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OBM Transplantation

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Review

Cardiac Allograft Vasculopathy: A Review of Risk Factors and Pathogenesis

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Academic Editor: Nandini Nair

OBM Transplantation
2018, volume 2, issue 1
doi:10.21926/obm.transplant.1801007

Received: August 31, 2017
Accepted: December 17, 2017
Published: January 14, 2018

Abstract: Heart transplant remains the gold standard therapy for patients with end stage heart disease and offers improved survival and quality of life. Significant progress has been achieved in improving one-year mortality after heart transplantation. Nonetheless, long-term graft survival has not changed significantly over the past few decades. Long term survival of heart transplant recipients is limited by chronic rejection, cardiac allograft vasculopathy (CAV), and malignancy. CAV is a major contributor for graft failure and mortality after the first year of in heart transplant recipients. CAV is a proliferative vasculopathy characterized by diffuse myointimal hyperplasia and progressive narrowing of the graft vessels. Both immune dependent and independent factors have been shown to contribute to the pathogenesis of CAV. Understanding these risk factors is essential in developing preventative and therapeutic strategies. Angiography with Intravascular ultrasound has become the key diagnostic tool in the early detection of CAV as well as prognostication. Echocardiographic assessment of allograft function in conjunction with coronary angiographic findings are used in assessing the severity of CAV. Adjustment of immunosuppression and statins remain the initial steps in the management of CAV.

Retransplantation is the definitive treatment for severe CAV, however, the paucity of organs along with increased mortality associated with retransplantation makes it a less desirable option. Remarkable progress has been achieved in the understanding of pathogenesis, risk factors for CAV and plaque morphology. Nevertheless, significant knowledge gaps persist in scientific understanding of risk factors, pathogenesis, prevention and treatment of CAV. Further research is warranted to fill these gaps, develop diagnostic modalities to facilitate early detection of CAV, and management strategies to Improve graft tolerance and immune modulation. This review focuses on summarizing the pathogenesis and risk factors for CAV.

Keywords

Cardiac allograft vasculopathy; Heart transplant; Pathogenesis and risk factors

Introduction

Cardiac transplant is a widely accepted therapy for select patients with end stage cardiovascular disease. Short-term survival following heart transplantation has improved with the evolution of transplant immunology & immunosuppressive therapy, advances in organ preservation & surgical techniques, as well as diagnosis & management of acute rejection. Despite achieving significant strides in short term survival, the challenges of long-term survival remain unresolved. Chronic rejection, cardiac allograft vasculopathy (CAV), malignancy and renal insufficiency hinder the long-term survival and are direct contributors to graft dysfunction and graft failure [1-5]. CAV remains one of the major causes of mortality and morbidity following the first year of cardiac transplantation [1, 2]. The International Society of Heart lung Transplantation registry reported 8% of incidence of CAV at one year following heart transplant and 29% and 48% at 5 and 10 years following the transplant respectively [1].

CAV is multifactorial in origin and is considered to be a form of chronic rejection previously due to the crucial role played by various alloimmune and autoimmune mechanisms in the pathogenesis of CAV [6-8]. Although immune mediated factors play a major role, several studies have demonstrated the role of traditional risk factors of coronary artery disease (CAD) in the progression of CAV [8-10]. Based on progress gained in this field, CAV is currently viewed as an "impaired response to vascular injury" resulting in altered permeability, migration of smooth muscle cells and fibroproliferation [10]. This results in diffuse concentric hypertrophy of the vessel wall and microvascular occlusion leading to pathologic remodeling of the transplant heart vasculature [8]. It affects epicardial, intramural arteries, and veins and causes diffuse luminal narrowing which could lead to myocardial infarction (MI) and graft dysfunction [11]. CAV can be indolent or may lead to clinical sequelae such as MI, decreased exercise capacity, heart failure, arrhythmia, and sudden cardiac death [12-14]. Clinical presentation is usually delayed as patients usually do not experience angina due to denervated status of the transplant heart and can have silent MI. It is imperative that surveillance angiography with Intravascular ultrasound (IVUS) is used to detect early CAV as sudden cardiac death, ventricular arrhythmias or heart failure could be the first clinical presentation in these patients [15, 16].

Definition and Diagnosis

CAV is a morphologically and clinically heterogeneous disease with significant phenotypic variation in angiographic manifestation and clinical presentation [17]. Routine angiographic surveillance is commonly performed in heart transplant recipients by many institutions across the United States. Varying angiographic descriptions are noted in the literature. Gao et al, described angiographic CAV based on type of lesion as Type A, B1, B2 and C lesions [18]. Costanzo et al, classified CAV into normal, mild, moderate and severe categories [19]. There was no uniform definition or description until International Society of Heart and Lung Transplant (ISHLT) formulated the definition and nomenclature for CAV (**Table 1**). ISHLT issued a consensus statement in 2010 stating that coronary angiography in conjunction with assessment of cardiac allograft function is likely to detect CAV with high degree of confidence [20].

Table 1 ISHLT recommendations for CAV nomenclature

ISHLT Grade	Degree of vasculopathy	Angiographic Characteristics	Allograft function
CAV0	Non-significant	No detectable lesions by angiography	
CAV1	Mild	Left main (LM) coronary artery < 50% Primary vessel < 70% Secondary vessel or branch stenosis < 70% including diffuse narrowing	No Allograft dysfunction
CAV2	Moderate	LM < 50% Single primary vessel > 70% Isolated branch stenosis > 70% involving 2 vessel systems	No Allograft dysfunction
CAV3	Severe	LM > 50% Two or more primary vessels > 70% stenosis isolated branch stenosis > 70% in all 3 systems ISHLT CAV1 or CAV2 with allograft dysfunction	Allograft dysfunction or Restrictive physiology

Modified and adapted with permission – Mehra et al [20].

A Primary Vessel is defined as the proximal and middle 1/3rd of the left anterior descending artery (LAD), the left circumflex (LCx), the ramus and the dominant or co-dominant right coronary artery (RCA) with the posterior descending (PDA) and posterolateral branches (PLB). A Secondary Branch Vessel is defined as the distal 1/3rd of the primary vessels or any segment within a large septal perforator, diagonals and obtuse marginal branches or any portion of a non-dominant RCA. Allograft dysfunction is described as left ventricular ejection fraction (LVEF) of 45% or less and is usually associated with regional wall motion abnormalities. Restrictive cardiac allograft physiology is described to be symptomatic heart failure with restrictive hemodynamic parameters as described below: Right atrial (RA) pressure > 12 mmHg, pulmonary capillary wedge pressure (PCWP) > 25 mmHg and cardiac index < 2.1 liters/minute/m^2; Or with following echocardiographic features: E /A velocity ratio > 2 in adults and a E/A ratio of > 1.5 in children; Shortened isovolumetric relaxation time denoted to be < 60 msec.

Despite pathological differences, CAV and traditional coronary artery disease (CAD) do share some similarities and have some common contributing factors (**Table 2**) [10, 21-23]. Immunologic

factors play a major role in the development of graft coronary artery disease (GCAD) or CAV, while metabolic and genetic factors play a dominant role in the development of traditional CAD. CAV is primarily a disease of intima and is characterized by diffuse intimal hyperplasia and fibrosis. The characteristic lesions that are seen in CAV are also noted in other solid organ transplants such as kidney, liver, and lung [24-26]. CAV is not a homogenous disease and lesions may vary morphologically ranging from lipid-rich atherosclerotic plaques to fibrointimal proliferation of the allograft vasculature [10, 17, 21, 22]. The atherosclerotic lesions seen in the allografts can be either donor derived lesions or de novo lesions developed after transplantation. Traditional CAD is usually characterized by focal eccentric hypertrophy and formation of fibrofatty plaques with disruption of the elastic lamina [21, 25, 27]. In contrast, in CAV, histologically the elastic lamina is primarily intact, and narrowing of the vasculature is circumferential rather than eccentric [10, 27-31]. Fibrofatty plaques could be seen in cardiac allografts, however, characteristic lesion of CAV is fibrointimal hyperplasia of the vessel wall leading to insidious narrowing of the vasculature of the allograft [10, 27-31]. While CAD typically takes several years to develop and propagate to clinically significant disease, CAV is rapidly progressive and may become clinically significant in weeks to months [10, 32, 33].

Table 2 Clinical and histopathological features of CAV vs. CAD

Feature	CAV	CAD
Presenting Symptoms	Usually asymptomatic Can present with heart failure or SCD	Angina or Anginal equivalent
Angiography	Diffuse disease Diffuse vessel narrowing leads to characteristic angiographic appearance described as "distal pruning"	Predominantly a focal proximal disease
Vessels involved	Epicardial arteries Intramuscular arteries Microvascular bed Veins	Epicardial arteries
Histopathologic features		
Intimal proliferation	Concentric	Eccentric
Internal elastic lamina	Intact	Severely disrupted
Calcium deposition	Uncommon (may be seen in the advanced stage)	Commonly seen

Immunobiology and Pathogenesis of Coronary Allograft Vasculopathy

CAV is an accelerated form of coronary vascular disease seen in the heart transplant recipients characterized by neo-intimal hyperplasia and fibrosis of graft vasculature and microvascular occlusion while sparing the recipient's native vasculature [27-34]. Immune mediated factors play a

dominant role in the initiation and propagation of CAV [35-37]. This is supported by the observation that distinct atheromatous disease of graft involves the coronary vasculature and extends to the graft aorta sparing the recipient aorta beyond the suture line. Other evidence of the role of immune mediated mechanisms is demonstrated by a lower incidence of CAV in combined organ transplants, such as heart-lung and heart-kidney recipients, when compared to isolated cardiac transplant recipients. It is suggested that in these combined heart-lung and heart-kidney transplants, the lung and renal system become the primary regions of interface between recipient and host immune systems; hence, graft coronary vasculature is relatively less affected [26, 38, 39]. Immunologic mechanisms that regulate CAV are complex and heterogeneous and involve cellular and humoral aspects of adaptive and innate immune response pathways [7, 9, 19, 35-37, 40-42].

Although the precise mechanism of CAV is not completely elucidated, a complex interplay of a wide array of immunologic and non-immunologic factors related to both donor and recipient result in the pathogenesis of CAV. The primary event in the pathogenesis of CAV is thought to be subclinical endothelial injury of the graft vasculature followed by exaggerated immune response and impaired repair mechanism [2, 43-51]. The endothelium serves as the barrier between the transplanted heart and circulating host immune cells. Endothelial dysfunction induces leukocyte adhesion, thrombus formation, vascular smooth cell proliferation, and impaired vasomotor tone and vascular homeostasis [46-52]. Endothelial injury and dysfunction leads to imbalance between endothelial derived relaxing factors (EDRFs) and endothelium-derived constricting factors (EDCFs). EDCFs promote inflammation and contribute to the development of atherosclerosis by attenuating the action of EDRFs [2, 8, 27, 29, 45-53].

The initial endothelial injury might result from ischemia-reperfusion injury or from host immune response to the cardiac allograft leading to activation of endothelium [53]. Any immunologic or non-immunologic triggered injury to the endothelium generates immune response after allo-recognition of foreign major histocompatibility complex (MHC) molecules expressed on the graft endothelium [54-56]. Subsequently, the graft vascular wall becomes the target of immune response inducing the remodeling of the allograft vasculature [57]. The immune response is interceded by either direct, indirect, or semi-direct pathways and results in activation of T lymphocytes, induction of cytokine secretion, formation of donor specific antibodies (DSAs) [44, 58]. This further bolsters the endothelial activation. Activation of endothelium leads to increased expression of MHC class II antigens and upregulation of adhesion molecules such as inter cellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule 1 (VACM-1) [59]. These adhesion molecules facilitate the adhesion of leukocytes to activated vascular endothelium and also promote mononuclear cell infiltration. Expression of VCAM-1 on intimal and medial smooth muscle cells has been observed in patients with allograft vasculopathy. ICAM-I and VCAM-I may also serve as co-stimulatory signals T cell stimulation during antigen presentation. Various immunoregulatory molecules in conjunction with chemoattractants stimulate the migration of lymphocytes, granulocytes, and monocytes to the intima of the graft vasculature [52, 60]. Immune response is further propagated by recruitment of macrophages and other pro-inflammatory cells on to the vessel wall. Activated macrophages elaborate cytokine production and growth factor secretion [9, 60, 61]. Intercellular communication and coordination between infiltrating cells, adhesion molecules, endothelium, and various components of the extracellular matrix are required for successful recruitment and transmigration of leukocytes. This is followed by altered permeability, smooth muscle cell proliferation and migration along with synthesis and deposition

of extracellular matrix [9]. This eventually leads to the characteristic vasculopathic changes of CAV i.e., fibromuscular proliferation of neointima.

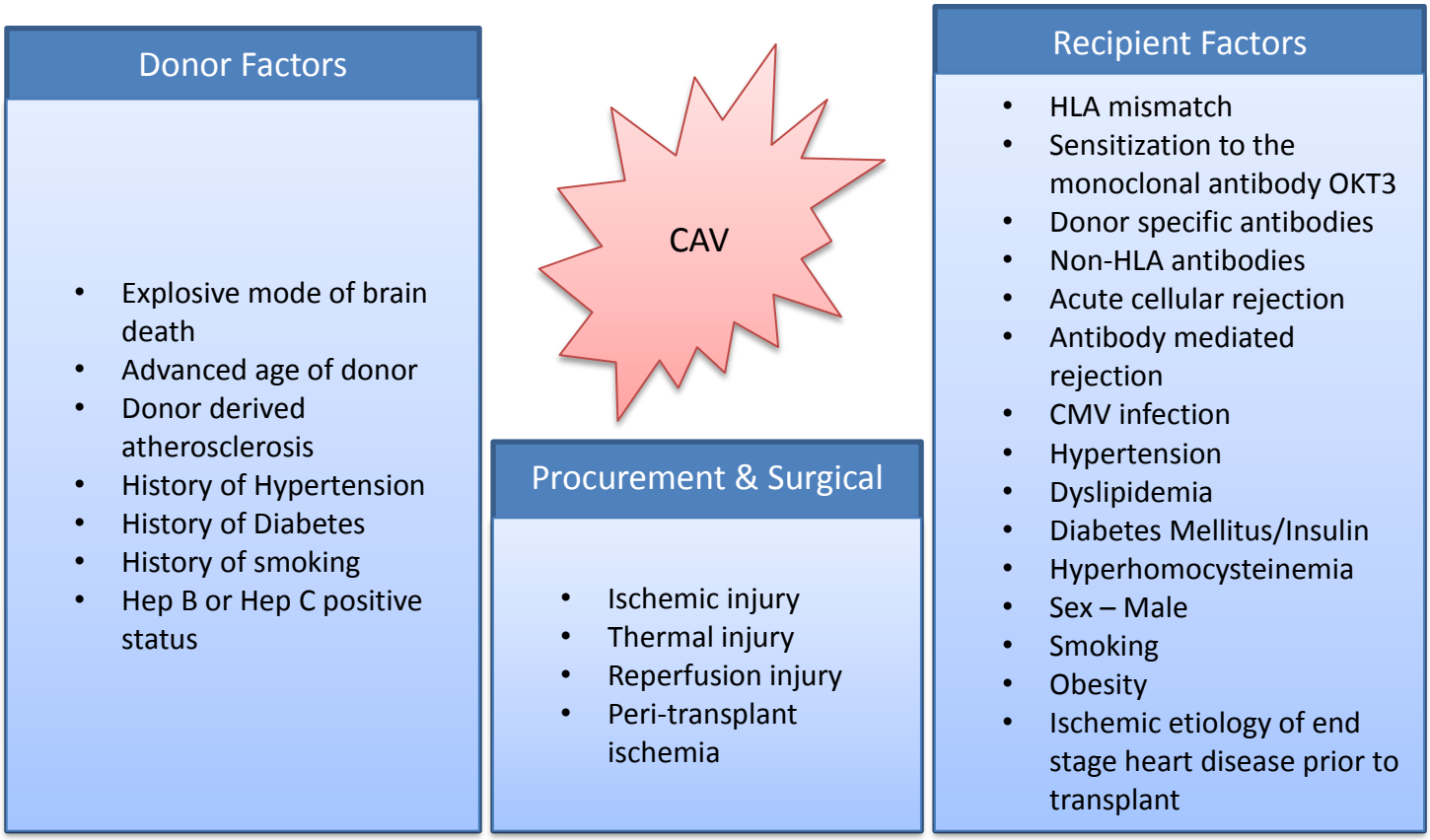
Antibody mediated rejection (AMR) or vascular rejection is associated with anti HLA and anti-endothelial antibody formation and has been linked to pathogenesis of CAV [6, 62-64]. Anti HLA antibodies can exert effects on allograft through complement dependent and independent pathways. High levels of circulating anti-HLA antibodies are associated with poor intermediate and long term survival. Presence of anti-endothelial antibodies is a strong determinant of CAV progression [6, 58, 62-68]. Presence of non-HLA antibodies against cardiac myosin and vimentin has also been associated with pathogenesis of CAV. The role of MHC-class-1-chain-related-A (MICA) antibodies in pathogenesis of CAV is imperfectly understood. However, increase in MICA expression is noted on the graft endothelial cells in patients with CAV [58].

Damaged endothelial surface can instigate platelet adhesion and aggregation and may serve as a nidus for thrombus formation. Platelets are integral players of inflammation and have been shown to regulate vascular permeability, leukocyte infiltration, hemostasis and thrombosis [67, 69]. Simpler et al, noted attenuation of circulating endothelial progenitor cells (EPCs) and increased number of endothelial cells derived from recipient's extracardiac progenitor cells in the coronary vasculature of the transplant recipients. Recipient derived extracardiac progenitor cells engage in endothelial cell repair and are capable of regenerating endothelium of the graft vessel leading to chimerism. Endothelium of allograft vasculature demonstrates a high degree of chimerism and this may contribute to the progression of CAV [70, 71]. Although immunologic mechanisms play a central role in pathogenesis of CAV, vasculopathy seen in cardiac allograft is a result of cumulative vascular injury induced by immune dependent and independent insults. Non-immunologic mechanisms that underlie the pathogenesis of CAV may become self-sustaining later in the disease process and could carry out the progression independently.

Risk Factors of CAV

Several risk factors have been implicated in the development of CAV. They are broadly categorized into immunologic risk factors and non-immunologic risk factors related to donor and recipient. Non-immunologic risk factors are primarily metabolic or otherwise described as traditional risk factors that play an important role in atherosclerotic vascular disease [72]. In addition, donor related factors such as donor mode of brain death, age of the donor and ischemic injury at the time of procurement play important roles in the development of CAV. **Table 3** summarizes the risk factors for CAV.

Table 3 Risk factors for CAV



Immunologic Factors

Immunologic risk factors have a major role in the genesis and progression of vasculopathic lesions of cardiac allograft. It had long been regarded as a form of chronic rejection until the concept of "response to injury" gained momentum [10]. MHC molecules are central targets of alloimmune response in solid organ transplant. The degree of (HLA) mismatch is a major factor in the development of CAV and correlates with its severity [73]. HLA-DR locus mismatch seems to carry more burden than HLA-A or HLA-B mismatch. Presence of DSA is a predisposing factor for the CAV development and has been reported to be an independent risk factor [74, 75]. Autoimmunity confers risk to the development of AMR and CAV. Antibodies against non-HLA antigens have gained attention in the pathogenesis of AMR and CAV [75-77]. Antibodies against cardiac self-antigens such as cardiac myosin and vimentin (cytoskeleton protein) are found to be associated with development of AMR and CAV and are considered to be independent risk factor for CAV [66-68]. Clinical studies have demonstrated a significant correlation between HLA mismatch, presence of DSA [44, 58] and increased anti-MICA levels to AMR and CAV in heart transplant recipients [66].

Cytomegalovirus (CMV) infection is another risk factor that is postulated to be associated with early CAV development. CMV infection is thought to mediate the effect by triggering the immune response rather than as a consequence of infection. Even a subclinical CMV infection or low-grade viremia can elicit immune response and could lead to rejection or CAV development [78-80]. CMV infection cause endothelial dysfunction by promoting local inflammation and increasing the

secretion of vascular adhesion molecules, altering the expression of MHC molecules on endothelial surface and impairing the nitric oxide production [79].

Both humoral and cellular rejections of transplanted heart contribute to the development of graft vasculopathy. The number and duration of acute rejection episodes is an independent risk factor associated with CAV development and progression. Although direct pathway of allorecognition plays a major role in the early rejection, chronic rejection is primarily driven by indirect pathway of allorecognition. Development of donor specific HLA antibodies has been associated with chronic rejection. Both acute cellular rejection (ACR) and AMR have been inferred in the pathogenesis of allograft vasculopathy [76-85]. Higher incidence of CAV is noted in heart transplant recipients with history of AMR than recipients without the history [76, 77, 84]. Heart transplant recipients who have experienced AMR are reported to have higher incidence of CAV [76, 77, 84]. In addition, AMR is associated with early onset of CAV. Number and severity of AMR episodes have been shown to have direct correlation with increased cardiovascular mortality.

Nonimmunologic Risk Factors

Various non-immunologic risk factors contribute to the development of CAV in heart transplant recipients. Several of these non-immunologic risk factors are the same conventional risk factors that contribute to the pathogenesis of atherosclerotic lesions. Hyperlipidemia, hypertension, diabetes mellitus, metabolic syndrome, smoking, and obesity are some significant non-immunologic risk factors that predispose cardiac transplant recipients to CAV [2, 9, 10, 43, 50, 61, 72]. Although these risk factors are not specific for transplant, there is increased occurrence of these risk factors in recipients of solid organ transplant. Immunosuppressive agents used in the management of heart transplant patients are known to cause or worsen pre-existing metabolic disorders.

Dyslipidemia

Dyslipidemia is a frequently observed metabolic abnormality in heart transplant recipients and prevalence is reported to be 60-80% in this population [1]. Hyperlipidemia is a commonly associated clinical condition in patients with atherosclerotic heart disease and is associated with poor outcomes. Numerous studies have shown the impact of dyslipidemia in pathogenesis and progression of CAV [86-88]. Immunosuppressive agents that are used in routine post-transplant care are known to cause or worsen pre-existing lipid abnormalities. Elevated plasma levels of triglycerides (TGs), low density lipoprotein cholesterol (LDL-C) levels and low levels of high density lipoprotein (HDL) levels are the common lipid abnormalities seen in the heart transplant recipients [43, 50, 61, 72, 88, 89]. Lipid metabolism in heart transplant recipients is influenced by various factors including choice of immunosuppressive regimen, genetic predisposition, pre-existing lipid abnormalities, age of the transplant recipient, and presence of other co-morbidities such as diabetes mellitus, obesity, chronic kidney disease (CKD), and proteinuria [90]. Steroid administration after heart transplantation and ischemic heart disease prior to transplant are both significant factors associated with post-transplant lipid abnormalities. Commonly used immunosuppressive agents in the post-transplant care such as corticosteroids, calcineurin inhibitors (CNIs) [91], proliferating signal inhibitors (PSIs)/mammalian target of rapamycin (mTOR) inhibitors [92, 93] and antiproliferative agents may influence lipid metabolism in heart transplant recipients. Although several immunosuppressive agents are known to cause dyslipidemia, mTOR inhibitors

and PSIs are associated with profound adverse lipid profiles. Despite causing significant lipid abnormalities, PSI agents have been shown to reduce the progression of CAV.

Hyperlipidemia in heart transplant recipients is usually treated with a 3-hydroxy-3-methyl-glutarylCoA (HMG-CoA) reductase inhibitor (i.e. statin). Therapeutic targets of cholesterol levels are poorly defined in heart transplant population. Nonetheless, efficacy and therapeutic benefit of statins in heart transplant recipients is established unequivocally [94-100]. In addition to their lipid lowering effects, statins exert their potential beneficial effects by their pleiotropic effects [101]. There are no definitive guidelines to guide therapy in transplant population. American College of Cardiology and American Heart Association (ACC/AHA) guidelines for hyperlipidemia management are extrapolated to these patients. It is also essential to address the secondary causes of lipid abnormalities such as hypo or hyperthyroidism, chronic liver disease, CKD, nephritic syndrome and diabetes. When adjustments are made to immunosuppressive regimen, close monitoring of lipid profile is recommended.

Hypertension

Hypertension is a commonly seen clinical condition in cardiac transplant recipients with a prevalence of 71% of cardiac transplant recipients having hypertension within a year of transplant and 91% within 5 years of transplant [1]. Although there is high prevalence of hypertension in cardiac transplant recipients, less than 50% of the patients achieve target blood pressure goals. Post-transplant hypertension plays a significant role in the onset of angiographic CAV. Hypertension in cardiac transplant recipients is multifactorial and various mechanisms are implicated in the genesis of hypertension [102-107]. The pathogenesis of hypertension in heart transplant recipients is multifactorial and complex. The denervated status of cardiac allograft results in impaired regulation of Renin-Angiotensin-Aldosterone System (RAAS) [102]. Corticosteroids and CNIs are the cornerstone of immunosuppressive therapy in heart transplant recipients [108-110]. These immunosuppressive agents used in routine post cardiac transplant care have deleterious effects on blood pressure [104, 109-111]. Introduction of CNIs shifted the paradigm of solid organ transplant. Although there is improved survival and reduced burden of rejection with CNI use, increased incidence of post-transplant hypertension is observed since the introduction of CNI therapy [112]. CNIs are known to cause hypertension in post-transplant patients by inducing endothelial dysfunction and imbalance between vasodilator and vasoconstrictive substances. Salt sensitivity and sympathetic hypertone also contributes to post transplant hypertension [106-108]. Diagnosis of hypertension prior to the transplant and advanced age are also predictive of future development of hypertension.

Obtaining a comprehensive medical history including the review of co-existing medical conditions such as renal insufficiency, thyroid or other endocrine disorders, and review of medications including concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) or erythropoiesis stimulating agents (ESAs) is essential in the management of hypertension in heart transplant population. Hypertension after heart transplant is preferentially treated with calcium channel blockers and angiotensin converting enzyme inhibitors (ACEIs) [91, 105, 113-116]. ACEIs can potentially achieve fluid homeostasis in heart transplant recipients, especially those receiving CNIs [105, 113-115]. There are no defined guidelines for blood pressure management in heart transplant recipients. However, Kidney Disease Improving Global Outcome (KDIGO) guidelines

defined for renal transplant patients can be extrapolated to heart transplant recipients [117]. Abnormal diurnal variations of blood pressures are noted in heart transplant recipients. Ambulatory blood pressure monitoring is advocated to facilitate the diagnosis of hypertension in post cardiac transplant patients [118].

Diabetes Mellitus

Diabetes mellitus is one of the most frequent co-morbidities noted in cardiac transplant recipients. Diabetes is a well-known conventional risk factor for atherosclerotic vascular disease and is associated with poor cardiovascular outcome [119, 120]. Diabetes mellitus and insulin resistance are frequently encountered metabolic complications in recipients of heart transplantation [119]. Heart transplant recipients may have pre-existing diabetes mellitus or may develop new onset diabetes mellitus after the heart transplant (NODAT) [119, 121]. Approximately 23% of heart transplant recipients develop post-transplant diabetes within one year of heart transplantation [1]. Several risk factors are identified to be the predisposing elements for the development of NODAT [122-124]. They are delineated below:

a) Blood glucose of >5.6 mmol/liter prior to the transplant [122]
b) Family history of diabetes
c) Pre-transplant over weight [124]
d) Requirement for insulin on the second day of post-transplant [122, 123]
e) Administration of immunosuppressive agents (CNIs and Corticosteroids) [125]
f) Asymptomatic CMV infection [126]

Immunosuppressive agents vary significantly in their potential to cause diabetes or worsen pre-existing diabetes [121, 127]. Although both CNIs and corticosteroids are significantly diabetogenic, the greatest risk of NODAT development is associated with the use of steroids [128-130]. Tacrolimus has been reported to be more diabetogenic than cyclosporine [131].

Heart transplant recipients with diabetes showed comparable rates of long term survival when compared with patients without diabetes [130, 132-136]. There was no significant difference in the incidence of infection or CAV. Studies have demonstrated either no significant difference or slightly low incidence of rejection in transplant patients with diabetes when compared with non-diabetic transplant patients. Some studies have shown higher incidence of infection in diabetic cardiac transplant patients compared to nondiabetic patients [129]. Discrepancies in the results of these studies are attributed to the limitations including defining criteria for the diagnosis of diabetes, therapeutic regimen used for the management of diabetes, target glycemic control and presence of any associated micro or macrovascular complications of diabetes [131, 137, 138]. Further studies are required to define the therapeutic targets and impact of glycemic control on development and prognosis of CAV.

Other Non-Immunologic Risk Factors

There are other non-immunologic risk factors that are known to contribute to the development if CAV. CKD, obesity and smoking have demonstrated risk association with development of CAV [2, 9, 10, 43, 50, 61, 72, 138]. Smoking causes endothelial dysfunction and is an important risk factor in the pathogenesis of both CAV and traditional CAD. CKD is a known risk factor for the progression of atherosclerotic vascular disease [10, 139, 140]. There is a high prevalence of hypertension and other metabolic abnormalities in patients with renal dysfunction. CNIs affect the

glomerular filtration and are identified as nephrotoxic agents [131]. Ischemic etiology of end stage heart disease prior to transplantation has been associated with increased risk of CAV. Advanced age of recipient offers a lower risk association with future development of CAV.

Hyperhomocysteinemia [141-147] and high C-Reactive protein (CRP) [148-152] levels are few of the novel risk factors that have been reported to contribute to the pathogenesis of the CAV. High levels of homocysteine can reduce the endothelial nitric oxide production and cause endothelial dysfunction [144, 146]. Hyperhomocysteinemia is associated with adverse cardiovascular outcomes. Although high levels of homocysteine are associated with development of CAV, efficacy of homocysteine lowering therapy has not proven to be beneficial [147]. CRP is an inflammatory marker and is known to induce smooth muscle cell proliferation by upregulating smooth muscle cell angiotensin I receptors and migration of smooth cells [148-152]. There has been a strong association between cardiovascular events and plasma CRP levels. High plasma CRP levels are associated with poor cardiovascular outcomes both in general and cardiac transplant recipients. However, further studies are warranted to define if there is a causal relationship between CRP elevation and CAV.

Donor Factors

Several donor factors including donor older age, male sex, and donor history of tobacco use confers increased risk of CAV [72, 141, 153-155]. Mode of brain death, and ischemic, and thermal injury to cardiac allograft also play an important role in the development of CAV. Donor age is an independent predictor of development of CAV in the allograft recipient [153-155]. Analysis by McGriffin et al., revealed that hearts obtained from donors aged above 35 posed a future risk of CAV development [153]. Various studies have demonstrated conflicting results on the impact of native vessel atherosclerosis of the donor heart in the development of CAV [156-160]. Maximal intimal thickness greater than 0.5 millimeters at one month after transplant is a strong independent predictor of mortality at one year [157, 158, 160]. Hepatitis B and C seropositive status of the donor is noted to be associated with higher rates of CAV in the heart transplant recipients [161, 162].

Mode of Brain Death

Cause and mechanism of brain death of the donor influence the cardiac function of the heart transplant recipients. Physiologic, metabolic, and neurohormonal alterations triggered by explosive nature of brain death adversely influence the cardiac hemodynamics and function. An explosive mode of brain death such as gunshot wound to the head or fatal intracranial hemorrhage leads to rapid progression of brain death. This promotes cytokine production, catecholamine surge, and evokes significant inflammatory response and endothelialitis [163-166]. Increased levels of circulating catecholamines stimulate the production of several pro-inflammatory cytokines, adhesion molecules, hormones, and inflammatory cells that are known to cause myocardial dysfunction. Explosive mode of brain death is considered to be an independent risk factor for both short and long term survival of cardiac allograft [163, 164]. Prudence is warranted in evaluating such donors; especially if additional risk factors are present. Nevertheless, there is significant scarcity of donor organs, therefore declining the organ based on mode of brain death may not be a viable solution. Further evidence is needed to see if hemodynamic management of brain dead donors could change this risk.

Ischemia-Reperfusion Injury

Ischemia and reperfusion injury causes denuding injury to endothelium and plays significant role in pathogenesis of CAV [167-172]. Graft ischemia and subsequent perfusion causes reperfusion injury. Reperfusion injury results in free radical production and these free radicals scavenge endothelium-derived nitric oxide (NO) and induce endothelial activation and dysfunction [167]. Solution used for cardioplegia at the time of procurement, quality of preservation and degree of thermal injury are some of the factors that influence the reperfusion injury. Cold ischemic time and total ischemic time influence the degree of the thermal injury encountered by the cardiac allograft. Perioperative ischemia at the time of transplant is associated with endothelial injury and stimulates matrix metalloproteinase production [169, 172]. Activation of matrix metalloproteinase system is associated with increased fibrosis and myocardial remodeling.

Conclusions

Long-term graft function and long-term success of cardiac transplantation is limited by CAV. Although significant progress has been made in the understanding of donor and recipient physiology, operative technique, transplant immunology and immunosuppressive pharmacology, CAV remains the Achilles heel of cardiac transplantation. Endothelial damage induced by various noxious stimuli followed by exaggerated repair response appears to be the inciting event in the pathogenesis of CAV. CAV is a multifactorial disease induced and propagated by ischemia-reperfusion injury, alloimmune responses to the allograft, de-novo autoimmunity to self-antigens, and classical risk factors. Repetitive denuding and non-denuding insults to endothelium leads to subendothelial cellular deposition, myointimal hyperplasia and vascular remodeling. Evolving understanding of various risk factors that influence endothelial cell modulation, smooth muscle cell proliferation and inflammation, may provide new insights into preventative strategies. Management of CAV is challenging, and therapeutic options are limited. Current strategies focus on aggressive modification of risk factors, institution of statins, adjustment of immunosuppressive regimen, and treatment of established vascular lesions. The future lies in developing the targeted approaches to prevent endothelial injury, early detection and development of immunomodulatory therapies to promote graft tolerance. There is an increased interest in developing and advancing organ preservation techniques, cytoprotective strategies of procured organs and perfusion technologies to reduce the ischemic time, thermal and reperfusion injury of the allograft.

Competing Interests

The authors have declared that no competing interests exist.

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