
P value		<.001	.468	.028	<.001	.001	.001
Annular diameter	22.1 ± 1.8	22.3 ± 1.8	22.3 ± 1.8	22.3 ± 1.7	22.5 ± 1.7	1.005	0.002
Difference†		0.2 ± 0.6	0.1 ± 0.3	0.1 ± 0.1	0.1 ± 0.3	(1.002-1.008)	(0.002-0.003)
P value		<.001	.493	.018	.013	.001	.001
LVOT diameter	21.5 ± 1.8	21.8 ± 1.8	21.8 ± 1.8	21.8 ± 1.8	21.8 ± 1.8	1.002	0.001
Difference†		0.3 ± 0.7	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	(1.000-1.005)	(0.001-0.002)
P value		<.001	.318	.318	.319	.001	.001
Aortic diameter	34.3 ± 4.1	34.1 ± 4.0	34.1 ± 4.1	33.9 ± 4.2	33.9 ± 4.7	−0.072	0.008
Difference†		0.1 ± 0.5	0.1 ± 0.6	−0.2 ± 0.9	0.1 ± 3.1	(−0.158 to 0.015)	(0.006-0.011)
P value		.286	.870	.009	.927	.104	.001
NYHA class							
1	0 (0.0%)	144 (72.7%)	144 (74.6%)	97 (63.0%)	45 (56.9%)		
2	64 (30.5%)	51 (25.7%)	45 (23.3%)	51 (33.1%)	22 (26.8%)	−0.172	0.008
3	86 (40.9%)	2 (1.0%)	3 (1.5%)	3 (1.9%)	9 (10.9%)	(−0.287 to −0.144)	(0.006-0.011)
4	63 (30.0%)	1 (0.5%)	1 (0.5%)	3 (1.9%)	5 (6.1%)	.001	.001

CI, Confidence interval; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; EF, ejection fraction; AV, aortic valve; LVOT, left ventricular outflow tract; NYHA, New York Heart Association. *Preoperative effect and time effect were evaluated with a longitudinal mixed-effect regression: the patient was considered a random effect; preoperative value and time from surgery to observation (in months) were considered fixed effects. Associated *P* value is shown. †Difference is calculated from the previous time point using paired data, with associated *P* value.

TABLE E2. Clinical outcomes classified by etiology and surgical procedure

Outcome	Patients	P value
Early mortality	12	
By etiology		
Endocarditis	9	.165
Rheumatic	3	
Congenital	0	
Other	0	
By technical procedure		.147
Freehand	1	
Miniroot	11	
Overall mortality	80	
By etiology		
Endocarditis	23	<.001
Rheumatic	23	
Congenital	19	
Other	11	
By technical procedure		.004
Freehand	12	
Miniroot	68	
Valve-related cardiac late mortality	36	
By etiology		.909
Endocarditis	20	
Rheumatic	8	
Congenital	6	
Other	2	
By technical procedure		.689
Freehand	8	
Miniroot	18	
Not valve-related late mortality	22	
Not cardiac mortality	10	
Reoperation	69	
By etiology		
Endocarditis	35	.272
Rheumatic	19	
Congenital	9	
Other	6	
By technical procedure		<.001
Freehand	32	
Miniroot	37	
Reoperation for SVD	57	
By etiology		
Endocarditis	30	.601
Rheumatic	15	
Congenital	7	
Other	5	
By technical procedure		<.001
Freehand	30	
Miniroot	27	

(Continued)

TABLE E2. Continued

Outcome	Patients	P value
MACCEs	115	
By etiology		
Endocarditis	51	.914
Rheumatic	31	
Congenital	21	
Other	12	
By technical procedure		.124
Freehand	36	
Miniroot	79	

SVD, Structural valve degeneration; MACCE, major adverse cardiac and cerebrovascular event.

TABLE E3. Characteristics of tear and wear

Characteristics of tear and wear	Patients with SVD (N = 69)
Right cusp	26
With calcifications	5
Left cusp	24
With calcifications	10
Right and left cusp	19
With calcifications	13

SVD, Structural valve degeneration.

TABLE E4. Clinical outcomes in childbearing age

Outcomes	Women in childbearing age who had children	Women childbearing age who did not have children	P value
Number of patients	37	7	
Overall death	17	5	.216
Valve-related cardiac death	4	0	.362
Structural valve degeneration	9	2	.812
Reoperation	10	2	.933
MACCEs	20	5	.395
Outcomes	Women in childbearing age who delivered after surgery	All ages women	P value
Number of patients	37	48	
Valve-related cardiac death	4	7	.607
Structural valve degeneration	9	5	.087
Reoperation	10	9	.364
MACCEs	20	19	.184

MACCE, Major adverse cardiac and cerebrovascular event.

TABLE E5. Multivariable Cox regression: overall mortality, cardiac-related mortality, MACCEs, and reoperation

Overall mortality	Hazard ratio	95% CI	P value	Test of proportional hazard assumption Overall model, $P = .232$
Male sex	0.94	0.43-2.07	.889	.724
Age	1.07	1.04-1.09	.001	.058
Etiology (ref. endocarditis)				
Rheumatic	0.77	0.17-3.48	.740	.761
Congenital	1.73	0.50-5.96	.382	.443
Degenerative	1.32	0.55-3.18	.524	.683
Freehand technique	0.61	0.24-1.57	.312	.976
Valve size	0.86	0.72-1.02	.096	.243
Preoperative ejection fraction	0.97	0.93-1.01	.198	.071
Cardiac mortality	Hazard ratio	95% CI	P value	Test of proportional hazard assumption Overall model, $P = .062$
Male sex	0.94	0.39-2.24	.892	.886
Age	1.06	1.03-1.09	.001	.052
Etiology (ref. endocarditis)				
Rheumatic	0.70	0.14-3.34	.655	.983
Congenital	1.27	0.30-5.31	.739	.231
Degenerative	0.72	0.21-2.44	.597	.829
Freehand technique	0.94	0.35-2.51	.903	.936
Valve size	0.84	0.69-1.03	.104	.078
Preoperative ejection fraction	0.95	0.91-0.99	.030	.059
MACCEs	Hazard ratio	95% CI	P value	Test of proportional hazard assumption Overall model, $P = .235$
Male sex	1.10	0.65-1.88	.704	.897
Age	1.00	0.98-1.01	.711	.543
Etiology (ref. endocarditis)				
Rheumatic	0.98	0.46-2.05	.957	.869
Congenital	0.59	0.27-1.26	.175	.611
Degenerative	0.94	0.45-1.94	.868	.351
Freehand technique	0.72	0.39-1.31	.289	.751
Valve size	0.93	0.82-1.06	.300	.444
Preoperative ejection fraction	0.981	0.95-1.01	.295	.053
Reoperation	Hazard ratio	95% CI	P value	Test of proportional hazard assumption Overall model, $P = .768$
Male sex	1.01	0.49-2.07	.971	.233
Age	1.00	0.98-1.02	.729	.263
Etiology (ref. endocarditis)				
Rheumatic	1.81	0.64-5.08	.257	.506
Congenital	0.88	0.33-2.33	.799	.895
Degenerative	1.33	0.49-3.62	.565	.925
Freehand technique	0.63	0.28-1.39	.259	.555
Valve size	0.79	0.67-0.95	.012	.342
Preoperative ejection fraction	0.96	0.91-1.01	.076	.585

Bold indicates statistical significance. *CI*, Confidence interval; *MACCE*, major adverse cardiac and cerebrovascular events.

TABLE E6. Effect of freehand/subcoronary implantation technique: Longitudinal analysis of echocardiographic data

Variable	Coefficient	95% CI	P value	Sigma_u	Sigma_e	Rho	Sigma2_u (95% CI)
LVEDD	−2.20	−3.71 to −0.70	.004	4.61	3.40	0.65	
LVESD	−2.14	−4.11 to −0.17	.033	6.28	2.11	0.89	
LVEF	2.99	1.15-4.83	.001	5.68	3.76	0.69	
Aortic valve gradient	2.29	1.15-3.43	.001	0.00	9.22	0.00	
Annular diameter	0.33	−0.19 to 0.86	.218	1.70	0.46	0.93	
LVOT diameter	0.35	−0.18 to 0.88	.198	1.71	0.43	0.94	
Aortic diameter	−0.64	−1.86 to 0.58	.306	3.88	1.59	0.85	
Aortic regurgitation grade	0.17	−0.15 to 0.49	.297				0.43 (0.24-0.76)
NYHA class	−1.01	−1.41 to −0.61	.001				0.72 (0.46-1.12)

Bold indicates statistical significance. *CI*, Confidence interval; *LVEDD*, left ventricular end-diastolic diameter; *LVESD*, left ventricular end-systolic diameter; *LVEF*, left ventricular ejection fraction; *LVOT*, left ventricular outflow tract; *NYHA*, New York Heart Association.