Allograft Vasculopathy Versus Atherosclerosis

Maziar Rahmani,* Rani P. Cruz,* David J. Granville, Bruce M. McManus

Abstract—Over the last 4 decades, heart transplantation (HTx) has evolved as a mainstream therapy for heart failure. Approximately half of patients needing HTx have organ failure consequent to atherosclerosis. Despite advances in immunosuppressive drugs, long-term success of HTx is limited by the development of a particular type of coronary atherosclerosis, referred to as cardiac allograft vasculopathy (CAV). Although the exact pathogenesis of CAV remains to be established, there is strong evidence that CAV involves immunologic mechanisms operating in a milieu of nonimmunologic risk factors. The immunologic events constitute the principal initiating stimuli, resulting in endothelial injury and dysfunction, altered endothelial permeability, with consequent myointimal hyperplasia and extracellular matrix synthesis. Lipid accumulation in allograft arteries is prominent, with lipoprotein entrapment in the subendothelial tissue, through interactions with proteoglycans. The apparent endothelial “intactness” in human coronary arteries of the transplanted heart suggest that permeability and function of the endothelial barrier altered. Various insults to the vascular bed result in vascular smooth muscle cell (SMC) activation. Activated SMCs migrate from the media into the intima, proliferate, and elaborate cytokines and extracellular matrix proteins, resulting in luminal narrowing and impaired vascular function. Arteriosclerosis is a broad term that is used to encompass all diseases that lead to arterial hardening, including native atherosclerosis, postangioplasty restenosis, vein bypass graft occlusion, and CAV. These diseases exhibit many similarities; however, they are distinct from one another in numerous ways as well. The present review summarizes the current understanding of the risk factors and the pathophysiological similarities and differences between CAV and atherosclerosis. (Circ Res. 2006;99:801-815.)

Key Words: allograft vasculopathy ■ atherosclerosis ■ cardiac transplantation ■ chronic transplant rejection ■ risk factors ■ pathogenesis

Allograft vasculopathy (AV) and atherosclerosis are atheromatous diseases with both stereotypic and uncommon features. Both diseases are characterized by increased cell adhesion molecular expression leukocyte infiltration, similar ambient cytokine profiles, aberrant extracellular matrix (ECM) accumulation,1–3 and the early and protracted buildup of extracellular and intracellular lipids.4 Intimal smooth muscle cell (SMC) migration, endothelial dysfunction and abnormal apoptosis are observed in both diseases. Emerging evidence also indicates that stem cells
may play a significant role in vascular repair and remodeling in both diseases.

Through the analysis of similarities and differences in phenotypes and biological mechanisms of atherosclerosis and cardiac AV (CAV), we hope to distill our understanding related to prediction, prevention, treatment, and management of these conditions. Such comparative features are summarized in the Table and Figure 1.

**Factors Affecting CAV and Atherosclerosis Outcomes**

Analyses of risk factors in heart transplant recipients with CAV, diagnosed predominantly by angiogram and more recently by intravascular ultrasound (IVUS) have identified both alloantigen dependent and independent factors.\(^5\)\(^6\) Alloantigen-dependent factors include the number of HLA mismatches, the number of rejection episodes, their duration, and their time of onset posttransplant.\(^7\) Alloantigen independent risk factors include hyperlipidemia, older donor age, sex, obesity, diabetes mellitus, hypertension, hyperhomocysteinemia (HHcy), cytomegalovirus (CMV) infection, ischemia/reperfusion (I/R) injury, and brain death.\(^5\)\(^7\) Hyperlipidemia and insulin resistance are the most significant nonimmunologic factors, occurring in 50% to 80% of the heart transplant population.\(^8\) These risk factors could be regrouped based on types of vascular pathology seen in cardiac allografts. For example, hyperlipidemias, diabetes, and smoking are risk factors common to atherosclerotic disease in allografts. On the other hand, the alloantigen dependent risk factors and CMV infection are more likely to be associated with vascular changes like endotheliitis and arteritis. As noted above, Figure 1 compares a number of known risk factors and mechanisms between atherosclerosis and CAV.

Immunological and nonimmunological factors are known to contribute to vascular injury and atherogenesis. Although several are unique to AV (I/R, donor age, organ quality, recipient age, donor brain death, major histocompatibility mismatch), many are similar in both AV and atherosclerosis (hyperlipidemia, diabetes, oxidative stress, hypertension, cytokine modulation, inflammation, C-reactive protein [CRP], infections, and other environmental stimuli such as smoking). The contributions of many of these factors to AV will be discussed in detail in subsequent reviews in this series of articles, and, therefore, only a selected few are discussed briefly in this review.

**I/R Injury**

I/R injury plays a significant role in endothelial dysfunction and the pathophysiology of CAV.\(^9\)\(^10\) The transplanted organ is vulnerable to I/R injury induced by graft ischemic time, quality of graft preservation during transport, hemodynamic status of the donor, catecholamines used for inotropic sup-

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### Histopathological Characteristics

<table>
<thead>
<tr>
<th>Features</th>
<th>CAV</th>
<th>Atherosclerosis</th>
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<tbody>
<tr>
<td><strong>Vessel involvement</strong></td>
<td></td>
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<tr>
<td>(1) Epicardial and intramural arteries are involved</td>
<td>(1) Major epicardial muscular arteries are involved</td>
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<td>(2) Veins can also be involved. The only vessels relatively unaffected are those with little or no muscular layer</td>
<td>(2) Largely affects the proximal epicardial coronary arteries. There is usually sparing of the intramyocardial vessels and arteries under muscular bridges</td>
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<td>(3) Diffuse and very extensive vessel involvement</td>
<td>(3) Veins are never involved</td>
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<tr>
<td>(4) Affects the proximal and distal epicardial vessels, as well as their branches</td>
<td>(4) Three layers, intima, media and adventitia, are involved</td>
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<td>(5) The media can be unaffected or almost completely replaced by fibrous tissue. As the intimal disease progresses in severity so does fibrosis of the media and adventitia.</td>
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<tr>
<td>(6) A disease of the intima, media, and adventitia</td>
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<tr>
<td><strong>Lesion pattern</strong></td>
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<tr>
<td>(1) Diffuse, concentric intimal thickening</td>
<td>(1) Focal, eccentric proliferative, and degenerative lesions of the intima of proximal coronary vessels</td>
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<tr>
<td>(2) Ranges from concentric, diffuse, intimal lesions to advanced fibrofatty plaques with degeneration</td>
<td>(2) Mostly fibrofatty plaques with ultimate necrotic coves and progressively thinned fibrous cap</td>
<td></td>
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<tr>
<td><strong>Initiation, progression, and complication</strong></td>
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<tr>
<td>(1) The initial lesions are SMC proliferation in the intima and accumulation of extracellular lipids</td>
<td>(1) Fatty streaks are seen initially</td>
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<td>(2) Accelerated progression of intimal proliferation and luminal stenosis during the early phase of the disease, with foam cell development</td>
<td>(2) Slow progression of lesion development (decades)</td>
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<tr>
<td>(3) Surface endothelial erosion is not characterized in this setting but may be a rare finding</td>
<td>(3) Surface endothelial erosion is seen</td>
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<tr>
<td>(4) Fibrous cap thinning and plaque rupture is a rare finding until late in the disease</td>
<td>(4) Thin fibrous cap and plaque rupture are frequently seen in intermediate to advanced lesions</td>
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Three sequential phases of graft ischemic time contribute to graft injury during transplantation: (1) the episode of warm ischemia on removal of the heart from the donor, (2) the cold ischemic interval associated with storage and preservation of the heart, and (3) the period of warm ischemia during engraftment. Paradoxically, although reperfusion is required to restore tissue oxygenation, significant damage can ensue during transplantation because of the associated oxidative burst that occurs during reperfusion.

Compelling evidence supports a molecular and cellular basis for a causal relationship between I/R injury during transplantation and the onset and progression of AV.11 I/R injury to endothelial cells (ECs) may provide the initial trigger for atherogenesis by stimulating platelet adhesion, release of growth factors, upregulation of major histocompatibility complex (MHC) class I and II expression, release of donor antigens, expression of adhesion molecules, and proliferation of vascular smooth muscle cells (VSMCs) (as reviewed by Valantine9). Thus, attenuation of I/R injury may be of great benefit to transplant recipients not only through the inhibition of direct cellular injury but also indirectly through the aforementioned factors that influence the alloimmune response.
Brain Death

A variety of donor-associated risk factors such as brain death can influence the short- and long-term outcomes of transplantation. Experimental and clinical studies have elucidated the complexities of the hemodynamic, metabolic, neurohormonal, and other physiological alterations following brain death and are reviewed elsewhere. This form of catastrophic central injury triggers elevated catecholamines, leading to peripheral vasoconstriction and also induces the release of hormones and proinflammatory cytokines and chemokines and adhesion molecules that are detected in the vessels of transplanted organs. Oxidative stress is also involved in brain death associated vascular injury that may contribute to CAV.

Shear Stress

Blood flow–induced shear stress acting on arterial walls plays a critical role in maintaining vascular homeostasis. ECs act as sensors of shear stress and regulate its levels by adapting the arterial dimensions to blood flow. To allow for variations in arterial geometry, such as bifurcations, shear-stress control is modified at certain eccentrically located sites to maintain low levels. In the presence of atherosclerotic risk factors, low shear stress contributes to endothelial dysfunction and plaque expansion, whereas normal-to-high shear stress is atheroprotective. Initially, lumen narrowing is prevented by vascular remodeling. However, over an extended period, prolonged unfavorable shear stress conditions augment plaque growth. As atheromas evolve, increasing tensile stress at the shoulder regions renders plaques susceptible to fissuring and thrombosis. Although the role of shear stress in atherosclerosis is well established, its role in AV is poorly understood.

Immune Factors

Both innate and adaptive immunity play important roles in both atherosclerosis and AV. A detailed overview of the mechanisms by which the immune system contributes to AV and atherosclerosis is beyond the scope of the current review and readers are encouraged to read one of the many excellent reviews that have been written on this topic. However, although the triggering mechanisms of endothelial injury and dysfunction and progression may differ between CAV and atherosclerosis, following endothelial activation, much of what is known concerning the infiltration of immune cells is similar between the 2 diseases. Endothelial injury and activation elicits the release of proinflammatory cytokines, chemokines, and expression of adhesion molecules, which fosters immune cell recruitment and transmigration of immune cells across the EC barrier and into the intima. The role of various immune components in atherogenesis is complex and will be the focus of 3 reviews in this series. As such, the current review will not delve into detail regarding the contributions and role of innate and adaptive immunity in atherogenesis.

Infection

Infection has been linked to the onset and progression of atherosclerosis and CAV. Infection in the context of atherosclerosis has been suggested to accelerate progression and activation of unstable plaques, while having no part in the onset of atherosclerosis. Several new studies have demonstrated specific infections, through activation or inhibiting players of the immune response, have accelerated atherosclerosis. In apolipoprotein E (apoE) knockout (KO) mice infected with Porphyromonas gingivalis, an increased macrophage infiltration and augmented atheromas were observed. The use of doxycycline in both infected and noninfected animals decreased atherosclerosis. The most compelling evidence linking infection to atherosclerosis progression, however, is the association between disease and the presence of the microorganisms Chlamydia pneumoniae and CMV. This first suggestion of infection was observed in the 1970s on noting the presence of monoclonal SMCs. Observed presence of Chlamydia in foci of tunica media calcifications suggested the hypothesis of infection of SMCs by Chlamydia as the initiating point in atherosclerosis. Another theory is the observed double-infection by both Chlamydia and CMV causing a synergistic increase in inflammatory response and perhaps speeding atherosclerosis progression. However, it has yet to be observed whether there is a causal relationship between infection and disease progression as antibiotic and antiviral medications against Chlamydia and CMV, respectively, failed to prevent atherosclerosis (as reviewed by Hansson). The link between infection and allograft rejection was first suggested in 1970. The same group later linked herpes virus infections (including CMV, herpes simplex, and herpes zoster) to rejection episodes. From 2 studies, no significant relationship has been determined between development of AV and Chlamydia infections. Subsequent associations were made with influenza and adenoviral infections; however, it is CMV which remains the hypothetical infectious player in the development of AV. CMV positivity around the time of transplantation is a major predictor of AV and posttransplant survival (as reviewed by Nieto). A recent human study pinpoints CMV infections causing episodes of endothelial dysfunction, whereas another goes further in demonstrating that CMV impairs the nitric oxide synthase (NOS) pathway to cause endothelial dysfunction.

Hyperlipidemia

Hyperlipidemia is commonly seen in cardiac transplant patients. Many of these patients are hyperlipidemic before transplantation. In addition, the immunosuppressive therapy given to patients, especially calcineurin inhibitors, can result in, or exacerbate preexisting dyslipidemia. Hypercholesterolemia, in a rabbit heterotopic cardiac transplant model, has been shown to be associated with AV, and transplanted coronary arteries were more affected by hypercholesterolemia than native coronary arteries. Hypercholesterolemia promotes fibrofatty proliferative changes to the intimal hyperplasia seen in most patients with CAV.

Hypercholesterolemia, hypertriglyceridemia, HHcy, hypertension, hyperglycemia, obesity, and insulin resistance occur with a high frequency in heart transplant patients. All of these abnormalities are associated with endothelial dysfunction and atherosclerosis in the general population. The link between the metabolic syndrome and the development of atherosclerosis and CAV has been shown to be attributed, at
least in part, to reduced NO availability. Data from observational studies, experimental models, and clinical trials indicate an important role for metabolic abnormalities in the pathophysiology of CAV. In many retrospective studies, hypertriglyceridermia has been identified as a predictor of CAV, indicating that the associated insulin resistance may be important in the pathophysiology of CAV. Long-term follow-up studies revealed that components of insulin resistance syndrome significantly predict subsequent development of CAV and cardiac events. Thus, hyperinsulinemia in persons without diabetes may be a marker for a cluster of metabolic abnormalities, including impaired insulin-mediated glucose uptake, visceral obesity, dyslipidemia, and hypertension. Through clinical trials of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), it has been demonstrated that metabolic abnormalities play an important role in endothelial injury and atherosclerosis. In addition to their lipid-lowering effects, statins restore endothelial-dependent vasodilator function in patients with classic risk factors for atherosclerosis, including those who have been identified for CAV as discussed previously. Two randomized trials highlighted in a recent review have demonstrated that patients treated with statins early after heart transplantation have a lower incidence and severity of AV. In both studies, patients receiving the statins experienced fewer and less severe acute rejection episodes and a survival benefit. These observations are consistent with the actions of statins in blocking inflammatory and immune responses. Recently, statins have been shown to suppress induction of MHC-II by interferon (INF)-γ, and this in turn represses the activation of T lymphocytes and other cell types, including human SMCs. These studies support the rationale for the use of statins as adjunctive immunosuppressive agents to specifically target the problem of CAV.

Hyperhomocysteinemia
Homocysteine is a byproduct of methionine metabolism and precursor to cysteine and taurine. Enzymes involved in converting homocysteine use cofactors folic acid and vitamins B12 and B6. There is an observed association between high levels of homocysteine (defined as hyperhomocysteinemia [HHcy]) and an increased risk of cardiovascular diseases. In solid-organ transplant recipients, HHcy is extremely common and occurs early with a rate as high as 80% to 90%. HHcy can damage cells by several mechanisms, but primarily by affecting the endothelium. HHcy results in reduced endothelial NO production, arterial response to vasodilators, and increased expression of procoagulant factors. The neutrophil/endothelium interaction is promoted in the setting of HHcy, allowing for the presence of more neutrophils in the intima. Several investigators have demonstrated that HHcy is associated with the development of CAV; however, prospective data on homocysteine-lowering interventions and CAV development have been lacking until recently. A more recent randomized trial of the folate therapy on de novo heart transplant recipients during the first 12 months after transplant, as detected by IVUS, does not seem to affect on early CAV onset.

Numerous studies suggest that homocysteine is a modifiable risk factor for atherosclerotic diseases. In general, epidemiologic studies show an independent and graded association between homocysteine levels and cardiovascular risk. However, recent large randomized clinical trials produced contradictory results. A recent study demonstrated that supplements combining folic acid and vitamins B6 and B12, did not reduce the risk of major cardiovascular events in patients with vascular disease after an average of 5 years of treatment. Another group also evaluated the efficacy of homocysteine-lowering treatment with B vitamins for secondary prevention in patients who had an acute myocardial infarction. Treatment with B vitamins did not lower the risk of recurrent cardiovascular disease after acute myocardial infarction. A harmful effect from combined B vitamin treatment was observed, which suggests that such treatment should not be recommended for native atherosclerosis or CAV.

Acute Rejection
Acute rejection as a cause or risk factor for CAV has been investigated by several authors. Some groups have reported an association between the severity and frequency of rejection and the severity of CAV; however, others have reported that episodes of acute rejection are not associated with the development of CAV. One proposed mechanism linking acute rejection to CAV is that the inflammatory process and tissue destruction from rejection result in endothelial damage, which initiates the process of CAV or potentiates the CAV already in progress.

Donor Related Diseases
The incidence of significant donor coronary artery disease (CAD) remains low, at approximately 2%. Donor CAD can serve as a starting point for CAV and may accelerate the disease process. Donor CAD can be important in the progression of the transplant patient in that it can progress independently of the CAV process. However, Botas et al found no significant difference in the rate of intimal thickening between patients with donor hearts having pre-existing CAD and those without. Thus, the impact of native vessel atherosclerosis on CAV remains controversial.

C-Reactive Protein
CRP is a protein marker found to be elevated in the blood during inflammation. In vitro experiments have identified several potential proinflammatory roles in cultured ECs, SMCs, and monocytes/macrophages by which CRP may promote atherosclerosis. Exogenous CRP induced the expression of adhesion molecules and decreased endothelial NOS (eNOS). Furthermore, CRP upregulates SMC angiotensin I receptors, thereby increasing reactive oxygen species and proliferation. In addition, monocytes/macrophages exposed to CRP increase release of tissue factor, potentially stimulating cell migration and adhesion to ECs and promoting the uptake of oxidized low-density lipoprotein (LDL).

The strong association of the plasma CRP level and cardiovascular events, a range of experimental evidence, and clinical data revealing lowering of CRP with some
preventive therapies and a concomitant reduction of cardiovascular events have led to the hypothesis that CRP is both a marker of, and a causal agent, in the development of atherosclerosis.51 Recent observations also suggest an association among plasma CRP levels and graft failure and CAV.52–54 The evidence that inflammation may be a central event in CAV and graft failure, independent of acute allograft rejection, is gaining acceptance. However, despite the fact that CRP is a well-proven clinical marker of increased cardiovascular risk both in native atherosclerosis and CAV, further experimentation is needed to clarify the causative link between CRP and either atherogenesis or CAV.

Other Risk Factors
Hypertension, smoking, diabetes mellitus, and other risk factors for atherosclerosis are associated with CAV. Hypertension in transplant patients can be present preoperatively or postoperatively secondary to immunosuppressive medication, such as cyclosporine (CsA). Hypertension causes endothelial injury by promoting the formation of intimal hyperplasia, which eventually gives rise to atherosclerotic lesions.

Histopathological Features of CAV and Atherosclerosis
The histopathological similarities and differences between these diseases (summarized in the Table) lie in several key features: fracture of plaques; geometry of luminal narrowing; and the tempo of each disease (see Figure 2).

Both diseases display fibrofatty plaques, and, in fact, histopathologic analyses show fibrofatty plaques in CAV are indistinguishable from spontaneously occurring atherosclerosis.55,56 In AV, a cellular infiltrate consisting of lymphocytes, macrophages, and modified SMCs is present, especially in the intima and adventitia.56 On gross examination they are visible as yellow streaks that follow the direction of blood flow. In fibrous atherosclerotic plaques, lipids are present both in macrophage and SMC foam cells and in the ECM. The intima is thickened because of accumulation of SMCs and ECM proteins. Lipids and macrophages are usually most frequent in the core region, which also contains T lymphocytes and occasional B cells and mast cells. SMCs and ECM are more abundant in the subendothelial region, often forming a fibrous cap covering the lipid and inflammatory cells in the deeper part of the plaque.

Although it occurs in both diseases, luminal narrowing is distinctive for each disease. Luminal narrowing in CAV is diffuse, typically concentric intimal thickening of both the major epicardial vessels and the intramyocardial vessels, with comparable severity from proximal to distal in the epicardial coronary tree.55–57 In the proximal region of epicardial arteries, the disease begins as concentric fibrous intimal thickening.56 In contrast, native atherosclerosis is usually a focal, eccentric proliferation of the intima of proximal coronary vessels. There is typically sparing of the intramyocardial vessels. Fatty streaks are seen initially. One of the predominant features of native atherosclerotic vessels as the disease progresses is the deposition of calcium and marked disruption of the elastic lamina. Rarely are veins involved in native atherosclerosis.

Another feature is the difference in the manifestations or tempo (rate or pace of progression and severity) of these diseases. In AV, changes in the intima can be seen as early as 1 or 2 weeks after transplantation. The lesion at this time has mild intimal thickening, early lipid insudation, mild fibrosis, and increases in ECM proteins may be present. In long-term survivors, fibrous and fibrofatty intimal lesions often diffusely involve large and small epicardial and intramural arteries.56 As the intimal disease progresses in severity so does fibrosis of the media. The major epicardial vessels are affected along their entire lengths from the base of the heart to the apex. Both arterial and venous structures can be involved by CAV. In the months following transplantation, intermediate lesions with accumulation of lipid-filled cells in the intima develop, and atheromatous plaques with well-formed lipid cores of cholesterol clefts and free-lying lipid debris can be seen. Native atherosclerotic plaques display a
very different tempo as compared with AV. Eccentric intimal thickening has been observed in newborn full-term infants, in whom the thickening occurs in areas of flow turbulence; however, it disappeared after 8 months of age.58 The plaques appear with impunity at puberty and may continue to progress to complicated lesions. According to a simplified version of the criteria previously set forth by the American Heart Association Committee on Vascular Lesions,59 plaque progression can be subdivided into 5 pathologically/clinically relevant phases and has been further elaborated to identify “plaque erosion” or the “vulnerable plaque.”60 Fatty streaks consist of intimal accumulation of macrophages filled with numerous lipid droplets. Complicated lesions are plaques that, in addition to lipids, inflammatory cells, and fibrous tissue, also contain hematomas and hemorrhage and thrombotic deposits. Complicated lesions are mainly a result of rupture of a fibrous plaque. Another possible cause may be bleeding from capillaries and venules entering the plaque from the adventitial vasa vasorum. Fissures, erosions, and ulcerations in the fibrous cap and luminal surface are other frequent characteristics. On the contrary, AV lesions are rarely known to rupture.

To further illustrate the concept of differential disease tempo for AV and atherosclerosis, the biological and clinical manifestations of these 2 diseases are presented in Figure 2. It is evident that AV has an accelerated, rapid development and the clinical signs and symptoms are seen shortly after the biological processes and pathologies develop. In contrast, native atherosclerosis manifests over several decades and the clinical horizons are usually detected at or beyond the sixth decade of life. Considering the major differences in disease tempo, cautious comparisons about the biology and pathogenesis can be made.

**Animal Models of CAV and Atherosclerosis**

Animal models have proven to be a valuable resource to study atherosclerosis and AV. An excellent review of the rabbit model of atherosclerosis by Brousseau and Hoeg61 highlights the human relevance: its apoB-containing lipoproteins are similar in composition to humans; apoB itself remains in its uncleaved form (apoB 100); cholesterol ester transfer protein (CETP) is ubiquitous in the plasma; and diet affects the induction and progression of atherosclerosis. The mouse, on the other hand, processes apoB (into apoB-48), expresses no CETP, and has naturally elevated high-density lipoprotein (HDL) plasma content thus increasing its resistance to atherosclerosis.61 The New Zealand white (NZW) rabbit has been used as a background for studying human apoA-1, human apoE2 and human lecithin: cholesterol acyltransferase (LCAT) proteins and their effects on atherosclerosis. The Watanabe Heritable Hyperlipidemic (WHHL) rabbit is a model for familial hypercholesterolemia (FH) as it lacks the LDL receptor (LDLR) and develops lesions with fewer genetically modified strains as compared with mice. Atherosclerosis models also provide easy comparisons to AV models as most studies of AV rely on rodents, although mice are preferred in atherosclerosis studies and rats are still preferred in AV studies. Rats, however, have shown to be resistant to the development of atherosclerosis and have fewer genetically modified strains as compared with mice. Thus more researchers are using mouse AV models to elucidate comparative mechanisms between atherosclerosis and AV as well as the genetic factors of AV. The congenic and consomic rat models developed and phenotyped at the University of Wisconsin–Milwaukee by Howard Jacob and his team may improve the utility of rats for research on atherogenesis in the native and transplanted heart.69

Most CAV models have used heterotopic cardiac transplantation or orthotopic artery transplantation into both mice and rats. Heterotopic cardiac transplantation is performed by the interposition of a donor heart into a nonphysiological position, such as the abdomen, in the recipient. In the abdomen, the donor vena cava and aorta are anastomosed to the recipient descending aorta and ascending vena cava, respectively.70 Although there is limited flow into the ventricles of this transplanted heart in spite of maintained genetically engineered versions available, ease of use, and cost of the animal. Such use of murine models will no doubt increase as the international project focused on knocking out every gene in the mouse evolves. Numerous recent studies have established the appropriateness of the use of C57BL/6 mice as the background for the transgenic and KO mice because this background is the most prone to the development of atherosclerosis.62 It is worth noting that nearly all such murine models have the limitation of comparatively high levels of HDL versus humans.

The successful creation of 2 knockouts, the apoE-KO mouse model63,64 and the LDLR-KO mouse model,65 have advanced the study of atherosclerosis, although both have disadvantages. The apoE-KO mice develop well-formed complex atherosclerosis similar to human plaques; however, this gene deletion causes a major elevation in circulating cholesterol. Many investigators use this knockout when studying other genes involved in atherosclerosis that are not involved in lipid metabolism.66 The major drawback to the apoE-KO model, however, is the difference in lipoprotein profiles as compared with most humans. In addition, drugs such as statins and fibrates may have disparate effects on these mice as compared with humans.66

The LDLR-KO mouse model compensates for the cholesterol composition; however, it does not develop complex “humanized” plaques without alteration to the diet.66 The LDLR-KO model has shown promise in bone marrow transplantation studies, a strategy not as effective in apoE-KO because apoE from transplanted bone marrow can rescue the KO characteristics. The creation of the apoE/LDLR double-KO mouse model allows the study of severe hyperlipidemia and atherosclerosis without the use of a modified lipid diet.67 It is easy to foresee a common practice of using this double KO model to study atherogenic genes. Similarly, the LDLR-KO crossed with an apoB transgenic mouse has proven useful for studies of atherosclerosis over the past number of years.68

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cardiac contractions, the myocardium is adequately perfused with recipient blood. As such, the vasculature and myocardium are exposed to the host immune system in a manner similar to clinical heart transplantation. There are numerous studies using the heterotopic heart transplant model that have addressed key risk factors highlighted in the previous sections. Wilhelm et al used a rat heterotopic heart transplant model to demonstrate that an upregulation of proinflammatory mediators, such as transforming growth factor (TGF)-β, is observed in brain dead donor rats, and not in non–brain dead control rats, and that this difference may lead to increased fibrosis. The rat heterotopic heart transplant model has also shown valuable for studying the association between CMV infections and the development of CAV. In particular, this model was useful in demonstrating that ganciclovir prophylaxis can attenuate how rat CMV infection affects CAV.

Researchers from our laboratory using the rat heterotopic heart transplant model demonstrated the progressive and ultimately profound inhibition of myogenic tone in allograft resistance arteries was a consequence of altered eNOS and inducible NOS (iNOS) activity and SMC damage. We have shown recently, using a mouse heterotopic model, that EC apoptosis contributes to the development of CAV and this cell death is through the granzyme B pathway. Another notable study demonstrated the acceleration of AV when using apoE-KO mice as recipients in a mouse heterotopic heart transplant model.

In the orthotopic arterial transplant model, blood flows through the artery under more or less normal physiological conditions. Arteries transplanted in this manner consistently develop intimal thickening and are used extensively to serve in arteries from native hearts in syngrafts and CsA-treated allografts. However, saline-treated allografts displayed progressive endothelial destruction, including large intercellular gaps, missing cells, and areas of bare ECM. Exfoliated surfaces were covered by platelets at various stages of adhesion, activation, and spreading. Similarly, numerous leukocytes were observed as either adherent to the endothelial lining or transmigrating into the subendothelial space. These findings indicate that, especially when immunosuppression is insufficient, early endothelial damage may promote vascular permeability and thereby initiate CAV. Thus, CAV can be initiated or exacerbated by several processes that can lead to denuding or nondenuding injury. These include I/R injury, immune activation, viral infection, and injury from immunosuppressive drugs.

Coronary endothelial vasodilator dysfunction is a common finding in cardiac transplant recipients and is an early marker for the development of intimal thickening and graft atherosclerosis. Paradoxical coronary vasoconstriction to acetylcholine in allograft recipients with and without angiographic evidence of CAV has been observed. Other investigators have observed abnormal responses (vasoconstriction and/or impairment in coronary blood flow response) to serotonin, substance P, cold-pressor testing, and exercise in AV. Notably, endothelial function in any one subject may not be diffusely disturbed after cardiac transplantation. The existence of coronary segments with functioning endothelium indicates that the coronary endothelium is not globally impaired in all cardiac transplant recipients and that endothelial function may not be irreversibly damaged. Indeed, Drexler et al have reported that intravenous administration of
l-arginine acutely improves endothelial vasodilator function of coronary conduit vessels if given at an early stage of AV.90 When the endothelium becomes diseased as is the case in both AV and atherosclerosis, the synthesis and bioactivity of the vasodilators are reduced and the balance tips in favor of endothelium-derived vasoconstrictors, such as endothelin and thromboxane.91 As a result of the impairment in endothelial vasodilator function, there is an increase in coronary vascular resistance, which can result in ischemia. However, as luminal narrowing ensues in CAV, unlike atherosclerosis, this reduced blood supply may progress with minimal levels of symptomatic discomfort and escape early detection in the transplant recipient, a matter of utmost concern.

Hasdai et al have found that coronary endothelial dysfunction in humans is associated with reversible myocardial perfusion defects.92 In transplant recipients, impaired coronary flow reserve is associated with subsequent reduction in left ventricular ejection fraction during a 2-year follow-up,93 suggesting that repetitive subendocardial ischemia during myocardial stress can cause a deterioration of ventricular function. Indeed, early epicardial endothelial vasodilator dysfunction predicts the development of visible vasculopathy (as imaged by IVUS) 1 year after transplantation.94 This is consistent with reports that coronary endothelial dysfunction in transplant and nontransplant patients is predictive of adverse cardiovascular events.95

Impairment of eNOS contributes to the pathological alterations in vascular reactivity and structure that are observed in atherosclerosis.96 Pharmacological inhibition or genetic deficiency of NOS inhibits endothelium-dependent vasodilation, impairs tissue blood flow, and raises the blood pressure.97 By contrast, enhancing NO production in the vessel wall slows or even reverses atherogenesis or restenosis.98,99 In preclinical models of AV, NO deficiency accelerates AV pathogenesis. The inducible form of NOS (iNOS) is expressed in the vessel wall of the aortic allograft and its inhibition significantly increases AV-associated intimal hyperplasia.97 Furthermore, early overexpression of iNOS by the use of ex vivo gene transfer completely prevents the development of structural changes in rejecting grafts.97

The literature supports a protective role for eNOS. In a murine chronic-rejection model, AV is accelerated in aortic allografts of eNOS-deficient mice.99 Additionally, Iwata et al demonstrated that intraoperative liposome-mediated gene delivery of eNOS to rabbit donor hearts can effectively reduce I/R injury while enhanced eNOS expression extends graft survival without immunosuppression.99 In further support, eNOS immunoreactivity is gradually lost after human heart transplantation,100 and reduced myocardial eNOS gene expression is associated with coronary endothelial dysfunction.101 In summary, endothelial dysfunction is an early feature of vascular disease that contributes to the pathogenesis of both atherosclerosis and AV.

The key similarities and differences in the role of ECs in atherosclerosis and CAV are as follows. (1) Experimental studies indicate the rapid development of AV in the absence of genetic dyslipidemia, whereas native atherosclerosis generally progresses very slowly. These findings signify the central role of altered endothelium in development of AV. (2) Evidence suggests that impairment of eNOS contributes to pathological alterations in vascular reactivity and structure observed in both AV and native diseases. (3) In considering the extent of endothelial disruption, increased vascular permeability in the allograft setting may allow larger numbers of lipoprotein particles to enter the subendothelial space with a higher influx rate as compared with native diseases. These events can be further accelerated posttransplantation by increased oxidative stress and dyslipidemia associated with transplantation. (4) Neovascularization of the atherosclerotic plaques may play a role in plaque progression and ruptures. However, its role is less prominent in AV. (5) Studies suggest that aging of the endothelium affecting vascular function and monolayer integrity alters its phenotype from an anti- to proatherosclerotic condition playing important roles on native atherosclerosis. (6) Vasomotor dysfunction in resistance vessels of allografts is more commonly documented than native vessels. Such dysfunction is correlated with a significantly increased risk of cardiovascular events. (7) Biochemical and biohumoral risk factors enhance shear forces and endothelial dysfunction near bifurcation of the coronary arteries in native disease. In contrast, diffuse involvement of coronary vasculature in AV underscores other mechanisms.

Role of SMCs in CAV and Atherosclerosis

Vascular SMC proliferation contributes to the pathobiology of atherosclerosis and is linked to other cellular processes such as inflammation, apoptosis, and matrix alterations.102 Recent studies have emphasized the involvement of inflammation in mediating all stages of atherosclerosis.19,84 However, in addition to inflammation, a key process of atherosclerosis involves the proliferation of SMCs. One precursor of lesion development in humans may be the focal accumulation of SMCs within the intima.103 The exact function of VSMCs in atherosclerosis is, however, still a subject of debate.103 In early atherosclerosis, VSMCs may contribute to the development of the atheroma through the production of proinflammatory mediators such as monocyte chemoattractant protein-1 (MCP-1) and vascular cell adhesion molecule (VCAM), and through the synthesis of matrix molecules required for the retention of lipoproteins.103 However, SMCs may also be important in maintaining the stability of the plaque through the formation of a firm fibrous cap. Indeed, in lipid-laden lesions in which the fibrous cap is thin and weak, there is evidence of SMC apoptosis, especially at the “shoulder” region, associated with inflammation.104 In addition, the local inflammatory milieu can induce expression of collagenase and inhibit expression of proteolytic inhibitors, thus rendering the fibrous cap weak and susceptible to rupture.19 In advanced lesions, fibroblasts and VSMCs with extracellular calcification form a fibrocalcific plaque.

SMCs constitute a significant portion of the atherosclerotic lesion. The origin of VSMCs in the atherosclerotic plaque is controversial. On the basis of observations in both humans and in animal models, the population of SMCs in intimal lesions has been proposed to arise from medial SMCs, adventitial cells, preexisting intimal clones, or precursor cells derived from the vessel wall itself or from circulating vascular progenitors.
The pathogenesis of CAV is believed to involve a chronic immune response of the recipient to the donor vasculature in which activated recipient immune cells damage the endothelium. Injured ECs secrete growth and chemotactic factors that recruit mononuclear cells that secrete inflammatory cytokines. This localized production of cytokines elicits activation of normally quiescent medial SMCs. As part of the SMCs' response to injury, they react to these soluble factors by transforming from a differentiated, contractile state to a dedifferentiated synthetic cell capable of migration, proliferation, and synthesis of cytokines and ECM. Histological changes that characterize AV confirm SMC migration from the media to the intima of the vessel. Intimal SMCs proliferate and synthesize cytokines, to which SMCs respond in an autocrine fashion. Proliferation and matrix deposition contribute to a loss of lumen diameter and vascular contractility and is responsible for most of the obliterative arterial intimal thickening present in solid organ allografts including CAV. It has been suggested that the cytokine-induced activation and proliferation of SMCs is the most critical cellular event in neointimal development. Accordingly, SMC activation, migration, and proliferation represent points of therapeutic intervention to attenuate most vascular proliferative diseases.

There are fundamental levels of proliferation control that are dependent on the environment of SMCs in the vessel wall, one of which is the vascular ECM (as reviewed by Hedin et al). This structural compartment can provide anchoring structures for SMCs that facilitate cell cycle progression by mitogens. In addition, the ECM can provide storage of mitogens and regulate interactions between mitogens or cytokines with their respective cell surface receptors. Most phenotypes of the SMCs in the media are quiescent, differentiated, and contractile cells, the primary function of which is to control vessel tone. Each individual cell is encased by a basement membrane composed of laminin, collagen type IV, entactin and the heparin sulfate (HS) proteoglycan (HSPG) perlecan. ECM components such as FN can promote the activation of freshly isolated SMCs into mitogen-responsive cells, whereas basement membrane components such as laminin retain the cells in a quiescent, differentiated state.

The key similarities and differences in VSMC phenotypes and biological mechanisms in atherosclerosis and CAV are numerous. (1) AV develops a predominantly SMC-rich neointima over a relatively short time period as compared with the naturally occurring multicellular atherosclerotic lesion that takes decades to develop (Figure 1). (2) Recent experimental and randomized clinical trials have shown that inhibitors of SMC proliferation such as sirolimus and everolimus can significantly retard CAV, although these approaches have not shown promising effects on prevention and/or progression of native atherosclerosis. (3) SMC apoptosis in normal as well as vascular proliferative diseases suggest a role for such in the maintenance of stable cell numbers in vessel walls. Directional atherectomy specimens have shown a paucity of apoptotic and proliferative cells in primary atherosclerotic plaques. In contrast, AV lesions have shown a greater extent of VSMC proliferation than in primary atherosclerotic lesions, which is supported by evidence from necropsy and atherectomy samples as well the results from various animal models. This difference is attributed to the low turnover of the cell population in native atherosclerotic lesions as compared with AV. (4) Although complex atherosclerotic lesions contain SMCs, the VSMC is the dominant cellular component of de novo AV lesions. Although analyses of models of murine atherosclerosis have provided evidence for the involvement of the proinflammatory cytokines in SMC accumulation, the relative effects are not always the same as those seen following allograft injury. For example, advanced lesions in apoE-deficient mice with reduced expression of interleukin-1 receptor α (IL-1Rα−/− mice) showed a small but significant reduction (15%) in α-SMC actin-positive area, in contrast to enhanced SMC proliferation and accumulation following allograft and wire-induced injury. (5) The functional role of phenotypic modulation of the SMC is likely to vary between AV and atherosclerosis as well as the stages of these 2 conditions. For example, this process presumably plays a maladaptive role in early lesion development and progression but may have a beneficial adaptive role in stabilizing plaques in mature eccentric atherosclerotic lesions. However, it may later contribute to plaque destabilization through apoptosis and/or activation of various protease cascades. These functional differences signify distinct roles for SMC phenotypic variation on the initiation, progression, and complications of the AV versus atherosclerosis lesions. (6) It is accepted that VSMCs undergo morphological changes leading to loss of their contractile properties and causing them to become “synthetic” cells. These changes are present in both AV and atherosclerosis. However, they appear to be faster to occur and more prominent in AV than atherosclerosis. (7) Studies in animal models have clearly demonstrated that circulating bone marrow–derived cells or adventitial fibroblasts can contribute to formation of the intimal lesions under some circumstances involving extensive medial necrosis or transplant rejection; however, the role of these circulating cells in formation of human atherosclerotic lesions is less convincing. Indeed, preliminary studies suggest they do not play a major role in most human lesions. Rather, the majority of SMCs within lesions appear to be derived from phenotypic modulation of preexisting SMCs in response to the plethora of alterations in environmental cues present within the atherosclerotic lesion.

**Role of ECM in CAV and Atherosclerosis**

The vascular ECM is a reinforced composite of collagen and elastic fibers embedded in a viscoelastic gel constituted by proteoglycans (PGs), hyaluronan, glycoproteins, and water. This network interacts with vascular cells and participates in vascular development and disease. Here we focus on the key similarities and differences of the major PGs of the vascular ECM and their biological mechanisms in native atherosclerosis and AV. Chondroitin sulfate (CS) and HSPGs are 2 main families of vascular PGs. The major CSPG in the arterial wall is versican, often accompanied by decorin and biglycan, members of a separate gene family. The main HSPG of the vascular wall is perlecan.
particular, biglycan is prominent in the intima and evolving atheroma with severe CAV, but not in native atherosclerosis. Similarly, versican accumulation occurs in the intima and media of vessels with CAV. Decorin is present primarily in adventitia of all vessels but also in the intima of those with native atherosclerosis. Intimal biglycan and versican deposits are positively associated with the extent of luminal narrowing in CAV when assessed by regression analysis. The distinctive staining patterns in both native and allograft disease indicate that the synthesis and distribution of these PGs are regulated by different local mechanisms.

We observed significant accumulation of lipids and foam cells in both intimal and medial walls of cardiac allograft coronary arteries. Prominent extracellular apoE, B, and (a) have been demonstrated immunohistochemically in transplant lesions distinct from those seen in atherosclerotic lesions. Specifically, transplant lesions display prominent intimal apo(a) and apoE immunoreactivity, whereas apoB is a more prominent feature in native disease. Of the 3 major arterial wall CSPGs, biglycan shows the strongest colocalization with retained epitopes for apoE, A-I, and B in human native atherosclerotic and CAV plaques. Versican epitopes are also in close proximity to retained apoproteins. Thus, on the basis of location alone, biglycan and versican appear to play roles in lipid and lipoprotein retention. The “response-to-retention” hypothesis of Williams and Tabas recognizes the central pathological role of subendothelial retention of atherogenic lipoproteins in native atherosclerosis. Although the role of lipoprotein/PG interactions have been well established in lipid retention of native atherosclerosis, the abovementioned observations support their putative roles in the initiation and progression of CAV.

HSPGs predominantly serve as potent negative regulators of coagulation, preventing hypercoagulable states and maintaining hemostasis. Furthermore, shed HS has the ability to activate a variety of antigen-presenting cells (APCs) and may also promote the development of the T-helper (Th) 1 type response seen in allograft rejection. Altogether, the evidences support the hypothesis that HSs has an important and extensive role in homeostasis and inflammation.

HSPG perlec an negatively correlates with SMC proliferation in vitro as well as in vivo animal model of postangioplasty injury. A recent study also showed that mice with heterozygote deletion of the perlecan gene in both apoE and LDLR-KO backgrounds had less atherosclerosis at 12 weeks but no significant difference in lesion size compared with littermate mice at 24 weeks, suggesting that loss of perlecan leads to less atherosclerosis in early lesions. Taken together, these results indicate that the endogenous perlecan contribute to SMC growth control during de novo intimal hyperplasia likely essential in vascular proliferative conditions such as AV.

The key similarities and differences in the role of ECM, especially PGs in atherosclerosis and CAV are as follows. (1) The profound early “insudation” of apolipoproteins along with uncertain endothelial “intactness” in allograft arteries very early posttransplant suggest that permeability of these vessel walls must be altered. Given the important roles of bone marrow perlecan in endothelial integrity, permeability, and inflammation, one can speculate the important role of perlecan in lipid imbibition of AV. However experimental studies do not support a crucial role of this PG in native atherosclerosis. (2) AV lesions have showed a greater extent of SMC proliferation than primary atherosclerotic lesions. Given the important roles of HSPG perlecan in de novo intimal growth, we suspect further essential role of this PG in AV as compared with native disease. (3) The central role of subendothelial retention of atherogenic lipoproteins in native atherosclerosis has been well established. Frequent accumulation of lipids and PGs in both the intimal and medial layers of AV has affirmed that aberrant expression of ECM components especially PGs may strongly promote lipid imbibition in the AV. Thus, it became important to consider PG/lipid interactions in the evolving story of CAV.

**Conclusion**

Atheromatous diseases impose the heaviest of health burdens worldwide. The impact of native atherosclerosis and its closely related conditions, postangioplasty restenosis and vein graft disease, continues to grow, despite progress in understanding the risks and pathogenesis. Similarly, as acute rejection as been better treated and managed, attention has been drawn to the persistent and recalcitrant issue of chronic rejection expressed in blood vessels as AV.

A few risk-related, pathological, and pathophysiological highlights are worth final notation with regard to the comparison of atherosclerosis and AV. A great number of similarities shared among all of these vascular diseases have been addressed in this review. The greatest distinction in risk and pathogenesis between atherosclerosis and AV resides in initiating immunological triggers in the allogeneic setting. This localizing alloimmune recognition confers the diffuse-ness of the AV process, proximally and distally, circumferentially, and into small vessels. Atherosclerosis, by comparison, is a more focal and unevenly distributed condition with more variability in the size and constituency of intimal, medial, and adventitial lesions. Another distinction rests with the route by which lipids and lipoproteins enter the vessel walls of affected arteries, mainly intracellularly (in monocytes) in atherosclerosis and extracellularly in AV. Although superficial endothelial erosions appear to be an occurrence of pathophysiological importance in atherosclerosis, it is not clear how often endothelial loss or disruption occurs in patients on typical immunosuppressive regimens. The role of thrombosis in converting chronic atherosclerotic disease to acute events appears on first face to differ from what is seen in AV. However, when AV is followed for long term, there is not only evidence of platelet-fibrin accumulation in intimal lesions of a more insidious nature than native atherosclerosis but also late thrombotic and frequently fatal events. The inflammatory constituency of atherosclerosis and AV has considerable similarity. There are observations in humans and in models to suggest that although the alloimmune trigger may be distinctive for vasculopathy, inflammatory amplification may occur in both, and, indeed, atherosclerosis may yet be more definitively shown to involve autoimmune mechanisms. The denervated state of the allograft no doubt affects the nature of vascular disease, in a fashion possibly
like denervated and vasa vasora-deficient vein grafts. The adventitia of coronary arteries where nerves and vasa vasora run is inflamed in both vascular diseases, however. Such inflammation plays an important role in the degree of transmural neovascular in-growth, the latter being a feature in both atherosclerosis and AV.

Finally, new questions and hypotheses are arising as a result of recent investigative observations. (1) Allograft coronary ECs can serve as stimulators as well as targets of inflammatory reactivity. Activation and dysfunction of the arterial endothelium may predict the development of CAV and may increase the risk of graft failure, mediated in part by dysregulation of the NOS pathway and NO deficiency within the allograft. Thus, the application of strategies directly restoring the NOS pathway offers potential for a more complete inhibition of CAV than has been achieved. (2) Vascular proliferative events are central in atherosclerosis and are linked to other cellular processes such as migration, inflammation, apoptosis, and ECM alterations. The contribution of vascular proliferation to the pathophysiology of CAV is also pivotal. Although the benefits and risks of antiproliferative therapy for atherosclerosis can be debated, inhibition of cellular proliferation by targeting cell cycle regulation for preventing CAV is a rational strategy. Additional research must uncover vascular-specific genes expressed in response to allograft injury and characterize their role in development of CAV. Additionally, pharmaceutical and clinical efforts must develop strategies capable of reducing vascular proliferation without attenuating the immune system. (3) The profound early insudation of lipids in human coronary arteries of the transplanted heart suggest that the permeability of these vessels must be correspondingly altered. Cumulative data support the view that profound lipid accumulation occurs in allograft arteries, with trapping in the subendothelial tissue, through interactions with PGs. This dysregulation of PG production leading to lipid entrapment and progressive AV is a testable hypothesis. (4) Early CAV manifests as some important functional changes in the arteries of the transplanted heart. Myogenic tone inhibition in cardiac allograft arteries is caused in part by excess vasoactive NO and in part by a defect in vascular SMC contractility. Excess NO can be derived from eNOS and iNOS isoforms. These changes predict a hemodynamic pattern within the rejecting heart that would favor myocardial edema, ventricular stiffness, and poor myocardial performance. Deterioration of myogenic tone in the resistance arteries of the transplant is extremely important as it provides a pathway of allograft injury that is not accounted for by the current methods of identifying allograft rejection.

The pathogenesis of atheromatous diseases remains a challenge. Although great progress has been made in understanding native atherosclerosis and AV, more work is still required to explain the mechanisms of initiation and progression. The vascular disease of allografts is a useful model of atheromatous disease, from which knowledge about native disease can be drawn, and vice versa. As donor ages have increased, the possibility of both conditions coexisting has made discernment of processes more challenging. Yet the use of models of both diseases, separately and concurrently, promises to teach us a great deal of the idiosyncratic and in-common factors that underpin these challenging problems.

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Maziar Rahmani, Rani P. Cruz, David J. Granville and Bruce M. McManus

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