Heart Transplant: Post Discharge Follow Up in a Developing Setup: an Update

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Abstract
Post heart transplant is a period where the recipient’s body and the donor heart are both in a state of adaptation fraught with several hazards. Cardiac transplant recipients have an average of one to three episodes of rejection in the first year after transplantation. Infections remain a significant cause of death after the first year. These infections are the result of a weakened immune system, and can develop from common bacteria and viruses in the community or from uncommon infections.

Keywords: Heart transplant; ATG; CMV

Introduction
Post heart transplant is a period where the recipient’s body and the donor heart are both in a state of adaptation fraught with several hazards. It requires the comprehensive involvement of the transplant surgeon and team, and the patient for mitigating the post transplant mortality and morbidity as well as increasing the chances of success and quality of the recipients life. For grasping the core issues which should be focused on the post discharge period, an overview of the primary areas of concerns during the follow up after Heart Transplant is essential.

1. Diagnosis and management of Rejections
2. Tailoring the immunosuppression regimen
3. Infections - Prophylaxis, Diagnosis, Treatment
4. Post Transplant Malignancies: Lympho-proliferative disorders
5. Cardiac Allograft Vasculopathy (Figure 1) [1].

Overview of Complications

Causes of death [2-7]
There are four major causes of death after cardiac transplantation, which occur at different times [2]

- Sudden (acute) rejection
- Infections other than cytomegalovirus
- Artery disease in the transplanted heart vessels (allograft vasculopathy)
- Lymphoma and other malignancies

Early mortality
Cardiac transplant recipients have an average of one to three episodes of rejection in the first year after transplantation. Between 50% and 80% of people experience at least one rejection episode. Acute rejection is most likely to occur in the first three to six months, with the incidence declining significantly after this time [2,3].

In the first year, most deaths are due either to acute rejection (18%) or infections (22%). Infections often develop as a result of the anti-rejection medications and weakened immune system that are required to prevent rejection.

Late mortality
Rejection is less common after the first year, and by four to five years after transplantation,
Follow up schedule [4].

Table 1: Follow up schedule [4].

<table>
<thead>
<tr>
<th>Test</th>
<th>1 month</th>
<th>1 month - 6 month</th>
<th>6 months to 1 year</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Biopsy</td>
<td>Weekly until 1 month</td>
<td>2nd weekly next 5 months</td>
<td>6th, 8th, 1 year</td>
<td>After 1 year, only if indicated</td>
</tr>
<tr>
<td>Renal Function and Immunosuppressive levels</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>Chest X-ray, ECHO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary Artery disease screening</td>
<td></td>
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</tbody>
</table>

less than 10% of deaths are the result of rejection (Tables 1,2) [2,3]. However, development of rapidly progressing coronary artery disease in the arteries of the transplanted heart (called allograft vasculopathy), becomes one of the most common causes of death by five years. The number of fatal cancers increases over time as well [4]. Infections remain a significant cause of death after the first year. These infections are the result of a weakened immune system, and can develop from common bacteria and viruses in the community or from uncommon infections [4]. Post-Transplant Lymphoproliferative Disease (PTLD) is a type of cancer that occurs in patients who use immunosuppressive medications. PTLD includes non-Hodgkin lymphoma. Most cases of PTLD occur in the first year after transplant. Among patients who develop lymphoma, the overall survival rates are between 25% to 35% in five years.

Immunosuppression

Maintenance immunosuppression after HT usually consists of

1) Corticosteroid
2) A (Calcineurin Inhibitor) CNI (Cyclosporin A or Tacrolimus)
3) An antimetabolite (Azathioprine [AZA] or Mycophenolate Mofetil [MMF]).

The m-TOR inhibitors, Everolimus (EVL) and Sirolimus (SRL) may also be used in clinical practice.

The mode of action of the drugs is mentioned in (Tables 3,4).

Rejection

The recipient’s body may reject a donor organ through hyperacute rejection, acute cellular rejection, or antibody-mediated rejection. The risk for developing rejection is the highest in the first six months following heart transplantation, with a decrease as the time from transplantation increases. Sex and age are both linked to rejection risk, with females and younger individuals being at higher risk.

A) Hyperacute rejection

During the immediate post-transplant phase, after cross clamp removal, hyperacute rejection may occur when the recipient has pre-existing donor directed Human Leukocyte Antigen (HLA) antibodies [7]. Hyperacute rejection is now uncommon as a result of both antibody screening prior to transplantation (Panel Reactive Antibodies (PRA)), and blood type matching [3,7].

B) Acute cellular rejection

This remains a frequent complication post-transplant. It involves recipient T-cells recognizing donor HLA molecules by means of antigen-presenting cells. Around 20% to 40% of patients will experience acute cellular rejection between 6 and 12 months post-transplant, though most patients are asymptomatic without allograft dysfunction.

C) Acute rejection

The clinical presentation of acute rejection varies widely. Patients may be asymptomatic or may have nonspecific clinical signs and symptoms, including fever, anorexia, leukocytoysis, and mild hypotension. In rare cases, acute rejection manifests with severe hypotension and circulatory collapse.

Table 3: Mechanisms of action and major side effects of maintenance immunosuppressive drugs in heart transplantation.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Effects</th>
<th>Major side effects (excluding infection and malignancy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcineurin inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Inhibition of the enzyme calcineurin</td>
<td>Prevention of proliferation and differentiation of T-cells</td>
<td>Drug-drug interactions, nephrotoxicity, neurotoxicity, hypertension, dyslipidemia, diabetes</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Inhibition of the enzyme calcineurin</td>
<td>Prevention of proliferation and differentiation of T-cells</td>
<td>Drug-drug interactions, nephrotoxicity, neurotoxicity, hypertension, dyslipidemia, gingival hyperplasia, hirsutism</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Inhibition of the cell cycle</td>
<td>Prevention of proliferation and differentiation of T-and B-cells</td>
<td>Leukopenia, gastrointestinal problems</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Inhibition of the cell cycle</td>
<td>Prevention of proliferation and differentiation of T-and B-cells</td>
<td>Pancytopenia, hepatitis, pancreatitis</td>
</tr>
<tr>
<td>Mammalian target of rapamycin inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>Inhibition of the enzyme mammalian target of rapamycin</td>
<td>Prevention of proliferation and differentiation of T-and B-cells</td>
<td>Drug-drug interactions, dyslipidemia, pancytopenia, delayed wound healing, oral ulcers, pericardial and pleural effusions</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Inhibition of the enzyme mammalian target of rapamycin</td>
<td>Prevention of proliferation and differentiation of T-and B-cells</td>
<td>Drug-drug interactions, dyslipidemia, pancytopenia, delayed wound healing, oral ulcers, pericardial and pleural effusions</td>
</tr>
</tbody>
</table>
Pathology

The primary process leading to acute rejection is acute cellular rejection, which is T cell mediated. Donor antigen presenting cells (APCs) may be directly recognized by recipient T cells, or donor antigens may cross into the recipient to be taken up by recipient APCs. The presentation of antigens to T cells via APCs causes conformational changes in the T cell receptor. In the presence of a costimulatory molecule, i.e., B7 (CD80 or CD86), on the APC interacting with CD28 on the T cell, promotion of T cell proliferation and cytokine production occurs. Following the sensitization of effector cells, there is a migration of lymphocytes into the allograft with subsequent activation of either the FAS-FAS ligand or perforin/granulolysin pathway resulting in myocyte death [2,3,7,8].

Diagnosis

Because these clinical signs and symptoms lack a high degree of sensitivity or specificity in the diagnosis of acute rejection, the gold standard diagnostic test is a tissue biopsy. Percutaneous endomyocardial biopsy is performed as a part of routine surveillance protocols after heart transplantation. A biotome is passed through a sheath in the right internal jugular vein and advanced through the tricuspid valve into the right ventricle, where tissue biopsies are taken [9]. Due to patchy involvement, 4-6 biopsies are taken. Possible frequent complication is Tricuspid Regurgitation as shown in (Figure 2) [9].

Alternative Noninvasive Techniques to Monitor Cardiac Allograft Rejection [10-15]

Emerging and promising techniques include magnetic resonance imaging, wall motion analysis with tissue Doppler imaging, electrical event monitoring with ventricular evoked response amplitude assessment, identification of peripheral blood markers of rejection (e.g., P-selectin, prothrombin fragments, B-type natriuretic peptides, troponin), imaging for necrosis with antimyosin antibody-based scintigraphy, and imaging for apoptosis with technetium 99 m-labeled annexin V. Cardiac biopsy grading as mentioned in (Table 5).
mediated rejection can be seen in as many as 25% of acute rejection cases (Figure 4) [4]. The principles of management for both ACR and AMR are same: aggressive hemodynamic management along with augmentation of the immunosuppressive regimen to maximize the effort against circulating DSAs and lessen B cell activity. Plasmapheresis, steroid therapy, rituximab, ATG, bortezomib, and IVIG are used in a variety of combinations, as shown in Figure 5 and Table 7 (I). Algorithm for treatment of Antibody-Mediated Rejection (AMR) in cardiac transplant recipients. Antithymocyte Globulin (ATG), Donor-Specific Antibody (DSA), IV Intravenous (IVIG), Intravenous as shown in Table 7 (II) Immunoglobulin, Intravascular Ultrasound (IVUS) [4].

**Infection**

An inherent complication of immunosuppression is increased risk for infection. In the first three years after transplantation, infection is the cause of death in 12% to 29% of patients. The pathogens involved vary depending on the time after transplantation [2]. Early infections in the first month after transplantation are commonly caused by bacteria and often manifest as pneumonia or urinary tract infections. Typical pathogens include Pseudomonas aeruginosa, Escherichia coli, and Staphylococcus aureus. However, the risk of infection decreases over time as immunosuppressive therapy is generally tapered the proportion of mortality attributable to infection is only 11% to 12% greater than 3 years out from heart transplantation.

**Cytomegalovirus [17-21]**

Cytomegalovirus (CMV) is the most common and clinically significant viral pathogen in heart transplant recipients. It may...
cause a variety of syndromes and has been implicated as a trigger for accelerated CAV. Heart transplant recipients are at high risk for CMV infection because cell-mediated immunity, which is necessary to combat CMV, is impaired by conventional immunosuppressive drugs. CMV infection may manifest either as primary infection or as reactivation of a latent infection. Primary CMV infection may develop in seronegative recipients receiving a heart from a CMV seropositive donor. Donor leukocytes or the allograft itself may harbor CMV and transmit it to the recipient. The risk of CMV infection is shown in Table 8 and its management approach in Table 9. In donor negative/recipient negative transplants, CMV disease is uncommonly seen under two circumstances: transfusion of viable leukocyte containing blood products from a seropositive donor or acquisition of virus in the community through intimate person-to-person contact.

Donor

In such cases, donor leukocytes or the allograft itself may harbor CMV and transmit it to the recipient. The risk of CMV infection is shown in Table 8 and its management approach in Table 9. In donor negative/recipient negative transplants, CMV disease is uncommonly seen under two circumstances: transfusion of viable leukocyte containing blood products from a seropositive donor or acquisition of virus in the community through intimate person-to-person contact. CMV infection can manifest as a mononucleosis-like syndrome, or it may be tissue invasive. The most common sites for tissue invasion are the lung, liver, and gastrointestinal tract. Less common sites include the retina and skin. Diagnosis made by measurement of viral load with either quantitative polymerase chain reaction or antigenemia assays; by direct culture of the virus from blood, urine, or tissue specimens; or by observation of characteristic histologic changes (enlarged cells containing nuclear inclusion bodies) [18,21].

Treatment

A combination of intravenous ganciclovir and hyperimmune globulin is used to treat CMV infection [21]. Several populations of cardiac transplant patients benefit from prophylactic treatment against CMV infection. Serologically mismatched patients seronegative recipient of heart from seropositive donor are treated with a combination of ganciclovir and hyperimmune globulin for weeks to months after transplantation [18,21]. Often, seropositive recipients are also treated with a course of ganciclovir to prevent reactivation infection. Prophylactic administration of intravenous ganciclovir when antilymphocyte antibody therapy is used to treat rejection reduces the risk for CMV disease to baseline levels.

a) High risk of CMV replication

CMV mismatch (donor positive, recipient negative). Cytolytic induction with ATG, use of MMF in maintenance immunosuppression:

- Antiviral prophylaxis: Valganciclovir per oral 900 mg OD or BD for up to 6 months after transplant (dose adjusted as per Kidney function).
- Surveillance of CMV replication - once a week to twice a month for 6 months post transplant: CMV early antigen pp65 in PMNC or CMV DNA by PCR.
- Replace MMF with Everolimus.

b) Low risk of CMV replication

- In centers where regular monitoring of CMV replication not possible - prophylaxis of Herpes virus with Acyclovir 800 mg thrice daily per oral.
In centers with access to regular diagnosis of CMV replication, if CMV replication is detected, pre-emptive therapy with Valganciclovir.

c) CMV disease

- Clinical manifestation after 2-4 weeks.
- Bone marrow suppression, gastroenteritis, fever, impaired kidney function.
- Treatment: IV Ganciclovir 5 mg/kg/day BD. Dose adjusted as per kidney function. Effect of therapy monitored by surveillance of CMV replication.

**Herpes simplex**

- Early after transplantation - mucocutaneous herpes simplex - painful aphthous disease in the mouth, lips, tongue.
- If only local aphthous ulcer - local application of Acyclovir ointment.

**EBV**

- If difficulty in swallowing – IV Acyclovir followed by oral application.

**Protozoal**

Protozoal pathogens that can appear after heart transplantation include *Pneumocystis carinii* and *Toxoplasma gondii*. Pulmonary infection with *P. carinii* can be prevented by routine postoperative prophylaxis with trimethoprim sulfamethoxazole or aerosolized pentamidine (for sulfa-allergic patients). Toxoplasmosis may occur in serologically mismatched patients (e.g., *T. gondii*-seronegative recipient of heart from *T. gondii*-seropositive donor) but may be prevented by prophylaxis with atovaquone.

**Pneumocystis jirovecii**

Interstitial pneumonia with severe hypoxemia. Diagnosis by
special staining or PCR of bronchoalveolar lavage specimen.

- **Toxoplasma gondii**: high risk when donor is toxoplasma antibody positive and recipient is negative. Diagnosis by PCR or detection of IgM antibodies (difficult due to immunosuppression).
- Antiprotozoal prophylaxis: TMP/SMZ 960 mg tabs twice a week up to 6 months post transplant.
- Treatment as in immune compromised status.

### Fungal Infections

Invasive fungal infections are uncommon after cardiac transplantation, but when they occur, they cause significant morbidity and mortality. Fungal pathogens include Candida albicans and Aspergillus. Treatment consists of fluconazole, itraconazole, or amphotericin B. The prevalent infections in relation to the time frame are enlisted in (Table 10).

### Malignancies

Another life-threatening consequence of long-term IS following transplantation is cancer. IS drug regimens predispose individuals to malignancy through several mechanisms, including impaired immune responses against malignant cells and oncogenic viruses. The incidence of malignancy increases with time following transplant, with 2.6%, 14.1%, and 27.9% of individuals developing any malignancy after 1, 5, and 10 years respectively [22]. This incidence is approximately 3 to 4-fold greater than age-matched controls in the general population.

Skin malignancies and lymphomas are the most commonly reported cancers, with skin malignancies affecting 19.8% of patients, and lymphomas 1.8% of patients 10 years following heart transplant. The most prevalent skin malignancies following transplant include basal cell and squamous cell carcinomas. In comparison, lymphomas are generally due to post-transplant lymphoproliferative disorder early post-transplant lymphoproliferative disorder (within 1 year of transplant), are most commonly caused by infection with Epstein-Barr virus and typically affect B-cells. Late post-transplant lymphoproliferative disorder (>1 year following transplant) is more likely to be Epstein-Barr virus negative and non-B cell. Other reported cancers following heart transplant include Kaposi’s sarcoma, adenocarcinoma, melanoma, as well as solid tumors affecting the prostate, lung, bladder, breast, cervix, colon, and kidney [18,22-25].

Risk factors for malignancy following heart transplant can be divided into general and cancer-specific categories. Generally, cancer risk following transplant is dependent on the duration and intensity of IS, as well as age [18,22-25]. In comparison, risk factors for post-transplant lymphoproliferative disorder include Epstein-Barr virus infection, high intensity of IS, and antibody induction therapy using OKT3 [18,22-25]. Malignancy is one of the most common causes of death 3-5 years following transplant. In fact, up to 24% of deaths after 5 years following transplant are directly caused by malignancy. This is especially true of individuals who develop lymphomas as compared to skin malignancies. Patients who develop malignancy may require a reduction in their IS doses, which can lead to acute rejection. Such reduction is often performed in the case of post-transplant lymphoproliferative disorder, as minimizing IS has been shown to improve overall survival. However, this survival benefit is at the expense of a 10% increased risk of sudden cardiac death due to acute rejection, highlighting the challenge in balancing IS versus cancer risk [2]. Current guidelines suggest that IS should not be reduced in patients with solid tumors that are unrelated due to the lymphoid system, due to a lack of sufficient evidence to support the benefit [2]. Either way, reductions in IS doses should be closely monitored and individualized in an attempt to balance malignancy versus allograft rejection [2]. Specific IS drugs may prevent the recurrence of malignancy. Proliferation signal inhibitors, such as sirolimus, have been shown to have anti-neoplastic properties in addition to their IS actions. This contrasts with the commonly used CNIs, which have been shown to promote malignancy independently of their IS functions [2].

### Screening

To prevent malignancy, all heart transplant recipients should receive age appropriate screening for breast, colon, and prostate cancer, as well as increased skin cancer screening with yearly dermatologic exams [16]. Furthermore, high-risk patients should be evaluated closely for the development of post-transplant lymphoproliferative disorder through regular screening of Epstein-Barr virus load [16]. For those at particularly high risk of malignancy, reduction in chronic IS should be done if possible. If cancer does occur, IS doses should be altered as appropriate, and patients should receive treatments specific to their cancer, such as chemotherapy.
or anti-B cell monoclonal antibodies in the case of post-transplant lymphoproliferative disorder. With regular screening and balanced, individualized interventions, it may be possible to reduce this common complication [16].

**Cardiac Allograft Vasculopathy**

The development of cardiac allograft vasculopathy remains the Achilles heel of cardiac transplantation.

Development of cardiac allograft vasculopathy represents the major determinant of long-term survival in patients after heart transplantation. Due to graft denervation, these patients seldom present with classic symptoms of angina pectoris, and the first clinical presentations are progressive heart failure or sudden cardiac death. The treatment of the established vasculopathy is disappointing, so the primary effort should be directed towards early prevention and diagnosis. Due to diffuse vascular changes, revascularization procedures are restricted only to a relatively small proportion of patients with favorable coronary anatomy. Severe vasculopathy has a poor prognosis and the only definitive treatment is retransplantation.

**Aetiopathogenesis**

The pathophysiologic features of CAV, although not completely understood, likely involve components of both immune-mediated and non-immune-mediated endothelial damage, and passenger “native vessel” atherosclerosis [26,27]. Histocompatibility mismatch, acute rejection episodes and chronic inflammation. The activation of CD4+ and CD8+ T cells leads to further synthesis of cytokines, which perpetuate the ongoing cascade of events that lead to CAV. The most important cytokines in allograft rejection are interleukin-2 (IL-2), interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-α). IL-2 induces T-cell proliferation and differentiation, IFN-γ activates macrophages, and TNF-α itself is cytotoxic to the transplanted heart. In addition, TNF-α act to increase MHC class I expression, while IFN-γ increases the expression of both MHC classes I and II molecules. Overall, these cytokines can lead to chronic graft rejection. IFN-γ and TNF-α also induce the leukocyte vascular cell adhesion molecule-1, which promotes monocyte adhesion and entry through the endothelium, leading to CAV.

**Non-immunologic factors**

Hyperlipidemia and insulin resistance are the most significant non-immunologic factors, occurring in 50% to 80% of the heart transplant population as shown in (Figure 6). Cause of donor brain death, Cytomegalovirus (CMV) infection, age, sex, obesity, dyslipidemia, Hyperhomocysteinemia (HHcy), Diabetes mellitus, hypertension, smoking and ischemia-reperfusion injury. Pathophysiology of Cardiac Allograft Vasculopathy (CAV) [26]. Congestive Heart Failure (CHF), Cholesterol (CHOL), Calcineurin Inhibitors (CNI), Diabetes Mellitus (DM), Hyperhomocysteinemia (HHcy), Hypertension (HTN), Myocardial infarction (MI). The endothelial damage involved in CAV can be categorized into either denuding or non-denuding injury. In non-denuding injury a rapid replacement of injured endothelial cells leads to endothelial dysfunction. Both immune-related and non-immune-related factors contribute to non denuding injury. In contrast, denuding injury is caused by ischemia-reperfusion injury during transplantation or during episodes of acute cellular rejection. This results in the loss of large stretches of endothelium along the vessel, which causes significant endothelial dysfunction.

Denuding injury allows for blood components and circulating cytokines to have direct contact with the subintimal layers. This can lead to significant proliferation of smooth-muscle cells. Therefore, CAV can be initiated or exacerbated by several processes that can lead to denuding or non-denuding injury. These include ischemia-reperfusion injury, immune activation, viral infection and injury from immunosuppressive drugs.

Hyperlipidemia is commonly seen in cardiac transplant patients for several reasons. Many of these patients are hyperlipidemia before transplantation. In addition, the immunosuppressive therapy given to patients, especially calcineurin inhibitors, may result in or exacerbate pre-existing dyslipidemia. Hypercholesterolemia promotes fibrofatty proliferative changes to the intimal hyperplasia seen in most patients with CAV [14].

In solid-organ transplant recipients, HHcy is extremely common and occurs early with a rate as high as 80% to 90%. HHcy can damage cells by several mechanisms, but primarily by affecting the endothelium. HHcy results in reduced endothelial nitric oxide production, impaired arterial response to vasodilators and increased expression of procoagulant factors. The neutrophil-endothelium interaction is promoted in the setting of HHcy, allowing for the presence of more neutrophils in the intima. All of these alterations in the endothelial wall are caused by alterations in the redox state induced by high homocysteine levels.

Hypertension, smoking, diabetes mellitus and other risk factors for atherosclerosis are associated with CAV. Hypertension in transplant patients can be present preoperatively or postoperatively secondary to immunosuppressive medication, such as cyclosporine. Hypertension causes endothelial injury by promoting the formation of intimal hyperplasia, which eventually gives rise to atheroarterial lesions.

**Diagnosis**

Cardiac denervation at the time of heart transplantation usually prevents transplant patients from experiencing angina, which is an important warning sign for heart disease. Only 10% to 30% of heart transplant recipients regain any innervation to the heart. Because of this lack of early clinical symptoms, transplant patients with CAV typically present late with silent myocardial infarction, loss of allograft function or sudden death [28]. Another difficulty faced by clinicians in diagnosing CAV is coronary remodeling and the diffuse nature of the disease. Angiography measures luminal diameter and compares the narrowing at plaques to normal reference diameters and previous angiograms in order to understand the severity and rate of disease progression. CAV, however, shows no initial decrease in luminal diameter due to vascular remodeling. Only when the process is more advanced does the lumen narrow and angiographic detection become possible. Since CAV involves the entire coronary arterial tree, angiography may convey the impression of less-than-actual vessel narrowing at plaque sites. Thus, angiography, although it is a good screening tool for CAD, often underestimates CAV, and in some patients with evenly distributed disease throughout the coronary tree, CAV can be missed altogether [26]. Despite the poor sensitivity of angiography, it is still widely used as a screening test for vascular disease. Johnson and associates developed a classification system [30] based on the varying morphologies in CAV to aid in its diagnosis using angiography. Briefly, type A lesions appear as discrete proximal tubular stenoses, type B as diffuse concentric
middle or distal stenoses, with type B₁ having an abrupt narrowing and type B₂ having a smooth concentric tapering. Finally a type C angiographic appearance indicates irregular vessels with distal lesions and loss of small branches. Diagnosis of CAV requires type B or C lesions and comparison with previous and recent angiograms to note disease progression (Figure 7). A more sensitive tool is Intravascular Ultrasonography (IVUS). IVUS is useful for detecting the extent of intimal thickening by imaging vessel wall structure rather than simply luminal diameter. IVUS has an axial resolution of 50 μm to 80 μm. Unfortunately, it is physically restricted to the larger epicardial arteries, and thus cannot be used to screen for CAV throughout the entire heart. One year after transplantation, IVUS detects CAV in 50% of patients whereas angiography detects disease in only 10% to 20% of patients [30]. With IVUS, normal coronary intimal thickness ranges between 0.10 mm and 0.30 mm. Hence, CAV is considered present when intimal thickness exceeds 0.3 mm or when the sum of the intimal and medial thickness exceeds 0.5 mm. At greater than 0.6 mm intimal thickening, patients are 10 times more likely to experience a cardiac event [30].

**Treatment**

Prevention & Risk Reduction, Early Diagnosis, Treatment and Disease Reversal [28-31].

**A) Pharmacotherapy**

1. **Statins:** Statins are a mainstay in pharmacotherapy for OHT patients given their cholesterol-independent immunomodulating effects. They are typically instituted by the end of the first week or during the second week after heart transplantation. Pravastatin is started with 20 mg/d and then increased to 40 mg/d if tolerated. Simvasta-tin is started with 5 mg/d and increased to 10 and 20 mg/d. The early initiation of statins is of utmost importance, as their later introduction in transplant patients did not have a favorable effect on graft prognosis although it reduced serum cholesterol level. The favorable effects of statins, besides lowering plasma lipids, may be explained with anti-inflammatory activity, cytokine suppression, and improvement of endothelial function [26].

2. **ACE Inhibitors and ARB:** Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARB) reduce the incidence of CAV by several mechanisms including a decrease of peripheral mononuclear cells that differentiate into smooth muscle-like cells, thereby theoretically altering a cascade of events critical to CAV advancement. Increased levels of Angiotensin II (AII) receptor messenger RNA (mRNA) may be involved in the pathogenesis of CAV via promotion of inflammation, extracellular matrix remodeling, apoptosis, and fibrosis.

   - **Antioxidant:** Vitamin C (2 x 500mg/day, Vit E (2 x 400IU/ day)
   - **Calcium Channel Blocker**
   - **Aspirin**

**B) Immunosuppression**

Immunosuppressive agents can decrease the risk of acute allograft rejection and smooth muscle cell proliferation and therefore may reduce the frequency and severity of CAV. In recent years, there has been an important transition to preferential use of TAC over cyclosporin and mycophenolate mofetil over azathioprine. When comparing immunosuppression with TAC as opposed to cyclosporin, studies have demonstrated greater prevention of acute allograft rejection with a TAC-based immunosuppression protocol [30, 31]. Proliferating Signal Inhibitor Sirolimus/Everolimus: The ISHLT guidelines recommend everolimus, sirolimus, or mycophenolate in the post-OHT period to minimize the onset and advancement of CAV [4].

**C) PCI**

Given the diffuse nature of CAV as well as involvement of the distal microvasculature, PCI is considered palliative despite high initial success rates (91% to 100%).

**D) Surgical revascularization**

Disappointing results due to diffuse and distal vessel involvement.

**E) Re-transplant**

CAV is a multifactorial disease that remains the major limitation to long-term survival after heart transplantation. Methods of diagnosis have improved significantly with the use of IVUS in addition to angiography [32,33]. Since treatment of CAV is limited and usually involves repeat transplantation, prevention of immunologic and non-immunologic risk factors is of critical importance. CAV is conceptually very similar to post-transplant disorders in other organs (e.g., bronchiolitis obliterans with organizing pneumonia, biliary cirrhosis).

**References**


