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Cardiac Allograft Vasculopathy and Insulin Resistance – Hope for New Therapeutic Targets

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Introduction

Cardiac allograft vasculopathy (CAV) is a major cause of death in patients surviving more than one year after heart transplantation (HT) 1-3. Although numerous immune-mediated and metabolic risk factors have been implicated in the pathogenesis of CAV, 4 to date no effective treatment is available to fully eliminate CAV and its related adverse outcomes. Thus, the main therapeutic strategy against CAV is the prevention and treatment of the factors known to trigger or accelerate the disease. An important cluster of CAV risk factors are those that occur as a consequence of insulin resistance, and manifest as part of the metabolic syndrome (Table 1). 5 Indeed, insulin resistance with its associated hypertension, dyslipidemia, diabetes and systemic inflammation, often affect HT candidates, and are frequent adverse effects of immunosuppressive therapy. Each of these consequences of insulin resistance, individually and collectively, appears to negatively affect the prognosis of HT patients. This article first summarizes the pathological features of CAV, and then reviews the contribution of the major components of insulin resistance in CAV development and progression. We focus on the few studies that have analyzed the impact of the individual metabolic abnormalities and inflammation, and on therapeutic strategies to minimize the clinical manifestation of insulin resistance after heart transplantation. The central role that insulin resistance appears to play in the pathophysiology of CAV suggest the opportunity for new therapeutic targets that increase insulin sensitivity, while also ameliorating the associated proinflammatory state.

Clinical and Pathological Features of CAV

The most common cause of death and retransplantation after heart transplantation is a rapidly progressive obliterative vascular disease involving the coronary arteries, termed cardiac allograft vasculopathy (CAV) 6. The characteristic pathological features of CAV have also been observed in the vasculature of kidney, liver and lung transplants that are chronically rejected, suggesting a similar mechanism for the disease process, regardless of the organ type. 7-9 Pathological studies indicate that the lesions of CAV are characterized by diffuse fibrointimal proliferation composed of vascular smooth muscle cells and inter cellular matrix, and a characteristic sparing of the internal elastic lamina which distinguishes

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it from native atherosclerosis (Figures 1 and 2). 2. The lesions are diffuse within the allograft, involving arteries, veins and great vessels 10-12, yet the disease is limited to the allograft. 13 Some observational studies suggest a correlation between CAV and acute rejection 14-16, but others have not confirmed a significant association. 17, 18 Due to cardiac denervation of the transplanted heart, patients with CAV are typically asymptomatic until presentation with sudden death or congestive heart failure. There is a pressing need for greater understanding of the disease process, which might cover targets for prevention and treatment. The metabolic consequences of insulin resistance syndrome are cluster of such potential targets

Insulin Resistance Syndrome in the Pathophysiology of CAV

Insulin resistance syndrome (IRS) is a descriptive term to describe the abnormalities and clinical syndromes which reflect a physiological abnormality that increases the likelihood that one or more of the following abnormalities will be present: glucose intolerance; dyslipidemia; endothelial dysfunction; procoagulant factors; hemodynamic changes; markers of inflammation; abnormal uric acid metabolism; increased testosterone secretion. The central physiological abnormality is due to impairment in the ability of insulin to stimulate glucose disposal, and is known to vary six fold in the population at large. 19 When insulin resistant individuals cannot secrete the amount of insulin needed to overcome the defect in insulin action, type 2 diabetes develops. However most of these individuals are able to sustain the level of compensatory hyperinsulinemia required to maintain normal or near normal glucose tolerance. Although compensatory hyperinsulinemia can prevent the frank development of hyperglycemia, insulin resistant/hyperinsulinemic individuals are at greatly increased risk for having some degree of glucose intolerance, a high plasma triglyceride (TG), a low high-density lipoprotein cholesterol (HDL-C) concentration, and essential hypertension, all of which arise as a consequence of differential tissues insulin sensitivity. Because not all tissues share the defect in insulin action, the cost of secreting the amount of insulin needed to overcome insulin resistance, located primarily in muscle and adipose tissue, is the adverse impact of the compensatory hyperinsulinemia on tissues that retain normal insulin sensitivity. In the face of muscle and adipose tissue insulin resistance, most other tissues in the body retain normal insulin sensitivity, and can become victims of the compensatory hyperinsulinemia. For example, hyperinsulinemia will act on the normally insulin sensitive kidney to decrease uric acid clearance, and increase sodium retention, resulting in the increased uric acid concentration and salt sensitivity that occurs in insulin resistant individuals. 20 Of particular relevance is the impact of hyperinsulinemia on the liver that is normally sensitive to insulin. This not only leads to the atherogenic lipoprotein phenotype that characterizes the insulin resistant state 21 but is also responsible for the accumulation of liver fat that results in non-alcoholic fatty liver diseases. 22 Several population-based studies have demonstrated that hyperinsulinemia, both fasting and post glucose challenge, predict the development of cardiovascular disease (CVD) in non-diabetic individuals. 23, 24 It has been shown that insulin resistance, as quantified by a specific measure of insulin mediated glucose uptake (IMGU), is predictive of increased CVD risk, and that this risk is present in one third of an apparently healthy population that has the greatest defect in insulin mediated glucose disposal. 25 Although the evidence linking the atherogenic profile of insulin resistant/hyperinsulinemic individuals to increased CVD is the most established, consideration of the non-lipid CVD risk factors is important for improved understanding of how the multiple component of the insulin resistance syndrome might impact the biology of vascular diseases.

Observational studies through out the past three decades of heart transplantation have consistently reported that hypertriglyceridemia is a major risk factor for CAV. 26, 27 Evidence from clinical studies conducted over the past decade suggest that elevated TG is

but one marker of insulin resistance in heart transplant recipients. We have demonstrated that CAV is accelerated in animal models of insulin resistance, independent of an alloimmune response. 28 Since long ago, it has been demonstrated that heart transplant recipients have elevated levels of hemostatic and proinflammatory markers, mirroring the findings in non-transplant insulin resistant individuals. 29 The published data confirms that heart transplant recipients are insulin resistant, and suggests that this state of impaired insulin action accelerates CAV.

Our group has demonstrated that the majority of non-diabetic long-term heart transplant patients have impaired glucose tolerance and elevated plasma insulin concentrations, consistent with insulin resistance. 27 Importantly, patients with a pretransplant diagnosis of ischemic heart disease had higher plasma glucose and insulin concentrations in response to oral glucose as well as higher fasting plasma triglyceride, cholesterol, and low-density lipoprotein cholesterol concentrations than did the normal age-matched control. In addition, high-density lipoprotein cholesterol concentrations were lower, and the ratio of cholesterol to high-density lipoprotein cholesterol higher than control values in patients with a pretransplant diagnosis of ischemic heart disease. Values for almost all variables were intermediate in patients with a pretransplant diagnosis of idiopathic cardiomyopathy and in most instances were significantly different from both. Thus, cardiac transplant recipients are dyslipidemic, relatively glucose intolerant, and hyperinsulinemic compared to normal volunteers. This underscores the ongoing state of insulin resistance after heart transplantation, and its possible impact in poor cardiovascular outcomes in this patient population.

In addition to evidence for insulin resistance, a typical pattern of dyslipidemia was observed in these patients, elevated triglyceride and decreased high-density lipoprotein (HDL) concentration. We noted that these abnormalities were most pronounced during the initial three months after transplant, and although they became less marked over time, were still demonstrable in the majority of patients at one year after transplant. The mechanisms underlying the development of insulin resistance after transplant is unclear, but is most likely the consequence of genetic predisposition, and the immunosuppressive drugs used to prevent acute rejection, notably corticosteroids and calcineurine inhibitors such as cyclosporine and Tacrolimus. Although it is recognized that calcineurine inhibitors can impair glucose metabolism, 30 several studies in kidney and liver transplant recipients suggest that among the immunosuppressive drugs, corticosteroids are the major contributors to the development of IRS. 31 Additionally, cardiac transplant recipients are known to demonstrate increased activation of the sympathetic nervous system that is generally attributed to the state of cardiac denervation; however, the presence of insulin resistance and the compensatory hyperinsulinemia could further enhance SNS activation.³²

Even prior to the introduction of cyclosporine as the primary immunosuppressive drug, we reported that elevated plasma triglyceride concentration was a major risk factor for CAV in heart transplant recipients whose major immunosuppressive regimen consisted of corticosteroids. 27 Subsequent studies in CSA treated heart transplant recipients confirmed a significant correlation of hypertriglyceridemia with the development of CAV including one from our institution in which elevated TG, Apo-lipoprotein-B, weight gain and donor age were found to be independent predictors of CAV. 33

In addition to the studies conducted at our institution, other retrospective, cross sectional and prospective studies have assessed the correlations of components of the insulin resistance syndrome (IRS) and obesity with the incidence and risk of developing CAV (see table 2).

In general, these studies have demonstrated that cardinal features of the IRS including hypertriglyceridemia, hyperinsulinemia and elevated plasma glucose levels are associated with the presence of CAV by angiography and intravascular ultrasound (IVUS). We have demonstrated that CAV defined as the presence of coronary artery intimal thickness $> 0.3\text{mm}$ was significantly correlated with many features of the IRS including elevated plasma insulin and glucose and insulin concentrations, fasting and after glucose challenge; elevated TG and low plasma concentrations of HDL-c. Importantly, these markers of the IRS predicted the development of severe CAD by angiography as well as mortality from cardiovascular complications during a 5-year follow-up period. Similarly, in a cross sectional analysis of 606 renal transplant recipients, De Vries and colleagues examined the relationship between the IRS as a single entity and long term allograft function. Among their study subjects, the presence of the IRS was highly correlated with impaired renal allograft function beyond one year post-transplant. Multivariate analyses demonstrated that systolic blood pressure and triglycerides contributed most to allograft dysfunction. 34

Many of the early studies focused predominantly on the role of hyperlipidemia and the impact of statins in blocking the development of CAV. Clinical trials using this approach have indeed documented amelioration of CAV progression and incidence, and a survival benefit 35. However, as demonstrated in a recent study by White et al 36 there is an ongoing proinflammatory milieu that persists despite the routine administration of statins. In this study, heart transplant recipients were found to have significant elevations in Factor VIII, Von Willebrand factor, fibrinogen, PAI-I, and CRP, in addition to elevated plasma markers of vascular endothelial cell activation, sVCAM, sICAM, E- and P-selectins. This proinflammatory milieu in heart transplant recipients has been reported in other studies and is entirely consistent with insulin resistance outside of the setting transplantation. Although the pattern of lipid and lipoprotein abnormalities suggested that the heart transplant patients enrolled in that study were insulin resistant, this factor was not evaluated. In a prospective cohort of 99 heart transplant recipients, we were able to demonstrate the clinical utility of triglycerides to HDL-c ratio greater than 3 – an easy to use marker of insulin resistance 37 – to identify patients with a higher prevalence of CAV. 38 Additionally, the presence of systemic inflammation, detected by elevated serum C-reactive protein levels, further refined the identification of patients with CAV, and combined with TG:HDL ratio > 3.0 identified a subgroup of patients with a 3-fold increased risk for subsequent cardiovascular events. Of note, in this series of patients, we found a significant correlation between markers of insulin resistance and systemic inflammation as detected by CRP, suggesting a pathophysiological link between immuno-inflammatory activation and insulin resistance.

In summary, the majority of heart transplant recipients are markedly insulin resistant and demonstrate many of the features of compensatory hyperinsulinemia, including the atherogenic and pro-inflammatory profile. Immunosuppressive drugs, genetic and environmental factors are major contributors to IRS, and the body of evidence leads us to hypothesize that insulin resistance in heart transplant recipients accelerates CAV. Future therapeutic strategies for IRS treatment and prevention include PPAR- agonists that act directly to improve insulin sensitivity. PPAR- is a nuclear transcription factor that regulates adipocytes differentiation, fatty-acids and triglycerides storage, and insulin-dependent glucose uptake. 39 A relatively new class of drug, thiazolidinediones, acts as an agonist of PPAR- , markedly improving cellular insulin sensitivity. Interestingly, inhibitors of type-1 angiotensin receptors, commonly used antihypertensive agents, enhance PPAR- activity, potentially improving markers of insulin resistance. 40 Although there is no evidence that such approach has any impact on CAV development, graft overexpression of angiotensin receptors predicts CAV, 41 and efficacy of a PPAR- agonist in reducing CAV in a rat model of HT. 42 These data provide a strong rationale for appropriately designed prospective studies to test the hypothesis that insulin resistance accelerates CAV.

Targeting Individual Components of IRS for Prevention of CAV

Hyperlipidemia

The epidemiological data correlating elevated plasma concentrations of LDL and/or triglyceride suggested potential therapeutic targets for preventing or slowing the progression of CAV. 33 Recent studies using intravascular ultrasound have shown a direct correlation between LDL plasma concentration and coronary intimal hyperplasia 43, 44, even in patients largely treated with statins 45. Further observational data from a recent multicenter study showed that high LDL cholesterol was an independent risk factor for graft-related mortality and non-fatal major cardiac adverse events, albeit not significantly correlated with angiographic coronary lesions. 46

Because the immunosuppressive drugs routinely used in the management of posttransplant patients induce dyslipidemia, the question has been raised as to which of these agents is most atherogenic. Although the mechanism is unclear, calcineurin inhibitors appear to have a greater impact than corticosteroids for increasing cholesterol absorption, 47 with no apparent difference between the two CNIs (cyclosporine and tacrolimus 48. However, other studies have found that plasma concentrations of HDL cholesterol were significantly higher in cyclosporine-treated patients. 49 The discordance of the data between immunosuppression levels and dyslipidemia make it unlikely that reduction of immunosuppressive agents alone will adequately address the control of hyperlipidemia and CAV.

To further complicate the issue of hyperlipidemia and CAV, is the observation that sirolimus and everolimus, mammalian target of rapamycin (mTOR) inhibitors, cause profound hypercholesterolemia and hypertriglyceridemia. 48 Yet this new class of immunosuppressive drugs has been shown to reduce the progression of coronary artery intimal thickening, a marker of CAV detected by IVUS, and decrease the incidence of major adverse cardiovascular events 50, 51 This beneficial effect of mTOR inhibitors was observed despite the high cholesterol and triglyceride levels in patients receiving statins to lower plasma lipid concentrations, Experimental models suggest that the increase in circulating lipids is overcome by decreased deposition in the vascular wall in animals simultaneously treated with mTOR inhibitors and statins (Corsini et al, personal communication).

Routine statin therapy, started immediately after heart transplantation has become the main prevention strategy for CAV, based on two randomized controlled trials. 35, 52 In a 12-month randomized study of 97 patients, those who received pravastatin in addition to immunosuppression early after cardiac transplantation had significantly lower mean cholesterol, LDL cholesterol and triglyceride levels; higher HDL cholesterol levels; less frequent cardiac rejection; better survival; and lower incidence of CAV when compared with a control group who did not receive a statin. 52 19 A 4-years prospective study of 72 heart transplant patients showed that those treated with simvastatin had significantly improved survival and a lower incidence of CAV compared with the control group who received dietary therapy but no statin. 35 In addition to the data from randomized clinical trials, the benefit of statins has also been demonstrated in several registries reporting real-life clinical practice. In these studies, a survival benefit of statin therapy, apparently independent from cholesterol plasma levels, has been reported. 53, 54 However, both studies report a rate of CK elevation greater than in the general population, indicating the need for caution because of their interaction with cyclosporine that may increase the risk of CK elevation and rhabdomyolysis. Among the different statins available, fluvastatin has been shown not to interact significantly with cyclosporine, to improve cardiovascular prognosis in kidney transplant with an appropriate safety profile. 55 Preliminary data suggests that where statins

are not tolerated or ineffective, the use of ezetimibe, an intestinal cholesterol absorption inhibitor, can effectively decrease LDL-c. 56 This specific mechanism may be particularly effective in antagonizing the increase in cholesterol absorption induced by calcineurin inhibitors. 47 However, whether LDL-c reduction obtained via a mechanism of action different from statins has any protective effect on prognosis or CAV development remains to be proven.

Hypertension

Hypertension is a common finding after heart transplantation. According to the data reported by the registry of the International Society for Heart and Lung Transplantation, 76% of patients are hypertensive at year 1 after transplant and 94% at 5 years. 3 Post-operative hypertension after heart transplantation has been significantly associated with the onset of angiographic CAV. 57 There is evidence that hypertension is a consequence of both immunosuppressive therapy, particularly calcineurin antagonists, and the denervation of cardiac volume- and chemo-receptors. 58. Amongst the CNIs, there is a suggestion that tacrolimus may be associated with less hypertension than is cyclosporine. 46, 59, 60 Post-transplant hypertension associated with calcineurin inhibitors can be managed effectively with anti-hypertensive therapy, but it may require use of more than 1 anti-hypertensive agent. Angiotensin converting enzyme inhibition (Captopril) normalizes blood pressure and fluid homeostasis in heart transplant recipients receiving cyclosporine, prednisone and azathioprine. This suggests that post-transplant hypertension is related to an inability to suppress the renin-angiotensin-aldosterone system when patients become hypovolemic. 61

Post-transplant hypertension associated with calcineurin inhibitors can be managed effectively with anti-hypertensive therapy, but it may require use of more than 1 anti-hypertensive agent. Indeed, anti-hypertensive medication has been associated with improved measures of CAV. In 57 cardiac transplant recipients followed angiographically after randomization to diltiazem or no calcium channel blocker, the average coronary artery diameter at 2 years was similar to baseline in the diltiazem group, but was significantly smaller in those not receiving a calcium channel blocker; the difference between the groups was significant. 62 Similarly, in 32 cardiac transplant recipients, intimal thickness at 1 year measured by IVUS was significantly greater in the untreated control group than in those who received calcium channel blockers, angiotensin-converting enzyme inhibitors or both. 63 These promising results from small randomized studies are supported by data from two observational studies in which the use of ACE-inhibitors was associated with less progression of plaque volume measured by IVUS. 64 Importantly, this protective effect was most evident if ACE-inhibitors were used in combination with calcium-channel blockers, and independent from blood pressure levels. 65

Diabetes

More than 30% of adult heart recipients are diabetic 1 year after transplant, and more than half of them developed diabetes after the transplant because of immunosuppressive therapy. 3, 66-68 The risk factors for new-onset diabetes include pre-transplant blood glucose of >5.6 mmol/liter; a family history of diabetes; pre-transplant overweight –which appears the most important pre-transplant risk factor 69– the need for insulin on the second day post-transplant; and immunosuppressive drugs, 68 particularly calcineurin inhibitors and corticosteroids. 48 More recently, it has been suggested that also asymptomatic CMV infection may predispose to the onset of post-transplant diabetes 70

The immunosuppressive agents vary considerably in their diabetogenicity. 48 Indeed, the type of immunosuppressive regimen used (steroids, cyclosporine or tacrolimus) was found to explain 74% of the variability in incidence of new-onset diabetes after transplantation

reported in different studies. Corticosteroids are associated with the greatest risk of developing new-onset diabetes after transplantation, with rates as high as 46% reported in kidney transplant recipients receiving high-dose prednisolone. 71 Higher doses of prednisolone have also been found to be a risk factor for the development of new-onset diabetes in heart transplant recipients. 68, 72 Amongst the calcineurine antagonists, tacrolimus has been reported to predispose to new-onset diabetes more frequently than does cyclosporine. 48, 73 However, results from randomized studies in heart recipients are inconsistent regarding the diabetogenic effect of tacrolimus. For example, a European-based trial in heart transplant patients reported a 20% incidence of new onset diabetes with tacrolimus, compared to 10% in the cyclosporine arm. This contrasts with data from a similar US based trial reporting that tacrolimus was only associated with worse glycemic control, and not an increase in new onset diabetes. 60, 74.

Discrepancies between studies may partially be explained by the variability in criteria used for diagnosis of diabetes, the degree of glycemic control obtained with anti-diabetic therapy, and the presence of diabetes-related complications. In particular, in a study from our group, we found that hemoglobin A1C, a marker of glycemic control, was associated with the severity of CAV, independently from the cumulative doses of diabetogenic immunosuppressive drugs, and of the presence of pre-transplant diabetes. 75 In a retrospective analysis of all the 20,000 patients who underwent heart transplant in the US between 1995 and 2005, post-transplant survival was not affected by diabetes per-se, but by the presence of diabetes-related complications, such as obesity, cerebrovascular accident, peripheral arterial disease. However, diabetic patients had only a slightly increased incidence of CAV, but much greater renal dysfunction as compared with non-diabetic patients, irrespectively of diabetes-related complications. 76 Additionally, in a single center report, only pre-transplant diabetes appeared to impact survival and not diabetes occurring after transplant 77. Notwithstanding the discordances between these observational studies, taken together these data suggest that the duration of diabetes and lack of aggressive glycemic control negatively impacts long-term graft survival. This hypothesis is also supported by the experimental evidence showing that metformin treatment prevents CAV development, in a diabetic rat model 28. However, randomized controlled trials are needed to determine the effect of anti-diabetic therapy on CAV development and on prognosis.

Conclusions

The ability of insulin to stimulate glucose disposal as measured by the steady state plasma glucose (SSPG) concentration, varies widely in apparently healthy individuals, and those at the upper tertile of the normal continuum of SSPG are at increased risk of CVD. The majority of heart transplant recipients are markedly insulin resistant and demonstrate many of the features of compensatory hyperinsulinemia, including the atherogenic and pro-inflammatory profile, and the clinical signs of the metabolic syndrome. Multiple lines of evidence lead us to hypothesize that insulin resistance in heart transplant recipients contributes significantly to the development of CAV. Immunosuppressive drugs, in particular corticosteroids and calcineurin inhibitors, seem to play a major role in predisposing to insulin resistance. Reduction of these immunosuppressive agents is a first step towards ameliorating the negative clinical impact of insulin resistance, an approach that has been effective in kidney transplant recipients, for reducing obesity, fasting insulin, and apolipoprotein B concentrations. 78 Nevertheless, we believe that a more aggressive approach directed at close monitoring and treatment of the metabolic abnormalities associated with insulin resistance syndrome is necessary to prevent CAV and improve long-term prognosis. In addition, specific therapies such as thiazolidinediones (TZD) compounds and metformin, shown to be effective in correcting insulin resistance (IR) and improving cardiovascular prognosis in the general population, 79 and in experimental models, 28, 42

offer new and promising therapeutic targets for CAV prevention that warrant testing in randomized controlled trials. If well designed, such trials will undoubtedly further our understanding of the pathophysiology of CAV.

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Figure 1.

Pathological features of CAV. This is a histological section from left anterior descending branch of the coronary artery of a patient who congestive cardiac failure eleven months after transplant, and died suddenly while being considered for re-transplant. It shows diffuse intimal proliferation (blue arrow) composed of smooth muscle and inflammatory cells, and interstitial matrix; sparing of the intimal elastic lamina (green arrow); medial layer (yellow arrow) which is normal; and adventitial layer (yellow arrow) containing inflammatory cells. The result is a slit-like lumen (black arrow) that lead to myocardial infarction and death.

Figure 2.

A typical, normally appearing coronary angiographic appearance (top panel), despite the presence of considerable intimal thickening detectable by intravascular ultrasound (IVUS) yellow arrow which limits the vessel lumen (green arrow).

Table 1

Abnormalities associated with insulin resistance	
Some degree of glucose intolerance	
-	Impaired fasting glucose
-	Impaired glucose tolerance
Dyslipidemia	
-	Triglycerides
-	HDL – C
-	LDL-particle diameter
-	Postprandial accumulation of TG-rich lipoproteins
Endothelial dysfunction	
-	Monocytes cell adhesion
-	Plasma concentration of cellular adhesion molecules
-	Plasma concentration of asymmetric dimethylarginine
-	Endothelial-dependent vasodilatation
Procoagulant factors	
-	Plasminogen activator inhibitor-1
-	Fibrinogen
Hemodynamic changes	
-	Sympathetic nervous system activity
-	Renal sodium retention
Markers of inflammation	
-	C-reactive protein
Abnormal uric acid metabolism	
-	Plasma uric acid concentration
-	Renal uric acid clearance
Increased testosterone secretion (ovary)	
Sleep disordered breathing	

Table 2

Reference	Component of Insulin Resistance Syndrome	N	Study Design	Gold Standard	Significant Findings (p<0.05)
Kato et al. JACC, 2004	Glucose Intolerance	151	cross sectional	angiography IVUS	HbA _{1c} (and BMI) associated with CAV by IVUS on multivariate analysis; HbA _{1c} associated with CAV by angiography on multivariate analysis
Valantine et al. Circ, 2001	Insulin Resistance TG and HDL	66	cross sectional prospective	angiography	High insulin and glucose levels associated with increased risk of CAV; MIT >0.3 mm associated with higher levels of TG and lower levels of HDL
Biadi et al. JHLT, 2007	Insulin Resistance TG and HDL	98	Prospective	angiography	TG/HDL ratio >3.0 and high CRP are associated with 3 fold increase in risk of developing CAV and subsequent cardiovascular events
Richenbacher et al. Transplantation, 1996	TG	116	retrospective	angiography IVUS	TG (and body weight) correlated with increased MIT at IVUS by multivariate regression; CAV progression at 1 yr associated with TG by regression
Mehra et al. JACC, 1995	TG	138	cross sectional prospective	IVUS	TG associated with increased risk of CAV by logistic regression
Senechal et al. JHLT, 2005	Atherogenic Triad	83	cross sectional	angiography	25 fold increase in the risk of CAV at angiography in the presence of the atherogenic triad by logistic regression
Kapadia et al. JACC, 2001	TG	93	Prospective	IVUS	TG were associated with progression of donor transmitted lesions at 1 yr but not on development of new lesions

Legend: BMI, body mass index; CAV, cardiac allograft vasculopathy; IVUS, intravascular ultrasound; TG, triglycerides; MIT, maximal intimal thickness; atherogenic triad, elevated fasting glucose, apo-B and small dense LDL