

REVIEW ARTICLE

Selection of Congestive Heart Failure Patients for Heart Transplant

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Heart failure is one of the most common causes of hospitalization in adult patients. With the recent technological advances and the use of new medications for controlling rejection, heart transplant has been established as a definite therapeutic measure for properly selected patients with advanced congestive heart failure. As there is an active transplant program in the Cardiovascular Center of Puerto Rico and the Caribbean, this review is intended to acquaint the

practicing physician with the required work up and management of patients referred for cardiac transplant. Emphasis is given to indications, clinical and psychosocial evaluation, optimization of medical therapy and to the absolute and relative contraindications.

Key words: Heart transplant, Heart failure, Peak MVo₂, Pulmonary vascular resistance

Heart failure is one of the most common causes of hospitalization in the United States. At present, nearly five million Americans have heart failure. The incidence has been increasing dramatically over the past decade, where hospitalizations for heart failure (CHF) has increased by 159% (1). This represents more than two million hospitalizations each year which imposes a huge burden to the national health care budget. Patients with severe heart failure have a 1- to 2-year mortality approaching 50% despite appropriate and advanced medical treatment. However, heart transplant has altered the course of end-stage heart disease with one, three and ten-year survival rates exceeding 85%, 80%, and 50%, respectively. Up to 1998, more than 55,000 such procedures have been performed in more than 330 centers worldwide, with nearly 3,000 cases done each year (2).

Advanced heart failure is present when patients with CHF exhibit symptoms that limit their daily life activity (New York Heart Association class III or IV) in spite of optimal medical treatment. The great majority of patients fulfilling these criteria have severe left ventricular systolic dysfunction with an ejection fraction lower than 25%. Although, diastolic heart failure could present with a

similar clinical symptomatic profile, this article is focused in patients with severe left ventricular dysfunction as prospective candidates for heart transplant. In recent years, new advances in the treatment of heart failure have been translated into a better quality of life and decreased mortality, however, for many of the patients in advanced CHF, cardiac transplantation remains the only hope for prolongation of life and survival.

A heart transplant program has been operating successfully in the Cardiovascular Center of Puerto Rico and the Caribbean since June 1999. Up to this date, 53 heart transplants have been performed in this institution with excellent results. This article is intended to provide the practicing physician with information on the criteria for the appropriate referral of patients that could benefit from this life-saving procedure. Historically, the age limit for heart transplantation has been set at 65 years old, although in some centers the age limit has been expanded to 70 years. The clinician, while considering patients for possible heart transplant, has to exclude potentially reversible causes of CHF such as; ischemic heart disease, metabolic disturbances, valvulopathies, sleep apnea and exposure to environmental factors including toxic drugs, tobacco and alcohol.

Optimization of Therapy

All conventional medical or surgical therapies should be used before a heart transplant is considered. Evaluation might reasonably include, in very few cases, endomyocardial biopsy to rule out other treatable causes

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of cardiomyopathy, especially for patients without ischemic heart disease. Therapeutic drugs that should be tried in congestive heart failure before considering a heart transplant include ACE-inhibitors, beta-blockers, diuretics, and a vasodilator such as hydralazine or nitrates as well as digitalis and aldosterone receptor blockers (3,4). The infusion of intravenous inotropic agents like dobutamine and milrinone are included on the maximum therapeutic regimen. Sodium nitroprusside and intravenous nitrates with or without inotropic agents might be drugs of choice in selected cases (2,9).

The introduction of cardiac resynchronization therapy to this population has improved the quality of life and has been shown to decrease the incidence of hospitalizations in selected patients (4). This option should be tried in patients with concurrent left bundle branch block and a QRS interval of more than 120 msec in duration that persist with congestive heart failure symptoms in spite of optimal pharmacological therapy.

Heart failure remains a progressive disease despite multiple procedures to improve survival, since fewer than 5% of the patients with advanced heart failure are eligible for cardiac transplantation. The use of *implantable mechanical support* devices can reverse life-threatening hypoperfusion when used as a bridge for patients awaiting transplantation (5,6). A unique aspect of end-stage heart disease, as opposed to other chronic conditions, is the availability of implantable cardioverter defibrillators. Successful defibrillation can decrease mortality in such patients (3). Although these devices are effective to treat life threatening arrhythmias, the appearance of tachyarrhythmias predict a rapid decline for some patients.

The appropriate role of *inotropic infusions* remains unclear. They are often administered with the expectation that they will enhance diuresis and improve left ventricular contractility during decompensation and hopefully, accelerate discharge. This assumption has been questioned as these medications are considered by some to promote potentially fatal arrhythmias. In some patients, infusions can not be weaned-off without experimenting clinical deterioration and a subsequent progressive development of renal dysfunction. Occasionally, patients are discharged on these infusions awaiting transplantation but for most of them, this approach complicates the clinical picture, making it difficult to distinguish whether it delays death or improves life. The expected survival in patients on some inotropic infusions is less than 50% at three to six months (1,3).

Patients with congestive heart failure who have survived episodes similar to those of sudden cardiac death and those with *malignant ventricular arrhythmias* are candidates for the use of an *implantable cardioverter*

defibrillator. In most cases, these devices are combined with *biventricular pacing*. Recent technological advances have lead to the development of *left ventricular assist devices*, approved as an alternative therapy in selected patients who are not candidates for transplantation and has also been used as a bridge for heart transplant. These devices must also be considered in the management of patients with chronic congestive heart failure as their use is correlated with a clinically meaningful survival and an shown improvement in the quality of life (1).

Clinical Considerations

The selection of a candidate for a heart transplant is ultimately decided from a clinical assessment that determines the patient is free of the established contraindications or that suffers from a severe cardiac disability refractory to expert medical management. The pathophysiology on these patients usually is related to symptoms of severe congestive heart failure, but occasionally is dominated by recurrent lethal arrhythmias or intolerable ischemic symptoms.

The selection of patients for a cardiac transplant based solely on a low (<25%) ejection fraction has become less reliable since the introduction of aggressive vasodilator therapy, since there are some patients with severe left ventricular dysfunction who are remarkably free of symptoms. In contrast, even symptomatic patients, when using the appropriate pharmacologic therapy can experience one and four-year survival of 98% and 84% respectively, whereas patients who are removed from the list of heart transplant candidates because of clinical improvement have been shown to have similar symptoms and survival data as those going on to transplantation (1).

Even though, it may be easy to identify the most severely ill heart failure patients with a poor prognosis for 6-month survival, when dealing with a large group of patients with symptomatic cardiomyopathy and ominous objective findings, (ejection fraction of <25%, a stroke volume of <40 ml and severe ventricular arrhythmias) timing for heart transplant may be somewhat difficult. Clinical class, although somewhat imprecise, consistently helps in establishing a general estimate of the prognosis.

For patients with a low ejection fraction and stable New York Heart Association class II symptoms, the reported yearly mortality has been from 10% to 15%. For class III it has been 15% to 25% and 30% to 50% or higher in class IV. Once the clinical classification of III and IV has been reached and the ejection fraction is lower than 25%, left ventricular dilatation becomes a better predictor of higher mortality at every stage of the disease (1,2). A ventricular dilatation more than 70 mm conveys a poor prognostic

sign. A two-year survival of only 20% with a ventricular dilatation greater than 80mm has been reported. The degree of preservation of the right ventricular function also predicts outcomes in advanced disease. Prognosis at every stage is worsened by any degree of renal dysfunction. Hyponatremia in these patients usually indicates an intense activation of reflex systems, primarily the rennin-angiotensin system, as a last resource to preserve perfusion. Multiple parameters of neurohormonal and cytokine activation such as serum norepinephrine, endothelin, and tumor necrosis factor α , are available to predict outcomes, although they are not routinely measured. Recently, the measurement of the brain natriuretic peptide has been available in hospitals and emergency rooms laboratories and it has been found to be useful in estimating clinical severity of heart failure and its prognosis.

Indications for Heart Transplant

The most frequent causes of requiring heart transplant are equally divided between ischemic and nonischemic cardiomyopathy. Both ischemic heart disease and idiopathic cardiomyopathy account each one for 45% of the cases, while valvular heart disease accounts for 3.4%. Retransplant occurs in 2.2% and congenital and miscellaneous in 1.6% each (9). The contraindications for heart transplant encountered vary depending on the program. Table 1 illustrates the absolute contraindications

has been modified progressively due to the technological advances in treatment of rejection-related morbidity. There have been reports with 70 yr/old-transplanted patients with no significant difference in early and medium-term outcomes in comparison with patients on the standard list. At present, most transplant programs have an upper age limit of 65 years including the Puerto Rico program. Nonetheless, Patients older than 50 years may warrant additional screening for comorbid conditions like coronary artery disease. The concurrent occurrence of diabetes or other systemic disease, such as chronic pulmonary disease, probably would render most heart failure patients older than 60 years as non candidates for heart transplantation.

Peak exercise oxygen consumption. The peak exercise oxygen consumption (MVo₂) as well as cardiac output response to exercise, have been established as valuable tools for the initial evaluation for the selection of patients for a heart transplant and are the most important current criteria for screening these patients (9).

Peak exercise oxygen consumption is a non-invasive index of peak exercise cardiac output. Although, it can be influenced by noncardiac factors such as muscle deconditioning, motivation, gender, age and obesity, at present it is considered as one of the most validated and reliable criteria for heart transplant screening (7).

There is a consensus that a peak MVo₂ of either less than 14 ml/kg/min or less than 55% of predicted peak MVo₂ should result in a strong consideration of listing for heart

Table 1. Contraindications for Heart Transplant

Age > than 70 years	Severe peripheral vascular or cerebrovascular disease
Recent cancer with uncertain status	Insulin-requiring diabetes mellitus with end-organ damage
Psychiatric illness with poor medical compliance	Active infection
Systemic disease that would significantly limit survival or rehabilitation	Sarcoidosis
Pulmonary hypertension with pulmonary vascular resistance > six Wood units or three Wood units after treatment with vasodilators	Amyloidosis
Irreversible hepatic, renal, or a pulmonary dysfunction	Muscular dystrophy
	ABO incompatibility

for heart transplant. Relative contraindications for heart transplant include nonmetastatic infective endocarditis, malignancy without recurrence, obesity with > 140 of ideal body weight, hypertension with target organ damage and severe osteoporosis.

Selection Criteria for Cardiac Transplantation

Age criteria. Initially, age criteria for a heart transplant was considered to be at an upper limit of 50 years. This

transplantation. Conversely, patients with a peak MVo₂ greater than 14 ml/kg/min can be safely deferred from cardiology for transplantation. A peak MVo₂ of less than 12 ml/kg/min predicts a very poor 1-year survival rate and warrants listing in nearly all contraindication-free cases (2,7,8).

Pulmonary vascular resistance. Orthotopic cardiac transplantation requires the presence of a low pulmonary vascular resistance, so that the normal right ventricle of the donor heart can adequately support the recipient's circulation after transplantation. Most programs use the

traditional measurement of the Wood unit and limit the value to six Wood units or less at rest or less than three Wood units with maximal vasodilatation (9). Other centers use the transpulmonary pressure gradient (mean pulmonary artery pressure minus mean pulmonary capillary wedge pressure) of ≤ 15 mm Hg. In those patients with values toward the upper limits, it is imperative to demonstrate, in the catheterization laboratory, that the resistance can be altered with oxygen, or vasodilators such as, inhaled nitric oxide and intravenous or inhaled prostacyclin.

If the pulmonary vascular resistance measurements persist elevated, in spite of optimal and tolerable ambulatory therapy, a strong consideration should be given to heart-lung transplantation. Repeated cardiac catheterization may be necessary semiannually to determine if the pulmonary vascular resistance has increased. Significantly elevated pulmonary vascular resistance and right-sided heart failure remain as problems even after orthotopic cardiac transplantation and are major causes of early postoperative mortality (2).

Although the evaluation of potential candidates for cardiac transplantation is difficult, the established criteria have led to certain predictable outcomes in terms of quality of life and survival of the transplanted patient. It is imperative that, as with any medical or surgical procedure, the final decision ultimately rests on the patient, in accordance with the concept of informed consent.

Psychosocial evaluation. An important aspect of the evaluation process is a comprehensive psychosocial assessment by a clinical social worker or psychologist. The ability of the patient to follow a complex medical regimen is extremely important. Family support is necessary to help patients go through numerous medical procedures and evaluations and also to maintain the complex but an essential medical regimen after transplantation (3).

Categorization of Patients for Heart Transplant

Once patients are selected for heart transplant, according to UNOS, classification status for heart transplantation (9), patients are categorized on the basis of size, ABO blood group, time on the waiting list and clinical status. For the UNOS categorization criteria the cardiologist and cardiovascular surgeons of the heart transplant program take into consideration technical aspects such as use of mechanical circulatory support, mechanical ventilation, use of ventricular assist devices and other items.

Conclusion

End-stage heart failure is a progressive and irreversible disease that affects an important percentage of our society. It alters the quality of life and makes life miserable and truncates years of productivity. However, cardiac transplant has become an important tool in modern management of end-stage heart failure. As an active heart transplant program in the Cardiovascular Center of Puerto Rico and the Caribbean is in operation, we have presented our experience and some basic information that will help the practicing physicians in Puerto Rico to select and refer their patients with end-stage heart failure for evaluation and possible heart transplant.

Main emphasis has been given to the importance of optimization of therapy and to the proper clinical assessment of the patient to be referred taking into consideration the indications of the procedure as well as the absence of absolute contraindications.

Important aspects to be considered in the selection criteria including age, peak exercise oxygen consumption (MV_{o2}), left ventricular ejection fraction, pulmonary vascular resistance determination, and psychosocial evaluation have been summarized.

End-stage heart failure is a progressive and irreversible disease that affects a significant percentage of our society, it deteriorates the quality of life of the patients and truncates years of productivity. However, cardiac transplant has become an important procedure in modern management of end-stage heart failure. We encourage physicians to join efforts in order to identify potential candidates and refer them on time for a detailed evaluation. Heart transplant benefits terminally ill patients that would otherwise undergo a fatal outcome in a few months.

Resumen

El fallo cardíaco es una de las causas más frecuentes de hospitalización en el adulto. Con los avances tecnológicos y el uso de nuevos medicamentos para controlar el rechazo de órgano, el trasplante cardíaco se ha establecido como una medida terapéutica concreta para pacientes con fallo congestivo avanzado que hayan sido seleccionados apropiadamente. Debido a que en el Centro Cardiovascular de Puerto Rico y el Caribe existe un programa activo de trasplante cardíaco desde junio de 1999, este artículo es dirigido a orientar a la población médica en la evaluación y manejo de pacientes que requieran ser referidos a un centro de trasplante. Se ha hecho énfasis en las consideraciones clínicas, indicaciones, optimización del tratamiento

farmacológico, evaluación psicosocial así como en las contraindicaciones y en los criterios de selección de pacientes.

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