Midterm results after aortic valve replacement with the autologous tissue cardiac valve

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Abstract

Objective: To assess midterm results after aortic valve replacement (AVR) with an autologous tissue cardiac valve (ATCV). This new technique was developed to construct a tissue prosthesis for AVR using the patients pericardium, harvested at the time of operation with negligible effect on operating time.

Methods: Briefly, glutaraldehyde tanned pericardium is mounted on a stent requiring no suturing. Between March 1994 and December 1996, 87 patients, 44/43 M/F and aged 70 ± 6 years had AVR for aortic stenosis (80%), aortic insufficiency (6%) and combined lesions (14%), one patient suffered from endocarditis. Additional coronary artery bypass was done in 25%, aortic root enlargement in 7%. Aortic cross clamp and cardiopulmonary bypass times were 69 ± 21 and 93 ± 29 min. All patients were followed by clinical examination and color flow Doppler echocardiography in 3–12 months interval. Follow up was 99% complete.

Results: There were five perioperative deaths (6%), none of them valve related. Eighty-one patients were followed up to a period of 52 months (mean interval 37.5 ± 1.3 months), one patient was lost for follow up. Overall survival was 86, 81, 79 and 71% at 12, 24, 36 and 48 months, respectively. There were 14 late deaths with eight (10%) valve related (four cerebral deaths, four sudden deaths). Sixteen patients (20%) had to be re-operated due to severe valve incompetence. Freedom from reoperation was 98, 97, 90 and 63% at 12, 24, 36, and 48 months, respectively. Valve incompetence occurred suddenly, without previous signs in the follow-up examinations. Selection and preparation of the pericardium, the way of fixation of the tissue ± brief immersion in glutaraldehyde ± and engineering problems might be responsible for this disastrous outcome. Conclusion: Due to these results we must state, that the ATCV did not fulfill our expectations and presently we can not recommend it as an aortic valve substitute. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Autologous pericardium, Cardiac valve, Bioprosthesis, Aortic insufficiency

1. Introduction

The use of the patients own pericardium for constructing a heart valve prosthesis is biologically more appealing than the use of animal tissue or of heterologous material. In the sixties the first experiences with autologous material by Senning [1] and Björk and Hultquist [2] failed because of the behavior of the untreated tissue and the inability of a standardized method to construct such a valve.

Love and coworkers recently developed a method to rapidly construct intraoperatively a stent mounted glutaraldehyde fixed autologous pericardial valve in a standardized fashion (Autogenics, Newbury Park, CA) [3]. Successful in vitro and in vivo experimental testing led to the first clinical trials in 1992 [4,5,6]. Nearly 500 valves were implanted in several European centers.

Our series of 87 consecutive patients undergoing aortic valve replacement with the autologous tissue valve represents the single greatest experience with this new device. Encouraging perioperative and short term results [7] were followed by a disappointing high percentage of primary tissue failure after 3 years follow up. Forty six explants worldwide correlate with our experience of nearly 20% explants.

We report in this paper technical aspects of valve construction, hemodynamic performance in the early period and mid term results. The modes of failure, concerning biomedical and engineering aspects are discussed.
2. Materials and methods

The autologous tissue cardiac valve (ATCV) is assembled in the operating room under sterile conditions. A thoroughly prepared thin piece of pericardium is excised and immersed in 0.625% glutaraldehyde buffered to pH 7 for 10 min and mounted on two mating stents. The tissue is clamped between inner and outer stent and does not require any sutures.

2.1. Mounting the valve

After opening the chest, in situ pericardium is cleared of overlying fatty tissue. A thin uniform piece is excised and after tanning in glutaraldehyde for 10 min, rinsed in three serial washes of saline. On standard cardio-pulmonary bypass the diseased aortic valve is excised and the aortic annulus sized. Size specific kits for 21, 23 and 25 mm valves are used for further construction. A corresponding geometric shape and eight 0.5 mm holes — used to align the tissue on the inner stent — are cut out of the pericardium. The tissue is placed on the inner stent aligning it by buttoning on two alignment stubs on each stent post. On one stent post the tissue overlaps to make a seam. The expandable outer stent is distended with a spreading tool and lowered over the tissue wrapped inner stent. The stents are made of thermoplastic Delrin TM and are covered with Dacron TM fabric. The valve is tested for exact leaflet coaptation in a test device. All tools are disposable. Details of construction are discussed previously [7]. In our series all valves were manufactured by one surgeon.

2.2. Morphological examination of the explanted valves

After removal, the bio-prostheses were fixed in glutaraldehyde in phosphate buffered saline 2.5% (4°C, pH 7.2). Photographs were taken of both inflow and outflow surfaces of the bio-prostheses, and a roentgenogram was made to determine distribution and intensity of calcium deposits. For light microscopy, fixed specimens were routinely embedded in paraffin wax, sectioned at 6 μm thickness and stained with hematoxylin and eosin, Goldner’s trichrom, Weigert’s resorcin fuchsin for elastic tissue and van Gieson’s silver method to demonstrate calcium deposits. All stainings were performed according to the directions in Romeis [8].

Immunohistochemistry was used to identify the nature of suspected endothelial cells. Sections were dewaxed and brought to water. Endogenous peroxidatic activities were blocked with 2% goat serum in phosphate-buffered salt solution (PBS) at room temperature for 20 min, incubation with the first antibody solution lasted for 1 h at room temperature (Anti-Human von Willebrand factor M616, Mouse, Dako, Glostrup).

After incubation and washing with PBS, first antibodies were coupled to appropriate biotinylated secondary antibodies and these were demonstrated by an avidin–bixin–peroxidase complex (ABC) method [9], using a commercially available ABC kit (Vectastain R, Vector Lab. Inc., Burlingame, CA). Reaction product was developed with a mixture of diaminobenzidinium tetrahydrochloride (0.04%) and H2O2 (0.002%) in 0.05 M Tris buffer, pH = 7.6. Immunostained sections were counter-stained with Mayer’s hemalun. Controls were run by omitting either the first or the second antibody.

For scanning electron microscopy, fixed specimens were washed in a 0.053 mol/l cacodylat buffer and dehydrated in a series of graded ethanols. After critical point drying with carbon dioxide, the specimens were sputtered with gold–palladium and examined with a Jeol JSM 5400 scanning electron microscope.

2.3. Patients

Between March 1994 and December 1996 the ATCV was implanted in 87 consecutive patients elected for bioprosthetic heart valve replacement. Informed consent was given by all patients. Complete clinical and echocardiographic assessment was performed before hospital discharge, after 3 months, and yearly thereafter. Patients were placed on oral anti-coagulation for the first 3 months.

There were 44 male and 43 female patients with a mean age of 70 ± 6 years (range 53–82). Predominant lesion was aortic stenosis in 80%, aortic insufficiency in 6% and combined valvular lesion in 14%. One patient had endocarditis. Patients with reoperation were excluded. The majority of patients (92%) were in NYHA classification III and IV. Associated diagnoses included diabetes in 15% of patients, hypertension in 22%, coronary artery disease in 31% and carotid artery disease in 7%. Preoperative cardiac catheterization data is shown in Table 1.

2.4. Statistical analysis

Data is given as mean and standard deviation where appropriate. Survival of patients and freedom from reoperation is calculated using Kaplan–Meyer methods. Student’s test was applied to test for differences in hemodynamic parameters between valve sizes.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patients characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>87</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>51</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70 ± 6</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>54 ± 16</td>
</tr>
<tr>
<td>NYHA III and IV (%)</td>
<td>92</td>
</tr>
<tr>
<td>Mean gradient (mmHg)</td>
<td>66 ± 19</td>
</tr>
<tr>
<td>Pure stenosis (%)</td>
<td>80</td>
</tr>
<tr>
<td>Additional CABG (%)</td>
<td>26</td>
</tr>
<tr>
<td>Bypass time (min)</td>
<td>93 ± 29</td>
</tr>
<tr>
<td>Cross clamp time (min)</td>
<td>69 ± 21</td>
</tr>
</tbody>
</table>
3. Results

Twenty eight (32%) patients received a 21-mm valve, in 35 patients (40%) a 23-mm valve was implanted and in 24 (28%) patients a 25-mm valve. Additional surgical procedures were performed in 31 patients (36%): coronary-artery bypass in 23 (26%) patients, and carotid endarterectomy in two (2%) patients. Root enlargement with a pericardial patch was performed in six patients (7%).

Cross clamp times of \(69^{±21}\) min are slightly higher than with both mechanical or stented biological valves. However, in our institution, the surgeon, constructing the valve, was also implanting it.

3.1. Hospital mortality and morbidity

There were five postoperative deaths (6%) within 30 days, all of them not valve related. Patients died suddenly after uneventful recovery. At autopsy severe left heart hypertrophy was found, with normal appearing valves.

Perioperative complications included need for implantation of a permanent pacemaker in three patients, and transient cerebral attacks in two patients.

3.2. Immediate postoperative results

Eighty-two patients were discharged from hospital in good condition.

Predischarge echocardiograms showed excellent hemodynamic performance of the valves with gradients comparable to other valves (Table 2). All but one patient had none or trivial valvular incompetence. One patient had insufficiency grade 3 due to paravalvular leakage. This patient was re-operated 6 months later.

3.3. Late mortality

Fourteen patients died during follow up period, 8 (10%) of them have to be considered as valve related deaths [10]. Four patients died a cerebral death, the other four suffered a sudden death. Survival estimates are 86, 81, 79 and 71% at 1, 2, 3, and 4 years, respectively. See Fig. 1.

3.4. Late results

Sixteen (20%) patients had to be re-operated for valve insufficiency. In one case a paravalvular leak, already existing immediately after operation, led to reoperation after 6 months. The other 15 cases were due to acute valvular insufficiency, caused by leaflet tear. All patients were under regular follow up control, the onset of symptoms lasted between a few days to 2 weeks. The majority of these events occurred between the 30th and 42d month postoperatively. Freedom from reoperation is 95% at 30 months and 74% at 42 months, respectively. See also Fig. 2. All patients were successfully re-operated.

Macroscopic evaluation of explanted bio-prostheses revealed with cuspal tears extending along the cuspal base from the commissural area to the central part of the leaflet, with smooth outflow surface and rough inflow surface in most cases (Fig. 3).

No calcification could be detected neither by X-ray analysis nor by histological methods. Microscopic analysis showed severe deterioration of the collagenous tissue. Collagen fibers were disseminated by insudated plasma proteins and erythrocytes. Cuspal hematomas could be

Table 2

<table>
<thead>
<tr>
<th>Valve size (mm)</th>
<th>n (%)</th>
<th>p. max</th>
<th>p. mean</th>
</tr>
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<tbody>
<tr>
<td>21</td>
<td>28 (32)</td>
<td>35 ± 12 mm Hg(^a)</td>
<td>19 ± 8 mm Hg(^a)</td>
</tr>
<tr>
<td>23</td>
<td>35 (40)</td>
<td>31 ± 9 mm Hg</td>
<td>20 ± 7 mm Hg</td>
</tr>
<tr>
<td>25</td>
<td>24 (28)</td>
<td>21 ± 7 mm Hg(^a)</td>
<td>13 ± 5 mm Hg(^a)</td>
</tr>
<tr>
<td>AI 0</td>
<td>69 (84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AI I</td>
<td>12 (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AI III</td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) P = 0.01 size 21 vs. 25. AI, aortic insufficiency.

Fig. 1. Kaplan-Meier. Overall survival at 1, 2, 3 and 4 years. Number of patients at risk at bottom line.

Fig. 2. Kaplan-Meier. Freedom from reoperation at 1, 2, 3 and 4 years. Number of patients at bottom line.
detected particularly near to the cuspal base. The autologous tissue looked compressed between the inner and outer stent and severely altered at the cuspal base (Fig. 4). No lymphocytes, macrophages or multinucleated giant cells were seen. Pericardial tissue appeared completely acellular, even the original fibroblasts disappeared. Scanning electron microscopical evaluation of the valvular surface revealed nearly complete reendothelialisation of the smooth outflow-surface.

Fig. 3. Explanted prostheses.

Fig. 4. Histological examination of the autologous tissue demonstrates severe disruption of the collagen fibers, especially near to the cuspal base. Note the cuspal haematoma (× 40).
Cells were characterized as endothelial cells by positive immuno-histochemical staining. In contrast, only rare endothelial cell in-growth could be seen at the rough inflow surface. Large areas of the inflow surface were covered with fibrin mesh and some activated platelets (Fig. 6).

The remaining 52 patients are under regular follow up and doing well. Mean follow up is $37 \pm 1.3$ months (maximum follow up 52 months). All patients but one are in New York Heart Association grade I or II. One patient had a prolonged reversible ischemic neurologic deficit (PRIND) 28 months after operation.
4. Discussion

Tissue valves were developed to answer the problems seen in mechanical valves, and they seemed to answer some problems well. There is no need for anticoagulation, they are quiet and have good flow characteristics. But the main disadvantage, limited durability, caused by tissue failure and calcification, still remains.

There are several patient and valve related factors, responsible for tissue calcification. Patient-related factors are age, calcium metabolism and associated renal disease. Valve related factors include inflammatory response, foreign tissue components, tissue preservation and mounting [11,12].

Early attempts by Senning [1] Bjork and Hultquist [2] to use fresh autologous pericardium and fascia lata eliminated inflammatory response and foreign tissue components, but led to thickening and shrinkage of the valve, endocarditis developed frequently.

Glutaraldehyde tanning, introduced by Carpentier in 1969 reduced antigenicity of heterograft valves – the immune response may at least in part contribute to the degenerative process – but did not eliminate it completely [13]. Interest in autologous pericardium was therefore renewed, to eliminate residual antigenicity.

Excellent mid to long term results using briefly glutaraldehyde tanned autologous pericardium in mitral valve reconstruction and aortic valve reconstruction seem to confirm this consideration [14,15].

Another problem was the non-standardized, time consuming and unreliable method of construction.

Relying on this knowledge Love and associates revitalized the concept to use briefly glutaraldehyde tanned autologous material. It is also the merit of this group to develop a method to construct an autologous tissue valve in the operating room in a simple, standardized and expedient fashion [3–6].

After extensive in vitro testing, the first clinical trials were initiated in 1992. Promising laboratory and clinical results let us start our series in 1992. Eighty seven consecutive patients between 1992 and 1994 were operated on. In 1996 we published results from the first 50 implants with encouraging early results [7].

In 1999, 3 years later, we have to strike a disillusioning balance: 15 patients had to be re-operated, because of valve failure due leaflet tears. In the majority of these patients failure occurred between the 30th and 42nd postoperative month without any previous notice.

This is in accordance with explant information, provided by the company in May 1998 reporting 46 explants (9.6%) out of 479 implants in 16 different hospitals with a mean duration of 33 months.

Analyzing the macroscopical and microscopical results of the explanted valves we face the following problems.

(a) Selection and preparation of the pericardium.

Function and performance of bioprosthetic heart valves depend critically on the mechanical properties of the leaflet tissue [16]. Apart from the importance of the fiber architecture of a pericardial sac, the thickness of the selected material is of major importance.

The selected location of the pericardium (left or right ventricle, apex etc.), is not solely responsible for this, as the thickness of the material is also responsible. Thickness varies substantially, depending not only on the location of harvest, but also on the age of the patient. Older patients have thicker pericardial sacks, and this fact influences not only the pliability of the material, but also the depth of invasion of glutaraldehyde. This is probably one of the reasons for failure in our series.

Whereas several groups achieved excellent long term results, using briefly glutaraldehyde tanned pericardium in aortic and valve surgery in young patients (mean age 20–30 years) [15], our group of patients has a mean age of nearly 70 years. This consideration leads to the next problem.

(b) The brief immersion.

The aim of glutaraldehyde tanning of autologous material is to stiffen the material, making it more suitable for constructing a valve and secondly to stop the abnormal cell metabolism, causing the inflammatory response of fresh untreated pericardium. Glutaraldehyde produces cross linking of collagen chains resulting in better tissue stability in long term implants [17]. On the other hand, glutaraldehyde moves very slowly through tissue [18,19]. Brief immersion (10 min in 0.625% glutaraldehyde) results in a kind of ‘surface glazing’ of the tissue. This may be enough for valve reconstruction and valve extension, the mechanical stress in a stented valve is obviously different. The dissemination of the collagen fibers, accompanied by plasma protein and erythrocyte insudation, as found in our microscopical analysis, does not guaranty sufficient mechanical stability of the bio-material.

(c) The engineering problem.

Love and colleagues developed a method to produce a valve rapidly and reproducibly in the operating room. Presupposition is, that the bio-material is clamped between two mating stents, avoiding the time consuming commissural sutures. In vitro testing has demonstrated, that the ATCV functions normally beyond 800 million cycles, the equivalent of 20 years of use [4]. But the authors describe the problems with autologous tissue with regard to accelerated wear testing. The tissue, even briefly in glutaraldehyde immersed, is not durable enough for the months, which are needed for testing in vitro – it putrefies and decays. So they used fully tanned bovine pericardium for their tests. Our macroscopical analysis of explanted valves shows clearly, that the autologous tissue looked compressed between the inner and outer stent and severely altered at the cuspal base, leading to insudation and cuspal hematomas just in there. This seems to be a completely different mode of failure compared to the problems observed in other pericardial valves as the early Ionescu–Shiley or Hancock valves.
rather inflexible stent and commissural stitches, concentrating stress, were responsible for these failures [20].

Also late mortality is considerably high. Among the eight valve related deaths, four of them are caused by cerebral attacks in patients with atrial fibrillation or flutter. Patients were not under warfarin. Four sudden unexplained deaths are also suspicious for acute valve insufficiency. All these patients had normal functioning valves in previous echocardiograms. But we know, that valve dysfunction occurs suddenly without previous notice. Under the six non-valve related deaths, two deaths were caused by myocardial dysfunction in severely impaired left ventricular function, two other fatal events were due to rhythm problems. Two patients died of senile cachexia.

On the other hand there are also two positive findings in our analysis: (1) no calcification could be found, neither by X-ray analysis nor by macroscopical or histological examination. (2) Scanning electron microscopical evaluation of the valvular surface revealed nearly complete reendothelialisation of the smooth outflow surface. In contrast only rare endothelial ingrowth could be seen on the rough inflow surface. If this observation is a mechanical problem due to different flow, stressed on the inflow compared to outflow surface, or if it is a biological problem due to the different surfaces of the pericardial sac is under discussion. Both facts speak well for the lack of antigenicity and good immunologic behavior of the bio-material.

In conclusion we can say, that the autologous tissue cardiac valve has failed in midterm results for several reasons. The lack of calcification and the possibility of reendothelialisation are encouraging. The valve is currently withdrawn from the market and is under complete reconstruction.

References