

Capturing echocardiographic allograft valve function over time after allograft aortic valve or root replacement

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Objective: This study describes echocardiographic allograft valve function over time in a cohort of patients who were prospectively followed after allograft aortic valve or root replacement, illustrating the use of longitudinal data analysis for assessing valve function over time.

Methods: Serial, standardized echocardiographic measurements of aortic regurgitation, aortic gradient, annulus diameter, left ventricular outflow tract diameter, and aortic diameter in 301 hospital survivors (mean age, 46 years; range, 16-83 years) after allograft aortic valve (N = 77) or root (N = 224) replacement were analyzed using nonlinear longitudinal models.

Results: Aortic regurgitation increased over time. At 15 years, 41% of patients had at least moderate aortic regurgitation. Younger patient age and subcoronary implantation technique were associated with increased aortic regurgitation. Aortic gradient increased over time (from 9.4 mm Hg at 6 months to 21.3 mm Hg at 15 years); both initial and increase in aortic gradient were greater in younger patients and after subcoronary implantation technique. Annulus diameter slightly increased (from 21.9 mm at 6 months to 22.4 mm at 15 years), whereas aortic diameter slightly decreased over time (from 34.3 mm at 6 months to 32.7 mm at 15 years). Left ventricular outflow tract diameter remained constant at 22 mm. Younger patients in the subcoronary implantation group had a larger annulus diameter.

Conclusions: Both aortic regurgitation and stenosis increase over time after allograft aortic valve or root replacement. Younger patient age and use of the subcoronary implantation technique are associated with increased regurgitation and stenosis. The use of nonlinear longitudinal models allows for an insightful analysis of allograft valve function over time. (J Thorac Cardiovasc Surg 2014;148:1921-8)

See related commentary on pages 1929-30.

Supplemental material is available online.

Allografts have been used for the replacement of the diseased aortic valve for more than 5 decades.¹ Although allografts were initially thought to be superior to xenografts,

today there is increasing evidence that allograft durability is comparable to other biological valve substitutes.^{2,3} Currently, their application is mainly in patients with complex cardiac and aortic root pathology in the setting of an active endocarditis.

The assessment of allograft valve performance over time is difficult. Echocardiographic measurements obtained over time after allograft implantation are usually dichotomized by using time-to-event methods and are reported as, for example, freedom from aortic regurgitation (AR) grade 1+ or 3+ at a certain follow-up time.^{4,5} Dichotomization of longitudinal data is often inappropriate because it leads to loss of information and incorrect statistical inferences. The 2008 guidelines for reporting mortality and morbidity after cardiac valvular interventions⁶ propose the use of longitudinal data analysis for series of assessments, such as repeated echocardiographic measurements of valve function to estimate its average temporal pattern and variability in a group of patients. Repeated measurement data have several important characteristics that are taken into account by longitudinal analyses methods but that are not taken into account by time-to-event methods.

The aim of this study is to describe echocardiographic allograft valve function over time in a prospective cohort

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Abbreviations and Acronyms

AR = aortic regurgitation

LVOT = left ventricular outflow tract

of patients who underwent allograft aortic valve or root replacement. This will be done by using and illustrating the use of advanced longitudinal data analysis techniques.

METHODS**Patients**

Between April 1987 and September 2010, a total of 347 patients underwent 356 aortic valve or root replacements with an allograft at the Erasmus University Medical Center, Rotterdam, The Netherlands (Table 1). After these 356 procedures, 301 hospital survivors had 1 or more standardized echocardiographic examinations. The small number of patients with repeat operations (n = 9) were considered as independent patients because the primary focus of this study was allograft valve function over time. Approval from the institutional review board (No. EMC00-813) was obtained for this prospective follow-up study, and all patients provided informed consent. The clinical outcome of the total cohort has been reported.³

Surgical Procedures

Surgical procedures were performed through a median sternotomy on cardiopulmonary bypass with moderate hypothermia (Table 2). Crystalloid cardioplegia and topical cooling were used for myocardial protection. Deep hypothermia and circulatory arrest were used in 32 patients with ascending aorta or arch pathology. Early in our experience, the subcoronary technique was used; since 1998, root replacement has become the technique of choice. Of the 356 procedures, subcoronary allograft implantation was performed in 94 patients⁷ and root replacement was performed as a freestanding root with reimplantation of the coronary arteries in 262 patients. From these patients, 1 or more standardized echocardiographic examinations were available for 77 patients who underwent the subcoronary allograft implantation technique and 224 patients who underwent the root replacement technique.

Echocardiographic Follow-up

Serial, standardized echocardiography has been performed at Erasmus University Medical Center in all patients aged 16 years or more who received human tissue valves since 1987. Postoperative echocardiographic examinations were scheduled at 6 months, at 1 year, and thereafter once every 2 years.⁸ A detailed description of the echocardiographic follow-up can be found in the [Online Methods](#) Supplement.

Statistical Analyses

All the analyses were performed using SAS9.1 (SAS Institute Inc, Cary, NC), and some plots were created using S-Plus6.2 statistical software (Insightful Corp, Lucent Technologies Inc, Palo Alto, Calif).

Analyses of clinical data

Presentation. Continuous variables are summarized as mean $\pm$ standard deviation, and comparison was done using the unpaired *t* test unless the data were not normally distributed (Kolmogorov-Smirnov test); in these instances, we used the Mann-Whitney *U* test for comparison. Categorical data are presented as proportions, and comparison was done using the chi-square test or Fisher exact test where appropriate. All tests were 2-sided, with an alpha level of 0.05.

Survival analyses. Overall nonparametric survival estimates were obtained by the method of Kaplan-Meier. A parametric method was used to resolve the number of phases of instantaneous risk of death (hazard function) and to estimate the shaping parameters.⁹ To identify risk factors for

death, multivariable analyses were performed in the multiphase hazard function domain.

In the multivariable analysis, factors modulating both hazard phases were considered simultaneously. Early risk factors are those found to increase the area beneath the early decreasing hazard phase, and late risk factors are those that increase the level of underlying increasing hazard. Within each hazard phase, we assume proportional hazards, but because the 2 hazard phases are operative across all time, this produces overall a nonproportional hazard model. Such a model is particularly appropriate for strongly time-varying hazard, as is evident for these events.

Reoperation analyses. Reoperation and multivariable analyses of patients who underwent reoperation were performed in a similar method used to study survival.

Analyses of echocardiographic data

Categorical echocardiographic measurement. To assess the temporal trend of likelihood of AR grades over time after surgery, follow-up transthoracic echocardiograms were analyzed longitudinally for percentages of patients in each AR grade across time. Because there is no practical method for continuous heart valve function assessment, a nonlinear cumulative logit mixed model^{10,11} was used to resolve a number of time phases on cumulative odds domain to form a temporal decomposition model and to estimate the shaping parameters at each phase. A longitudinal cumulative logistic mixed model^{12,13} for repeated measurements (SAS PROC NLMIXED; SAS Institute Inc) was used to implement the temporal decomposition model and to estimate the patient-specific probabilities for being in each AR grade. These patient-specific estimates were then averaged to obtain the percentages of patients (prevalence) in each grade. These methods were applied because they simultaneously solve multiple challenges of continuously collected echocardiographic data (eg, repeated measurements for each patient, variable time of recording, censoring by death).

Continuous echocardiographic measurement. To assess the temporal trend of aortic valve gradient, annulus diameter, aortic diameter, and left ventricular outflow tract (LVOT) diameter over time after surgery, follow-up transthoracic echocardiographic measurements were analyzed longitudinally for change in mean response across time.¹⁴ A nonlinear longitudinal mixed model regression^{12,13} (SAS PROC NLMIXED; SAS Institute Inc) was used to analyze these continuous repeated measurements.

RESULTS**Perioperative Details**

Table 2 shows the perioperative details. There were 4 patients (all root replacements) who required coronary artery bypass grafting because of problems related to the reinsertion of the coronary arteries. The detailed causes were as follows: In 1 patient the left coronary artery button was too small, causing coronary ostium stenosis; 1 patient had annular calcifications extending up to the right coronary ostium that was thin-layered and ruptured after reimplantation; 1 patient had right ventricular dysfunction due to kinking of the reimplanted right coronary artery; and in 1 patient, the attending surgeon made the decision to perform coronary artery bypass grafting on the basis of his observations of suboptimal coronary flow causing malperfusion of both the right and left coronary arteries. Hospital mortality was 5.9% (21/356 surgical procedures).

Clinical Follow-up

During follow-up, another 79 patients died (2.1%/patient year): Deaths were not valve related and were noncardiac in

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