Outcome of hearts with cold ischemic time greater than 300 minutes.  
A case-matched study

Fotios A. Mitropoulos*, Jonah Odim, Daniel Marelli, Kalyani Karandikar, David Gjertson, Abbas Ardehali, Jon Kobashigawa, Hillel Laks

Heart Transplant Program, University of California, Los Angeles Medical Center, Los Angeles, CA, USA

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Abstract

Objective: Expansion of potential donor pool may be facilitated by using cardiac allografts with long ischemic time. Early graft failure and potential relation to transplant coronary artery disease remains a concern. We sought to evaluate outcomes of heart transplantation in recipients of donor allografts with prolonged ischemia time. Methods: The study group consisted of 46 (mean age, 52 years) consecutive patients at UCLA from 1994 to 2002 that underwent heart transplantation with ischemia time > 300 min. This group was compared to a case-matched control group of 46 (mean age, 51 years) patients identified from our database during this time frame for the following factors: UNOS status, congenital heart disease diagnosis, preop inotropes, pretransplantation creatinine > 1.5 and recipient age. Primary endpoint was mortality and secondary were rejection rate and transplant coronary artery disease. Allografts were perfused and stored in cold University of Wisconsin solution. Results: Mean donor ages of the study and case-matched control group were 34 ± 15 and 34 ± 14 years, respectively. Mean ischemia times were 388 (range, 301–600 min) and 173 (range, 96–236 min), respectively. The death incidence rate per 100 transplants per year was 9% for the study group and 7.4% for the matched group (Z = 0.50). Thirty-day mortality for the study and case-matched groups were 4.3 and 2.1%, respectively (P = 0.9). Late mortality was 16.5 and 18.5%, respectively (P = 0.9). The risk of death after 30 days was 7.5 and 5.8%, respectively (P = 0.5, log-rank). One-year incidence of acute cellular rejection in the study and case-matched groups were 2 and 4.5% (P = 0.36), respectively. One-year incidence of transplant coronary artery disease in the study and case-matched groups were 4.3 and 5.4%, respectively (P = 0.68). Conclusions: Donor hearts with ischemia time greater than 300 min provide comparable early and intermediate outcomes given judicious and careful donor and recipient matching and our current techniques of myocardial preservation and modified reperfusion.

Keywords: Prolong ischemia time; Cardiac allograft; Orthotopic heart transplantation

1. Introduction

The success of orthotopic heart transplantation (OHT) for patients with end-stage heart disease in combination with the limited donor availability has resulted in a dramatic increase of the waiting lists and waiting times. At UCLA, efforts to shorten waiting times have focused on expanding the donor pool by broadening the standard donor criteria to include: older donors, high-dose inotropic support (dopamine > 10 μg/kg per min), hearts with coronary artery disease (CAD), left ventricular hypertrophy (LVH), depressed ejection fraction (EF), suspected myocardial contusion, recent cardiac arrest, reused donor hearts, donors with hepatitis B or C positive and prolonged ischemia time [1,2]. The usual accepted time limit for organ preservation in human heart transplantation is up to 4-5 h. Prolonged donor ischemic times (PIT) have been associated with need for higher inotropic support within the first 48 h postoperatively, depressed postoperative left ventricular ejection fraction (LVEF), right ventricular dysfunction, prolonged hospital stay, increased graft dysfunction, higher morbidity and early mortality [3-8]. Preservation with the University of Wisconsin solution (UW) and the improvement in myocardial reperfusion techniques have resulted in less myocardial injury as a result of ischemia and acceptance of non-standard donor hearts [9,10].

There is paucity of clinical data in the literature evaluating the impact of prolong ischemia time (> 300 min) on the immediate mortality, incidence of transplant coronary artery disease (TCAD) and rejection rate in a sizeable series of adult patients with long-term follow-up. In this study, we reviewed the outcome of patients that received cardiac allografts with cold ischemia time (CIT) greater than 300 min and compared with a case-matched group of patients who received allografts with CIT < 240 min.
2. Patients and methods

2.1. Study population

2.1.1. Matched case-control study

Between 1994 and 2002, 48 patients who received cardiac allografts with cold ischemic time greater than 300 min were identified from our database at UCLA Medical Center. Forty-six patients comprise the long ischemia time (LIT) study group (group A), since two patients were excluded (one due to the ventilator status and the other one due to the lack of sufficient follow-up data at that time). Twelve patients were transplanted during the first half of the study period and 34 over the second half.

They were matched with 46 randomly selected controls (group B) whose donor’s ischemia time was less than 240 min identified from our database during the same time frame for the following factors: UNOS status, congenital heart disease diagnosis, preoperative use of inotropes, pretransplantation serum creatinine > 1.5 and recipient age (Table 1).

The Twentieth Official Adult Heart Transplant Report from the Registry of the International Society for Heart and Lung Transplantation identified the following risk factors for mortality within 1 year for adult heart transplants performed between '01/1999 and 06/2001' [11].

<table>
<thead>
<tr>
<th>Factor</th>
<th>Cardiac allograft ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 300 min</td>
</tr>
<tr>
<td>N</td>
<td>46</td>
</tr>
<tr>
<td>UNOS status I</td>
<td>32 (70%)</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Intravenous inotropes</td>
<td>14 (30%)</td>
</tr>
<tr>
<td>Pretransplant serum creatinine &gt; 1.5</td>
<td>11 (24%)</td>
</tr>
<tr>
<td>Recipient age, mean (SD)</td>
<td>52 (17)</td>
</tr>
</tbody>
</table>

Since these factors are so significantly associated with mortality, elimination from the study groups or random matching of the patients for these factors would allow the identification of the other factors (such as the donor ischemia time) and their impact on outcome.

2.1.2. Exclusions

Since all the recipients in the long ischemia group were not on the ventilator, ventilated recipients were excluded from the matching process. Patients less than 16 years of age were excluded. Patients with inadequate follow-up were excluded as well.

2.2. Listing and donor allocation

Candidates for orthotopic heart transplantation are discussed on a weekly multidisciplinary conference and accepted by a consensus opinion. Donors and recipients are matched for ABO blood type compatibility and size. Panel reactive antibodies (PRA) are routinely performed. Patients with greater than 10% PRA undergo prospective cross-matching. If broadly positive (> 25%) and/or previous positive prospective crossmatch, preoperative plasmapheresis and/or treatment with intravenous immunoglobulin (IVIG) are performed in an effort to reduce the level of circulating antibodies.

2.3. Preservation and operative technique

Thyroid hormone infusion (T4) was started several hours prior to organ retrieval. Donor hearts were perfused with UW solution at a constant pressure of 60 mmHg over a 7-10 min period (8-10 cm³/kg), and were transported immersed in hypothermic UW solution at 4 °C. At the time of implantation, cold plasmalyte solution was infused into the left ventricle to aid in topical cooling and de-airing. Reperfusion consisted of leukocyte-depleted, aspartate/glutamate enriched, warm blood cardioplegia solution (Buckberg solution) for a total of 3-4 min followed by warm blood cardioplegia for 4-10 min at a pressure of 60 mmHg. Bicaval anastomosis was used for the right atrium. Postoperatively patients receive inhaled nitric oxide if the mean pulmonary artery pressure was greater than 25 mmHg and left atrial pressure < 12 mmHg [12].

An experienced cardiac surgeon with expertise in thoracic organ procurement is usually involved. Frequently, the procurement team spends considerable time in the field optimizing the donor.

2.4. Immunosuppression

Methylprednisolone (7 mg/kg) is given at the time of reperfusion and again upon separation from the cardiopulmonary bypass followed by a dose of 125 mg every 12 h for three doses. Oral prednizone is initiated at 1 mg/kg per day and tapered to 0.1 mg/kg per day. For patients with few rejections at 6 months complete weaning from steroids is attempted and has been achieved in ~70% of selected recipients.

Since 1998 Mycophenolate mofetil at a dose of 1000 mg twice a day and since 2001 Tacrolimus at a dose of 1 mg/kg have been the standard postoperative immunosuppressive regimen. Induction therapy is not utilized routinely.

Sample spleen and lymph nodes are obtained from all donors at procurement and lymphocytes are tested against serum from recipients. Right heart catheterization and myocardial biopsies are performed weekly for the first month, every 2 weeks for 2 months, monthly for 3-6 months and bimonthly up to the first year post-transplant. TCAD is monitored with annual coronary angiography and intravascular ultrasound. All patients are discharged on pravastatin and aspirin as well [13].
2.5. Statistical analysis

Data analysis was performed using STATA (Stata Corporation, College Station, TX). Indicated data are reported as mean±SD. Differences in matched proportions were compared using McNemar’s and Fisher exact tests. All tests were two-sided and a significant P-value was defined less than 0.05.

Survival and transplant coronary artery disease free rates were analyzed with standard Kaplan-Meier actuarial techniques along with a log-rank P-value. Early mortality was defined as death within 30 days post-transplant. Late mortality was defined as any death occurring later than 30 days post-transplant. Hospital mortality was defined as any death that occurred while the patient was still in the hospital following his original OHT procedure.

3. Results

3.1. Donors

Mean donor ages of the study and case-matched control group were 34±15 and 34±14 years, respectively. Mean donor ischemia time was 388 (range, 301–600) and 173 (range, 96–236 min), respectively. The donor causes of death in the LIT study group (n=40) and the case-matched control group (n=46) included blunt head trauma in 35 vs 30%, drug overdose in 3 vs 0%, atraumatic intracranial bleeding in 30 vs 37%, gunshot wounds in 28 vs 22%, and due to other causes in 4 vs 8%, respectively (Table 2). There was no statistical significance between these two groups (P=0.80 by Fischer’s exact).

3.2. Recipients

Group A consisted of 46 patients with a mean age of 52 years that received cardiac allografts with cold ischemia time >300 min. This group was compared to case-matched control group of 46 patients with a mean age of 51 years that received allografts with IT <240 min.

The mean value of the preoperative mean pulmonary artery pressure was 22.1 mmHg (range, 8–49) for the study group and 23.1 mmHg (range, 15–38) for the case-matched group (P=0.29).

Thirty-day mortality for groups A and B were 4.3 (2/46) and 2.1% (1/46), respectively (P=0.9). Late mortality was 16.5% (7/43) for group A and 18.5% (8/43) for group B (P=0.9).

The death incidence rate per 100 transplants per year was 9% for the study group and 7.4% for the matched group (P=0.5). The risk of death after 30 days was 7.5% for the study group and 5.8% for the matched group (P=0.5, log-rank).

The conditional 1-year incidence of biopsy-proven (Grade 3A or greater) acute cellular rejection for groups A and B was 2 and 4.5%, respectively, and was not statistically significant (P=0.35%). Kaplan-Meier estimates of actuarial rejection-free survival rates are shown in Fig. 1.

The prevalence of TCAD was 1.1% for group A vs 2.3% for group B (P=0.27). The 1-year incidence rate of TCAD in the LIT and case-matched groups were 4.3 and 5.4%, respectively (P=0.68).

Kaplan-Meier estimates of actuarial TCAD-free survival rates are depicted in Fig. 2.

Three-year survival for group A was 76.1 and 78.2 for group B. The cause of death for group A is shown in Table 3.

4. Discussion

The current era of heart transplantation has demonstrated improved survival for all age groups. This has been
attributed to a variety of factors such as better allograft preservation, perioperative use of nitric oxide, improved and standardized immunosuppressive protocols, appropriate use of antibiotics and antiviral agents for prophylaxis and treatment of infection, as well as the use of statins to decrease the severity of TCAD. [1,2,13,14]

Whether these improvements can allow prolongation of the ischemia time in an effort to counteract the shortage of donors remains a critical question that seeks a timely answer.

The use of allografts with ischemia times greater than 4.5 h has been associated with a need for higher inotropic support within the first 48 h, reduced postoperative left ventricular ejection fraction, right ventricular function, prolonged hospital stay, increased graft dysfunction, and higher morbidity and early mortality [3–8]. It is believed that although LIT could negatively affect the postoperative course the long-term outcome might not be adversely affected. Available clinical data in the literature are conflicting and limited by small number of patients without significant long-term follow-up. Endpoints that are of significant clinical relevance and pertinent to the use of are the immediate and long-term mortality, incidence of TCAD and rejection rate.

Since 1992, we have used cardiac allografts with IT greater than 300 min in 46 patients. Being located in Los Angeles we have traveled and procured organs from the Northeast and Southeast United States, Hawaii, and as far as Alaska. This policy has resulted in an average of six extra grafts per year.

Kawauchi et al. found that pediatric patients who received donor hearts with ischemia time greater than 4 h when compared to a group with IT <4 h demonstrated diminished cardiac function in the first postoperative week (primarily posterior wall diastolic movement) with functional recovery after the second week [15]. Serum cardiac myosin light chain levels were also higher during the first week in the LIT group but the difference was not evident beyond the first week in either group [16]. Of note was the fact that inotropic support was required for 5.3 ± 3.7 days for the long ischemia time group vs 3.9 ± 3.3 days for the short ischemia time group (not statistical significant).

In our series, the mean duration of inotropic support was 3.4 days for the study group and 3.3 days for the matched group (P=0.35). Nitric oxide was required in 4/46 and 3/46 patients, respectively.

Ischemia–reperfusion injury or extensive cytokine release could explain the temporary myocardial dysfunction [7]. Since the phenomenon of postoperative myocardial dysfunction is temporary, oversized allografts could provide a solution for this problem.

Briganti et al. compared a group of patients with IT less than 240 min to a group with IT 240–300 min and to a group with IT greater than 300 min. They found a statistical significant decrease in left ventricular function in the greater than 300 min group compared with the less than 200 min group (P=0.01), which did not translate into long-term compromised functional recovery [8].

Scheule et al. compared pediatric patients with IT >8 h to those with IT less than 90 min. They found no difference in the length of inotropic support, rejection episodes, TCAD, hospital readmissions or late outcome. The duration of cardiopulmonary bypass was longer in the group with the long IT which they attribute to planned longer reperfusion time [17]. The Loma Linda group over the years has made a considerate effort to prolong ischemia times with significant results [15-17].

Although we included patients with congenital heart disease in our study age less than 16 years was an exclusion criterion. Our analysis included primarily adult population.

Multi-institutional studies concluded that long IT was an independent risk factor for early mortality post-transplantation (P=0.0003, relative risk 1.19), and advocate cautious extension of criteria for donor acceptance but with an anticipated greater risk in the presence of diffuse echocardiographic wall motion abnormalities and long anticipated ischemic time, particularly in older donors given inotropic support. The adverse effect of a longer ischemic time was most notable after 4 h (1-month survival rate 71% for more than 4 h vs 85% for less than 4 h, P=0.0003) [5,6].

On the other hand, Pflugfelder et al. studied 219 transplant patients and found that long ischemia time (>3 h) did not negatively affect 1-year survival [18].

Del Rizzo reports on 128 patients with IT greater than 4 h and found no effect on survival. Cardiac allograft ischemia time did have an effect on survival if the donor age was >50 years and was used into urgent recipients [4]. These data

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Table 3  
Cause of death in the long ischemia time group

<table>
<thead>
<tr>
<th>No.</th>
<th>Diagnosis</th>
<th>Ischemic time</th>
<th>Survival</th>
<th>Follow-up</th>
<th>Donor status</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dilated CM</td>
<td>425</td>
<td>53.8</td>
<td>52.9</td>
<td>Standard</td>
<td>Other</td>
</tr>
<tr>
<td>2</td>
<td>Ischemic CM</td>
<td>398</td>
<td>36.8</td>
<td>36.2</td>
<td>Non-standard</td>
<td>Graft failure–MSOF</td>
</tr>
<tr>
<td>3</td>
<td>Ischemic CM</td>
<td>515</td>
<td>2.1</td>
<td>2.1</td>
<td>Non-standard</td>
<td>MSOF</td>
</tr>
<tr>
<td>4</td>
<td>Ischemic CM</td>
<td>498</td>
<td>0.1 (2 days)</td>
<td>0.1</td>
<td>Non-standard</td>
<td>Infection</td>
</tr>
<tr>
<td>5</td>
<td>Valvular CM</td>
<td>383</td>
<td>23.8</td>
<td>34.9</td>
<td>Non-standard</td>
<td>Hepatic failure</td>
</tr>
<tr>
<td>6</td>
<td>Dilated CM</td>
<td>389</td>
<td>24.3</td>
<td>29</td>
<td>Standard</td>
<td>Other</td>
</tr>
<tr>
<td>7</td>
<td>Ischemic CM</td>
<td>324</td>
<td>1.2</td>
<td>1.2</td>
<td>Standard</td>
<td>Graft failure–rejection</td>
</tr>
<tr>
<td>8</td>
<td>Viral</td>
<td>461</td>
<td>15.3</td>
<td>15.3</td>
<td>Standard</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>9</td>
<td>Ischemic CM</td>
<td>312</td>
<td>3.8</td>
<td>3.8</td>
<td>Standard</td>
<td>Graft failure–rejection</td>
</tr>
<tr>
<td>10</td>
<td>Dilated CM</td>
<td>521</td>
<td>5.7</td>
<td>5.7</td>
<td>Non-standard</td>
<td>Infection</td>
</tr>
<tr>
<td>11</td>
<td>Alcoholic CM</td>
<td>313</td>
<td>0.2</td>
<td>0.2</td>
<td>Non-standard</td>
<td>Graft failure–rejection</td>
</tr>
</tbody>
</table>

CM, cardiomyopathy; MSOF, multiple system organ failure; survival and follow-up are in months, ischemia time in minutes.
illustrate that donor risk factors should be considered additive.

Mullen et al. from Canada compared two groups with IT less and greater than 4 h and found no significant difference in the 30-day, 90-day or actuarial survival between these two groups (P = 0.014, 0.027 and 0.27, respectively) [19].

The small number of patients and incomplete follow-up flaws single institution studies. On the other hand, multi-institutional registries compile data from centers with wide range of volume, individual institutional policy, experience and variability.

In an effort to answer these questions we design the study in such a way so that the ischemia time will be the only factor under question by comparing the study group to case-matched group and an unmatched group from the same database during the same time period [14].

In our study, the 30-day and late mortality for the study and case-matched groups were 4.3 (2.46) vs 2.1% and 16.5 vs 18.5%, respectively (P = 0.9 for both variables). The death incidence rate per 100 transplants per year was 9 and 7.4%, respectively (P = 0.5). The risk of death after 30 days was 7.5 for the study group and 5.8% for the matched group (P = 0.5, log-rank). None of these values reached statistical significance.

It has been hypothesized that ischemia plays a pathogenetic role in cardiac allograft vasculopathy [20]. Data from a rat cardiac allograft model showed that progression to chronic vasculopathy is principally an immunologic process accelerated by an ischemic insult to the allograft and mediated in part by T cells and macrophages [21].

The group from Columbia in a very elegant study compared four groups based on their donor ischemia time and found that prolong IT did not adversely affect long-term outcome and that there was no significant difference in freedom from TCAD among the four groups [14]. Although the group of patients with IT > 300 was small (17 patients) they conclude that it can be safely extended to 5 h [14].

In our series, 1-year conditional incidence of biopsy-proven (Grade 3A or greater) acute cellular rejection in the groups A and B were 2 and 4.5%, respectively (P = 0.36). The 1-year incidence of TCAD was 4.3 and 5.4%, respectively (P = 0.68). These data support the hypothesis that in the current era long ischemia time does not affect the incidence of rejection or TCAD.

In summary, we can conclude that donor hearts with ischemia time greater than 300 min provide comparable early and intermediate outcomes given judicious and careful donor and recipient matching and our current techniques of myocardial preservation and modified reperfusion. We believe that donor hearts with prolong ischemia time should not be a contraindication for OHT. Careful evaluation of these allografts should be undertaken, taking into consideration the left ventricular ejection function, presence of LV hypertrophy, coronary anatomy, donor age, stability of the donor, UNOS status and co-morbidities of the recipient since the presence of more than one donor or recipient risk factors appear to have an additive effect.

Acknowledgements

The authors would like to acknowledge the contribution of all the members of the UCLA Heart Transplant team. In particular, we would like to express our deepest appreciation to the transplant coordinators for their hard work.

References


Appendix A. Conference discussion

Dr. A. Pavie (Paris, France): We know everything of the UCLA transplantation program, but we are a little frustrated after your presentation because you didn’t give us any data on the acute choice of such donor. You increase the ischemia time, but probably you choose an excellent donor using other criteria. We were also pleased to know how you weaned the patient from extracorporeal circulation, with which drugs and at which doses do you need sometimes cardiac assistance.

No time for reply.