Early donor management increases the retrieval rate of hearts for transplantation in marginal donors†

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Received 14 September 2013; received in revised form 15 January 2014; accepted 18 February 2014

Abstract

OBJECTIVES: Organ donations continue to fall, failing to meet the clinical requirements for heart transplantation. Furthermore, the pathophysiology of brain stem death including hormonal and inflammatory changes may lead to significant donor heart injury. Early donor management may potentially alleviate these changes and therefore increase the number of available hearts for transplantation. We aimed to investigate whether early management of borderline donors can increase the heart retrieval rate.

METHODS: Between September 2011 and February 2013, we performed early donor management of 26 potential heart donors in the intensive care units of the respective donor hospitals. At the time of referral donors were considered as borderline based on high-dose inotrope requirements, history of hypertension and cardiopulmonary resuscitation. Our management protocol included insertion of a pulmonary artery catheter and performance of cardiac output studies, weaning noradrenaline and commencing arginine vasopressin, and administration of tri-iodothyronine, methylprednisolone and insulin. Our primary end-point was donor heart acceptance, depending collectively on the results of cardiac output studies, cardiac contractility and coronary artery patency at the time of retrieval operation.

RESULTS: We retrieved 14 (56%) borderline hearts after donor management (Group A) with a 30-day survival rate of 86%. Twelve (44%) organs were declined due to poor heart function (n = 8; 66.7%; P < 0.001) and/or palpable coronary artery disease (n = 4; 33.3%; P = 0.018) (Group B). The mean age of Groups A and B was 42.77 and 47.78 years, respectively (P = 0.19). Most of the female donors, i.e. 10 (83%), were declined, and only 4 (27%) were accepted (P = 0.005). Majority of patients in both groups (Group A: 71.4%; n = 10; and Group B: 66.7%; n = 8) were on high-dose noradrenaline (>0.08 μg kg⁻¹ min⁻²) at the time of donor offer. Group A had a mean cardiac output of 6.29 and 3.09 l/min for Group B (P = 0.01). A positive smoking history was present in 28.6% (n = 4) and 33.5% (n = 4) in Groups A and B, respectively (P = 0.793). Cardiopulmonary resuscitation was performed on 3 (21.4%) patients in Group A and 2 (16.7%) in Group B (P = 0.759). A history of hypertension was present in 7.1% (n = 1) of the Group A and 33.3% (n = 4) of the Group B donors.

CONCLUSIONS: In our study, we were able to retrieve more than half of the potential heart donors as a result of early active donor management without impacting on the post-transplant recipient outcome. Early active donor management may assist in increasing the number of heart transplantations, thus warranting further investigation.

Keywords: Heart transplantation • Organ donor • Donor management • Early donor management

INTRODUCTION

Heart transplantation is an established treatment option with excellent long-term outcomes in patients with end-stage heart failure. However, donor organ shortage remains a major problem and there is an imbalance in the supply and the demand [1, 2] for donor hearts. Changing donor demographics with an increasing number of older donors, who may have comorbid conditions, may further contribute to this imbalance in Western Europe, and this problem is exaggerated in the UK. This leads to an increase in waiting list mortality [3]. Furthermore, not all donor referrals materialize to successful organ retrievals as assessment of the donor in the operating theatre does not allow adequate time for donor optimization, which may in turn lead to poor retrieval rate. Accepting a marginal donor graft may also increase the risk of development of primary graft dysfunction (PGD) following transplantation. Recipient centres are most likely to turn down such an organ due to the increased risk of PGD.

The pathophysiology of brain stem death (BSD) includes haemodynamic, hormonal and inflammatory changes leading to cardiovascular instability and poor organ perfusion that may result
in donor organ injury [4]. The hormonal changes after brain stem death usually include drop in the circulating level of cortisol, insulin, thyroxine (T₄) and tri-iodothyronine (T₃) [1]. It has also been shown that excessive catecholamines used for haemodynamic support of the patients prior to brain death have a depressant effect on the heart [5]. As a result many potential heart donors do not meet the criteria for donor selection. There is a window of opportunity that exists from the time of confirmation of brain death to irreversible damage to all organs. During this period, attention to detail and optimization may improve organ function, thereby increasing the retrieval rate. Early donor management with hormone replacement therapy including steroid, T₄ and vasopressin can alleviate post-BSD hormonal and inflammatory changes and therefore improves donor organ function and increases the number of available hearts for transplantation [4,5].

Our aim in this retrospective study is to investigate whether early donor management of marginal donor hearts can increase the retrieval rate without affecting the post-transplant outcome on the recipients.

MATERIALS AND METHODS

Study design

In the UK, each transplant unit is responsible for heart retrieval within its specified zone [6]. Traditionally, the retrieval team is sent out once all the organs are offered and accepted, and a theatre time set at the donor hospital. As this process of donor assessment does not allow adequate period for donor management, we started a consultation process with the local/zonal hospital intensive care units (ICUs). After obtaining the support of the NHS Blood and Transplant (NHS-BT), North West intensive care society in the UK and the local clinical lead for organ donation (CLOD), we introduced the concept of ‘early donor management in the ICU’. It took 6 months of consultation to get acceptance by the local hospitals to initiate this process. Our team included a fully trained transplant fellow accompanied by a specialist nurse in organ retrieval (SNOR). The retrieval team carried with them all necessary equipment and consumables required to institute donor management. Following initiation of optimization, either the SNOR or the fellow continued the management and stayed with the donor until retrieval.

We retrospectively analysed all potential donor heart offers between September 2011 and February 2013 to the Transplant Unit at the Wythenshawe Hospital, Manchester. We received 86 offers of heart donors. All offers fulfilled the following criteria: local retrieval zone, within 2 h drive, age between 16 and 65, consented for organ donation, available information about the cause of brain death, medical history, comorbidity, haemodynamic state and inotropic support, results of blood investigations and blood gases, ECG and chest X-ray. Offers from donors with a history of ischaemic or valvular heart disease, poor left ventricular (LV) function (ejection fraction <30%) and active infection were turned down as per the inclusion criteria (Table 1).

Assessment and donor management

After gathering all relevant information, the team attended the marginal donor to initiate early management in the ICUs at their hospitals. Our management protocol includes insertion of pulmonary artery catheter to measure the intracardiac pressures and cardiac output studies. Following that all donors received T₃ (4 µg as a bolus and then infusion at 0.3 µg/h), methylprednisolone 15 mg/kg and insulin infusion 1 unit/h (blood sugar maintained between 6 and 10). We aggressively weaned off noradrenaline and other inotropes after starting arginine vasopressin (1 unit bolus and then infusion at 0.5–5 units/h). Intravenous fluids as well as diuretics were given on an individual basis guided by the central venous pressure and urine output. Blood transfusion was used if donor haemoglobin was <10 g/dl.

We continued our active management in the ICU until the time of retrieval operation. The details of the protocol have been published before [1]. In summary, the aim of our active management is to achieve a cardiac index >2.5 l/min/m², central venous pressure and pulmonary capillary wedge pressure <12, mean arterial pressure between 65 and 85 mmHg, and systemic vascular resistance from 800 to 1200 dyn/cm/s. Cardiac output and haemodynamic studies were repeated prior to retrieval. The final decision for donor acceptance was after intraoperative assessment. After sternotomy, the heart was assessed for chamber hypertrophy, palpated for any coronary artery disease and visually assessed for contractility and dilatation.

Statistics and end-points

The primary end-point of our study was the acceptance and suitability of the donor heart for transplant that depended also on the intraoperative findings of coronary disease and heart contractility. The secondary end-point was the improvement of cardiac output and haemodynamic state after commencement of the management.

We divided the marginal heart donors into two groups; Group A, where we could retrieve the hearts, and Group B, where the hearts were not usable and were not retrieved.

Statistical analysis was done using SPSS, version 20.0. P-values were calculated by two-tailed Student’s t-test and Pearson’s χ² tests. P-values <0.05 were considered significant.

RESULTS

During the study period we received 86 heart offers, of which we initially accepted 51 (64%) and refused 35 as they were outside the inclusion criteria (Table 1). The donor details and their outcomes have been demonstrated in Figure 1.

Demographics

Twenty-five of these 51 (49%) donors were non-marginal heart donors who did not undergo early management. The remaining

<table>
<thead>
<tr>
<th>Table 1: Donor inclusion criteria</th>
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<tbody>
<tr>
<td>(1) Age &gt;16 or &lt;65</td>
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<tr>
<td>(2) No history of ischaemic or valvular heart disease</td>
</tr>
<tr>
<td>(3) No major thoracic trauma</td>
</tr>
<tr>
<td>(4) Confirmed permission for heart donation</td>
</tr>
<tr>
<td>(5) No active infection</td>
</tr>
<tr>
<td>(6) In our local zone within 2 h drive</td>
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</tbody>
</table>
26 of the 51 (51%) were considered as marginal organs, either because the donor was on high inotropic support, or had a history of hypertension or episodes of cardiopulmonary resuscitation for cardiac arrest or a combination of any of those factors, for which we conducted early donor management. The 26 marginal heart donors were divided into two groups based on whether the hearts were retrieved (Group A) or not retrieved (Group B). The donor demographic parameters for the marginal group were presented in Table 2.

The mean age of Groups A and B was 42.77 and 47.78 years, respectively ($P = 0.19$). There was no significant difference in smoking history between groups, 28.6% ($n = 4$) of Group A, and 33.5% ($n = 4$) of Group B ($P = 0.005$). Cardiopulmonary resuscitation for cardiac arrest was performed on 3 (21.4%) patients in Group A and 2 (16.7%) patients in Group B ($P = 0.285$). Only 1 (7.1%) donor in Group A was hypertensive, while 4 (33.3%) donors of the declined group were having high blood pressure; however, this was not statistically significant. Most patients (Group A: 71.4%; $n = 10$; and Group B: 66.7%; $n = 8$) were on high-dose noradrenaline ($>0.08 \mu g \text{kg}^{-1} \text{min}^{-1}$) at the time of donor offer.

The donors were managed for a total duration of $3.5 \pm 2.42$ h in the ICU prior to retrieval. The duration of management was significantly longer for Group A retrieved donors ($4.95 \pm 2.2$ h) compared with Group B non-retrieved donors ($1.77 \pm 1.3$ h; $P = 0.002$).

**Heart retrieval rate and post-transplantation outcome**

We retrieved 14 (54%) of the 26 borderline hearts after donor management. From the standard non-marginal donors, 14 of 25 hearts were retrieved and transplanted (56%), while 11 were rejected after intraoperative assessment. There was no significant difference in the number of hearts retrieved between the two groups ($P = 0.88$).

The 30-day post-transplantation survival rate for the recipients who had received the hearts from the marginal donors was 86% (12/14 survived). This does not differ from the recipients who had received the hearts from the non-marginal donors (11/14...
survived, 79%; $P = 0.62). We noted in our study that most of the female donors, i.e. 10 (83%), were declined and only 4 (27%) were accepted ($P = 0.005).

Haemodynamic data and operative findings

Haemodynamic studies at the beginning of management and the ones prior to retrieval showed improvement in cardiac output and reduction in systemic vascular resistance especially in the retrieved group, while the other parameters remained nearly stable. Group A (retrieved hearts) had a mean cardiac output of 6.29 l/min, while that for Group B was 3.09 l/min (declined hearts); $P = 0.01$. The donor haemodynamic parameters are presented in Table 3.

All those 14 donors had good biventricular contractility and no palpable coronary lesions. Of the 12 unusable heart donors, 8 were declined due to poor function (66.7%; $P < 0.001) and 4 due to palpable coronary artery disease (33.3%; $P = 0.018) (Table 4).

DISCUSSION

The physiological changes after brain death can lead to instability and organ injury, which results in decrease in donor numbers [7]. These changes include haemodynamic instability, endocrine abnormalities, hypothermia, coagulopathy, pulmonary dysfunction and electrolyte imbalances [7]. Brain death and increased intracranial pressure might be associated with bradycardia [8], which is followed by increased sympathetic stimulation and marked vasoconstriction, which leads to increase in systemic vascular resistance and tachycardia, the phenomenon called ‘catecholamine storm’ [9, 10]. After this storm the sympathetic tone decreases, which results in vasodilatation that leads to organ hypoperfusion, including the heart [11].

Norepinephrine is the commonly used vasopressor to treat post-brain death hypotension that happens due to a vasoparetic phenomenon, which is cardiotoxic at the same time [12]. The use of norepinephrine has been further demonstrated to be associated with initial organ non-function after heart transplantation [13]. A significant decrease of vasopressin levels may worsen hypotension [14, 15], while vasopressin replacement was shown to conserve haemodynamic stability and decrease the need for catecholamines [16]. After BSD there is commonly a drop in the circulating levels of cortisol, insulin and T4. T3 may also decrease along with normal T4, low thyroid-stimulating hormone levels and elevated reverse T3, which may lead to the ‘sick euthyroid syndrome’. T3 was shown to improve the contractile performance of the depressed heart after preceding high-dose epinephrine [17]. Moreover, the inflammatory process and the hyperglycaemia noted post-brain death due to drop in mentioned hormones levels have been reported to be attenuated by methylprednisolone and insulin infusion, respectively [6]. According to these physiological changes, it can be concluded that haemodynamic instability does not necessarily mean primary cardiac dysfunction. Therefore, the donor hearts especially from the marginal ones should be assessed according to load-independent indices of cardiac function. Early donor management has been reported to improve the cardiac performance in potential heart donors [4], which in consequence, increases the number of the transplantable hearts from the pool of donors [1].

**Table 3: Haemodynamic studies results**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (retrieved hearts) (N = 14)</th>
<th>Group B (declined hearts) (N = 12)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP 1</td>
<td>75 ± 18</td>
<td>78 ± 35</td>
<td>0.57</td>
</tr>
<tr>
<td>MAP 2</td>
<td>73 ± 27</td>
<td>72 ± 38</td>
<td>0.95</td>
</tr>
<tr>
<td>CVP 1</td>
<td>09 ± 4</td>
<td>05 ± 2</td>
<td>0.86</td>
</tr>
<tr>
<td>CVP 2</td>
<td>08 ± 3</td>
<td>07 ± 4</td>
<td>0.52</td>
</tr>
<tr>
<td>SVR 1</td>
<td>1153 ± 87</td>
<td>1312 ± 149</td>
<td>0.53</td>
</tr>
<tr>
<td>SVR 2</td>
<td>965 ± 398</td>
<td>1187 ± 167</td>
<td>0.71</td>
</tr>
<tr>
<td>PCWP 1</td>
<td>11 ± 3.0</td>
<td>7 ± 4.6</td>
<td>0.97</td>
</tr>
<tr>
<td>PCWP 2</td>
<td>7 ± 5.1</td>
<td>13 ± 2.1</td>
<td>0.03</td>
</tr>
<tr>
<td>CO 1</td>
<td>4.2 ± 1.4</td>
<td>3.0 ± 2.4</td>
<td>0.58</td>
</tr>
<tr>
<td>CO 2</td>
<td>6.2 ± 2.5</td>
<td>3.1 ± 3.3</td>
<td>0.01</td>
</tr>
</tbody>
</table>

MAP: mean arterial pressure; CVP: central venous pressure; SVR: systemic vascular resistance; PCWP: pulmonary capillary wedge pressure; CO: cardiac output.

**Table 4: Results after the final assessment**

<table>
<thead>
<tr>
<th></th>
<th>Group A (retrieved hearts) (N = 14)</th>
<th>Group B (declined hearts) (N = 12)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor left ventricle</td>
<td>0</td>
<td>8 (66.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0</td>
<td>4 (33.3%)</td>
<td>0.018</td>
</tr>
<tr>
<td>Cardiac output (mean) l/min</td>
<td>6.29 ± 2.54</td>
<td>3.09 ± 3.38</td>
<td>0.01</td>
</tr>
</tbody>
</table>
More than 25% of the heart donor offers we received were either on high-dose inotropes, had a history of cardiac arrest upon the last admission, or a history of hypertension. Consequently, they were considered as marginal hearts for transplant and deemed to be unsuitable by standard criteria and, on initial offer, a majority of them could have been turned down by the recipient units. With our early donor management protocol, which includes hormone replacement therapy, management of fluid balance and inotropes, the heart function and the haemodynamic state improved significantly and we managed to retrieve more than 50% of those hearts and transplant them successfully, and there were only 2 cases of in-hospital mortality among those 14 retrieved hearts. A literature review shows that hormone replacement therapy and aggressive haemodynamic management post-BSD increase the rate of conversion and the graft survival [2]. In a large retrospective study, 701 of 10 292 potential donors received hormone replacement therapy that contributed to a statistically significant increase in the number of transplantable hearts by 4.7% [4].

About two-thirds of declined hearts in our study were rejected because of poor heart contractility, which suggests that echocardiography is important in the pre-donation assessment. A randomized controlled trial of 66 patients showed that normal LV function on echocardiography predicts haemodynamic suitability for transplant, and more than half of the subnormal ones showed improvement after management, and this suggested that both echo and pulmonary artery cardiac output study should be used routinely [18]. The remaining one-third of those hearts in this study were rejected because of palpable coronary artery disease (CAD). Unfortunately, in the UK, routine coronary angiography is not performed on donors and the retrieval surgeons have to use the subjective method of palpating coronary arteries to rule out any CAD. This is mainly due to the lack of availability of catheter labs in most of the smaller district general hospitals and a major proportion of UK donors come from such smaller centres. Routine donor screening with coronary angiography has been shown to pick up 7% of patients with severe CAD who otherwise would have been unidentified by the traditional method of palpation [19]. Screening by coronary angiography in donors over the age of 40 years can identify significant CAD and the reduction in the number of abandoned transplant runs due to the identification of CAD by the retrieval surgeon can compensate the cost of performing angiography [20].

Although the role of T3 infusion on multiorgan donors to improve donor heart function has been reported to be not effective [1], its influence in hypothyroid donors and its effect in the recipient post-reperfusion have not been studied yet. For these reasons, we still continue to use T3 infusion for all multiorgan donors in the UK. Many studies investigated the outcome of donor–recipient sex matching and the effect on survival [21]. We noted in our study that 83% of the declined hearts were from female donors; this needs to be further investigated. On multivariate analysis, none of the parameters, including gender, demonstrated any significant difference in predicting transplant usability of the heart.

Finally, machine perfusion is an established option for organ preservation in kidney transplantation, but its role in cardiac transplantation is still under investigation and its effect remains unproven. In contrast, our approach to donor management is extremely simple and, by concentrating on our efforts to optimize the donor after BSD, we have demonstrated that the heart retrieval rate can be increased without impacting on the recipient outcome. Although this process of sending out a team early to the donor hospital is labour intensive and has operational difficulties, it is still, we believe, a better, more physiological and less expensive option. As our aim during optimization is to maintain normal homoeostasis, it should also be beneficial not only for cardiothoracic organs but also for all other organs retrieved for transplantation. As Western Europe and the UK are faced with an increasing number of older donors, this may be one of the options to keep the heart transplantation activity with a good outcome.

In summary, our study demonstrated that early active donor management improved the suitability of potential donor hearts for transplant and increased the pool of donor hearts. Following the successful implementation of our strategy, the cardiothoracic transplant advisory group (CTAG) in the UK has recently started the ‘UK Scout Pilot project’. The same protocol has been used to optimize all the heart donors in the UK in all other transplant units. The result of this project is eagerly awaited.

**Study limitations**

We recognize that our study is retrospective and has a relatively small sample size. However, it still shows the importance of giving attention to detail and optimizing the basic physiological parameters in the donor to salvage over half of marginal donors. This should definitely increase not only the quantity of donor hearts, but also the quality of organs transplanted, thereby reducing the incidence of PGD. In spite of the extensive experience of our team, we do recognize that intraoperative assessment of heart contractility could be quite subjective, and so we are training our staff to use the echocardiogram routinely in donor assessment.

**ACKNOWLEDGEMENTS**

We acknowledge Joanne Hasan from the Transplant Unit Audit Department for her help in collecting recipient outcome data, and we are also grateful to all our Specialist nurses in organ retrieval for their contribution towards making early donor management in the ICU a success.

Conflict of interest: none declared.

**REFERENCES**


APPENDIX. CONFERENCE DISCUSSION

Dr J. Dinkhuysen (São Paulo, Brazil): We have applied a new strategy for heart transplantation: we use a bicalval bipulmonary implantation technique in all patients; in about 35 cases we did this with the heart beating in normothermia. We first did the aortic anastomosis and recovered the beatings, and the ischaemic time was between 40-60 minutes. The results have improved and the implant times are not different when compared with cardioplegia. This work is published in the Brazilian Journal of Cardiovascular Surgery.

Dr M. Antunes (Coimbra, Portugal): Can I ask you a question? These are usually multorgan donors. What was the impact on other organ retrieval? Do you have any information about that?

Dr Abuanzeh: We focused our study mainly on the heart, but we are in the process of doing a multicentre study to investigate whether this process could affect the renal and liver transplants as well. In this study, we didn’t have complete information about the other organs, just an input from the other centres that all the organs that were taken during this early donor management were transplanted successfully in their centres, but we didn’t investigate what exactly the effect was on the liver and kidneys.

Dr Antunes: Another figure that impressed me, or which I found strange, is that in period number 1, out of 66 or 64% of accepted donors, you could only retrieve 33%, that means half of them. Why was there a subsequent rejection rate?

Dr Abuanzeh: No. We could retrieve 33% of the 64.

Dr Antunes: Yes.

Dr Abuanzeh: Mainly they either had poor LV function or coronary artery disease. We know that the brainstem difficulty affects the contractility of the heart. There are many studies talking about the drop in thyroxine. Other studies talk about the catecholamines as cardiodepressants. And usually in most of the hospitals they use catecholamines to support the haemodynamic status of patients before declaring them as brainstem dead patients. So we noticed that, and there are many studies talking about catecholamines, especially the noradrenaline and adrenaline are really cardiodepressant. So that’s why before replacing the catecholamines and improving the function of the heart, most of them, they were declined.

Dr R. Venkateswaran (Manchester, UK): I am one of the co-authors of the paper. Historically in the United Kingdom, unfortunately, the donor management was the part that was most neglected. As soon as a donor is identified, it gets the least priority because it is another bed for another patient waiting to occupy the intensive care unit.

So the weaning of noradrenaline, optimizing the preload, reducing the afterload, so the basic things; it’s not rocket science. Unfortunately, it is not done. That’s why sending a dedicated fellow who basically does all these things using invasive parameters, it made the difference, and you can clearly see that our transplant numbers have almost doubled since the introduction and with a great result.

And now UK wide, it’s been adopted. And the UK Scout pilot project started in April 2013, so all the transplant units send their teams to manage donors early in their zone.

Dr W. Brinkman (Dallas, TX, USA): I may have missed it in the talk, but did you report that there has been a change in your outcomes in the recipients with the change in your donor allocation strategy?

Dr Abuanzeh: Yes, I may have missed that.

Dr Abuanzeh: Yes. We studied the in-hospital stay of the patients. We focused on the mortality rate. All of them were successfully transplanted. Just one patient passed away because of sepsis and multiorgan failure. Otherwise, they did very well.

Dr Brinkman: Any longer term follow-up?

Dr Abuanzeh: The programme started recently, so we don’t have data about long-term follow-up.

Dr S. Jaber (Amman, Jordan): Why don’t you do echocardiography before retrieving the heart? It would define and give you more information. I mean, it’s mandatory I think.

Dr Abuanzeh: Exactly. Before starting this programme, we were not doing echocardiography, and we noticed that most of the patients or many of the patients, two-thirds, were refused because of poor LV function. So we are adding the echo to be part of our pre-donor assessment, I mean, pre-offering the patient for donation.