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Task Force 4: Function of the Heart Transplant Recipient

JAMES B. YOUNG, MD, FACC, CHAIRMAN, WILLIAM L. WINTERS, JR., MD, FACC, CO-CHAIRMAN, ROBERT BOURGE, MD, FACC, BARRY F. URETSKY, MD, FACC

Introduction

Heart transplantation affords a remarkable degree of rehabilitation for patients with end-stage heart failure and all of its attendant hemodynamic abnormalities and functional limitations. In highly selected patients this surgical procedure is vastly superior to other existing forms of therapy in improving functional capacity and survival. Cardiac allografts, however, do not function totally normally and exercise tolerance in transplant recipients is somewhat less than might be expected. It is important to understand the implications of the altered physiology of the denervated heart because of its relation to exercise tolerance, physical rehabilitation, postoperative complications and pharmacotherapeutic intervention.

Heart transplant recipients often have severe psychologic dysfunction caused by symptoms from their previous cardiac disease, the stresses imposed by these symptoms and concern regarding impending death. In most cases, heart transplantation results in resolution or marked improvement of cardiovascular symptoms and anticipated survival. Therefore, exploring quality of life after transplantation also is important.

Physiology

The function of the orthotopically transplanted heart is a complicated interplay of ventricular loading conditions, intrinsic myocardial contractile capability, circulating catecholamine levels, denervation (with, in some cases, partial reinnervation), donor/recipient size relation, pulmonary performance and atrial function. Table 1 summarizes many of the issues relevant to function of the transplanted heart.

Table 1. Factors Affecting Function of the Transplanted Heart

Hemodynamic
  Donor/recipient body size relation
  Donor/recipient atrial asynchrony
  Early postoperative restrictive physiology
  Late postoperative restrictive physiology
Denervation
  Afferent denervation
    Altered reflex control of peripheral vasoconstriction/vasodilation
    Altered Na^+/H_2O regulation via central nervous system–dependent
      vasopressin, renin, angiotensin, aldosterone secretion
    Absence of anginal syndrome during ischemia
  Efferent denervation
    Absent vagal nerve control
    Rapid heart rate at rest
    Attenuated heart rate response to exercise
    Hypersensitivity to circulating catecholamines
Altered hormonal milieu
  Atrial natriuretic peptide secretion changed
  Elevated exercise circulating catecholamines
Myocardial injury/maladaptation
  Organ preservation/recovery injury
  Intraoperative complications
  Rejection
  Ventricular hypertrophy
  Hypertension (increased ventricular wall stress)
  Allograft arteriopathy (ischemia)

Canine Transplant Models

Insight into hemodynamic characteristics of transplanted hearts was first gained from study of canine models. Mann, et al. (1) suggested in 1933 that cardiac function after heart transplantation would be excellent if the "biologic factors" now known to be tissue rejection causing organ demise could be identified and controlled. Autotransplantation models (complete cardiac excision with subsequent reimplantation) clarified the impact of cardioplegia, ischemia and denervation on subsequent cardiac performance (2–5). Immediately after autotransplantation, right and left heart pressures are elevated but gradually return to control levels, sometimes over several weeks (6,7). Likewise, exercise tolerance approaches that of control animals with time (4,6).

Other observations have included the fact that dogs with an autotransplant have increased total blood volumes compared with values in control dogs (8,9). A blunted diuretic and natriuretic response to volume expansion in denervated cardiac canine preparations has been demonstrated (9), and it is apparent that the interruption of afferent neural fibers mediating, in part, volume homeostasis creates a decrease in the opposition of sympathetic renal stimulation. A new volume steady state develops that translates into fluid retention and altered cardiac loading conditions (7–9). It also has been shown (10) that denervation of the heart causes myocardial catecholamine levels to diminish as early as 1 week after autotransplantation in animal models. This observation has also been confirmed by analyzing biopsy specimens taken serially after heart transplant in humans (11).

Hemodynamics in Humans

Any evaluation of heart transplant physiology must be considered in light of the fact that the implants are probably functioning far more normally than the organs they replaced. Furthermore, these transplanted organs demonstrate remarkable, though not entirely normal, functional reserve. The first reports of heart transplantation in humans provided some data regarding hemodynamics, but it has become clear that rejection plays an important role in confounding observations in this regard. Early reports (12) suggested that cardiac output was usually depressed soon after transplantation and that maintenance of a high central venous pressure was essential to maintain cardiac output. More recently, atrial dynamics have been noted to be abnormal (13). Because of the midatrial anastomosis between donor and recipient hearts, varying portions of donor and recipient atria are present, and the native atria do not contract synchronously with the allograft atria because native sinus node electrical activity is not transmitted across the atrial suture lines. Consequently, less than the expected 15% to 20% normal atrial contribution to net stroke volume is often noted.

Initial reports summarizing hemodynamic follow-up after heart transplantation (14,15) noted that intracardiac pressures usually were normal at rest, but that ventricular diastolic pressure increased dramatically during exertion. Recent publications have focused on the evolutionary changes in hemodynamic patterns noted in patients receiving a cyclosporine-based immunotherapeutic protocol (16–18). Complicating factors, such as rejection and arterial hypertension, have been emphasized. A restrictive hemodynamic pattern has been documented early after heart transplantation that resolves within days or weeks (19). Interestingly, a subclinical, latent restrictive hemodynamic state may persist for much longer, but may require volume challenge to unmask (18). The presence of persistently impaired ventricular filling late after transplantation (seen in 10% to 15% of patients) has been linked to the incidence of graft rejection (20). Another explanation, that is, donor-recipient size mismatch, may also account for the observation of restrictive hemodynamic patterns. Donor size is often 20% to 30% less than that of the recipient. Hosenpud et al. (21) reported a significant negative correlation between donor to recipient weight ratio and heart rate at rest, right atrial pressure and pulmonary capillary wedge pressure 3 months after transplantation. Patients receiving a heart from a donor weighing substantially less than the recipient had higher resting values for heart rate and ventricular filling pressures than that of other patients.

A variety of echocardiographic techniques have given us insight into the anatomic and functional characteristics of the transplanted heart (20,22,23). In studies performed when rejection is absent, ejection fraction remains within normal limits over at least a 4-year follow-up period, but substantial increases in cardiac volume and end-systolic wall stress are

noted even in the absence of increased myocardial mass (19). St. Goar et al. (24) utilized Doppler echocardiographic techniques early after heart transplantation to assess left ventricular diastolic function serially. Isovolumetric relaxation time, pressure half-time and peak left ventricular early filling rates suggest that restrictive myocardial physiology and elevated left heart filling pressures are present early postoperatively. As noted in previous hemodynamic studies, this pattern normalizes over the first postoperative month (18,19,22). These early abnormalities do not appear to correlate with preoperative pulmonary pressure or vascular resistance, duration of cardiopulmonary bypass time, total ischemic time or age of the donor heart.

Maintenance of generally normal values for left ventricular ejection fraction at rest many years after transplantation has also been documented with fluoroscopic analysis of surgically implanted radiopaque myocardial markers (25,26). An appropriate increase in cardiac output during low intensity exercise, resulting from augmentation of end-diastolic volume and stroke volume, has been demonstrated in these reports. At more intense exercise levels, heart rate and contractility are augmented as well, probably because of increasing circulating catecholamines.

Utilizing rest blood pool radionuclide angiography, Verani et al. (27) demonstrated that systolic ventricular performance of the transplanted heart, assessed by measurement of right and left ventricular ejection fractions, was comparable to that of normal subjects. Rest peak diastolic filling rate and time to peak diastolic filling rate were normal as well. During exercise, significant increases occurred in left and right ventricular ejection fractions and peak diastolic filling rate, but peak left and right ventricular ejection fractions were significantly lower than those of normal subjects. It can be concluded that heart transplant patients have mildly impaired ventricular function reserve that requires maximal exercise stress to uncover.

One characteristic of the denervated transplanted heart without tonic vagal input is a high heart rate at rest (95 to 115 vs. 60 to 100 beats/min in normal subjects). The rate accelerates more slowly than normal during exercise and tends to be lower at the same level of exercise than is seen with the innervated heart (22). The rate does not respond to physiologic stimuli such as carotid sinus massage or innervation-dependent pharmacologic stimuli such as atropine.

As suggested, heart transplant recipients have diminished maximal exercise tolerance compared with that of normal subjects, and this probably results from subnormal ejection fraction and cardiac output augmentation in response to exercise as well as an exaggerated increase in intracardiac filling pressure during exercise (27–29). Elevated intracardiac filling pressure in the setting of normal or reduced left ventricular volume suggests that the orthotopically transplanted heart functions on a ventricular pressure-volume curve that is steeper than normal and shifted leftward. As previously suggested, this type of hemodynamic profile implies that the ventricles are less compliant than normal,

owing either to myocardial changes (such as rejection) or to the presence of a relatively small donor heart. Furthermore, it suggests that cardiac performance during exercise is unusually dependent on loading conditions, which in turn are related to postural changes (28–30).

Patients with chronic heart failure frequently develop skeletal muscle atrophy with metabolic abnormalities of muscle function. Intrinsic muscle oxidative problems become apparent and these residual abnormalities may be exacerbated by immunotherapy after transplantation. Because this skeletal muscle "failure" occurs in advanced heart failure, it is possible that patients tested after heart transplantation have residual peripheral skeletal muscle effects of previous congestive heart failure that limits their peak exertional capabilities (31,32). With increasing exertion, anaerobic metabolism is common before peak exercise levels are reached in transplant recipients. Savin et al. (33) demonstrated that transplant patients had higher peak lactate levels and ventilatory equivalents but lower peak oxygen uptake and peak work rates than those of normal control subjects. Exercise after transplantation eventually does induce tachycardia and evidence of an increased contractile state, probably because of increased circulating catecholamines. Still, the maximal cardiac output achieved is generally lower than that seen in normal persons (25,27) because of a blunted heart rate response as well as lower peak stroke volume (28–30). Despite these physiologic observations, the majority of transplant patients are, in fact, capable of performing most desired physical activities, as is discussed in the Quality of Life section.

Cardiac Allograft Denervation

As noted in animal models of orthotopic heart transplantation, human donor heart cardiectomy with subsequent orthotopic transplantation creates both afferent and efferent cardiac denervation (3,4,7). Afferent nerve interruption alters cardiovascular homeostasis by impairing renin-angiotensin aldosterone regulation and impeding the normal vasoregulatory response to changing cardiac filling pressure (34). Furthermore, absence of afferent signaling eliminates the subjective experience of angina pectoris during periods of ischemia (35). Cardiac efferent innervation mediates sympathetic and parasympathetic nervous system effects on the heart. The absence of vagally mediated parasympathetic influences causes heart rate at rest to be higher and eliminates the influence on the heart of vagal signaling from the central nervous system (22). Loss of autonomic innervation blunts the usual rapid changes in heart rate and contractility seen during exercise, hypovolemia or vasodilation (36 and Verani et al. [unpublished observations]).

Because the denervated cardiac graft relies on enhancement of ventricular performance through stimulation of myocardial beta-adrenergic receptors by circulating catecholamines (34), administration of beta-adrenergic blocking drugs may be deleterious during stress situations. Verani et

al. (unpublished observations) characterized the effect of acute beta-adrenergic blockade in heart transplant patients. Beta-adrenergic blockade produced a decrease in ventricular performance at rest in transplant patients and control subjects, characterized by lower values for stroke volume index, cardiac index and ejection fraction in both groups, with the changes generally similar except for a greater decrease in ejection fraction in the transplant recipients. This decrease was caused by a reduction in heart rate and, quite likely, contractility. As the ejection fraction decreased in the heart transplant patients, end-systolic volumes increased substantially. In the normal patients there was a reduction in heart rate because there was only a minimal reduction in ejection fraction and no change in end-systolic volume. These observations emphasize that in the denervated heart transplant patient, circulating hormones appear crucial to maintain reasonable exercise performance.

The response of the denervated heart to other forms of stress is also important to consider. In a canine model of the denervated heart, Tsakiris et al. (36) demonstrated that acute hypertension was well tolerated with only a slight decrease in cardiac output and a small increase in left ventricular end-diastolic pressure, but hypotension was less well tolerated with minimal reflex increase in cardiac output because of little heart rate response. Mohanty et al. (37) demonstrated that baroreflex-induced volume regulation after cardiac transplantation is impaired. Volume unloading induced with a lower body negative pressure apparatus produced minimal reduction in forearm blood flow and only a slight increase in forearm vascular resistance, because orthotopic heart transplantation permits portions of the native atria with their accompanying sympathetic and parasympathetic innervation to remain. This observation suggests that nerves arising in the ventricle rather than in the atrium or pulmonary vasculature constitute the afferent limb of this reflex. Furthermore, it has been suggested (21) that the inability to vasoconstrict blood flow to nonworking muscles plays a role in limiting the maximal exercise capacity of heart transplant patients. Scherrer et al. (38) have further suggested that the cyclosporine-induced hypertension seen in heart transplant recipients is associated with increased peripheral sympathetic nerve discharge and suggested that this effect of cyclosporine may be exaggerated in heart transplant patients because of cardiac denervation.

There is evidence that reinnervation occurs in some patients late after orthotopic heart transplantation. It has been demonstrated by immunohistochemical technique that most human cardiac allografts remain extrinsically denervated but appear to contain viable intrinsic nerve fibers (39). Ischemia-induced subjective chest pain (classic angina pectoris) in heart transplant recipients has been reported (35) and suggests that some heart transplant recipients have at least partial afferent reinnervation. A study by Stark et al. (35) demonstrated a tyramine-induced cardiac epinephrine release response indicative of reinnervation in two patients with angina pectoris and allograft arteriopathy. Wilson et al.

(40), in a study of norepinephrine release in patients in response to tyramine and sustained handgrip, concluded that it was likely that sympathetic reinnervation commonly occurs late after transplantation but that the pattern of reinnervation is extremely variable. How frequent and how physiologically significant such reinnervation is remains to be elucidated.

Electrocardiographic and Electrophysiologic Changes

Serial electrocardiographic (ECG) changes have been noted in the transplant recipient. Indeed, the earliest method of monitoring heart transplant rejection utilized serial quantification of ECG voltage (41,42). It is generally accepted in the cyclosporine era that the sensitivity and specificity of electrocardiography are not acceptable for diagnosis and surveillance of rejection.

Electrocardiographic abnormalities, however, are frequently observed. Leonelli et al. (unpublished observations) demonstrated that 73% of first postoperative ECGs evidenced changes from normal, with a predominance of right bundle branch block. Patient or donor age, ischemic time and prior drug therapy did not differ significantly between transplant patients with normal or abnormal early postoperative ECGs. Electrocardiograms can undergo evolutionary changes during the initial posttransplantation hospital period and Leonelli et al. (unpublished observations) also noted that patients with progressive deterioration of conduction manifest by widening QRS complexes or worsening of a preexisting conduction defect had a higher early mortality rate.

Approximately 20% of heart transplant patients demonstrate sinus node dysfunction with slow or no spontaneous depolarization and these individuals characteristically have junctional rhythms with lower rest heart rates than those of the majority of transplant recipients (usually <70 beats/min) (43). Sinus node dysfunction may be caused by ischemic injury during graft retrieval, by rejection or by allograft arteriopathy. Furthermore, sinus node dysfunction has been described in patients who died early or late after cardiac transplantation (44) and some patients require permanent pacemaker implantation for persistent sinus node dysfunction (43–45). In addition to the usual indications for permanent pacemaker implantation, some programs recommend permanent pacing in heart transplant patients with unexplained recurrent syncope or near syncope, particularly in the setting of allograft arteriopathy, as sinus node dysfunction may be intermittent and difficult to document (44).

Electrophysiologic studies performed in heart transplant patients (46,47) demonstrate that atrioventricular (AV) node conduction times are similar to those of normal subjects, both at rest and during atrial pacing. AH and HV intervals are also normal. Usually, the AV node alters conductivity relative to the rate of stimulation. This characteristic still is apparent in the denervated heart (47) but, whereas the

changes occur almost instantaneously in an innervated heart, they require more time (several seconds) to occur in a transplanted heart. Collectively, observations such as these emphasize that AV node impulse transition control is an intrinsic function, with autonomic innervation enhancing this activity rather than being critical to the underlying function.

Arrhythmias in the heart transplant patient are not common and tend to be either bradyarrhythmias, as previously noted, or tachycardias that are usually supraventricular. Experimental models have suggested that cardiac denervation is antiarrhythmogenic, particularly in terms of ischemia-related ventricular arrhythmias (48). There seems to be a low prevalence of ventricular arrhythmias in long-term survivors of both orthotopic and heterotopic heart transplantation and most investigators would agree that the occurrence of ventricular arrhythmias is most commonly associated with development of allograft arteriopathy (49,50). Atrial arrhythmias, in contrast, are frequently associated with rejection episodes. Bradyarrhythmias may also occur with coronary artery disease and should be considered in patients complaining of nonspecific "weak" spells or presyncopal episodes. Sudden death in the absence of coronary artery disease or acute rejection is quite rare in transplant recipients.

Effect of Drugs on the Transplanted Heart

Because of the existence of denervation, drugs affecting physiologic responses through autonomic nervous system stimulation are not usually effective in the transplanted heart. For instance, since the effect of atropine is mediated by a parasympatholytic mechanism, it does not speed the ventricular rate in bradycardia (51). Likewise, edrophonium, a cholinesterase inhibitor, has no effect on heart rate (52). Sympathomimetic agents such as isoproterenol that directly stimulate myocardial receptors have the normal or expected effects on heart rate and contractility.

Increased sensitivity of the denervated transplanted heart to parenterally administered beta-adrenergic agents such as isoproterenol has been noted (53). Exaggerated sensitivity to acetylcholine in denervated canine models also has been reported (54). Because acetylcholine and the endogenous nucleoside adenosine have similar cardiac electrophysiologic effects, Ellenbogen et al. (55) used adenosine and demonstrated that the denervated donor sinus node had greater sensitivity to exogenous adenosine than did the recipient innervated node. Thus, care should be exercised to prevent bradyarrhythmia if this agent is to be used during diagnostic scintigraphic study.

Because the electrophysiologic effects of digoxin are primarily on sinoatrial and AV nodes and mediated by way of the sympathetic nervous system, this drug has little electrophysiologic activity in the transplanted heart (56). The inotropic effect of digoxin, which is not being mediated by way of the autonomic nervous system, seems to remain intact.

Some antiarrhythmic agents (quinidine and disopyramide, for example) have vagolytic effects that increase rest heart rates in nontransplant patients. These changes are not observed in the denervated heart and, instead, decreased sinus rate and increased AV conduction times are generally observed when these drugs are used in transplant recipients (57,58).

The dihydropyridine calcium channel blocker nifedipine when used in heart transplant patients produces minimal reflex increase in heart rate coincident with decrement in blood pressure due to vasodilation and has also been shown to produce a slight decrease in the AH interval (59). Verapamil produces a slight increase in the AH interval (59) and diltiazem causes a small decrease in heart rate (60). These effects on conduction are very minor and do not cause substantive electrophysiologic changes in the denervated heart.

Endocrine Activity

Atrial natriuretic peptide is normally secreted by the heart and involved in volume homeostasis. It increases in response to atrial distension in normal humans and patients with multiple pathophysiologic conditions. In heart transplant patients, plasma atrial natriuretic peptide levels are elevated (61) and, although atrial natriuretic peptide release increases with atrial stretch in transplant patients, levels are higher than might be expected by atrial stretch alone. The mechanism responsible for the elevation has not been totally clarified.

Confounding Issues

Several factors may alter the function of the transplanted heart. Most important is rejection with its myocarditis, humoral antibody production and complement system activation. These events directly impair cardiac contractility and may also affect coronary blood flow. During acute rejection, coronary vascular reserve is compromised and varying degrees of systolic and diastolic ventricular dysfunction have been observed. Treatment of rejection often reverses these abnormalities, resulting in improved graft function (62,63). However, biventricular diastolic dysfunction has been observed in some patients even after resolution of histologic rejection. Other long-term changes apparent in the patient after transplantation include increased left ventricular afterload and hypertrophy due to hypertension, which in turn contributes to alteration in long-term heart function.

Allograft arteriopathy is particularly prevalent during long-term follow-up and also can contribute to functional impairment. Systolic left ventricular dysfunction can occur in the setting of graft ischemic heart disease and coronary angiographic findings define a high risk subgroup for subsequent cardiac events, such as acute myocardial infarction, heart failure resulting from myocardial infarction, and sudden cardiac death (64).

Heterotopic Heart Transplantation

Heterotopic heart transplantation has been performed much less frequently than orthotopic procedures, comprising <2% of all heart transplant procedures in the Registry of the International Society for Heart and Lung Transplantation (65). The procedure is, nevertheless, important to consider because it may have a therapeutic niche (66,67). Generally, heterotopic procedures have been performed in the setting of very elevated pulmonary artery pressure or when the donor size seems inadequate in relation to that of a potential recipient. The hemodynamic function of the heterotopic heart transplant involves additional physiologic variables, such as the contribution to overall cardiac output of the native heart and different loading conditions, particularly pulmonary hypertension. Because both donor and native hearts are beating in parallel, but not synchronously, hemodynamic assessment of relative contributions of native and donor hearts in these patients is most difficult. Heterotopic implants have been demonstrated to be capable of completely supporting a patient's circulation when the native heart becomes asystolic or develops ventricular fibrillation (67). Clearly, this type of heart transplant can provide hemodynamic support adequate enough to ameliorate many of the heart failure abnormalities noted in end-stage left ventricular dysfunction. Regression of pulmonary hypertension and elevated pulmonary vascular resistance can occur over several weeks, and seems similar to the resolution seen in orthotopic heart transplant recipients (66).

Summary

The transplanted heart is denervated, except as noted herein, and in the absence of rejection, coronary artery disease or hypertension, it performs in similar but not entirely identical fashion to that of normal hearts at rest. Diastolic dysfunction is common early and may recur at a late stage in some patients. Cardiac reserve during exercise is adequate but generally less than normal. Augmentation of cardiac performance does occur and seems to result from endogenous elevation of catecholamines and changes in diastolic loading conditions. However, in view of preoperative functional limitations apparent in end-stage heart failure, patients undergoing successful heart transplantation have a remarkable improvement in cardiac performance.

Recommendations

The Task Force recommends that the following be undertaken by the transplant community:

1. Develop evaluation standards for heart transplant recipients so that functional performance characteristics at various times after heart transplantation can be objectively quantified in uniform fashion and disability due to graft malfunction identified.

2. Develop a universal functional classification of heart transplant recipients that is more precise than the New York Heart Association categories. These criteria should be based on noninvasive measures of systolic and diastolic function as well as exercise capacity.

3. Determine the relation to disability of functional performance characteristics after heart transplantation.

4. Encourage funding of clinical physiologic studies to develop methods to improve function of the transplanted heart.

Quality of Life After Heart Transplantation

Analyses of benefits after heart transplantation have overwhelmingly focused on survival. Because transplantation is usually performed in patients with end-stage heart failure having a high probability of death within a short period of time, the merit of this operation in terms of conferring improved survival is now considered great; survival rates of 80% to 90% at 1 year and 60% to 70% at 5 years are to be expected (65,68). Whereas heart transplantation was previously considered an appropriate option only in patients unlikely to survive 6 months, patients today sometimes are considered candidates for heart transplantation if they have a 50% survival likelihood at 24 months (69). It seems that as more patients are placed on waiting lists for heart transplantation and waiting times lengthen, the acuity of illness of these patients may be lessening, as is addressed by Task Force 3. Assessing quality of life variables after transplantation, therefore, becomes extraordinarily important, particularly when comparing the physiologic outcome after transplantation with functional capacity possible after modern, aggressive pharmacologic management of heart failure (69,70). In such assessment it is crucial to remember that quality of life judgments are frequently subjective and if a patient's premorbid quality of life is poor, it is unlikely to be significantly changed by a heart transplant procedure.

It is apparent that improvement in quality of life after heart transplantation can be dramatic for many persons who return to a productive working environment and more normal family unit. However, the residual psychologic trauma of suffering a devastating and near-fatal illness treated with an unusual operation cannot be dismissed lightly. Furthermore, the ongoing and indefinite medical therapy required to maintain immune tolerance of the graft can cause a variety of side effects as well as devastating complications. Living in fear of these problems surely takes its toll emotionally in many patients. Patients may become depressed and grieve over loss of a normal body image. Guilt can become apparent when patients recall that a healthy, usually young, person died to make the transplant procedure possible (71).

Quality of life after heart transplantation can be assessed both subjectively and objectively (72); simply listening to patients' stories is important (71). Still, such variables as survival, overall health status, ability to return to work and functional capacity can serve as objective measures of quality of life. Subjective and more personal measures might include a patient's perception of his or her well-being, happiness or general satisfaction with life. Of course, such

Table 2. Quality of Life Outcomes After Heart Transplantation

Indicators	Outcome
Objective	
Employment (% of patients)	32 to 50
Physically active (% of patients)	80 to 85
Subjective	
Life satisfaction (score)*	5.11 (5.55)§
Well-being (score)†	11.11 (11.77)§
Psychologic affect (score)‡	5.49 (5.68)§

*Range of values 1.0 to 7.0, where 7.0 = positive satisfaction. †Range of values 2.1 to 14.7, where high score = positive well-being. ‡Range of values 1.0 to 7.0, where 7.0 = positive effect. §Values for the general population of the United States in parentheses. All data are from Evans (68,72).

perceptions are clearly dependent on a patient's preoperative personality matrix. Assessing quality of life variables can be very difficult and hazardous, yet some general conclusions have been drawn.

The National Transplantation Study

The National Transplantation Study, funded in large part by the United Network for Organ Sharing, the Health Care Financing Administration and the Social Security Administration (68), recently explored quality of life after heart transplantation in detail (Table 2). The final report was wide ranging, analyzing information from 85% of all transplant programs in the U.S. In this study, patients' physical activity levels and functional rehabilitation after cardiac transplantation were generally considered to be adequate. The National Transplantation Study, indeed, estimated that 80% to 85% of surviving heart transplant recipients are physically active (based on global measures of activity) and this activity level was no different from that reported by kidney, liver or pancreas transplant recipients. Only 32% of patients were employed after heart transplantation, but this, again, is not different from employment estimates after kidney transplantation (31% to 46%) or liver transplantation (10% to 47%). The report suggests that because heart transplant recipients are physically active and, theoretically, capable of working, barriers to employability are important in limiting gainful and meaningful employment. This opinion has been expressed elsewhere as well (71). For example, employers may be hesitant to hire heart transplant recipients, fearing compromised employee health and, therefore, reliability. Also, insurers might adversely rate group health insurance holders when they hire transplant recipients, thus affecting employers' hiring decisions. Evans (68,72) points out that patients undergoing solid organ transplantation have employment records similar to those of others who have had serious diseases such as myocardial infarction or cancer, suggesting, again, that lack of insurability may correlate with lack of employability.

In fact, many subjective measures of posttransplantation quality of life are similar to those reported for the U.S. population in general. Indeed, almost 90% of patients analyzed in the National Transplantation Study indicated they were normal or had only minimal signs or symptoms of disease. Evans tabulated subjective quality of life scores focusing on life satisfaction, well-being and psychologic affect (72). When heart, kidney, liver and pancreas transplant patients are compared amongst themselves, as well as to the general population, little difference exists between all of these populations with regard to their scores. For example, using a range of values of 2 to 15 where a higher score indicates positive well-being, heart transplant patients scored 11.11, pancreas transplant patients 11.07 and kidney transplant patients 11.01. These data should be compared with the general population score of 11.77. Furthermore, only 7.2% of heart transplant patients rated their health status as poor.

Though patients' self-assessed health status after heart transplantation is quite satisfactory, functional limitations are sometimes evident. This might be expected based on the observation that posttransplantation peak exercise capacity often is subnormal (as discussed in the previous section) and heart transplant patients require long-term treatment with drugs such as steroids and cyclosporine, which may predispose them to musculoskeletal difficulties such as weakness, myalgias, osteopenia or aseptic necrosis of weight-bearing joints. Additionally, mood alterations seem related to these medications. As upper limits of age for heart transplant candidates increase, limitations simply associated with a more aged transplant population might be anticipated. Although Evans (72) reported that patients felt well and perceived themselves as healthy, 66% stated they were limited in some way from doing something they desired. However, only 1% of patients needed help in eating, dressing, bathing or using the toilet, and only 9% of patients needed assistance in traveling around their community. Health problems restricted 7% to bed or the home most of the day; 34% had trouble walking several blocks or climbing stairs because of health; 43% had trouble bending, stooping or lifting; 47% reported they were limited in their work load at their job or around the house; and 52% reported an inability to do certain amounts of physical labor, housework or school work. These data suggest that at least 50% of heart transplant patients could adequately perform employment tasks; however, slightly less than 33% actually return to the workplace.

Many other factors are apparent when analyzing why patients do not return to work, including lack of desire to return to the same job, unemployment before transplantation, economic uncertainties and, as mentioned, employer reluctance to rehire heart transplant patients. Related to this employment issue is the fact that 63% of heart transplant recipients are receiving medical disability benefits, whereas only 45% of kidney transplant patients receive such support (68,72); however, kidney recipients are generally younger.

The United Kingdom Heart Transplant Study

The United Kingdom Heart Transplant Study also assessed quality of life (73,74). Overall, during evaluation before heart

transplantation, only 8% of patients rated quality of life "high," whereas 67% studied 3 months after transplantation gave their life quality an equivalent "high" score. This report suggested that 84% of patients had problems at their job before transplantation compared with 50% of patients after transplantation, 94% had difficulties looking after their home before the procedure compared with 20% after the procedure and 84% had problems with their sex life before the procedure compared with 29% afterwards (all p < 0.01).

This study used the Nottingham Health Profile Survey to quantify the health status of heart transplant patients and compare it with that of nontransplant control subjects (74). Mean scores for the variables studied were similar at 1 and 2 years after transplantation when compared with values in the "normal" population control groups, with the exception that transplant patients had more difficulty sleeping. Variables reported included physical mobility, pain, sleep, energy, social isolation and emotional reactions.

Other Studies

Analysis of outcome after heart transplantation in the Stanford program also indicated that transplant recipients achieve reasonable functional capacity and rehabilitation in consistent fashion (75–78). Negative changes noted in these patients after transplantation generally occurred with respect to the patient's financial situation, physical appearance (self image) and sexual functioning (although the latter was not always a statistically significant observation). Again, it was pointed out that patients were discriminated against in the labor force.

Further assessment of quality of life after orthotopic heart transplantation was reported by Bunzel et al. (79). In their study, patients were asked to evaluate postoperative improvement or deterioration and satisfaction with the level reached utilizing a scale quantifying nine distinct areas, including physical, emotional, mental, vocational, sexual, financial, leisure, partnership and overall quality of life. Again, distinct improvement in almost all dimensions except patients' financial situation was reported. Improvement in physical status was ranked best.

Financial Factors and Quality of Life After Heart Transplantation

Because financial stress and difficulties adversely affect quality of life after heart transplantation, it is important to understand the cost of these procedures and payment mechanisms. In 1988 dollars, the median heart transplant procedure charge reported by Evans (68) in the National Transplantation Study was $91,570. This charge should be compared with $39,625 for kidney, $145,795 for liver and $134,881 for heart-lung transplants, but does not include charges incurred before the procedure or the long-term cost of follow-up care. These costs compare very favorably to expenses incurred in most devastating illnesses. Although

today most private insurers cover heart transplantation, there is no certainty that reimbursement will be sufficient to pay charges. Still, the day of coverage denial because of an "experimental" label the operation carried seems to have ended when Medicare coverage was extended to include heart transplantation. Indeed, in 1985 only 55% of private insurers provided heart transplant benefits, whereas 84% did in 1988 (68). Currently, a more prominent problem seems to be coverage caps that limit insurance payments and, thus, a patient's available resources. For example, only 72% of payers reimbursed 80% of hospital charges in 1988. Although Medicare provides coverage to eligible participants for heart transplantation, the Diagnosis Related Group (DRG) payment is low, and coverage for medications is restricted. Furthermore, Medicaid coverage for heart transplantation is not universal, with 22% of states not offering reimbursement for this service in 1990 (68). Long-term medication cost coverage is often unavailable. Loss of insurance benefits or a prohibitive rise in premiums can occur after transplantation as well, but data quantifying this problem seem unavailable. It is not surprising, therefore, that patients report a negative impact on their quality of life precipitated by disease-generated financial impecunity.

A stable financial situation is what most cardiac transplant patients believe to be required to have an acceptable quality of life (80,81). Therefore, returning to work after heart transplantation is quite important. The study of Meister et al. (80) reviewed the data on 40 heart transplant patients with respect to their return to work status. Patients were classified into four groups: those who were able to return to work (32%), those who were retired (25%), those who were medically disabled (7.5%) and those who were termed "insurance disabled" (36%). The latter patients were those who could have gone back to work but did not because of financial limitations. They were dependent on disability income or government-subsidized health care, and return to work would cause them to lose disability income or health care benefits. These patients are usually considered medically uninsurable by potential new employers and therefore cannot hope to earn enough money to cover medical costs. Thus, they remain disabled to continue their health care benefits.

Further insight into social rehabilitation and likelihood of returning to work after heart transplantation was provided by Paris et al. (81). Of 250 patients at seven heart transplant centers from different geographic regions in the U.S., 45% were employed, 36% unemployed, 13% medically disabled and 6% retired. The majority of employed patients had returned to their previous workplace (87%). Of the unemployed, only 16% had made job applications and 63% had no plans to seek further employment. Variables predicting likelihood of not returning to work included the length of medical disability before transplantation, the patient's perception of being physically unable to work and the potential loss of health insurance or disability income.

Preoperative Psychosocial Factors and Postoperative Outcome

There may be some relation between preoperative psychopathology and outcome after transplantation. One of the largest reviews of quality of life after heart transplantation was a multicenter survey of psychologic problems related to the surgical procedure in 595 patients reported by McAlear et al. (82). Before the procedure, the most significant difficulties were depression and increased family unit stress. This high prevalence of anxiety and depression in patients with heart failure has been confirmed (83). Mai et al. (84) also suggested a correlation between presence of significant preoperative psychiatric diagnosis and poor outcome. Preoperative psychiatric symptoms do not seem to predict major postoperative psychiatric complications, but reduced coping skills reflected by the diagnosis of personality disorders or organic brain syndrome were associated with behavioral problems capable of jeopardizing long-term outcome (85). Postoperatively, denial expressed toward graft implantation, as well as euphoria, gratitude, curiosity, guilt, anxiety and a feeling of changed body image, is often seen (71,86,87). It has been suggested that denial serves a protective and adaptive function in heart transplant recipients.

Shapiro and Kornfeld (86) reported similar observations but emphasized the frequency of postoperative psychiatric disorders and psychosocial difficulties. In their study, 51% of patients had an affective illness characterized by mood lability, irritability and grandiosity. Major depressive difficulties, noted in 11%, may have been associated with steroid administration. Anxiety disorders were also frequent (noted in 26% of the patients), but they usually were not persistent or debilitating. Delirium was noted postoperatively in 4%. Also observed with some frequency were sexual dysfunction and an inability to return to the work force.

Tabler and Frierson (87) expanded on sexual concerns patients have after heart transplantation. These difficulties were generally related to the psychologic impact of altered roles and responsibilities, body image concerns, loss of autonomy with adverse effects on self-esteem, physiologic effects of medication with respect to sexual functioning, decreased libido, changes in mood, performance anxiety and residual fear of death. It was believed that identification of these issues in any specific patient with appropriate counseling and education would reduce complaints.

Pediatric Patients

Few data are available assessing quality of life in pediatric heart transplant recipients. Starnes et al. (88) indicated that growth delay was observed in a few patients <10 years of age but that rehabilitation occurred in all patients who were discharged from the hospital. All survivors in their study were said to be active without physical limitations or restrictions. Psychosocial evaluation of a small group of pediatric transplant patients utilizing the Personality Inventory for Children, the Eyberg Child Behavior Inventory and other

tools suggested that, despite the emotional and physical trauma of end-stage cardiac illness, patients who survived were reasonably compensated and able to function at a level appropriate for their age (89). Bailey et al. (90) indicated that growth development and psychosocial adaptation had been adequate in their series of 43 patients <12 years of age.

Summary

Although psychosocial and quality of life evaluation variables can be difficult to quantify precisely, most data support the view that patients' lives are vastly improved after heart transplantation, not only in terms of prolongation, but also in the sense of quality and well-being. Although difficulties persist, such as employability, financial stress and certain physical limitations, heart transplantation clearly remains an important and very worthwhile procedure.

Recommendations

The Task Force recommends that the following be undertaken by the transplant community:

1. Develop policy and a document designed to educate patients and their families about life after heart transplantation, including return to mainstream activities and employment.

2. Develop policy and a document designed to educate employers about capabilities of heart transplant recipients, with specific respect to their employability.

3. Develop policy and an educational document that defines significant functional impairment after heart transplantation with respect to physiologic, emotional and psychiatric variables.

4. Define barriers to return to work, including a study of patients' functional capacity, loss of disability insurance and inability to pay for health care costs.

5. Develop strategies to reduce the barriers to return to work after heart transplantation.

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Task Force 5: Complications

LESLIE W. MILLER, MD, FACC, CHAIRMAN, ROBERT C. SCHLANT, MD, FACC, CO-CHAIRMAN, JON KOBASHIGAWA, MD, FACC, SPENCER KUBO, MD, FACC, DALE G. RENLUND, MD, FACC

Introduction

Improvements in immunosuppression and recipient selection have been associated with increased short- and long-term survival rates with heart transplantation. A number of complications, however, do occur after heart transplantation (1), most of which can be traced to relative inadequate or excessive dosing or intrinsic properties of immunosuppressive medications. The following section is a brief overview of these complications.