Long-term clinical outcomes after aortic valve replacement using cryopreserved aortic allograft

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Background: Although the frequency of biological valve use in treating aortic valve disease is increasing, the critical limiting factor, ''structural deterioration,'' remains unresolved. Analysis of long-term outcomes after implantation of cryopreserved aortic allografts will yield further information related to the durability of the aortic allograft, possibly suggesting mechanisms underlying or strategies to prevent or treat the structural deterioration of biological valve substitutes.

Methods: A total of 840 cryopreserved aortic allografts implanted in the last 35 years were reviewed with clinical follow-up completed in 99% of the consecutive series. By June 2010, 285 implanted allografts had been surgically explanted, 288 patients died before allograft removal, and 267 patients are under continued follow-up.

Results: Cryopreserved aortic allografts were durable for more than 15 years in the middle-aged and older patient population. The estimated median time until structural deterioration was 20 years post-implantation, and 2 allografts have been functioning well for more than 30 years. Structural deterioration was independently related to the young age of the recipient, elderly age of the donor, severe obesity in the recipient, history of blood transfusion in the recipient, and full-root implantation technique. Infection of the implanted allograft necessitating reintervention rarely occurred. Reintervention for the allograft demonstrated 2% in-hospital mortality.

Conclusions: Cryopreserved aortic allografts were durable for more than 15 years. Structural deterioration of aortic allografts was related to multiple factors. The age of the recipient and the donor, obesity and blood transfusion history of the recipient, and implantation technique were identified as the most important factors contributing to allograft failure. (J Thorac Cardiovasc Surg 2014;148:65-72)

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Severe aortic valve disease is one of the major causes of cardiac death worldwide, whereas aortic valve replacement using a mechanical or biological valve substitute remains the gold standard treatment.[1] Biological valve substitutes have a number of clinical advantages over mechanical valves, including nonrequirement of anticoagulant therapy and absence of noise. However, structural deterioration remains the ''Achilles' heel'' of biologic prostheses because of the requirement for often complex reoperation and the associated morbidity and mortality confronting the patient.[2] Structural deterioration of biological valve substitutes consistently shows atherosclerosis-like inflammatory changes regardless of valve substitute types,[3,4] indicating that common mechanisms or processes contribute to progressive valve failure, although factors related to the structural deterioration are not fully understood.

The aortic allograft is one of the alternative biological valve substitutes used in clinical practice over the last 50 years,[5,6] although the use of the aortic allograft is not widely accepted because of the limited supply, variable implantation techniques contributing to uncertainty of the function, durability of the valve,[7] and prospect of a challenging reintervention.[8] At The Prince Charles Hospital, the cryopreserved aortic allograft has been implanted in a variety of patients as a treatment for severe aortic valve disease and has been the primary choice of valve substitute since 1975 when Queensland Heart Valve Bank was established to collect, prepare, store, and catalogue the allograft for implantation.[5] We explored the long-term outcomes of all patients after implantation of this single valve substitute, the ''aortic allograft.'' The aim was to identify factors influencing allograft durability and to explore putative mechanisms that may help to prevent or treat structural deterioration of biological valve substitutes.

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Abbreviation and Acronym
AS = aortic stenosis

MATERIALS AND METHODS

Cohort and Data Collection

The prospective database contained 7973 aortic valve and root replacement surgeries performed in The Prince Charles Hospital between January 1975 and December 2008. The cryopreserved aortic allograft was used as the valve substitute in 852 cases (11%). Clinical progress of the patients was followed up with annual visits to the institutional or local physicians. Medical charts and referral letters, including serial echocardiographic studies, were reviewed to obtain the data, which were further supplemented by telephone interviews of patients under the care of distant physicians. Data collection was performed between January 2010 and June 2010. Mortality data also were gathered by request to the National Death Registry in December 2010. The study was approved by the institutional ethics committee (reference number HREC/09/QPCH/152).

Study End Points

A total of 285 allografts were surgically explanted by June 2010, and 288 patients died before removal of their aortic allograft, with explant and death defined as primary end points of this study. A further 267 patients who did not reach the primary end points were under continued follow-up until June 2010, and 12 patients were not contactable for or refused clinical assessment as of June 2010. Therefore, clinical follow-up was completed in 98.6% of total, consecutive cryopreserved aortic allografts in The Prince Charles Hospital. This gives an overall total of 840 allografts retrospectively studied from January 1975 to June 2010. Secondary end points assessed included other adverse cardiac events, such as structural/nonstructural failure and infection of the implanted allograft, which were defined according to the guideline.[9]

Treatment Strategies and Surgical Techniques

Surgical strategies in The Prince Charles Hospital to treat severe aortic valve disease have been consistently to replace the aortic valve using a mechanical or biological valve substitute. However, there were several evolutions through the study period. First, choice of the valve substitute has been modified according to the availability and the concerns related to the durability of the valve substitutes.[5] Until the early 1990s, the aortic allograft was the primary choice of valve substitute in any patient whose aortic annular anatomy was suitable for allograft implantation, regardless of the patient's age, although the use of the allograft was deferred in a number of patients because of limited availability or inadequate anatomy. In the mid to late 1990s, the use of the allograft was gradually limited by operating surgeons who were concerned about allograft durability. Since 2000, the aortic allograft has been used only in neonates, infants, small children, or patients with severe infective abscess in the aortic annulus.

Second, the pattern of aortic valve pathologies has gradually altered over the 3 decades in line with changes in the patient population. Rheumatic valvular disease was predominant in the first decade of the study, whereas endocarditis predominated in the last decade. Therefore, the characteristics and background of the cohort are substantially different among the eras of surgery (Table 1). Finally, surgical techniques to implant the allograft have been markedly modified over the 3 decades (Table 2). The subcoronary implantation technique was the surgical strategy in the first decade, when the allograft was sized 3 mm less than the valve annulus dimension. In the second decade, operating surgeons applied the full-root implantation technique, implanting an allograft sized the same as the native valve annulus dimension. This was done to achieve more consistent technical results to match congenital pathology with asymmetric annulus morphologies compared with the subcoronary technique, in which there is often difficulty in achieving perfect cusp alignment, resulting in some degree of incompetency. In addition, the intellect at this stage was to foster allograft integrity by maintaining the allograft valve in its natural position. In the process of this change, the inclusion-cylinder technique also was used, albeit briefly. Selection of the allograft was primarily dependent on the size of the native annulus, which was intraoperatively measured. No consistent attempt was made to match age, sex, or blood group.

No patients received immunosuppressive medications post-allograft implantation. Allograft infection was essentially treated in the same clinical manner as native aortic valve endocarditis, for which antibiotics were the first choice of treatment unless septic thromboembolism or large vegetation on the allograft was evident.[5] Reintervention for the allograft was indicated when the implanted allograft presented with structural/nonstructural deterioration or medically uncontrollable infection, or the heart developed end-stage heart failure requiring cardiac transplantation.

Statistical Analyses

Continuous variables are presented as mean ± standard deviation or median (interquartile range). Categoric variables are shown as the percentage of the sample. Comparisons between the groups divided into the era of surgery were performed using 1-way analysis of variance followed by Dunn's multiple comparison test (Tables 1 and 2). Predictors of in-hospital mortality were identified using multivariate logistic regression, where potential predictors were those showing a P value less than .10 in a single variable analysis (Table E1). Survival, freedom from structural deterioration, and freedom from allograft infection were estimated using the Kaplan–Meier method (Figures 1, 2, and E1). Predictors of survival and structural deterioration were identified using a Cox proportional hazard model (Table 3). The potential predictors in a multivariate Cox proportional hazard model were those with a P value less than .10 in a single variable model (Tables E2 and E3). Statistical analysis was performed with GraphPad Prism 4 (GraphPad Software Inc, La Jolla, Calif) and StatView-J 5.0 (SAS Institute Inc, Cary, NC).

RESULTS

In-Hospital Outcomes of Aortic Allograft Implantation

In-hospital mortality after aortic allograft implantation occurred in 21 patients (2.5%), including deaths in the operating room in 5 patients. A further 11 patients showed evidence of ventricular problems, with 9 having global dysfunction and 2 having tachyarrhythmia. Cerebrovascular accidents occurred in 3 patients, and overwhelming sepsis occurred in 2 patients. Risk factors of in-hospital mortality were older age, hypertension, smoking history, and New York Heart Association functional class III or IV (Table E1).

Implantation of Aortic Allograft to Treat Active Infective Endocarditis

Aortic allografts were implanted in 101 patients to treat active endocarditis. Sixty-seven patients (66%) had a native aortic valve endocarditis, and 34 patients (34%) had an infection of a previously implanted valve substitute, such as a prosthesis in 23 patients and an allograft in 11 patients. The subcoronary technique was used in 33 cases of native endocarditis and 5 cases of valve substitute infection. In contrast, the full-root technique was used in 33 cases of native endocarditis and 29 cases of valve substitute