Cardiac Allograft Vasculopathy: Pathogenesis and Role of Coronary Computed Tomography Angiography in the Diagnosis and Surveillance

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Abstract: Cardiac allograft vasculopathy (CAV) is an entity unique to the cardiac transplant patients and remains the leading cause of mortality after the first year of transplantation causing chronic allograft rejection. It is an accelerated form of coronary artery disease, occurring diffusely, starting from the small distal vessels and ultimately extending to intramyocardial and epicardial vessels of the allograft. Multiple traditional metabolic risk factors known to cause atherosclerosis have been identified as a trigger for CAV. Moreover, several nontraditional environmental risk factors such as viral infections, donor's age, underlying cardiac disease and mechanism of donor brain death have also been implicated. The pathogenesis of CAV is complex with involvement of both immunological and non-immunological mechanisms and still remains poorly understood. Clinical diagnosis of CAV is difficult as symptoms of angina are usually lacking because of denervated nature of the allograft and it is identified when the graft is already compromised. Currently, invasive testing stands as the gold standard for its diagnosis; however its utility has been questioned. Coronary CT angiography (CCTA) has emerged as a promising noninvasive tool for the diagnosis of CAV. This review discusses the risk factors, pathogenesis and diagnosis of CAV and utility of CCTA in its diagnosis and surveillance.

Keywords: Cardiac allograft vasculopathy, coronary computed tomography angiography, cardiac transplant.

INTRODUCTION

Cardiac transplantation has emerged as an effective treatment modality for patients with end stage heart failure. Over 5,000 heart transplants are performed every year worldwide [1], and about 50% of those are performed in the United States alone [2]. Significant advances in cardiac transplantation and post transplant care over the last three decades have led to substantial improvement in the overall survival of cardiac transplant patients. As the long-term survival of transplant recipients continues to increase, cardiac allograft vasculopathy (CAV) has emerged as an important cause of morbidity and mortality after the first year of heart transplantation. CAV may begin during the first twelve months after cardiac transplantation and has been reported as an independent predictor of mortality [3]. Despite the fact that CAV is one of the leading causes of late graft failure; its exact pathogenesis remains unclear. Many believe that CAV is the result of a chronic allograft rejection; however increasing evidence shows involvement of both immunological and non-immunological mechanisms [4]. In the current era, coronary angiography is the gold standard method for its diagnosis. Increasing efforts are being made to study non-invasive imaging techniques for its diagnosis. Coronary computed tomography angiography (CCTA) has emerged as a noninvasive tool to assess coronary artery disease in symptomatic patients with low to intermediate pretest probability of obstructive CAD and there is growing evidence that CCTA might be a valuable tool in the early detection of CAV.

This review focuses on pathogenesis of CAV and the usefulness of CCTA in the diagnosis and surveillance of CAV.

WHAT IS CAV?

Cardiac Allograft Vasculopathy is an entity unique to cardiac transplant patients and remains the leading cause of mortality after the first year of transplantation causing chronic allograft rejection. It has been referred to as the Achilles heel of cardiac transplantation by many authors [5]. It is a rapidly progressive form of diffuse coronary artery disease (CAD) starting from the small distal vessels and ultimately extending to intramyocardial and epicardial vessels of the allograft [6]. It is characterized by predominantly concentric intimal proliferation sparing the internal elastic lamina, causing luminal narrowing, occlusion of smaller arteries and ischemic graft failure [7, 8]. This is in contrast to traditional native coronary artery atherosclerosis that is a relatively focal process and is usually characterized by eccentric intimal proliferation and disruption of the internal elastic lamina. CAV affects about 8% of the transplant recipients by one year, 30% by five years,

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and 50% by ten years after transplantation [1, 9]. It has a high mortality rate (about 90%) in the first year of diagnosis in patients with 3-vessel CAV [10] and the only definitive treatment is re-transplantation, which by itself has a poor prognosis. Therefore, research efforts should focus on the early detection and targeted treatment interventions of CAV.

RISK FACTORS

Multiple traditional metabolic risk factors known to cause atherosclerosis can trigger development of CAV [11]. These include pre-existing hyperlipidemia, hypertension, and diabetes. Sanchez *et al*. [11] showed that dyslipidemia of the recipient is strongly associated with development of CAV and that the other metabolic risk factors such as age, sex, body mass index, diabetes mellitus, hypertension and smoking are only weakly associated.

Environmental risk factors have also been linked to the development of CAV. Of these, viral infections have been studied extensively with cytomegalovirus being the best-described [12]. Risk factors such as the donor's and recipient's age and sex, underlying cardiac disease, doses of immunosuppressive agents, HLA mismatch [13, 14], also play an important role in the development of CAV [13, 15]. Mehra *et al.* showed that explosive brain death of the donor is a significant determinant of late development of CAV in transplant recipients and also affects long-term survival of the allograft [16].

PATHOGENESIS

The pathogenesis of CAV is complex and remains poorly understood. Both immunological and non-immunological mechanisms have been found to play a role in its pathogenesis [17].

Immunological

CAV has long been understood as a process of chronic rejection with an overwhelming role of alloimmunity in its pathogenesis. The observation that CAV affects the donor arteries and not the recipient arteries supports alloimmunity as the main process in CAV. The alloantigen-dependent risk factors include HLA mismatches and the number and duration of acute rejection episodes [13, 14]. HLA matching has been found to be an independent predictor of survival in heart transplantation [18]. Both innate and acquired components of the immune system have been implicated in the pathogenesis of CAV [19]. The first target of the immunological activation is the endothelium and the inflammation caused by the release of various cytokines and chemokines results in migration and proliferation of smooth muscle cells causing intimal thickening and fibroblast activation triggering fibrosis [20].

Non-Immunological

Several non-immunological factors have been implicated in the development of CAV after cardiac transplantation.

a) Cytomegalovirus Infection

CAV occurs more frequently in patients who develop cytomegalovirus (CMV) infection with or without symptoms after transplant [21]. These patients typically have a more severe form of CAV compared to patients without CMV infection [21]. The risk of developing CMV infection varies with the immunosuppressive agent being used. For example, higher incidence of CMV infection was found with mycophenolate mofetil compared to azathioprine [22] while the incidence remained similar with use of cyclosporine and tacrolimus [23, 24]. Prophylactic use of ganciclovir has been shown to reduce intimal thickening, decrease progression of CAD and offer a survival benefit [25]. Ganciclovir in combination with hyper-immune CMV globulin has proven to be more effective than ganciclovir alone [26].

b) Metabolic Factors

The prevalence of conventional cardiovascular risk factors such as diabetes, hypertension and hyperlipidemia is likely to be higher in the cardiac transplant patients compared to the general population. The use of corticosteroids and immunosuppressive chemotherapeutic regimens also contributes to the development of diabetes and hypertension after transplant. New onset diabetes occurs in about one-third of patients post transplant [27], while hypertension requiring treatment occurs in majority of patients within six months of cardiac transplant [28].

c) Ischemia-Reperfusion Injury

Ischemia disrupts the blood supply causing anaerobic cell metabolism, depletion of energy molecules and dysfunction of ATP dependent membrane channels. As reperfusion occurs, highly reactive oxygen free radicals are generated which cause activation of endothelial cells [29]. These activated cells produce mediators such as platelet-activating factor (PAF), and surface adhesion

molecules. These lead to attachment of circulating leukocytes with the endothelial cells resulting in direct endothelial cell damage. These leukocytes further release cytokines that results in proliferation of smooth muscle cells and contributes to development of graft vasculopathy [30].

d) Other Donor and Recipient Related Factors

Graft injury can occur in cases of brain death, donor maintenance and organ retrieval and preservation process [31]. Pre-existing CAD even in young donors is frequent. However, donor transmitted lesions have not been reported to cause accelerated graft vasculopathy in current studies [32].

CLINICAL PRESENTATION

The diagnosis of CAV is clinically difficult as symptoms of angina are mostly absent because of the denervated nature of the allograft. Thus, it is usually identified late when the graft is already compromised. The typical presentation of CAV includes shortness of breath, decrease in exercise capacity, syncope, heart failure, ventricular arrhythmias or sudden cardiac death which could be the initial presentation of the disease [33]. Studies have shown that timely alterations in the immunosuppressive regimen can delay the development and progression of CAV and even cause its regression [34]. With the advent of newer immunosuppressive agents, early diagnosis has become imperative as it can facilitate the essential modifications in the medication regimen before reaching a stage where revascularization or retransplantation will be the only alternative.

DIAGNOSTIC TESTING

In the past, CAV was diagnosed with histopathological examination only. Currently, coronary angiography stands as the gold standard for the evaluation of CAV and is the norm for surveillance in cardiac transplant patients. However, coronary angiography lacks sensitivity in identifying the extent and severity of CAV when compared with histopathologic examination [35] and intravascular ultrasonography [36]. The associated risks that invasive procedures carry and the risk of contrast-induced nephropathy have led to the advent of research for non-invasive imaging modalities that could identify CAV in its primitive stages.

Several noninvasive test modalities including the treadmill exercise test, dobutamine stress echocardiography, and myocardial perfusion scans have also been studied for early diagnosis however their modest diagnostic accuracy is the major limitation [37, 38]. Coronary CT angiography (CCTA) is an upcoming noninvasive modality in detection of CAV.

Invasive Testing

Coronary angiography is currently considered the gold standard for the evaluation and surveillance of CAV [39]. It is universally available for both the adult and pediatric population and it is applicable at any time after a cardiac transplantation. An angiogram may be considered within a month after cardiac transplant to establish a baseline of the coronary anatomy. Abnormal findings at that time suggest native coronary artery disease of the donor and not CAV. Thereafter; patients should undergo coronary angiography a year after the cardiac transplant. Surveillance is recommended every other year in patients without CAV and on a yearly basis in those with disease [40]. Some transplant centers alternate coronary angiography with non-invasive tests such as such as dobutamine stress echocardiography or myocardial perfusion imaging to limit the radiation exposure [39].

Despite its advantages, coronary angiography is an invasive test and as such carries its associated risks. It has also been shown to underestimate the presence of disease compared to histopathologic studies or intracoronary ultrasound [41]. In the transplant patients, stenosis may develop in a concentric fashion and mimic the normal coronary arteries. In other cases severe intimal thickening may be compensated by remodeling and enlargement of the vessel and thus missed by angiography, which provides direct visualization of the vessel lumen only.

Apart from its diagnostic purposes, coronary angiography provides significant prognostic information: In a study by Yacoub *et al.* absence of angiographic disease was a significant predictor of cardiac event-free survival in heart transplant patients [42, 43].

Intravascular Ultrasound (IVUS)

Intravascular ultrasound (IVUS) has been used for imaging of the coronary anatomy in post-transplant patients. IVUS allows measurements of both the actual lumen diameter and the thickness of the intima and media and thus provides invaluable information about the onset, severity and progression of CAV [36]. IVUS has high sensitivity and negative predictive value

however its routine use as a screening tool for CAV is not recommended based on the latest guidelines [39, 42]. The rate of progression and severity of CAV assessed by IVUS has been shown to have prognostic implications for the risk of heart failure, myocardial infarction, death and re-transplantation, however the detailed information provided by IVUS does not trigger changes in the clinical practice that would change those outcomes. Furthermore, its use is costly, invasive, time consuming, riskier and allows the assessment of proximal epicardial arteries only [41].

Diagnostic Cardiac Catheterization and Fractional Flow Reserve

Coronary flow reserve (CFR) measures the increase in coronary blood flow in response to a vasodilator agent. The reduction of CFR indicates the development of CAV and helps in detection of the disease before angiographic changes occur. Currently CFR is the standard for the early detection of CAV however it is an invasive procedure and does not allow the study of side branches or distal segments of the vessels.

Non-Invasive Testing

Stress Testing

In patients with a normal angiogram that are considered low-risk for the development of CAV non-invasive testing can be used to minimize the surveillance angiographies [39]. Exercise ECG, thallium scintigraphy and exercise radionuclide ventriculography are also used in patients with advanced renal failure to reduce the administration of contrast. These tests have low sensitivities but good negative predictive value: Patients with a normal stress test have been shown to be free of adverse events. Dobutamine echocardiography has been shown to have better sensitivities and specificities compared with the other non-invasive tests [37]. Lewis *et al.* evaluated patients on a yearly basis with dobutamine echocardiography. Their data suggested an abnormal test serves as an important predictor of subsequent cardiac events while a normal test identified a subset of low risk patients [37, 44].

Coronary CT Angiography

Cardiac CT angiography (CCTA) has arisen as a non-invasive test for the assessment of the coronary anatomy allowing visualization of the wall of the coronary arteries and thus potentially detecting CAV in earlier stages compared to coronary angiography [45, 46]. In a recent study published in the New England Journal of Medicine, CCTA was able to accurately identify the presence and the severity of obstructive coronary artery disease [47]. However, the negative and positive predictive value of 83% and 91% respectively of the CCTA reveal that coronary angiography cannot be replaced as the gold standard for the assessment of post-transplant patients [47].

Limitations of the CCTA include the high radiation exposure, with an average radiation dose of 10-20mSv (when performed with retrospective gating) [48] compared to 5-6mSv [49] that is the average radiation dose of invasive angiography, and the concerns that increased doses of radiation could translate into higher risk of cancer in this patient population that is of high risk given the prolonged use of immunosuppressant medications [42, 50, 51]. The risk of contrast-induced nephropathy (CIN) is also noteworthy: Higher doses of contrast are used in CCTA compared to conventional coronary angiography with the majority of the post-transplant patients having a degree of renal dysfunction at baseline. The denervated hearts lack vagal tone and usually do not respond well to the beta-blockers given to slow the heart rate for obtaining optimal CCTA images. Furthermore the use of beta-blockers in these patients has raised safety concerns with regards to their use in this patient population [50]. Based on the current evidence, the routine use of CCTA for the assessment of CAV is not recommended as there is currently limited evidence on its diagnostic accuracy and prognostic value in the post-transplant survival [52].

Magnetic Resonance Imaging (MRI)

Magnetic resonance perfusion imaging (MRI) using gadolinium based contrast has the advantage of being a non-invasive test without exposing patients to radiation. Currently MRI does not have the resolution to accurately define the coronary anatomy the way CCTA or coronary angiography do; however; it has been validated as a tool to quantify myocardial perfusion reserve (MPR) in patients with a diagnosis of CAV. Studies have shown that MPR matches the reduced coronary flow reserve as assessed by angiography [42].

Biomarkers

Because inflammation causes endothelial injury, measurement of inflammatory cytokines in the serum could theoretically help in the detection of CAV.

Elevated C-reactive peptide (CRP) and brain natriuretic peptide (BNP) levels have been associated

with increased risk of developing CAV and increased mortality [53, 54]. Persistent elevation of troponin-I after cardiac transplant was also associated with an increased risk of CAV and graft failure. Other cytokines associated with endothelial injury such as ICAM-1, VCAM-1, endothelin, vascular endothelial growth factor (VEGF) and even von-Willebrand factor are currently being studied as potential biomarkers and therapeutic targets for CAV [42, 55].

Based on the guidelines, measurement of biomarkers is not currently recommended for detection or evaluation of the severity of CAV given the lack of concrete evidence about their specificity and reproducibility [39].

MANAGEMENT OF CAV

Once diagnosed, treatment options for CAV are somewhat limited and have only minimal impact. Therefore, management of CAV focuses on early surveillance and primary prevention with optimal immunosuppression and aggressive control of cardiovascular risk factors.

Conventionally, immunosuppressive agents of the calcineurin inhibitor class have been the cornerstone in reducing rejection. mTOR inhibitors such as sirolimus and everolimus have antiproliferative actions and have been shown to decrease incidence and progression of CAV [34, 56]. The use of antiplatelet agents is not well studied in this population, however aspirin is empirically used for possible microthrombi, which can form at the sites of endothelial injury in the coronaries in CAV. Statins are part of standard care for post-transplant patients: they help not only in lowering cholesterol, but have been found useful in the transplant patients given their immunosuppressive and anti-inflammatory properties [57].

Revascularization interventions are limited due to diffuse nature of the disease in CAV. Percutaneous revascularization can be considered for focal disease however has not been shown to be beneficial compared to medical therapy alone. Retransplantation has been considered as a treatment option for patients with advanced CAV. One recent study showed survival benefit when retransplantation was performed in patients with CAV for associated systolic graft dysfunction compared to medical therapy alone [58]. However, retransplantation is associated with the challenges of organ shortage and the increased risk of CAV compared to first transplantation. Thus, current consensus recommendation is that it should be reserved only for selected patients with advanced CAV [59].

CONCLUSION

CAV is a major cause of death in heart transplant patients. Invasive testing remains the gold standard in its diagnosis, however the emerging noninvasive modalities hold great potential in reliable detection of CAV and reducing the need for invasive testing. Surveillance measures and primary prevention strategies are crucial as the treatment of CAV is limited.

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