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Human Tissue Valves in Aortic Position

Determinants of Reoperation and Valve Regurgitation

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***Background*—**Human tissue valves for aortic valve replacement have a limited durability that is influenced by interrelated determinants. Hierarchical linear modeling was used to analyze the relation between these determinants of durability and valve regurgitation measured by serial echocardiography.

***Methods and Results*—**In adult patients, 218 cryopreserved aortic allografts were implanted with the subcoronary (85) or the root replacement technique (133), and 81 patients had root replacement with a pulmonary autograft. Mean follow-up was 4.2 years (SD 2.7; range, 0 to 10.5). Patient age, operator experience with subcoronary implantation, and allograft diameter were independent predictors for reoperation. With repeated color Doppler echocardiography, the severity of aortic regurgitation was assessed by the jet length method and the jet diameter ratio. Multilevel hierarchical linear modeling was used to estimate initial aortic regurgitation (intercept), its change over time (slope), and the effect of 11 potential determinants of durability on aortic regurgitation. With the jet length method, the intercept was 0.94 grade and the slope was 0.11 grade per year. With the jet diameter ratio, the intercept was 0.34 and the annual increase was 0.01. Subcoronary implanted valves had more initial aortic regurgitation, but progression of aortic valve regurgitation did not differ from root replacement. At midterm follow-up, recipient age <40 years was the only independent predictor of aortic regurgitation.

***Conclusions*—**Subcoronary implantation has a learning curve, resulting in more initial aortic regurgitation and early reoperation compared with root replacement. In both techniques, progression of aortic regurgitation over time is small but accelerated in young adults. **(*Circulation*. 2001;103:1515-1521.)**

Key Words: valves ■ aorta ■ echocardiography ■ epidemiology

Aortic allograft and autografts have gained popularity for aortic valve replacement (AVR) in adults, and good long-term results have been reported.[1–9] Valve function is determined by interrelated determinants, including patient and donor valve characteristics and whether the subcoronary implantation or aortic root replacement technique is used.[10]

The incidence of reoperation has been used to assess the results of either surgical technique but represents a crude end point. Serial echocardiographic examinations could offer a noninvasive means to monitor the process of valve degeneration by assessment of aortic regurgitation. Analytical techniques, such as hierarchical linear models (HLMs), are required to take into account the above-mentioned determinants of valve function and the variation of echocardiographic measurements over time. This prospective, serial color Doppler echocardiographic study assesses aortic regurgitation after allograft or autograft implantation and its changes over time.

Methods

Patients

From 1987 to July 1999, 299 human tissue valves (218 cryopreserved aortic allografts and 81 autografts) were implanted in the aortic position in 296 adult patients in the Erasmus Medical Center Rotterdam. Eighty-five allografts were implanted with the subcoronary implantation technique (SIT) in 84 patients, and 133 allografts were used for aortic root replacement in 131 patients. The pulmonary autograft was used for aortic root replacement in 81 patients. Patient and operative characteristics are displayed in Table 1.

The SIT was mainly used in isolated valve pathology. Initially, each sinus of Valsalva was scalloped (32); later, the non–coronary sinus was preserved (53).[11] Root replacement with allograft or autograft was performed as a freestanding root. Allograft root replacement was performed for major root pathology in 78 patients (59%). Pulmonary autograft root replacement was mainly used in young adult patients with isolated valve pathology, but major aortic root pathology existed in 12%. Surgical procedures were performed on cardiopulmonary bypass with moderate hypothermia. Crystalloid cardioplegia and topical cooling were used for myocardial protection. Deep hypothermia and circulatory arrest were used in selected patients with ascending aorta or arch pathology.

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Success with the SIT is related to the surgeon's experience, and a learning curve has been reported.[12,13] The first 10 subcoronary implants of each surgeon were considered to represent the learning period.

Allograft Characteristics

Cryopreserved aortic allografts were allocated by Bio Implant Services Foundation, The Netherlands. The allografts were prepared from heart-beating or non–heart-beating donors. Valves were initially cryopreserved with glycerol solution but in recent years with DMSO solution. The technique for dissection, quality coding, decontamination, and cryopreservation has been reported.[14] Mean donor age was 39 years (SD, 12; range, 12 to 61). The mean internal diameter of the allografts was 23 mm (SD, 2.1; range, 19 to 28).

Echocardiographic Study

Serial, standardized echocardiography has been done since 1987. The severity of aortic regurgitation is estimated by the jet length method on a scale of 0 to 4. With this method, the severity of the regurgitation may be overestimated.[15,16] Therefore, since January of 1993, the severity of aortic regurgitation is also estimated by measuring the ratio of the maximal regurgitant jet diameter to the systolic left ventricular outflow tract diameter directly under the aortic valve in the parasternal long-axis view (jet diameter ratio).[15,17]

The echocardiographic examinations were initially performed with different echocardiographic equipment. Since January 1993, all examinations are performed by two experienced technicians on a Vingmed CFM 750 ultrasound system with a 3.25-MHz transducer to limit intermachine and interobserver variability.[17] The color Doppler examination is started at low gain and increased until white noise appears in the left ventricular cavity. The flow velocity is set between 0.7 and 1.0 m/s, depending on the depth. The threshold of the flow velocity is set at 0.25 m/s. Diameters are measured on-line on the video screen from frozen images by planimetry with the use of a trackball. The mean values of measurements from two cardiac cycles are noted.

Postoperative echocardiographic examinations are scheduled at 6 months, at 1 year, and thereafter once every 2 years.

Follow-Up

The mean duration of follow-up of all patients surviving the initial hospitalization was 4.2 years (SD, 2.7; range, 0 to 10.5 years). Sixty hospital survivors with the SIT (74%) and 46 with a root replacement (22%) had an echocardiographic follow-up of ≥5 years. The closing date for inclusion of events and echocardiographic examinations was September 1, 1999.

Statistical Analysis

Data are expressed as mean±1 SD. Means were compared by 1-way ANOVA. χ^2 testing was used to compare categorical variables. All tests were 2-sided, with an α level of 0.05. Survival and freedom from reoperation for aortic valve failure were analyzed with the method of Kaplan-Meier.[18] The survival of a patient started at the time of aortic valve operation and ended at death (event) or at last follow-up (censoring). The analysis of allograft or autograft survival started at the time of implantation and ended with graft failure (reoperation, valve-related death) or at the last follow-up (censoring). The differences between curves were evaluated with the log-rank test.

After univariate analysis, a multivariate analysis of patient survival and aortic valve–related reoperation was performed with the Cox proportional hazard regression model.[19] Backward stepwise selection with a value of $P<0.10$ was applied for inclusion of the variables in the Cox model.

The echocardiographic data were analyzed with a multilevel HLM.[20] This model provides a regression line with an intercept and slope for individual patients (Figure 1). The square root of the jet diameter ratio was calculated to minimize the influence of outliers and to normalize the distribution.

TABLE 1. Patient and Operative Characteristics (n=299)

	Allograft Root (n=133)	Subcoronary Allograft (n=85)	Autograft Root (n=81)
Age, y			
Mean	47	47	31*
SD	15	14	9
Range	16–75	19–83	16–52
Sex, % men	76%	70%	60%
Creatinine, mean (SD)	98 (50)	116 (112)	77 (19)*
Hypertension	15%	14%	4%†
Cause			
Rheumatic/degenerative	8%	28%	11%†
Congenital	23%	29%	62%
Endocarditis	29%	35%	6%
Aneurysm	15%	0%	1%
Dissection	12%	0%	0%
Other	13%	7%	20%
NYHA class			
I	26%	12%	35%†
II	26%	28%	42%
III	24%	48%	21%
IV	17%	5%	1%
V (cardiogenic shock)	8%	7%	1%
Preoperative heart rhythm			
Sinus rhythm	96%	92%	100%
Atrial fibrillation	3%	4%	0%
Heart block	1%	2%	0%
Other	1%	2%	0%
Prior AVR	23%	6%	14%†
Urgent operation‡	17%	2%	1%†
Left ventricular function			
Good	68%	78%	80%†
Impaired	24%	18%	10%
Moderate	4%	5%	9%
Bad	5%	0%	1%
Pump time, min	214 (89)	177 (40)	221 (72)
X-clamp time, min	144 (50)	133 (31)	153 (29)
Circulatory arrest, min	42 (35) n=25		38 (37) n=2
Concomitant procedures			
None	41%	68%	84%†
Coronary artery bypass graft	11%	13%	4%
Mitral valve operation	5%	9%	1%
Extended root	27%	0%	3%
Other	17%	9%	9%

*$P<0.05$ by ANOVA; †$P<0.05$ by χ^2 testing. ‡Urgent indicates <24 hours after diagnosis. SD in parentheses.

Covariables were examined by complete case analysis. Patient characteristics included age, hypertension, New York Heart Association class, left ventricular function, prior aortic valve surgery, aortic root pathology, and urgent operation (See Tables 1 and 2). Surgical variables included the SIT versus root replacement technique and the

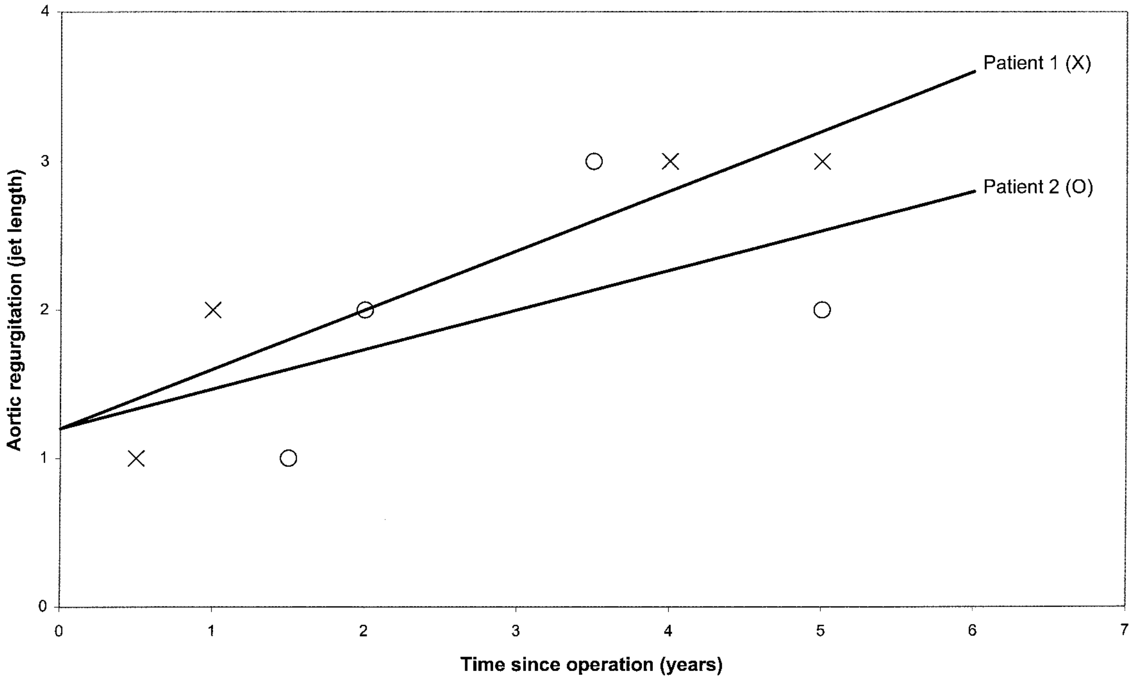

Figure 1. HLMs estimate of a regression line with intercept and slope for individual patients. Intercept reflects initial severity of aortic regurgitation; slope reflects its change. Patient 1 is example of missing examinations in a specified interval after operation. Patient 2 shows variability of regurgitation over time (see text).

learning curve of the surgeon. Valve characteristics included cryopreservation solution, allograft diameter, quality code (good, n=94; moderate, n=123; missing, n=1), donor age ≥40 years (n=112), and type of donor (heart beating, n=161, non–heart beating, n=57).

The following definitions for covariables were used. Hypertension was defined as diastolic pressure >95 mm Hg or medically treated; urgent operation, operation within 24 hours after examination by the surgeon; quality code, based on macroscopic allograft characteristics and qualified as good or moderate (poor quality valves were discarded); heart-beating donor, time between circulation stop and cardiectomy <2 hours. The remaining valves were defined as being from non–heart-beating donors.

Results

Patient Survival

The hospital mortality rate for the SIT was 4.7% (4 of 85 patients); for aortic root replacement with an allograft or an autograft, 4.5% (6 of 133 patients) and 3.7% (3 of 81 patients), respectively. Five-year patient survival after subcoronary implantation and aortic root replacement with allograft or autograft was 91% (95% confidence limits [CL], 85% to 97%), 85% (95% CL, 77% to 93%), and 96% (95% CL, 92% to 100%), respectively. Patient survival was better in the autograft group compared with the group with the SIT or allograft root replacement (log-rank test, $P=0.03$).

Reoperation

Five-year freedom from aortic valve–related reoperation after the SIT was 87% (95% CL, 80% to 94%) and for allograft or autograft root replacement, 96% (95% CL, 92% to 100%) and 94% (95% CL, 86% to 100%), respectively. Reoperation after the SIT was performed for severe aortic regurgitation in 11 patients and for late aortic stenosis in 1. Nine patients had nonstructural (technical) valve failure and 3 patients had structural valve failure. After allograft root replacement, 5 reoperations were necessary in 4 patients. In 2 patients, aortic regurgitation was due to structural valve failure. Another patient underwent a first reoperation for a pseudoaneurysm and late replacement of the allograft for nonstructural valve failure. Finally, in 1 patient, a vegetation from the proximal anastomosis was removed. Three autografts were replaced for severe aortic regurgitation, 2 for progressive dilation of the autograft root and 1 for recurrent acute rheumatic fever.

The results concerning reoperation after allograft root and autograft root replacement were merged for comparison with the SIT group.

Multivariate analysis determined patient age <40, the surgeon's learning curve, and an allograft diameter >25 mm as independent risk factors for reoperation (Table 2).

Aortic Regurgitation on Color Doppler Echocardiographic Analysis

In the analysis of the jet length and jet diameter ratio, we found an initial aortic regurgitation (intercept, 0.94 and 0.34, respectively) for all implanted valves, with a moderate progression of the regurgitation severity (slope, 0.11 and 0.01, respectively, Table 3). Analysis of the severity of aortic regurgitation revealed no differences between allograft or autograft root replacement; subsequently, these were considered as one group,

Jet Length Method

From April 1989 until September 1999, 887 echocardiographic examinations in 252 patients were performed. Two or more echocardiograms were available in 217 patients (86%). The number of echocardiographic examinations was 852

TABLE 2. Freedom From Aortic Valve–Related Reoperation at 5 Years Stratified for Covariables

Analyzed Variables	Freedom From Aortic Valve–Related Reoperation	95% CL	HR Univariate	HR Multivariate (Full Model)
Patient age				
<40 y (n=135)	89%	83–95%	2.5 (0.0–6.5)	3.7 (1.3–10.2)
≥40 y (n=164)	96%	93–99%	*P*=0.06	*P*=0.01
Learning curve				
Unexperienced (n=37)	80%	67–93%	4.0 (1.5–10.1)	6.4 (1.2–33.9)
Experienced (n=262)	95%	92–98%	*P*=0.02	*P*=0.03
Allograft diameter				
19–25 mm (n=183)	95%	92–98%	3.9 (1.5–10.5)	4.6 (1.5–13.7)
>25 mm (n=35)	81%	67–95%	*P*=0.03	*P*=0.01
Type of operation				
SIT (n=85)	87%	80–94%	2.5 (0.9–6.5)	1.0 (0.2–4.6)
Root (n=214)	95%	91–99%	*P*=0.06	*P*=0.99 (NS)
Cryopreservation method				
Glycerol (n=32)	80%	66–94%	2.8 (1.0–8.0)	1.7 (0.4–7.1)
DMSO (n=180)	95%	91–99%	*P*=0.04	*P*=0.49 (NS)

(mean, 3.9; range, 1 to 8), with a mean follow-up of 4.4 years (SD, 2.4; range, 0.4 to 10.3 years).

Mean initial aortic regurgitation was 0.94 grade, and an average yearly increase of 0.11 grade was found (Table 3). The severity of aortic regurgitation varied considerably during follow-up within patients (variance around the regression line=0.20). The differences between patients were even larger (variance of differences between the individual regression lines=0.42).

The SIT showed more initial aortic regurgitation (1.23 grade) than root replacement (0.83 grade; $P<0.001$, Table 3). The severity of aortic regurgitation remained relatively stable during the observation period, giving a rise of only 0.11 grade per year, independent of implantation technique.

Further analysis of covariables was undertaken while controlling for confounding effects of the implantation technique, by including the type of operation as a covariable in the model (Table 4). None of the factors tested had an effect on initial aortic regurgitation after operation. Patient age was the only factor that had an effect on progression of aortic regurgitation. Patient age >40 years was associated with less progression of aortic regurgitation (Figure 2).

Jet Diameter Ratio

From March 1993 to September 1999, 660 echocardiographic examinations were performed in 215 patients for analysis by the jet diameter ratio. One hundred seventy-one patients had ≥2 echocardiograms during follow-up. The number of echocardiographic examinations was 616 (mean, 3.6; range, 1 to 8 echocardiograms), with a mean follow-up of 4.5 years (SD, 2.3; range, 0.4 to 10.3 years).

Mean initial aortic regurgitation was 0.34 grade, with an average yearly increase of 0.008 grade (Table 3). Variance of the severity of aortic regurgitation within and between patients was 0.01 and 0.03, respectively.

Patients after the SIT tended to have more initial aortic regurgitation compared with patients after root replacement (Δintercept=0.04, $P=0.07$, Table 3). No difference in the progression of aortic regurgitation between groups was seen.

The data of the jet diameter ratio from all operated patients are plotted with the average regression lines from the HLM analysis for the subcoronary group (Figure 3A) and the root replacement group (Figure 3B). The influence of covariables was analyzed while correcting for the confounding of operative technique by inclusion of implantation technique in the regression models (Table 4). No significant effects of covariables were observed.

Discussion

AVR with human tissue valves in patients with aortic valve or root disease is the preferred intervention in the younger age

TABLE 3. Hierarchical Linear Model Analysis for Aortic Regurgitation on Color Doppler Echocardiography

	Jet Length Method				Jet Diameter Ratio			
Variables	Intercept	*P*	Slope	*P*	Intercept	*P*	Slope	*P*
All valves (n=217)	0.94	<0.001	0.113	<0.001	0.34	<0.001	0.008	0.02
Type operation								
SIT versus root (Δintercept)	0.40	<0.001	−0.003	NS	0.04	0.07	−0.010	NS
Learning curve vs more experienced (Δintercept)	0.29	NS	−0.016	NS	−0.008	NS	0.006	NS

TABLE 4. Hierarchical Linear Model Analysis for Aortic Regurgitation Adjusted for Type of Operation

	Jet Length Method				Jet Diameter Ratio			
Variables	ΔIntercept	*P*	ΔSlope	*P*	ΔIntercept	*P*	ΔSlope	*P*
Age at operation	−0.06	NS	−0.08	0.01	−0.02	NS	0.004	NS
Hypertension	−0.04	NS	−0.01	NS	0.01	NS	0.014	NS
Left ventricular function	0.16	0.20	0.03	NS	0.01	NS	−0.00	NS
Previous AVR	−0.10	NS	0.02	NS	−0.06	NS	−0.02	NS
Aortic root pathology	−0.11	NS	0.00	NS	−0.05	NS	−0.01	NS
Urgent operation	0.08	NS	0.04	NS	0.05	NS	−0.003	NS
Cryopreservation method	−0.04	NS	0.05	NS	−0.04	NS	0.004	NS
Allograft diameter	−0.07	NS	0.04	NS	0.00	NS	0.00	NS
Quality code	0.08	NS	0.01	NS	0.04	NS	0.01	NS
Donor age	0.04	NS	−0.00	NS	0.02	NS	0.00	NS
Type donor	0.14	NS	0.03	NS	0.00	NS	0.00	NS

group. Human tissue valves are reported to have excellent hemodynamic performance, no need for lifelong anticoagulation, a low risk of thromboembolism, and reduced infectious complications.[1–9] Nonetheless, human tissue valves have a limited durability that may necessitate reoperation.

An important determinant of durability is the method of preservation of the aortic allografts. The techniques that apply chemical preservation, irradiation, and freeze-drying have been replaced by immediate transplantation, by fresh-wet storage in an antibiotic solution, or by cryopreservation. As a consequence of these changes, the durability of these valves improved considerably.[2,3,5] Other reported determinants with a negative influence on durability are young recipient age, previous xenograft valve implantation, donor age, large aortic root diameter, and the surgeon's learning curve.[1,3,5,12,13] Another determinant that is still under debate for both allograft and autograft valves is the choice of the surgical technique: subcoronary implantation or root replacement. These determinants of durability should be taken into account when reporting on early and late human tissue valve function.[10]

The most common end point for valve failure is reoperation, which may underestimate the actual incidence of valve dysfunction. With echocardiographic assessment of the severity of aortic regurgitation, valve dysfunction could be analyzed in a time-dependent model with the Kaplan-Meier method to estimate freedom of valve failure. Unfortunately, the Kaplan-Meier method is not ideal for analysis of echo-

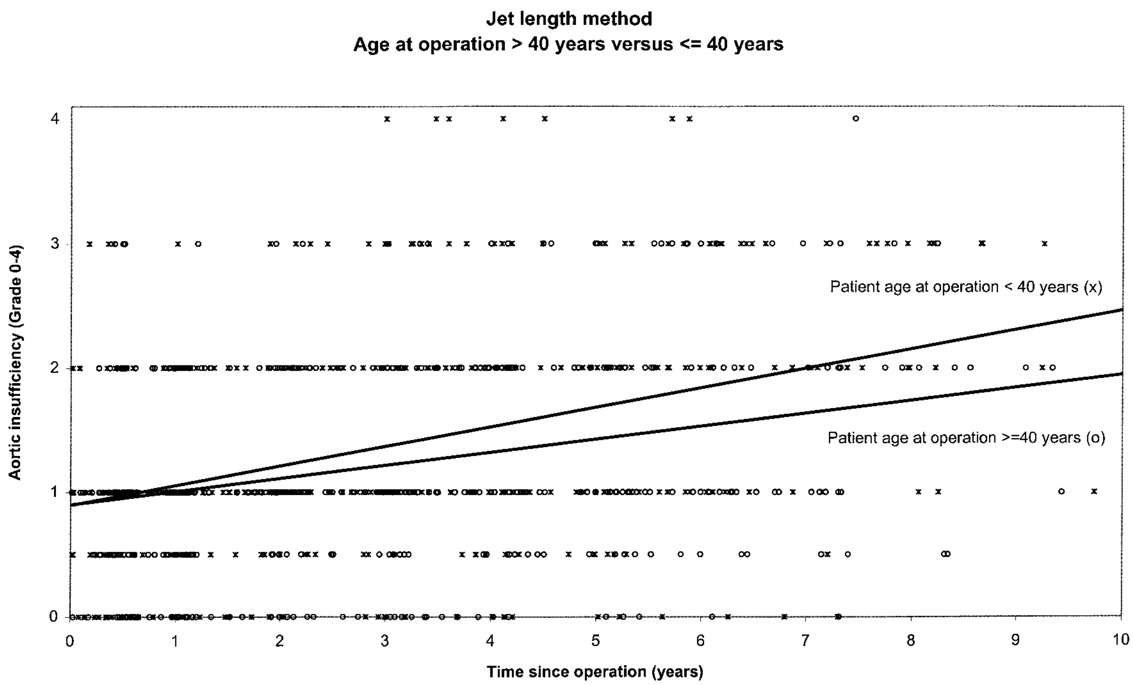

Figure 2. All aortic regurgitation measurements over time as measured by jet length method in patients <40 years (upper trend line) versus patients ≥40 years (lower trend line) at time of operation.

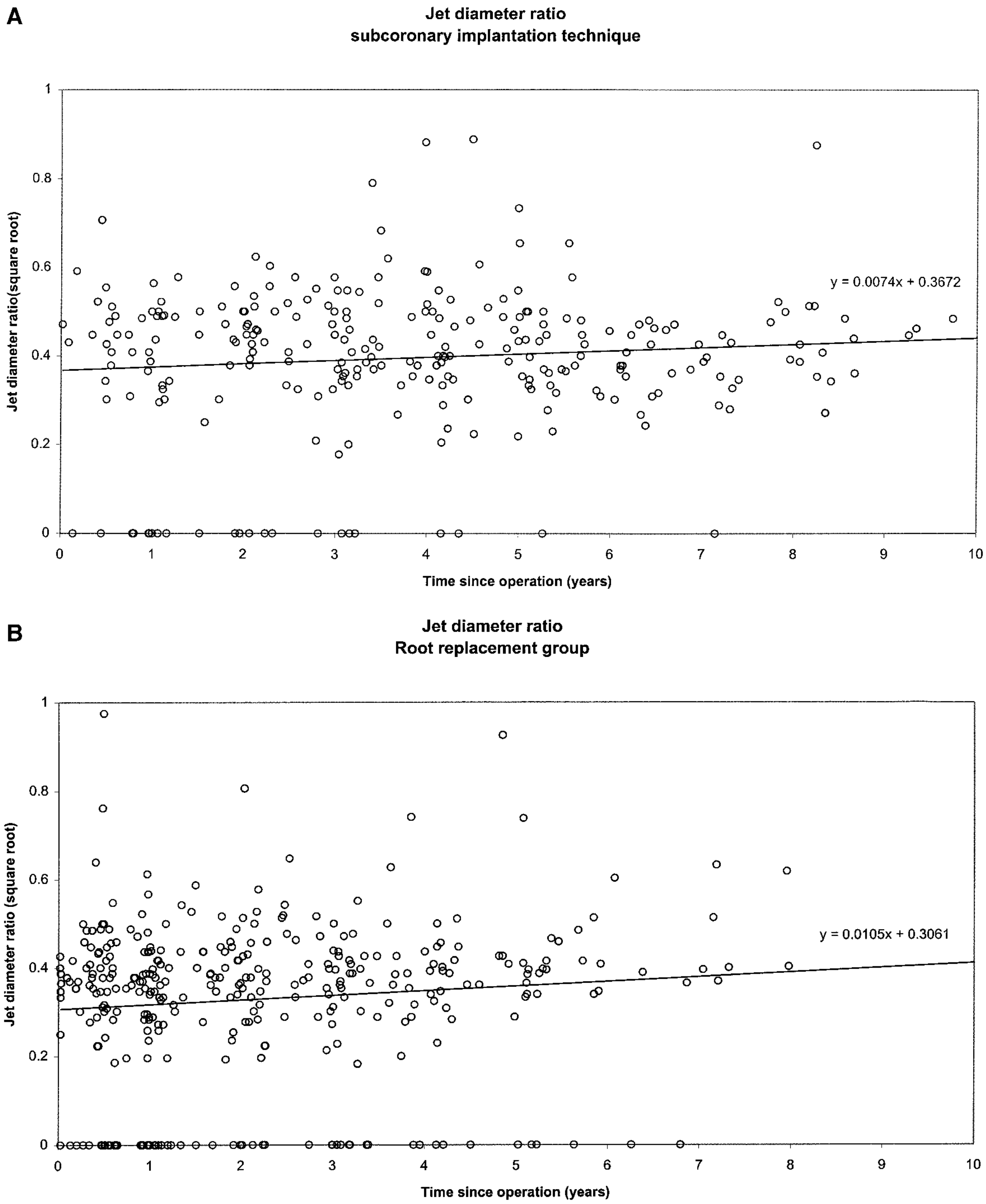

Figure 3. Data on aortic regurgitation after subcoronary implantation (A) and root replacement technique (B) measured by jet diameter ratio during follow-up. Horizontal line represents regression line calculated by HLM.

cardiographic data for the following reasons. First, time of follow-up should be used as a continuous variable. However, echocardiographic data are usually available within a certain time frame, and data after specified intervals of the operation may be incomplete. More importantly, the use of the Kaplan-Meier method can be misleading in the analysis of classified echocardiographic data because of the variability over time of the severity of aortic regurgitation within each patient. Therefore, censoring for moderate to severe aortic regurgitation may occur too early. Also, data on patients with less than moderate to severe or severe aortic regurgitation are not used to observe changes in regurgitation (reflecting the process of valve degeneration) over time. The HLM takes into account the variable follow-up time and intrapatient changes in the severity of aortic regurgitation over time.[20] It determines the initial severity of aortic regurgitation (intercept) and changes in severity over time (slope), reflecting the behavior of implanted human tissue valves. The influence of determinants of durability in human tissue valves can be studied with changes in intercept and slope as end points.

One determinant of durability is the implantation technique. Some authors favor root replacement over the subcoronary implantation technique because they hypothesize that early regurgitation is minimized by the preservation of the aortic root geometry as a functional unit.[2,3,21] Others are less concerned with aortic incompetence after the SIT but prefer to avoid the early risk of more radical root resection and the late risk of aortic root calcification with progressive loss of radial extensibility.[6] On the other hand, limited experience of the surgeon with the SIT may result in premature failure of the valve. This series confirms the influence of the surgeon's experience on the incidence of early reoperation after the SIT. A learning curve for the subcoronary implantation technique is not a uniform finding in the surgical literature.[6] However, in clinics with a resident training program, this aspect is a disadvantage compared with replacement of the entire root.

In parallel with the findings based on the incidence of reoperation, more initial aortic regurgitation during echocardiographic examination was found after subcoronary implantation. The surgeon's experience is an important risk factor, and a learning phase is apparent. However, after this phase, more initial aortic regurgitation was detected on echocardiography with the SIT. This is an additional argument in favor of root replacement.

Minimal progression of the severity of aortic regurgitation, as expressed by the slope of the regression line, was found during this medium-term follow-up study of aortic allografts and autografts. The only independent risk factor for progression of echocardiographic aortic regurgitation was patient age <40. This is in accordance with our finding that younger patient age is an independent risk factor for valve-related reoperation. Lund et al[22] recently described a similar relation between patient age and redo valve replacement. No effect of other covariables on late valve degeneration was observed at this period of follow-up. The importance of these variables may become evident in the next decade.[10]

The surgeon's learning curve is an important limitation of the subcoronary implantation technique. We found more early reoperations and initial aortic regurgitation with the subcoronary implantation technique compared with aortic root replacement. The progression of aortic regurgitation is small for both implantation techniques during medium-term follow-up but is accelerated in younger patients. In our hospital, the subcoronary implantation technique is no longer in use.

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