REVIEW

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Long-term medical complications of heart transplantation: Information for the primary care physician

ABSTRACT

As heart transplantation becomes much more common primary care physicians will play a key role in preventing, detecting, and treating the short-term and long-term complications of this procedure. These complications include chiefly graft rejection and accelerated coronary artery disease, but also dyslipidemia, hypertension, diabetes mellitus, kidney failure, gout, osteoporosis, and malignancy.

KEY POINTS

Acute rejection is the leading cause of death in the first posttransplant year, but in the long term the leading cause is coronary artery disease, followed by malignancy.

Statins appear to increase the survival rate. We therefore recommend that all heart-transplant recipients take a statin, regardless of lipid level, with a goal LDL level less than 100 mg/dL.

Heart-transplant recipients should undergo coronary angiography every year to screen for coronary artery disease. Dobutamine stress echocardiography may emerge as an alternative, noninvasive test.

Because the immunosuppressant drugs cyclosporine and tacrolimus are nephrotoxic, the blood levels of these drugs should be monitored, as should the serum creatinine level. Urinalysis should also be performed to check for albuminuria.

CARDIAC TRANSPLANTATION has become practical for many more patients with end-stage heart disease, offering extended survival and improved quality of life. More than 26,000 have been performed in the United States since 1988.

Successful long-term care is a team effort involving the patient, the transplant team, and the primary care physician. Although a successful transplant alleviates the patient's primary problem of heart failure, it introduces a new set of potential long-term complications, primarily related to long-term immunosuppression with drugs such as cyclosporine, tacrolimus, azathioprine, muromonab-CD3, and corticosteroids.

The primary care physician plays an important role in:

- Managing preexisting and posttransplant medical problems that need long-term follow-up such as diabetes, hypertension, hyperlipidemia, and osteoporosis
- Watching for posttransplant complications such as infection, rejection, coronary artery disease, and malignancy, and providing appropriate referral to the cardiac transplant team if these arise
- Providing health maintenance, including annual physical examinations, appropriate cancer screening, and vaccinations
- Providing appropriate antibiotic endocarditis prophylaxis for heart-transplant recipients undergoing dental, genitourinary, or gastrointestinal procedures
- Addressing psychological issues and counseling patients and families.

Conversely, the transplant physician can help the primary care physician. In particular,

we recommend consulting with the transplant physician before prescribing any new medication, because immunosuppressant drugs have extensive interactions.

This article reviews these long-term complications and their management, with special attention to the role of the primary care physician. It also discusses the issue of retransplantation. However, because the issue of posttransplant infection is such a large topic and was reviewed by Avery in the June 1998 issue of the *Cleveland Clinic Journal of Medicine*,[1] the topic will not be addressed here.

FIRST DAYS: HEART DYSFUNCTION

A key concern in the first days after heart transplantation is the function of the graft.

Several physiologic factors influence the function of the newly transplanted cardiac allograft, including allograft denervation, ventricular loading conditions, the hormonal milieu, myocardial injury, donor-recipient size relation, pulmonary performance, and atrial function.[2]

Diastolic dysfunction is common early after heart transplantation, as revealed by serial evaluations of ventricular function by Doppler echocardiography.[3] Hemodynamic studies also show a restrictive pattern that usually resolves within days or weeks but may persist or recur later owing to cell-mediated rejection or hypertrophy.[4]

Consider consulting the transplant physician before prescribing new medications

During the first week after cardiac transplantation, mitral, tricuspid, and aortic regurgitation generally increase in severity.[5] These valvular regurgitations are usually asymptomatic at rest, except for tricuspid regurgitation, which is associated with right-sided heart failure in more than half of cases.

FIRST YEAR: ACUTE REJECTION

Rejection is the leading cause of death in the first year after heart transplantation and accounts for approximately 20% of all deaths.[6] Hence, it is important to monitor for acute rejection and ensure that the immunosuppressive therapy is adequate, especially during the critical initial 6-month period when the incidence of rejection is at its peak.

Most rejection episodes are asymptomatic. However, any hemodynamic compromise should alert the primary care physician to the presence of acute rejection.

Endomyocardial biopsy

Endomyocardial biopsy remains the gold standard for diagnosing acute rejection after cardiac transplantation. The most commonly used grading scheme is that of the International Society of Heart and Lung Transplantation.[7]

Biopsy schedule. How often to perform surveillance biopsies varies from one center to another. In general, the schedule is:

- Every week during the first month
- Every 2 weeks during the second month
- Every 6 to 8 weeks from the third month for 1 year
- Every 4 to 6 months thereafter.

After a treated episode of rejection, a biopsy is generally repeated within 14 days to assure adequate treatment.

Complications of biopsy. Endomyocardial biopsy is generally considered safe, with some procedural risk but few significant long-term sequelae.[8] Relatively common complications include flail tricuspid leaflets, reported to occur in 6% to 14% of patients and necessitating tricuspid valve repair in those with symptomatic right heart failure.[9] Coronary artery fistula formation has been reported in 2.9% of patients; most of these fistulae close spontaneously without long-term clinical sequelae.

Less common complications include arrhythmias (0.25%) and conduction abnormalities (0.2%). Relatively rare complications include hepatitis B transmission and venous thrombosis.

Noninvasive tests for rejection

A variety of noninvasive tests for rejection (eg, echocardiography, radionuclide angiography, heart rate variability, myocardial impedance measurement) have been investigated but lack adequate sensitivity. Serologic studies (eg, interleukin-6 and troponin measurements) also have proved unreliable to date.[10]

Tissue Doppler imaging, a new technique, measures myocardial relaxation velocities and gives an estimate of ventricular filling pressures. Since allograft rejection results in increased myocardial stiffness and abnormal

myocardial relaxation, tissue Doppler imaging has been useful for diagnosing rejection,[11] and may have a role as a screening test if ongoing research confirms its sensitivity and specificity.

LONG-TERM: CORONARY ARTERY DISEASE

New coronary artery disease is very common in heart transplant recipients and accounts for much of their long-term mortality and morbidity. Angiographic studies reveal coronary artery disease in approximately 42% of patients by 5 years.[12] However, this incidence may reach 80% if evaluated by intravascular ultrasonography.[13]

Angiography indicated yearly

Current practice after cardiac transplantation is to perform coronary angiography yearly, a surveillance interval in which progression of coronary artery disease can be observed. In addition, angiography should be performed any time a myocardial infarction (MI) is suspected, because MIs can present in a subtle and atypical manner.[14] Thus, a high index of suspicion is required.

Noninvasive tests for coronary artery disease

In general, noninvasive tests for transplant-associated coronary artery disease (eg, exercise electrocardiography and exercise radionuclide ventriculography) have inadequate sensitivity and specificity and their results do not correlate well with cardiac event-free survival following transplantation.

Dobutamine stress echocardiography (DSE). In a recent study,[15] 22 heart transplant recipients underwent serial DSE. During a mean follow-up of 32 months, 8 (73%) of 11 patients with persistent inducible wall-motion abnormalities on DSE either died, had an MI, or developed coronary artery disease, compared with 0 of 11 patients with transient wall-motion abnormalities or normal studies ($P < .001$). These data suggest that DSE might be a useful noninvasive test for coronary artery disease in this population.

Thallium-201 imaging has been advocated, but its role remains questionable.

HYPERTENSION

Hypertension develops after cardiac transplantation in 70% to 90% of cyclosporine-treated patients and 30% to 50% of tacrolimus-treated patients.[16] In addition, at the Cleveland Clinic, at least one third of cardiac transplant recipients have a history of hypertension before transplantation.

The mechanisms of heart-transplant hypertension include altered renal vascular reactivity and sympathetic nervous system activation.[17] In the normal (nontransplanted) heart, volume receptors respond to fluid expansion with signals for the kidney to increase natriuresis and diuresis. But because the transplanted heart is denervated, this reflex is interrupted, leading to a salt-sensitive type of hypertension.[18] Corticosteroids play a minor role in the pathogenesis.

Treating hypertension

Generally, blood pressures consistently higher than 140/90 mm Hg should be treated, as recommended by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[19]

Titrated monotherapy with either an angiotensin-converting enzyme (ACE) inhibitor or a calcium channel blocker may be effective in about 50% of patients, as described in the only randomized prospective clinical trial of antihypertensive treatment performed in heart transplant recipients.[20] Of note, however:

- Some patients are prone to hyperkalemia due to the combined effect of cyclosporine and ACE inhibition on the kidney, limiting the use of ACE inhibitors and mandating serial electrolyte measurements after starting these drugs.
- Diltiazem, verapamil, and amlodipine decrease the metabolism of cyclosporine. This effect allows one to use lower doses of cyclosporine, and hence, reduce cost, but may require initially more frequent cyclosporine-level monitoring.

Combination therapy with both an ACE inhibitor and a calcium channel blocker is commonly used and effective.[20] In some patients, however, hypertension cannot be controlled adequately even with maximally

Have a high index of suspicion for acute MI in heart transplant patients

tolerated doses of both calcium channel blockers and ACE inhibitors. People with hard-to-control hypertension requiring multiple agents often require diuretics as part of the regimen. The final tier of management would be to add an alpha-blocker such as clonidine or doxazosin in refractory cases.

Beta-blockers are usually avoided after heart transplantation because they tend to reduce exercise performance.[21]

HYPERLIPIDEMIA

Hyperlipidemia occurs in 60% to 80% of heart-transplant recipients.[22] Its cause is multifactorial and could be related to preexisting lipid abnormalities, cyclosporine therapy, and corticosteroid therapy. Corticosteroid withdrawal has been associated with lower cholesterol levels.

Elevated triglycerides may be a stronger risk factor than elevated cholesterol in transplant coronary artery disease, although the point is controversial.[23] Most likely, immune and ischemic mechanisms of endothelial injury in the setting of hyperlipidemia play a role in the development of coronary artery disease.

All transplant recipients should receive a statin

Treating dyslipidemia

Gemfibrozil. Lipid-lowering therapy using gemfibrozil, targeted to lowering triglyceride levels, appears to confer a survival benefit in cardiac transplant recipients who survive beyond the first year.[24]

Statins also appear to increase survival. In a prospective randomized trial,[24] patients who received pravastatin early after heart transplantation had a lower incidence of clinically severe acute rejection episodes, resulting in a significant improvement in 1-year survival (94% vs 78% in the control group, $P = .02$).[24] Follow-up at 5 years showed a continued survival benefit in patients receiving pravastatin (83% vs 62%).[25] A similar survival benefit was observed with simvastatin in a randomized prospective trial.[26] This observed survival benefit is probably a class effect shared by all statins.

In vitro studies revealed that pravastatin inhibits natural-killer cell cytotoxicity and acts synergistically with cyclosporine to inhibit cytotoxic lymphocyte activity. These findings suggest that pravastatin may increase survival in part by combating acute and chronic rejection.

Therefore, a statin is advised in all patients after cardiac transplantation, even with a normal lipid profile. Dosing should be titrated to achieve the goals recommended by the National Cholesterol Education Program (eg, LDL < 100 mg/dL).[27]

Side effects of statins. The combination of cyclosporine and a statin increases the risk of rhabdomyolysis (dissolution of muscle) over that with a statin alone. However, this combination has been shown to be safe in heart-transplant patients.[28] Combining lovastatin and gemfibrozil can also predispose to rhabdomyolysis, and this combination should in general be avoided. Rhabdomyolysis may present as vague muscle weakness and fatigue.

Another potential side effect is liver toxicity. It is thus recommended that creatine kinase and liver enzyme determinations be performed twice a year in all transplant recipients receiving statins.

RENAL DYSFUNCTION

Nephrotoxicity remains a serious clinical challenge with cyclosporine and tacrolimus use. The greatest decrease in the glomerular filtration rate occurs in the first 3 to 6 months. In a study of 2,088 Medicare beneficiaries, the annual risk of end-stage renal disease was 0.37% in the first year after transplantation, increasing to 4.49% by the sixth year.[29]

Chronic cyclosporine nephrotoxicity is characterized by a decrease in glomerular filtration rate, afferent arteriolopathy, and striped tubulointerstitial fibrosis.[30] Preexisting histologic changes in patients with advanced heart failure may mimic some features of "cyclosporine nephrotoxicity." Tacrolimus nephrotoxicity shares similar functional and structural features seen with cyclosporine nephrotoxicity.[31]

The mechanism by which cyclosporine and tacrolimus damage the kidneys may be inhibition of calcineurin, which may explain in part the increased systemic vascular resistance, due to effects on vascular smooth muscle and indirect effects mediated by increased sympathetic nervous system activation.

Preventing and monitoring for renal failure

Close monitoring of blood levels of cyclosporine and tacrolimus is critical to limit progressive decline in renal function, as there is no known treatment that is uniformly effective in preventing or reversing nephrotoxicity. The target therapeutic blood level of cyclosporine during the first 3 months after transplantation is 300 to 350 ng/mL; for tacrolimus the target range in the first month is 15 to 20 ng/mL.

In patients at high risk for nephrotoxicity (as determined by serum creatinine measurements), we delay starting tacrolimus or cyclosporine after transplantation and instead give cytolytic induction therapy (eg, muromonab-CD3) to spare the kidneys.

Close monitoring of renal function is essential, with serum creatinine measurements, urinalysis to screen for significant proteinuria, and early referral to a nephrologist if these findings are abnormal.

OSTEOPOROSIS

Transplant recipients rapidly lose bone mass and have high fracture rates. Within 2 months after heart transplantation, approximately 3% of whole-body bone mineral density is lost, mostly due to decreases in trabecular bone in the spine and hip. Up to 35% of patients have a fracture during the first year.[32]

Cyclosporine, tacrolimus, and glucocorticoids all cause bone loss, glucocorticoids particularly in the first 6 to 12 months of use.

Preventing and treating osteoporosis

Bone densitometry studies are helpful in identifying patients at risk for osteopenia and fractures. Treatment of osteoporosis in heart transplant patients should be directed towards preventing bone loss. In view of the morbidity associated with osteoporosis, patients at highest risk should be treated even before transplantation.

Postmenopausal women should generally receive estrogen replacement. In a recent prospective randomized study of 16 cardiac transplant recipients, exercise training restored bone mineral density towards pretransplantation values when started early after transplantation.[33] Prophylactic use of calcium carbonate and alfa-calcidol after cardiac transplantation is an effective regimen that reduces bone loss and may decrease osteoporotic complications. Bisphosphonates (eg, alendronate) and calcitonin nasal spray are among the main agents used to treat overt osteoporosis and can be used in heart transplant recipients.

GOUT

Gouty arthritis is the most frequent rheumatological complication among cyclosporine-treated organ-transplant recipients. Before transplantation, gout is observed in 6% of patients[34]; afterward, 70% to 80% of patients have hyperuricemia and 8% to 17% have gouty arthritis.

Posttransplant gout is often polyarticular and often has an accelerated clinical course. Symptoms and findings may be atypical, owing to immunosuppression.

Treating gout

Treatment of gout is often complicated by renal insufficiency and interactions with immunosuppressant drugs.

Colchicine is generally effective in treating acute episodes and preventing recurrent episodes. However, an interaction between colchicine and cyclosporine can lead to a rare but serious complication, myoneuropathy, especially if the patient has renal insufficiency. Therefore, if colchicine is used, the dose should be reduced, cyclosporine levels should be monitored closely, and patients should be evaluated for signs of neuromuscular toxicity.[35]

Transplant recipients rapidly lose bone mass and have high fracture rates

Allopurinol can interact with azathioprine to cause another potential life-threatening condition, pancytopenia.[36] Since allopurinol blocks the xanthine oxidase pathway by which azathioprine is metabolized, potentially toxic levels of azathioprine may result. On the other hand, mycophenolate is not metabolized by the xanthine oxidase pathway and can be used safely in combination with allopurinol.

Corticosteroids may be the most effective and safest approach in patients who are receiving cyclosporine and azathioprine and who have renal dysfunction.

Nonsteroidal anti-inflammatory drugs are generally *not* used, owing to their propen-

sity to precipitate acute cyclosporine-induced renal toxicity.

MALIGNANCY

Malignant diseases develop in 3% to 18% of heart-transplant recipients, with an estimated risk of 1% to 2% per year.[37] Malignancy ranks second to coronary artery disease as a cause of mortality, accounting for 10% to 23% of all deaths following heart transplantation. Cutaneous malignancy is the most common type, seen in up to 17% of patients, with a predominance of squamous cell carcinoma.

If a patient has a history of malignancy before transplantation, his or her risk of dying of a malignant disease is 12% at 3 years after transplantation, compared with 2% in patients without a pretransplant history of malignancy ($P = .0001$).[38] Hence, it is extremely important to follow the American Cancer Society screening recommendations both before and after transplantation. The primary care physician plays an important role in malignancy surveillance by performing regular annual evaluations including, in women, pelvic examinations and Papanicolaou smears.

Avoid NSAIDs in patients receiving cyclosporine

Posttransplant lymphoproliferative disorder (PTLD), a frequently fatal complication, occurs in 1.7% to 6% of cardiac transplant recipients.[39] The peak occurrence of PTLD is 3 to 4 months after transplantation. A strong association of PTLD with Epstein-Barr virus was observed in several series. The use of muromonab-CD3, which may reduce the rejection rate, has been shown to increase the risk of lymphoma more than eightfold.[40] This association remains contentious and has been challenged.

The initial management of PTLD usually involves reducing the amount of immunosuppression, which may be effective in a proportion of cases. Nonresponding patients may require aggressive combination chemotherapy, but the mortality rate is approximately 80% in this situation.[41]

DIABETES MELLITUS

Preexisting diabetes mellitus used to be a contraindication to heart transplantation, owing to concern about increased infection rates and worsening diabetes mellitus with corticosteroid use. Now, however, an estimated 12% of heart transplant recipients have a prior history of diabetes,[42,43] although patients with end-organ complications of diabetes (retinopathy, severe peripheral vascular disease, end-stage renal disease) are not considered suitable candidates.

Approximately 8% of heart-transplant recipients develop diabetes after transplantation.[42,43] Hyperglycemia is more frequent in patients receiving tacrolimus than in patients receiving cyclosporine.

Diabetes becomes more labile and harder to control after transplantation. However, even though diabetic patients need higher insulin doses after transplantation than before, they have a long-term survival rate similar to that of nondiabetic patients, and no increased risk of rejection, lethal infection, renal dysfunction, or graft atherosclerosis.[42,44]

If a patient develops diabetes after transplantation, oral glycemic agents may serve as a first-line strategy for treatment.

ANTIBIOTIC PROPHYLAXIS

Heart-transplant recipients undergoing dental, genitourinary, or gastrointestinal procedures should receive antimicrobial prophylaxis, according to guidelines from the American Heart Association.[45]

PSYCHOLOGICAL ISSUES

Heart transplantation is a psychosocially demanding process that carries tremendous psychological distress during the waiting period for a donor organ. A thorough psychosocial evaluation of the transplant candidate is thus essential to determine the patient's ability to cope with a number of stressors, including compliance with the medical regimen, the wait for a donor, the surgical procedure itself, and adaptation to life with a new organ.

However, despite such a thorough screening, a few patients may have significant psychopathology that remains undetected. Postoperative psychiatric complications range from organic mental syndromes to depression. Hence, patients need systematic psychosocial support both before and after transplantation.[46]

WHO MIGHT BENEFIT FROM RETRANSPLANTATION?

If a transplanted heart fails, the patient's only option is to undergo retransplantation.

But retransplantation raises many ethical and fiscal issues. Organs for transplantation are scarce, and patients are 20% less likely to survive 1 year after a second transplantation than after a first transplantation. Is it therefore fair for a patient to receive a second heart transplant? Is it cost-effective? Is it the optimal use of a scarce resource? Rigorous and consistent criteria are needed to select the "ideal" candidate for retransplantation—ie, one who is likely to do well.

The International Society for Heart and Lung Transplantation registry[47] found four factors predictive of survival after repeat heart transplantation:

- Accelerated coronary artery disease as the cause of allograft failure (coronary artery disease is the main cause of graft failure and the most common reason to consider retransplantation, followed by rejection and primary graft failure[48])
- An interval longer than 6 months between transplants
- No need for mechanical ventilatory assistance before transplantation
- Second transplantation after 1985.

Patients with these predictive variables had an anticipated 1-year survival rate of 64%, which is still significantly less than the 85% 1-year-survival rate expected with first transplants. Thus, defining the ideal candidate poses a dilemma to the transplant team.

The primary care physician can help by relaying information to the transplant center about the patient's health maintenance status and compliance, issues that are equally important in the decision process.

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