Allosensitization in bridge to transplant Novacor left ventricular assist device patients: analysis of long-term outcomes with regard to acute rejection and chronic allograft vasculopathy

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Received 5 September 2007; received in revised form 27 March 2008; accepted 31 March 2008; Available online 23 May 2008

Abstract

Background: The true relevance of allosensitization in patients benefiting from left ventricular assist device (LVAD) as bridge to transplant (BTT) is still debated. Available registry data referred to numerous devices precluding LVAD-specific analysis. Therefore, we studied all patients with Novacor LVAD prior to transplantation. Methods: From 1985 to 2006, 37 Novacor LVADs were implanted as BTT, with 30 patients surviving to transplantation (81%). Post-LVAD sensitization was determined for anti-HLA-class I and class II IgGs. Study endpoints were overall survival and/or graft loss, >3A cellular rejection and chronic allograft vasculopathy (CAV). The results from LVAD patients were compared to non-LVAD primary heart transplant recipients (n = 318). Results: After LVAD insertion, 5 out of 27 patients available for analysis developed anti-HLA antibodies (18.5%). The mean anti-HLA titer after Novacor LVAD implantation was 14% [SD 31]. Actuarial 5- and 10-year patient/graft survival for LVAD and non-LVAD transplant recipients were 73% and 55%, and 70% and 55%, respectively (p = NS). Overall prevalence of rejection >3A was 23.3 % (LVAD group) and 18.9% (non-LVAD group) (p = NS). At follow-up, the respective incidence of CAV was 8% (LVAD group) and 32.4% (non-LVAD group) (p < 0.01). However, mean follow-up was significantly different for LVAD and non-LVAD patients, 46 vs 90 months (p < 0.001). Conclusion: In this study, allosensitization occurred infrequently after Novacor LVAD implantation. Secondly, analysis of outcome variables shows that Novacor-LVAD BTT patients can anticipate similar survival to non-LVAD patients, thus minimizing the impact of allosensitization after LVAD implantation.

Keywords: Assist device; Transplantation; Rejection; Allograft vasculopathy

1. Introduction

Since the mid 1990s, the number of cardiac transplantations performed each year keep on declining, mostly because of donor shortage as well as improvement in heart failure patient management. The progressive increase in recipient age, and this recurrent cumulative imbalance between request and offer, has led to a lengthening on the waiting list [1], thereby increasing the need for LVAD support as bridge to transplant therapy (BTT) for evolving class NYHA III and IV patients [2].

Left ventricular assist devices, due to their specific physical properties, their blood-contacting surface and the frequent need for blood product support [3,4], have been shown to be responsible for allosensitization through up-regulation of the immune system and an increased antibody production [5,6], though its true impact on transplantation outcome is still a matter of debate [7—13]. Allosensitization can translate into an increase in cellular and/or humoral immunity [5,6], putting the transplant recipient at risk for both acute and chronic rejection.

Since the initiation of our long-term LVAD program, we electively used the Novacor LVAD device (World Heart Corporation, Ottawa, Canada) because of its high reliability, durability and effectiveness in providing mechanical support for end stage heart failure patients [14].

The aim of this study was to analyze our institution's experience in LVAD and non-LVAD primary transplant recipients with regard to patient and/or graft survival, cellular rejection and chronic allograft vasculopathy (CAV), a multifactorial disease in which chronic humoral rejection has been incriminated [15—17].
2. Material and methods

2.1. Study population and sample collection

From 1985 through February 2007, 348 patients underwent a primary cardiac transplantation at the U.C.L. Saint Luc Hospital for end-stage heart failure.

Of those 348 patients, 30 patients (8.6%) had a Novacor LVAD implanted as a bridge to transplant (BTT). The mean duration (SD) of support was 172 (±111) days, and there was a total of 5703 patient-days of support. Survival to transplant was 81% (7 deaths/37 patients). Indeed during the same time period, 7 additional patients had Novacor LVAD implantation as a bridge but died while on support awaiting transplantation. We compared the 30 Novacor LVAD surviving patients to the 318 consecutive non-BTT patients who received a primary heart transplantation during this same period.

Information necessary for the study was collected from the patient operative reports, the hospitalization charts and our transplantation database. All patients are regularly followed at our transplantation clinics and additional information was gathered through contacts with the referring cardiologist. Follow-up was completed from January 2007 until March 2007 and is 100% complete, with a median time of 37 months for LVAD patients and 87 months for non-LVAD patients (p = 0.001).

The Committee on Human Rights in Research (Institutional Review Board) of Cliniques Universitaires Saint-Luc approved this study.

2.2. Selection of variables

Transplantation variables included in the analysis were: recipient’s age, sex, blood group and type of cardiomyopathy, as well as donor’s age, sex and blood group, pre- and post-transplantation anti-HLA antibodies, initially referred to as panel-reactive antibodies (PRAs), and finally immunosuppressive therapy.

Outcome variables analyzed were mortality and/or graft loss (combined end-point), cause of death: graft loss, grade ≥3A cellular rejection and chronic allograft vasculopathy.

2.3. Immunosuppression

All patients received an induction treatment with one course of rabbit anti-thymocyte globulin (3 mg/kg) (RATG, Fresenius AG, Bad Homburg, Germany) administered immediately before transplantation. Additional doses of antithymocyte globulin were administered after transplantation up to day 5 depending upon the absence or presence of early postoperative renal dysfunction. In the early period of our transplantation program, following surgery, patients were initially treated with a conventional triple drug immunosuppressive protocol: cyclosporine (CsA) (3—8 mg/kg/d), azathioprine (2 mg/kg/d) and steroids. From 1995 on, antiproliferative agent has been largely switched from azathioprine to mycophenolate mofetil (MMF), administered orally at a dose of 1 g twice daily. During transplantation and in the early postoperative period, methylprednisolone was started intravenously and a shift to oral administration was done as soon as possible. Since 2000, two major modifications of the protocol occurred: (a) selected patients, especially young patients and female recipients were started on tacrolimus (oral dose of 0.075 mg/kg/bid, adjusted to blood trough levels), and (b) whether on CsA or on tacrolimus, an early steroid withdrawal protocol was initiated (progressive tapering of the oral steroid dose and a wean off at 6 months in the absence of treated rejection episode).

2.4. Detection of anti-human leukocyte antigen (HLA) antibodies

During the first decade of our transplantation program (1985—1995), anti-HLA antibodies were very rarely searched for and in patients in whom allosensitization was suspected, only prospective cross-match with donor lymphocytes and/or splenocytes was performed for donor selection.

Since the late 1990s, panel-reactive antibodies against B and T lymphocytes were almost systematically assessed during the implantation phase of the left ventricular assist device before transplantation. After transplantation though, follow-up measurements were irregularly realized depending both on the pre-transplantation anti-HLA status and/or clinical events. Patient’s sera were first heat-treated to remove immunoglobulin M reactivity, and than tested by complement-dependent cytotoxicity against a comprehensive 65—70 member cell panel of HLA-typed donors selected to represent most of the defined HLA specificities. Positive reactions were quantitatively expressed as a percentage of total T-cell panel using cytotoxicity by standard dye-exclusion assay (PRAs). In the LVAD group, PRA values pre-transplantation were available in 27/37 patients, and in the non-LVAD group, PRA values pre-transplantation were available in 95/318 patients.

Besides conventional PRA measurements, solid phase immunoassays were used to determine the presence of class I and class II antibodies, including the LAT mixed antigen tray (LAT-M) ELISA (One Lambda, USA) and the LAT 1240/240 to determine anti-HLA specificities. In all instances, kit protocols were followed as per manufacturers’ instructions.

Among the entire cohort, 61 patients had post-transplantation sera available for analysis. There were 20/30 LVAD-BTT recipients and 14/318 non-LVAD transplant recipients. From early on, we have set the threshold for allosensitization at the 10% level for PRAs. Therefore, in this study, patients with anti-HLA titers equal or less than 10% were considered not sensitized.

2.5. Endomyocardial biopsies

Routine surveillance endomyocardial biopsies were performed weekly during the first month, every second week for the next 2 months, monthly until month 6, and than every 6 weeks up to 1-year post-transplantation. The grading of the biopsy specimens was done according to the International Heart and Lung Transplantation criteria [18]. High-grade cellular rejection was defined pathologically as grade 3A or 3B.

2.6. Detection of transplant-associated coronary allograft vasculopathy (CAV)

All patients had a protocol coronary angiography at 8—12 weeks after transplantation and afterwards on an annual
basis. With the use of coronary angiography, CAV is usually classified as absent, mild, moderate, or severe according to the amount of stenosis in the most severely affected vessel. In this study, our definition of significant CAV was a lesion greater than 50% of a proximal or mid portion of one major coronary graft vessel [10,19,20]. In order to precisely determine the date of occurrence of graft vasculopathy, all angiographies were serially reviewed and compared with each patient’s prior exam. Patients who died within the first year and those with missing angiography data were not included in the data analysis, leaving overall 273/348 patients with at least two consecutive exams.

2.7. Statistical analysis

Unless specified, continuous variables were reported as the mean ± SD and categorical variables as proportions.

Survival was calculated from the date of transplantation to the date of follow-up (or death/graft loss). For each patient, the date of the first acute cellular rejection grade 3A or greater was recorded as well as the number of rejection episodes. For patients presenting with CAV, the number of days was calculated from the date of transplantation to the first documentation of a significant lesion as described above.

For analysis of descriptive statistics and categorical variables, Chi-square or Fisher’s exact test were used as appropriate whereas for analysis of continuous variables of normal distribution, Student’s t-test was used. Time between events analysis was performed according to Kaplan—Meier method, univariate analysis by the log-rank test and Cox regression model were used to compare these data. The level of statistical significance was set at a p value <0.05. All statistical analyzes were performed with SPSS version 14.0 software (SPSS, Inc., Chicago, IL).

3. Results

3.1. Patient’s features (Table 1)

Between 1985 and February 2007, 348 adults underwent a primary cardiac transplantation at our center. Of those, 30 patients had a LVAD implanted as a bridge, and survived to transplantation, whereas 7 additional patients had Novacor LVAD implantation as a bridge but died while on support awaiting transplantation. During the same period, 318 patients were transplanted without bridge. The demographics of both groups are given in Table 1.

In the LVAD group, 34 of the LVAD patients were male (91.9%), as compared to 249 male (78.3%) in the non-LVAD group. Patients with assist device tended to be slightly younger (mean 45 ± 11 years) than the non-LVAD patient (49 ± 14 years, p = 0.09). The distribution of the recipients’ blood group was similar in both groups. The most frequent etiology of heart failure for patients in the LVAD group was idiopathic dilated cardiomyopathy (52.8%), whereas in the non-LVAD group, the main indication for transplantation was ischemic heart disease (44.2%) (p = 0.17).

The donors’ sex and age were evenly matched in the two groups, as well as the donors’ blood group. Overall, 93% had an identical ABO match, 7% were ABO compatible.

<table>
<thead>
<tr>
<th>Table 1 Demographics</th>
<th>LVAD group</th>
<th>non-LVAD group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n)</td>
<td>37</td>
<td>318</td>
<td></td>
</tr>
<tr>
<td>Recipients sex</td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Male</td>
<td>34 (91.9%)</td>
<td>249 (78.3%)</td>
<td></td>
</tr>
<tr>
<td>Mean age at transplantation (years, SD)</td>
<td>45.0 ± 11.7</td>
<td>49.0 ± 14.0</td>
<td>0.09</td>
</tr>
<tr>
<td>Recipients blood group</td>
<td></td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>A</td>
<td>15 (40.5%)</td>
<td>147 (46%)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>3 (8%)</td>
<td>32 (10%)</td>
<td></td>
</tr>
<tr>
<td>AB</td>
<td>2 (5.5%)</td>
<td>12 (4%)</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>17 (46%)</td>
<td>127 (40%)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>DCM</td>
<td>19 (52.8%)</td>
<td>108 (34.1%)</td>
<td></td>
</tr>
<tr>
<td>ICM</td>
<td>15 (41.7%)</td>
<td>140 (44.2%)</td>
<td></td>
</tr>
<tr>
<td>Median waiting time (days)</td>
<td>98</td>
<td>124</td>
<td>0.28</td>
</tr>
<tr>
<td>Donor sex</td>
<td></td>
<td></td>
<td>0.74</td>
</tr>
<tr>
<td>Male</td>
<td>19 (65.5%)</td>
<td>198 (62.5%)</td>
<td></td>
</tr>
<tr>
<td>Donor mean age (years, SD)</td>
<td>29.7 ± 8.8</td>
<td>32.8 ± 13.1</td>
<td>0.21</td>
</tr>
<tr>
<td>Donor blood group</td>
<td></td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>A</td>
<td>14 (48.3%)</td>
<td>139 (44.0%)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>3 (10.3%)</td>
<td>25 (7.9%)</td>
<td></td>
</tr>
<tr>
<td>AB</td>
<td>1 (3.4%)</td>
<td>6 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>11 (37.9%)</td>
<td>146 (46.2%)</td>
<td></td>
</tr>
<tr>
<td>Year of transplantation</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1985—1995</td>
<td>3 (10.0%)</td>
<td>197 (61.9%)</td>
<td></td>
</tr>
<tr>
<td>1995-ongoing</td>
<td>27 (90.0%)</td>
<td>121 (38.1%)</td>
<td></td>
</tr>
<tr>
<td>Death or retransplantation</td>
<td>8 (26.7)</td>
<td>165 (51.9)</td>
<td>0.008</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Sudden death</td>
<td>1 (12.5%)</td>
<td>31 (22.0%)</td>
<td></td>
</tr>
<tr>
<td>Cardiac related</td>
<td>4 (50%)</td>
<td>15 (10.6%)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>1 (12.5%)</td>
<td>17 (12.1%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (25%)</td>
<td>49 (34.8%)</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>0</td>
<td>29 (20.6%)</td>
<td></td>
</tr>
</tbody>
</table>

As shown in Table 1, both groups were very similar, except for the year of transplantation. All but three patients were implanted with a ventricular assist device after January 1995, whereas 61.9% of the non-BTT group were transplanted before that date.

Median waiting time was 118 days for the overall cohort of patients. Median waiting time was 98 days for LVAD patients and 124 days for non-LVAD patients (log-rank, p = 0.28).

Regarding sensitization, overall, median waiting time was 86 days for pre-transplantation high PRA patients and 132 days for pre-transplantation low/negative PRA patients (log-rank, p = 0.98). In the VAD subgroup, median waiting time was 178 days for pre-transplantation high PRA patients (n = 4) and 98 days pre-Tx low/negative PRA patients (n = 21) (log-rank, p = 0.34)

3.2. Patient/graft survival

Overall survival was similar in LVAD and non-LVAD patients. Death or graft loss (re-transplantation) occurred in eight patients in the LVAD group (26.7%) whereas in the non-LVAD group, 165 patients (51.9%) have either died or been re-transplanted. Causes of death were significantly different between the two groups. Post-transplantation, half the
patients with LVAD died of cardiac-related causes, in the non-BTT group causes of death were sudden death and cardiac-related in 32.6% and secondary to neoplasm in 20.6% (p = 0.02). Patients who died while on support (7 out of 37), were slightly younger (39.7 ± 15.9 years) than those that survived to transplantation, the main cause of death being stroke/intra-craniial bleeding and infection.

The survival curves for both groups are similar (Fig. 1). Actuarial patient/graft survival for the LVAD at 3, 5, 7 and 10 years are 79.4%, 73.3%, 73.3%, and 55%, and the non-LVAD group respectively 75.1%, 69.7%, 65.9% and 55.1% (log-rank, p = 0.67).

3.3. Allosensitization

There was no significant difference between both groups concerning allosensitization before surgery: in the LVAD group 5 out of the 27 patients (18.5%) available for analysis had high PRA (PRA >10%, anti-class I or anti-class II), while 24 patients out of the 95 available in the non-LVAD group (25.3%) were allosensitized before undergoing transplantation (p < 0.47). In the LVAD group, the mean PRA before transplantation was 13.9% (±32.4), and the 23/30 LVAD patients with PRA analysis who were successfully transplanted had a mean PRA level of 10.8% (±28.3), after a mean duration of support of six and a half months. Analysis of PRA levels reveals that anti-HLA titers did not increase significantly neither after VAD implantation nor after transplantation, as shown in Table 2.

3.4. Freedom from 3A rejection (Fig. 2)

The incidence of rejection grade 3A or greater did not differ significantly between the LVAD and non-LVAD group.

There were 7 episodes in the LVAD group (23.3%) and 60 in the non-LVAD group (18.9%). Freedom from 3A rejection at 3, 5, 7 and 10 years was 70.6% at all time points for the LVAD group, respectively 81.4%, 80%, 77.8% and 74.9% for the non-LVAD group (log-rank, p = 0.55) (Fig. 2).

3.5. Freedom from chronic allograft vasculopathy (Fig. 3)

As already stated above, there was a significant difference in the follow-up duration between both groups, the LVAD subgroup having mostly been transplanted after 1995. This being stated, chronic allograft vasculopathy (CAV) developed in 2/30 LVAD patients (8%) and 80/318 patients in the non-LVAD group (31.5%), and freedom from significant angiographic CAV at 3, 5, 7 and 10 years was 100%, 100%, 83.3% and 66.7% in the LVAD group, respectively and 97.8%, 95.2%, 86.9% and 75% in the non-LVAD group (log-rank, p = 0.76).

We further analyzed patients from the two groups transplanted during the same period (1995—2006) and again could not demonstrate any correlation between CAV and LVAD implantation (data not shown).

3.6. PRA pre- and post-transplantation and survival

For the entire cohort, pre-transplantation sera were available in 122 patients, 2 from LVAD patients who died prior to transplantation. Post-transplantation, sera from 61 patients were also available for analysis. There were 20 sera collected in LVAD patients and 41 sera collected from the control group of non-LVAD patients.

As shown in Fig. 4a and b, a pre-transplantation high PRA level was not associated with a decreased survival (log-rank, p = 0.83), but there was a significant association between

Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Age at Tx (years) mean ± SD</th>
<th>Duration of LVAD support (days) mean ± SD</th>
<th>PRA pre-Tx in % mean ± SD</th>
<th>PRA post-Tx in % mean ± SD</th>
<th>Mean difference in PRA (%) HLA Class I</th>
<th>Mean difference in PRA (%) HLA Class II</th>
<th>p value Class I/Class II</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVAD group (27/37 pa)</td>
<td>45.0 ± 11.7</td>
<td>172.3 ± 111.1</td>
<td>4.19 ± 18.5</td>
<td>13.9 ± 32.4</td>
<td>9.72 ± 20.5</td>
<td>7.79 ± 23.9</td>
<td>0.02/0.09</td>
</tr>
<tr>
<td>LVAD group Tx (25/30 pa)</td>
<td>46.2 ± 10.5</td>
<td>190.1 ± 101.5</td>
<td>0.68 ± 2.8</td>
<td>10.83 ± 28.3</td>
<td>10.15 ± 22.3</td>
<td>8.38 ± 25.3</td>
<td>0.00/0.02</td>
</tr>
<tr>
<td>LVAD group no Tx (2/7)</td>
<td>39.7 ± 15.9</td>
<td>96.0 ± 126.1</td>
<td>48 ± 67.9</td>
<td>50 ± 70.7</td>
<td>0.48 ± 6.9</td>
<td>0.39 ± 7.5</td>
<td>0.00/0.00</td>
</tr>
<tr>
<td>No LVAD group (95 pa)</td>
<td>48.2 ± 15.0</td>
<td>N/A</td>
<td>1.72 ± 7</td>
<td>8.42 ± 18.4</td>
<td>6.70 ± 16.7</td>
<td>4.23 ± 15.3</td>
<td>0.04/0.04</td>
</tr>
</tbody>
</table>
patient/graft survival and the appearance of post-transplantation anti-HLA antibodies with a 1-year survival of only 70% for the latter group (log-rank, \( p = 0.005 \)). Among the 10 patients with PRA > 10% postoperatively, 3 patients died shortly after transplantation. Two patients died unexpectedly from sudden death while still on the surgical ward, one with a proven cardiac electromechanical dissociation and the second from a proven humoral rejection (histology and retrospective B and T cell cross-matches), whereas the third died from primary graft non-function.

4. Discussion

In this study comparing Novacor LVAD patients to primary heart transplant recipients, we found that the implantation of a left ventricular assist device was not correlated to any increase in anti-HLA antibody production. In our experience, our unselected LVAD bridge— to transplant patients had an excellent 81% survival rate to transplantation, a rate that compares favorably to recent published series where rates from 49% to 66.7% were reported [10,21].

As in the Baran et al. study [10], our LVAD population was predominantly represented by male (91% and 96%, respectively), reflecting the bias due to the need for space accommodation with this first generation LVAD.

The incidence of sensitization (PRAs > 10%) at any time during the LVAD implantation period prior to transplantation was 18.5% (5/27 patients) and close to the 13% rate recently reported by the Cleveland group [20]. The mean level of anti-HLA class I and class II pre-transplantation were 4.2 ± 18% and 13.9 ± 32% respectively. Such results are very similar to those reported by Baran et al. (mean PRA level: 14.8%), who also exclusively reported on Novacor LVAD patients [10].

We could not demonstrate any difference in pre-transplant sensitization between our LVAD and non-LVAD groups, where an unanticipated 23% rate of high PRAs was found. We have no likely explanation for this figure, which is higher that the 5—10% rate generally found in an immunologically naïve population [20,22].

Importantly, this 18.5% sensitization rate is much lower than the one reported when using other types of devices. Most US studies with the Heartmate LVAD have reported allosensitization rates ranging from 40% to 66% [9,21—23]. One hypothesis for this lack of sensitization is that the texture of the inner surface of the Novacor device does not allow the formation of a pseudo-intima that might contain T cells and dendritic cells, as it has been shown for the Heartmate [24], thus avoiding activation and up-regulation of both T and B cell populations. Because this study did not address specifically the aspect of blood products transfusion, we cannot rule out that differences between blood product transfusion management between US centers and our own center, such as the systematic use of leukocyte-depleted red blood cells and/or platelets obtained from apheresis could have impacted on our comparative low prevalence of sensitization [3,4].

As a direct consequence of this neutral immunogenicity, our Novacor LVAD patients did not suffer an increase in the mean waiting time prior to transplantation.

Analysis of Kaplan—Meier actuarial curve of freedom from rejection \( \geq 3A \) in both LVAD and non-LVAD groups did not reveal any statistically significant difference between the two groups. At 3 years, 29.4% of LVAD patients and 19.6% of non-LVAD patients had experienced at least one episode of rejection \( \geq 3A \). Those rejection rates are lower than the one reported elsewhere [8—10,20,23] and most likely reflect the systematic use of polyclonal antibody induction immunosuppression.

As in the Gonzalez et al. study, we have found that the risk of developing significant CAV was similar for both LVAD and non-LVAD heart transplant recipients [20]. At 7 years post-transplantation, by angiography, 16.9% of LVAD and 13.1% of

Fig. 3. Freedom from chronic allograft vasculopathy (CAV) in LVAD and non-LVAD patients.

Fig. 4. (a) Patient and/or graft survival according to pre-transplantation allosensitization \( (n = 120) \). (b) Patient and/or graft survival according to post-transplantation allosensitization \( (n = 61) \).
non-LVAD patients had developed significant CAV. Our 37 months median time of follow-up in the VAD group does not allow us to discuss this point further and will require a follow-up study. For the entire cohort, our freedom from angiographic CAV at 5 and 10 years were 86.8% and 47.4% and are in agreement with the literature when keeping in mind that mild CAV was recorded as negative in our study [10,20].

Notably, patients with high PRA pre-transplantation had similar patient and/or graft survival than non-sensitized patients. Although Itescu et al. reported an increased incidence of rejection, no information was available on patient outcome in their study [23]. To mention, during that study period, we did not administer any immunomodulatory drugs (intravenous immunoglobulins or cyclophosphamide) before transplantation to any sensitized patients, but a negative prospective cross-match was required for the 28 patients with high pre-transplantation PRA levels (>10%). Our results showing a negative prognostic value on patient/grant survival with post-transplantation patient’s sensitization (10 pa/61 or 16.4%), appears in agreement with Tambour et al.’s recently published study [25] although our experience was limited to a fraction of our cohort. As stated earlier, all our in-hospital deaths in this subgroup were cardiac-related.

Obviously, our study limitations is its retrospective design, the absence of transfusion requirements data, the incompleteness of pre/post sera sampling as well as the lengthy time (more than 20 years) over which this study spans. However, we believe that the accuracy of follow-up data as well as the high percentage of serial angiographic evaluation allows us to safely address the questions of rejection and chronic allograft vasculopathy in this rapidly growing cohort of patients with LVAD implantation as bridge to transplantation. There still remains valuable unanswered questions on the mechanisms and on the true specificity to anti-human leukocytes antigens [21], all of which will be better addressed in multi-institutional prospective studies.

In summary, this study has shown that allosensitization occurred infrequently after Novacor LVAD implantation. Analysis of outcome variables revealed that Novacor LVAD bridge to transplantation patients can anticipate similar long-term survival to non-LVAD patients, without suffering an incremental risk for either severe acute cellular rejection or chronic allograft vasculopathy, thus minimizing the impact of allosensitization after LVAD implantation.

References

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Appendix A. Conference discussion

Dr G. Laufer (Innsbruck, Austria): Are you aware of any different rates in sensitization among the different support devices?

Dr Poncelet: No. In fact, our unit, since the inception of the VAD program, has basically used the Novacor and we have no other devices that we are using, so we have no experience with the others, so that’s why I just reported one device type.

Dr Laufer: Do you have any ideas from the literature about differences?

Dr Poncelet: Well, most of the published studies have been done with the HeartMate, because the American experience is mostly based on the HeartMate I. And so in the manuscript, when I discuss about the rate of sensitization between assist devices, what has been shown in the experimental studies is that if you put polyurethane, which is the inner layer of the HeartMate I, and if you put T cells in contact with the polyurethane, you will have a B & T cell activation. And so that is one of the hypotheses for the high rate of PRAs in the HeartMate I group.

Dr D. Tixier (Paris, France): Maybe I missed it, but what were the results of the crossmatch that you performed before transplant in your two groups?

Dr Poncelet: For the entire cohort, any patient who had a high PRA, greater than 10%, VAD or non-VAD patient, did have a T-cell crossmatch prior to accepting the donor and therefore they were all negative. There were no transplantations across a positive crossmatch.

Dr Tixier: So it’s very difficult to deal with sensitization since we don’t know exactly the targets. As you probably know, the PRA is not any more admitted as a standard to compare the different groups because it’s a very vague evaluation of the sensitization. Wouldn’t you go back, if you still have some sera, to look at the targeted antigens that you have and see if there is any correlation with the donor’s antigen that you transplanted while the antibody is there and the donor’s antigen, then you would be able to compare and to see if there is any difference in survival, if you have an antibody against the antigen. Otherwise it’s a vague figure of sensitization, as you mentioned, either to albumin or to plastic or whatsoever, and it does not help us to understand exactly what is going on and if we can do something to help the outcome of these patients. And how do you explain that you have no differences?

Dr Poncelet: Two points. The first one is with respect to the assist device patients. The problem is that with the increased amount of, let’s say, anti-HLA antibodies that were diagnosed by our hematology laboratory, we were more and more restrictive in the acceptance of potential donors, so that we were fearing that we would increase the time before giving an organ to our assist device patients. So that was one of the primary aims to perform this study.

Now, as you suggested, and it is totally right, our current research manager is focusing on retrieving data on class I and class II HLA antigens both in the donor and the recipient, and we will go back and see whether we can have further information on antibody allospecificity. So that’s the next work to be done.

Dr G. Dellgren (Stockholm, Sweden): You said that you didn’t monitor the risk of humoral rejection. You didn’t do any C4 coloring or similar investigations. However, my guess would be that for patients being sensitized, the risk of humoral rejection is higher than that of cellular rejection. Anyway, those patients that eventually had a rejection, I presume you checked in those if they also had signs of humoral rejection. So did you find any signs of humoral rejection in those patients that rejected?

Dr Poncelet: I must confess that we have not looked into the data specifically, and we can try to go back and see. So far we haven’t done the correlation between the humoral and cellular component of the acute rejection episodes. But it’s a good suggestion. We could do it and see.