The effect of a donor’s history of active substance on outcomes following orthotopic heart transplantation

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Abstract

Objective: To review the short-term and long-term outcomes of using heart donors with a history of substance abuse. Methods: Retrospective chart review was performed of heart recipients over an 8-year span. Charts provided demographics, mechanisms of donor death, and history of substance abuse. Additionally, charts were quarried for post-operative echocardiography and coronary angiogram results, serologic tests, and survival. Results: Between January 1997 and December 2005, 689 heart transplants were performed, 150 (21.8%) had a history positive for substance abuse. The mean donor age was 34.5 years (range 16—62 years); most common cause of death was traumatic head injury in 87 donors (58.0%). Most patients (76.0%) had a history of 1 ppd smoking for ≥5 years, 89 (59.3%) had a history of inhaled drug use, 75 (50.0%) alcohol abuse, and 12 (8.0%) intravenous drug use. At a mean follow-up of 8.3 days, 68 hearts (45.3%) had normal, 36 (24.0%) mild, 23 (15.3%) moderate, and 10 (6.7%) severe ventricular dysfunction by echocardiography. Furthermore, 110 hearts (73.3%) had normal coronaries, 20 (13.3%) had mild, and 2 (1.3%) had evidence of moderate coronary artery disease (CAD) on coronary angiogram at a mean follow-up of 9.8 months (range 0.1—43.7 months). All recipients who received organs from known hepatitis B, or C positive, donors converted to positive serologies. Overall post-transplant survival for the group was 89.8% at a mean follow up of 43.3 months (range 5.8—108.6 months). Conclusions: A history of donor substance abuse does not have a negative impact on overall survival, cardiac function, risk of transplant associated coronary artery disease (TCAD). In patients who receive organs from virus positive donors, the risk of viral conversion is high, but survival seems not to be influenced.

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1. Introduction

In 1995, work by Copeland [1] produced what most transplant centers recognize as the traditional criteria for an appropriate heart transplant donor. However, because of the large disparity between the number of patients listed and the number available of donors, some have added to these criteria marginal donors in hopes of expanding the donor pool [2].

But, despite the available information associated to the positive impact these marginal donors have on the donor pool, and post-transplant outcomes, some centers continue to decline donors with good functioning grafts secondary to a history of substance abuse. Therefore, we conducted the following study in hopes of determining the impact substance abuse had on graft function, transplant coronary artery disease, risk of viral transmission, and survival following orthotopic heart transplantation.

2. Methods

2.1. Patient selection

A retrospective chart review was performed on all patients who underwent an orthotopic heart transplant at Cleveland Clinic between January 1997 and December 2005. Through this review we identified all donors who had a past history of substance abuse. A donor with a history of substance abuse was defined as that individual who either drank more than two alcoholic drinks (i.e. 24 oz of beer, or 2 oz of hard liquor) per day for more than a year, or smoked one pack of cigarettes per day for more than 5 years, or had a...
history of habitual marijuana, cocaine, methadone, opiate, or intravenous heroin use. The history of illegal substance abuse was obtained through family member interviews. Unfortunately, the amount of time using these drugs could not be determined for obvious social reasons. However, all patients in this subgroup had positive toxic screens at the time of transplantation.

Following the identification of these donors, recipient charts were used to obtain donor demographics, donor cause of death, risk of donor-to-recipient viral transmission, post-transplant echocardiograms, surveillance coronary angiograms as well as short- and mid-term outcomes.

2.2. Technique of donor organ procurement

All procurements were performed by a dedicated procurement team. Donors were selected based on our standard criteria which includes ejection fraction >40%, no significant motion wall abnormalities, no valvular pathology, and no evidence of significant coronary artery disease as determined by either coronary angiography, history, or direct palpation. Upon arrival to the donor institution, this team proceeded to review all data pertaining to the donor.

As an institutional policy, all donors require a pre-procurement echocardiogram. If the interpretation of this study was difficult, an intra-operative echocardiogram was requested, and performed by the hosting institution when possible. Pre-procurement coronary angiography was performed only when the donor was 40 years of age or older.

Once all data were reviewed, donor hearts were inspected visually and by palpation. After this initial evaluation, findings were immediately communicated to the transplant surgeon.

At the time of procurement, an antegrade cardioplegia needle is inserted into the ascending aorta. The ascending aorta is cross-clamped, and 2 l of cold modified crystalloid cardioplegia solution is used to arrest the heart. Following donor cardiectomy, the organ is closely inspected for any pathology. Subsequently, the donor heart is placed in a sterile container, and transported in ice in a portable cooler.

Once the organ arrives to our institution, it is removed from the container, and passed onto the operating field. Orthotropic heart transplants were performed by either a bicaval or bi-atrial technique depending on surgeon preference.

2.3. Immunosuppressant therapy

Plasmapheresis and OKT3 were used selectively in the pre-transplant period as a means of desensitizing patients with an elevated panel of reactive antibodies, or as induction therapy. All patients received 1 g of methylprednisolone at transplantation. Post-transplant plasmapheresis was used selectively in those patients with a worrisome anti-HLA antibody panel. Maintenance immunosuppression consisted of a three-drug combination of cyclosporine, azathioprine, and prednisone, with mycophenolate mofetil largely replacing azathioprine since 1997.

2.4. Post-transplant echocardiogram

All patients underwent post-transplant echocardiography prior to discharge. This test is routinely ordered on post-transplant day 5. For this study, we only reported on this predischARGE echocardiogram in hopes of avoiding any changes in graft function which might be associated to graft dysfunction secondary to rejection in the post-transplant period.

Ventricular function was reported by an experienced echocardiographer who was blinded to the history of the donor. Graft function was defined as normal if ejection fraction was greater than 55%, mild dysfunction if ejection fraction ranged between 45% and 54%, moderate dysfunction if ejection fraction ranged between 30% and 44%, and severe dysfunction if ejection fraction was less than 30%.

2.5. Surveillance coronary angiography

Coronary angiograms were conducted as part of a surveillance protocol aimed at identifying and treating transplant-associated coronary artery disease (TCAD). Each patient underwent a baseline coronary angiogram at 1 month following transplantation, with a yearly angiogram thereafter. The severity of TCAD was defined as (1) trivial TCAD if <10% intraluminal disease was detected at coronary angiography; (2) mild TCAD if 10–20% intraluminal disease was detected in a single epicardial vessel, or 10% disease in more than one epicardial vessel; (3) moderate TCAD if 30–40% disease was detected in a single epicardial vessel, or 30% disease in more than one epicardial vessel; or (4) severe TCAD if >50% disease was detected in a single epicardial vessel, or 40% disease in more than one epicardial vessel.

2.6. Statistics

Values are presented as the absolute number of events detected.

Percent of the total are presented in parentheses. Ranges are provided for ordinal variables. Each abused substance is reported rather than the individual who used it. We realize that most substance abusers use more than one substance, and this might have a cumulative effect on the outcomes of grafts rather than if one substance were used. The Social Security Death Index was queried to determine survival. If this query failed to confirm a patient’s death, then the individual was assumed to be alive. This study was conducted with the written approval of the Cleveland Clinic’s Institutional Review Board.

3. Results

3.1. Substance abuser demographics

Between January 1997 and December 2005, 689 orthotopic heart transplants were performed at our institution. Among these, 150 (21.8%) hearts were used from donors with a history of active substance abuse. The mean age of these donors were 34.5 years (range 16–62 years).
The most common cause of death among substance abuse donors was traumatic head injury (58.0%). Other causes of death within this group included 26 (17.3%) intracranial cerebral hemorrhages, 21 (14.0%) anoxic brain injuries, and 15 (10.0%) subarachnoid hemorrhages. One donor (0.7%) died as a result of an acute cerebral embolism.

3.2. Distribution of substances abused

Most donors in this study abused tobacco (Fig. 1). Among the 150 donors with an active history of substance abuse, 114 (76.0%) smoked tobacco habitually and 75 (50%) donors abused alcohol. With regards to marijuana use, 78 donors (52.0%) used this drug habitually, and another 41 (27.3%) donors inhaled cocaine. Intravenous heroin use was found in 9 (6.0%) donors, and 4 (2.7%) donors had a history of active methadone use. A history of opiate abuse was found in 11 (7.3%) of donors.

Overall, approximately 66% donors used more than one substance. This included 44 donors who abused two substances, 36 donors who abused three drugs, 16 donors who abused four drugs, 2 donors who abused five drugs, and 2 donors who habitually used six drugs.

3.3. Outcomes

3.3.1. Short-term outcomes

The overall 30-day post-transplant survival was 98.0%. Only three patients died during this period. Causes of death included one from graft dysfunction, and two from septic shock. Interestingly, all of these patients were bridged on a ventricular assist device. At a mean follow-up of 43.3 months, the overall survival rate was 89.8%.

The prevalence for either hepatitis B or C was 6% (9 out of 150). A total of six patients converted to hepatitis C secondary to the transplant. All donors associated to these events were known to be hepatitis C carriers. Only one (16.5%) recipient died at follow-up secondary to hepatitis C. However, all other recipients are alive and without any evidence of liver dysfunction at the most recent follow-up.

Among recipients who converted to hepatitis B, all are well at follow-up and none has developed active hepatitis.

3.3.2. Predischarge ventricular function

At a mean of 8.3 days (range 0—44 days) post-transplant echocardiograms were obtained in all patients. Left ventricular function was categorized as normal in 68 (45.3%) of recipients (Fig. 2). Only 36 (24.0%) recipients had mild graft dysfunction at discharge; however, 23 (15.3%) of recipients had moderate and 10 (6.7%) had severe graft dysfunction at discharge. The substance abuse history of donors whose predischarge echo showed moderate graft dysfunction included tobacco, alcohol, marijuana, and cocaine. Similarly the substances abused by those donors with severe dysfunction were tobacco, alcohol, and marijuana. Among this latter subgroup of donors, two donors used two drugs, one used three drugs, and one used four drugs.

3.3.3. Risk of TCAD

At a mean follow-up of 9.8 months (range 0.1—43.7 months), 110 (73.3%) recipients had no evidence of TCAD on coronary angiography (Fig. 3). There were 20 (13.3%) recipients who developed mild TCAD, and 2 (1.3%) who were found to have moderate TCAD. Among these later two recipients, substances abused by one donor included tobacco, alcohol, and cocaine, while the other simply abused tobacco.
4. Discussion

Expanding donor selection criteria have been viewed by some as a potential solution for the severe organ shortage afflicting allo-transplantation [2]. Extended donor criteria are aimed at increasing the donor pool by using marginal donors who would under conventional transplant guidelines be declined as potential organ donors. In heart transplantation, these donors include older aged donors [3–8], patients with a history of coronary artery disease [9–12], patients with a history of viral infection (i.e. hepatitis B or hepatitis C) [2,13,14], and patients with a social history of substance abuse [15–18]. However, the wide use of this strategy has been slow to gain popularity due to reports suggesting that using these donors might have a negative impact on post-transplant outcomes. For instance, chronic use of alcohol has been shown to impact post-heart transplant graft function and survival. Freimark et al. [15] reported the post-heart transplant outcomes between two groups of patients depending on whether the donor was or was not an alcoholic abuser. This study showed that heart transplant recipients who received an organ from an alcohol abuser had significantly lower 1- and 2-year survival when compared to the non-alcoholic group. The authors postulated the presence of subclinical cardiomyopathy may be a contributing factor associated to these results. In another study published by Houyel et al. [18], patients receiving hearts from chronic alcoholics had a greater risk of early graft dysfunction compared to a non-alcoholic abuser cohort. However, this did not translate into a survival disadvantage. Conversely, our work does not support these findings. Most patients in this study had good functioning grafts at the time of discharge, and only 7% had evidence of severe graft impairment. Furthermore, survival in this group was excellent (89.6%) at a mean follow-up of nearly 4 years.

Cocaine use has been associated to similar findings in the literature. While one report based on a single case report warns about the potential implications on outcomes associated to using donor hearts from a patient with a history of cocaine abuse [17], a large single-center study raises questions about these concerns [16].

There is ample evidence to support the association of tobacco abuse and cardiovascular disease. Ironically, there is scant data supporting the deleterious effects of this combination on outcomes following heart transplantation. Reasons for this might lie on the fact that most donors with a strong history of smoking, but no drug abuse, are older and undergo coronary angiography as part of their donation work up. If coronary artery disease is found, these donors are not considered suitable by most transplant programs and are discarded. Our own policy is similar, and we seldom consider these donors for transplantation. However, while our results do support the safety of using donors with a history of tobacco abuse, we also acknowledge that these donors are younger, and have not been exposed to the long-term effects of tobacco. In addition, while we do not routinely consider angiography on donors younger than 40 years of age, if a donor has a strong history of smoking and we were to palpate calcium on the coronaries of the donor heart at the time of procurement, we would automatically turn down that organ offer.

One of the major concerns about donors with a history of substance abuse lies in the transmission of viruses. Previous reports have linked the seropositive hepatitis B or C donor to both an increased risk of accelerated coronary artery vasculopathy and death [13,14]. In our own experience, hepatitis B was not associated to a greater risk of death at follow-up; however, one death occurred in a patient known to convert to hepatitis C. At our latest follow-up, it did not seem evident that transmission of these viruses had any effect on graft function or transplant coronary artery disease. We do acknowledge our numbers are small and that a longer follow-up may be needed to confirm these findings.

In conclusion, a history of substance abuse associated with a potential heart transplant donor does not have a significant influence on overall post-heart transplant survival, graft function, or risk of TCAD. Furthermore, the prevalence of viral infection can be low, in a carefully selected donor population. However, care must be taken in underestimating the impact of hepatitis C on outcomes following transplantation, as this strategy might be reserved for those patients in which all other alternatives are futile. Nevertheless, these data should encourage other centers to use this group of donors at the time of organ offer.

References

Appendix A. Conference discussion

**Dr C. McGregor (Rochester, Minnesota, USA):** In your patients who had hepatitis C-positive donors, you said they converted, I think, but only one of them died. Clearly, we need to know what the follow-up is and how many of those patients have viral C hepatitis who are still alive.

**Dr Shea:** I would like to take the opportunity to speak a little about hepatitis C donors in this case. We're talking about the case that a hepatitis C-positive donor is transplanted into a hepatitis C-negative recipient. At our institution, historically, there have been 30 of these transplantations performed. In 1999 Ong published, in Hepatology, results following 28 patients at our institution who received hepatitis C-positive organs. None of these were treated pre-transplant for hepatitis C. Twenty-three of the 28 patients were found post-transplant to have active viremia by RT-PCR. Seven of the 23 went on to develop hepatitis C liver disease, 3 of which developed chronic hepatitis and 4 developed acute fibrosing cholestatic hepatitis. And risk factors identified for developing the acute fibrosing cholestatic hepatitis were the use of MMF and increased viral load, leading to decreased survival.

In 2004, Yamani published in the Journal of Heart and Lung Transplantation that there was increased risk of mortality and a three times risk associated with moderate to severe post-transplant vasculopathy.

And then Kathleen Lake reported at the ISHLT that hepatitis C-positive donors do not lead to the statistically significant difference in survival.

So at our institution, we first obtain informed consent from the patients and make sure that they understand the risks, alternatives, and benefits associated with receiving a hepatitis C donor. And then there is no use of interferon-gamma, they follow the post-transplant viral load by RT-PCR, and they avoid the use of MMF.

So typically, at our institution, hepatitis C donors are not used. And the reasons for that are because patients are aware and concerned about developing cirrhosis and hepatocellular cancer. And there's also the issue of surgeons' bias to preserving the use of hepatitis C-positive donor organs for status 1-A recipients.

**Dr McGregor:** So that it begs the question of your summary slide a little bit.

**Dr S. Kucuker (Ankara, Turkey):** Are these patients receiving any antiretroviral drug therapy during the course of their follow-up?

**Dr Shea:** Well, I guess I can speak a little bit about hepatitis B where therapy is used. In a hepatitis B-positive donor, all recipients are immunized against hepatitis B. And the recipient is premedicated prior to transplant with diphenhydramine acetaminophen. Hepatitis B immune globulin is given IV intraoperatively and post-operatively for 7 days. The patient is monitored post-transplant by a quantitative hepatitis B viral DNA analysis, liver function tests, hepatitis B surface antigen, and hepatitis B surface antibody for 3 months regardless of quantitative donor HPV DNA results. Additionally lamivudine is given daily if the quantitative HPV DNA results are positive.