Heart Transplantation: New Challenges for the 21st Century

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Since the first heart transplant in 1967, this surgical procedure has seen great vicissitudes. The initial difficulties inherent to any pioneering activity in the field of medicine were complicated by results considered unacceptable by many cardiologists and heart surgeons of the time. The 12- and 36-month survival rates of the first 82 patients of the Stanford group were 48% and 25%, respectively.[1] The high rates of death due to graft rejection were the cause of this worldwide discredit, and comments such as "heart transplantation: that great speculation of the future" were common in medical circles. The introduction during the 1980s of cyclosporine as an immunosuppressive therapy led to the increasing number of heart transplants, far above what was thought possible just a few years previously. The great speculation had finally become a reality, with much improved survival rates, now standing at 82% at 1 year and 68% at 5 years.[2] Heart transplantation thus became unquestioned as the only possibility for patients with advanced heart failure, often refractory to all types of drug therapy. Furthermore, the greater understanding of the underlying neurohormonal hyperactivity in the pathophysiology of heart failure and its prognosis, as well as the role of therapy aimed to control and modulate this activity, have resulted in substantial changes in the expectations of patients with advanced heart failure.

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SELECTION OF CANDIDATE PATIENTS FOR HEART TRANSPLANTATION

The important advances in pharmacologic therapy, especially in the use of beta-blockers, and in surgery for heart failure—automated implantable cardioverter defibrillator (AICD), cardiac resynchronization, mechanical circulatory assistance, and artificial hearts—have led to reconsideration of the indications for heart transplantation. Compared with medical therapy, the benefit of heart transplantation is only seen in patients with severe disease and more likelihood of dying during the first year of follow-up (COCPIT study).[3] In an attempt to help with this difficult decision, many heart transplant teams now use complex algorithms to score the risk. However, the indication for such an important operation as a heart transplant cannot be based solely on a mathematical formula. The traditional criteria for including a patient on the waiting list for a heart transplant are applied to patients who are at medium- to high-risk according to the heart failure survival score (HFSS), which groups 7 parameters, including peak oxygen uptake.[4] Other teams consider oxygen consumption <14 mL/min/kg as the main criteria for inclusion on the heart transplant waiting list. These criteria are currently being questioned because the administration of such drugs as beta-blockers, spironolactone, or new inotropic substances have led in recent years 55% of those patients with an oxygen uptake of 10-14 mL/min/kg now to be considered at low risk, according to the HFSS, as their survival is similar to that of patients who have a heart transplant (88% at 1 year).[4] These patients, therefore, are now no longer candidates for heart transplantation, although they require a very close clinical follow-up to be able to make a correct reevaluation at all times. The incorporation of natriuretic peptides (BNP, NT-proBNP) for the diagnosis and prognosis of patients with heart failure resulted in a significant clinical advance. With time, their use and evolution may help optimize medical therapy and define a subgroup of

patients with persistently high values who could be candidates for other treatments, such as heart transplantation.

Another approach would be to determine which of the 2 types of therapy (medical or surgery) provides a better quality of life, assuming that both afford equal survival. The answer is not easy; beta-blockers have led to improved indices in quality of life in the most important studies, whereas heart transplant patients see their capacity to work limited and have ventilatory disorders, psychological problems and difficulties in their relationships, which occasionally limit the benefits derived from the operation. Most of these problems (obesity, myopathy, osteoporosis, and neurotoxicity) are associated with the side effects of corticosteroids and calcineurin inhibitors.

Alternatives therefore need to be sought for low-risk patients with an indication for a heart transplant. The recently published results of the COMPANION study[5] showed that patients with heart failure and a wide QRS complex have a 20% reduction in the primary end point (death or hospitalization from any cause) after cardiac resynchronization, with or without an AICD. The study also showed a clear improvement in exercise capacity, heart failure symptoms and quality of life. We may thus be able to state that cardiac resynchronization should be considered before heart transplantation in patients who fulfil the criteria for heart transplantation.

Many patients in heart transplant programs have a high risk of sudden death, despite optimal treatment with angiotensin-converting enzyme inhibitors and beta-blockers. Although these drugs have shown to reduce the rate of sudden death, this remains the major cause of death in functional class III patients, who are sometimes candidates for a heart transplant. The most common etiology of sudden death is malignant ventricular arrhythmia, followed by bradyarrhythmia. The placement of an AICD to prevent sudden death in these patients is controversial. The report by Kadish et al[6] shed some light on this obscure side of heart failure. Of 458 patients with dilated cardiomyopathy and ventricular arrhythmia (ventricular extrasystole and nonsustained ventricular tachycardia), the 229 who received optimal pharmacologic therapy plus an AICD experienced a significant reduction in death from arrhythmia compared with the other 229 treated with drugs alone. There were 17 sudden deaths from arrhythmia: 3 in the AICD group compared with 14 in the optimal therapy group (RR=0.20; 95% CI, 0.06-0.71; *P*=.006). Subgroup analysis showed that the implantation of an AICD only reduced the risk of death significantly in patients with NYHA functional class III or men. These results are clinically important, but we should not forget their economic burden. The authors of the study do not advocate the indiscriminate implantation of an AICD in these patients, but recommend the use of these devices on a case-by-case basis after determining the individual risk profile.[6]

Another important aspect is the management of patients with advanced heart failure or cardiogenic shock using mechanical ventricular assistance or provisional or definitive artificial hearts. Although these measures are mainly used as a bridge to heart transplantation, initial results with the implantation of an artificial heart as a definitive therapy are encouraging for these types of patients, or even for patients who are not candidates for a heart transplant. The possibility of recovering ventricular function and the progressive withdrawal of these mechanical support systems by intensifying pharmacologic therapy already exists. In the future, the application of cell or gene therapy in patients with these types of support may obviate the need for a heart transplant.

Little doubt exists concerning the efficacy of heart transplantation in patients with functional class IV or cardiogenic shock, but the indication for a heart transplant in class III patients or patients with a certain stability is becoming more and more questioned. Until just a few years ago, the superiority of heart transplantation in these patients was assumed to be clinically evident. Nowadays, however, the scientific community is calling for a prospective, randomized study to compare optimal medical therapy with heart transplantation.[7] This proposal is further warranted due to the increasingly reduced number of heart donors and the growing number of patients on the waiting list, as well as the rise in emergency indications. A national consensus is therefore required in cooperation with international scientific societies.

CLINICAL MANAGEMENT OF POSTTRANSPLANT COMPLICATIONS

The pathophysiology of the transplanted heart and the lifetime requirement for immunosuppressive therapy favor the appearance of additional diseases. Patients with heart transplants therefore require strict clinical control. In this issue of the REVISTA ESPAÑOLA DE CARDIOLOGÍA, Perez-Villa et al[8] present the confirmation that despite eliminating the cause of heart failure, the expected normalization of the neurohormonmal activity fails to materialize. The authors show that during the first few posttransplant months no important reduction takes place in plasma levels of angiotensin II (AT-II), endothelin or aldosterone, whereas a significant reduction was noted in the levels of vasodilating peptides (natriuretic atrial peptide and adrenomedullin). Our knowledge of the pathophysiology of heart failure suggests that this unfavorable neurohormonal profile may well contribute to the genesis of the most

common posttransplant diseases. Those diseases associated with neurohormonal hyperactivity are systemic and pulmonary hypertension, salt and fluid retention, and endothelial dysfunction as a factor related with graft vessel disease. From the clinician's point of view, high blood pressure may be the most interesting section related with this hyperactivity, since 72.8% of heart transplant patients have hypertension at 1 year and 94.6% at 5 years. The cause of this hypertension is multifactorial, and includes prior hypertension, the effect of immunosuppression, sympathicotonia, and nephrotoxicity. Nevertheless, loss of the cardiorenal reflex secondary to cardiac denervation is an important factor in the inability to suppress the renin-angiotensin-aldosterone (RAA) system, thereby leading to posttransplant hypertension and poor homeostasis of body fluids.[9] The retention of salt and fluids is due to an alteration in the normal diuretic and natriuretic response to volume expansion. The use of angiotensin-converting enzyme inhibitors, such as captopril, reverts this anomaly. These alterations in homeostasis cannot be attributed solely to cyclosporine or other immunosuppressive agents, as these anomalous responses to hypervolemia and the infusion of saline have not been seen in patients with a liver transplant who followed the same immunosuppression regimen.[9] It has been suggested that the hypertensive effect of calcineurin inhibitors, such as cyclosporine and tacrolimus, may be due to increased systemic vascular resistance secondary to the presence of generalized arterial vasoconstriction. This pathophysiologic response may be due to adrenergic activation and activation of the RAA system, which would corroborate the findings of the study mentioned previously[8] and those of other authors.[10] The finding of persistently raised levels of endothelin[8] should be added to our prior knowledge of abnormal endothelial control of vessel tone and the reduction of nitric oxide activity after transplantation. Endothelin, a powerful vasoconstrictor released by the endothelium, has been related with a poor prognosis before heart transplantation, after which it participates in the pathophysiology of pulmonary and systemic hypertension, in acute rejection and in graft vessel disease, although some researchers doubt this action. The use of antiendothelin drugs, such as bosentan, for the early and delayed treatment of these complications remains to be determined. From what we have seen and from our knowledge of the pathophysiology involved, the treatment of posttransplant hypertension should be based on the restriction of salt and the use of angiotensin-converting enzyme inhibitors or AT-II.

The process of cardiac reinnervation, described some time ago, improves the cronotropism and inotropism of the transplanted heart. A Spanish group[11] has recently shown cardiac reinnervation in 31% of the patients studied by scintigraphy with ^{123}I-metaiodobenzylguanidine. It would be interesting to determine the behavior of the RAA system in these patients and whether differences exist compared with those patients who remain denervated. Cardiac denervation may play an important role in exercise limitation experienced by patients with a heart transplant. Programs of rehabilitation and physical training attempt to counteract this clinical problem.[12]

One controversial aspect is the possible association between hyperactivity of the RAA system and graft vessel disease, which together with tumors, remains the most important cause of late post-heart-transplant death. The etiology and pathogenesis of vessel disease, which is detected angiographically in 30%-50% of patients at 5 years, involve immunological questions together with several other factors, including classical cardiovascular risk factors (diabetes mellitus, hypertension, dyslipidemia, and obesit), plus graft ischemia and cytomegalovirus infection. AT-II is a powerful activator of fibrosis and endothelial proliferation, as well as smooth muscle cells. The costimulatory efffects of AT-II have also been reported in the immunological response to activation of mediators such as TGF-β, TNF-α, IL-6, VCAM-1, and P-selectin. An increase and upregulation of the AT1 receptors of AT-II have recently been reported in biopsies from heart graft tissues. These findings suggest that the presence of high posttransplant levels of AT-II may contribute to the genesis and development of graft vessel disease. Consequently, the pharmacologic blockade of AT-II would slow progression of graft vessel disease; this has already been been demonstrated in animal studies, though not yet in humans. The only drugs which have so far proven to be protective of graft vessel disease are HMG-CoA reductase inhibitors, rapamycin, and micophenolate mofetil.

Other important complications also appear during the follow-up of heart transplant patients. The management of these problems is complex, because they are related with the therapy for transplant patients and usually cause a high degree of death and disease. The most important complications are dyslipidemia, new onset diabetes mellitus, nephrotoxicity due to the immunosuppresssive drugs, and neoplasias.[2]

Hyperlipidemia, a very common metabolic disorder which occurs in 50% of heart transplant patients at five years, has a multifactorial cause.[2] The relative importance of each of these factors is difficult to determine, but a fat-rich diet, genetic predisposition and immunosuppressive drugs, especially steroids and calcineurin inhibitors (cylosporine and tacrolimus) all play a primordial role. Many heart transplant centers now include the

use of m-TOR inhibitors, such as sirolimus and everolimus. The powerful vascular antiproliferative effect of these inhibitors, which have their maximum expression in the reduction of graft vessel disease, is dampened by their hyperlipidemic effect. The clinical repercussion of hyperlipidemia in heart transplant patients is its association with the development of graft vessel disease. Therapeutic management involves HMG-CoA reductase inhibitors and changes in the immunosuppression regimen, such as reduction or withdrawal of steroids.

The incidence of diabetes mellitus in heart transplant patients reaches 32% at 5 years post-transplant.[2] As with hyperlipidemia, the etiology and pathogenesis of diabetes mellitus is related with the use of corticoids, cyclosporine, and more especially tacrolimus. Diabetes mellitus causes morbidity (infections) and is associated with graft vessel disease. The treatment is the same as for other patients with diabetes mellitus and the changes in immunosuppression therapy are oriented towards withdrawal of steroids and the replacement of tacrolimus by other immunosuppressive drugs.

Nephrotoxicity, with some degree of kidney failure, affects 22% of heart transplant patients, of whom 2% are on dialysis and 0.4% have also received a kidney transplant.[2] Calcineurin inhibitors (cyclosporine and tacrolimus) are largely to blame for this severe problem. Management, therefore, should include reduction or withdrawal of these drugs with the introduction of m-TOR inhibitors (sirolimus or everolimus) associated with mycophenolate mofetil.

Neoplasias are now the second leading cause of long-term death in heart transplant patients. At 5 years, 8.8% of heart transplant patients have some type of cancer; 53% skin cancer, 35% solid organ cancer, and 12% lymphoma.[2] The relative risk of developing type B lymphoma is 300 times greater than in the general population. Early detection is vital because the death rate is very high, despite radical therapy. This high death rate is due not only to the tumor itself but also to acute graft rejection following the necessary reduction of immunosuppression. m-TOR inhibitors, such as sirolimus and everolimus, have shown an antineoplastic effect in several studies and are used at various heart transplant centers as immunosuppressive agents for these patients.

Finally, other types of relatively common problems can also seriously affect the quality of life in heart transplant patients. These problems, which include neurotoxicity, osteoporosis, and digestive complications, all have their origins in the use of immunosuppressive drugs and their management should thus include changes in immunosuppressive therapy.

FINAL CONSIDERATION

We can conclude from the above that heart transplantation is effective but not exempt from complications due to the use of immunosuppressive drugs. Nevertheless, many of these complications can also be attributed to neurohormonal hyperactivity, which remains after heart transplantation, and to cardiac denervation.

Most heart transplant centers in Spain are now becoming multidisciplinary units for the evaluation of patients with heart failure. Improvements in medical management and new surgical techniques, such as cardiac resynchronization, implantation of an AICD and mechanical circulatory assistance, mean that heart transplantation is the last option to be considered after all possible therapeutic alternatives have failed. Heart transplantation is limited more and more by the low number of heart donors and the problems of posttransplant disease associated with life-long immunosuppresive therapy. Even so, heart transplantation, when correctly indicated, has magnificent results, which may even be spectacular in some types of patients.

Finally, we believe that we should be more daring in awareness of the prognosis of advanced heart failure and the involvement of other health care professionals in its prevention and early diagnosis, thereby preventing heart failure from becoming one of the most severe epidemics of the 21st century, as it was in the 20th century.

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