Review

What is the optimal prophylaxis for treatment of cardiac allograft vasculopathy?

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Abstract

Coronary artery disease in the transplanted heart, also known as cardiac allograft vasculopathy (CAV), is one of the major causes of mortality late after transplantation. It affects up to 50% of all heart transplant recipients within 5 years of surgery. The mechanisms of CAV are multifactorial and include both immune and nonimmune factors. Ischemia of the graft at the time of transplantation is one of the more important nonimmune factors, because this leads to endothelial cell injury. Immune factors involving cellular and humoral rejection can further insult the vascular endothelial cell, leading to a cascade of immunologic responses. The optimal treatment prophylaxis for CAV has not been established. The treatment approach to this major post-transplant complication includes modification of risk factors through medical therapies and strategies. The early use of diltiazem and/or pravastatin or simvastatin has been demonstrated to be effective in reducing the development of CAV, but does not completely prevent it. There are many ongoing studies involving newer immunosuppressive agents that may hold promise for the future.

Keywords: cardiac allograft vasculopathy, heart transplantation, prophylaxis

Introduction

Cardiac allograft vasculopathy (CAV) is an accelerated form of obliterative coronary artery disease that occurs in heart transplant recipients and is one of the leading causes of mortality among long-term transplant patients. It occurs in 5–10% of heart transplant recipients each year and consequently up to 50% of these patients have angiographically confirmed atherosclerosis within 5 years of transplant surgery. As the donor heart is denervated, heart transplant recipients usually have silent myocardial ischemia and may present with congestive heart failure symptoms and/or sudden death. There is no effective treatment for CAV except that of retransplantation. However, because of the scarcity of donor organs, retransplantation raises serious ethical questions. Therefore, emphasis has been placed on prophylaxis, which may be achieved by treating the various risk factors. This manuscript will briefly review the risk factors and the believed pathogenesis of CAV and explore the optimal prophylaxis therapies for this major post-transplant complication.

ACE = angiotensin-converting enzyme; CAV = cardiac allograft vasculopathy; HLA = human leukocyte antigen; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; IVUS = intravascular ultrasound.

Background and risk factors

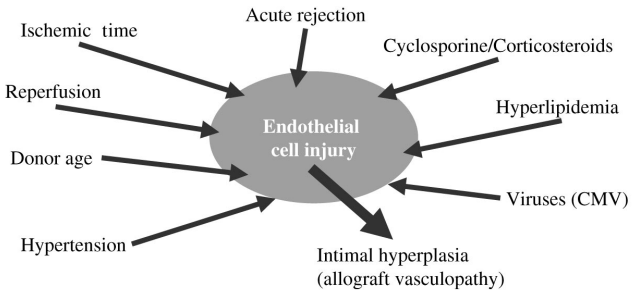
Histologically, CAV is characterized by concentric intimal proliferation and diffuse narrowing along the entire length of the vessel, as opposed to the discrete focal lesions usually seen in native coronary artery disease. Other differences seen in CAV, as opposed to native coronary artery disease, include rapid development (months to years), intact appearance of the elastic lamina, rarity of calcification, distal disease more severe than proximal disease, and rarity of the development of collateral vessels [1].

Numerous risk factors have been associated with the development of CAV. Accumulating data suggest that this disease process is predominantly immune-mediated. Reported immune risk factors include increased levels of cytotoxic B-cell antibodies, increased anti-human leukocyte antigen (HLA) antibodies, more acute cellular and humoral (antibody-mediated) rejection, cytomegalovirus infection, sensitization to the monoclonal antibody OKT3, and detection of early and persistently elevated soluble interleukin-2 receptor levels [2]. Many nonimmune risk factors have also been associated with the development of CAV [3,4]; these include hyperlipidemia, diabetes, recipient age and gender, obesity, pretransplant diagnosis, and donor ischemic time.

Among nonimmune risk factors for CAV, cholesterol and triglycerides have been the most reported [3,5]. The mechanism by which increased lipids might lead to greater intimal thickness may be linked to an immune process. Oxidized low-density lipoprotein leads to stimulation of macrophage activation, DNA synthesis in smooth muscle cells, expression of HLA-DR antigens, and interleukin-2 receptor expression in resting T cells. Activated macrophages and endothelial cells mediate low-density lipoprotein oxidation, which can stimulate macrophages further to secrete cytokines and growth factors that, in turn, may promote intimal thickening [6].

Historically, the diagnosis of CAV has been made with coronary angiography. But because CAV is concentric, longitudinal, and diffuse, the coronary angiogram may not detect early development of the disease process. The angiogram simply fills the coronary artery with contrast, but does not detect diffuse thickening in the coronary arterial wall. Therefore, coronary angiography lacks the sensitivity necessary for detection of early CAV. Intravascular ultrasound (IVUS) is a new imaging technique that provides quantitative information on vessel wall morphology and lumen dimension [7]. When used in the heart, an ultrasound catheter is moved over a guidewire that has been inserted into a coronary artery. An ultrasound transducer at the tip of this catheter obtains a 360-degree view of the artery intima and media, and the image is recorded on videotape. Quantitative measurements can then be made. It has been demonstrated that IVUS can detect severe intimal thickening in patients whose angiograms appear normal. IVUS has been reported to be the gold standard for early detection of CAV and for assessment both of prognosis and of the effects of therapy [8,9]. However, concern as to the reliability of IVUS in predicting CAV in the long-term has recently arisen. A longitudinal prospective study of 20 patients studied by IVUS at 2 months, 1 year, 2 years, and 3 years after heart transplant demonstrated that in a majority of patients, early intimal thickening in the first year is accompanied by constrictive remodeling (reduced lumen area). Over the subsequent 2 years, further constrictive remodeling is seen despite a decrease in intimal area. This might reflect both intimal and advential scarring [10], which would explain the decreasing lumen area in the absence of an increase in intimal area.

Figure 1



Proposed mechanisms in the development of CAV. Endothelial cell injury has been proposed as the event that initially triggers proliferation of smooth muscle cells and macrophages (see text for description).

Pathogenesis

The precise mechanisms for the development of CAV are unclear; but it appears to be multifactorial. A central event leading to the development of CAV appears to be endothelial cell injury [2]. This can occur early during organ procurement and reperfusion, both of which can cause ischemia in endothelial cells. Other factors, such as acute cellular and humoral rejection, hypertension, viral infections, hyperlipidemia, and even immunosuppressive agents [11] can lead eventually to endothelial cell injury, consequent intimal hyperplasia, and the development of CAV (Fig. 1).

Vascular endothelial cell damage causes a cascade of immune responses. These might include the coincident upregulation of complement, inflammatory mediators and cytokines [6]. Circulating host antibodies, particularly immunoglobulin G and antibody-antigen complexes, can affect the endothelium further. Platelets can then accumulate on exposed collagen, causing initiation of the clotting cascade. Various mediators, including thromboxane, leukotrienes, platelet-derived growth factor, and platelet-

activated factors, are released by injured endothelial cells. Subsequently, circulating leukocytes infiltrate tissues by means of the activities of adhesion molecules. There is loss of the endothelial cell barrier with subsequent lipid accumulation. Multiple signals cause the migration of macrophages and smooth muscle cells into the intima of the coronary artery. These cells transform into foam cells, causing intimal thickening and subsequent vessel lumen obliteration.

Therapy

In general, it can be said that if severe CAV occurs, treatment has not been satisfactory. Therefore, emphasis has been placed on prophylaxis. The current prophylaxis options for CAV include modification of risk factors through various medical therapies and strategies. Table 1 lists the main areas at which treatment has been targeted. The modification of potential risk factors includes the treatment of hypertension, hyperlipidemia, obesity and diabetes, promotion of exercise programs, and abstinence from smoking. Although modification of these risk factors in native coronary artery disease has been found to be beneficial, there is little data to support the efficacy of these measures in preventing CAV. Single-center studies have demonstrated that primary prevention with a specific calcium channel blocker or lipid-lowering agent may be beneficial.

Table 1

Therapeutic modalities to treat cardiac allograft vasculopathy

Antiproliferative agents:	
	Angiopeptin
	Low-molecular weight heparin
Antimetabolites:	
	Methotrexate
Antithrombotic agents:	
	Hirulog
	Antithrombin III
Monoclonal antibodies:	
	Growth factors
	Adhesion molecules
	Cytokines
Antihypertensive agents:	
	Calcium channel blockers
	ACE inhibitors
	New immunosuppressive agents
	Use of photopheresis
Lipid-lowering agents:	
	HMG-CoA reductase inhibitors

Calcium channel blockers

The use of calcium channel blockers was investigated by Schroeder *et al* [12], who randomly allotted 116 heart transplant patients either diltiazem or no calcium channel blocker immediately after transplantation, and assessed these patients with quantitative coronary angiography at 1 and 2 years after transplant surgery. The patients treated with diltiazem were less likely to demonstrate a significant decrease in coronary artery luminal diameter in their follow-up angiograms when compared with baseline values. At 5-year follow-up [13], there was a significant difference in freedom from both death and angiographic CAV (56% in the diltiazem group versus 30% in the control group). A major limitation of this study was the use of angiography, since one cannot sufficiently control for variations in vascular tone. In addition, coronary angiography is relatively insensitive in detecting early intimal thickening. Mehra *et al* [14] reported on an IVUS study of 32 consecutive heart transplant patients who were treated either with a calcium channel blocker, an angiotensin-converting enzyme (ACE) inhibitor or a combination of these drugs and compared with a control group who did not receive any of these drugs. In the treated groups, therapy was initiated within 1 month of transplantation as a result of the development of hypertension. At 1-year follow-up, coronary artery intimal thickness was significantly greater in the untreated control group than in the treated groups.

Cell and animal studies provide supporting evidence that calcium channel blockers may be beneficial in limiting CAV. D'Ambrosio *et al* [15] have demonstrated that diltiazem enhances production of interleukin-1B and slightly reduces production of interleukin-6 in mixed lymphocyte cultures. This suggests that diltiazem modulates monokine production and may exert effects on monocytes and possibly on other antigen-presenting cells. Finally, Atkinson *et al* [16] reported that the calcium channel blocker amlodipine could significantly decrease narrowing in the coronary arteries of the rat heterotopic transplant model as evaluated by digitized morphometry. Smooth muscle cell migration and proliferation may involve calcium-dependent mechanisms. Calcium channel blockade also has been reported to stabilize endothelial function and inhibit platelet aggregation with a decrease in the release of platelet-derived growth factors [17]. Therefore, use of calcium channel blockers may result in a decrease in the development of the intimal thickening that characterizes CAV.

Cholesterol lowering agents

Hypercholesterolemia is common after cardiac transplantation, and many studies have associated it with the development of CAV [3]. A study at our institution [18] evaluated the use of pravastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, in primary prevention of hyperlipidemia in heart transplant recipients. Ninety-seven heart transplant patients were randomized to pravastatin or no HMG-CoA reductase inhibitor within 2 weeks of transplant. Twelve months after transplantation, the pravastatin group had significantly lower mean cholesterol levels than the control group (193 ± 36 versus 248 ± 49 mg/dl), surprisingly less frequent cardiac rejection accompanied by hemodynamic compromise (three

versus 14 patients), better survival (94% versus 78%), and a lower incidence of CAV as determined both by angiography and autopsy (3 versus 10 patients). In a subgroup of study patients, IVUS measurements at baseline and 1 year after transplantation showed significantly less progression of intimal thickness in the pravastatin group compared to the control group. In another subgroup of patients, the cytotoxicity of natural killer cells was significantly lower in the pravastatin group than in the control group (9.8% versus 22.2% specific lysis). This study suggests that the role of pravastatin in decreasing CAV may not only relate to cholesterol lowering, but also to an unexpected immunosuppressive effect. Interestingly, the inhibition of natural killer cells by other HMG-CoA reductase inhibitors has been demonstrated *in vitro* [19]. Other studies have demonstrated beneficial effects of HMG-CoA reductase inhibitors on the development of CAV. Wenke *et al* [20] conducted a randomized trial of simvastatin in 72 heart transplant patients and demonstrated a lower incidence of CAV in simvastatin-treated patients. After 4 years of this study, CAV was observed in 18% of the simvastatin-treated patients as compared to 42% of control patients. In addition, IVUS performed at baseline and at 1-year revealed less progression of intimal thickness in the simvastatin group (170 mm^2 versus 370 mm^2 in the control group).

Pravastatin inhibits the HMG-CoA reductase enzyme and thereby reduces the production of mevalonate. This subsequently lowers cholesterol production and reduces isoprenylation of certain proteins such as ras and ras-related proteins. Ras-related proteins play important roles in T cell activation and effector function, which are pivotal in the development of allograft rejection during organ transplantation [21]. These findings of an added immunosuppressive effect of pravastatin (via inhibition of isoprenylation) may in part explain the anti-rejection properties as well as the decreased development of CAV observed in the pravastatin-treated cardiac transplant patients. In addition to inhibition of isoprenylation, there may be other mechanisms by which pravastatin reduces the development of CAV. In a study by Maggard *et al* [22], using a rat model, pravastatin decreased coronary arterial intimal lesions while depressing IgG alloantibody levels, suggesting a role for the humoral immune response in the development of CAV, as reported by others [23,24]. Pravastatin may also have direct vascular effects on intimal proliferation. In another rat study by Maggard *et al* [25], pravastatin-treated rats as compared with controls had significantly less degradation of laminin and fibronectin and had fewer graft-infiltrating macrophages, particularly within the arterial intima and perivascular areas. This suggests that the macrophage may also play a major role in the pathogenesis of CAV. The specific mechanisms for these findings in the rat studies are not clear, but could be related to the inhibition of isoprenylation by pravastatin as previously mentioned.

Other therapies

The somatostatin analog angiopeptin has been demonstrated to have an inhibitory effect on the proliferation of smooth muscle cells in experimental studies [26]. Other experimental data have shown that angiopeptin inhibits the release of insulin-like growth factor, which may inhibit the proliferation of smooth muscle cells after vascular injury. Wahlers *et al* [27] studied 54 heart transplant patients who received angiopeptin injections, but found similar survival and angiographic coronary atherosclerosis when compared with historical controls.

Photopheresis, a technique that has been in use for several years to treat cutaneous lymphoma (mycosis fungoides), is being investigated as a new therapeutic strategy to modulate the immune response. With photopheresis, patients are given oral 8-methoxy-psoralen and white blood cells are subsequently harvested via apheresis techniques. The psoralen-bound white blood cells are then irradiated with ultraviolet light and subsequently reinfused into the patient. It is postulated that these treated white blood cells cause a host autoregulatory T cell response, which may have a beneficial effect on the development of intimal thickness. In a randomized trial by Barr *et al* [28] of 23 cardiac transplant recipients, photopheresis was found to reduce intimal thickening as measured by IVUS. A larger multicenter study is currently in progress. Photopheresis may be a promising technique, although it is expensive and time-consuming (patients receive photopheresis for 4 h during 2 consecutive days; and the procedure is performed at least once monthly for the first year) and therefore may find limited use.

Newer immunosuppressive agents are currently being studied and many have the potential to decrease the development of CAV. In rats with heterotopic heart transplants, recent studies suggest that treatment with mycophenolate mofetil [29], 15-deoxyspergualin [30], or rapamycin [31] can diminish the severity of CAV. The mechanisms of these apparently beneficial effects are not known but appear to reflect more than a decreased incidence of acute rejection. Mycophenolate mofetil reportedly blocks purine synthesis and prevents the proliferation of both T lymphocytes and B lymphocytes, therefore blocking both the cellular and humoral responses. A multicenter, double-blind, randomized trial using mycophenolate mofetil versus azathioprine, in combination both with cyclosporine and prednisone in 650 heart transplant patients, did not reveal significant differences between groups in the development of CAV by angiography or IVUS at 3 years. However, the number of patients developing CAV was small and therefore more time may be needed to demonstrate differences. Multicenter studies with rapamycin are currently ongoing, with results on CAV becoming available within the next 2 years.

An impaired anticoagulant pathway has been associated with the development of CAV. Aziz and colleagues [32] have demonstrated in the rat heterotopic heart model that rats treated with cyclosporine and low-molecular-weight heparin have reduced frequency and severity of CAV as well as reduced graft rejection. Research interest in antithrombin III has demonstrated the impressive inhibitory activities of these agents in the period after coronary angioplasty. Experience in heart transplant patients has not yet been reported.

Clinical research has also focused on the use of monoclonal antibodies, antimetabolites, and ACE inhibitors. Monoclonal antibodies target specific growth factors, adhesion molecules, and cytokines. Future studies using this advanced technology will probably require several monoclonal antibodies because the etiology of CAV is diverse. Antimetabolites, such as methotrexate, have been used empirically by many transplant physicians to treat patients with CAV. The rationale is to add more immunosuppression with the current belief that CAV is predominantly immune-mediated. However, there have been no randomized trials using methotrexate for patients who develop CAV. Most anecdotal experiences do not show clear benefit. Studies by Mehra *et al* [14,33] have suggested a benefit of captopril, an ACE inhibitor, in CAV. In the rat heterotopic heart transplant model, Kobayashi *et al* [34] demonstrated that rats treated with captopril had a lower incidence of cellular and vascular rejection, minimal intimal proliferation, and reduced smooth muscle cell proliferation. It is suggested that captopril may mediate this vascular response through a paracrine renin-angiotensin mechanism or a suppressive effect on platelet-activating factor. In the DBA/2 to B10.D2 mouse cardiac allograft model used by Furukawa *et al* [35], which is an MHC compatible combination that differs in background genes only and allows 70% graft survival on day 70 without the use of immunosuppressive drugs, both captopril and the angiotensin II receptor antagonist TCV-116 demonstrated a beneficial effect. Both drugs tended to improve day 70 graft survival and significantly decreased both intimal thickening, and perivascular and interstitial fibrosis, in allografts. This study suggested that angiotensin II is directly involved in intimal thickening and fibrosis and that the beneficial effect of an ACE inhibitor is unrelated to the accumulation of tissue bradykinin activity. Convincing clinical evidence is still lacking to support the routine use of ACE inhibitors in cardiac transplant patients to decrease the development of CAV.

Conclusion

The mechanisms leading to CAV are undoubtedly multiple. They probably involve ischemic events that occur at the time of transplantation and both immune and nonimmune factors that occur postoperatively. Endothelial cell injury appears to be central to the pathogenesis of CAV. A multitude of immune responses subsequently occur, leading to smooth muscle cell and macrophage transformation into foam cells, which results in intimal proliferation and ultimately in obliteration of the vessel lumen.

Medical therapy to prevent this major complication has progressed slowly. The early use of diltiazem and/or pravastatin or simvastatin appears to be the current optimal prophylaxis for decreasing the incidence of CAV, but does not completely prevent its development. Multicenter studies with mycophenolate mofetil, rapamycin, and other newer agents may hold promise for the future. It is clear that whatever intervention is applied, it must be started at the time of transplantation, as the cascade of events determining CAV begins by this time.

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