Factors affecting the yield of cardiac valve allografts from living unrelated donors

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Abstract

Objective: Allografts are the valve of choice for fertile women, patients with infective endocarditis and those with small aortic roots. However, the supply of valves is problematic and widespread usage is restricted by limited availability. Allograft valves are available from cadaveric donors and from the explanted hearts of transplant recipients. Potentially, hearts from these patients could be an excellent source of usable aortic and pulmonary valves. However, little information is available on the suitability of such donors, the procurement rate of allograft valves from this source, or the factors that limit the yield of implantable valves from explanted hearts.

Method: In order to examine some of these issues, we have carried out a retrospective study on the explanted hearts offered to the East Anglian Tissue Bank by Papworth hospital. Papworth hospital carries out 90 heart and heart-lung transplants per year. Over a 2 year period, the tissue bank was offered 72 hearts from this programme. Results: Of the 72 hearts offered, 58 were accepted for subsequent dissection and further examination. A total of 14 hearts were refused. The main reasons for refusal were extensive cardiectomy trauma (4 hearts) and abnormal valve morphology (four hearts). Of the 116 valves from those hearts accepted for dissection, 55 valves were rejected upon further examination. Reasons for rejection included: cardiectomy trauma (26 valves), abnormal morphology (22 valves), procurement/dissection trauma (7 valves). Of the 61 valves banked, four were subsequently rejected due to positive or incomplete microbiology. Procurement trauma fell to 0% in the last 12 months of the study but cardiectomy trauma remained constant and was related to previous cardiac surgery. Overall, the yield of implantable valves was 0.8 valves/donor. However, the yield showed considerable variation, from 1.0 valves/donor for donors diagnosed as cardiomyopathy to 0.5 valves/donor for donors with ischaemic heart disease who had undergone previous cardiac surgery. Conclusion: It is possible to predict the likely yield of explanted heart valves from different groups of heart transplant recipients, based on diagnosis and previous history. The yield of usable valves could be increased by avoidance of injury, both during cardiectomy and subsequent removal of the valves; this is achievable through appropriate training. © 1998 Elsevier Science B.V.

Keywords: Heart valves; Tissue donors; Tissue procurement; Transplantation

1. Introduction

In 1962, Ross [1] and Barratt-Boyes [2], both independently, used an orthotopic aortic allograft to replace the aortic valve in a human patient. The replacement of diseased aortic valves with allografts is now well established and they have become the valve replacement of choice for patients with infective endocarditis, small aortic roots and for fertile women contemplating pregnancy. Good results are now achieved using antibiotic-treated, cryopreserved allografts [3]. Advantages include excellent haemodynamic characteristics, resistance to the development of endocarditis, relative freedom from thromboembolic events, the infrequent requirement for anticoagulant therapy and long term
freedom from valve-related complications. Long-term follow-up has demonstrated that durability exceeds that of porcine xenografts [4,5].

However, the supply of allografts has always presented problems and widespread usage is restricted by limited availability. Currently, allograft valves are obtained mainly from cadaveric donors. However, hearts excised from recipients of heart transplants may also be an excellent source of valves [6], but little information is available concerning the rate of procurement of usable valves from living donors or the reasons that result in valves from this source being rejected [7,8].

In order to examine these issues, we have performed a retrospective study of 75 hearts offered to the East Anglian Tissue Bank by Papworth Hospital. We have determined the overall valve procurement rates from heart transplant recipients and attempted to identify the donor groups most likely to provide a satisfactory yield of implantable valves. We have also examined those factors which contribute to potentially usable valves being discarded.

2. Methodology

The East Anglian Tissue Bank began accepting explant tissue for cardiac valve cryopreservation in March 1993. Since then, all transplant recipients have been offered the opportunity to donate. Donation was by informed consent, with additional consent being sought for HIV testing. The selection policy was that which the bank had followed since its inception. This study covers a 2 year period.

2.1. Donor criteria

Potential donors were under 60 years of age, free from active transmissible disease and extracranial malignancy. Donors with degenerative neurological disease, autoimmune disorders or those who had received pituitary-derived human hormones were excluded.

2.2. Microbiology

All explant heart valve donors were screened for anti-HIV1/2, HIVp24Ag, HBsAg, anti-HBe, anti-HCV and syphilis, both at the time of donation and 3 months post-transplant. Tests for antibodies to Chlamydia, Coxiella burnetii and enterovirus IgM (Coxsackie A/B and echovirus) were also conducted at the time of transplant. Any confirmed positive test for any of these markers was grounds for rejection of the valves.

2.3. Heart and cardiac valve assessment

All tissue from explant heart donors was assessed following the protocol outlined in Fig. 1. Hearts from donors fitting the donor criteria underwent a preliminary assessment prior to dissection. Hearts were rejected if they failed to meet warm ischaemic and transportation criteria or showed evidence of abnormal valve morphology or iatrogenic damage. The criteria for rejection of valves at dissection were as follows:

- Congenital malformations leading to dysfunction
- Calcified deposits on the leaflets or commissures
- Extensive deposits of non-calcified atheroma on the leaflets or commissures
- Large fenestrations on the cusps or small fenestrations on the cuspal edge if accompanied by incompetence of the valve
- Moderate to severe thickening or thinning of the leaflet
- Fusion of the leaflets
- Mechanical damage to the valve itself

2.4. In-process bacteriology

Samples of the transport solution, together with post-disinfection and co-processed tissue samples, were tested for aerobes/anaerobes, yeast, fungi and mycobacteria. Valves were rejected according to strict guidelines: no valves were released for issue if any organisms were detected in the post-disinfection or co-processed tissue samples. In common with US banks, valves were also rejected if yeast, fungi, Clostridia, Pseudomonas, Staphylococcus aureus or β-haemolytic Streptococcus were associated with the heart tissue prior to disinfection. A positive result from the transport solution for any of the above organisms resulted in rejection of the valves, even if the results from the post-disinfection tissue samples were negative.

2.5. Preservation protocol

All solutions used were sterile and tested for endotoxin by the use of a chromogenic LAL test. Following explantation, the heart, or heart valve block was placed in sterile transport solution at +4°C. All hearts were dissected within 48 h of procurement under aseptic conditions in a Class 100 laminar flow hood. The valves were disinfected for 24 h in Hanks balanced salts solution containing the following antimicrobial agents: gentamicin, imipenem, vancomycin, polymyxin B and nystatin. The valves were then transferred to a class 100 laminar flow hood within a clean room environment, washed to remove residual antibiotics and equilibrated in Hanks solution containing dimethyl sulphoxide (DMSO, 5%). Following equilibration, the valves, now in 10% DMSO, were sealed within a double bag and cryopreserved.
by controlled rate cooling. Valves were stored below $-180^\circ\text{C}$ in the gas phase above liquid nitrogen.

Using data supplied by the donor files held by the tissue bank and the patient records on the Papworth Hospital Transplant Database, we have examined the outcome of all the hearts offered to the tissue bank over the stated period.

### 3. Results

During the period of the study, 87 heart and 38 heart–lung transplants were performed at Papworth Hospital. A total of 72 hearts were offered for valve donation (69 from heart and 3 from heart–lung transplant recipients). Of these patients, 63 were male (87.5%), nine were female (12.5%) and age ranged from
15 to 60 years. The indication for transplantation was ischaemic heart disease in 30 patients (42%), cardiomyopathy in 35 patients (48%) and seven patients with miscellaneous diagnosis (10%). Of these patients, 25 (34.7%) had undergone previous cardiac surgery.

3.1. Rejected hearts

Of the 72 hearts offered to the East Anglian Tissue Bank, 14 (19%) were rejected. Four hearts were rejected prior to dissection due to obvious damage induced during cardectomy. Procedural irregularities accounted for another four hearts: two were rejected due to the use of unsuitable transport media and two were received outside the ischaemic time limits set by the tissue bank. A further four hearts were rejected due to abnormal morphology (one donor heart was shown to have a bicuspid aortic valve and an abnormal pulmonary valve on ex-situ examination; one heart showed extensive calcification of both valves; one patient with valvular heart disease had undergone previous valve replacement; one donor heart was from a re-transplant). The remaining hearts were required for histological examination and were returned to Papworth hospital without examination.

3.2. Rejected valves

Of the 116 valves dissected from those 58 hearts accepted by the bank, 55 (47%) were rejected for reasons shown in Table 1. Iatrogenic damage was the most common cause of rejection: rejected valves divided equally between aortic and pulmonary valves. A total of 26 valves were damaged during cardectomy, seven during dissection of the valves. There were two common sites for damage at cardectomy (accounting for over 50% of the valves lost). The first was at the level of the coronary sinuses; aortic valves showed cuts sustained from scissors which often extended as far as the valve leaflets. The second site for damage was in the area of the commissural posts, where the conduit had been cut too close (< 5 mm) to the top of one or more commissures. This was particularly prevalent amongst pulmonary valves. Damage sustained at valve dissection, although initially a common cause for rejecting the valve, fell to 0% during the last 12 months of the study; surgical injury remained constant. The incidence of cardectomy related valve damage was greatest in the donor group with ischaemic heart disease, especially in those who had undergone previous cardiac surgery.

Twenty-two valves were rejected due to abnormal morphology; 64% of these being aortic valves. The most common morphological abnormality leading to rejection was calcification/atheroma (commissural and leaflet). This occurred in fifteen valves (12 aortic, 3 pulmonary) and was more common in the donor group who had been transplanted for ischaemic heart disease. Pronounced fenestration of the leaflet (5 valves), and myocardial abnormalities (2 valves) accounted for the remaining valves.

Only four valves were rejected following cryopreservation: two valves (from a single donor) on serological evidence of past Chlamydial infection and two where microbiological results were inconclusive or incomplete.

3.3. Yield of implantable valves

The rate of procurement of implantable valves by donor age is shown in Table 2. There was little effect of donor age: such differences as there were, probably reflected differences in the age of onset and progression of the heart and lung diseases diagnosed within the donor group as a whole.

Yield as a function of donor diagnosis is shown in Table 3. The yield from donors transplanted for cardiomyopathy (1.0 valves/donor) was substantially higher than the overall procurement rate from donors diagnosed with ischaemic heart disease (0.6 valves/donor). The sub-population of donors with ischaemic heart disease who had undergone previous cardiac surgery showed an even lower procurement rate (0.5 valves/donor). The negative effect of previous cardiac

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Cardiectomy trauma</th>
<th>Procurement trauma</th>
<th>Abnormal morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aortic</td>
<td>Pulmonary</td>
<td>Aortic</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>3</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>HHD (No previous surgery)</td>
<td>4</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>HHD (previous surgery)</td>
<td>5</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>13</td>
<td>4</td>
</tr>
</tbody>
</table>

*a Ischaemic Heart Disease
*b Four valves were discarded following cryopreservation.
surgery on the yield of implantable valves is shown in Table 4.

3.4. Procurement strategy

The effect of adopting various strategies on procurement rate is shown in Table 5. The current strategy of accepting all donors regardless of diagnosis or previous cardiac surgery yielded 0.8 valves/donor. Excluding hearts from the donor group in which the most valves were lost, donors with ischaemic heart disease, would only have a marginal effect on the yield of implantable valves per donor, as would excluding those with previous cardiac surgery. However, eliminating cardiectomy damage would significantly increase the procurement rate per donor.

4. Discussion

The increased use of allograft valves is related to their excellent long-term durability and relative freedom from valve-related complications. However, more widespread application is limited by graft availability. The excised hearts of transplant recipients have been recognised by some as being an excellent source of valves [6,7] and the potential that this source has to supply clinical need is considerable: in 1993 alone, 3300 heart transplants were reported to the Registry of the International Society for Heart and Lung Transplantation [9]. However, some centres question retrieval of valves from explanted hearts, citing poor yield and economic factors amongst the reasons for not accepting hearts from this source.

In the preparation of allograft valves, most of the processing costs are incurred in the retrieval and dissection phases before many of the abnormalities associated with the rejection criteria become apparent [10]. Thus,

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**Table 2**
Allograft valve procurement rate vs. donor age

<table>
<thead>
<tr>
<th>Donor age</th>
<th>Number of donors (n = 72)</th>
<th>Number of valves procured (n = 61)</th>
<th>Valve procurement rate per donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>16–25</td>
<td>5</td>
<td>3</td>
<td>0.6</td>
</tr>
<tr>
<td>26–35</td>
<td>6</td>
<td>8</td>
<td>1.3</td>
</tr>
<tr>
<td>36–45</td>
<td>10</td>
<td>8</td>
<td>0.8</td>
</tr>
<tr>
<td>46–55</td>
<td>31</td>
<td>27</td>
<td>0.9</td>
</tr>
<tr>
<td>56–60</td>
<td>20</td>
<td>15</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**Table 3**
Allograft valve procurement rate vs. donor diagnosis

<table>
<thead>
<tr>
<th>Donor diagnosis</th>
<th>Number of donors (n = 72)</th>
<th>Number of valves procured (n = 61)</th>
<th>Valve procurement rate per donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyopathy</td>
<td>35</td>
<td>36</td>
<td>1.0</td>
</tr>
<tr>
<td>Ischaemic heart disease (no PCSa)</td>
<td>10</td>
<td>8</td>
<td>0.8a</td>
</tr>
<tr>
<td>Ischaemic heart disease (+PCS)</td>
<td>20</td>
<td>11</td>
<td>0.5</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>7</td>
<td>6</td>
<td>0.9</td>
</tr>
</tbody>
</table>

a Previous cardiac surgery.
b Combining ischaemic heart disease with and without PCS gave a valve procurement rate per donor of 0.6.

**Table 4**
Allograft valve procurement rate in relation to previous cardiac surgery

<table>
<thead>
<tr>
<th>Donor status</th>
<th>Number of donors (n = 72)</th>
<th>Number of valves procured (n = 61)</th>
<th>Valve procurement rate per donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous surgery</td>
<td>25</td>
<td>16</td>
<td>0.6</td>
</tr>
<tr>
<td>No previous surgery</td>
<td>47</td>
<td>45</td>
<td>0.9</td>
</tr>
</tbody>
</table>

**Table 5**
Effect of changing the procurement strategy on allograft valve procurement rate

<table>
<thead>
<tr>
<th>Donor strategy</th>
<th>Number of donors available</th>
<th>Number of valves procured</th>
<th>Valve procurement rate per donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current strategy</td>
<td>72</td>
<td>61</td>
<td>0.8</td>
</tr>
<tr>
<td>Exclude ischaemic heart disease</td>
<td>42</td>
<td>42</td>
<td>1.0</td>
</tr>
<tr>
<td>Exclude donors with previous cardiac surgery</td>
<td>47</td>
<td>45</td>
<td>0.9</td>
</tr>
<tr>
<td>Eliminate cardiectomy trauma</td>
<td>72</td>
<td>103</td>
<td>1.4</td>
</tr>
</tbody>
</table>
establishing criteria for excluding poorly yielding donors prior to processing would be advantageous. Although some criteria related to valve acceptability and clinical outcome, notably donor age [11], are applied, little information is available concerning other factors that may influence suitability and the likely yield of implantable valves from this source.

Some centres only recover the most widely used allograft — the aortic valve. In this study, 27 hearts (47% of those accepted for processing) yielded implantable aortic valves. This is lower than a similar study on valves obtained from explanted hearts, where a yield of 55% was achieved after adjusting for cardiectomy damage [7]. However, that study did not differentiate by donor diagnosis. If only donors with a diagnosis of cardiomyopathy are considered, then the yield of aortic valves from processed hearts in our study is similar (58%).

The significance of donor age on the yield of implantable valves is difficult to assess since the number of donors in the younger age groups is small. Apparent differences between the yield for younger donors (26–35) and those aged > 55 may be attributable to the different disease states (and notably the age of onset) for which the patients required transplantation. Similarly, donors in the older age groups (46–55 and 55–60) produced too few valves to show a statistical difference between the age groups. The upper age limit for valve donation varies between tissue banks, with most setting the upper limit either at 55 or 60 years of age. Yacoub et al. reported an increased rate of valve degeneration in recipients of valves retrieved from donors over the age of 55 [6]. Further studies, with larger sample sizes, are required before the question of an acceptable upper age limit can be answered.

Yield was affected by two factors: the type of heart disease leading to transplant and whether the donor had undergone previous cardiac surgery. The yield was almost twice as high in those patients diagnosed as cardiomyopathies (1.0 valves/donor) as compared to donors with ischaemic heart disease (0.6 valves/donor). Many donors in the latter group had also undergone previous cardiac surgery, further reducing the yield to 0.5 valves/donor when only these patients were considered. Valves from patients with ischaemic heart disease were also more likely to be rejected for abnormal morphology (usually excessive atheroma or calcification) than those from patients with cardiomyopathy.

Considerable wastage occurred due to preventable causes, in particular, iatrogenic injury during cardiectomy. It was the main reason for rejecting hearts at the preliminary stage of assessment and during valve dissection. It was particularly prevalent in the donor group who had undergone previous cardiac surgery (usually coronary artery by-pass grafting). Patients in this group yielded only 0.6 valves/donor compared to 0.9 valves/donor in the group without surgery. The need to take care in avoiding damage to the aortic valve and sinuses of Valsalva, particularly if previous cardiac surgery has been undertaken, has been noted previously [7]. Heightening awareness of the need for particular care in removal of hearts required for valve recovery, could reduce losses considerably and increase the yield per donor. We have stopped short of recommending specific cardiectomy procedures, but have emphasised the need for care during removal of the explant heart and the need to ensure that a suitable length of conduit is left on the valves. This must be impressed on all staff involved in cardiac excision. Those surgeons within the hospital who require allograft valves play a particularly important role in educating their colleagues in this regard. Clear criteria must be laid down by the tissue bank and constant audits undertaken to reduce cardiectomy trauma.

While eliminating cardiectomy trauma would appear to significantly increase yield, other factors must be considered. Firstly, valves were only assessed on the basis of a single rejection criterion. That is to say, if valves were rejected for cardiectomy damage, no assessment as to their morphological acceptability was performed. Thus the true yield, in circumstances where cardiectomy damage has been minimised, is difficult to determine, as the group which would most benefit from improved technique is that in which anatomical abnormalities, especially extensive atheroma and calcification, are high: donors with ischaemic heart disease.

The yield of implantable valves from donors with ischaemic heart disease is low. Not only are considerably more valves rejected due to iatrogenic damage (particularly where there is a history of previous cardiac surgery), but the incidence of aortic valve rejection for non-congenital abnormalities in donors with ischaemic heart disease was also high. Considering these factors, retrieval of cardiac valves from donors with ischaemic heart disease, especially those who have undergone previous cardiac surgery, appears unwarranted. Altering the procurement strategy to exclude this donor group would not significantly alter the overall yield of implantable valves, but would reduce costs associated with recovery.

Abnormal or unacceptable morphology was the second most likely reason for valves to be discarded. Morphological criteria for rejecting valves vary from bank to bank, but from a clinical perspective the effect of morphological abnormalities on clinical outcome is largely unknown and potentially usable valves may be discarded unnecessarily. Currently, under the Human Organ Transplant Act 1989, UK heart valve banks supply information to the United Kingdom Transplant Support Services Authority (UKTSSA). However, this is comprised mainly of information relating to the donor and recipient of the allograft, no data concerning the morphological criteria on which valves are assessed or the effect that these criteria may have on clinical outcome is collated, except within the confines of the individual tissue bank. Though attempts to collate
data across centres have been made [5], little is known about tissue banks policies concerning quality criteria. We believe that it is time for the introduction of a national or international register documenting assessment criteria, quality and clinical outcome of allograft valves, similar to that which already exists for commercially prepared valves.

References