SPECIAL ARTICLE

Spanish Heart Transplantation Registry. 17th Official Report of the Spanish Society of Cardiology Working Group on Heart Failure, Heart Transplantation, and Associated Therapies (1984-2005)

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Introduction and methods. This article summarizes the general characteristics of heart transplantation in Spain and the results achieved, once data for 2005 have been included.

Results. In the course of the last year, 287 heart transplantations were performed, which brings the total to 4967 since 1984.

Clinically, the typical Spanish heart transplant patient is male, aged about 50 years, has blood group A or O, has non-revascularizable coronary disease or idiopathic dilated cardiomyopathy, and is in New York Heart Association functional class IV/IV.

The percentage of emergency heart transplants carried out was 22%, which is considerably lower than in the previous year (i.e., 35%) and slightly lower than the average for the last 5 years (i.e., 23%). The early mortality rate was 10%, which is similar to that in the previous year and lower than the average for the last 5 years (i.e., 12%).

After adding the 2005 results to those of previous years, the survival probabilities at 1, 5, and 10 years were 75%, 65%, and 50%, respectively. On calculating survival curves for separate historical periods, a significant improvement could be seen for the last 5 years, in which the 1- and 5-year survival probabilities were 80% and 70%, respectively. The most frequent cause of death in the first month was acute graft failure; in the first year, infection and rejection were most common; and, in the long term, tumors and the combination of graft vascular disease with sudden death.

Conclusions. Comparative analysis of survival rates showed that short-, medium-and long-term outcomes in Spain are consistent with those reported in the world literature, including a continuing trend towards better survival over the years.

Key words: *Heart transplantation. Registry. Survival.*

Registro Español de Trasplante Cardiaco. XVII Informe Oficial de la Sección de Insuficiencia Cardiaca, Trasplante Cardiaco y Otras Alternativas Terapéuticas de la Sociedad Española de Cardiología (1984-2005)

Introducción y métodos. En este artículo se describen las características generales y los resultados obtenidos con el trasplante cardiaco en España tras incluir los datos del último año.

Resultados. En 2005 se realizaron 287 trasplantes que, junto con los realizados desde 1984, hacen un total de 4.967.

El perfil clínico medio del paciente que recibe un trasplante en España corresponde a un varón de aproximadamente 50 años, de grupo sanguíneo A o 0, con enfermedad coronaria no revascularizable o miocardiopatía dilatada idiopática y situación funcional IV/IV de la New York Heart Association.

El porcentaje de trasplantes cardiacos urgentes fue del 22%; esta cifra fue muy inferior a la del año previo (35%) y ligeramente menor que la media de los últimos 5 años (23%). La mortalidad precoz fue del 10%, cifra similar a la del año previo e inferior a la media de los últimos 5 años (12%).

Tras incorporar los resultados del pasado año a los previos se obtuvo una probabilidad de supervivencia al primero, quinto y décimo año del 75, el 65 y el 50%, respectivamente. Al separar las curvas de supervivencia por períodos se objetivó la importante mejoría en los últimos 5 años, con valores al primero y quinto años del 80 y el 70%. La causa más frecuente de fallecimiento en el primer mes fue el fallo agudo del injerto, en el primer año la infección y el rechazo, y a largo plazo los tumores y el combinado de enfermedad vascular del injerto con muerte súbita.

Conclusiones. El análisis comparativo de la supervivencia muestra que los resultados a corto, medio y largo plazo son superponibles a los publicados en la literatura científica mundial, con una progresiva tendencia hacia una mejora de la supervivencia con los años.

Palabras clave: *Trasplante cardiaco. Registro. Supervivencia.*

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INTRODUCTION

This article is the customary annual update analysis describing results of heart transplantations carried out in Spain between the first such procedure, performed in May 1984, and 31 December 2005.[1-16]

This registry includes all heart transplants performed by all teams at all centers in Spain. It is, therefore, an accurate account of the status of heart transplantation in the country. The report's reliability is founded on the nationwide use of a similar database constructed on mutually agreed principles, which unifies possible responses and standardizes variables.

Heart Transplants Performed

Eighteen heart transplantation centers supplied data for the registry (Table 1) although only 17 are actively performing transplants at present. Since 2001, the number of active centers in Spain has remained stable. Most transplantation teams believe that there are too many centers and that it would be unwise to increase their number. New centers take a long time to acquire the experience necessary to ensure good results and this outweighs the benefit to patients of having shorter distances to travel.

In the 21 years that heart transplantation procedures have been being performed in Spain, the total number of operations has reached 4967. Figure 1 presents the distribution of the number of heart transplants per year. Of these, 96% were isolated orthotopic transplants. Table 2 shows the distribution of transplants by procedure type.

TABLE 1. **Spanish Registry on Heart Transplantation, 1984-2005. Centers Reporting**

1. Hospital Santa Creu y San Pau, Barcelona
2. Clínica Universitaria de Navarra, Pamplona
3. Clínica Puerta de Hierro, Madrid
4. Hospital Marqués de Valdecilla, Santander
5. Hospital Reina Sofía, Córdoba
6. Hospital La Fe, Valencia
7. Hospital Gregorio Marañón, Madrid
8. Fundación Jiménez Díaz, Madrid
9. Hospital Virgen del Rocío, Seville
10. Hospital 12 de Octubre, Madrid
11. Hospital Juan Canalejo, La Coruña
12. Hospital de Bellvitge, Barcelona
13. Hospital La Paz, Madrid
14. Hospital Central de Asturias
15. Hospital Clínic, Barcelona
16. Hospital Virgen de la Arrixaca, Murcia
17. Hospital Miguel Servet, Zaragoza
18. Hospital Clínico, Valladolid

Heart Transplant Recipient Profile and Baseline Heart Disease

In Spain, the profile of the average heart transplant recipient is that of a man of approximately 50 years of age with blood group A or O. Percentages of pediatric transplant recipients, older adults or women are rather low. Figure 2 presents the general characteristics of transplant recipients. Ischemic heart disease and idiopathic

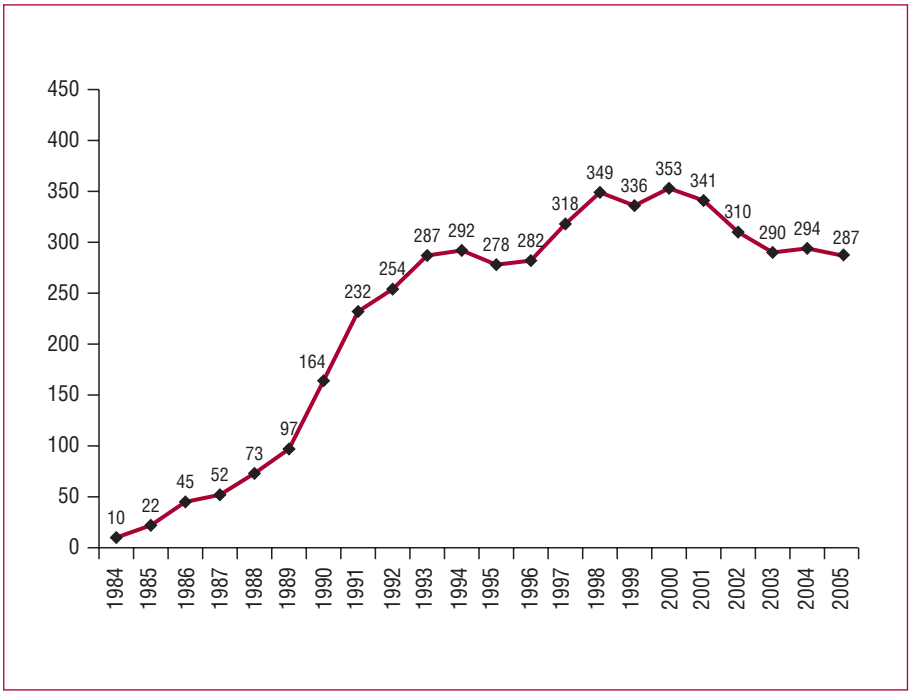

Figure 1. Number of heart transplants per year.

TABLE 2. **Spanish Registry on Heart Transplantation, 1984-2005. Procedure Types**

Orthotopic heart transplants	4764
Heart retransplantations	108
Simultaneous transplantations	
Heart-lung	55
Heart-kidney	35
Heart-liver	4
Heart-liver-pancreas	1
Total	4967

dilated cardiomyopathy are the most frequent indications for transplantation. Together, they account for 72% of all causes. With the exception of valvular heart disease (10%), other specific causes are relatively infrequent. Figures 3 and 4 show the distribution of pathologic processes that are indications for heart transplantation.

Waiting List Mortality and Urgent Transplantation

In 2005, the waiting list mortality was 8%. The percentage of patients excluded from transplant after placement on the waiting list was 20%. Figure 5 shows the annual percentages of waiting list patients who received a transplant, were removed from the list without receiving one, or died before receiving one.

The percentage of indications for urgent transplantation has varied, sometimes substantially, over the years. Often, there has been little apparent reason for these changes. In 2005, urgent transplants accounted for 22% of procedures.

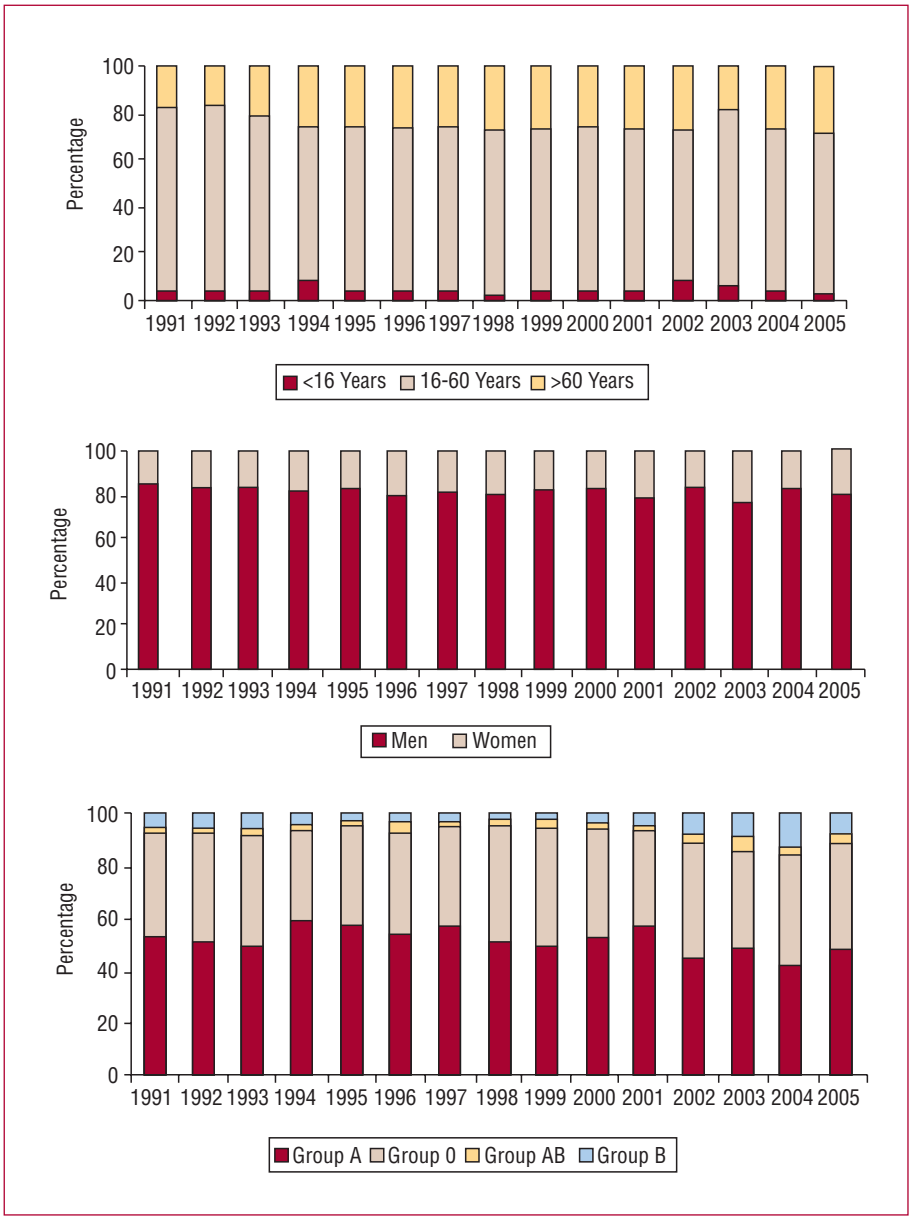

Figure 2. Annual distribution by age (top), gender (center), and blood group (bottom).

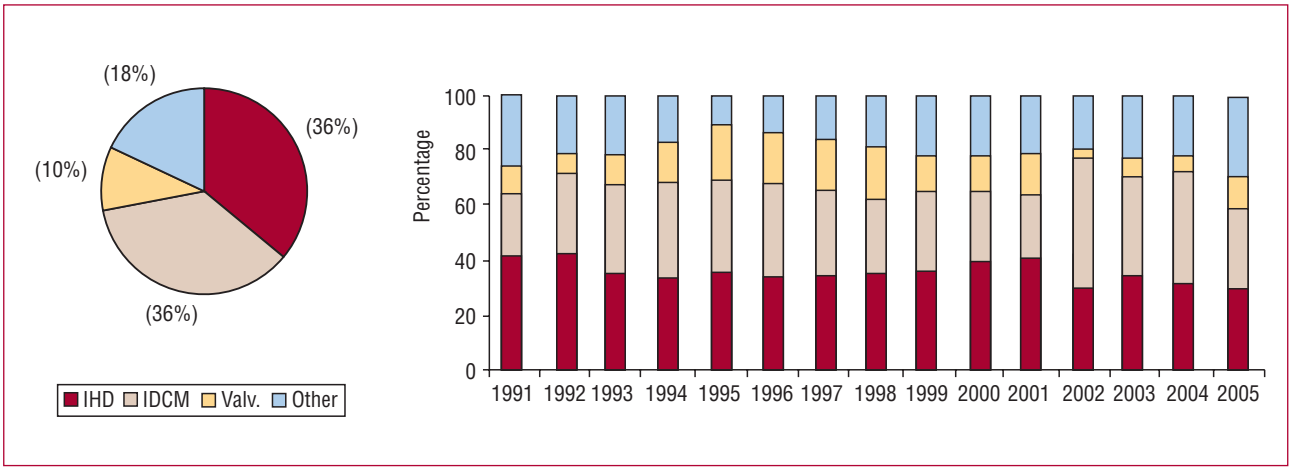

Figure 3. Baseline illness indicating transplantation and annual distribution. IHD: ischemic heart disease; IDCM: idiopathic dilated cardiomyopathy; Valv.: valvular heart disease.

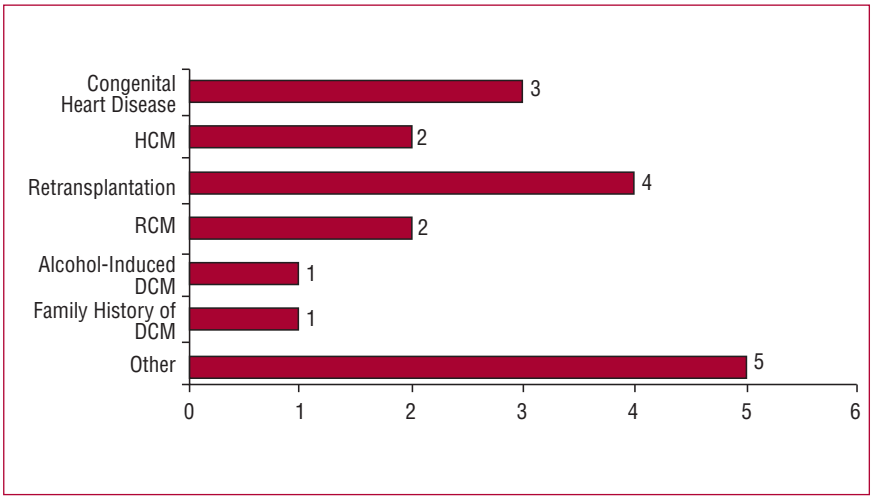

Figure 4. Less frequent diseases indicating transplantation. The number at the end of each column represents the corresponding percentage of the total. DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; RCM: restrictive cardiomyopathy.

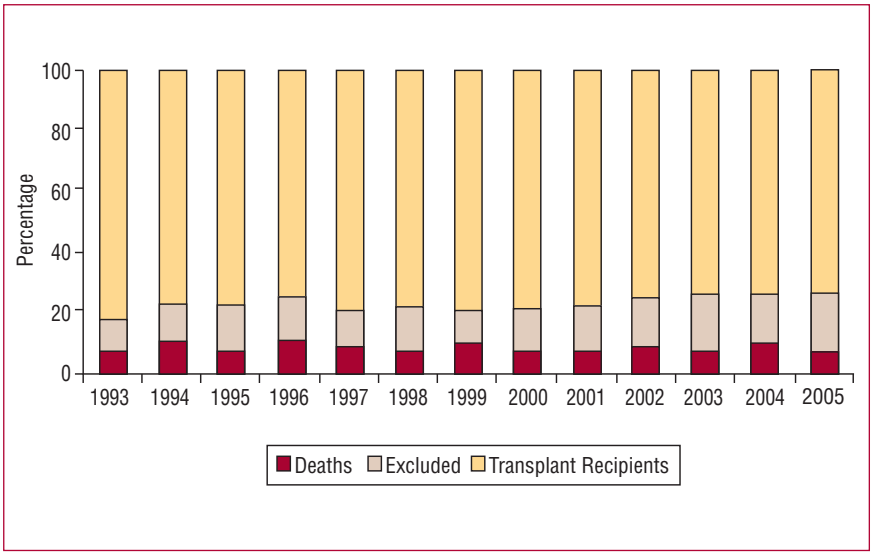

Figure 5. Percentage annual distribution of transplant recipients, patients who died and patients removed from waiting lists.

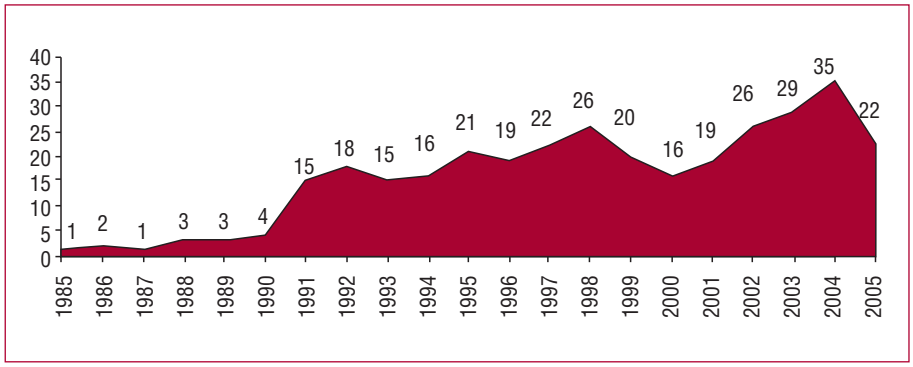

Figure 6. Annual changes (percentage) in indication for urgent transplantation.

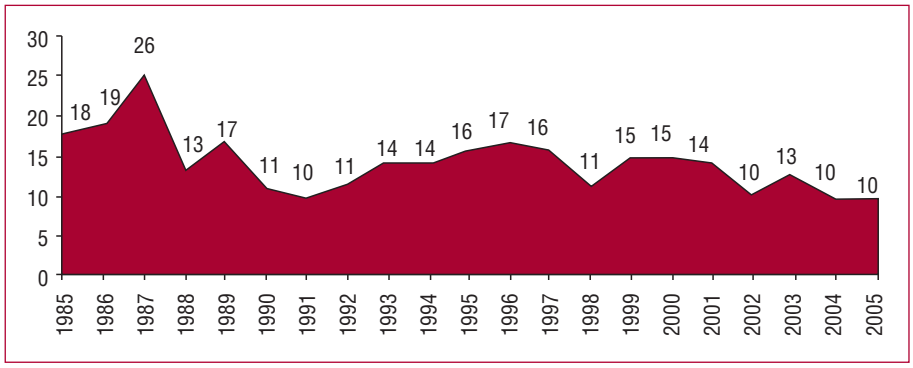

Figure 7. Year on year percentage evolution of early mortality rate.

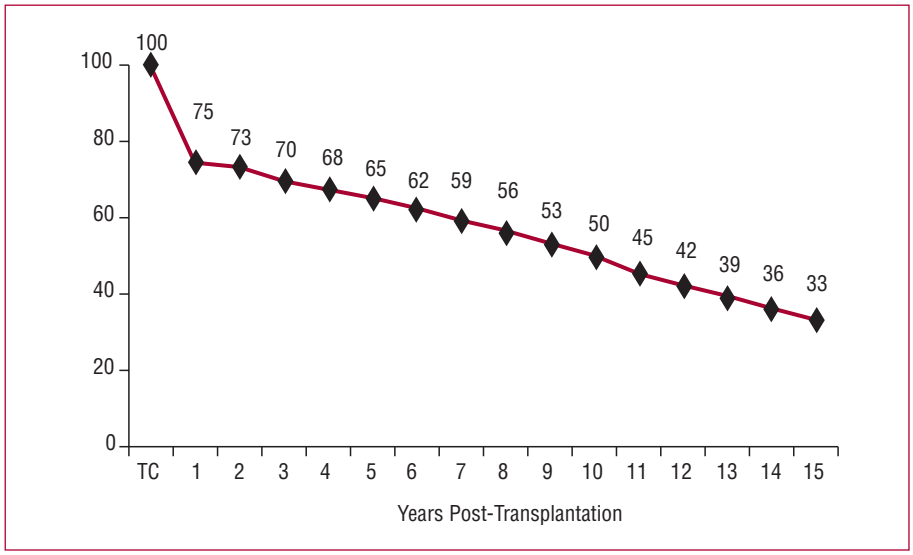

Figure 8. Actuarial survival curve (Kaplan-Meier).

This is clearly fewer than 2004 (35%) and is also below the mean for the last 5 years (23%). Figure 6 shows the evolution of indications for urgent transplantation over the years.

RESULTS

Survival

Early mortality (the early 30 days post-transplantation) was 10% in 2005. Figure 7 shows the evolution of early mortality over the years.

When survival rate data for 2005 were added to those of previous years, we obtained 1-, 5-, and 10-year actuarial survival rates of 75%, 65%, and 50% respectively, with an average recipient survival of 10 years. Figure 8 shows the actuarial survival curve with an initially sharp decrease over the first year (essentially due to the first month) followed by a less marked decline of approximately 2.8% per year. Figure 9 shows that substantial differences exist when the overall survival curve is analyzed by periods.

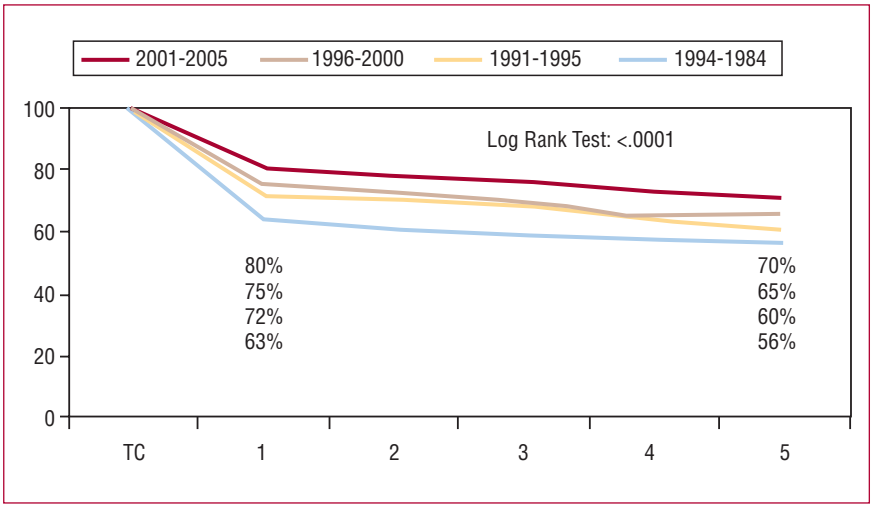

Figure 9. Survival curve by periods. The percentages correspond to 1- and 5-year survival from the most recent period (at the top) to the initial period (at the bottom).

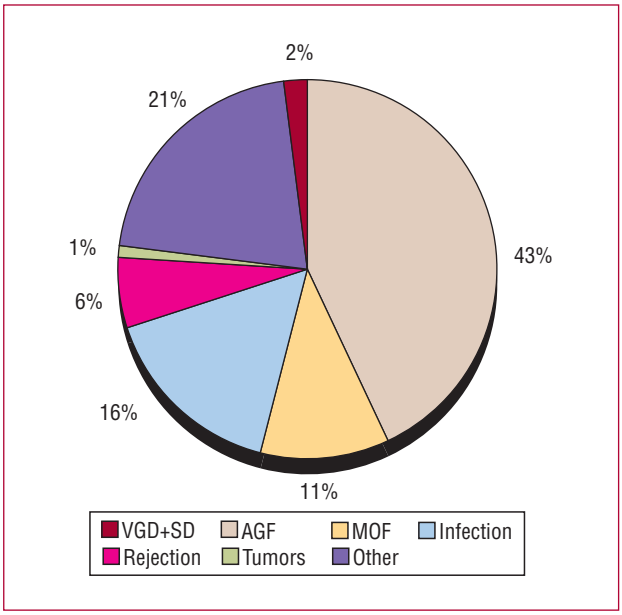

Figure 10. Causes of early mortality. VGD+SD: vascular graft disease and sudden death; AGF: acute graft failure; MOF: multiple organ failure.

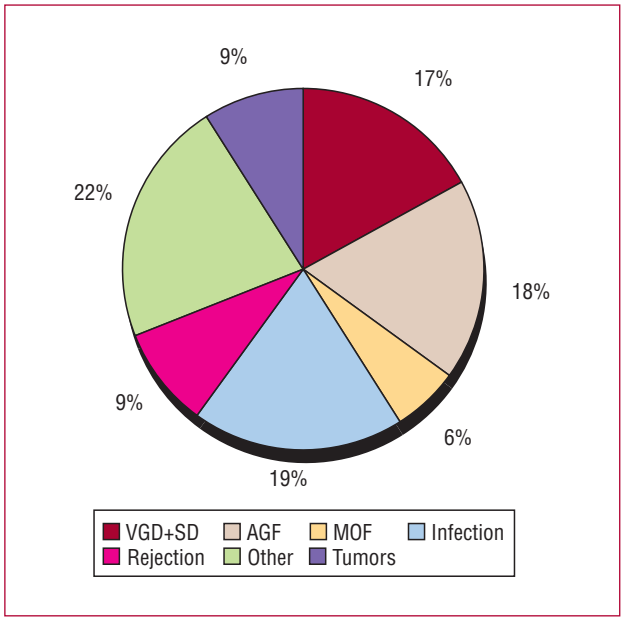

Figure 11. Causes of overall mortality. VGD+SD: vascular graft disease and sudden death; AGF: acute graft failure; MOF: multiple organ failure.

Causes of Death

The most frequent cause of death during the early period was acute graft failure (43%). Figure 10 shows the distribution of causes of death at the early 30 days.

The most common causes of overall mortality were infections (19%), acute graft failure (18%), and the combination of vascular graft disease and sudden death (17%). Figures 11 and 12 show the incidence of causes of overall mortality.

When causes of mortality are distributed by periods, differences can be seen at the early 30 days (acute graft failure), 1 month to 1 year (infections and rejection), and >1 year (tumors and the combination of sudden death with vascular graft disease). Figure 13 shows the distribution of causes of mortality by periods.

DISCUSSION

In Spain, the early days of heart transplantation are long gone and today we can call on a wealth of experience with this procedure. Our results are on a par with those achieved in other countries both in Europe and around the world. Analysis of the Registry of the International

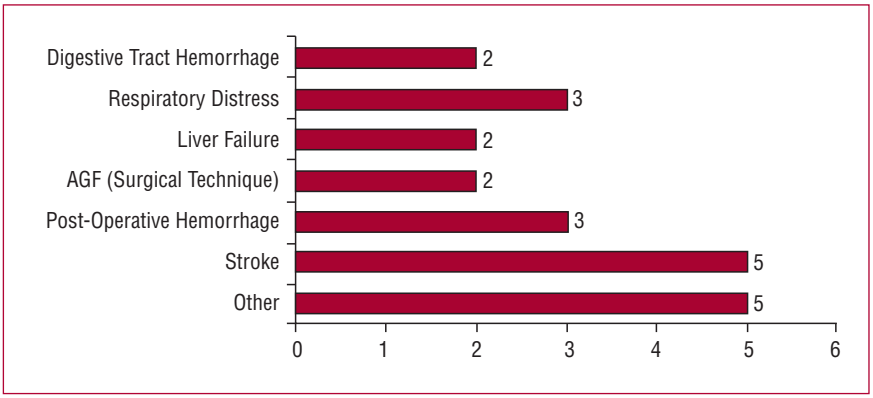

Figure 12. Less frequent causes of overall mortality. The number to the end of each of the columns represents percentage with respect to the total. AGF: acute graft failure.

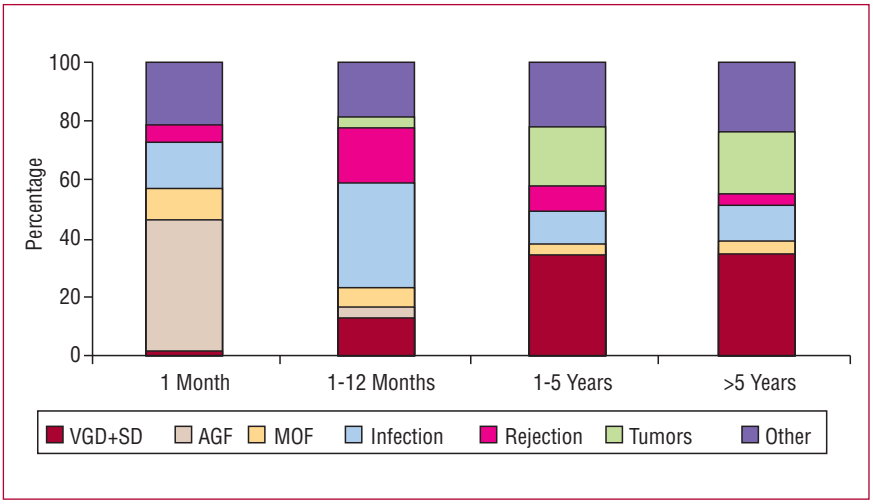

Figure 13. Causes of mortality by periods. VGD+SD: vascular graft disease and sudden death; AGF: acute graft failure; MOF: multiple organ failure.

Society for Heart and Lung Transplantation annual report[17-19] demonstrates this clearly.

An important advantage of our Registry is that it is compiled from on a standardized database which only permits a previously agreed range of responses. All teams update results annually and submit figures to the Registry coordinator who, using custom-built software, introduces the data into a common database for subsequent analysis of variables. We believe this method greatly enhances the reliability of our results and avoids errors of the kind so often found in non-standardized databases.

In 2005, the number of active transplantation centers in Spain remained stable. We are thankful that this is the case despite the fact that it still causes concern for most teams because the number of optimal donors has remained constant whereas the number of transplants per center has fallen. The fact that fewer transplant procedures are being performed leads to the underuse of resources in hospitals equipped to undertake a great number of transplants and to a longer learning process needed to achieve adequate results. The only tangible benefit for patients is the convenience of being able to undergo transplantation without having to travel far from home.

Since heart transplantation began in Spain, the number of procedures per year has increased steadily. The period 1989-1993 saw the greatest increase in transplantations with the number of procedures rising from 97 to 287 per year. Since 1993, the rate of increase has fallen and only in 2000 did we see the transplants per year rate pass 350. Considered at the time a probable plateau, this figure now seems excessively high as in the last 3 years procedures have stabilized at around 300 per year, despite an increase the age limit for donors.[20]

The future of simultaneous heart-lung transplants is still unclear and this procedure has yet to become firmly established. Few teams perform heart-lung transplants and few procedures are carried out each year. In 2005, only 2 such operations were performed in Spain whereas 2004 had seen 7 interventions of this type. The development of these procedures is complicated by the lack of donors, the technical difficulties involved, the high level of organ "consumption" and the substantially worse prognosis associated with it by comparison with separate heart and lung transplantation. Of the other simultaneous procedures, heart-kidney transplants are the most advanced (35 procedures in total).

Prior to 2005, ischemic heart disease had been the most frequent indication for transplantation in Spain. In some international registry reports the most frequent cause is dilated cardiomyopathy. This difference is probably a question of terminology as ischemic heart disease accompanied by substantial ventricular dilation is defined as dilated cardiomyopathy. The present analysis has seen an increase in the percentage of patients receiving transplants for idiopathic dilated cardiomyopathy and it is now on a par with ischemic heart disease, each of them representing 36% of causes of transplants.

The importance of waiting list mortality may be underestimated as it only includes patients who die while on the list, ignoring those removed due to severe decompensation with multiple organ failure who die after removal from the list. In 2005, the number of patients who died and the number who were excluded from the waiting list were 8% and 20%, respectively. Consequently, the figure we should consider when evaluating the real impact of waiting list mortality currently stands at 28%.

Urgent heart transplantations are somewhat controversial as they are operations with specific characteristics (recipients in worse clinical condition, less-than-ideal donors, longer periods of ischemia) that entail a worse prognosis than programmed transplants. In 2005, the percentage of urgent transplants fell markedly (22% in 2005 vs 35% in 2004). This figure stands slightly below the mean for the last 5 years (23%). The cause of such a substantial fall is not entirely clear but, without doubt, to a considerable extent the increase in restriction criteria agreed by transplant teams in early 2005 has been influential. Indication for urgent transplantation has been questioned given that it offers poorer results. However, the transplant teams are of the opinion that this option should continue to exist, in a controlled form, as it is the only therapeutic option available to the subgroup of patients with advanced heart failure and uncontrollable acute decompensation. In any event, we must remember, as European guidelines on acute heart failure recommend, that it is better to stabilize heart failure rather than indicate for urgent transplantation.[21]

Over the years, overall survival has shown a clear trend towards progressive improvement. However, logically, the number of patients added to the Registry each year represents a comparatively smaller percentage of the total. Thus, the chances of finding substantial changes in 1 year are very remote and analysis of survival by eras is more illuminating.

When evaluating this Registry and comparing it with others we must remember that it includes all transplantation procedures and reliably portrays the reality of transplantation in Spain. However, analyses are global and also include high risk transplants (urgent transplants, older age group recipients, pediatric transplants, retransplants, heterotopic transplantations, combined heart-lung, heart-kidney, heart-liver, and other simultaneous transplantations).

In 2005, early mortality (the early 30 days) was 10%, which was lower than the mean for the last 5 years (12%). The most frequent cause of early mortality was acute graft failure which accounts for 43% of deaths during this period. Despite being a postoperatory problem, the impact of acute graft failure is so great that it causes a substantial number of deaths at >1 month too. It is of interest to observe that mortality due to rejection (early mortality 6%, late mortality 9%) is notably less than that caused by infections (early mortality 16%, late mortality 20%). Perhaps transplant teams should consider reducing overall immunosuppression regimens despite the fact that it might lead to a higher number of rejection episodes. From a clinical perspective, at least, these are usually more controllable.

To conclude, we can state that:

1. In recent years, the annual volume of heart transplantations has fallen despite the inclusion of older and older donors. The number of procedures seems to have stabilized at almost 300 per year.

2. Heart-lung transplantation has not yet become firmly established in Spain. There are few such transplantations each year.

3. In general, (early and late) survival rate figures are similar to those published in international registry reports and have improved year on yearly, especially in the last 5 years.

4. We should continue to try to reduce the high incidence of acute graft failure. This would have a highly positive effect on the probability of immediate post-operative and overall survival.

5. Given that infection is a greater cause of morbidity and mortality than rejection, we should pay it more attention to it and situate it among the principle objectives of general studies and of clinical trials of drugs.

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