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Evaluating the donor pool: impact of using hearts from donors over the age of 49 years

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Abstract The shortage of hearts for transplantation has led to the use of organs from older donors in many centres. Despite the lack of coronary angiography on potential organ donors, hearts from carefully selected donors over 49 years of age have been used at this centre since 1988. In the study reported here looked at the impact of this strategy on morbidity and mortality. Between May 1988 and August 1996, 400 first heart transplants were performed, 35 recipients (31 male, 4 female; age 51 ± 5.9 years) received hearts from donors over 49 years of age (group 1) while 365 (310 male, 55 female; age 49 ± 9.7 years) had younger donors (group 2). The mean ischaemic time was 189 min (± 63.1) in group 1 and 180 min (± 59.2) in group 2 (n.s.). The main aetiology of heart failure in groups 1 and 2 was coronary artery disease in 46% and 51%, and dilated cardiomyopathy in 40% and 45% respectively (n.s.). There were no differences in the duration of stay on the intensive care unit or in hospital between the groups. One-year survival was 79% in group 1 and 82% in group 2 (n.s.) and actuarial 5-year survival 69.% and 67%, respectively. Six patients in group 1 (17%) and 45 patients in group 2 (12%) died in the first 3 months; of these primary donor organ failure accounted for 50% in group 1 and 13.3% in group 2 (n.s.). Episodes of acute rejection (in the first 3 months) were similar in the two groups: 1.4 and 1.6 per 100 patient days, respectively. Infection rates were also similar: 0.5 and 0.6 per 100 patient days, respectively. The prevalence of coronary artery disease on surveillance coronary angiography at 2 years was 23% in group 1 and 9% in group 2 ($P < 0.005$). There was a greater proportion of CMV antibody donors in the older donor group, but the association between donor age and coronary artery disease persisted after adjusting for CMV status in multivariate analysis. Too few patients underwent angiography thereafter for valid comparisons. In summary, recipients of organs from donors aged 49 years and over can expect comparable survival rates and morbidity levels to recipients of organs from younger donors, at least in the first 2 years postoperation. There is evidence that older donors confer a significantly higher risk of cardiac allograft vasculopathy which may result in a greater attrition rate thereafter. Careful follow-up of these patients after 2 years is required.

Key words Donor · Age · Vasculopathy

Introduction

Cardiac transplantation has evolved into an accepted mode of therapy for patients with severe heart failure. The shortage of donor organs has led to a great increase in the number of patients waiting for transplantation. [1]. In the early years of cardiac transplantation restrictive criteria were applied to ensure optimal selection of donor organs [2–4]. In order to increase the donor pool, there has been a trend to using hearts from older donors in many centres including ours [5–9]. There is some evidence [10] that donor age > 55 years is an adverse prognostic factor while other studies have shown acceptable survival and morbidity using donors above this age [11]. At our centre we now harvest hearts from donors up to 60 years of age. In the United Kingdom it is generally not possible to perform coronary angiography on potential donors. This increases the risk of using donor hearts with preexisting coronary artery disease.

Registry data reports have provided information from a large number of procedures but may be subject to wide variation in the completeness and accuracy of reporting and outcome between centres with varying degrees of expertise. We report here retrospective study of the results from a single large centre with complete prospective data collection and follow-up, comparing outcomes in transplant recipients of hearts from donors aged 50 years and above with those receiving hearts from younger donor.

Methods

Patient population

The first accepted donor aged > 49 years was in May 1988 at this centre. All 400 consecutive patients who underwent first orthotopic heart transplantation between May 1988 and August 1996 were included in this analysis. Transplants prior to this time were excluded to ensure that the two groups arose contemporaneously, so that changes in patient management over time should have affected the two groups to a similar extent. Patients undergoing second transplants were treated as organ failures at the time of retransplantation and not studied further. Recipients were divided into two groups as follows: group 1 consisted of 35 recipients of hearts from donors aged more than 49 years (mean 53.6 years, range 50–61 years); group 2 consisted of 365 recipients of hearts from donors aged ≤ 49 years (mean 30.4 years, range 9–49 years).

All patients were followed-up at Papworth Hospital for at least 6 months (range 6 months to 9 years). The two groups were compared with respect to acute outcomes such as survival, rejection and infection episodes and for development of coronary allograft vasculopathy.

Donor selection criteria

At this institution donors are comprehensively assessed. The heart is deemed to be unsuitable if there is a history of uncontrolled hypertension, cardiac disease or associated symptoms, prolonged smoking, alcohol or drug abuse, or if there is any direct cardiac injury or ECG changes not explained by brain stem death. This information is evaluated along with direct observation of the donor heart and palpation of the coronary arteries for atherosclerosis. More in-depth evaluation with echocardiography and/or coronary angiography is not performed for logistical reasons.

Recipient selection criteria

Patients with poor prognosis due to heart disease are usually referred for cardiac transplant assessment when they are symptomatic with NYHA class III or IV, despite optimal therapy: Indications for heart transplant listing are ejection fraction on MUGA scanning of < 20%, peak oxygen consumption on exercise less than 14 ml/kg per min, age less than 60 years for patients with ischaemic heart disease and dilated cardiomyopathy. Relative contraindications are significant dysfunction of other organ systems and evidence of systemic disease likely to affect postoperative survival. When a donor becomes available a recipient is selected according to ABO compatiblity and size. Where more than one potential recipient is available the final decision is made on the basis of waiting time and expected patient prognosis.

Immunosuppression

Immunosuppression is with triple therapy using cyclosporin, azathioprine and prednisolone. Cyclosporin is titrated to give a trough blood level of 300–400 μg/ml, and azathioprine is titrated to give a white blood cell count of 4.5 to 5.5/mm^2. The prednisolone starting dose is 1 mg/kg per day and is tapered to 0.2 mg/kg per day. An attempt is made to wean patients off prednisolone after the first 3 months. Rabbit antithymocyte globulin was used as routine induction therapy until August 1993 and thereafter in selected patients with significant renal impairment.

Acute rejection

A rejection episode is defined as immunologically mediated dysfunction of the transplanted organ requiring augmented immunosuppression. This is usually associated with histological rejection of ISHLT (International Society of Heart and Lung Transplantation) grade 3 or higher. Rejection episodes are treated with 3-day courses of IV methylprednisolone (500 to 1000 mg). According to protocol, cardiac biopsies are performed on days 7–10 and weeks 2, 3, 4, 6, and 8 and thereafter at 3, 4, 6, 8, 10, and 12 months. Additional biopsies are undertaken if clinically required.

Acute infection

Infectious episodes are defined as clinically evident infectious diseases that require treatment and are usually confirmed with positive culture tests and/or histological evidence.

Cardiac allograft vasculopathy

Cardiac allograft vasculopathy (CAV) is diagnosed as any degree of abnormality on coronary angiography. Coronary angiography is routinely performed 2 years after transplant. If the 2-year angiogram is normal it is repeated at year 4 and yearly thereafter. If the

Table 1 Patient characteristics

	Group 1 (donor > 49 years)	Group 2 (donor < 49 years)	*P*-value
Number of patients	35	365	
Recipient gender (M:F)	31:4	310:55	0.25
Recipient age (years), mean (SD)	51 (5.9)	49 (9.7)	0.08
Donor gender (M:F)	18:17	249:116	< 0.001
Donor age (years), mean (SD)	54 (3.1)	30 (10.6)	< 0.001
Preoperative diagnosis			
Ischaemic heart disease	16 (45.7)	186 (50.9)	= 0.07
Cardiomyopathy	14 (40)	166 (45.4)	
Other	5 (14.2)	18 (4.9)	
Ischaemic time (min), mean (SD)	189 (63.1)	180 (59.2)	0.39
Length of overall stay (days), mean (SD)	27 (9.3)	27 (13.0)	1.00
ICU stay (days), median (interquartile range)	2 (1–3)	2 (1–3)	0.54

2-year angiogram shows any stenosis it is repeated yearly to monitor the progression of disease.

Statistical analysis

Background characteristics of the two groups were summarized using means (standard deviations) or medians (interquartile ranges) for continuous measurements and frequencies, with percentages for categorical data. The two groups were compared using Student's-test and the Mann-Whitney *U*-test or Chi-squared test for contingency tables as appropriate. Actuarial survival and freedom from CAV rates were calculated using the life table method. Curves for the two groups were compared using the Cox-Mantel test. Multivariate log rank tests were used to adjust for potentially confounding factors such as CMV status. Infection and rejection episodes are expressed as the rate per 100 patient days within 3-month periods and compared using linear rate methods.

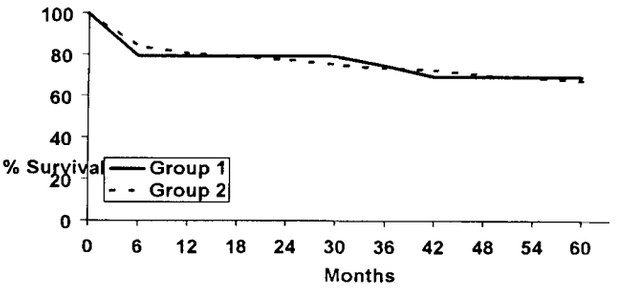

Fig. 1 Actuarial survival (— group 1, older donors; ----- group 2, younger donors). The difference between the groups was not significant

Results

Table 1 shows the characteristics of the patients in the two groups. There were no significant differences between the two groups in terms of recipient age, sex and preoperative diagnosis profile. In addition, donor ischaemic times were similar and postoperative stay in ICU and overall length of stay were the same. There was a significant difference in the proportion of female donors who made up 49% of older donors and 32% of younger donors.

Survival

Figure 1 shows actuarial survival curves for the two groups. Overall there was no significant difference in survival rates ($P = 0.53$) with 12-month survival rates close to 80% in both groups. During the study period there were 120 deaths; 51 in the first 3 months and 69 thereafter. Of the early deaths, 6 patients (17%) had older donors and 45 patients (12%) had donors less than 50 years ($P = 0.59$). Of the late deaths, 4 (11%) had older donors and 65 (18%) younger donors ($P = 0.84$). Causes of death for the two groups are shown in Table 2.

Of the group 1 deaths within 3 months, 3/6 (50%) were attributable to primary donor organ failure. At autopsy one patient had evidence of left ventricular hypertrophy and in the other two patients no pathology could be found to account for organ dysfunction. Of the groups 2 deaths within 3 months, 6/45 (13%) were attributable to primary donor organ failure. At autopsy none of the donor hearts had atherosclerotic changes demonstrable in the coronary vasculature. The difference was not statistically significant (Fisher's exact test, $P = 0.11$).

Of the group 1 deaths after 3 months, 2 (50%) were due to CAV at 2510 and 1221 days posttransplant, respectively. Correspondingly of the group 2 deaths, 24 (37%) were due to CAV at a mean of 1124 (range 150–2951) days posttransplantation.

Table 2 Causes of death

	Group 1 (donor > 49 years)	Group 2 (donor < 49 years)
Death < 90 days	6 (17%)	45 (12%)
Acute rejection	0	7
Infection	2	14
Organ failure	3	6
Elevated PVR	1	8
Cerebrovascular event	0	3
Pancreatitis	0	4
Sudden cardiac death	0	2
Aneurysm	0	1
Death > 90 days	4 (11%)	65 (18%)
Acute rejection	0	5
Infection	0	10
Organ failure	0	0
Coronary occlusive disease	2	24
Malignancy	0	8
Sudden cardiac death	0	4
Cerebrovascular event	0	4
Pancreatitis	0	2
Coronary artery disease	0	1
Aneurysm	0	1
Unknown	2	6
Total	10/35 (28.5%)	110/365 (30.1%)

Rejection

The rates of rejection were recorded at 3-monthly intervals for the two groups for the first year after operation. In the 35 patients from group 1 entering the first 3-month interval there were 38 events (1.4 events per 100 patient days). In the 365 patients in group 2 entering the first 3-month interval there were 496 events (1.63 events per 100 patient days). These differences were not statistically significant. There were no deaths from acute rejection in the group 1 patients while seven deaths in group 2 were attributable to acute rejection during this period. Beyond 3 months, there were no deaths from acute rejection in group 1 and five deaths from acute rejection in group 2.

Infection

The rates of infective episodes were recorded and compared for the two groups in the first 3 months after operation. In group 1 patients there were 14 infective episodes in the first 3 months in 35 patients (0.52 per 100 patient days) and in group 2 patients there were 193 infective episodes in the first 3 months in 365 patients (0.64 per 100 patient days). This difference was not statistically significant. Infection was the cause of death in 2 patients (5.7%) in group 1 and in 24 patients (6.5%) in group 2.

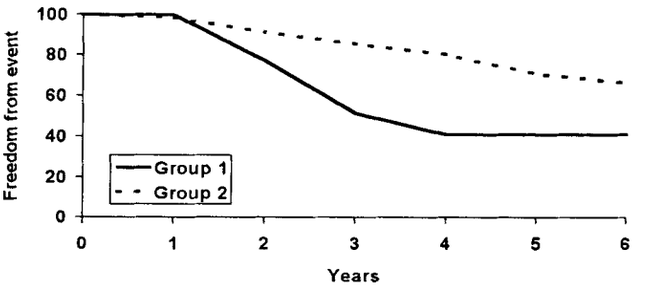

Fig. 2 Actuarial cardiac allograft vasculopathy (— group 1, older donors; ---- group 2, younger donors). The difference between the groups was significant ($P < 0.005$)

Cardiac allograft vasculopathy

Surveillance coronary angiography was commenced at 2 years after transplantation. Significant graft atherosclerosis was found in 22% (5/26) of group 1 and 7% (18/272) of group 2 at 2 years. This difference was statistically significant ($P < 0.005$). Beyond 2 years there were insufficient numbers of patients undergoing angiography for further analysis to be carried out. Figure 2 compares actuarial CAV between the two groups.

Discussion

Older donor age has traditionally been seen as a barrier to organ donation and as a risk factor for development

of CAV [12, 13]. Indeed we were unwilling at our centre to accept hearts from older donor aged more than 49 years until 1988 for this reason. This study was undertaken at a time when the demand for the scarce number of donor hearts available is increasing. Despite UK figures [1] that show a 12% increase in the number of cardiac donors aged more than 41 years between 1988 and 1995, the donor pool has not expanded sufficiently rapidly to meet the requirements of transplant centres.

It must be recognized that since 1988 our policy regarding older donors has developed on a case by case basis. Allocation of hearts from donors over the age of 49 years has been on the basis of recipient match and need rather than recipient age. This is in contrast to the policy at several centres at which a policy of allocating older organs to older recipients has been pursued [6–9, 14]. With this in mind, research at a number of centres into the effect of donor age on morbidity and mortality has given encouraging data [5–7, 15].

In this study our 1- and 5-year survival in recipients of older donor hearts is comparable to our other patients and to that reported by other centres [6, 9, 15]. Several studies have looked at the effect of using older donors. Comparison is made difficult by the fact there is no consensus on what constitutes an "older donor". Mulvagh et al. [5] studied a group of patients who received hearts from donors over 35 years (35–49 years) of age and compared them with the results using younger donors. There was no significant difference in survival, coronary artery disease or left ventricular function between the two groups. The older donor hearts were used in older recipients. Ibrahim et al. [15] studied a group of 40 patients receiving hearts form donors over the age of 40 years (range 40–62 years) and found no effect of donor age on outcome. Schuler et al. [9] reported their experience of using hearts from donors older than 35 years (range 36–54 years) and reported no difference in survival, ventricular function or coronary artery disease.

The impact of donor age on CAV remains contentious. Neither Mulvagh et al. nor Luciani et al. [6] were able to demonstrate a correlation between age and accelerated graft atherosclerosis, but McGiffen et al. [13] and Gao et al. [12] in relatively small studies found that older donor age may be a significant predisposing factor for the development of coronary disease in the transplanted heart. Our results suggest a significant difference in the prevalence of CAV between the two groups on surveillance coronary angiography at 2 years posttransplant. There was a greater proportion of CMV antibody-positive donors in the older donor group but the association between donor age and allograft vascular disease persisted after adjusting for CMV status in multivariate analysis. While we did not carry out intravascular ultrasound examinations in our patients, we do not believe the message would have changed significantly. Our study was limited by a relatively short duration of follow-up in the recipients of older donor hearts which makes analysis of the long-term sequelae of allograft vascular disease difficult. Further follow-up of these patients is needed to assess the impact of older donor organs on long-term survival.

We conclude that there is a need to maintain an open mind with regard to the use of hearts from older donors and that assessment of these donors on a case by case basis is essential. Where donor coronary angiography is feasible, it will obviously help decision making. We concur with the conclusions of Pflugfelder et al. [7] and Ibrahim et al. [15] who recommend extra vigilance when selecting donors with risk factors such as increased age. Nevertheless, we feel that increasing demand for cardiac transplantation will inevitable lead to the use of older donors. Careful follow-up and analysis of data from larger numbers of patients may define the risks and benefits of expanding the donor pool in this way.

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