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Cardiac Allograft Vasculopathy: An Ongoing Challenge in the Care of Heart Transplant Recipients

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1. Introduction

Cardiac allograft vasculopathy (CAV) represents the most common cause of late graft failure and limits the long-term success of heart transplantation. It is the most common cause of death, in addition to malignancy, in patients who survive the first year after transplant (Taylor *et al*., 2006). CAV is a diffuse, accelerated form of coronary artery disease in the transplanted heart. Despite improvements in immunotherapy, the incidence of angiographically detected CAV has not changed appreciably over the past two decades. CAV is associated with a relentless course after heart transplantation and immunological and non-immunological interventions have only partially modified its natural history. Treatment of CAV is limited, highlighting the importance of preventive therapies. Re-transplantation for advanced disease is the only definitive therapy, but is limited to select patients. In this chapter, we will review the epidemiology, natural history, clinical manifestations, screening and diagnostic strategies for CAV while emphasizing current treatment strategies designed to prevent or slow the progression of this disease.

2. Pathology

CAV was first described in 1970 as a diffuse, obliterative, accelerated form of arteriosclerosis (Bieber *et al.,* 1970). Pathologically, CAV is distinctly different from traditional coronary atherosclerosis (Table 1). It is characterized by diffuse, concentric intimal smooth muscle hyperplasia involving the entire circumference and length of the vessel, and deposition of neointima in the major epicardial vessels and microvasculature, which progressively obstructs the affected vessel lumen (Figure 1). CAV is further distinguished microscopically as having intense cellular proliferation, composed mainly of smooth muscle cells and inflammatory infiltrates (monocytes and lymphocytes). Specific populations of lymphocytes co-localized with CAV lesions include recipient CD4+ T cells, thus suggesting a role for major histocompatibility complex (MHC) II antigen recognition and processing in the development of CAV. Populations of macrophages and CD8+ T cells have also been localized in CAV lesions, whereas recipient B-cells are rare.

The endomyocardial biopsy has limited sensitivity in the recognition of vasculopathy because it samples only the smallest of intramyocardial arteries and arterioles, which often

do not show histologic features of CAV. Reported histologic changes seen in the small arteries in endomyocardial biopsies include concentric intimal thickening with or without foamy macrophages, subendothelial accumulation of lymphocytes, and perivascular fibrosis (Pardo *et al.,* 1997). Evidence of myocardial ischemia, such as myocytolysis, frank coagulation necrosis, and healing ischemic lesions as well as interstitial, perivascular, and replacement fibrosis can be seen (Neish *et al.,* 1992). Identification of myocardial injury should raise the suspicion of CAV as the cause of graft dysfunction. The absence of these findings, however, does not necessarily rule out the presence of CAV.

3. Pathogenesis

The development of CAV represents a complex interaction between acute and chronic immune activation via an allo-immune pathway and alloantigen-independent non-immune mechanisms that ultimately lead to inflammation and endothelial injury, the precursor to CAV. (Figure 2). Immunologic events appear to be most important, since CAV develops in the donor's coronary arteries but not the recipient's vasculature. The donor coronary artery endothelial cells express major histocompatibility complex (MHC) class I and class II antigens, and thus appear to be primary targets of the cell-mediated and humoral immune responses. These antigens are thought to be recognized by recipient CD8+ and CD4+ T cells and these activated lymphocytes secrete cytokines (interleukins, interferons, and tumor necrosis factors), which promote proliferation and further activation of allo-reactive T cells, monocytes, and macrophages. Macrophages are then recruited to the intima where they elaborate cytokines (IL-1, IL-6, tumor necrosis factor TNF alpha) and growth factors [platelet derived growth factor (PDGF), insulin-like growth factor-I (IGF-I), transforming growth factor-alpha (TGF-alpha), TGF-beta-1], leading to smooth muscle cell proliferation and synthesis of extracellular matrix (Libby P & Tanaka H, 1994).

T cell activation also stimulates the expression of adhesion molecules, [intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), P-selectin] thereby "activating" endothelial cells, enabling recruitment of proinflammatory cells from the vasculature and the initiation of the immune response and subsequent development of CAV. (Briscoe *et al.,* 1995)

Pathologic characteristic	CAV	Native CAD
Lesion morphology	Diffuse, concentric (variable)	Focal, proximal, eccentric
Vessels involved	Intramyocardial, epicardial branches	Epicardial, spares intramyocardial branches
Collateral vessels	Minimal	Often extensive
Initial Lesion	Smooth muscle proliferation	Fatty streaks
Internal Elastic Lamina	Intact	Disrupted
Endothelial lymphocytes	Sometimes	Absent
T-cell location	Subendothelial	Edge of plaque

Table 1. Characteristics of cardiac allograft vasculopathy compared to traditional coronary atherosclerosis in the native heart.

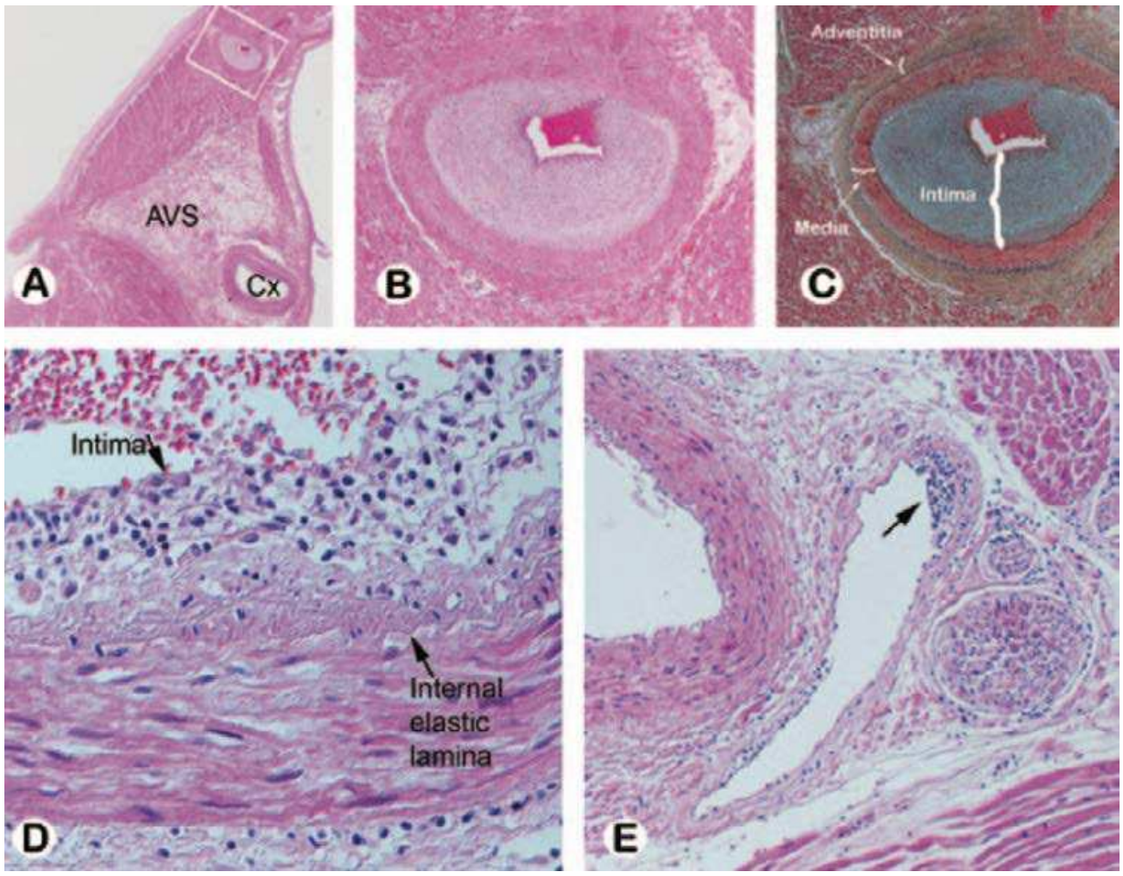


Fig. 1. Cardiac allograft vasculopathy. (A) Photomicrograph of the left atrium and ventricle with the left circumflex (Cx) artery noted at the atrioventricular sulcus (AVS) from a patient who died of CAV 3 years post transplant. (B,C) Intramyocardial branch of circumflex artery (from inset A) supplying the atrium shows marked intimal proliferation with preservation of the elastic lamina and normal medial layer (hematoxylin-eosin (B) and Movat pentachrome (C)). (D,E) Subendothelial lymphocytic infiltration is seen in a small epicardial artery (D) and in an intramyocardial vein (arrow E). Reprinted from Tan CD, Baldwin WM, Rodriguez ER. Update on Cardiac Transplantation Pathology. Arch Pathol Lab Med. 2007;131:1169-1191 with permission from *Archives of Pathology and Laboratory Medicine.* Copyright 2007. College of American Pathologists.

Non –immune mechanisms implicated in the development of CAV include inflammatory injury due to recipient hypertension, dyslipidemia, diabetes and insulin resistance, and obesity, in addition to ischemia-reperfusion injury during organ procurement. Endothelial cell dysfunction resulting from inflammatory injury predisposes to thrombosis, vasoconstriction, and vascular smooth muscle cell proliferation. Reperfusion injury increases expression of endothelin 1, which is associated with post-transplant ischemic fibrosis and subsequent development of arteriopathy, in addition to generating free radicals that promote the expression of such inflammatory adhesion molecules and subsequent leukocyte recruitment (Ferri *et al.,* 2002). More research is needed in the field of organ preservation, possibly targeting specific cellular processes to minimize reperfusion injury. Endothelial injury and dysfunction, regardless of the

mechanism, seems to be the key inciting event and the common pathway for the development of CAV.

4. Risk factors

Many risk factors for the development of CAV have been identified and can be broadly divided into donor-specific factors, recipient-specific factors and donor-recipient factors, with the latter being predominantly immune mediated (Table 1).

4.1 Donor factors

Donor factors include a history of hypertension, diabetes, male sex, and history of tobacco use. Older donor hearts confer a higher risk of CAV development compared to younger donor hearts, and this risk appears most significant with donors older than 50 years (Al-Khaldi *et al.,* 2006; Nagji *et al.,* 2010).

Donor mode of death has also been shown to have associations with the development of CAV. Explosive modes of brain death, including gunshot wound to the head, accidental head trauma, or a rapidly progressive intracranial hemorrhage have also been associated with development of CAV after transplantation (Mehra *et al.,* 2004a). It has been demonstrated that rapid brain death induces a calcium overflow injury that affects conduction tissue, coronary artery smooth muscle, and myocardial cells (Cohen *et al.,* 2007; Novitzky *et al.,* 1988). There is also a generalized activation of macrophage-associated cytokines, an up-regulation of immunoregulatory and adhesion cell molecules with subsequent endothelial inflammation and dysfunction, in addition to increased levels of circulating catecholamines, all of which may negatively impact the graft response after heart transplantation (Segel *et al.,* 2002; Takada *et al.,* 1998).

The role of transmitted native vessel atherosclerosis is controversial and conflicting. Studies utilizing serial coronary artery intravascular ultrasound (IVUS) found donor lesions did not significantly change after transplantation (Jimenez *et al.,* 2001). However a maximal intimal thickness ≥ 0.5mm at baseline (1 month post transplant) was one of the strongest predictors of plaque progression at one year in another study (Yamasaki *et al.,* 2011). In another observational study, donor lesions (defined by intimal thickness > 0.5mm by IVUS at 1 month post transplant) did not have a greater increase in intimal thickness compared to other sites without donor lesions, however the incidence of angiographically apparent CAV up to three years after transplant was higher in patients with donor transmitted lesions with no apparent effect on 3 year mortality (Li H *et al.,* 2006).

Hepatitis C infection (HCV) in donor hearts increases recipient mortality with mortality rates in one study of 16.9% at 1 year, 41.8% at 5 years, and 50.6% at 10 years, compared to recipients of hepatitis C negative donors who had 8.2%, 18.5%, and 24.3% mortality, respectively (Gasink *et al.,* 2006). Recipients with HCV-positive donor hearts were more likely to die secondary to CAV. Other studies also note higher rates of CAV in recipients of HCV + donor hearts, possibly related to HCV viremia in a significant proportion of these recipients; the exact mechanism however, is not completely understood (Haji *et al.,* 2004). Hepatitis B seropositivity (HBV) has been correlated with increased rates of CAV. In one observational study, HBV seropositivity, defined as either the donor or recipient being hepatitis B core antibody positive, was associated with higher rates of CAV at 1 year

compared to cases where neither the donor nor recipient were HBV seropositive (Haji SA *et al.,* 2006).

4.2 Recipient factors

Recipient factors that are associated with the development of CAV include male sex, pre-transplant ischemic heart disease, and higher body mass index (Costanzo *et al.,* 1998; Taylor *et al.,* 2007). Traditional cardiac risk factors in the recipient including hypertension, diabetes, dyslipidemia and smoking also increase the risk of developing CAV (Sanchez *et al.,* 2008). Importantly, hypertension, dyslipidemia and diabetes are commonly induced post transplant as side effects of immunosuppressant therapy with calcineurin inhibitors and steroids. The prevalence of hypertension increases after transplant from 74.4% at one year to 98.5% at 10 years (Taylor *et al.,* 2007). The incidence of diabetes after heart transplant ranges from 15% to 20% (Martinez-Dolz *et al.,* 2005).

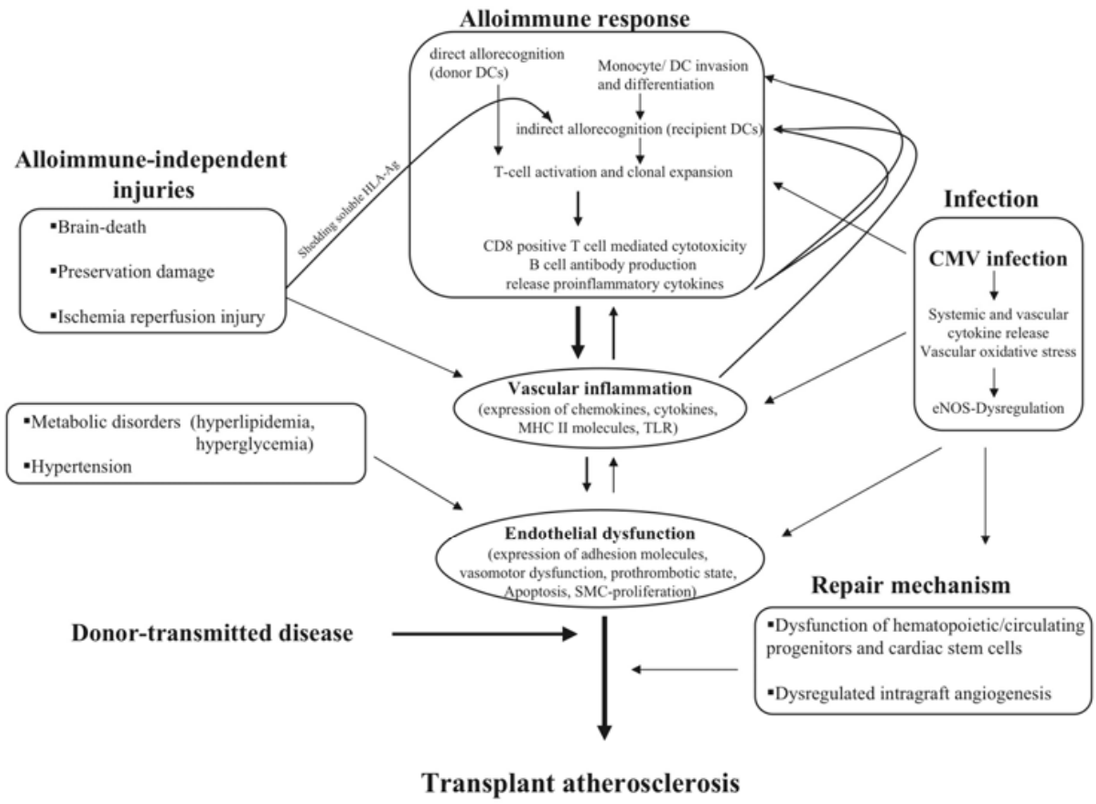


Fig. 2. Pathobiology of Cardiac Allograft Vasculopathy. Reprinted from Schmauss D and Weis M. Cardiac allograft vasculopathy: recent developments. Circulation 2008;117:2131-2141 with permission from Wolters Kluwer Health. Copyright 2008.

4.3 Donor-recipient factors

Donor-recipient factors that increase risk of CAV include episodes of high-grade cellular rejection during the first year after transplantation, HLA-DR mismatches, antibody mediated rejection (including asymptomatic AMR), and cytomegalovirus (CMV) infection.

The total cellular rejection score at six months increases the risk of CAV by almost threefold (Raichlin *et al.,* 2009). The total cellular rejection score is assigned based on ISHLT grading as 0R = 0, 1R = 1, 2R = 2, 3R = 3, and normalized by dividing the cumulative scores for the total number of biopsies taken during the 6 month intervals. Antibody-mediated rejection increases the incidence of CAV by 10% at one year and by 36% at five years (Michaels *et al.,* 2003). Asymptomatic AMR, defined as histologic evidence of AMR, including endothelial swelling, interstitial hemorrhage, interstitial edema and neutrophil infiltration and/or immunoperoxidase staining showing CD-68 positive macrophages within capillary cells and C4d complement coating the walls of the myocardial capillaries, in patients without symptoms or any evidence of graft dysfunction, increases the risk of developing CAV compared to those with no AMR (We *et al.,* 2009).

CMV disease appears to increase the risk of early-onset CAV –an effect that may be mediated via immune mechanisms rather than a direct consequence of the infective organism (Weill *et al.,* 2001). CMV infection in endothelial cells, such as those lining the donor coronary arteries, leads to a local proinflammatory state and subsequent increased production of vascular cell adhesion molecule (VCAM)-1, alterations in cell surface MHC I and II molecules, and an increase in proinflammatory cytokines and growth factors. This causes endothelial cell/smooth muscle cell proliferation and narrowing of the vessel lumen. CMV may also cause endothelial dysfunction leading to CAV by impairing the nitric oxide synthase pathway. (Hosenpud *et al.,* 2003; Koskinen 1993; Van Dorp *et al.,* 1989). Nitric oxide prevents vascular inflammation and lesion formation in the vessel wall by inhibiting platelet and leukocyte adherence and by suppressing vascular smooth muscle cell proliferation. CMV infection of the endothelium increases expression of endothelial surface adhesion molecules and promotes mononuclear adhesion, activation, and transendothelial migration within the vasculature. In addition, CMV is a stimulus of plasma ADMA (asymmetric dimethylarginine) accumulation, the endogenous inhibitor of nitric oxide synthase. (Weis M *et al.,* 2004)

Donor Factors
Age (>50 years), Sex (male) and Mode of Death
History of hypertension, diabetes, smoking
? Donor Transmitted Atherosclerosis
Hepatitis B & C infection
Recipient Factors
Age (>40 years), Sex (male)
Hypertension, dyslipidemia, obesity, smoking
Insulin resistance/Diabetes
Hepatitis B
Donor – Recipient Interaction
Rejection (cellular and antibody mediated)
CMV disease

Table 2. Risk factors for the development of cardiac allograft vasculopathy

5. Clinical manifestations

Early CAV is clinically silent, and ischemia is usually not evident until the disease is far advanced. Patients are most often diagnosed by routine angiographic surveillance or loss of

allograft function by surveillance imaging with negative rejection studies. Clinically, patients present with heart failure symptoms and are found to either have new onset systolic or diastolic dysfunction in the absence of acute cellular or antibody mediated rejection, or may present with ventricular arrhythmias and sudden cardiac death. Patients rarely present with chest pain, due to de-innervation of the cardiac allograft at the time of transplantation. However, 25-40% of patients develop some degree of re-innervation post transplant, manifest primarily by return of heart rate response and less often, ischemic chest pain (De Marco *et al.*, 1995).

6. Epidemiology and natural history

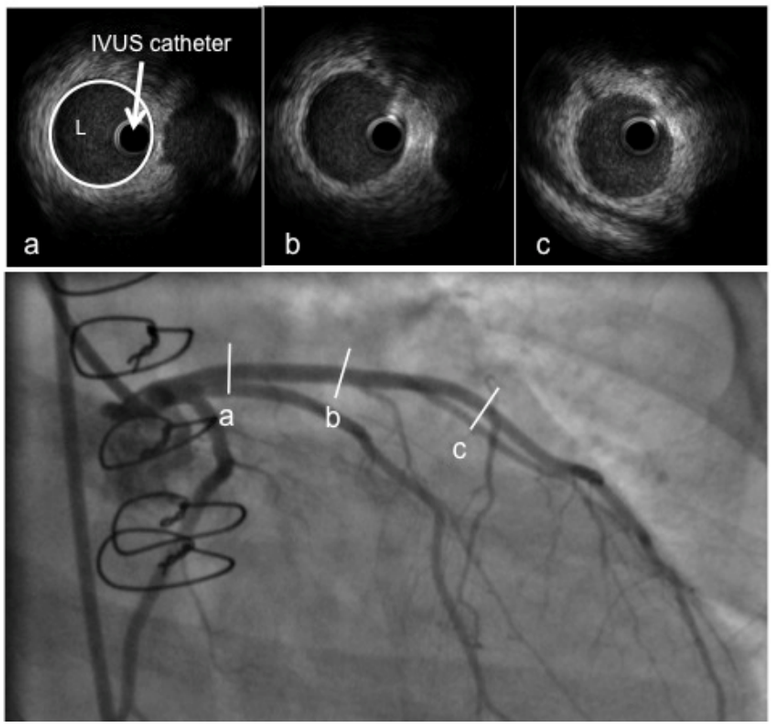
CAV is detectable by coronary angiography in approximately 10% of heart transplant recipients within the first year, in 32% - 50% by 5 years, and in an even greater number of recipients when detected by intravascular ultrasound (Pflugfelder *et al.,* 1993). Once mild disease is identified angiographically, the likelihood of progression to severe CAV within 5 years is approximately 19% (Costanzo *et al.,* 1998). Lack of development of CAV at 1 year post-transplant identifies a group who are likely to remain free of clinical events through 6 years of follow up (Luyt *et al.*, 2003). In patients with at least 1 focal stenosis ≥40%, survival was 67% at 1 year, 44% at 2 years, and 17% at 5 years. With 3 vessels involved, survival was 13% at 2 years (Keogl *et al.,* 1992). The overall likelihood of death or re-transplantation as a result of CAV is approximately 50% for severe CAV (Costanzo *et al.* 1998).

Graft function is an important component in evaluating severity of CAV. Patients with CAV and LV dysfunction have significantly lower 5-year survival compared with CAV patients without LV dysfunction (60% vs. 90%) (Stork *et al.,* 2006). Patients with restrictive cardiac physiology [E to A velocity ratio >2, shortened isovolumetric relaxation time (<60msec), shortened deceleration time (≤150ms), or restrictive hemodynamics (right atrial pressure >12mmHg, pulmonary capillary wedge pressure >25mmHg, cardiac index <2.0)] in the presence of preserved LV systolic function and CAV also have a lower 5-year survival than heart transplant patients without restrictive physiology (Itagaki *et al.,* 2007).

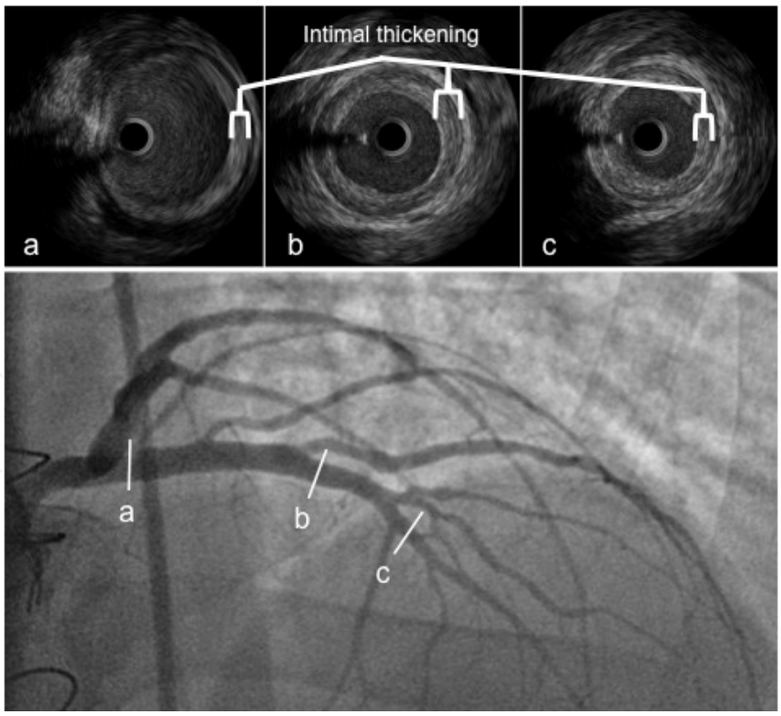
7. Diagnosis

Coronary angiography and assessment of cardiac allograft function remains the cornerstone for diagnosis of CAV. Anatomic abnormalities characteristic of CAV include gradual, distal, diffuse, concentric tapering ("distal pruning") of the major epicardial arteries with obliteration of the small branching vessels. Discrete epicardial stenoses are less likely (Figure 3). As early CAV is asymptomatic, routine screening with annual coronary angiography (with or without intravascular ultrasound) is standard practice among the majority of transplant centers in the first 3-5 years post transplant. After this time period, there are different practice patterns for assessment of CAV, depending on individuals' risk factor profile for CAV, graft function, renal function, and clinical status. As CAV is a concentric process, early disease may be overlooked if prior angiograms are not compared. For this reason, baseline angiography is usually performed 4-6 weeks post transplant.

In 2010, the ISHLT working group proposed standardized nomenclature for CAV (Table 3) (Mehra *et al.,* 2010). This system defined CAV as not significant, mild, moderate, and severe based on angiographic appearance. Angiography is a very useful test for detecting lesions



(A)



(B)

Fig. 3. Angiography and IVUS imaging demonstrating (A) normal coronary arteries and (B) cardiac allograft vasculopathy. (L= coronary artery lumen).

located in epicardial arteries and the main branches, however the main limitation of angiography is low sensitivity, especially in those mild cases in which an apparently normal examination can underestimate the presence of CAV. This is primarily due the vascular remodeling that occurs early in the disease in which there is no compromise in luminal diameter (Nissen 2001). Repeated angiography is recommended for the follow-up of patients with moderate lesions or for patients with symptoms leading to the suspicion of CAV.

Intra-vascular ultrasound (IVUS) at coronary angiography has been evaluated as an adjunctive modality for assessing and diagnosing early CAV. Angiography depicts only a 2-dimensional silhouette of the lumen whereas IVUS allows a reproducible view of both actual lumen diameter, as well as the appearance and thickness of the intima and media. As the intima begins to thicken, the vessel area enlarges as a compensatory mechanism to preserve luminal area. Therefore, 'angiographically normal' coronary arteries may in fact have significant CAV.

IVUS parameters include intimal thickness, intimal index, and change in maximal intimal thickness at a reference point, total atheroma volume, and percentage of atheroma volume. IVUS can detect occult disease in angiographically normal sites and has emerged as the optimal diagnostic tool for early detection. CAV is considered present when the intimal thickness is >0.3mm (Rickenbacher *et al.,* 1995). The presence of moderate to severe intimal thickening by IVUS is predictive of the future development of angiographically apparent CAV. IVUS-detected maximal intimal thickness (MIT) greater than 0.3mm at 1 year is associated with a 4-year actuarial survival of 73% versus 96% among those with less than 0.3mm of intimal thickening (Rickenbacher *et al.,* 1995). A change in MIT of ≥ 0.5mm at a specific site in the coronary tree within the first year after transplant predicts outcomes at 5 years related to the development of angiographic CAV, mortality and myocardial infarction (Kobashigawa *et al.,* 2005; Tuzcu *et al.,* 2005). Death or graft loss occurred in 21% versus 6%, non-fatal major adverse events or death/graft loss in 46% versus 17% and angiographically apparent disease in 65% versus 33% in those with a change in MIT ≥ 0.5mm between baseline and 1-year (Kobashigawa *et al.,* 2005) versus those with a lesser degree of intimal thickening. With >0.6mm intimal thickening, patients are 10 times more likely to experience a cardiac event and for those who developed cardiac events, 62% of patients had 'normal' angiograms (Mehra *et al.,* 1995).

In patients with stable graft function and no history of CAV, most centers alternate coronary angiography with dobutamine stress echocardiography after 3-5 years; reserving invasive catheterization to every other year. The sensitivity and specificity of dobutamine stress echocardiography compared with coronary angiography and IVUS for detecting CAV is approximately 80% and 88% respectively (Derumeaux *et al.,* 1995; Spes *et al.,* 1999). A normal DSE incorporating M-mode measurement of wall thickening predicts an uneventful clinical course (Spes *et al.,* 1999).

Computed tomographic angiography, although useful in detecting traditional atherosclerosis, has limitations in heart transplant recipients. The major drawbacks with the routine use of 16 or 64 slice multidetector CT in this population include the high heart rate of most heart transplant recipients (due to cardiac vagal denervation) that may compromise imaging quality, contrast-induced nephropathy and radiation. However, compared with

ISHLT CAV_0 (not significant)	No detectable angiographic lesion
ISHLT CAV_1 (Mild)	Angiographic left main (LM) <50%, or primary vessel with maximum lesion of <70%, or any branch stenosis <70% (including diffuse narrowing) without allograft dysfunction
ISHLT CAV_2 (Moderate)	Angiographic LM <50%; a single primary vessel ≥ 70% stenosis, or isolated branch stenosis ≥ 70% in branches of 2 systems, without allograft dysfunction
ISHLT CAV_3 (Severe)	Angiographic LM ≥ 50%, or ≥ 2 primary vessels ≥ 70% stenosis, or isolated branch stenosis ≥70% in all 3 systems; or ISHLT CAV 1 or 2 with allograft dysfunction (defined as LVEF ≤ 45%, usually in the presence of regional wall motion abnormalities) or evidence of significant restrictive physiology (which is common but not specific)

Table 3. The International Society for Heart and Lung Transplantation Recommended Nomenclature for Cardiac Allograft Vasculopathy. 'Primary vessel' denotes the proximal and middle 33% of the LAD, circumflex, ramus and the dominant or co-dominant right coronary artery with the posterior descending and posterolateral branches. 'Secondary branch vessel' includes the distal 33% of the primary vessels or any segment within a large septal perforator, diagonals and OM branches or any portion of a non-dominant RCA. Restrictive physiology is defined as symptomatic heart failure with echocardiographic E to A velocity ratio >2, shortened isovolumetric relaxation time (<60msec), shortened deceleration time (<150msec) or restrictive invasive hemodynamics (right atrial pressure >12mmHg, pulmonary capillary wedge pressure >25mmHg, cardiac index <2L/min/m^2)

IVUS, the sensitivity, specificity, positive and negative predictive values for the detection of CAV by dual source CT were 85%, 84%, 76%, and 91% respectively (Schepis *et al.,* 2009). Magnetic resonance coronary angiography, at present, shows limited sensitivity for detecting CAV and positron emission tomography (PET) has not yet been well studied (Muehling *et al.,* 2003).

Serum biomarkers provide important clues to molecular and structural changes within the transplanted heart. The role of inflammation has been demonstrated by the elaboration of inflammatory cytokines in patients with CAV. Elevated CRP levels have been shown to be associated with increased risk of developing CAV, suggesting a link between systemic and local inflammation within the coronary artery of the transplanted heart (Arora *et al.,* 2010; Raichlin *et al.,* 2007). However, it is not clear if CRP is merely a marker or if it is involved in CAV pathogenesis. Persistently elevated troponin I levels after heart transplantation are associated with an increased risk of development of CAV (Labarrere *et al.,* 2000). Elevated BNP has also been correlated with the development of CAV (Mehra *et al.,* 2004b). BNP may be useful in combination with angiographic findings in predicting outcomes, with 50% of patients with high BNP levels and angiographic CAV experiencing cardiac death (Tsutsui *et al.,* 2001). Biomarkers may hold predictive correlation, but are not used routinely for the evaluation of CAV.

8. Prevention and treatment

Therapeutic options in CAV can be thought of in terms of prevention and treatment. Medical therapy aims to slow, halt, or even reverse the intimal proliferation, concentric luminal loss and arterial obliteration that characterize CAV. Preventive therapy targets traditional cardiac risk factors (diabetes mellitus, hyperlipidemia and hypertension) and aggressive treatment of rejection episodes. Rapidly progressive CAV within the first year after heart transplant strongly predicts all-cause mortality, myocardial infarction, and the subsequent development of angiographically severe CAV. Accordingly, prophylactic strategies must be implicated very early to induce significant improvement in long-term prognosis.

Statins have been associated with reduced progression of CAV, and routine administration of statins to all patients after transplant has clearly reduced the mortality and progression of the disease (Wenke *et al.,* 2003). A meta-analysis based on the published results of three randomized clinical trials determined that the use of statins decreased 1-year mortality following heart transplantation from 17.1% to 5.4% (Mehra *et al.,* 2004c). The introduction of routine anti-CMV drugs to all CMV seropositive patients (donor or recipient or both) for at least 3 months and in some centers up to 6 months has lowered the incidence of CMV infection and its impact on the graft. In a randomized study, patients receiving gancyclovir were significantly more likely to remain free of CAV for 5 years post transplant (Valantine *et al.,* 1999).

There are small studies that suggest calcium channel blockers, such as diltiazem, are effective in slowing the progression of CAV (Schroeder *et al.,* 1993). ACE inhibitors have been associated with plaque regression and improved survival for established CAV , however pre-emptive therapy with ACE inhibitors has unknown preventative effects (Bae *et al.,* 2006). Currently, there is little definitive evidence to suggest that calcium channel blockers or ACE inhibitors are effective in reducing the incidence or slowing the progression of CAV.

Diabetes is common in cardiac transplant recipients and most heart transplant patients are markedly insulin resistant and demonstrate many of the features of compensatory hyperinsulinemia, including the atherogenic and proinflammatory profile of the metabolic syndrome (Potena L & Valantine H, 2007). Patients with high plasma glucose or insulin concentrations after oral glucose intake have greater intimal thickness and are less likely to be free of CAV and have significantly lower survival during 5 years of follow up than patients with low glucose and insulin levels (Valantine *et al.,* 2001). Specific therapies shown to be effective in correcting insulin resistance, such as the thiazolidinediones, offer potential new therapeutic targets for CAV prevention, however the clinical studies are lacking.

Owing to the diffuse nature of vasculopathy, conventional therapeutic approaches including percutaneous coronary intervention and coronary artery bypass grafting are optional only late in the course and are not always successful or even feasible.

Immunosuppression continues to represent the principal means of pharmacologic prophylaxis against and treatment of allograft vasculopathy, with the development and introduction of the proliferation signal inhibitors (PSI) sirolimus and everolimus representing the greatest advance achieved to-date in this field. PSI's are powerful immunosuppressant drugs that inhibit cellular proliferation and have shown the ability to

reduce, and even reverse, coronary intimal growth in established CAV and reduce the incidence of CAV in *de novo* transplant patients through a variety of mechanisms, including a reduction in CMV infection and decreased rejection episodes. (Eisen *et al.,* 2003; Keogh *et al.,* 2004).

In a prospective multi-center randomized double blind control trial, patients who received everolimus, cyclosporine and steroids versus azathioprine, cyclosporine and steroids had a significant reduction in the incidence of CAV at 12 months (35.7% versus 52.8%), fewer grade ≥ 3A cellular rejections (21.3% versus 30.6%) and CMV infection (12% versus 41.4%) (Eisen *et al.,* 2003). Similar results were found with sirolimus (Keogh *et al.,* 2004). The long-term results of both studies demonstrate a trend toward a lower incidence of severe vasculopathy in the group that is maintained on PSI with patients treated with everolimus having significantly lower rates of major cardiovascular events related to CAV compared to patients treated with azathioprine (7.9% vs. 13.6%) (Eisen *et al.,* 2006; Keogh *et al.,* 2007).

The available data suggest the efficacy of PSIs in reducing the incidence of CAV; however, up to 30-40% of patients in the clinical trials had to discontinue the PSI during the first year because of poor tolerability. Complications and side effects include bacterial and viral infections (17-30%), oral ulcerations, pericardial effusions (up to 25%) and pleural effusions (15-40%), hematologic abnormalities including anemia and thrombocytopenia, impaired wound healing, acne, and pedal edema. Adverse events may be related to the dosing regimen (high vs. low dose) and timing (immediately post transplant vs. delayed introduction). A recent study with lower serum concentrations of everolimus (3-8ng/mL) report a lower drop-out rate of 15% (Lehmukuhl *et al.,* 2009). At this time, it remains unclear whether patients should be transitioned to a PSI-based immunosuppressant regimen once sternal healing has occurred.

In relation to the pharmacologic treatment of established CAV, aggressive control of traditional cardiac risk factors is important; however, the PSIs represent the most important advance. Studies in which patients with established CAV were switched to a PSI from MMF or azathioprine demonstrated a significant reduction in CAV-related adverse events (5% vs. 25%) including death, percutaneous coronary intervention (PCI), myocardial infarction, or angiographic progression of the disease 2 years following the transition and a reduction in plaque size compared to progression (Mancini *et al.,* 2003; Segovia *et al.,* 2004). Larger studies are needed to corroborate these initial findings; however, it is generally accepted practice that patients with established CAV are transitioned to PSI.

The treatment of established CAV represents a clinical challenge. Non-pharmacologic treatment includes PCI, coronary artery bypass grafting (CABG), and retransplantation. Percutaneous and surgical revascularization is limited by the diffuse coronary involvement, the infrequency of focal lesions with suitable distal targets, and the high mortality rates with surgical intervention (up to 30-40%) (Musci *et al.,* 1998; Patel *et al.,* 1997). PCI is associated with excellent short-term results, however is associated with high restenosis rates. With the advent of drug eluting stents, preliminary studies suggest much lower restenosis rates. (Lee *et al.,* 2008). PCI remains a palliative therapy, as CAV is a diffuse and progressive disease process. It may be appropriate to perform PCI in patients with discrete focal lesions with abnormal graft function or evidence of stress-induced functional significance by stress imaging. Retransplantation is the only definitive therapy for CAV; however, survival is lower than after primary heart transplant and the probability of CAV in the retransplanted

heart is higher than in de novo transplants (up to 50% at 3 years) (Musci *et al.,* 1998; Srivastava *et al.,* 2000). Re-transplantation is reserved for highly selected patients with CAV.

9. Summary

The development of CAV has been described as the Achilles heel of cardiac transplantation. The increased mortality observed in the years after the diagnosis of CAV reflects that fact that, at present, the management of these patients represents a clinical challenge. Diagnosis is heavily reliant on invasive testing and early diagnosis and preventive strategies are crucial, but remain ineffective in many cases. Statins, antihypertensive drugs, and anti-CMV agents have all demonstrated a modest beneficial reduction in CAV; however, the proliferation signal inhibitors represent the best prevention and treatment options available at this time. Current research focuses on identification of novel agents that are effective in preventing the development and progression of CAV, and non-invasive techniques for CAV diagnosis.

10. References

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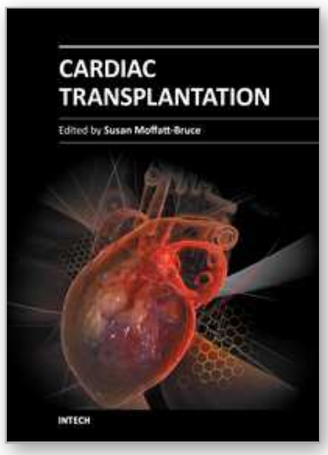

Cardiac Transplantation
Edited by Dr. Susan Moffatt-Bruce

ISBN 978-953-51-0000-3
Hard cover, 154 pages
Publisher InTech
Published online 10, February, 2012
Published in print edition February, 2012

We are truly in an era of change not only in terms of technology but in the type of patient we are caring for. That is why I feel this book is exciting in that it presents the team approach to the transplant patient. I am confident that the pioneers of cardiac transplantation would be pleased with our response to challenges in healthcare today and be pleased with the final product.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Brian Clarke and Kiran Khush (2012). Cardiac Allograft Vasculopathy: An Ongoing Challenge in the Care of Heart Transplant Recipients, Cardiac Transplantation, Dr. Susan Moffatt-Bruce (Ed.), ISBN: 978-953-51-0000-3, InTech, Available from: http://www.intechopen.com/books/cardiac-transplantation/cardiac-allograft-vasculopathy-an-ongoing-challenge-in-the-care-of-heart-transplant-recipients

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