



## **Cardiac Transplantation: Eligibility and Listing Criteria in Canada 2012**

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# Cardiac Transplantation: Eligibility and Listing Criteria in Canada

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## Introduction

Cardiac transplantation is the treatment of choice for patients who have 1) severe end-stage heart failure despite maximal medical therapy and/or 2) complex congenital heart disease not amenable to surgical palliation at reasonable risk. With improvements in organ preservation, anti-rejection regimes, and post-transplant management, survival rates post cardiac transplantation are very good. Unfortunately, there is an ever-enlarging gap between the supply and the demand for transplantable organs, a gap which is made more severe by expanding indications and less conservative listing criteria for cardiac transplantation. In Canada, it is estimated that 50% of patients listed for cardiac transplantation will never receive a donor organ. Many of these patients will be removed from the active transplant list because of progressive deterioration and multi-organ failure that renders them unable to survive transplantation, and others (20–30%) will die while on the transplant list. Although the number of patients listed for cardiac transplantation has increased by >25% over the last decade, the number of donor organs has remained static. Even with our expanded acceptance criteria for donor hearts, the gap between the number of patients who would benefit from cardiac transplantation and the number of available hearts is growing. In 2008 166 cardiac transplants were performed in Canada, in 9 adult cardiac transplant centres and 2 additional pediatric cardiac transplant centres.<sup>1</sup>

## Indications for Cardiac Transplantation

The Canadian Cardiac Transplant Network and the International Society of Heart and Lung Transplantation have recently reviewed the listing criteria for cardiac transplantation, in light of advances in medical, surgical, and device therapy for patients with late-stage heart failure.<sup>2,3</sup>

### Transplantable conditions

In general, cardiac transplantation can be considered in patients with late-stage heart disease who have received optimal medical and surgical (if appropriate) therapy, and *who have an unacceptable quality of life and poor anticipated survival*. Typically, this would include patients with:

- late-stage heart failure due to any cause;
- refractory life-threatening arrhythmias despite optimal medication, surgical, and device therapy;
- refractory angina not amenable to further revascularization;
- complex congenital heart disease with failed surgical palliation or not amenable to surgical palliation at acceptable risk.

## Assessment of the potential cardiac transplant recipient

**Cardiopulmonary exercise testing (CPX)** is routinely used as an objective assessment of functional limitation and prognosis, and is valuable in determining candidacy for cardiac transplantation. CPX testing results alone, however, do not constitute candidacy for transplantation, and must be used in conjunction with a complete clinical assessment. The currently accepted indication for transplantation is a peak  $\text{VO}_2 < 10 \text{ ml/kg/min}$ , providing anaerobic threshold was achieved.<sup>2</sup> A relative indication for transplantation, in those patients who have significant functional limitations due to heart failure, is a peak  $\text{VO}_2$  of 10–14 ml/kg/min in patients intolerant of beta blockers, 10–12 ml/kg/min in patients on beta blockers, or those with a peak  $\text{VO}_2$  of <50% of their maximum predicted value.<sup>2</sup>

In patients with borderline  $\text{VO}_2$  values, the **Heart Failure Survival Score (HFSS)** may be used to evaluate prognosis and assess candidacy for transplantation. The HFSS is a predictive model using 7 clinical characteristics, and can stratify patients into low, medium, and high risk for poor transplant-free survival.<sup>4</sup> These variables include: (1) presence of ischemic etiology of heart failure; (2) resting heart-rate value; (3) left ventricular ejection fraction; (4) mean arterial blood pressure; (5) presence of intraventricular conduction delay; (6) peak  $\text{VO}_2$  value; and (7) serum sodium level.

In the paediatric population, objective testing and the HFSS are generally not applicable and existing literature and clinical experience need to be utilized in a specialized centre to determine prognosis, identify patients with the greatest risk of dying and identify those who will derive the most benefit from heart transplantation.<sup>5</sup>

In the setting of fetal listing for cardiac transplantation, assessment should include a detailed fetal echocardiogram for diagnosis, a detailed anatomic antenatal ultrasound for other anomalies, amniocentesis for genetic and metabolic testing, and maternal blood for viral exposure and other infectious surveillance.

## Contraindications to Transplantation

In addition to assessment of patient prognosis, the evaluation of candidacy for cardiac transplantation includes careful workup for potential contraindications. It is important to note however, that for the most part these contraindications are not absolute and decisions regarding candidacy should be made on an individual basis by the cardiac transplant program.

**Pulmonary Hypertension** is the only hemodynamic contraindication to transplantation. The presence of significantly increased pulmonary artery pressure is a critical issue in the determination of candidacy. The potential for right heart failure is significant in the early post-operative stages of cardiac transplantation in the presence of refractory elevation of pulmonary artery pressure. As much as 20% of early post-cardiac transplantation deaths are attributable to right heart failure.<sup>6</sup> Prior to a patient being listed for cardiac transplantation, a right heart catheterization is mandatory to assess pulmonary artery pressure, and to identify

whether high pulmonary artery pressures are reversible with therapy. A vasodilator challenge should be administered when the PA systolic pressure is >50 mmHg, and when either the transpulmonary gradient (PA mean - PA wedge pressure) is >14 mmHg or the pulmonary vascular resistance is >3 Woods units (while maintaining a systolic arterial pressure of 85 mmHg).<sup>2,3</sup> In the paediatric population, differing thresholds and criteria for acceptable levels of pulmonary hypertension exist. Assessment of candidacy with this regard should be done in an experienced paediatric cardiac transplant centre.

**Age** is not an absolute contraindication to cardiac transplantation. Although the current guidelines suggest that patients should not be considered for cardiac transplantation if they are 70 years of age or older, patients over the age of 70 have had acceptable outcomes after cardiac transplantation if they are otherwise in excellent physical condition (i.e., no other significant medical problems).<sup>7</sup>

**Obesity** is associated with higher post-cardiac transplant mortality and morbidity, and it is recommended that severely obese patients not be listed for transplantation until they have achieved a BMI of <30kg/m<sup>2</sup>.<sup>2</sup>

**Malignancy**, specifically active neoplasm from origins other than the skin, is an absolute contraindication to transplantation. Although the general recommendation is that the patient be in remission for 5 years prior to being considered for transplantation, a pre-transplant cancer history should be assessed individually, with input from the treating oncologist regarding the risk of tumour recurrence, particularly in the setting of post-transplant immunosuppression.<sup>2</sup> In the paediatric population, there is precedence for cardiac transplantation within 2 years post-malignancy in the setting of low risk malignancies with high response rates to treatment.

**Diabetes with end-organ damage**, other than non-proliferative retinopathy, is a relative contraindication to transplantation. Of particular concern are those diabetics with autonomic dysfunction and those with hypoglycemic unawareness. Uncontrolled diabetes despite optimal therapy (HbA1c >7.5) is also considered a relative contraindication.<sup>8</sup>

**Renal dysfunction** is common in the heart failure population, and may be secondary to poor renal perfusion or related to underlying conditions such as diabetes, hypertension, or primary renal disease. In many of these cases the renal function can be expected to improve with restoration of adequate blood flow, but the use of calcineurin inhibitors post transplant may be associated with deterioration in renal function. Irreversible renal dysfunction with serum creatinine of >150 µmol/l (2 mg/dl) or creatinine clearance of <40ml/min has been considered a relative contraindication to cardiac transplantation.<sup>2</sup> However, multi-organ transplantation (i.e., heart and kidney) has been performed, and may be considered in appropriate candidates.

**Peripheral vascular disease** is considered an absolute contraindication, based on the severity of lesions, and the associated symptoms. In some cases surgical intervention (particularly carotid lesions) may be performed to allow listing for transplantation however, the progression of peripheral vascular disease may be accelerated after cardiac transplantation.<sup>9</sup>

Active **tobacco and substance abuse** is a contraindication to transplantation. Active tobacco smoking is a risk factor for adverse outcomes after transplantation, particularly when it comes to coronary artery vasculopathy and malignancy<sup>10</sup>. It is recommended that tobacco abstinence be monitored for a minimum of 6 months prior to a patient being listed for transplantation, and every 1–3 months afterwards.<sup>2,3</sup> Unfortunately, about 24% of patients who receive a cardiac transplant will return to smoking post-operatively.<sup>11</sup> For those patients who abuse alcohol or other substances, a similar program of monitored abstinence is required prior to listing for transplantation. Active substance abuse is an absolute contraindication to transplantation.

Active **infection** is also an absolute contraindication to transplantation. HIV infection has been considered an absolute contraindication to transplantation in the past, but more recently patients with stable, treated HIV in the absence of significant active disease have been transplanted with reasonable results<sup>12</sup>. The Canadian Cardiac Transplant Network considers HIV infection to be a relative contraindication to cardiac transplantation at this time. With the advent of effective antiviral therapy, patients who are carriers of Hepatitis B and C may be considered for cardiac transplantation, providing there is no evidence of hepatic cirrhosis.<sup>13</sup>

**Psychosocial issues** should be evaluated, so these issues can be identified and addressed prior to transplantation. This assessment should focus on compliance, quality of life, comprehension, and social situation. The goal is to identify those factors that would have a negative impact on post-transplant survival.

**Severe pulmonary or liver disease**, or any other significant organ dysfunction that would limit the quality of life or survival benefit to be gained from cardiac transplantation, is a contraindication to cardiac transplantation. Multi-organ transplantation may be considered in appropriate circumstances. Concomitant lung and heart transplant is the most common multi-organ (with heart) transplantation, and requires a separate discussion of indications and listing protocol.

**Immuno incompatibility** testing is mandatory prior to listing for transplantation. Although a high panel reactive antibody (PRA) is not a contraindication to transplantation, it is associated with a marked decrease in availability of suitable donors. Strategies to reduce PRA in highly sensitized patients are being developed and evaluated but are beyond the scope of this paper. High PRA is most likely to be present in multiparous females, patients who have received numerous blood transfusions, those with mechanical circulatory assist devices, and patients with complex congenital heart disease having undergone previous palliative surgery (especially with the use of autologous homograft material).

**ABO-incompatibility** in the setting of cardiac transplantation is generally an absolute contraindication except in the infant population given the immaturity of the immune system and the delayed production of isohemagglutinins. ABO-incompatible cardiac transplantation should only be undertaken in an experienced paediatric cardiac transplant centre.

**Chromosomal, neurologic or syndromic abnormalities** that are severe and/or progressive with an early mortality are absolute contraindications to cardiac transplantation. Nonprogressive or slowly progressive systemic diseases and genetic syndromes with life expectancies into the 3<sup>rd</sup> or 4<sup>th</sup> decade (genetic or metabolic cardiomyopathies) are no longer considered absolute contraindications.

**Fetal listing** is contraindicated if the fetus has not reached an age of pulmonary maturity, is not greater than 35 weeks gestation, and has not reached an estimated fetal weight of greater than 2.5 kilograms.

## **Process of Assessment for Cardiac Transplantation**

Adult cardiac transplant programs currently exist in Halifax, Montreal, Quebec City, Toronto, London, Ottawa, Edmonton/Calgary, and Vancouver. Paediatric cardiac transplant programs currently exist in Toronto, Montreal and Edmonton. Patients from outside of these geographic areas are referred to the nearest transplant centre for assessment. While it is often possible for a portion of the pre-transplant investigations to be performed outside of the transplant centre, the patient is usually required to undergo a significant portion of the assessment at the transplant centre.

Considerable expertise is required to determine whether a patient is a suitable transplant candidate. This requires a multi-disciplinary approach, to build a relationship between the patient and the transplant centre and to facilitate post-transplant management. Good communication between the transplant centre and the referring physicians is essential.

While some patients are referred for emergent transplantation listing, many others will be referred as they progress in their disease, to the point where it is anticipated that their functional status will imminently decline. For non-emergent candidates, the assessment process should include thorough evaluation of all of the prognostic investigations and potential contraindications. In patients for whom emergent listing is contemplated (cardiogenic shock, acute mechanical circulatory support, etc.) the assessment process is by necessity abbreviated. In these cases, the following assessments are key:

- Assessment of neurologic status. Patients must be deemed neurologically intact prior to listing for transplantation. If there is either doubt about the neurologic status or potential for significant neurologic impairment, strategies for bridge to candidacy (i.e., short-term circulatory support) may be considered, and the patient then re-evaluated over time.
- Assessment of infection and infection risk.
- Assessment of blood group for listing purposes.
- Assessment of pulmonary artery pressure, and documentation of the absence of irreversible pulmonary hypertension.
- Careful consultation with patient and family. It is important that the patient and family be aware of the risks and benefits of transplantation, and of the therapeutic commitments necessary for successful management after transplantation. When a

patient is not able to give informed consent, the family must be consulted about the patient's stated or probable wishes.

## Timing of Referral for Transplantation

- 1) Potential transplant patients should be referred to a cardiac transplant centre for evaluation in the setting of severe chronic cardiac disability  $\pm$  evidence of reduced organ perfusion only after they have undergone optimization of medical, surgical, and device therapy.
- 2) Patients with acute severe cardiac decompensation may be referred for evaluation when there is failure to respond to conventional therapies, and where the primary process is cardiac, in the absence of irreversible failure of other organ systems. Examples would include documented dependence on IV inotropic support to maintain adequate organ perfusion, or refractory cardiogenic shock.
- 3) Patients being considered for acute Mechanical Circulatory Assist (MCA) device implantation should be evaluated for cardiac transplantation candidacy as part of the MCA assessment.

If referring physicians have questions about their patients' suitability or the timing of referral for cardiac transplant assessment, the cardiac transplant program should be contacted directly for discussion and guidance.

## Listing Status for Cardiac Transplantation

When patients have been listed for transplantation, they are assigned a listing status according to their disease stability and the likelihood of survival without transplantation. The following status criteria have been developed by the Canadian Cardiac Transplant Network for listing of cardiac transplant recipients across the country.<sup>4,5</sup> **The criteria below are to be applied to patients for whom a decision has already been made about the appropriateness of cardiac transplantation. It is not meant to represent criteria for listing. All patients must be proven neurologically eligible for listing.**

### Status Criteria: Adult Cardiac Transplantation

#### *Status 4*

- 1) Mechanically ventilated patient on high-dose single or multiple inotropes  $\pm$  mechanical support (eg. Intra-aortic balloon pump, extra-corporeal membrane oxygenation (ECMO), abimed BVS5000, or biomedicus), excluding long-term ventricular assist devices (VAD).
- 2) Patient with VAD malfunction or complication, such as thromboembolism, systemic device-related infection, mechanical failure, or life-threatening arrhythmia.

- 3) Patient should be recertified every 7 days as a Status 4 by a qualified physician, if still medically appropriate.

#### **Status 4S**

- 1) High PRA (>80%)

#### **Status 3.5**

- 1) High-dose or multiple inotropes in hospital, and patients not candidates for VAD therapy or no VAD available.
- 2) Acute refractory ventricular arrhythmias.

#### **Status 3**

- 1) VAD not meeting Status 4 criteria.
- 2) Patients on inotropes in hospital, not meeting above criteria.
- 3) Heart/Lung recipient candidates.
- 4) Cyanotic congenital heart disease with resting saturation <65%.
- 5) Congenital heart disease – arterial-shunt-dependent.
- 6) Adult-sized complex congenital heart disease with increasing dysrhythmic or systemic ventricular decline.

#### **Status 2**

- 1) In-hospital patient, or patient on outpatient inotropic therapy not meeting the above criteria.
- 2) Adult with cyanotic CHD: resting O<sub>2</sub> saturation 65–75% or prolonged desaturation to less than 60% with modest activity (i.e., walking).
- 3) Adult with Fontan palliation with protein-losing enteropathy.
- 4) Patients listed for multiple organ transplantation (other than heart-lung).

**Status 1.** All other out-of-hospital patients.

## **Pediatric Cardiac Transplantation**

### **General Principles for the Paediatric Age Group (fetal – 18 years):**

1. The option for listing across compatible blood groups (i.e. ABO-incompatible heart transplantation), should exist in any paediatric patient in whom it is clinically appropriate. Eligibility for ABO-I listing is to be determined by a transplant physician or surgeon with the appropriate clinical expertise.
2. Organ allocation will be made preferentially to postnatal patients regardless of status. There may be circumstances where an *in utero* patient is deemed to have “life threatening CHD not amenable to medical or surgical temporizing therapy” and may be listed as a Status 4 at the discretion of the listing program. Allocation of a donor organ to an *in utero* patient ahead of any postnatal patient (regardless of listing status) will require mandatory discussion physician-to-physician. The program with the Status 4 patient should be notified as per the principles of organ sharing and initiate

the discussion regarding the possibility of reallocation of the donor heart to the *in utero* candidate. *In Utero* listing: prenatal testing should confirm that the fetus is viable and medically suitable to receive a transplant; the risk of associated complications becomes appropriately low at approximately 35-36 weeks gestational age; waiting time recommences at the time of birth.

3. Hearts from donors less than 18 years of age will be first considered for recipients less than 18 years of age (pursuant to size, blood type and clinical status). However, a suitable-sized paediatric donor may be better suited for a higher status older recipient and consideration for reallocation should proceed as per the principles of organ sharing.

### **Status Criteria: Pediatric Cardiac Transplant**

#### ***Status 4***

- 1) VAD in a patient <8 kg
- 2) Mechanically ventilated on high dose single or multiple inotropes  $\pm$  mechanical support (eg. IABP, ECMO, abiomd BVS5000, or biomedicus), excluding VADs
- 3) VAD malfunction or complication such as thromboembolism, systemic device-related infection, mechanical failure, or life threatening arrhythmia
- 4) Patients should be recertified every 7 days as a Status 4 by a qualified physician if still medically appropriate

#### ***Status 4S***

- 1) High PRA (>80%)

#### ***Status 3.5***

- 1) Hospitalized patient with a VAD
- 2) Less than 6 months of age with congenital heart disease – prostaglandin dependent
- 3) High dose or multiple inotropes in hospital *and* patients not candidates for VAD therapy or no VAD available
- 4) Acute refractory ventricular arrhythmias

#### ***Status 3***

- 1) VAD not meeting Status 4 criteria including outpatient VAD
- 2) Less than 6 months of age with congenital heart disease
- 3) Cyanotic congenital heart disease with resting saturation less than 65%
- 4) Congenital heart disease – *arterial* shunt dependent (i.e. Norwood)
- 5) Patients on inotropes in hospital, not meeting above criteria
- 6) Inpatient with CPAP/BIPAP support *for HF management*
- 7) Heart-Lung recipient candidates

#### ***Status 2***

- 1) At Home with intermittent CPAP/BIPAP support *for HF management*
- 2) In Hospital *for management of heart disease/HF* not meeting the above criteria
- 3) Growth failure: <5<sup>th</sup> percentile for weight and/or height OR loss of 1.5 SD of expected growth (weight or height)

- 4) Cyanotic congenital heart disease with resting saturation 65-75% OR prolonged desaturation to less than 60% with modest activity (i.e. walking, feeding)
- 5) Fontan palliation with protein-losing enteropathy or plastic bronchitis
- 6) Multiple organ transplant recipient candidates

### **Status 1**

- 1) All other out of hospital patients
- 2) *In Utero* (congenital heart disease or heart failure)

All Status 4 patients, whether adult or pediatric, are reviewed semi-annually at a meeting of representatives from a majority of transplant centres (i.e. Canadian Cardiac Transplant Network meetings) as a means of quality assurance.

## **Organ Sharing: A Nation-wide Agreement to Promote Optimal Donor Heart Allocation**

The Canadian Cardiac Transplant Network has endorsed and formalized a system whereby hearts are allocated nation-wide to the patients most in need of transplantation. A nation-wide list is distributed to all Organ Procurement Organizations (OPOs) across Canada, on which patients are identified according to their listing status (see above). The principle of the organ-sharing agreement, as outlined by the Canadian Cardiac Transplant Network, is as follows:

*The OPO will offer the donor heart to the Canadian site with the highest status recipient in the geographic area. The OPO will also notify the Canadian program(s) with a potentially appropriate Status 4 or 4S recipient(s) nationwide of the potential donor heart. If there are competing potential recipients, mandatory discussion in a timely fashion, physician to physician, will ensue to allocate the organ, **the principle being that the recipient with the longest current listing as Status 4 be given priority.** If consensus is not reached, final allocation will be made by the center to which the heart was originally offered.*

*If an organ becomes available in a province without a cardiac transplant program (adult or pediatric), it will be offered to the program with the longest listed patient from that province. That transplant program will then follow the established organ allocation algorithm.*

*All out-of-country donor hearts will be offered nationally to all programs with eligible Status 4 or 4S recipients. If there are competing Status 4 candidates, mandatory discussion is required in a timely manner, physician to physician, prior to allocation of the donor heart. If consensus is not reached, final allocation will be made by the centre with the **recipient with the longest current listing time as Status 4.**<sup>4</sup>*

## Summary

The goal of cardiac transplantation is to improve survival and quality of life in patients with end-stage cardiac disease. The greatest limitation to transplantation at this time is lack of donor availability. Patients who are felt to be potential candidates for cardiac transplantation should be referred for evaluation at a cardiac transplant program, where they will be assessed for listing suitability. This is an extensive process which may, however, be abbreviated in emergent situations, and which in any case requires significant expertise and a multi-disciplinary approach. Once a patient is listed for transplantation, close monitoring and regular reassessment of clinical status is mandatory. The members of the Canadian Cardiac Transplant Network have developed Listing Status criteria to ensure consistent status listing for patients awaiting cardiac transplantation in Canada. Appropriate allocation of donor hearts across Canada is promoted by a nation-wide organ sharing agreement. The fact that this system works so well is a tribute to the members of Canada's cardiac transplantation programs, who continue to work cohesively to set standards and promote best practices for cardiac transplantation across the country.

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