

# Cardiac Transplantation: The Role of the Primary-Care Physician

The care of a patient following cardiac transplantation requires a team approach, involving the transplant center and the family physician. This requires the primary-care physician to have adequate knowledge of the basics of transplantation.



By Lynn P. Straatman, MD, FRCPC

## *History of Cardiac Transplantation*

Over the past decade, cardiac transplantation has evolved into an acceptable therapy for patients with end-stage cardiac disease not amenable to conventional therapy. The care of the patient following

transplantation requires a team approach, involving the transplant center and the family physician. This requires the primary-care physician to have adequate knowledge of the basics of transplantation.

The history of cardiac transplantation dates back to the 1940s when the understanding of transplant biology evolved and successful immunosuppressive protocols in renal transplantation forged the way for successful cardiac transplantation. The first successful canine orthotopic cardiac transplantation, using a biatrial approach, was published in 1950.<sup>1</sup> In 1966, Christiaan Barnard performed the first successful human cardiac transplantation in Cape Town, South Africa. The advent of new immunosuppressive agents in the 1970s lead to the establishment of cardiac transplantation as a treatment option for end-stage heart failure.

### **About the author...**



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Table 1

## Minimal Listing Criteria For Cardiac Transplantation

### Indications

- Advanced functional class (NYHA\* class III to class IV).
- Patients with a peak  $VO_2^{**}$  of 15 ml/kg/min maximum or 55% of predicted  $VO_2$  for age and gender.
- Poor one-year survival.
- Failure of maximal medical therapy and alternative or conventional surgery.
- Capacity for rehabilitation after transplantation.

### Contraindications

- Pulmonary hypertension:
  - Pulmonary vascular resistance 5 Wood's units
  - Transpulmonary gradient 15 mmHg
  - Pulmonary vascular resistance index 6 Wood's units
- Age — not an absolute contraindication, but with increasing age there should be more intensive screening for comorbidities.
- Psychosocial — any behavior that would jeopardize the successful outcome.
- Obesity — body mass index >140% of ideal body weight.
- Cardiac cachexia — body mass index < 60% of ideal body mass index.
- Malignancy — all patients with a pre-existing non-basal cell carcinoma require oncology assessment regarding grade, duration of remission and prognosis.
- Osteoporosis — risk of osteoporosis should be screened and treated prior to listing for cardiac transplantation.
- Renal insufficiency.
- Primary systemic disease.

\*NYHA: New York Heart Association \*\* $VO_2$ : Volume of oxygen utilization

Adapted from: Miller LW: Listing criteria for cardiac transplantation: Results of the American Society of Transplant Physicians – National Institute of Health Conference. *Transplantation* 1998; 66:947-51.

Improvements over the past several years in anti-rejection therapy and organ preservation have resulted in improved survival rates. The 2001 report of the International Society of Heart and Lung Transplantation states that the current one-year survival is 80%. The patient half-life (time to 50% survival) is 9.1 years. In those patients who survive the first year, the patient half-life is 11.6 years.<sup>2</sup>

There exists a significant gap, however, between the supply and demand for transplantable organs. Recent reports indicate that, among those patients currently listed for transplant in Canada, only 50% will eventually receive a transplant. The number of transplantations in this country has remained constant at 160 to 180 per year.<sup>3</sup> It is estimated there are as many as 5,000 patients in Canada < 65 years of age, who

would benefit from transplantation. The current listing criteria for transplantation are extremely strict.

The indications and contraindications for cardiac transplantation have recently been reviewed and the Canadian Cardiovascular Congress has published a consensus document. These criteria were designed to identify those patients who are at the greatest risk of dying and who will derive the most benefit from cardiac transplantation. All patients who demonstrate severe end-stage heart failure through exercise-testing merit a formal evaluation, including an assessment of comorbidities that either alone, or in combination, may represent relative or absolute contraindications to transplantation (Table 1).<sup>4</sup>

The improvement in patient survival is due to improvement in immunosuppressive protocols. The goal of post-transplant immunosuppressive therapy is to prevent cardiac rejection and graft dysfunction, while at the same time minimizing toxicity. Combinations of immunosuppressive agents are commonly used to achieve this goal. Many transplant centers have adopted an individualized approach to immunosuppression, rather than one protocol for every patient.<sup>5</sup>

Steroids, calcenurin agents (*e.g.*, cyclosporin A, tacrolimus [FK506]), purine antimetabolites, azathioprine and mycophenolate mofetil are used in an individualized manner to minimize symptoms. Each drug has a unique site of action within the immune response cascade as well as its own adverse effects (Table 2). Newer drugs, such as sirolimus, have been developed to inhibit at a later stage in the immune cascade and are synergistic with cyclosporin and mycophenolate mofetil.<sup>6</sup>

### *Complications Following Cardiac Transplantation*

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Morbidity surrounding transplantation is primarily due to the adverse effects of drugs and immunosuppression. Hypertension is extremely common post cardiac transplantation, occurring in 68% of recipients at both one and five years follow-up. Hyperlipidemia, both secondary to immunosuppressive therapy or as a pre-existing risk factor for coronary disease, is present in approximately 40% to 45% of recipients by one year following transplantation. The use of agents, such as pravastatin, has been studied in this population and the use of lipid-lowering agents is strongly recommended in all patients. Diabetes and renal dysfunction continue to be a source of significant morbidity post-transplantation. At five-years follow-up, approximately 2% of patients are reported to be on chronic dialysis.<sup>2</sup>

Rejection remains an important cause of morbidity and mortality post-transplantation.<sup>7</sup> Acute rejection consists of both a non-specific and an antigen-specific immune response. While the majority of rejection episodes are asymptomatic, hemodynamically compromising rejection can occur. This is defined as a decrease in the ejection fraction of > 10% and/or the presence of clinical signs of ventricular dysfunction. Endomyocardial biopsy is the gold standard for the diagnosis of cardiac allograft rejection.<sup>8</sup> There is a standard grading system for rejection developed by the International Society for Heart & Lung Transplantation.

Chronic rejection is due to chronic vascular injury to the graft. This is demonstrated by circumferential thickening of the vascular endothelium, resulting in concentric arterial narrowing that eventually leads to graft

Table 2

## Immunosuppressive Medications Used In Cardiac Transplantation

Drug	Mode of Action	Side Effects	Indications
Corticosteroids	Nonspecific (block expression of several cytokine genes)	<ul style="list-style-type: none"> <li>• Osteoporosis</li> <li>• Cataracts</li> <li>• Glucose intolerance</li> <li>• Hypertension</li> <li>• Cushingoid face</li> </ul>	<ul style="list-style-type: none"> <li>• Induction</li> <li>• Maintenance</li> <li>• Acute rejection</li> </ul>
Cyclosporin	Inhibits production of IL-2* and the generation of cytotoxic T cells**	<ul style="list-style-type: none"> <li>• Nephrotoxicity</li> <li>• Hepatotoxicity</li> <li>• Hypertrichosis</li> <li>• Gingival</li> <li>• Hyperplasia</li> <li>• Neuropathy</li> </ul>	<ul style="list-style-type: none"> <li>• Maintenance</li> </ul>
Tacrolimus	Inhibits T cell function by impairing release of IL-2 and other cytokines	<ul style="list-style-type: none"> <li>• Nephrotoxicity</li> <li>• Neurotoxic</li> <li>• Nausea</li> <li>• Diarrhea</li> </ul>	<ul style="list-style-type: none"> <li>• Maintenance</li> </ul>
Azathioprine	Inhibits antigen stimulation of proliferation of lymphocytes	<ul style="list-style-type: none"> <li>• Bone marrow suppression</li> <li>• Hepatotoxicity</li> <li>• Pancreatitis</li> </ul>	<ul style="list-style-type: none"> <li>• Maintenance</li> </ul>
Mycophenolate Mofetil	Reversible inhibitor of the <i>de novo</i> pathway of purine synthesis	<ul style="list-style-type: none"> <li>• Nausea</li> <li>• Vomiting</li> <li>• Diarrhea</li> <li>• Increased CMV</li> </ul>	<ul style="list-style-type: none"> <li>• Maintenance</li> </ul>
Polyclonal Antibodies	Attaches to circulating circulating	<ul style="list-style-type: none"> <li>• Fever</li> <li>• Chills</li> </ul>	<ul style="list-style-type: none"> <li>• Induction</li> <li>• Rejection</li> </ul>
Monoclonal Antibodies	Binds with CD3 complex on T cell and interferes with Ag*** recognition and decreases cell proliferation	<ul style="list-style-type: none"> <li>• Fever, chills</li> <li>• Bronchospasm</li> <li>• Hypotension</li> <li>• Pulmonary edema</li> <li>• Rash</li> <li>• Headache</li> </ul>	<ul style="list-style-type: none"> <li>• Induction</li> <li>• Rejection</li> </ul>

\*IL-2: Interleukin 2 \*\*T cell: Thymic cell \*\*\*Ag: Antigen

Adapted from: Haverich A, Frimpong-Boateng K, Schafers HJ, et al: Individualized immunosuppression in heart transplant recipients. *Transplant Proc* 1987; 19(1 Pt 3):2514-5.

Table 3

## Possible Presentations of Acute Allograft Rejection

### Symptoms

- Decreased exercise tolerance
- Fatigue
- Shortness of breath
- Fever

### Physical Signs

- Hypotension
- S<sub>3</sub>\* gallop
- Increased jugular venous distention
- New onset of edema

### Electrocardiology

- Bradyarrhythmias
- Atrial flutter or fibrillation
- Low voltage

\*Third heart sound

Adapted from: Kirklin JK, Bourge RC, McGiffin DC: Recurrent or persistent cardiac allograft rejection: Therapeutic options and recommendations. *Transplantation Proc* 1997; 29(supp A):40S-4S.

ischemia.<sup>9</sup> This process is termed allograft or transplant coronary disease (Table 3). After the first year post-transplantation, coronary disease is the most common cause of morbidity and mortality. It is important to note that the classical symptoms of coronary artery disease (CAD), such as angina, do not occur due to cardiac denervation. Classical symptoms of advanced transplantation CAD include congestive heart failure, myocardial infarction and sudden death. Transplantation coronary disease etiology is multifactorial, including both immune and non-immune mediated factors. Non-immune factors include cytomegalovirus (CMV) infection, hypercholesterolemia, elevated homocys-

teine and advanced donor age.<sup>10</sup>

Infections are an important cause of morbidity and mortality following transplantation. The timing of infections, relative to the date of transplantation, can help predict the type of infection present. Infections occurring in the first month after transplant are usually related to the surgical procedure and include surgical site infections, infections from indwelling catheters and ventilator associated pneumonias.

Between the first and sixth month after transplantation, the common opportunistic infections that occur include CMV, herpes simplex virus (HSV), pneumocystis carinii and toxoplasmosis. Beyond six months, community-acquired infections are most common, including influenza, pneumococcal pneumonia and reactivated varicella-zoster viral infection.<sup>11</sup>

Malignancy is more common post-transplant and is also multifactorial related to the following:

- Immunosuppressive medications;
- Chronic viral infections; and
- Reactivation of previous cancer that is in remission or idiopathic.

Post transplant lymphoproliferative disease (PTLD) is an immune-mediated lymphoma, which occurs only after transplantation. Epstein-Barr virus is considered to play a major role in the development of most PTLT. Primary infection conveys the highest risk for development of PTLT. Other risks for development of early PTLT include immunosuppression (especially with OKT3 [muromonab-CD3]), age of the recipient and type of organ transplanted. Symptoms such as fevers, sweats or neurological manifestations, along with lymphadenopathy or organomegaly, may be signs of disease. The diagnosis is made based on histological criteria. The treatment of PTLT consists of

lowering immunosuppressive therapy, followed by the addition of anti-viral agents, monoclonal antibodies or interferon.<sup>12</sup>

Skin malignancies, such as squamous cell carcinoma, basal cell carcinoma and Kaposi's sarcoma, are the most common malignancies following transplant. Skin cancers are linked to duration and level of immunosuppression, older age at transplant and exposure to ultraviolet radiation.<sup>13</sup> There is also an increase in other malignant tumors following transplantation.<sup>14</sup>

## *Cardiac Physiology Post-Transplantation*

Cardiac physiology post-transplantation is unique. Resting hemodynamics differ significantly, both acutely and chronically, from normal subjects. In addition, neural mechanisms undergo changes as a result of surgical denervation. Afferent control mechanisms and efferent responses are both altered. Examples of altered cardiovascular responses include altered cardiovascular response to exercise, altered responses to cardiac pharmacological agents and altered cardiac electrophysiology. Immediately after transplantation, cardiac filling pressures, such as right atrial and pulmonary artery pressures, are elevated. These hemodynamic abnormalities improve with time, but never completely normalize.

In the normal heart there is afferent and efferent innervation. Cardiac transplantation, however, severs afferent fibers, as well as the efferent fibers of the sympathetic and parasympathetic nervous system. As a result of the afferent denervation there is a lack of angina, alterations of peripheral autonomic response and changes in sodium and water balance. Loss of efferent fibers results in a resting tachycardia and a blunted chronotropic response to stresses such as exercise. The transplanted heart

Table 4

### Indications for Referral or Consultation to the Transplant Center

- Suspected allograft rejection
- Allograft dysfunction
- New onset of renal dysfunction
- Fever without an obvious cause
- Complicated infection
- Perceived cardiac events (myocardial infarction, syncope, complicated arrhythmias or sudden death)
- Malignancy other than skin cancers
- Medication changes (due to potential interactions with immunosuppressive agents)
- Possible noncompliance

Adapted from: Wagoner LE: Management of the cardiac transplant recipient: Roles of the transplant cardiologist and the primary care physician. *Am J Med Sciences* 1997; 314(3):173-82.

is dependent on heart rate to maintain adequate cardiac output. Immediately post-transplantation, sinus node function may be delayed and the transplanted heart must be supported by pharmacological methods or cardiac pacing.<sup>15</sup>

## *Role of the Primary-Care Physician*

The best overall approach in the management of the post-transplantation patient is a team approach among the transplantation and primary-care physicians. Studies have shown patients who do better post transplantation have a primary-care physician. In Canada, many patients live a great distance from a transplantation center, therefore many situations, such as infections, immunizations and non-cardiac surgery, have to be dealt with


### Case Discussion

The patient underwent formal transplantation evaluation, including a right heart catheterization, abdominal ultrasound, femoral and peripheral Doppler ultrasound and a psychosocial assessment.

John was able to wait at home for his transplant for the first eight months. Worsening heart failure, however, resulted in his admission to the hospital for inotrope stabilization and bridge to transplantation. Nine months after being accepted for transplantation, John received a new heart. Bleeding, renal insufficiency and worsening diabetes (requiring insulin) complicated the immediate post-transplant course. Fourteen days after his heart transplant, John was discharged. He was able to begin a cardiac rehabilitation program eight weeks after transplant.

closer to home.<sup>16</sup> There are several reasons to refer a patient to the cardiac transplantation center (Table 4). The general rule is, if in doubt, call the transplantation center first. Most issues can be dealt with through simple communication between the two physicians caring for the patient.

Perhaps one of the greatest roles of the primary-care physician is to aid in the increased public awareness of organ donation and transplantation through patient education. The organ donation rate in Canada is 15.4 donors per million population. This is significantly lower, when compared to other countries, such as Spain which has a donor rate of > 31 donors per million population.<sup>17</sup> This is due to increased public awareness and increased effort by trauma centers to identify potential donors.

Cardiac transplantation has evolved over the past several years. Advances in immunosuppressive therapy, organ preservation and complication surveillance has continued to improve outcomes. Cardiac transplantation remains a treatment and not a cure. Alternatives to cardiac transplantation, such as ventricular assist devices, total artificial hearts, cell transplantation  and xenotransplantation are being studied.

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