When to Consider Heart Transplant

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INTRODUCTION

　　Cardiac transplantation continues to be the treatment of choice for suitable patients with refractory heart failure; survivors of the procedure are very likely to be encountered by a diverse group of medical personnel. Shumway and colleagues developed surgical techniques for the procedure as early as 1966, and Barnard performed the first clinical human cardiac transplant in 1967. And yet, the survival benefit of cardiac transplantation as compared with conventional treatment in advanced heart failure has never been tested in a prospective randomized trial.(1, 2)

　　Many advances have occurred in the management of cardiac transplant recipients, including new immunosuppression modalities, therapies for chronic rejection, and improved operative and cardiac preservation techniques. Three-year survival from 1975 to 1981, prior to the routine use of cyclosporine, was 40%, compared with 70% in the era from 1982 to 1994, representing the early use of cyclosporine. Indeed, the number of heart transplants worldwide reached a peak of about 4,500/year in 1994. Since then, the number of procedures has declined, while patient survival has continued to improve. Unfortunately the rate of identification of potential organ donors has not kept pace with the demand created by transplant waiting lists. There is a 10 to 20% incidence of deaths per year on the transplant waiting list. As a result, other modalities for the treatment of Stage D heart failure have been created and are being assessed in clinical trials. Since patients referred for heart transplant have usually failed one, if not more, of these newer therapeutic options and now lack any other medical or surgical alternatives, they are becoming progressively older and more ill, with increasing medical co-morbidities, which has significantly increased the risk of cardiac transplantation.(3) Likewise, there has been an expansion in the selection criteria for donors to increase the number of organs available.(4) These changes have shifted the selection of patients for heart transplant toward higher acuity recipients while providing less ideal organs than in the past.

　　Nevertheless, the purpose of performing a heart transplant for an individual patient is to both prolong life and to improve the overall quality of life. Thus, it is imperative for the referring physician to understand the potential benefits a cardiac transplantation might confer on a recipient as well as co-morbidities that may portend an unsatisfactory outcome. In addition, an attempt must be made to assess the likelihood of imminent death for the patient and to balance that risk against

those encountered following cardiac transplant surgery. Finally, prospective transplant recipients should be given all other therapies that have been shown to improve outcome, both with respect to overall survival and quality of life, prior to a consideration of heart transplant.

MANAGEMENT OF HEART FAILURE

There is a reasonable, world-wide concordance about the appropriate management of dilated, end-stage cardiomyopathy in patients with refractory heart failure.(5-7) (Figure 1.) The fundamentals of care involve patient education, judicious use of salt and fluid restriction, and some combination of angiotensin antagonists, beta-adrenergic antagonists, and diuretics. In patients with more persistent symptoms and hospitalizations, this foundation of drug therapy may be supplemented with aldosterone antagonists, non-specific vasodilators such as nitrates and/or hydralazine, digitalis, and intermittent intravenous inotropes. In the last few years, implanted device therapy has significantly improved both the duration and quality of life with the use of cardiac resynchronization pacemakers (CRT) and implantable cardio-defibrillators (ICDs).(8-10) Thus, optimal medical and device therapy should be applied to patients according to guideline criteria before a consideration of transplant. Moreover, there are a variety of investigational and possibly, high-risk surgical procedures that are increasingly being employed in this population of patients to avoid the need for cardiac transplantation.(11, 12)

Physicians need to utilize all of the above therapies, according to heart failure guidelines, prior to the consideration of heart transplant. Since many of these therapies take time to effect both an improvement in functional capacity and to have a salutary effect on ventricular function, there are some patients who either are too sick to benefit from these drugs or can not tolerate them. Table I lists the other potential patient populations, besides those with Stage D or end-stage chronic heart failure, who might need consideration for heart transplant, and outlines an algorithm with which to approach such patients.
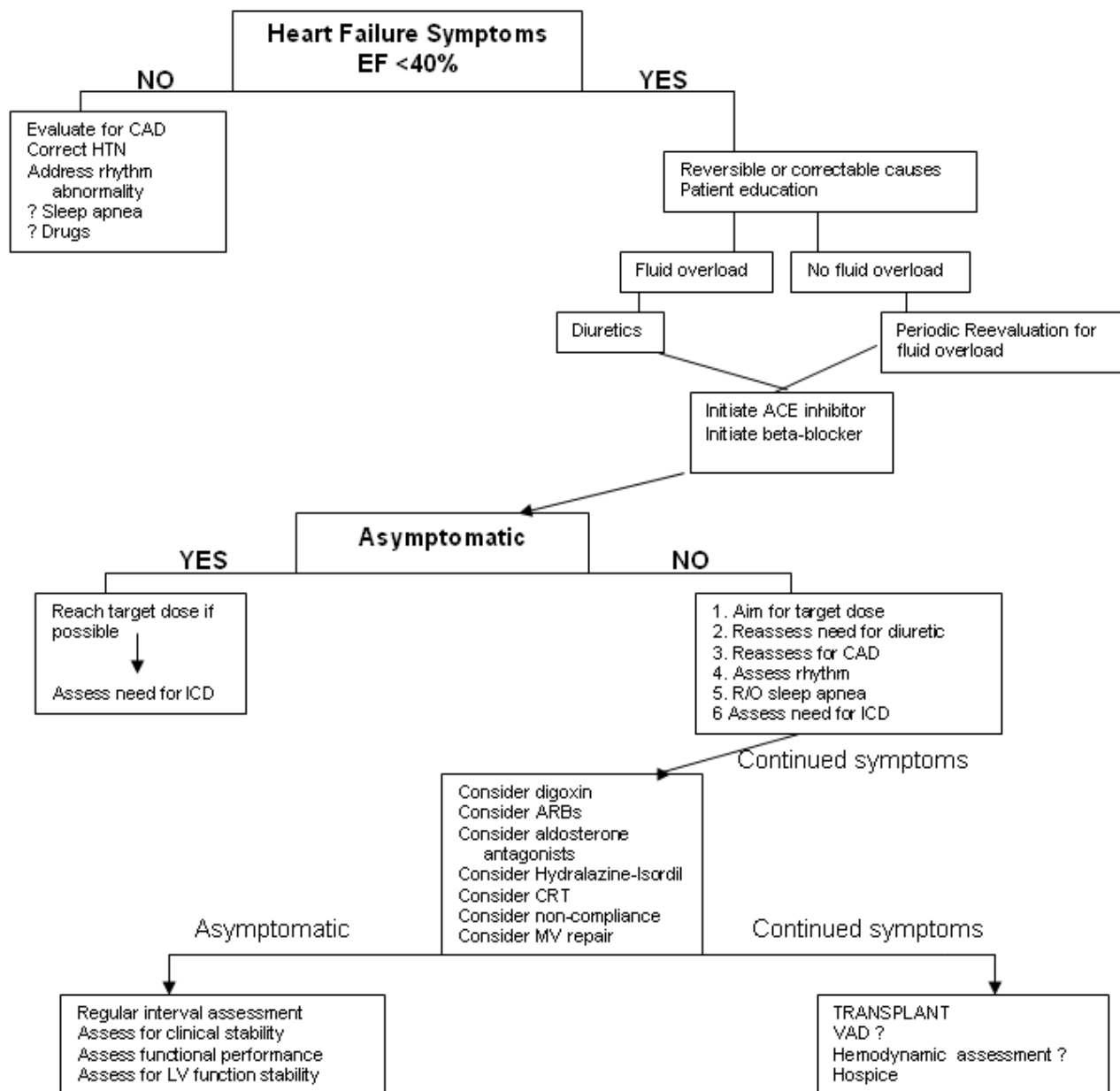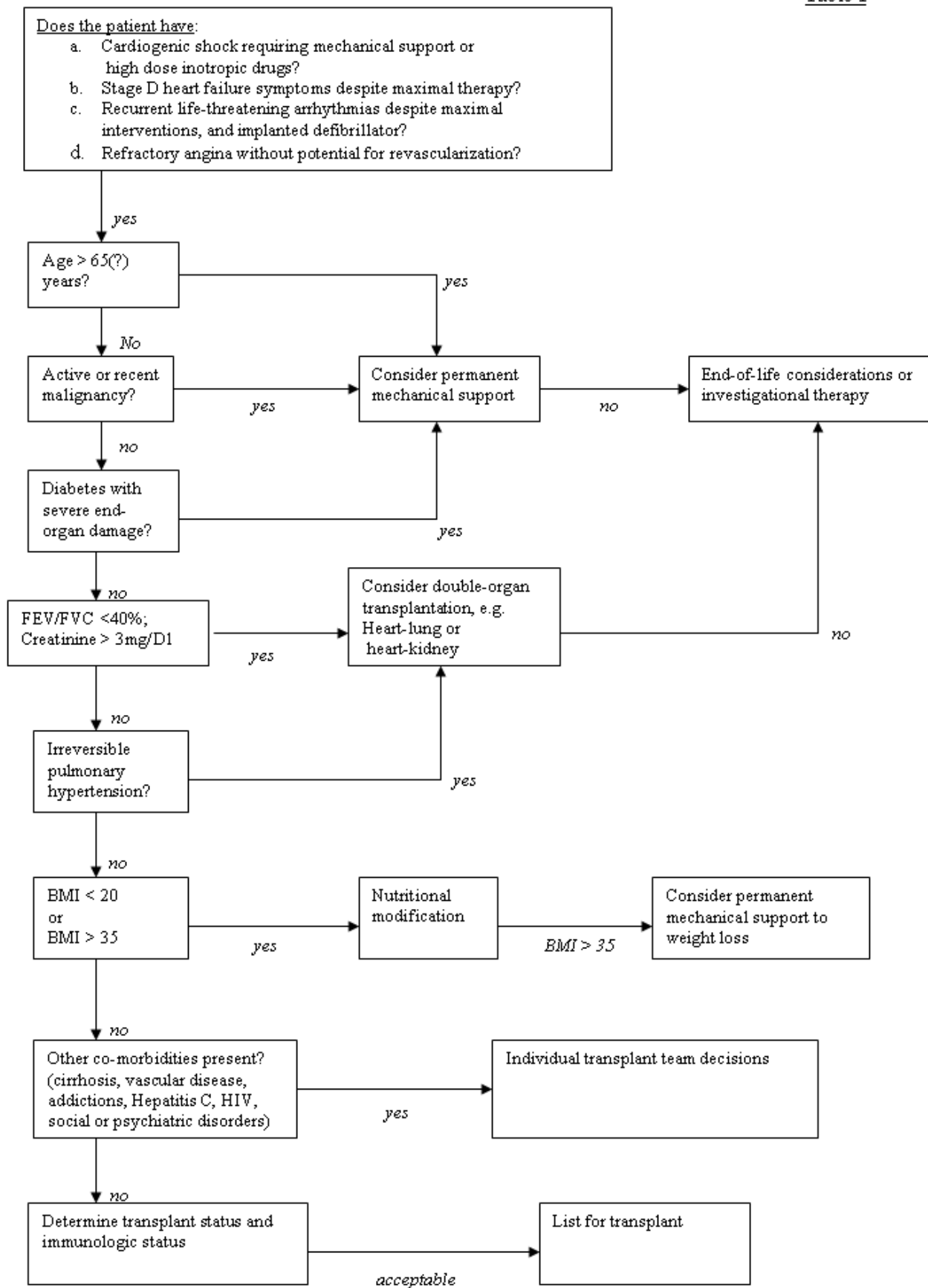
Figure 1. Optimal management of heart failure.

Heart Failure Symptoms
EF <40%

NO

YES

Evaluate for CAD
Correct HTN
Address rhythm
    abnormality
? Sleep apnea
? Drugs

Reversible or correctable causes
Patient education

Fluid overload

No fluid overload

Diuretics

Periodic Reevaluation for
fluid overload

Initiate ACE inhibitor
Initiate beta-blocker

Asymptomatic

YES

NO

Reach target dose if
possible

Assess need for ICD

1. Aim for target dose
2. Reassess need for diuretic
3. Reassess for CAD
4. Assess rhythm
5. R/O sleep apnea
6 Assess need for ICD

Continued symptoms

Consider digoxin
Consider ARBs
Consider aldosterone
    antagonists
Consider Hydralazine-Isordil
Consider CRT
Consider non-compliance
Consider MV repair

Asymptomatic

Continued symptoms

Regular interval assessment
Assess for clinical stability
Assess functional performance
Assess for LV function stability

TRANSPLANT
VAD ?
Hemodynamic assessment ?
Hospice

Table I

Does the patient have:
- a. Cardiogenic shock requiring mechanical support or high dose inotropic drugs?
- b. Stage D heart failure symptoms despite maximal therapy?
- c. Recurrent life-threatening arrhythmias despite maximal interventions, and implanted defibrillator?
- d. Refractory angina without potential for revascularization?

yes ↓

Age > 65(?) years? — *yes* →

No ↓

Active or recent malignancy? — *yes* → **Consider permanent mechanical support** — *no* → **End-of-life considerations or investigational therapy**

no ↓

Diabetes with severe end-organ damage? — *yes* ↑

no ↓

FEV/FVC <40%; Creatinine > 3mg/D1 — *yes* → **Consider double-organ transplantation, e.g. Heart-lung or heart-kidney** — *no* →

no ↓

Irreversible pulmonary hypertension? — *yes* ↑

no ↓

BMI < 20 or BMI > 35 — *yes* → **Nutritional modification** — *BMI > 35* → **Consider permanent mechanical support to weight loss**

no ↓

Other co-morbidities present? (cirrhosis, vascular disease, addictions, Hepatitis C, HIV, social or psychiatric disorders) — *yes* → **Individual transplant team decisions**

no ↓

Determine transplant status and immunologic status — *acceptable* → **List for transplant**

Accordingly, suitable patients for consideration either have: 1. Stage D heart failure symptoms despite maximal therapy, as discussed above; 2. Cardiogenic shock requiring mechanical support or high dose inotropic/pressor drugs; 3. Recurrent life-threatening arrhythmias despite maximal interventions, including implanted defibrillators; or, rarely, 4. Refractory angina without potential for revascularization. Several models have been proposed to help risk stratify patients with heart failure into those most urgently requiring transplant, using both invasive and noninvasive methods, but are really only applicable to those patients with chronic heart failure symptoms. The most potent predictor of outcome in ambulatory patients with heart failure is a symptom limited metabolic stress test to calculate peak oxygen consumption, or peak VO2. (13-16) A peak VO2 of less than 10 ml/kg/min indicates a poor prognosis, with a survival that is less than that of a transplant. Non-ambulatory patients who require continuous intravenous inotropic support that can not be weaned, or require mechanical support to maintain adequate cardiac index, are more obviously at risk for a poor outcome without transplant. These patients, however, often manifest signs and symptoms of end-organ failure of the pulmonary, hepatic and renal systems that may signal an ominous prognosis even with the transplant procedure. In reality, therefore, there are two disparate populations of patients considered for transplant: those who come to the transplant deliberations electively and those who arrive precipitously, on the verge of imminent death. Either way, the subsequent decisions about the patients' suitability for transplant require a similar approach

AGE

 In the past, patients older than 60 years of age have been excluded from consideration for transplantation. Advances in post-transplant care have improved outcomes in older patients and many centers have demonstrated survival in this age group comparable to younger patients undergoing transplantation. In addition, some data suggest that older patients have less donor organ rejection, which most likely represents immunosenescence in this older population.(17-19) Therefore, an increasing tendency to perform transplantation in older patients has been observed in recent years. In 2002, 10% of patients undergoing cardiac transplantation were more than 65 years old.(20)

PREVIOUS MALIGNANCY

Active neoplasm from origins other than skin has been an absolute contraindication to cardiac transplantation due to limited survival rates. There is also concern that immunosuppression after transplant might reactivate any pre-existing neoplasm in remission.(21, 22) Currently, only

those patients with cancers that have been in remission for 5 years, or those with low-grade cancers, such as prostate, may be acceptable for transplant evaluation. The 5-year remission threshold to safely proceed with transplant appears somewhat arbitrary and depends on the type of pre-existing neoplasm. In these patients needing cardiac transplantation, collaboration with oncology must occur to assess each patient as to their risk of tumor recurrence. Cardiac transplantation may be considered when tumor recurrence is low based on tumor type, response to therapy, and negative metastatic workup.

DIABETES MELLITUS

In the proceedings from the 24th Bethesda Conference, insulin-dependent diabetes mellitus (IDDM) with end-organ damage was a secondary exclusion criterion for heart transplantation.(19) However, diabetic patients without severe, secondary end-organ disease (retinopathy, neuropathy, or nephropathy) have undergone transplantation successfully with excellent intermediate results. Because of these reasonable to very good results, diabetes mellitus (without end-organ damage) is not considered an absolute contraindication.(18) Nevertheless, the ISHLT registry demonstrates an approximately 20-40% increase in one- and five-year mortality in even carefully selected diabetic patients. . In general, uncontrolled diabetes (Hgb A_{1C} > 7.5), despite optimal education and expert consultation, should be considered a relative contraindication for transplantation.

It is important to be aware of the patient's diabetes status because corticosteroid therapy may worsen glucose intolerance or induce diabetes mellitus. In patients with insulin-dependent diabetes mellitus, higher doses of insulin may be needed. Persons with diabetes mellitus who are treated with oral agents may require insulin after heart transplantation.(23, 24)

RENAL FUNCTION

Irreversible renal dysfunction with serum creatinine > 2 mg/dL or creatinine clearance < 50 mL/min was considered in the Bethesda Conference as a secondary exclusion criterion. However, when serum creatinine was evaluated as a continuous variable, no specific level was identified beyond which the risk of heart transplant was unacceptable. Two-thirds of U.S. centers assess a serum creatinine of > 3 mg/dL as an absolute contraindication for transplantation. Other centers world-wide use higher values of serum creatinine or lower values of creatinine clearance to determine candidacy.

Current surgical skills and immunosuppressive strategies now permit combined heart and kidney transplantation. (25)Such combined organ transplantations challenge current indications

and contraindications for heart transplantation and could be seen as experimental, especially in light of the shortage of organ donors. Additional testing in patients with a decreased measured glomerular filtration rate include a renal ultrasound (to assess renal size and chronicity), renal artery ultrasound (to assess for intrinsic renovascular disease), and urinalysis for proteinuria (to assess for nephrotic syndrome).

LUNG FUNCTION

Patients with severe pulmonary dysfunction (e.g., FEV1 < 1, or FEV/FVC < 40%)) should not be considered heart transplant candidates. First, their functional outcome after transplant is often less than satisfactory because of ongoing symptoms of breathlessness. Second, they carry a much higher risk in the peri-operative period, and usually have a much higher risk of subsequent pulmonary infections. Likewise, mechanical ventilation in cardiogenic shock is a severe risk factor for poor post-implant outcome. Recent pulmonary embolism or inflammatory parenchymal infiltrates can lead to the development of infective foci difficult to treat in the immediate post-transplant period.(18) Some highly selected patients with both pulmonary and cardiac failure may be appropriate candidates for heart-lung transplantation.

PULMONARY HYPERTENSION

Right heart failure is a common occurrence and a cause of morbidity and mortality after cardiac transplantation. Contemporary registry data from the ISHLT indicate that approximately 20% of early deaths after cardiac transplantation are attributable to right ventricular failure. Large cohort analyses have demonstrated that elevated pulmonary vascular resistance (PVR) is an incremental risk factor from low to high values.(23, 26) A variety of PVR-based variables have been analyzed and correlated with outcomes, including both static measures of pulmonary artery resistance and provocative/dynamic measures after pharmacological challenges.

Patients with chronic heart failure most commonly develop pulmonary hypertension due to elevated left ventricular end-diastolic pressure, and subsequently develop elevated left atrial pressure and pulmonary venous hypertension. This is considered to be a reactive form of pulmonary hypertension. Usually the pulmonary artery pressures fall rapidly when the left heart is "unloaded" either pharmacologically or mechanically. This is the basis of "vasodilator challenges" which most commonly, as in the case of nitroprusside, nitroglycerin, and nesiritide, reduce pulmonary capillary wedge and pulmonary artery pressures. However, pulmonary venous hypertension can lead to irreversible pulmonary arterial hypertension, as evidenced by fixed, elevated PVR. Numerous studies have shown, however, that reversible pulmonary hypertension is

associated with worse outcomes. Patients with fixed, elevated PVR may have concomitant lung disease, obstructive sleep apnea, or chronic pulmonary thromboembolic disease. Each of these potential causes should be considered and excluded.

The 2004 ISHLT registry report demonstrated that when comparing survival in patients with PVR of 1 to 3 Woods units versus PVR of > 5 Woods units, outcomes were better in the low PVR group. Acute studies are performed by administering a vasoactive agent (e.g., nitroprusside, nitroglycerin, nesiritide, prostacyclin, or nitric oxide) and documenting an acute reduction in the PVR usually in conjunction with a fall in pulmonary artery systolic pressure. When an acute vasodilator challenge is unsuccessful, hospitalization with continuous hemodynamic monitoring may be considered, as often the PVR will decline after 24 to 48 hours of treatment consisting of diuretics, inotropes, and vasoactive agents. Some patients may require prolonged therapy for weeks before an acceptable reduction in the PVR is obtained. Serial hemodynamic studies should be performed more frequently in patients with marginal initial reductions in the PVR despite aggressive therapies to determine their ongoing acceptability for cardiac transplantation. Pulmonary artery hypertension and elevated PVR should be considered as a relative contraindication to cardiac transplantation when the PVR is > 5 Woods units or the transpulmonary gradient exceeds 16 to 20 mm Hg. Again, some patients in this category may be evaluated for the possibility of heart-lung transplant.

BODY WEIGHT INDEX

Obese patients have a greater risk of morbidity and mortality after open-heart surgery. This is manifested in poor wound healing, increased risk of infection, lower extremity thrombosis, and pulmonary complications. Several methods may be used to measure obesity, which include body mass index (BMI), percent ideal body weight (PIBW) and direct measure of adiposity. BMI is measured as weight in kilograms divided by height in meters squared and PIBW is weight expressed as a percentage of the mean ideal weight for a given height and sex. Both have been found to be associated with outcomes.

In cardiac transplantation, one study reported that 55 obese (BMI > 30 kg/m^2) patients demonstrated nearly twice the 5-year mortality of 351 normal-weight or overweight recipients (53% vs. 27%, respectively, $P = 0.001$). (18, 27, 28) Previous reports have demonstrated that obesity is a risk factor for the development of transplant coronary vasculopathy. In a multicenter study of 4,515 cardiac transplant patients, preoperative obesity (> 140% of PIBW) was associated with increased 4-year mortality in males ($P < 0.001$) and a trend towards increased mortality in females.

These obese patients also had increased infections after cardiac transplantation. The increased infection rate was observed in both males and females under 55 years of age, and in patients with ischemic heart disease. In this study, pre-heart transplant BMI and PIBW were not associated with acute rejection or cardiac allograft arteriopathy after transplant.

Overall, it appears that pretransplant BMI > 30 kg/m^2 or PIBW > 140% are associated with poor outcome after cardiac transplantation. Therefore, for those severely obese patients, weight loss should be mandatory to achieve a BMI < 30 kg/m^2 or PIBW < 140% prior to listing for cardiac transplantation.

OTHER CO-MORBIDITIES

A psychosocial evaluation is performed to exclude contraindications for transplant, other co-morbidities are excluded or considered and studies are done to determine immunologic status. The co-morbidities that may negatively impact on a transplant team's decision to further consider a potential recipient include hepatitis C or cirrhosis (or any active hepatitis), vascular disease, advanced neuropathy, HIV status, addictions to alcohol or illicit drugs, and social or psychiatric disorders. Importantly, appropriate counseling of the patient excluded from heart transplant should include end-of-life preparation and discussions about possible investigational approaches.

The major ethical argument for the use of psychosocial criteria is the same as for medical criteria, i.e., allocating scarce donor organs to those most likely to benefit. However, there are fewer data on the reliability and validity of psychosocial criteria and on the ability of such evaluations to predict outcome after transplantation. Care must be taken to ensure that psychosocial factors predictive of outcome are not confused with judgments of an individual's social worth.

Neurocognitive and social assessment concentrates on four areas: compliance, comprehension, quality of life, and social evaluation.(29) Compliance, the capacity to adhere to a complex lifelong regime of drug therapy, lifestyle changes and regular follow up, is a crucial element in attaining long-term success after transplantation. Comprehension, the ability to understand explanations of relatively complex procedures and instructions about pre-transplant and post-transplant care and ultimately to give informed consent is perhaps the most controversial area. Quality of life assessment focuses on the patient's perception of happiness, well-being, and perhaps the desire for long-term survival. Social evaluation aims to identify whether the patient has family or friends who will support him/her through what is obviously a difficult period and who are willing to make long-term commitments for the patient's welfare.

Abdominal ultrasound should be obtained to screen for kidney size, gallbladder disease due to its association with high morbidity after transplantation, and any incidental abdominal findings. If there are any lesions or other suspicious findings on ultrasound or chest radiograph, an abdominal or chest computed tomography (CT) scan should be obtained.

Patients who are over 50 years of age or who have particular risk factors for cerebrovascular or peripheral vascular disease should undergo carotid Doppler ultrasound and ankle brachial index (ABI) studies. Other screening tests, such as sigmoidoscopy or colonoscopy should be performed in appropriately aged patients. Patients with signs or symptoms of intestinal angina should undergo mesenteric artery Doppler ultrasound to assess for occlusive vascular disease. Potential recipients over the age of 50 and those with other risk factors such as patients taking steroids or perimenopausal woman should have a dual energy x-ray absorptiometry (DEXA) scan. If the screening DEXA scan shows severe osteoporosis, further work-up for osteoporosis should be obtained.

Dental examination and ophthalmologic examinations should be obtained on a yearly basis to evaluate for potential problematic lesions or abscesses. Ophthalmologic consultation to determine the presence of retinopathy should be obtained at least annually in diabetic patients.

An immunologic evaluation includes a determination of ABO blood type and antibody screen, a panel reactive antibody level (PRA) and human leukocyte antigen (HLA) typing.(30-32) The presence and levels of anti-HLA antibodies is determined by cytotoxic testing in which the recipient's serum is incubated with lymphocytes from 30 to 60 individuals representing a wide range of HLA antigens. The PRA value is expressed as a percentage of cell panel members that undergo cytolysis, and is considered positive if greater than 10% of the wells (cell panel members) undergo cytolysis. Enzyme-linked immunoassay (ELISA) and flow cytometry can also determine PRA and are more sensitive than the cytotoxic test. The most common cause of sensitization, or elevated PRA levels, is pregnancy, however, sensitization can also occur with transfusions, prior transplantation, or insertion of a ventricular assist device. Patients with a PRA > 10% should have a prospective cross match at the time of transplant, as elevated PRA levels increase the risk of rejection following transplant.

LISTING FOR TRANSPLANT

The cardiac transplant screening or evaluation process may take place in the outpatient clinic or in a semi-urgent, hospitalized setting. Transplant centers typically have a transplant selection committee composed of physicians, surgeons, nursing personnel, social workers or psychiatrists, and even lay personnel who meet regularly to review each potential transplant recipient. Once the committee decides a patient is appropriate, the patient's listing criteria are officially registered with an organ procurement organization, the specifics of which are determined by the transplant policies of each country. Waiting times for a suitable donor organ are dependent on the severity of the recipient's heart failure, the blood group type and the size of the patient. Currently, the longest waiting times are for those patients with a large frame and/or body weight and blood group type O.

SUMMARY

Cardiac transplant is a complicated, expensive and uncommon procedure for a select group of patients with severe heart failure. Nevertheless, the operation has the potential to return a previously pre-morbid patient to become a fully functioning member of society. Cardiac transplant continues to be an important option in the scope of care for patients with Stage D heart failure.

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