Ten-year experience with cryopreserved aortic allografts in the surgical treatment of aortic valve pathologies

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Aortic valve replacement; Cardiac surgery; Endocarditis.

Background. **The aim of this study was to evaluate the performance of cryopreserved aortic allografts (CAA) in the treatment of adult aortic valve pathologies.**

Methods. **Between May 1992 and October 2002, 122 CAA were implanted in 119 adult patients with pathologies of the aortic valve. The mean age of the patients was 38.03 ± 13.6 years (range 17-78 years). Thirty had had previous cardiac surgery. The principal indication was endocarditis (n = 45). In 66 patients one or more associated pathologies were present including: an abscess of the left ventricular outflow tract (n = 32), an aneurysm of the ascending aorta (n = 22), mitral incompetence (n = 10), and coronary artery disease (n = 3). The indications for surgery were elective in 77 cases and urgent in 45. The CAA was implanted as a total root replacement in 46 patients and as a free-hand in 76. In 66 patients an associated procedure such as a left ventricular outflow tract reconstruction (in 27 cases) was performed.**

Results. **The in-hospital mortality was 5.73% (7/122). In one patient the CAA was replaced before discharge with another CAA because of a mediastinitis with endocarditis by *Candida albicans*. At the follow-up of the 114 patients discharged from the hospital (mean 50.11 months, range 1-126 months), 6 patients died and 6 were reoperated. The actuarial 10-year survival, reoperation-free, endocarditis-free, structural degeneration-free rates were respectively 83.88, 81.70, 86.30, and 92.80%.**

Conclusions. **From our experience we conclude that CAA are good substitutes for aortic valve replacement and even in desperate situations exhibit an acceptable long-term performance.**

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Introduction

The cryopreserved aortic allografts (CAA) are one among the numerous devices available for aortic valve replacement (AVR). Although they have been introduced into clinical practice since 1962[1,2], the interest in their use has fluctuated widely with time and even today the precise indications remain controversial. Since there has been a continuous evolution in the techniques of sterilization, preservation and even of the surgical implantation of CAA, there are not many long-term follow-up studies available to evaluate the risk of early structural degeneration, especially in young patients, and to identify the factors that dictate their long-term durability. The arguments that make CAA a good device for AVR are their excellent hemodynamic profile[3], resistance to infection[4-7] and durability[3]. The factors that militate against their widespread use are their limited availability, greater surgical complexity with a prolonged operative time and increased risk of early mortality or of aortic incompetence due to technical error and the concerns regarding the risk of calcification in young patients[8]. Moreover, stentless xenografts in middle- or advanced-aged patients[9] and the Ross operation in young patients are good alternatives[10-13].

We report our 10-year experience with CAA for AVR in adult patients. We think that three factors render our experience peculiar: 1) all the CAA came from one Tissue Bank (Tissue Bank of the Veneto Region) that maintained the same techniques of procurement, processing, cryopreservation and thawing along these 10 years; 2) all the patients were operated by only two surgeons (CV and FR) who adopted absolutely similar operative techniques and indications; 3) a high percentage of patients constituted a high-risk population with acute native or prosthetic aortic valve endocarditis and this fact stresses, in our opinion, the characteristics of the CAA.

Methods

Between May 1992 and October 2002, 122 CAA were implanted in 119 patients operated at the Cardiac Surgery Department of the Treviso Regional Hospital. The mean age of the patients (90 males and 29 females) was 38.03 ± 13.6 years (range 17-78 years). The most frequent hemodynamic lesion was aortic incompetence (n = 89), followed by aortic mixed lesions (n = 20) and aortic stenosis (n = 13). Prosthetic or native endocarditis was the most frequent etiology (n = 45), followed by congenital bicuspid aortic stenosis (n = 27) (Table I). The etiologic agent responsible for the endocarditis lesion most frequently encountered was *Staphylococcus aureus* (n = 11), followed by coagulase-negative *Staphylococcus* (n = 8), *Candida albicans* (n = 3) and *Gemella morbillorum* (n = 2); other pathogens were isolated in 11 patients while in the remaining patients the agent was not identified. Two young patients presented with an immuno-mediated lesion of the aortic valve: one male with a thrombosis due to an alteration of proteins S and C, and a female with an aneurysm of the ascending aorta due to a Takayasu syndrome. Thirty patients had undergone previous cardiac surgery: 11 of them had a mechanical prosthesis, 5 an aortic or pulmonary homograft, and 4 a bioprosthesis; other previous cardiac operations included: aortic valve reconstruction in 5 cases, and 1 case each of David operation, vascular prosthetic ascending aorta replacement for type A dissection, composite graft replacement of the aortic valve and ascending aorta for type A dissection, repair of a traumatic ascending aorta lesion, and aortic decoarctation. Forty-five patients were in preoperative NYHA class I, 32 in II, 9 in III, 10 in IV, and 26 in V. The indications to surgery were considered elective in 77 cases and urgent in 45. The most frequent associated pathology was related to the complications of the endocarditis and was the presence of abscesses in the left ventricular outflow tract (LVOT) in 32 cases so extensive in 20 as to produce a ventriculo-aortic discontinuity. Other associated pathologies were dilation or aneurysm of the ascending aorta (n = 22), mitral incompetence (n = 10), and coronary artery disease (n = 3). All patients underwent preoperative transthoracic echocardiography to determine the diameters of the aortic annulus, of the sinuses of Valsalva, of the sino-tubular junction and of the ascending aorta beyond the sino-tubular junction. All the CAA implanted were provided by the Tissue Bank of the Veneto Region. Their internal diameter was 2 mm less than that of the recipient aortic annulus as measured at preoperative echocardiography.

All the operations were performed with total hypothermic cardiopulmonary bypass and aortic cross-clamping. Myocardial protection was ensured by intermittent antegrade (retrograde in the last 2 years) infusion of cold blood cardioplegic solution. Two patients were operated with a period of deep hypothermic circulatory arrest with selective cerebral retroperfusion. After removal of the native or prosthetic aortic valve, the aortic annulus was measured with a Hegar dilator. Comparison between the data of the diameters of the aortic annulus as measured at preoperative echocardiography and using the Hegar dilator during surgery revealed only minimal differences. As a consequence, the internal diameter of the implanted CAA correlated well with that of the recipient aortic annulus (the means of the two diameters were respectively 23.0 ± 2.2 vs 26.2 ± 2.8 mm). In all the patients operated for acute endocarditis, cultures of the aortic valve and of the periaortic tissues were routinely obtained.

In 76 patients the CAA was implanted with the Ross free-hand technique (leaving the aortic wall of the CAA in correspondence of the non-coronary sinus intact), while in 46 we adopted the so-called "button Bentall" technique. In all cases the proximal suture was made with interrupted 4-0 gore-tex stitches and was reinforced with a strip of autologous, cryopreserved homologous or xenologous pericardium. The most frequent associated operation was the reconstruction of the LVOT with autologous, cryopreserved homologous or xenologous pericardium in 27 patients (Table II). Transesophageal echocardiography was performed at the end of surgery in all patients.

All the patients were treated with teicoplanin and ceftriaxone intravenously until the fifth postoperative day. Blood cultures were not routinely performed in the absence of clinical symptoms and signs of infection except in patients operated for acute endocarditis.

No patient but one (in whom reconstruction of the mitral valve and of the left atrium was performed using xenologous pericardium) received anticoagulant therapy.

All the patients were followed with medical and echocardiographic examination at 3, 6 and 12 months after surgery and then once yearly.

Table I. Indications for surgery.

Endocarditis	45
Bicuspid aortic valve restenosis	27
Rheumatic fever	16
Prolapsing aortic valve	16
Congenital malformation of the aortic valve	13
Type A acute aortic dissection	4
Trauma	1

Table II. Associated procedures.

Left ventricular outflow tract reconstruction	27
Mitral valve reconstruction	7
Plicature of the aortic annulus	8
Plicature of the ascending aorta	3
Coronary artery bypass grafting	3
Aortic arch replacement	1

For a more accurate analysis of the results the patient population (TG) was divided into two groups: group 1 included 45 patients operated upon for endocarditis and group 2 (75 patients) all the patients with an indication other than endocarditis or immuno-mediated aortic pathology.

The operative and long-term mortality and complications were registered following the recommendations of Edmunds et al.[14].

Statistical analysis was performed using the SPSS statistical package (SPSS Inc., Chicago, IL, USA). The two-tail Student's t-test was used for comparison of the means, the Fisher's exact test and Pearson's test for comparison of categorical variables, while the actuarial curves were calculated by means of Kaplan-Meier analysis.

Results

Early results. Seven patients died during the early postoperative period and the operative mortality for TG was 5.73%. The operative mortality for group 1 was 13.3% (6 patients). All the patients underwent emergency operation for acute endocarditis. One patient with acute endocarditis on the native valve and a LVOT abscess with ventriculo-aortic discontinuity, submitted to AVR with a free-hand implanted CAA, mitral valve repair and LVOT reconstruction died of septic shock. A second patient with a *Candida albicans* acute endocarditis on a mechanical prosthesis (implanted 1 month before because of acute endocarditis) who received a free-hand CAA died of septic shock. The other 4 patients died of low output syndrome and bleeding; all the patients presented LVOT abscesses with ventriculo-aortic discontinuity: 3 patients had previous cardiac surgery, 1 patient, at the fifth procedure, had a composite graft with a mechanical prosthesis, while 2 had a CAA (one of them was a drug addict at his third operation while the second was a drug addict with positive serology for HCV and HIV). In group 2 we observed only one death, a young patient with an anomalous coronary artery origin who was submitted to total root replacement with a CAA and died of low output syndrome and bleeding. The operative mortality of group 2 was 1.3% and was significantly different from that of group 1 ($p < 0.01$).

The most frequent postoperative complication registered for TG was bleeding (8 patients), followed by low output syndrome (6 patients), acute myocardial infarction (3 patients), and severe neurological damage (1 patient). One patient in group 2 had a *Candida albicans* mediastinitis complicated by an endocarditis on the CAA. This was replaced on postoperative day 21 by another CAA. The patient was discharged in good conditions and after 3 years she is well without any antibiotic therapy.

Late results. For all the 114 patients discharged alive from the hospital, the mean follow-up was 50.11 months (range 1-126 months) and 99.6% complete. We registered 6 late deaths, 5 of them in group 1. Three of these patients operated for prosthetic endocarditis died within the first 3 postoperative months. One patient discharged with severe neurological damage died of unknown causes; in the second, in treatment with dicumarol, the cause of death was cerebral hemorrhage (at autopsy) and the third who was submitted to CAA replacement of an ascending aorta and arch prosthesis implanted for a type A dissection and infected by a *Candida albicans* mediastinitis died of rupture of the dissected abdominal aorta (autopsy report). A fourth patient died at postoperative month 56 probably of arrhythmia. At necroscopy the CAA did not present any gross morphological alterations. The fifth patient, an intravenous drug addict, died at reoperation for *Staphylococcus aureus* acute endocarditis of the CAA implanted 78 months before. With regard to group 2, 1 patient died in a traffic accident 24 months postoperatively. At 126 months the survival for the total group was 83.88% with a statistically significant difference between group 1 (66.59%) and group 2 (98.4%) as shown in figure 1.

Six patients were reoperated. Two patients underwent a second operation at 24 months: one for a thrombosis of the CAA implanted for an immuno-mediated thrombosis of the native aortic valve and the second for a perivalvular leak due to a technical error. Two patients operated for acute endocarditis underwent reoperation at 36 and 56 months respectively for severe calcification of the CAA. Two more patients were respectively reoperated at 70 and 78 months postoperatively for a new acute endocarditis (by a different pathogen) of the implanted CAA. Hence, the freedom from reoperation for the entire group was 81.70% at 126 months with a difference between group 1 (63.89%) and group 2 (98.40%) (Fig. 2).

During follow-up, 3 patients presented with endocarditis: the 2 patients mentioned above of group 1 and 1 patient of group 2 at 6 months. In this latter case the endocarditis was successfully managed with medical treatment. After 2 years the CAA is working perfectly without any sign of dysfunction. The freedom from endocarditis for the total group was 86.3%. In group 1 the freedom was 79% at 126 months while in group 2 it was 98.9% (Fig. 3).

The freedom from structural dysfunction for TG is shown in figure 4: at 126 months, 92.8% of the overall patient population was free from structural failure with a statistically significant difference between group 1 (85.3%) and group 2 (100%).

As shown in figure 5, the cumulative freedom from death and CAA-related complications markedly differed between the two groups: while 95.27% of the patients in group 2 were free, those in group 1 exhibited only a 57.87% freedom (70.25% for the overall population).

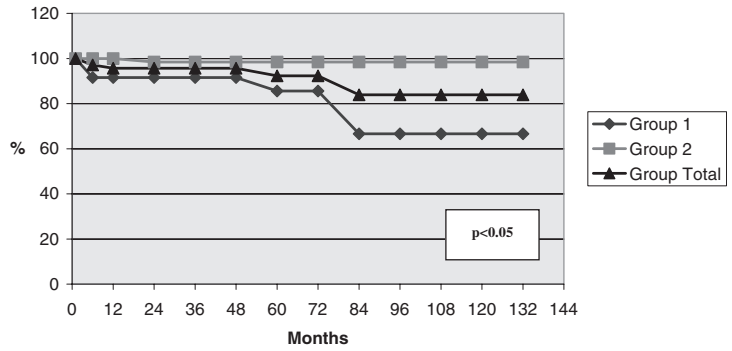

Figure 1. *Actuarial survival curves for the three groups of patients.*

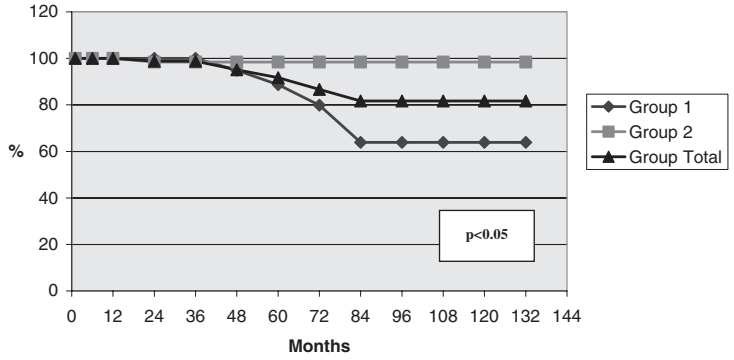

Figure 2. *Actuarial reoperation-free curves for the three groups of patients.*

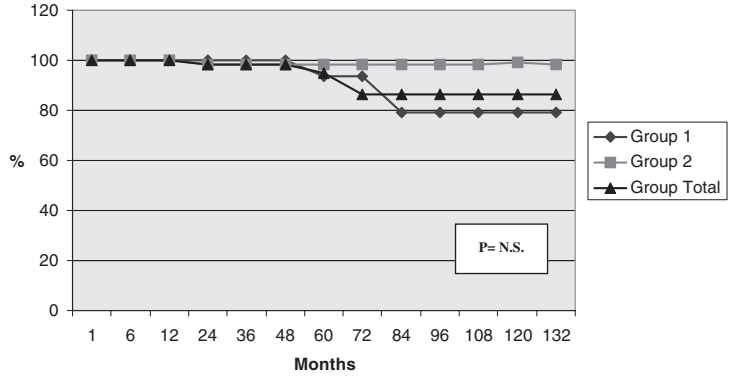

Figure 3. *Actuarial endocarditis-free curves for the three groups of patients.*

All the patients are in NYHA functional class I or II. The results of the long-term echocardiographic examinations revealed that 97.30% of patients had no trivial or only mild aortic incompetence. One patient operated for a Takayasu syndrome presented with severe incompetence of the CAA, partially destroyed by a probable immunological reaction, 24 months after surgery. A more than moderate stenosis (mean gradient > 20 mmHg) was observed in 2 patients.

Discussion

Early results. The operative mortality in our experience was strongly influenced by the indications to surgery, by the preoperative status of the patient and by the surgical anatomy. The highest mortality was observed in patients operated on an emergency basis for acute native or prosthetic aortic valve endocarditis with extensive destruction of the LVOT tissues. The 13.3% mortality observed in group 1 patients is similar to that

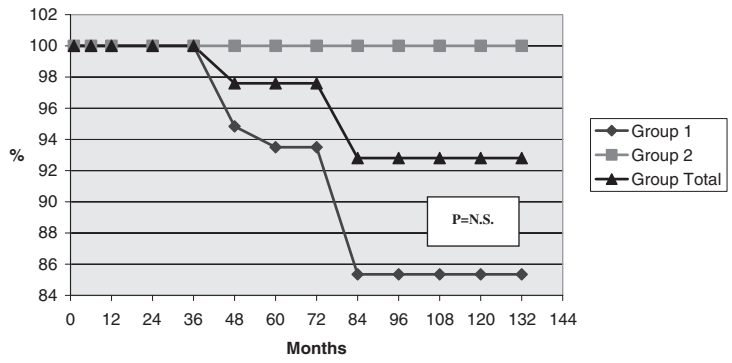

Figure 4. *Actuarial structural dysfunction-free curves for the three groups of patients.*

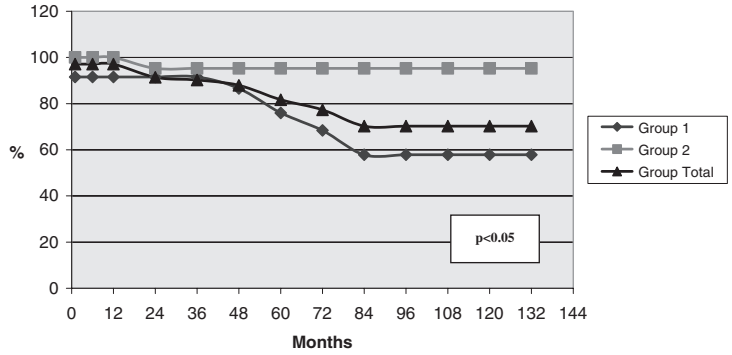

Figure 5. *Actuarial death and prosthesis-related event-free curves for the three groups of patients.*

reported by other authors[4-7,15-27]: the major series on the surgical treatment of native or prosthetic aortic valve endocarditis reported an operative mortality that ranges from 4 to 48%. The desperate clinical or anatomic situations of this group of patients, such as the presence of preoperative septic shock, multiorgan failure syndrome and the finding of a ventriculo-aortic discontinuity, dictate their fate. On the other hand, we observed only one operative death in patients who underwent an elective AVR with a CAA. This death occurred during the first 2 years of our experience and since then in the last 8 years the operative mortality in group 2 has virtually been 0%. The excellent operative results of CAA have been confirmed in the literature[3,8,28-36] and hence we may affirm that even if the implantation of a CAA is technically more challenging and requires longer aortic cross-clamping, cardiopulmonary bypass, and operative times than a simple standard AVR, this fact does not translate into a greater operative mortality or morbidity. The total mortality of our series is higher than that reported in other series, but this is conditioned by the extremely high percentage of patients operated for infection (45/122). The operative technique of CAA implantation, free-hand vs total root replacement, did not influence the operative mortality neither in our nor in other series[3,8,29-40]. It is worthwhile to stress that in no patient the presence of a more than trivial incompetence of the CAA at intraoperative transesophageal echocardiography obliged us to replace the CAA with a standard mechanical or biological prosthesis.

Late results. The long-term results in our experience were conditioned on the one hand by the prevalence of patients operated for acute endocarditis and on the other by the young age of the population. As a consequence, if young age (mean age < 40 years) has a positive impact on the 126-month survival of the whole population (that is about 84% and very similar to that reported by other authors[3,8,29-40]), when we separately analyzed the long-term survival related to the presence or not of preoperative endocarditis, we found a dramatic difference between the two groups. However, the 66.59% 10-year survival of patients in group 1 compares favorably with that of other series in the literature in which the patients operated for endocarditis received a mechanical or a stented biological prosthesis[19,20,23,24]. The 98.4% 10-year survival in group 2 is very high and depends on the young age and the good conditions of the patients and consequently a comparison with the long-term survival of other series in which a standard aortic bioprosthesis was implanted does not make sense[41-43].

The CAA are considered non-thrombogenic devices with no specific need for early or long-term anticoagu-

lant therapy. In our experience, only one patient received early anticoagulant therapy because of the necessity of an associated procedure on the mitral valve and unfortunately died of cerebral hemorrhage within a few months of surgery. This event reinforced our choice to go through any effort to avoid administering anticoagulant therapy. In our experience, we did not observe any thromboembolic or hemorrhagic event (besides the aforementioned one) and this confirms the excellent flow characteristics of CAA[3].

The resistance to CAA to infections is well documented[4-7] as is their ability to eradicate the infection when used in patients with prosthetic or native aortic valve endocarditis[6,7,16,17,21,22]. In our experience too, even when used in desperate situations with a widespread destruction of the LVOT tissues, the patients with a CAA present a low incidence of postoperative primary or recurrent endocarditis: the freedom at 10 years for group 1 was 79% and 98.9% for group 2. For this reason, we continue to adopt the CAA as the device of first choice in patients with acute native or prosthetic aortic valve endocarditis. However, we observed an increased incidence of structural deterioration among group 1 patients. The fact that CAA in patients operated for endocarditis present an accelerated calcification, especially in younger subjects, has been reported by other authors[44]. Young age is one of the most important risk factors for precocious structural degeneration, but our follow-up is probably too limited to confirm these data. Four young ladies in our experience had one or more pregnancies with no signs of structural degeneration of the CAA.

Apart from one patient in whom failure of the CAA was due to a technical error, the indications to reoperation were mainly related to the presence of preoperative endocarditis. Four patients in group 1 underwent reoperation: 2 patients for a new endocarditis and 2 patients for an accelerated structural deterioration. The fact that in the 2 patients operated for an immuno-mediated lesion of the aortic valve the CAA presented a precocious failure, deserves particular consideration. Of course, this is our limited experience and even though in the literature we did not find any article dealing with this aspect, we still wish to spend a word of caution about the use of CAA in patients with an immunological pathology of the aortic valve.

In our experience and differently to what reported by other authors[3,8,31-36], the long-term performance of CAA was not influenced by the technique of implantation, age of the CAA donor or age of the recipient.

In conclusion, our experience confirms that the use of CAA in the treatment of aortic valve pathologies is safe and produces good early and long-term results. Despite the technical difficulty in implantation, the early operative mortality in elective surgery is extremely low. The long-term results are satisfactory and the patients with CAA have a good quality of life even though the probability of developing structural degeneration and undergoing reoperation is very high especially in patients aged < 25-30 years. When used in the challenging field of native or prosthetic aortic valve endocarditis, CAA offer satisfactory early results with a good probability of performing a radical operation with complete eradication of the infection as documented by the low early-phase risk of recurrent endocarditis. Of course, even the CAA may get infected over time if the patient persists in using intravenous drugs and hence a strict surveillance of these patients is mandatory. Nevertheless, in desperate cases such as in the presence of septic shock or massive tissue destruction, CAA are of course an excellent weapon in the surgical armamentarium. Unfortunately, their use cannot always favorably modify the natural history of the disease.

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