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When and why do heart transplant recipients die? A 7 year experience of 1068 cardiac transplants

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Abstract. This mortality study deals with the 1068 heart transplants (1054 patients) performed in Italian Units from November 1985 to April 1992. The death rate was 19.7% and the actuarial survival was 89% at 1 month, 83% at 1 year and 74% at 6.5 years. Recipients who died had been less often transplanted for dilated cardiomyopathy, were older (44.1 vs. 41.7 years) and more often male (84.5 vs. 72.7%). Analysis of the causes of death was restricted to orthotopic transplantations (1029/1068 procedures, 195/208 deaths). Deaths were grouped within four intervals: peri-operative (≤ 1 month, 50.0% of deaths), early (>1 month ≤ 3 months, 17.2%), intermediate (>3 months ≤ 2 years, 22.6%) and late (>2 years, 10.2%). The prime causes of death were mostly post-operative graft failure (whose effects brought about 64% of peri-operative deaths, 28% of early and 7% of intermediate deaths), post-operative complications (10% of peri-operative deaths), acute rejection (10% of total deaths, distributed in all the periods), graft arteriopathy (6% of early, 36% of intermediate and 58% of late deaths), infections (17% of deaths, occurring in all periods but late) and malignant tumours (7% of deaths), lymphomas being the first to occur and Kaposi's sarcoma occuring only in the intermediate period. Repeat transplantation had a poor outcome (death rate 71.4%), two-thirds of the re-transplanted patients' deaths being due to early graft failure and a third to late relapsing graft vasculopathy.

Key words: Cardiac transplantation – Mortality – Allograft rejection – Graft arteriopathy – Tumours

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Introduction

Post-mortem examinations have made a major contribution to the understanding of the pathology of cardiac transplantation (Uys et al. 1979). Continual changes in the age distribution of recipients, immunosuppressive therapy, supportive treatment of patients maintained on the waiting list, donor ischaemic times and recipient monitoring make careful evaluation more and more necessary (McManus 1992). Because of the relatively low death rate of heart transplant recipients, it has become mandatory to perform multi-centre studies (McManus 1992) in order to gather sufficient information. The limitation of these studies, however, lies in collecting data from different, often barely comparable, sources.

The purpose of the present paper is to report the mortality data of the eleven Italian cardiac transplantation units in their first 7 years of activity (1985/1992). Such a multi-centre study has the advantage of reporting a large series (208 deaths out of 1068 transplants) which was collected from a homogeneous population, undergoing the same monitoring procedures.

Materials and methods

We studied 1068 heart transplants performed on 1054 patients (14 recipients were re-transplanted) from November 1985 to April 1992. The patients underwent surgery in the eleven transplant units which have been authorised in Italy since 1985.

Most patients underwent orthotopic transplantation (1029/1068; 96.4%), but 13 heterotopic (1.2%), 12 heart-lung (1.1%) and 14 orthotopic re-transplants (1.3%) were performed. In 4 orthotopic transplants the donor's heart was obtained through a domino procedure. Since orthotopic transplants represent the large ma-

jority of our series, the study of the causes of death was restricted to this procedure only, to obtain a more homogeneous group without losing considerable information.

All the recipients were treated with a similar immunosuppressive procedure (triple therapy with cyclosporine A, prednisone and azathioprine) and monitored with a schedule of endomyocardial biopsies (Gallo et al. 1992a). The working formulation (Billingham et al. 1990) for the nomenclature of rejection was first adopted in a pilot study (Gallo et al. 1992c) and is currently in use in all the units.

The present multi-centre study was set up by the first author by sending to all the sections of pathology of the transplantation units a questionnaire for each deceased patient. Data about all the 208 died recipients were collected and subsequently analysed.

The chi-square method was used for comparison of percent ratios. Actuarial survival rates were computed according to the Kaplan and Meier's (1958) estimate. A $p<0.05$ was considered statistically significant.

Results

During the first 6.5 years, 208 patients died of the 1054 transplanted (death rate 19.7%). Half of the deaths occurred within the first post-operative month; the cumulative death rate rose to 67% at 3 months, to 81% at 1 year and to 90% at 2 years. That means that only 10% of deaths occurred after the second follow-up year. The actuarial survival rate (Fig. 1) is 89% at the end of the first post-operative month, 86% at 3 months, and 83% at 1 year. After the first year, the survival percentage falls slightly but steadily to a mean rate lower than 2% per year, reaching 74% at 6.5 years.

Many pre-transplant risk factors affect survival. One of these is the spectrum of pathology which requires the transplant: in our series, idiopathic dilated cardiomyopathy (Table 1) was significantly rarer among dead patients than in alive recipients and the opposite was true (although not significantly) for ischaemic, valvular and congenital heart disease and for myocarditis. Age at transplantation also influences survival: surviving recipients were younger than non-survivors (41.7 vs. 44.1 years). This may simply reflect the age difference according to the underlying disease: in our series (Gallo et al. 1992a) the mean age of patients transplanted for dilated cardiomyopathy (42.3 years) was lower than that of the subjects transplanted for valvular (45.0 years) or ischaemic (48.7 years) heart disease. Male patients had a worse outcome: they represented 72.7% of living recipients but this rate rose to 84.5% among the dead, the difference being highly significant ($p<0.01$). In our series, heart-lung transplantation seemed to show the best survival rate (83.3%) but this conflicts with the worldwide experience (Kriett and Kaye 1991) and may be explained by this procedure being rather recent in our experience and the follow-up thus being short. Orthotopic transplantation had a good outcome (80.3% survival), followed by heterotopic (76.9%) and domino (75.0%) transplants. Repeat transplant had a poor overall outcome (28.6%).

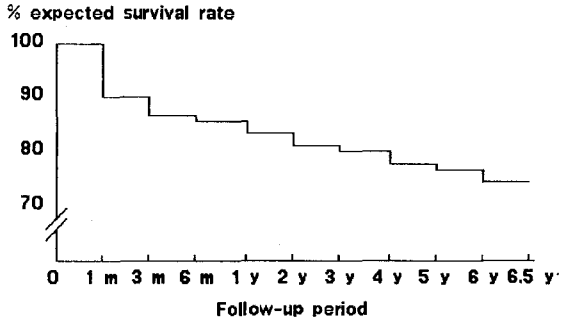

Fig. 1. Kaplan-Meier probabilities of survival after cardiac transplantation. The curve refers to our entire series of 1054 patients

Table 1. Distribution of pathologies that required transplantation in alive and deceased patients

Pathology	Per cent distribution		Statistical significance
	in alive patients	in deceased patients	
Dilated CM	50.9	37.1	*
Ischaemic HD	34.1	40.6	NS
Valvular HD	5.2	8.6	NS
Congenital HD	2.0	4.1	NS
Hypertrophic CM	2.2	2.0	NS
Endocardial Fibroelastosis	1.7	1.5	NS
Restrictive CM	1.3	2.0	NS
Myocarditis	0.7	1.5	NS
Cardiac Tumours	0.5	0.5	NS
Arrhythmogenic CM	0.1	0.5	NS
Others	1.3	1.6	

CM, Cardiomyopathy; HD, heart disease; * $p<0.01$; NS, $p>0.05$

Major pre-existing pathologies of the graft were occasionally detected at the post-mortem examination of the recipient: type C (Schutz et al. 1990) atherosclerotic stenoses (>70%) of the epicardial coronary arteries in three short-term survivors, arrhythmogenic cardiomyopathy in three hearts, and an isolated post-inflammatory scarring of the tricuspid valve in one heart. One heart had a large ventricular septal defect that had caused Eisenmenger's syndrome. It had been evaluated as suitable for a domino procedure and was implanted after closing the defect but, unfortunately, the recipient died of pump failure.

An intriguing feature which was not rare in our short-term survivors and was at times attributed to a pre-transplant pathology, was a marked and diffuse myocardial hypertrophy, often accompanied by histological findings of non-specific myocardial disarray in the mid-septal region. Hypertrophy was sometimes so severe (Fig. 2) that an unaware pathologist might attribute it to pre-transplant hypertrophic cardiomyopathy. By measuring the ventricular thickness (Silver and Freedom 1991) hypertrophy was found in 39% of our post-mortem series: the mean values of the ventricular thickness were 0.64 cm on the right and 1.81 cm on the left respectively. Histological examination confirmed the existence of myocardial hypertrophy and disclosed different additional features according to the timing of death. In short-

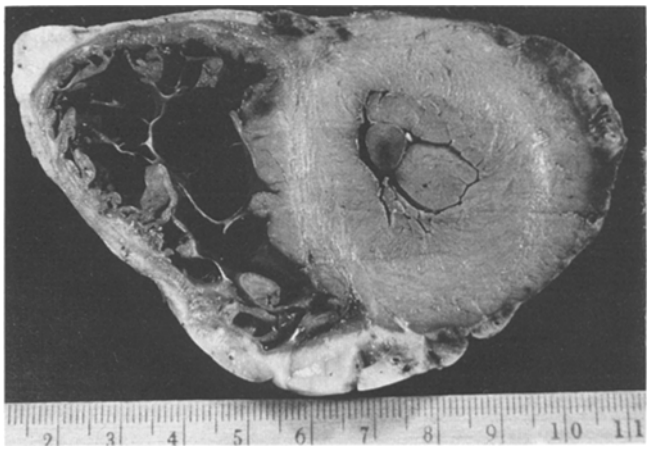

Fig. 2. Donor's heart. The recipient died of congestive failure, due to pulmonary hypertension, on the fifth post-operative day. The heart is sectioned according to an echocardiographic short-axis plane: the left ventricle exhibits an evident myocardial hypertrophy, with a reduced cavity. The right ventricle is dilated. The histological examination confirmed the presence of hypertrophy, associated to areas of haemorrhagic reperfusion necrosis: one of them is visible at a macroscopic level within the posterior papillary muscle

term survivors (63% of patients with hypertrophy) the main histological findings were multifocal reperfusion necrosis (47%), acute rejection (23%) or infective myocarditis (12%). In early and intermediate-term survivors (30%) further examples of acute rejection (25%) as well as graft arteriopathy (75%) were observed; in late-survivors (7%) only graft arteriopathy was present.

Other pre-transplant risk factors are said to affect the short or long-term survival of recipients, but were not evaluated in the present pathological study.

Our analysis of the pathology at death of recipients is restricted to orthotopic transplantation only (195/208 deceased patients). The data were mainly drawn from the post-mortem examination, which was performed in 159/195 patients (81.5%). In the remaining cases autopsy was impossible because the patient died suddenly at home, or consent was denied. The prime cause of death could be definitively determined on pathological or clinical grounds in 186/195 cases.

The distribution of pathologies observed at the post-mortem examination varies substantially according to the survival time. We subdivided the 186 patients whose cause of death was determinable into four groups (Table 2): peri-operative deaths (within the first month after

Table 2. Per cent distribution of the prime causes of death, subdivided by survival intervals, in the group of orthotopic transplant recipients

Prime cause of death	Timing of death				Total $n=186$
	Peri-operative ≤ 1 month $n=93$	Early >1 month ≤ 3 months $n=32$	Intermediate >3 months ≤ 2 years $n=42$	Late >2 years $n=19$	
Graft failure					
Pump failure	30	16	5	–	19
Multi-organ failure	18	6	2	–	11
Pulmonary hypertension	16	6	–	–	9
Total	64	28	7	–	39
Postoperative complications	10	–	–	–	5
Acute rejection	9	19	5	11	10
Graft arteriopathy	–	6	36	58	15
Infections					
Bacterial	8	6	7	–	7
Fungal	2	6	5	–	3
Viral	2	16	7	–	5
Protozoal	1	3	2	–	2
Total	13	31	21	–	17
Tumours					
Lymphoma	–	3	3	11	2
Kaposi's sarcoma	–	–	7	–	2
Pulmonary carcinoma	–	–	7	5	2
Other cancers	–	–	–	11	1
Total	–	3	17	27	7
Others	4	13	14	4	7

transplantation; 93 patients; 50.0%) early deaths (after the first month but within the third month; 32 patients; 17.2%) intermediate deaths (>3 months ≤2 years; 42 patients; 22.6%) and late deaths (>2 years; 19 patients; 10.2%).

We defined the prime cause of death as the disease which initiated the process eventually leading to death. For example, a patient with Kaposi's sarcoma, whose immunosuppressive therapy was accordingly reduced, died of acute rejection; nevertheless, Kaposi's sarcoma was regarded as his prime cause of death.

A different spectrum of pathologies occurred according to the time elapsed from transplantation to death (Table 2). In 64% of patients who died in the peri-operative period, the new heart was not able to cope with the recipient's poor general condition (Table 2). A further 10% died of post-operative complications, such as haemorrhage, graft compression, cerebrovascular accident, or aortic dissection. Acute rejection and infection were respectively responsible for 9% and 13% of deaths. In the early period, 28% of patients died from the consequences of peri-operative graft failure (Table 2). Infections were the most frequent cause of death (31%). Untreatable acute rejection accounted for 19% of deaths, but graft arteriopathy in the setting of chronic rejection caused deaths even in this early period (6%). Some tumours were present. In the intermediate period some mortality (7%) imputable to the late sequelae of peri-operative graft failure was still evident (Table 2). The frequency of fatal episodes of acute rejection dropped to 5%, whereas graft arteriopathy became the most frequent cause of death (36%). Mortality for infections fell (21%) whereas that for tumours rose (17%). In the late period there was no mortality for infections (Table 2), the causes of death being substantially limited to graft arteriopathy (58%) and tumours (27%). Two occurrences (11%) of late acute rejection were also recorded; in one case this was due to voluntary discontinuance of therapy by the patient.

Repeat transplant had a poor outcome overall (survival being limited to 28.6%). In dead patients re-transplantation had been required because of post-operative graft failure at a short interval (1 day–2 months) from the former transplantation, or for graft vasculopathy (8 months–2 years). Two-thirds of subsequent deaths were due to graft failure (on the average within 1 month from re-transplant) and the other third to relapsing graft arteriopathy (at a median interval of 10 months from re-transplant).

Discussion

The Italian heart transplantation project proved to be successful; our survival rates are fully comparable with those of other outstanding centres (Laufer et al. 1988; McCarthy et al. 1989; Olivari et al. 1990; Primo et al. 1991; Uretsky et al. 1987; Yacoub et al. 1990). Cardiovascular pathologists joining the project made a major contribution to these results, examining thousands of endomyocardial biopsies (Gallo et al. 1992a) and performing many post-mortem examinations, with a high autopsy rate (83.6% for the whole series, 81.5% for orthotopic transplants), comparable with that of other units (Graham 1992). Even if some of the reported results are self-explanatory, others may deserve a brief discussion.

It is well-known that ischaemic (Sharples et al. 1991), valvular (Sharples et al. 1991) or congenital heart disease (Trento et al. 1989) and myocarditis (O'Connell et al. 1990) adversely affect transplant outcome. In our series, patients transplanted for idiopathic dilated cardiomyopathy had a significantly ($p<0.01$) better outcome (Table 1). In our opinion, this happens because the disease is limited to the heart and the patient will not necessarily have undergone previous surgery. This reduces the risk of both post-operative complications and a multi-organ failure syndrome.

Male patients have a significantly higher overall mortality rate, but male recipients are said to be particularly prone to graft arteriopathy and female ones to fatal acute rejection (Sharples et al. 1991). In our series there was a 0.8% rise in male rate among patients dying of graft arteriopathy and a 5.6% rise in female rate among those dying of acute rejection. Both figures lack statistical significance ($p>0.05$).

Although repeat transplantation is still associated with a poor outcome, with a 49% 1 year actuarial survival rate in the world series (Kriett and Kaye 1991) and a 28.6% overall survival rate in ours, there is growing evidence (Ensley et al. 1992) that in selected patients re-transplantation gives encouraging results.

We were surprised to find some pathology in the donor heart, although this had been observed in other series (Ninet et al. 1991; Pomerance and Stovin 1985). This finding is now unsurprising since after showing a sharp rise from 1981 to 1986, the world-wide number of heart transplants has gone up only very slightly in the last years (Kriett and Kaye 1991) because of a shortage of donors. Consequently the limit age of acceptable donors is being raised (Primo et al. 1991): the presence of native atherosclerotic lesions in the grafts is accordingly going to become more and more frequent with the growing age of donors (Primo et al. 1991).

Arrhythmogenic cardiomyopathy was observed three times in our series. It was an unexpected finding in one patient who died of right ventricular failure due to pulmonary hypertension, on the second post-operative day. In a second case, the diagnosis was made at pathological examination of a donor's heart that was not implanted because it had suddenly arrested during the harvesting procedures. A third patient died of an unexplained biventricular dysfunction, 2 months after transplantation, and the transplanted heart was found to exhibit a biventricular adipose infiltration (Gallo et al. 1992b).

Myocardial hypertrophy is a frequent finding at the post-mortem examination of recipients. In long-term survivors, it is usually associated with graft arteriopathy (Crawford et al. 1992) or with the effects of long-lasting pre-transplant ischaemia (Imakita et al. 1987). In short-term survivors, myocardial hypertrophy has been observed in combination with the myocellular necrosis

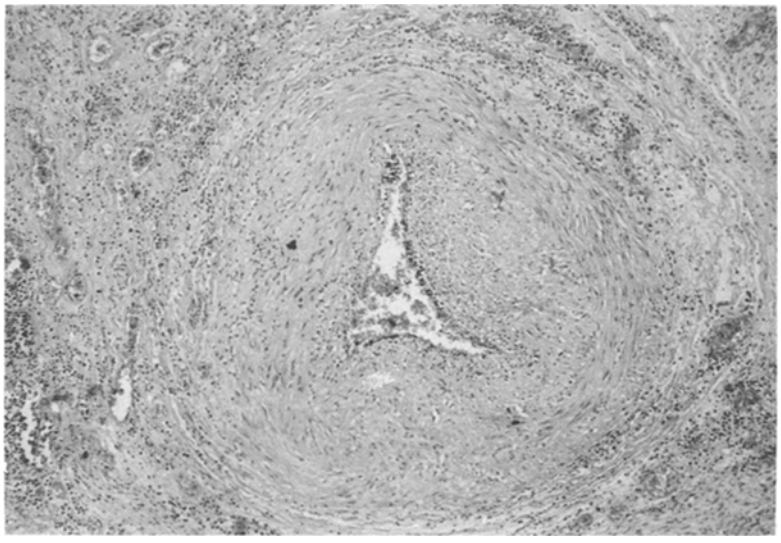

Fig. 3. Endarteritis of a coronary branch. Lymphocytes are scattered through the wall; the lumen is centrally narrowed by a diffuse proliferation of smooth muscular cells. The recipient died of allograft vascular disease 25 months after transplantation. H & E, ×40

caused by acute rejection. In our experience, hypertrophy was associated with many non-specific features eventually leading to myocellular death: early reperfusion necrosis, acute rejection, infective myocarditis and late ischaemic necrosis due to graft arteriopathy.

For statistical purposes, a distinction between early and late deaths is frequently made, and peri-operative deaths are often noted separately. Although, in small series, it may be difficult to couple the likely causes of death with the survival timing (Helmuth et al. 1991) this is certainly possible and useful in larger studies (Kriett and Kaye 1991). We subdivided the follow-up period into four intervals (Table 2). Our timing subdivision is similar to that proposed by Olivari et al. (1990) but we preferred to extend the intermediate period up to the end of the second post-operative year, because of the homogeneity of diseases observed in this interval.

In the world series (Kriett and Kaye 1991), post-operative graft failure and early complications are responsible for nearly 60% of deaths occurring within the first 2 weeks after transplantation. Graft failure seems to be of even greater importance in our series, since it caused 64% of deaths within the peri-operative period, and its effects extended for the subsequent periods. However, our mortality figures for graft failure are enlarged, as well as those for infections are reduced, by the definition of prime cause of death we adopted. Actually, graft failure was often the first but crucial event in a long chain of events leading to death, usually through a saprophytic infection, some weeks or even months later.

As in the world series (Kriett and Kaye 1991) so in ours the prevalence of fatal infective episodes varied according to the survival intervals, being greatest in the early period. The distribution of the microbiological agents differs in different periods (Table 2). It has been observed that bacterial infections prevail in the first 3 post-operative months (Cooper et al. 1983; Primo et al. 1991) whereas fungal infections occur later and viral infections may be early or late (Cooper et al. 1983). In our series, bacterial infections were relatively frequent in all the periods except the late (when no fatal infections were observed) and prevailed in the first post-operative month (Table 2). Viral infections (mostly by cytomegalovirus) were most frequently assumed to be the prime cause of death in the early period. Protozoal infections (Toxoplasmosis), although not being infrequent rarely caused death.

Our data on acute and 'chronic' rejection are difficult to compare with those of other series since some authors join them together under the common heading of rejection (Kriett and Kaye 1991) others separate them and identify 'chronic' rejection with the graft arteriopathy (Addonizio et al. 1990; Olivari et al. 1990) and still others treat graft arteriopathy as distinct from chronic rejection (Graham 1992). In the present paper, and for classification purposes, we identified chronic rejection with the allograft vascular disease due to coronary endarteritis (Fig. 3).

Malignant tumours are an important cause of death in long-term survivors, but may also occur very early. Interestingly enough, distinctive tumours develop in different survival intervals. Non-Hodgkin's lymphomas are usually the earliest tumours to occur, even within the third post-operative month (Davies et al. 1991; Graham 1992): in our series one patient died of a lymphoplasmocytoid polymorphic lymphoma on day 50 post-operation and another one of a B-type, diffuse, large cell lymphoma on day 159, but in the latter case the donor had been unexpectedly found to be affected by chronic lymphocytic leukaemia at post-mortem examination. We observed Kaposi's sarcoma only in the intermediate period, as if this tumour was associated with recent-onset immunodeficiency states. Other cancers (most often pulmonary carcinomas) were the prime cause of neoplastic deaths in cardiac transplantation recipients. For those whose origin is not usually related to oncogenic viruses or immunodeficiency states, the question arises of whether they existed before transplantation. This hypothesis is supported by the observation of occult carcinomas in short-term survivors detected in other autopsy

series (Graham 1992) and in ours: a male, 38-year-old, recipient who died of graft failure within the peri-operative period, was unexpectedly found to be affected by a 7 cm diameter papillary carcinoma of the thyroid gland.

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