

Heart transplantation and its long-term outcomes

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ABSTRACT

Heart transplantation increases quality of life and life expectancy in patients with end stage heart failure. Patients diagnosed with severe heart failure via cardiopulmonary function tests are candidates for heart transplantation. Immunosuppressive treatment administered after transplantation is a three-drug treatment method used to weaken the recipient's immune system in order to prevent rejection of the transplanted organ. While early-term complications of heart transplant include primary graft incompatibility, right ventricular failure, and infections, malignancies and cardiac allograft vasculopathy (CAV) are among late-term complications. The past decade has revealed 50% increased incidence of post-transplant CAV which is difficult to diagnose and treat to this day.

Keywords: Cardiac allograft vasculopathy, heart transplant complications, heart transplant, immunosuppressive treatment, transplantation rejection.

HEART TRANSPLANTATION

The first human-to-human heart transplantation was perceived as a speculation for a long time until it was performed in 1967 by Christiaan Barnard and was later widely accepted in the medical community, given the positive outcomes of long-term survival and quality of life in patients.^[1]

Heart transplantation is the gold standard treatment in patients with end stage heart failure that is unresponsive to treatment,^[2] and is the third most commonly performed organ transplantation procedure in organ transplantation centers.^[3,4]

Heart transplantation may be considered in patients with symptoms of heart failure at rest or during mild physical activity despite undergoing all treatments, frequent hospitalizations, and in those with unsatisfactory response to medical and surgical treatments. However, these factors alone are insufficient. In the cardiopulmonary function test, which plays a critical role in the decision-making process for transplantation, the patient's

respiratory, circulatory, and musculoskeletal systems are all tested and evaluated in order to estimate the recipient's status and potential complications following transplantation.

During the cardiopulmonary test, the patient is given an exercise in the form of pedal cycling, yielding data on the amount of oxygen and carbon dioxide volumes, general respiratory adequacy and muscle metabolism during exercise stress.^[5,6] In particular, the maximum oxygen consumption (VO_2) is higher and ventilation/carbon dioxide production slope is lower in heart failure patients compared to healthy people, showing strong resemblance to the later stages of heart failure.^[6,7]

Some of the medical requirements and contraindicatory factors of heart transplantation are provided in Table 1. In addition to the listed factors, presence of other diseases accompanying heart failure such as infections or neoplasms should be treated to reevaluate transplantation.

Table 1. Some medical requirements for heart transplantation and factors that prevent transplantation

Indication	Contraindication
VE/VCO ₂ >35	Severe psychiatric disease, incompilance to treatment
VO ₂ ≤12 mL/kg/min (with beta blocker use)	Severe peripheral vascular disease, substance abuse
VO ₂ ≤14 mL/kg/min (without beta blocker use)	Severe renal failure
Persistent functional class III or IV	Severe cerebrovascular disease
Ischemic disease with angina unresponsive to treatment that cannot be treated with revascularization	Severe pulmonary heart disease
VAD or unresponsive HF during inotropic use	Pulmonary hypertension (PVR >5 Wood units)
Persistent or unresponsive ventricular arrhythmia	Incompatibility between donor and recipient in ABO cross-match test

VO₂: Maximum oxygen consumption volume; VE/VCO₂: Ratio of respiration volume to carbon dioxide volume; VAD: Ventricular assist device; HF: Heart failure; PVR: Pulmonary vascular resistance; Functional class: WHO rated classes of pulmonary hypertension.

High-risk factors such as pre- and post-transplantation peripheral vascular disease (PVD),^[8] pre-transplantation renal failure (PRF),^[9,10] and cerebrovascular accidents (CVAs)^[11] play a critical role in the decision-making process of transplantation. Furthermore, corticosteroid drugs included in post-transplantation immunosuppressant treatment increases levels of blood sugar in diabetes patients, making treatment difficult. However, the main factor that prevents transplantation is presence of any end organ failure.^[12]

Early-term complications and immunosuppressive treatment

Currently, the one-year survival rate following heart transplantation is around 90%,^[13] however elderly patient age due to increased life expectancy has increased tendency to poor outcomes such as primary tissue mismatch or antigen-related mismatch.^[13-15]

Early term complications include primary tissue mismatch, which accounts for 36% of deaths within the first 30 days,^[16] right ventricular insufficiency^[17] which causes pulmonary hypertension and is responsible for 50% of early complications, and infections induced by opportunist pathogens especially due to immunosuppressive therapy^[5] which occupy the largest majority.

Endomyocardial biopsies are performed to detect the early stages of organ rejection. These biopsies can identify three types of organ rejection: hyperacute, cellular, or humoral (or antibody-mediated) rejection.^[18] Hyperacute humoral

rejection caused by previously formed antibodies against the donor (HLA or ABO) is a rare but very severe form of organ rejection. Acute cellular rejection, characterized by inflammatory cells found in the myocardium, is the most common form of organ rejection and its severe forms require additional immunosuppressive treatment.^[19] Acute humoral rejection or antibody-mediated rejections generally manifest as anti-HLA antibodies in

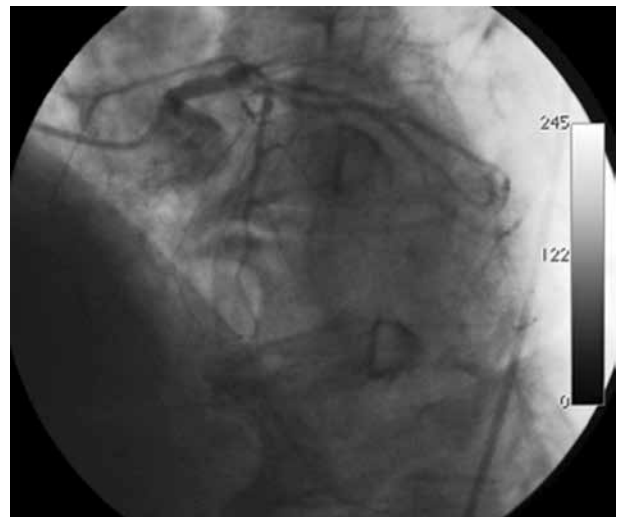


Figure 1. Coronary angiography of a cardiac allograft vasculopathy patient who underwent heart transplantation six years ago. Diffuse narrowing of the left anterior descending artery of the heart and disappearance of the distal end of the left circumflex artery is shown.^[35] Cardiac allograft vasculopathy disrupts the vasculature of the transplanted heart with a stiffening effect. Prolonged smooth muscle cell proliferation, inflammatory cell and fat accumulation cause thickening of the circumferential vessels of the heart.^[34]

the transplanted organ or tissue's vascular endothelium.^[20] However, in some cases, anti-HLA antibodies in conjunction with non-HLA antibodies can cause acute humoral rejection. One example of this is angiotensin II hormone receptor antibody. The angiotensin II hormone, responsible for maintaining the body's overall fluid content, functions with a G protein-bound type 1 angiotensin receptor (AT1R)^[21] on the surface of vascular endothelial cells in the body. This receptor's antibody is a non-HLA AT1R antibody which significantly increases the risk of acute antibody-mediated rejection and acute cellular rejection if it has elevated levels together with the HLA type antibody, HLA-donor-specific antibodies (DSA).^[22,23]

Immunosuppressive treatment is a three-drug treatment method used to weaken the recipient's immune system after transplantation to prevent organ rejection. The drugs used in immunosuppression include calcineurin inhibitor (CNI) (cyclosporin or tacrolimus), antimetabolite agent (mycophenolate mofetil [MMF] or azathioprine), and corticosteroid to be used for a period of one year after transplantation in gradually decreasing doses.^[24] Antiproliferative agents (PSIs) and mTOR inhibitors (sirolimus and everolimus) are novel drugs used in immunosuppressive treatment compared to conventional drugs.^[25] mTOR inhibitors (sirolimus and everolimus) has been shown to decrease cardiac allograft vasculopathy (CAV) progression and probability.^[26,27] and risk of neoplasm and viral infections as late term complications.^[28,29]

Cardiac allograft vasculopathy and other late-term complications

Malignancies and CAV are the most common late-term complications. Post-transplantation malignancies are more common in heart transplant compared to other organ transplants. This is because more prophylactic drugs are used in immunosuppression.^[30,31] Skin cancer accounts for about 50% of all post-transplant malignancies and is the most common type.^[32] Lymphoproliferative disorders, Kaposi sarcoma, and tumors are other significant post-transplant malignancies.^[33]

Cardiac allograft vasculopathy is the largest cause of late-term complications after heart transplantation. It has 8% incidence rate in the

first year after transplant, 30% in the first five years, and 50% in the first 10 years.^[16]

Cardiac allograft vasculopathy is a slow progressing disease that is initially asymptomatic or manifests symptoms nonspecific to CAV and therefore, difficult to diagnose. When symptoms initially occur, the disease has already progressed to later stages and irreversible myocardial damage may lead to sudden death. Tissue disorders seen in routine echocardiographic follow-up or annual angiography may indicate CAV. However, since angiography is not sensitive to some changes in vascular structure caused by the disease, it may be inadequate for identifying CAV. Therefore, intravascular ultrasonography (IVUS) used to see the inside of the vessel is accepted as the gold standard for CAV diagnosis.^[34,35]

Heart transplantation cases

A total of 350 routine coronary angiographies were conducted on 105 patients over an 18-month period. Tissue disorders that may be indicative of CAV were identified in 43 of the patients. Of these 43 patients, 15 had serious damage due to over 50% narrowing of the coronary vessel. Age of these patients ranged between 27 and 68 years and all of them were male. Nine of those patients underwent PTCA (percutaneous transluminal coronary angioplasty). Cyclosporine and prednisone were administered to all and azathioprine was administered to seven of the patients. Within the first month after the initial PTCA, ischemic disorders were detected in all nine patients with dobutamine stress echocardiography. In addition, three of the patients developed myocardial infarction. All patients were administered daily aspirin with doses ranging from 100-250 mg. Over the next four years, a total of 23 surgical operations (PTCA and stent implantation) were performed on 37 critical stenoses. All additional interventions were successful with no bleeding complications. Over the next 6-47 months, angiographic follow-ups and additional procedures including PTCA and stent implantations were performed. As a result, no cardiac death occurred between 7 and 51 months after the first procedure. One patient died 21 months after the first PTCA procedure due to myeloma. No new myocardial infarction cases occurred. Two patients with dyspnea were treated with balloon angioplasty and symptoms

resolved. A 60-year-old patient was offered a recommendation for retransplantation.^[36]

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