Special article


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A B S T R A C T

Introduction and objectives: The purpose of this report is to present the results obtained with heart transplantation since this therapeutic modality first began to be used in Spain in May 1984.

Methods: A descriptive analysis was performed of all heart transplantation performed until December 31, 2010.

Results: The total number of transplants is 6,291. The average clinical profile of the Spanish heart transplant patient in 2010 was that of a 53-year-old male diagnosed with nonrevascularizable ischemic heart disease accompanied by severely depressed ventricular function and poor functional status. The implanted heart was typically from a 39-year-old donor who had died from brain hemorrhage. The average time on the waiting list was 99 days. Mean survival time has progressively increased over the years. Whereas for the overall series, the probability of survival at 1, 5, 10, and 15 years was 78%, 67%, 54%, and 40%, respectively, over the past 5 years the probability of survival at 1 and 5 years was 85% and 73%, respectively. The most frequent cause of death was acute graft failure (16.5%), followed by infection (15.9%), the combination of graft vascular disease and sudden death (13.7%), tumors (11.9%), and acute rejection (7.8%).

Conclusions: The transplantation survival rates obtained in Spain, especially in recent years, position heart transplant as the treatment of choice in irreversible heart failure patients without other established medical or surgical options.

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R E S U M E N

Introducción y objetivos: El propósito de este artículo es presentar los resultados del trasplante cardíaco desde que se inició esta modalidad terapéutica en España en mayo de 1984.

Métodos: Se ha realizado un análisis descriptivo de todos los trasplantes cardíacos realizados hasta el 31 de diciembre de 2010.

Resultados: El número total de trasplantados fue de 6,291. El perfil clínico medio del paciente intervenido para trasplante en España en 2010 fue el de un varón de 53 años, diagnosticado de cardiopatía isquémica no revascularizable con depresión grave de la función ventricular y situación funcional avanzada, al que se implantó un corazón de 39 años procedente de un donante fallecido por hemorragia cerebral y con un tiempo en lista de espera de 99 días. El tiempo medio de supervivencia se ha incrementado con los años. Así, mientras en la serie total la probabilidad de supervivencia tras 1, 5, 10 y 15 años es del 78, el 67, el 54 y el 40% respectivamente, en los últimos 5 años la probabilidad de supervivencia tras 1 y 5 años es del 85 y el 73%, respectivamente. La causa más frecuente de fallecimiento es el fallo agudo del injerto...
INTRODUCTION

As has been the custom for our section since 1991, we present a descriptive analysis of the results of heart transplantation (HT) performed in Spain from May 1984, when this therapeutic modality was initiated, to December 31 of the year prior to the publication.1–21

This registry includes all HTs performed by all teams at all centers in Spain (Appendix) and is therefore an accurate account of the status of this technique in Spain. The report’s reliability is supported by the use by all HT teams of a similar database, established by consensus, which standardizes variables and possible responses.

METHODS

Patients and Centers

Nineteen centers provided their data to the registry (Table 1), although 18 centers are currently performing transplantations.

During more than 25 years of transplantation, 6291 HTs have been performed. Figure 1 shows the distribution in the number of HTs per year. Of these, 94% were isolated orthotopic transplants. Table 2 shows the distribution of HTs according to procedure type.

Design

The database includes 175 clinical variables with data on recipients, donors, surgery, immunosuppression, and follow-up.

(16.5%), seguida de infección (15.9%), el combinado de enfermedad vascular del injerto y muerte súbita (13.7%), tumores (11.9%) y rechazo agudo (7.8%).

Conclusiones: La supervivencia obtenida en España con el transplante cardíaco, sobre todo en los últimos años, lo sitúa como el tratamiento de elección para cardiopatías irreversibles en situación funcional avanzada y sin otras opciones médicas o quirúrgicas establecidas.

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<table>
<thead>
<tr>
<th>Table 1</th>
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<tbody>
<tr>
<td>Spanish Registry on Heart Transplantation, 1984-2010. Centers Participating.</td>
</tr>
<tr>
<td>1. Hospital Santa Cruz y San Pablo, Barcelona</td>
</tr>
<tr>
<td>2. Clínica Universitaria de Navarra, Pamplona</td>
</tr>
<tr>
<td>3. Clínica Puerta de Hierro de Majadahonda, Madrid</td>
</tr>
<tr>
<td>4. Hospital Marqués de Valdecilla, Santander</td>
</tr>
<tr>
<td>5. Hospital Reina Sofia, Córdoba</td>
</tr>
<tr>
<td>6. Hospital Universitario y Politécnico La Fe, Valencia</td>
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<tr>
<td>7. Hospital Gregorio Marañón, Madrid</td>
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<tr>
<td>8. Fundación Jiménez Díaz, Madrid</td>
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<tr>
<td>9. Hospital Virgen del Rocio, Seville</td>
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<tr>
<td>10. Hospital 12 de Octubre, Madrid</td>
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<tr>
<td>11. Hospital Universitario A Coruña, A Coruña</td>
</tr>
<tr>
<td>12. Hospital de Bellvitge, L’Hospitalet de Llobregat, Barcelona</td>
</tr>
<tr>
<td>13. Hospital La Paz, Madrid</td>
</tr>
<tr>
<td>14. Hospital Central de Asturias, Oviedo</td>
</tr>
<tr>
<td>15. Hospital Clinic, Barcelona</td>
</tr>
<tr>
<td>16. Hospital Virgen de la Arrixaca, El Palmar, Murcia</td>
</tr>
<tr>
<td>17. Hospital Miguel Servet, Zaragoza</td>
</tr>
<tr>
<td>18. Hospital Clínico, Valladolid</td>
</tr>
<tr>
<td>19. Hospital Vall d’Hebron, Barcelona</td>
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</tbody>
</table>

Order according to start of transplantation operations.

Each year, centers send data to the Director of the Registry, who organizes the statistical methodology with the company hired for this purpose (currently ODDS, SL). Audits of the centers are also organized periodically to check the data. The audits are performed by an independent external company that randomizes the centers and HTs, extracting a representative sample and checking the reliability of the submitted data.

In 2008, the registry was submitted to the Committee for Biomedical Research Ethics of the Hospital Universitario y Politécnico La Fe, Valencia and was approved. Additionally, the
registry is being submitted to the Ministry of Health and Consumer Affairs (Ministerio de Sanidad y Consumo) to ensure compliance with the Spanish Data Protection Law 15/1999 (Ley Orgánica de Protección de Datos 15/1999).

**Statistical Analysis**

Variables are presented as mean (SD) and percentages. Survival curves were calculated using the Kaplan-Meier test, and were compared using the log rank test. A P<.05 was considered significant. The survival analysis was performed without including retransplants or combined transplants.

**RESULTS**

**Heart Transplant Patient Profile**

In Spain, the clinical profile of the average heart transplanted patient is a 53-year-old male, with blood type A or O and diagnosed with ischemic heart disease or idiopathic dilated cardiomyopathy. Table 3 shows the clinical profile of isolated HT recipients distributed by age, with retransplants analyzed separately.

**Waiting List Mortality and Days to Transplant**

In 2010, waiting list mortality was 5%. The percentage of patients excluded from HT after inclusion in the list was 15%. Figure 2 shows the annual percentage of patients who, after being added to the waiting list, received HT, were removed from the list without HT, or died before receiving a transplant.

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### Table 2

<table>
<thead>
<tr>
<th>Type of Transplant</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>De novo heart transplants</td>
<td>5980</td>
</tr>
<tr>
<td>Heart retransplants</td>
<td>182</td>
</tr>
<tr>
<td>Combined transplants</td>
<td>73</td>
</tr>
<tr>
<td>Heart-kidney</td>
<td>49</td>
</tr>
<tr>
<td>Heart-liver</td>
<td>7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>6291</strong></td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Type of Transplant</th>
<th>&lt;16 years</th>
<th>≥16 years</th>
<th>Retransplants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>277</td>
<td>5490</td>
<td>143</td>
</tr>
<tr>
<td>Males, %</td>
<td>62.3</td>
<td>82.1</td>
<td>77.5</td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>6 (5.7)</td>
<td>53.2 (11.9)</td>
<td>50.5 (13.9)</td>
</tr>
<tr>
<td>BMI</td>
<td>15.7 (4.8)</td>
<td>25.4 (4)</td>
<td>25 (4.1)</td>
</tr>
<tr>
<td>Baseline etiology, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD:</td>
<td>1.5</td>
<td>34.6</td>
<td>33.1</td>
</tr>
<tr>
<td>HT:</td>
<td>33.8</td>
<td>29.9</td>
<td>16.6</td>
</tr>
<tr>
<td>CHD:</td>
<td>0.7</td>
<td>9</td>
<td>11.5</td>
</tr>
<tr>
<td>VHD:</td>
<td>40.4</td>
<td>1.3</td>
<td>38.8</td>
</tr>
<tr>
<td>Others:</td>
<td>23.6</td>
<td>25.2</td>
<td></td>
</tr>
</tbody>
</table>

### Blood type

- A: 54.4
- B: 6.9
- AB: 4.4
- O: 34.3

### NYHA functional class III-IV / IV

- 67.6
- 61.1
- 69.8

### Creatinine > 2 mg/dl

- 2.9
- 5.3
- 27.7

### mPAP, mmHg

- 29 (13)
- 30.3 (11.1)
- 27.1 (9.8)

### PVR, WU

- 2.9 (1.7)
- 2.5 (4.1)
- 2 (1.4)

### Bilirubin >2 mg/dl

- 19.6
- 15.6
- 22

### GOT/GPT >x2, mg/dl

- 21.6
- 25.5
- 29.3

### ID diabetes mellitus

- 0.7
- 13.6
- 18

### HBP

- 1.9
- 27.9
- 41.7

### Hypercholesterolemia

- 3.3
- 37.3
- 43.4

### Moderate-severe COPD

- 1.8
- 10.8
- 7.9

### Previous HS

- 27.4
- 24.6
- 100

### Treatment with inotropic drugs

- 67.3
- 33.8
- 55

### Mechanical ventilation

- 31.5
- 10.3
- 32.4

AGF, acute graft failure; ARe, acute rejection; BMI, body mass index; CHD, congenital heart disease; COPD, chronic obstructive pulmonary disease; GOF (AST), aspartate aminotransferase; GPT (ALT), alanine aminotransferase; GVD, graft vascular disease; HBP, high blood pressure; HS, heart surgery; ID, insulin dependent; IDCm, idiopathic dilated cardiomyopathy; IHD, ischemic heart disease; mPAP, mean pulmonary artery pressure; NYHA, New York Heart Association; PVR, pulmonary vascular resistances; VHD, valvular heart disease; WU, Wood units. Values are given as mean (SD) and percentages. Combined transplants are not included.

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![Figure 2](image-url). Patient outcomes following inclusion on the heart transplantation waiting list.
The mean HT waiting time for 2010 recipients was 99 days. Figure 3 shows the evolution of this waiting time over the last 19 years.

Cause of Death and Mean Donor Age

Most hearts that are currently implanted come from donors who died due to cerebral hemorrhage. The mean donor age in 2010 was 39 years (Figs. 4 and 5).

Urgent Transplantation

The rate of indications for urgent HT in 2010 was 34%. Figure 6 illustrates how this HT option has evolved over the years.

Ventricular Assistance

The rate of patients transplanted with assistance has increased over the years. In the last 5 years, it reached 21.9%. The distribution
by periods and by type of assistance implemented can be seen in Figure 7.

**Immunosuppression**

In Spain, most patients who received HT were administered immunosuppressive therapy by induction. The various drugs used and the distribution by periods can be seen in Figure 8.

*De novo* immunosuppressive maintenance therapy and changes made during the transplanted patient’s evolution are shown in Figure 9.

**Survival**

Early mortality (first 30 days after HT) was 18% last year (Figure 10). This mortality is higher than the mean of the 5 previous years (14%).

By incorporating 2010 survival data to those of previous years, we obtained a 1-month actuarial survival rate of 88%, and 1-, 5-, 10-, 15-, and 21-year rates of 78%, 67%, 54%, 40%, and 27%, respectively (Figure 11). Survival by periods showed better results in the last stages, with 1- and 5-year survival rates of 85% and 73%, respectively (Figure 12).

Survival curves differed according to etiology indicating HT (Figure 13). The degree of urgency also influenced the survival probability (Figure 14).

**Causes of Death**

The most frequent cause of death (Figure 15) was early graft failure (16.5%), followed by infection (15.9%), combined graft vascular disease and sudden death (13.7%), tumors (11.9%), and acute rejection (7.8%).

By distributing causes of mortality into several periods, differences can be seen between the first month (early graft failure), the first month to the first year (infections) and after the first year (tumors and the combination of sudden death with chronic rejection). Figure 16 shows the causes of mortality distributed by periods.

![Figure 6](http://www.revespcardiol.org) Year-to-year evolution of urgent heart transplantations.

![Figure 7](http://www.revespcardiol.org) Distribution of the type of pretransplant ventricular assistance by periods. ECMO, extracorporeal membrane; VAD, ventricular assistance device.

![Figure 8](http://www.revespcardiol.org) Induction immunosuppression. Drugs used.

![Figure 9](http://www.revespcardiol.org) Maintenance immunosuppression. Variations in clinical course by drug type. Immunosuppression at transplantation and at end of follow-up. MMF, mycophenolate mofetil; MPS, mycophenolate sodium; RAPA, rapamycin.
cooperation with all Spanish transplant teams, creating a consensus of response possibilities. Each year, all teams update their data and send them to the Registry Director who collates the data and sends them to an independent statistics company for analysis. We believe that this method confers high reliability on the results and avoids errors, which are quite common in nonstandardized databases. In 2007, we increased the number of variables analyzed per patient to 175. In 2008, the registry was submitted to the Biomedical Research Ethics Committee of Hospital Universitario y Politécnico La Fe, Valencia, and was approved. In the near future, there are plans to formalize the registry in the Spanish Ministry of Health and Consumer Affairs to give it legal coverage and ensure adequate protection of patient healthcare data. For the sake of greater quality and reliability of data, we plan to continue auditing centers through independent external companies that ensure maximum data validity.

Currently, there are 18 centers performing transplantations. The fact that centers in Spain are authorized for HT without an appropriate needs assessment study is of great concern to many transplant teams. This is because the number of optimal donors in Spain has shown a clear declining trend, thus decreasing the ratio of HTs to centers. On one hand, the reduction in the number of HTs causes underutilization of resources in hospitals that are prepared for a large number of surgeries, and on the other hand, lengthens the learning curve to achieve adequate results. The only benefit for patients is the convenience of not having to travel far from home, which would not be an advantage in those cases where an authorized center is already nearby. The health authorities who decided to open more centers should assess whether proper optimization of resources is being achieved in these “times of crisis.”
teams, who are aware of this problem, are attempting to broaden the selection of possible donors. In fact, last year donors who were accepted for HT were older (39 years vs 37 years, in 2010 and 2009, respectively).

The waiting time for obtaining a compatible organ has tended to decrease (99 days in 2010, 106 days in 2009, and 111 days in 2008). This decrease was due to the progressive increase in urgent HTs. With an increasing proportion of urgent HTs, which involve shorter waiting times than elective HTs, the overall time is shortened. However, the waiting times for elective HTs increase disproportionately.

The clinical profile of patients has not changed in recent years. We separated HTs into 3 groups (pediatric, adult, and retransplantation) since they have distinct clinical characteristics. Pediatric patients are transplanted for congenital heart disease and idiopathic dilated cardiomyopathy, have higher pulmonary resistance, and lack cardiovascular risk factors. Meanwhile, retransplants tend to be performed for graft vascular disease, with greater organic deterioration and more risk factors. This may be a greater contribution to the worse prognosis than the fact that this is a second HT.

Urgent HTs are somewhat controversial since these interventions, due to their characteristics (recipients in worse clinical condition, less optimal donors, and longer periods of ischemia), involve a worse prognosis than those performed in a scheduled manner. In recent years, the number of urgent HTs has increased markedly (34% in 2010 vs 23% in 2005). The percentage of patients who undergo urgent HT varies from one area to the next and changes markedly from one year to the next. The causes of these fluctuations and varying geographical distribution are not completely obvious. However, it seems clear that the low number of donors and the better maintenance of critical patients (ventricular assistance) make this more of a possibility. The indication for urgent HT has been questioned since it obviously offers worse results. Nevertheless, transplant teams believe that the indication should remain, although in a “controlled” manner. To ensure the maximum possible survival for patients who are transplanted under critical situations, we should keep in mind that it is better to stabilize heart failure before indicating urgent HT, as recommended by the European guidelines on heart failure. Also, HT should not be considered as treatment for unstable acute heart failure,\textsuperscript{26} due among other reasons to the time it takes to get a donor even with this degree of urgency.

The proportion of patients who arrive at HT with some type of ventricular assistance has increased progressively, especially in the last 5 years. Intra-aortic balloon counterpulsation remains the most widely used system although its use has not increased in the last 5 years. The use of extracorporeal membrane oxygenators and pulsatile devices has increased significantly. In the last 5 years, more than half of emergency transplanted patients were implanted with some type of ventricular assistance. These devices are crucial for maintenance and stabilization of patients with acute heart failure prior to HT, and it is therefore advisable that all transplant teams have access to them for their most critical patients. In addition, they are very useful when dealing with severe graft failure immediately following implantation. This complication is becoming increasingly frequent due to the worse condition of the recipient, less optimal donors, and longer periods of ischemia inherent in the degree of urgency of the recipient and the greater distance to the organ.

Induction immunosuppression has been used in most HTs. Since transplants were first performed, the most commonly used treatment has been OKT3 antilymphocyte antibodies (35% in the overall series) although currently interleukin-2 antagonists are used more often (85% of HTs performed in the last 5 years). The maintenance immunosuppressive therapy currently used is

Last year, the number of HTs fell once again (243 in 2010 vs 274 in 2009) due to the progressive trend towards a reduced number of donors. There is no single explanation for this decrease, but it seems clear that lower mortality due to traumatic brain injury linked to traffic accidents along with better control and handling of patients in multiple trauma units play major roles. With the decreased number of donors, the possibilities for HT decrease and the number of patients on waiting lists increases. Thus, the proportion of patients with advanced heart failure who, once included in the list, cannot be transplanted and are removed from the list (due to death or deterioration) reaches 20%. The transplant
the so-called triple combination: cyclosporine vs tacrolimus, azathioprine vs mycophenolate mofetil, and steroids. However, the introduction of other immunosuppressants, such as rapamycin, everolimus, mycophenolate acid, and more recently, extended-release tacrolimus, is common during patient evolution. Of these, the administration of everolimus has increased the most. It is administered to 2.8% of patients at the start of HT and in up to 21.3% of HTs that have concomitant renal dysfunction, tumors, or graft vascular disease.

The early mortality rate rose last year (18% in 2010 vs 16% in 2009), with an increasing trend over the last 4 years. This may be related to an increased number of emergencies and use of ventricular assistance, with the patients arriving at the HT in more critical condition. The early period is probably the most important for improving survival since the survival curve stabilizes after the first months following HT.

Over the years, overall survival has shown a clear trend towards progressive improvement. However, and not surprisingly, the number of patients added to the registry each year represents a smaller proportion of the total. Therefore, the probability of large changes in a year is very low, making analysis of survival by time periods more productive. In recent years, survival has improved significantly compared to the earliest periods. However, there is “stagnation” in the survival curve, which has been attributed to the worst clinical condition of recipients and less optimal organs with longer periods of ischemia. Nevertheless, survival is much greater than that conferred by advanced heart failure without HT, even for high-risk groups.

The indication for HT is clearly related to survival. Patients diagnosed with idiopathic dilated cardiomyopathy have higher survival rates than those transplanted for other reasons because they are younger and have lower prevalence of cardiovascular risk factors.

The most frequent cause of death was acute graft failure (16.5%), followed by infection (15.9%), a combination of graft vascular disease and sudden death (13.7%), tumors (11.9%), and acute rejection (7.8%). However, the cause of death is usually related to the time since the HT, and thus the most frequent cause of death during the first month is graft failure. From the first month to the first year, the most frequent cause is infection and rejection. After that, the most frequent cause is a combination of sudden death and chronic rejection, infections, and tumors. This distribution of causes of death has not changed in recent years and should lead us to reflect on the need for achieving “balanced” immunosuppression, since death due to failure in preventing rejection is 7.8% while death due directly to excessive immunosuppression (infection and tumors) is 27.8%.

CONCLUSIONS

The survival rates of the Spanish Registry on Heart Transplantation are similar to those of other registries. Nevertheless, efforts need to be increased to improve survival rates during the early periods, which will result in significant overall improvements.

Ventricular assistance has experienced major growth. These devices keep recipients in suitable condition until compatible organs can be found. However, since waiting times for organs can sometimes last for weeks, long-term ventricular assist devices are needed to avoid patient deterioration and maintain good patient conditions until the HT.

There is still a major imbalance between the complications that immunosuppression prevents (rejection) and those it favors (tumors, infection). In the coming years, these problems need to be addressed and immunosuppression must be customized according to the specific characteristics of each patient.

ACKNOWLEDGEMENTS

Statistical analysis was carried out by ODDS, SL, thanks to an unconditional grant by Novartis Trasplante.

CONFLICTS OF INTEREST

None declared.

APPENDIX. SPANISH REGISTRY ON HEART TRANSPLANTATION 1984-2010. COLLABORATORS

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REFERENCES