Late durability of decellularized allografts for aortic valve replacement: A word of caution

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Early outcomes of decellularized allografting (DAVA) performed for aortic root replacement (ARR) have been promising. Da Costa and colleagues¹ reported only 1 reoperation among 38 patients, but follow-up was relatively short (19 months). Assessment of the durability of DAVA requires long-term follow-up.

METHODS

After receiving approval by the appropriate Institutional Review Boards, we reviewed patients who underwent ARR with DAVA between March 12, 2002, and October 6, 2004, at Mayo Clinic, Rochester, Minnesota and Missouri Baptist Medical Center, St Louis, Missouri. We compared outcomes between those patients and patients who underwent ARR with a standard cryopreserved allograft during the same period. The primary outcome was reoperation, and the secondary outcome was survival.

Pathologic Analysis

Sections of excised valve and cusp tissue from the DAVA were stained with hematoxylin and eosin and Verhoeff-Van Gieson stains. Graft analysis (performed by J.J.M. and C.L.) involved grading of inflammation, fibrosis, calcification, recellularization, and degeneration.

Statistical Analysis

Descriptive statistics for categorical variables are reported as frequency and percentage, and continuous variables are reported as mean $\pm$ standard deviation or median (range). The Kaplan-Meier method was used to calculate survival and freedom of reoperation estimates. All statistical tests were 2-sided, with the α level set at 0.05 for statistical significance.

RESULTS

Forty-two patients (74% men; mean age, 49 ± 17 years) underwent ARR with a DAVA. Aortic valve reoperation was required in 37% of the survivors (15 of 41). Indications were endocarditis (26%; $n = 11$ of 42), aortic valve regurgitation associated with aortic aneurysm (12%; $n = 5$), isolated

Kaplan-meier curves for freedom from reoperation. Curves vary significantly at 10 years ($P = .06$).

Central Message

Patients receiving a decellularized aortic allograft had a freedom from reoperation at 10 years of 51% (95% CI, 34%-76%), compared with 80% (95% CI, 60%-100%) in those who received a standard cryopreserved allograft ($P = .06$).

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aortic valve regurgitation (31%; $n = 13$), aortic valve stenosis (29%; $n = 12$), and aortic dissection causing aortic valve regurgitation (2%; $n = 1$). Twenty-nine patients underwent ARR with a cryopreserved allograft. Indications for operation in these 29 patients included endocarditis (21%; $n = 6$), aortic aneurysm (10%; $n = 3$), aortic valve regurgitation (14%; $n = 4$), aortic valve stenosis (55%; $n = 16$). The prevalence of preoperative endocarditis in this group was similar to that in the group of patients who received DAVA ($P = .20$). Aortic valve reoperation was required in 4 of the 24 control patients (17%), including 2 patients with regurgitation and 2 with stenosis.

Of the 10 valves with sufficient tissue for analysis, 7 had edematous degeneration and calcification of the valve. Mild recellularization was present in the other 3 valves. Adventitial fibrosis and neointimal fibroplasia were identified in all cases. Fibrosis and calcification have been reported as modes of failure in cryopreserved allografts (Figure 1).

Freedom from reoperation at 5 years postsurgery was 92% (95% CI, 84%-100%) in the DAVA group and 100% in the control group. Freedom from reoperation at

FIGURE 1. Histopathologic findings of DAVAs in tissue sections stained with hematoxylin and eosin (*left column*) and corresponding Verhoeff-Van Gieson elastic (*right column*) stains, showing (A and B) full-thickness degeneration of the valve cusp and (C and D) marked calcification of the tubular component of the graft. (Original magnification, 40 $\times$.)

10 years postsurgery was 51% (95% CI, 34%-76%) in the DAVA group and 80% (95% CI, 60%-100%) in the control group ($P = .06$) (Figure 2). Overall 5- and 10-year survival rates were 90% (95% CI, 80%-100%) and 76% (95% CI, 61%-93%), respectively, in the DAVA group, compared with 72% (95% CI, 57%-90%)

and 57% (95% CI, 38%-79%) in the control group ($P = .09$).

DISCUSSION

Early outcomes in the patients undergoing ARR with DAVA were promising. A Brazilian study reported a

FIGURE 2. Kaplan-Meier curves for freedom from reoperation. Patients implanted with a DAVA had a 92% (95% CI, 84%-100%) freedom from reoperation at 5 years postimplantation, compared with 100% in the control group. Freedom from reoperation at 10 years postoperatively was 51% (95% CI, 34%-76%) in patients receiving a DAVA, compared with 80% (95% CI, 60%-100%) in the control group ($P = .06$).

98% freedom from reoperation at an average of 19 months of follow-up.¹ In our study at 5 years, patients with DAVA had a 92% freedom from reoperation. Further, early hemodynamic performance appears to be favorable, with a mean aortic valve gradient of 8.8 ± 6.3 mm Hg in patients with DAVA assessed at an average of 30 months.² Long-term outcomes are not favorable, however. At 10 years, freedom from reoperation in the patients receiving DAVA was 51%, substantially lower than that in the patients receiving a standard cryopreserved allograft.

Based on the pathologic studies, modes of failure appear to be similar with DAVA and standard allografts. In explanted DAVAs, fibrosis and calcification were seen, with only minimal recellularization in the minority of cases. These findings likely reflect a final pathway of degeneration, but initiating mechanisms are unclear. There are several theoretical causes of the initial injury. First, the decellularization process may be damaging to tissue.³ The decellularization process of the valves used in our study (CryoLife, Inc, Kennesaw, Ga) is different from that used in the study reported by da Costa and colleagues.¹ Long-term follow-up studies from that group may provide insight into whether the decellularization method affects allograft durability. Sterilization of decellularized valves could have a detrimental effect on durability as well. In an animal study, we demonstrated that sterilization with gamma radiation, even at doses as low as 3000 Gy, irreversibly damages decellularized porcine valves.⁴ The sterilization

procedure for the allografts implanted in this study was proprietary, and strength testing after sterilization should be made available.

Long-term survival was generally similar in the 2 groups of patients. Overall 10-year survival was 76% in the DAVA group, compared with 57% in the control group ($P = .09$). The decreased survival of control patients is likely due to their older age (7 years). Moreover, all of the DAVA implantations at one institution were performed as part of a study and as such, allografts were used in some patients who otherwise might not have received an allograft.

In conclusion, this study identified a strong trend for late reoperation in the DAVA group. Given the dramatic change in valve durability beyond 5 years, new tissue-engineered valves should be studied over the longer term before their use becomes widespread.

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