Cardiac Allograft Vasculopathy: The Achilles' Heel of Long-term Survival after Cardiac Transplantation

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Over the past 40 years, cardiac transplantation has evolved as the single best long-term option for eligible candidates with end-stage heart failure. Approximately 2000 transplants are performed annually in the United States, and with the institution of calcineurin-based immunotherapy, surveillance biopsies, and programmatic-based patient care, life expectancy at 1 and 12 years is 85% and 50%, respectively. Cardiac allograft vasculopathy (CAV) is the number one cause of death after the first year of transplantation. The incidence of CAV remains as high as 50% at 5 years, with life expectancy significantly abbreviated once it is recognized. Although current immunotherapy has reduced the likelihood of cellular rejection, it has not impacted CAV substantially. Better treatment of established risk factors and the advent of newer antiproliferative immunotherapy may hold promise in treating CAV. However, future therapies must address the multitude of mechanisms underlying CAV. This manuscript reviews the pathophysiology, clinical manifestations, screening, and diagnostic strategies for cardiac allograft vasculopathy while emphasizing current treatment paradigms designed to stave off or retard the progression of CAV.

Introduction

Experimental cardiac transplantation began as early as 1907 and the first successful human transplantation was performed in 1967. However, the lack of appropriate immunosuppression and techniques to monitor rejection in association with the high rates of fatal infections dampened the initial enthusiasm for cardiac transplantation as a realistic option for end-stage heart disease. The application of cyclosporine-based immunotherapy and the development of transvenous endomyocardial biopsy techniques in the 1980s finally allowed the number of transplant recipients surviving beyond the initial 12 months to exceed those who died within the same time frame [1]. The success of standardized triple-regimen immunotherapy, advent of safe endomyocardial biopsy techniques, and institution of key programmatic organizations, including the United Network of Organ Sharing (UNOS), have allowed for continued growth in human cardiac transplantation throughout the 1990s. Statistics on transplanted individuals from the most recent UNOS national data reveal a 1-year national survival average of 86.1% [2], and in select clinical investigations documented survival exceeds 90% at 1 year [3].

Currently, 2000 transplants are performed annually in the United States, a number that has not changed appreciably over the past 10 years, primarily due to donor availability. Voluntary cumulative data for nearly 70,000 patients submitted to the International Society of Heart and Lung Transplantation (ISHLT) since 1982 indicate that 50% of transplant recipients will be alive in 12 years [4••], and a significant proportion of them enjoy an excellent quality of life, with 40% returning to work.

Balancing the success of cardiac transplantation for end-stage heart failure is the long-term morbidity and mortality associated with this therapy. Recent data indicate that within 8 years of cardiac transplantation, 97.7% patients will have hypertension, 35.6% will have renal dysfunction, 91.2% will have hyperlipidemia, 36.5% will have diabetes, and 26.2% will have a malignancy [4••]. Cardiac allograft vasculopathy (CAV) will develop in 45.7% of transplant recipients at 8 years. Statistics indicate the major obstacle for long-term survival after the first year of cardiac transplantation is CAV. Primary CAV accounts for 18% of all deaths and contributes to roughly half of all graft dysfunction leading to death (14.5%) at 5 years. Despite improvements in immunotherapy, the incidence of angiographically detected CAV has not changed appreciably over the past two decades. In fact, the latest data from the ISHLT registry reveal only a slight decrease in CAV at 1 year when comparing the period of 1994 to 1999 (8.7%) with 2000 to 2003 (7.0%), perhaps owing to an increase in the use of mycophenolate mofetil and rapamycin over this time period. Therefore, future advancements in the field of cardiac transplantation must address the concerns of CAV.

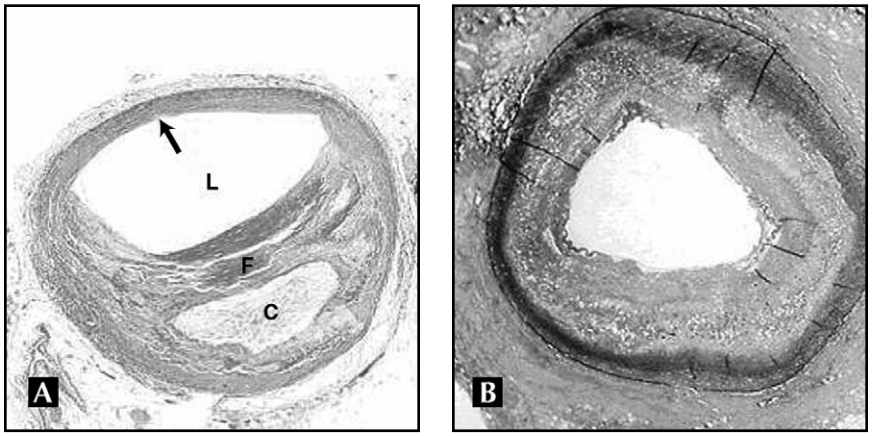

Figure 1. A, Native vessel atherosclerosis panel. **B,** Transplant arteriopathy. C—lipid core; F—fibrous cap; L—lumen.

This manuscript reviews the pathophysiology, clinical manifestations, screening, and diagnostic strategies for CAV while emphasizing current treatment paradigms designed to stave off or retard the progression of this disease. It is not, however, intended to provide an exhaustive reference toward the understanding of CAV, and where appropriate the authors will direct readers to relevant sources.

Epidemiology

Cardiac allograft vasculopathy was first described in 1970 [5] as a diffuse, obliterative, accelerated form of arteriosclerosis. It is the third leading cause of death, after infection and rejection, in the first year after transplantation and, together with graft failure, is the leading cause of death beyond the first year. Angiographic evidence of arteriopathy ranges from 8% to 11% at 1 year, 19% to 27% at 2 years, 26% to 44% at 3 years, 42% to 50% at 5 years, and up to 80% at 8 years [6–9]. However, given the diffuse subintimal nature of the inflammatory process, angiography is inherently insensitive in detecting arteriopathy. Intimal thickening, which is a prognostic marker for the development of CAV, is detectable by intravascular ultrasound (IVUS) in 75% of patients at 1 year [10], and by 5 years all grafts have evidence of graft vasculopathy [11].

Once vasculopathy develops, long-term survival is reduced significantly [12]. Patients with angiographic evidence of arteriopathy are 3.5 times more likely to suffer a cardiac event than those without disease [13]. In addition, arteriopathy that develops within 2 years is associated with more rapid progression to ischemic events than CAV after 2 years [14].

Pathology

Cardiac allograft vasculopathy is characterized by the deposition of neointima in association with vascular smooth muscle cells, which progressively obstructs the affected vessel lumen. This process is not unique to cardiac allograft coronary vessels but is ubiquitous to all solid organ transplantation vascular beds. The pathologic findings of vasculopathy are, however, restricted to the allograft (ie, the changes of arteriopathy begin distal to the anastomosis).

In contrast to the focal, asymmetric, frequently calcified pattern of native vessel arteriosclerosis, CAV is diffuse, involving the entire circumference and length of the vessel, including small intramyocardial branches (Fig. 1). CAV is further distinguished microscopically as having intense cellular proliferation, composed mainly of smooth muscle and inflammatory infiltrate (monocytes and lymphocytes). A descriptive study documented the presence of smooth muscle cells, lipid-laden macrophages, and lymphocytes adjacent to donor endothelium from six patients with an ante-mortem diagnosis of CAV. Specific populations of lymphocytes co-localized with CAV lesions include recipient CD4+ T cells; thus invoking a major histocompatibility complex (MHC) II antigen recognition and processing physiology. Furthermore, populations of macrophages and CD8+ T cells have also been co-localized with MHC II–secreting endothelial cells, whereas recipient B-cells are rare. Seminal work by Gao et al. [14] has characterized CAV and identified and correlated early and late microscopic lesions with specific angiographic patterns.

Risk Factors

Conflicting data exist regarding risk factors for the development of CAV, likely representing variations among study populations, immunosuppressant used, and inadequate sample size. However, a variety of large datasets, such as the ISHLT registry, have helped to identify recurring risk factors that are associated with CAV. These are broadly divided into three categories: 1) donor specific, 2) recipient specific, and 3) donor-recipient interaction, with the latter being immune mediated.

Identified donor factors for the development of CAV within 3 years of transplantation are hypertension, male sex, older age, and prior blood transfusion. Among those who did not have arteriopathy at 1 year after transplant, donor risk factors for the development of arteriopathy at 7 years were diabetes, death from cerebrovascular events, older age, and male sex.

Recipient factors identified for the development of arteriopathy at 3 years are male sex, younger age, and higher body mass index. Among individuals without arteriopathy at 1 year, recipient risk factors for the development of arte-

riopathy at 7 years were transplantation for coronary artery disease, younger age, and higher body mass index.

Donor-recipient factors for CAV include episodes of high-grade rejection during the first year after transplantation and HLA-DR mismatches [4••]. Positive recipient cytomegalovirus (CMV) serologic status [7] and antecedent CMV infections appear to increase the risk of early-onset transplant arteriopathy [2] and may be mediated via an immune mechanism rather than a direct consequence of the infective organism.

Many of the risk factors highlighted in the preceding text implicate the role of traditional risk factors in the development of arteriopathy. Hypertension requiring treatment occurs in most cardiac transplant recipients by 6 months post-transplant, and new-onset diabetes after transplantation occurs in up to 32% of transplant recipients [15]. Elevation of low-density lipoproteins (LDL) to greater than 130 mg/dL is observed in 60% to 80% of heart transplant recipients [16]. Both cyclosporine and prednisone, which are mainstays in current immunosuppression, contribute to the dysmetabolic state present in heart transplant recipients.

The role of transmitted native vessel atherosclerosis is less certain. However, data exist whereby similar numbers of patients with and without donor lesions developed de novo CAV [17]. Similarly, studies utilizing serial IVUS found donor lesions did not significantly change after transplantation [18], whereas de novo intimal thickening progressing to obstruction occurred over the 3 years of follow-up. The authors do not believe that native arteriosclerosis plays a significant role in the development of CAV.

Reperfusion Injury

Allografts by virtue of ischemia during procurement, transport, and implantation undergo anaerobic metabolism. The resultant depletion of ATP causes energy-dependent ion channels and pumps to dysfunction and leads to uncontrolled sodium and calcium entry into both cardiomyocytes and endothelial cells. Furthermore, reperfusion results in the generation of free radicals that foster the expression of inflammatory adhesion molecules and subsequent leukocyte recruitment. The role of free radical injury is supported by studies indicating efficacy of antioxidant therapy in preventing progression of transplant arteriopathy [19] and in murine models with upregulation of superoxide dismutase or treatment with mimetic agents [20,21]. Reperfusion injury increases expression of endothelin 1, which is associated with post-transplant ischemic fibrosis and subsequent development of arteriopathy [22]. Clearly, more research is needed in organ preservation techniques, possibly targeting specific cellular processes to minimize reperfusion injury.

Prothrombotic State

Allograft vasculopathy is characterized by the presence of a prothrombotic microvasculature [23••]. Fibrin deposition, which is absent in normal hearts, is present in approximately 50% of allografts when transplanted or within the first weeks after transplantation. Seminal work by Labarrere et al. [23••] has revealed that myocardial fibrin deposition identified from routine endomyocardial biopsies within the first 3 months after transplantation is associated with persistent elevation in cardiac troponin (a marker of myocardial injury). Furthermore, when present and sustained in the first 3 months, fibrin deposition predicts a more aggressive form of cardiac allograft vasculopathy [24]. Depletion of tissue plasminogen activator, over-expression of tissue plasminogen activator inhibitor, and loss of vascular antithrombin all play a role in fibrin deposition [25,26]. The prothrombotic and antifibrinolytic milieu created early after transplantation facilitates the generation of thrombin and fibrin within the allograft microvasculature. Steps occurring subsequent to these early thombotic events may bear similarities to native vessel atherosclerosis (ie, thrombosis leading to reperfusion leading to hyperplasia leading to remodeling).

Remodeling

There are two mechanistically inter-related processes that occur in CAV that contribute to the degree of luminal compromise (positive and negative remodeling). Although traditionally intimal thickening (negative remodeling) has been the focus of research, recent observations indicate that impaired positive remodeling also contributes to net lumen loss. Select studies have shown that negative remodeling occurs early after transplantation [27], whereas others purport that CAV is associated with impaired late positive remodeling [28–30]. Arteriopathy may, therefore, represent an overactive intimal hyperplasia (negative remodeling) in association with an under-compensation of positive remodeling. In a 5-year IVUS-based study of subjects followed after primary cardiac transplantation, Tsutsui et al. [30] documented that early positive remodeling offsets the process of neointimal hyperplasia (negative remodeling). However, after the first year negative remodeling predominates, resulting in lumen narrowing. The specific signals governing the timing and degree of negative or positive remodeling are presently under investigation. However, distinct from native vessel atherosclerosis (in which the stimulus for negative remodeling appears to be plaque rupture, inflammation and repair), CAV does not require plaque presence at all. One postulate set forth includes that the same signals perpetuating intimal hyperplasia initiate a cascade of pathways that adversely affect the ability of the coronary vessel to positively remodel.

Immunogenic Activation

The number of HLA mismatches and the duration, severity, and number of high-grade rejection (< 3A) episodes correlate with the development of cardiac allograft vasculopathy [4••,18,31••,32••,33,34]. Therapies that reduce the incidence of rejection appear to reduce the occurrence of CAV as well, suggesting an association between the two phenomena.

Inflammatory cells and a variety of cytokines and adhesion molecules are localized to the microvasculature and expressed peripherally among patients with CAV. CD4-positive and CD8-positive T lymphocytes, natural killer cells, and antigen-presenting elements, including macrophages, dendritic cells, and endothelial cells expressing HLA-DR, are represented within CAV lesions. The proinflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, and the chemokine macrophage chemoattractant protein-1 (MCP-1) are elevated in transplant patients with arteriopathy when compared with transplant recipients without CAV [35,36]. Furthermore, increased serum soluble intercellular adhesion molecule 1 (ICAM-1) levels, a critical cytokine for leukocyte adhesion and translocation across an intact endothelium, are correlated with severity of arteriopathy [37].

Most recently, humoral immunity has been associated with CAV. Specifically, survival is not only reduced in transplant recipients who develop anti-HLA class II antibodies [38•,39], but the incidence of arteriopathy is greatest among patients who manifest humoral rejection [40,41••]. It is known that antibodies against endothelial cell surface molecules, such as MHC class I and ICAM-1, activate vascular endothelium [42] and antiendothelial antibodies, which target vimentin [43,44], resulting in vascular antithrombin depletion. The net effect of these processes is biochemical evidence for myocardial damage and CAV [45]. Therefore, mechanisms targeting the production of select cytokines, their cellular receptors, and/or anti-HLA class II antibodies would be postulated to ameliorate the initial steps in the development of CAV. However, we do not believe that the redundancy intrinsic to the immune system easily lends itself to a single target approach.

Viral Infections

A seminal paper by Grattan et al. [46] documented the long-term outcome of 210 CMV-free cardiac allograft recipients compared with 91 patients who had at least one episode of active CMV infection; both graft loss and death caused by transplant arteriopathy were more common in those who were CMV positive. Studies have since shown that CMV can infect native vascular cells, as well as host-derived components of neointimal lesions, and subsequently alter expression of MHC, adhesion molecules, cytokines, and growth factors so as to evade detection [33]. Select studies have found that allografts with more CMV infections have impaired compensatory remodeling [47•]. Pathologically, CMV viral inclusion bodies are seldom demonstrated CAV lesions. On the other hand, endothelial dysfunction mediated via nitric oxide pathways appears to worsen among seronegative recipients of CMV-positive donors [48,49]. Interestingly, adenovirus particles or the serologic indicators of their infection and bacterial lipopolysaccharide have been demonstrated to be associated with CAV [50]. The accumulation of data implies the systemic consequences of viral infections, rather than the specific infectious organism, has greater implications for CAV.

Renin-angiotensin System

Authorities argue that the renin-angiotensin system (RAS) also participates in the development of allograft vasculopathy [51]. Angiotensin II, the primary effector molecule, is known to induce intimal proliferation and fibrosis (via production of a number of growth factors), increase production of plasminogen activator inhibitor-1, enhance oxidative stress, increase lipid loading into foam cells, and increase expression of redox-sensitive gene products. Animal models demonstrate inhibitors of the RAS have beneficial implications on CAV by preventing myointimal proliferation, improving endothelial dysfunction, and reducing vascular inflammation in animal models [52–55]. The authors advocate utilization of the inhibitors of the RAS system (either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) for the treatment of post-transplant hypertension in the appropriate patient.

Unifying Process

Events leading to the development of CAV are demonstrated as early as graft procurement; the inflammatory response is in response to immune or non–immune-mediated injury [56]. Once the allograft is transplanted, an immediate elevation in plasma levels of high-sensitivity C-reactive protein (CRP) and heat shock protein is observed and is predictive for the development of angiographic-evident CAV and ischemic events leading to graft failure [57,58]. Despite the strong association of hsCRP and heat shock protein with CAV, a direct causal role is uncertain. Among patients with established CAV, CRP is the serum and localies to CAV lesions to induce endothelial dysfunction [59]. However, the authors believe that these observations are a marker of the disease progression rather than a causative factor.

Irrespective of the cause of inflammation, endothelial injury and dysfunction precedes the development of arterial lesions evident from both animal and human studies [60,61]. Segments that progress to CAV first show decrements in endothelial-mediated relaxation compared with controls [62•]. Furthermore, coronary segments with endothelial dysfunction appear to have a greater increase in intimal and overall luminal maximal thickness (ie, luminal narrowing) [63]. The appearance of markers of endothelial activation, namely ICAM-1, consistently predicts the development, progression, and extent of disease [64]. Endothelial dysfunction resulting from impairment of the nitric oxide synthase pathway in cardiac allografts perpetuates vascular inflammation resulting in CAV. Furthermore, segments demonstrating impaired response to acetylcholine have a higher representation of mRNA for toll-like receptors [65].

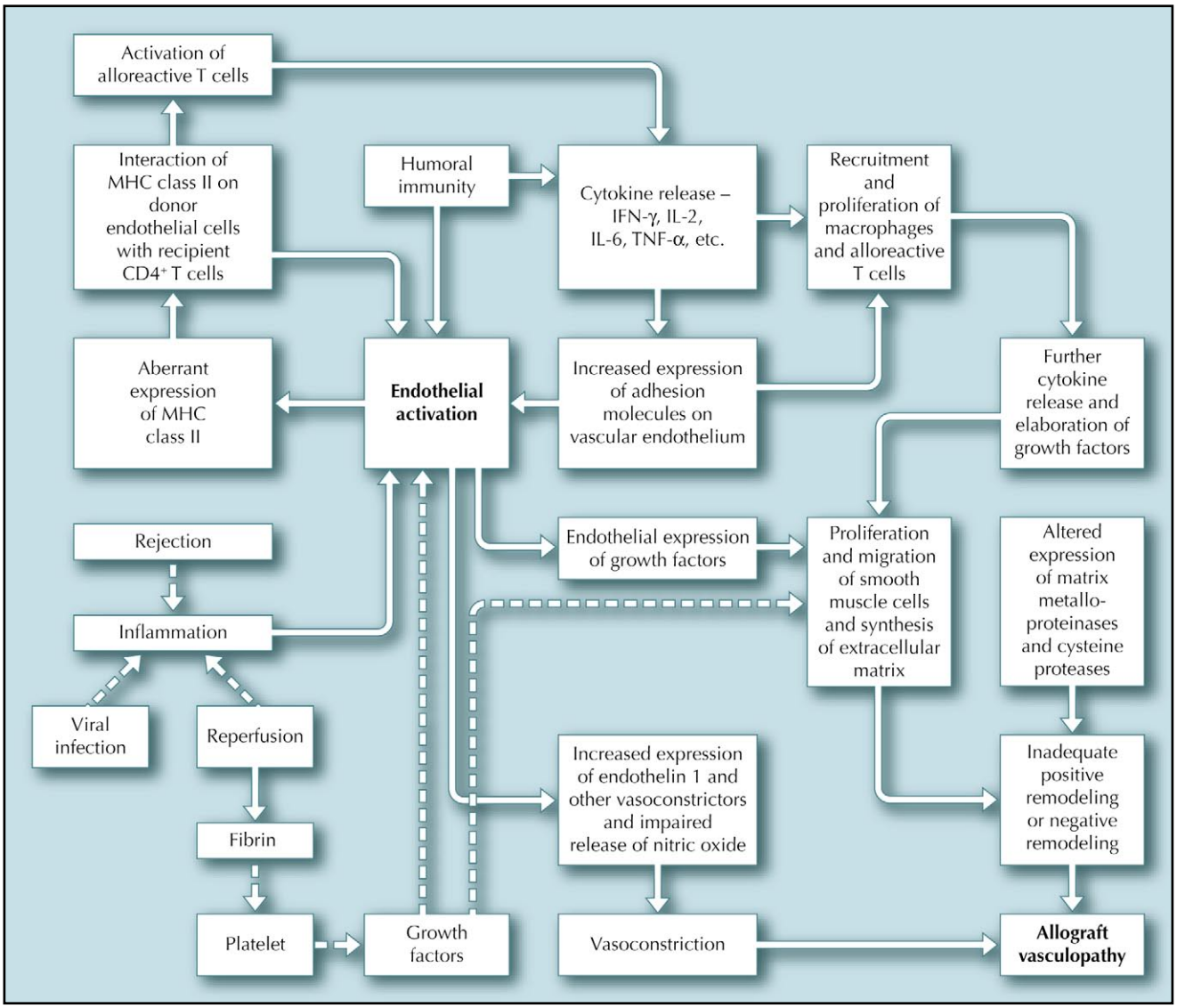

Figure 2. Model for the pathogenesis of arteriopathy. *Dotted lines* are hypothetical considerations. Growth factors include vascular endothelial growth factor and platelet-derived growth factor. IFN—interferon; IL—interleukin; MHC—major histocompatibility class; TNF—tumor necrosis factor.

These same receptors bind oxidized low-density lipoprotein, heat shock proteins, bacterial toxin, and particles and lead to activation of downstream pathways progressing to CAV.

The endothelium serves a dual role, both as the target of immune response and the interface for antigen presentation. In particular, CD4-positive T cells directly, and indirectly through antigen presenting cells, recognize allo-antigens on endothelium. These highly activated lymphocytes actively release proinflammatory cytokines including IL-1, IL-2, TNF-α, and interferon-γ (IFN-γ), which upregulate the expression of ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1), facilitating lymphocyte migration across the endothelium. Destruction of endothelium leads to expression of donor-specific MHC class II epitopes, further enhancing activation of CD4-positive T cells. The presence and activation of these cellular and chemical elements is associated with the development of earlier and more severe CAV. This same pattern of activation may also occur as a consequence of classical immune injury (ie, cellular rejection), viral infections (ie, CMV), or simply by ischemia reperfusion injury at the time of transplantation. The positive feedback loop created by immune injury, chemokines, and antigen-specific cellular elements results in the elaboration of growth factors and specific tissue matrix metalloproteinases. The final stage in this process is the migration of smooth muscle cells and fibroblasts that secrete basement membrane–causing neointimal hyperplasia. Figures 2 and 3 represent a summary of the mechanisms described.

Experimental models support the pivotal role of the interaction between CD4 T cells and MHC class II epitopes in the development of arteriopathy [66]. Animal models clearly demonstrate that the inhibition of key regulatory elements, namely ICAM-1, VCAM-1, leukocyte function-associated antigen-1, and IFN-γ, via monoclonal

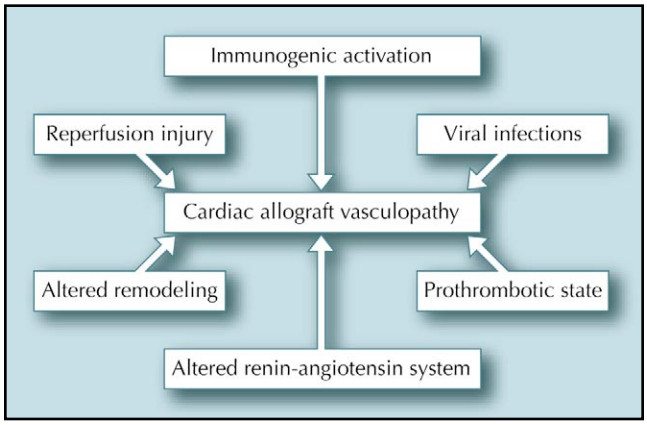

Figure 3. Individual components implicated in the pathogenesis of transplant arteriopathy.

antibodies retards the development of arteriopathy. Blockade of platelet-derived growth factor and vascular endothelial growth factor activity through stimulation of specific tyrosine kinases inhibits the development of arteriopathy. Furthermore, the genetic knockout models resulting in the absence of either ICAM-1, MHC II, IFN-γ, Stat4 (a signal transducer and activator of transcription that regulates TH1 differentiation), and chemokines CCR-1 and CCR-5 in rodent models are associated with attenuation in neointima formation [67–72]. Finally, IL-10, a regulator for the development of specific TH2 cell type, appears to protect against the development of arteriopathy [73]. Table 1 summarizes a number of experimental animal models that currently shape our understanding of arteriopathy.

Diagnosis and Screening

Due to the denervated state of the post-transplant heart, the majority of CAV presents insidiously. In a series of 54 patients with arteriopathy, over 50% had no symptoms [74]. Patients present atypically with occult enzymatic myocardial infarction or congestive heart failure. These facts provide the impetus for annual surveillance angiography at most transplant centers. However, angiography is limited by the fact that CAV is diffuse, circumferential, and involves the entire coronary vascular bed. Therefore, the disease process lacks a discrete stenotic segment that one may compare with the rest of the vessel.

Intravascular ultrasound is more sensitive at detecting arteriopathy. In a study of 29 patients in whom annual angiograms, IVUS, and angioscopy were performed, CAV was detected by IVUS in 76% versus 10% by conventional arteriogram [75]. Concordant data from a cohort of 60 subjects revealed intimal thickening was apparent in all patients beyond 1 year, with 63% having moderate to severe thickening [1] compared with a detection rate of only 35% by conventional angiogram [76]. Furthermore, IVUS-detected mean intimal thickness of greater than 0.3 mm at 1 year is associated with a 4-year actuarial survival of 73% versus 96% among those with less than 0.3 mm of intimal thickening [77]. An increase in intimal thickness of at least 0.5 mm in the first year after transplantation is a reliable indicator of both the development of CAV and 5-year mortality rates [78].

Cardiac MRI and Cardiac CT

Emerging technologies such as cardiac MRI may be used to obtain coronary anatomy or assess perfusion reserve. A pilot study using magnetic resonance angiography in 16 heart transplant patients revealed overall sensitivity for detection of significant disease was 56%, specificity was 82%, and negative predicative value was 88% [79]. Using perfusion reserve, transplant arteriopathy was excluded by a reserve ratio greater than 2.3 with 100% sensitivity, 85% specificity, and 100% negative predictive value [80] after excluding patients with hypertrophy and prior rejection.

Traditional CT relies on detection of calcification, which correlates with presence of disease in native vessel artherosclerosis. Calcification in CAV is less common; thus data on the use of electron beam computed tomography is variable, and failure to detect some patients with severe arteriopathy has been observed [81–83]. At the time of this manuscript, limited data were available on the role of CT angiography [84].

Dobutamine Echocardiography

Regional motion abnormalities are more common in patients with moderate to severe intimal hyperplasia, thus allowing dobutamine stress echocardiography (DSE) to effectively diagnose established CAV [85]. Compared with angiograms and IVUS, stress echocardiography has a sensitivity of 64% to 72%, specificity of 88% to 91%, and negative predictive value of 62% to 85% for detection of arteriopathy [86,87•]. Most importantly, however, a normal stress echocardiogram predicts an uneventful course with the same sensitivity and negative predictive as IVUS (both 100%) [86].

At the Methodist Hospital in Houston, we have adopted an approach utilizing the high sensitivity of dobutamine echocardiography as a screen for the detection of cardiac allograft vasculopathy. Routine annual angiography is not performed at our institution between years 1 to 5 after transplant; rather patients are subjected to annual dobutamine stress echocardiograms. If results indicate ischemia or resting wall motion abnormalities, further diagnostic testing is performed. Thereafter, because of the high likelihood of CAV, annual angiography is routinely performed as a diagnostic and, if needed, a therapeutic modality. A review of over 550 transplants at our program, with 150 patients screened using DSE, has validated this approach as safe with equal outcomes as compared with annual catheterization. We do not know whether screening for cardiac allograft

Table 1. Representative experimental models delineating pathogenesis of arteriopathy

Pathophysiologic element	Mechanism	Evidence
Ischemia reperfusion injury and resultant endothelial activation		
Decreased SOD expression	Increased free radical generation	Reduced GCAD indices in murine models with induction of SOD-1 expression [20] or introduction of mimetic m40401 [21]
Altered pkC expression	Activation of endothelium with production of inflammatory cytokines and adhesion molecules	Improved GCAD indices in a murine model with Γ-pkC activation and Δ-pkC inhibition [74]
Endothelin	Increased endothelin post-transplant results in endothelial dysfunction	Reduced endothelial dysfunction with intermittent perfusion of a porcine model with endothelin receptor blocker [102]
Decreased cAMP	Increased leukocyte adhesivity, increased superoxide and decreased nitric oxide levels	cAMP infusion reduced severity of GCAD at 60 days [103]
Decreased nitric oxide expression	Increased free radical generation and reduced nitric oxide levels	Endothelial NOS gene transfer suppressed VCAM-1 and ICAM-1 expression in a rabbit model [104]
Post-transplant pro-thrombotic state		
tPA depletion	Depletion of tPA causes a prothrombotic state post-transplant	tPA gene transfer significantly decreased intimal hyperplasia in grafts [105]
Immune mediated endothelial activation		
ICAM-1, LFA-1 and VCAM-1 expression	Increased migration of lymphocytes and macrophages	Infusion of antibodies inhibited development of GCAD [106] and increased long-term graft acceptance [107]
T cell activation and mononuclear cellular infiltration		
IFN-Γ	Activation of lymphocytes and macrophages	Monoclonal antibodies inhibited GCAD in murine models [108,109]
CD-154	CD-40 mediated T-cell activation	Monoclonal antibodies inhibited GCAD in murine models [108,109]
MCP-1	Recruitment of mononuclear cells that precede GCAD	Anti–MCP-1 gene therapy attenuated GCAD indices in a murine model [110]
Altered balance between CD4 T-cell subsets	Increased expression of IFN-Γ and decreased TGF-β and IL-10 activity is noted in arteriopathy	Hepatocyte growth factor, which reversed this imbalance, inhibited development of arteriopathy in a murine model [111]
Polymorphonuclear cellular infiltration		
CXCR-2 [CCR2]	PMN infiltration precedes subsequent T-cell infiltration	In a murine model, blockade prolonged allograft survival [112]
Growth Factors with resultant neointimal formation		
VEGF and PDGF expression	Neointimal proliferation with luminal thickening and recruitment of cellular infiltrate through proinflammatory effects	Tyrosine kinase inhibitors PTK787 and imatinib retarded subsequent arteriopathy in a rat model [113] Angiopoetin-1 gene transfer decreased development of allograft arteriosclerosis [114]
cdk 2	cdk-2 mediates smooth muscle cell proliferation	Anti-sense cdk-2 oligodeoxynucleotide inhibited neointimal formation in murine allografts [115]
E2F	Transcription factor E2F is involved in the coordinated transcription of cell-cycle regulatory genes	Double-stranded DNA with specific affinity for E2F prevented neointimal thickening in a murine model [116]
Inhibition of vascular remodelling		
MMP-2	MMP-2 is a principal MMP throughout the progression of the vascular remodeling in CAV	Anti–MMP-2 ribozyme decreased luminal occlusion in a murine model [117]

cAMP—cyclic AMP; CAV—cardiac allograft vasculopathy; GCAD—graft coronary artery disease; ICAM—intercellular adhesion molecule; IFN—interferon; LFA—lymphocytic function-associated antigen; MCP—macrophage chemoattractant protein; MMP—matrix metalloproteinase; NOS—nitric oxide synthase; PDGF—platelet-derived growth factor; pkC—protein kinase C; PMN—polymorphonuclear neutrophilic; SOD—superoxide dismutase; TGF—transforming growth factor; tPA—tissue plasminogen activator; VCAM—vascular cell adhesion molecule; VEGF—vascular endothelial growth factor.

vasculopathy with DSE can be extended beyond 5 years. Anecdotally, we are using DSE to screen for CAV in select patients with relative contraindications for angiography (eg, elevated creatinine, poor vascular access, dye allergy).

Treatment

Initial concern with the use of statins among patients after solid organ transplantation stemmed from data regarding the higher rates of rhabdomyolysis. The inhibition of the cytochrome P-450 (CYP450 3A) pathway by cyclosporine results in greater bioavailability of most statin preparations. However, numerous series demonstrating the incidence of rhabdomyolysis were based solely on higher-dose statin regimens. The cumulative incidence of rhabdomyolysis with lovastatin and simvastatin has been reported as 1.1% and 1.4%, respectively [16].

Statins do not treat CAV. Rather, two separate randomized, controlled clinical trials have indicated that when instituted early after cardiac transplantation, statin therapy delays the development of CAV. A number of other intriguing observations regarding the effects of statin therapy after heart transplantation are worth mentioning. Kobashigawa et al. [88] documented not only a lower incidence of hemodynamically significant rejection at 12 months, but an overall improvement in survival with pravastatin therapy among 97 primary cardiac transplant recipients. Furthermore, angiographic- and necropsy-proven arteriopathy was less evident in the pravastatin arm, and IVUS performed in a subset of patients showed that maximal intimal thickness was also significantly less compared with placebo [88]. Of note, there were no reported cases of rhabdomyolysis despite treatment maximized to 40 mg/d of pravastatin in all patients. Not surprisingly, LDL levels were significantly lower in the pravastatin arm; however, the benefit was achieved regardless of baseline LDL, suggesting a possible pleiotropic effect of pravastatin therapy [88]. Concordant data from Wenke et al. [89] documented that simvastatin as compared with placebo significantly improved survival among 72 primary cardiac transplant recipients at 48 months (88.6% vs 70.3%) and is associated with a reduction in the incidence of arteriopathy (16.6% vs 42.3% for simvastatin vs placebo, respectively). An intracoronary ultrasound substudy from this same cohort also revealed less intimal thickening in the intervention group [89]. In 2003, the same authors published 8-year follow-up data and found that although lipid levels were comparable, the incidence of arteriopathy (24.4% vs 54.7%) and overall survival (88.6% vs 59.5%) favored simvastatin therapy [90]. Again, no cases of rhabdomyolysis were observed over the 8-year period.

Two separate clinical trials exist comparing simvastatin with pravastatin. Results indicate lower total LDL levels with simvastatin therapy but a nonsignificant trend toward reduced mortality in the pravastatin arm [91,92], again underscoring the potential nonlipid effects of statin therapy. No data are currently available for differences that may exist in these two statins with regard to long-term therapy.

Cumulative data from over 1186 patients in the Heart Transplant Lipid Registry [93••] found a highly significant reduction in overall mortality and fatal rejection among the 79% of who were on statin therapy. No significant difference in the distribution of causes of death was noted.

Current data indicate that the lower doses of statins are safe and effective therapy, with daily doses of 10 mg for simvastatin, 20 mg for lovastatin, 40 mg for pravastatin, 10 mg for atorvastatin, and 40 mg for fluvastatin being generally regarded as upper limits on therapy with concomitant cyclosporine-based therapy.

Cytomegalovirus Prophylaxis

Data on CMV prophylaxis are derived from two clinical trials. One is a post hoc analysis of 131 cardiac transplant patients randomized to ganciclovir or placebo. At a mean of 4.7 years of follow-up, arteriopathy was present in 43% of the ganciclovir arm versus 60% in the placebo arm [94]. The other trial included 80 heart and heart-lung transplant recipients who were either CMV seropositive or were receiving grafts from seropositive donors [95]. Compared with matched historic control patients, intimal thickness was lower in patients receiving CMV hyperimmune globulin, and the number of patients with intimal thickness greater than 0.3 mm was 15% versus 56%. Actuarial survival was 91% versus 63%, favoring combined therapy. The data do not strongly support the implementation of therapeutic modalities that target CMV unless donor recipient status dictates therapy.

Sirolimus and Everolimus

Sirolimus is a macrocyclic triene antibiotic originally developed as an antifungal agent and later recognized to alter signal transduction pathways, resulting in blockade of the cell cycle in the late G1-S phase. Sirolimus inhibits the proliferation of T and B cells as well as other nonlymphoid tissues, such as endothelial cells, fibroblasts, and vascular smooth muscle cells [96]. Several randomized clinical trials exist evaluating the role of sirolimus and its sister compound everolimus for the treatment of CAV.

Among 46 primary transplant recipients with established CAV, sirolimus administered in a randomized manner substituting for azathioprine or mycophenolate mofetil revealed fewer severe rejection episodes among those treated with sirolimus. Importantly, catheterization scores for CAV progressed in the standard-therapy arm, whereas sirolimus treatment stabilized CAV [97•]. Concordant data from Keogh et al. [98] among 136 primary cardiac transplant recipients demonstrated a lower overall incidence of cellular rejection within 12 months. A subset of patients with 6-week and 6-month paired IVUS

data documented that parameters of CAV progressed significantly among azathioprine-treated patients whereas sirolimus-treated patients did not. Individuals followed for 2 years continued to confer these early benefits.

The largest trial using an agent in this class of immunosuppressants was conducted by a multinational tour de force of 52 transplant centers [99•]. A total of 634 primary cardiac transplant recipients were randomized in a double-blind, double-dummy manner to treatment with everolimus (0.75 mg or 1.5 mg twice daily) or azathioprine in the background of standard cyclosporine- and prednisone-based therapy. Although the primary endpoints of death, graft loss, re-transplant, loss to follow-up, and hemodynamic-equivalent rejection episode was statistically lower in the two everolimus arms, the difference was driven primarily by rejection episodes. Overall mortality was not statistically different among the three treatment groups, rather, a statistically higher incidence of bacterial infections in the high-dose everolimus arm was noted. Importantly, with regard to CAV, change in maximal intimal thickness at 12 months was 0.1 mm with azathioprine (standard dose of 1–3 mg/kg), 0.04 mm with 1.5 mg/d of everolimus, and 0.03 mm with 3 mg/d of everolimus at 12 months. Furthermore, CAV defined as an increase in maximal intimal thickness of at least 0.5 mm in at least one matched slice was present in 35.7% of patients receiving 1.5 mg/d of everolimus, 30.4% of patients receiving 3 mg/d of everolimus, and 52.8% of patients receiving azathioprine (standard dose of 1–3 mg/kg). Long-term outcome from this investigation is pending; however, if progression of IVUS markers of CAV is a surrogate for mortality due to CAV, then the promise of everolimus therapy may be fulfilled and our current paradigm of immunotherapy will change.

Revascularization

Because of the diffuse nature of the disease, CAV does not lend itself easily to percutaneous or bypass approaches to revascularization. In the absence of randomized data, percutaneous coronary intervention when employed judiciously (eg, for angioplasty, artherectomy, and intracoronary stenting) is as efficacious in allograft vasculopathy as in native vessel artherosclerosis and provides a means for palliation. However, new lesions or pre-existing lesions continue to develop after angioplasty [100]. The use of coated stents holds the promise of a lower incidence of restenosis in at least one study [101•]. Although retransplantation is an option for refractory nonrevascularizable CAV, long-term outcomes, particularly for those individuals with early and aggressive CAV, are not as favorable as primary cardiac transplantation. Furthermore, societal questions regarding organ utilization in an era of limited organ availability are actively debated on the local and national level.

Conclusions

Our understanding of cardiac allograft vasculopathy continues to improve, and over the past decade important mechanisms have emerged that have spurred newer treatment modalities that appear to have an impact on both the development and progression of CAV. Ongoing research efforts are targeting the underlying mechanisms established in the development of CAV. It is important to realize that most clinical trials in this field have not translated to a decrease in the incidence of overall death or death attributed directly to CAV. The authors believe that the promise of long-term success after cardiac transplantation can only be achieved after carefully designed, randomized clinical investigations with long-term follow-up are performed.

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