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REVIEW

Coronary microvasculopathy in heart transplantation: Consequences and therapeutic implications

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Abstract

Despite the progress made in the prevention and treatment of rejection of the transplanted heart, cardiac allograft vasculopathy (CAV) remains the main cause of death in late survival transplanted patients. CAV consists of a progressive diffuse intimal hyperplasia and the proliferation of vascular smooth muscle cells, ending in wall thickening of epicardial vessels, intramyocardial arteries (50-20 μm), arterioles (20-10 μm), and capillaries (< 10 μm). The etiology of CAV remains unclear; both immunologic and non-immunologic mechanisms contribute to endothelial damage with a sustained inflammatory response. The immunological factors involved are Human Leukocyte Antigen compatibility between donor and recipient, alloreactive T cells and the humoral immune system. The non-immunological factors are older donor age, ischemia-reperfusion time, hyperlipidemia and CMV infections. Diagnostic techniques that are able to assess microvascular function are lacking. Intravascular ultrasound and fractional flow reserve, when performed during coronary angiography, are able to detect epicardial coronary artery disease but are not sensitive enough to assess microvascular changes. Some authors have proposed an index of microcirculatory resistance during maximal hyperemia, which is calculated by dividing pressure by flow (distal pressure multiplied by the hyperemic mean transit time). Non-invasive methods to assess coronary physiology are stress echocardiography, coronary flow reserve by transthoracic Doppler echocardiography, single photon emission computed tomography, and perfusion cardiac magnetic resonance. In this review, we intend to analyze the mechanisms, consequences and therapeutic implications of microvascular dysfunction, including an extended citation of relevant literature data.

Key words: Heart transplantation; Cardiac allograft vasculopathy; Microvascular function; Coronary flow reserve; Endothelial dysfunction

Core tip: In this review, we intend to analyze the mechanisms, consequences and therapeutic implications of microvascular dysfunction in heart transplantation recipients, including an extended citation of relevant data from the literature. We think that this manuscript could be of interest for many research workers and physicians working in the field of cardiovascular surgery, cardiology and transplant medicine.

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INTRODUCTION

Heart transplantation (HT) is the most effective treatment for patients with end-stage heart failure. Recently, early survival after HT has been improved through the

use of immunosuppressive therapy and updated surgical procedures. Unfortunately, late survival is still limited by the onset of malignancies and cardiac allograft vasculopathy (CAV). CAV is a specific form of coronary artery disease that affects heart transplanted patients and is characterized by an early, diffuse intimal proliferation of both the epicardial and microvascular vessels, resulting in epicardial coronary artery stenosis and small vessel occlusion[1]. The 29th Official Adult Heart Transplant Report, edited by the Registry of Heart and Lung Transplantation, noted a relatively small decrease in the cumulative incidence of CAV: at 7 years after transplant, 37% of the patients transplanted between 2003 and June 2010 had CAV, compared with 42% of those transplanted between April 1994 and 2002. In fact, CAV affects 8% by year 1, 30% by year 5 and 50% by year 10 after transplant[2]. This decrease seems to be related to newer approaches to CAV treatment, such as targeting lower low-density lipoproteins (LDL)-cholesterol levels or the use of mammalian target of rapamycin (mTOR) inhibitors or drug-eluting coronary stents[3]. The 1-year survival rate after HT is 81%, and the 5-year survival rate is 69%, with a median survival of 11 years for all HT patients and 13 years for those surviving the first year. CAV causes approximately 10%-15% of the deaths between years 1 and 3 after HT and contributes to potentially more deaths resulting from graft dysfunction[4]. Epicardial coronary artery disease is detectable by intravascular ultrasound (IVUS) during coronary angiography. Coronary microvascular function can be assessed by transthoracic Doppler echocardiography (TDE) measuring coronary flow reserve (CFR)[5]. Understanding the physiopathology of endothelial and microvascular dysfunction in CAV plays a crucial role in the development of new therapies.

THE ROLE OF ENDOTHELIAL FUNCTION

Coronary endothelial vasodilator dysfunction is a common finding in HT recipients and is an early marker for the development of intimal thickening and graft atherosclerosis. Since 1988, a paradoxical coronary vasoconstriction to acetylcholine in allograft recipients with and without angiographic evidence of CAV has been observed[6]. Subsequently, other investigators have observed abnormal responses (vasoconstriction and/or impairment in coronary blood flow response) to serotonin, substance P, cold-pressor testing, and exercise[7-10]. The impairment of endothelial function is time-dependent. Endothelial dysfunction is caused by both immunological and non-immunological risk factors[11]. The immunological response is the principal initiating stimulus and results in endothelial injury and dysfunction and altered endothelial permeability, with consequent myo-intimal hyperplasia and extracellular matrix synthesis. Non-immunological events, including ischemia/reperfusion time, donor age, donor brain death, infections (*i.e.*, Cytomegalovirus, CMV) and traditional risk factors such as hypertension, dyslipidemia and diabetes, contribute to maintaining inflammatory responses and to extend vessel damage[12-14].

Immunological response

Alloimmune injury is initiated when donor major histocompatibility antigens expressed on the surface of graft endothelial cells interact with recipient dendridic cells, resulting in a chronic immune response[15]. Recipient $CD4^+$ lymphocytes recognize donor major histocompatibility complex (MHC) class Ⅱ antigens on the cell's surface (HLA-DR, DP and DQ) and are activated. This process leads to a cascade of cytokines, such as Interleukin-2 (IL-2), IL-4, IL-5, IL-6, interferon-γ (IFN-γ), and tumor necrosis factor α and β (TNF-α, TNF-β), which promote the proliferation of alloreactive T cells and stimulate the expression of other cytokines and adhesion molecules (*i.e.*, intercellular adhesion molecule-1, ICAM, and vascular cell adhesion molecule-1, VCAM) by the endothelium with leukocyte adhesion to the vessel wall. As a result, the activated macrophages and lymphocytes in the intima of the artery secrete platelet-derived growth factor and transforming growth factor, which stimulate the proliferation of smooth muscle cells (SMCs) and vascular remodeling[16]. Non-human leukocyte antigen (HLA) allo- and auto-antibodies are an increasingly recognized component of the immune response. They are often directed against angiotensin type-1 receptor and the endothelin-1 type A receptor and may alone induce endothelial activation, trigger proinflammatory, and both proproliferative and profibrotic responses[17-19].

Nitric oxide pathway

Cytokines and growth factors lead to coronary endothelial vasodilator dysfunction through the dysregulation of the L-arginine-nitric oxide pathway, resulting in the reduced synthesis and bioactivity of the vasodilators in favor of endothelium-derived vasoconstrictors such as endothelin (ET) and thromboxane. Endothelium-derived nitric oxide (NO) is the most potent endogenous vasodilator known. It induces vasodilatation by stimulating soluble guanylate cyclase to produce cyclic guanosine monophosphate and inhibits platelet and leukocyte adherence to the vessel wall. IFN-γ is the determinant mediator, linking endothelial dysfunction to structural changes in transplanted human arteries through the down-regulation of endothelial NO synthase (eNOS) expression, inducible-NOS (iNOS) activation and potentiating growth-factor-induced SMC mitogenesis. The iNOS is not a normal constituent of quiescent healthy cells but is expressed in a wide variety of cell types that have been exposed to bacterial endotoxin or combinations of inflammatory cytokines. Under conditions of reduced availability of L-arginine (the NO precursor), the product of iNOS is the superoxide anion, which can increase local oxidative stress and exacerbate the inflammatory process[10,20,21]. The increased production of reactive oxygen species (ROS) is considered a major determinant of reduced levels of NO[22]. In human cardiac allografts, enhanced endomyocardial iNOS mRNA expression is accompanied by the expression of nitrotyrosine protein, suggesting peroxynitrite-mediated vessel damage. Importantly, dietary L-arginine has been shown to attenuate the structural changes of CAV *in vivo*

and has been associated with the down-regulation of insulin-like growth factor- I and IL-6[10]. Recently, great importance has been attributed to the ratio of L-arginine/asymmetric dimethylarginine (ADMA), which is an endogenous NO synthase inhibitor. ADMA is normally produced by the hydrolysis of proteins and degraded by the oxidant-sensitive enzyme dimethylarginine dimethyl aminohydrolase (DDAH)[23]. An increase in the ADMA levels of HT patients has been observed due to an oxidative impairment of the DDAH. The loss of endothelium-derived NO permits the increased activity of the pro-inflammatory transcription nuclear factor kappa B (NF-κB), resulting in the expression of leukocyte adhesion molecules[22].

Non-immunological mechanisms

Non-immunological risk factors for endothelial dysfunction are the same as those observed in non-transplanted patients, such as CMV infections, diabetes and dyslipidemia. CMV infection of seronegative HT recipients plays an important role in CAV development. It increases the ADMA levels, generates ROS and, through NF-κB activation and TNF-α production, induces proinflammatory cytokines and destabilizes the mRNA message for eNOS[24]. Donor- or recipient-related factors (*e.g.*, age/gender, pre-transplant diagnosis) and factors related to surgery (*e.g.*, ischemia-reperfusion injury) also increase the risk of CAV[25,26]. Diabetes mellitus is present in 28% of recipients at 1 year after HT and in 40% of patients at 5 years after HT[4]. Risk factors for new-onset diabetes include pre-transplant blood glucose of > 5.6 mmol/L, a family history of diabetes, being overweight, and the pre-transplant use of immunosuppressive drugs, particularly calcineurin inhibitors and corticosteroids[27].

Insulin resistance impedes the removal of triglycerides (TG) from very-low-density lipoproteins (VLDL) that are in circulation, resulting in hypertriglyceridemia and high VLDL concentrations. This impedance increases the transfer of cholesterol from high-density lipoproteins (HDL), thus decreasing the HDL concentrations and forming small cholesterol-depleted LDL[28]. These small dense LDL particles are rich in TG but contain relatively little cholesterol and are not readily cleared by the physiological LDL receptor; these particles are highly atherogenic[29]. Markers of metabolic syndrome such as a TG/HDL ratio of ⩾ 3 and levels of C-reactive protein (CRP) > 3 mg/L are considered markers of insulin resistance and may lead to endothelial dysfunction and the development of CAV[28]. Hyperlipidemia occurs frequently in HT recipients, with pre-existing or similar conditions to treatment with calcineurin inhibitors and corticosteroids. Hyperlipidemia leads to an increased intimal thickening, but there is only limited evidence that shows its direct association with CAV development[28]. Importantly, the benefits from statin therapy are well documented. Early treatment has been reported to be beneficial to first-year survival and has helped reduce severe rejection, thereby decreasing the development of CAV[30]. Statins inhibit MHC Ⅱ induction by IFN-γ on primary human endothelial cells and monocytes-macrophages and may exert a dampening effect on MHC Ⅱ-mediated T lymphocyte activation[31].

HISTOPATHOLOGICAL FEATURES

The precise interaction between host and donor endothelium remains unclear, but there is a significant amount of data showing a partial re-endothelization from recipient-derived cells, possibly as a response to allogenic stimuli causing vascular injury[32-34]. Endothelial chimerism (the coexistence of both donor and recipient endothelial cells) has been shown to be much higher in the microcirculation than in larger vessels, with a predilection for small epicardial and intramyocardial vessels, which had a notable 3- to 5-fold-greater chimerism than their larger counterparts. The high degree of endothelial chimerism may have immune implications for myocardial rejection or graft vasculopathy[33-37]. It has been hypothesized that this replacement could lead to a decrease in alloreactivity with a positive influence on graft outcome, but further studies are needed[38].

A study conducted by our group investigated the correlation between levels of human endothelial circulating progenitor cells (EPCs) and microvascular dysfunction, as evaluated by CFR. We demonstrated that EPCs in both the circulation and the graft decrease significantly in HT recipients with microvascular damage. A possible explanation for this may involve humoral factors that occur in a chronic low-grade rejection and influence mobilization, migration, and cell survival[39,40].

Hiemann *et al*[41] established a grading system of microvasculopathy in post-transplantation biopsies by light microscopy. The endothelial layer was defined as the mono-cell layer at the inner part of the blood vessel wall. The presence of a thin layer of cells whose diameter was less than the diameter of the endothelial cell cores was considered normal. Endothelial cells were graded as thickened if the diameter of the cell layer was at least as thick as the endothelial cell cores. The wall layer (media) was defined as the poly-cell layer adjacent to the endothelium. The wall was graded as normal if its diameter was less than the luminal radius. Wall thickening was classified as non-stenotic if the ratio of the luminal radius to wall thickness was < 3 but ⩾ 1, and stenotic wall thickening was graded if this ratio was < 1 (Table 1). Stenotic microvasculopathy was diagnosed if there was evidence of microvascular stenosis due to either endothelial thickening or wall thickening in at least one blood vessel per field of view on endomyocardial biopsies[41].

MICROVASCULOPATHY: DIAGNOSTIC TOOLS

Microvascular disease can be detected in HT recipients using both invasive and non-invasive techniques. The international society of heart and lung transplantation (ISHLT) guidelines has suggested CFR during coronary

Table 1 Different definitions of microvasculopathy

Author	Microvessels diameter (μm)	Microvasculopathy assessment
Drakos *et al*[97]	< 60	Microvascular density (number of microvessels/total tissue analysis area)
Escaned *et al*[96]	< 100	Arteriolar density, capillary and arteriolar obliteration index
Hiemann *et al*[41]	10-20	Luminal radius/medial thickness < 1

angiography as an option for detecting microvascular disease in HT recipients who are suspected of having CAV, but its routine use has not yet been widely instituted[31,42]. CFR is the ratio of the maximum stress flow (during intravenous adenosine vasodilator stress) to the rest flow for a given arterial distribution with or without a stenosis or diffuse narrowing, and it could be performed in more quickly and less expensively using TDE[43,44]. Our group demonstrated that microvascular dysfunction, as evaluated by CFR measured in the distal portion of the left anterior descending coronary artery (LAD), correlates with intimal hyperplasia measured by IVUS in patients with physiologically normal epicardial coronary arteries[45-47].

Dobutamine stress echocardiography (DSE) is a useful technique for HT recipients unable to undergo an angiogram for CAV detection. For CAV detection, the sensitivity and specificity of DSE have been shown in different studies to vary from 67% to 95% and from 55% to 91%, respectively[48-50]. However, its ability in detecting microvascular graft disease is still uncertain[51].

Another noninvasive test is dual-source computed tomography, which showed a sensitivity of 100%, a specificity of 92%, a positive predictive value of 50%, a negative predictive value of 100%, and a global accuracy of 93% in detecting CAV. Similar to DSE, its predictive value in microvascular dysfunction is not well established[52].

Magnetic resonance perfusion imaging with myocardial perfusion reserve (MPR) analysis showed a significant correlation with CFR when invasively evaluated.

Muehling and colleagues analyzed the resting endomyocardial/epimyocardial perfusion ratio (Endo/Epi ratio), which is decreased in impaired coronary circulation. CAV can be excluded by an MPR of > 2.3 with a sensitivity and specificity of 100% and 85%, respectively, and an Endo/Epi ratio of > 1.3 with a sensitivity and specificity of 100% and 80%, respectively[53,54].

MEDICAL TREATMENT

CAV prevention requires a combination of immunosuppressant agents, the prevention of CMV infection and a reduction in common cardiovascular risk factors[25,42,55].

Endothelial dysfunction is an early marker and contributes to the development of CAV[6,56-58]. Standard immunosuppression after cardiac transplantation includes a calcineurin inhibitor (CNIs, such as cyclosporin or tacrolimus) in combination with an antiproliferative agent [mycophenolate mofetil (MMF) or azathioprine (AZA)] with or without corticosteroids[59]. Cyclosporin (Cy-A) was the first immunosuppressive drug that had an important impact on the result of clinical HT by reducing the incidence and severity of rejection. Cy-A is known to impair endothelial function by increasing the release and response to vasoconstrictors, impairing the synthesis of NO, and generating free radicals. It may also result in increased ET levels and an impaired vascular response to NO[60-63]. Kobashigawa *et al*[64] showed that the five-year survival and incidence of angiographic CAV were similar between groups treated with microemulsion Cy-A- or tacrolimus. In a study by Meiser *et al*[65], a more pronounced intimal proliferation was detected in the group treated with Cy-A and MMF than in the tacrolimus-MMF-treated group. Moreover, microvascular endothelial function deteriorates more in Cy-A-treated patients than in tacrolimus-treated patients, a finding that correlates with the enhanced ET-1 concentration and reduced vascular remodeling[65-67]. The progression of CAV is slower in patients randomized to receive MMF instead of AZA. The combination of Cy-A and MMF was associated with a 35% reduction in 3-year mortality or graft loss compared with patients treated with Cy-A and AZA[68]. MMF-treated HT patients, when compared to AZA-treated patients, both treated concurrently on Cy-A and corticosteroids, have significantly less progression of first-year intimal thickening[69]. In terms of CAV prevention, MMF is superior to AZA in both combinations. A trend toward improved survival in MMF patients was noted. The lower number of rejection episodes in the MMF groups may have contributed to these results.

MMF is associated with the reduction of leukocyte adhesion to the graft endothelium and inhibition of the proliferation of SMCs[70-72]. Rapamycin therapy has been associated with improved coronary artery physiology at the level of both the epicardial artery and the microvasculature soon after HT[73]. Proliferation signal inhibitors (PSIs), *e.g.*, sirolimus and everolimus, may have the potential to reduce the incidence of microvasculopathy and, later, of CAV. In a 2-year randomized clinical trial, the use of sirolimus was associated with fewer acute rejection episodes and a significant absence of the progression of intimal plus medial proliferation compared with the use of AZA[74,75]. These drugs were also associated with a lower rate of CMV infection[76,77]. The occurrence of malignancies after HT is a well-described consequence of immunosuppression that affects the long-term prognosis of HT recipients. Patients on mTOR inhibitors, a class of drugs that has been experimentally proven to have both immunosuppressive and potent antitumor effects, developed significantly fewer malignancies, as expected due to the drug's mechanism of action[78]. In a recent retrospective study, Fröhlich *et al*[79] demonstrated that statin use is also protective against malignancies. Hypercholesterolemia and hypertriglyceridemia may occur in HT recipients who are treated with sirolimus, but the presence of these side effects did not appear to impair its ability to slow the progression of CAV[80]. Everolimus is an analog

of sirolimus. Several studies demonstrated a decreased severity and incidence of CAV in HT recipients receiving immunosuppressive therapy with everolimus. It was compared with AZA in the largest trial conducted thus far for HT, which randomized 634 patients. This study showed that both average intimal thickening by IVUS and the incidence of acute rejection at 6 mo after HT were significantly lower in patients receiving everolimus[74,81,82]. Prophylaxis consisting of CMV hyperimmune globulin plus ganciclovir has been associated with decreased intimal thickening and reduced coronary artery disease[83].

Of the recommendations made by the ISHLT regarding CAV management, only statin therapy had a level of evidence A[42]. In several studies, cholesterol and TG have been proven to directly correlate with the development and progression of CAV[84]. It is currently advocated that statins should be given soon after HT, when the most rapid expansion of intimal hyperplasia occurs. Different statins have been associated with the reduced progression of CAV. Simvastatin improved the 8-year survival in HT recipients[85]. A one-year trial in 92 patients randomized to pravastatin or no 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor showed not only lower mean cholesterol levels but also less intimal thickening by IVUS as well as less frequent high-grade acute rejections and rejections with hemodynamic compromise[86].

The vasculoprotective effects of statins are likely mediated by multiple immunogenic effects. The immunomodulating effects of statins in the presence of Cy-A include the suppression of T-cell responses[87], the reduction of chemokine synthesis by mononuclear cells in the peripheral bloodstream, and the inhibition of the expression of *MHC-II* genes[88]. Simvastatin inhibits the proliferation of SMCs, which is an important process in the pathogenesis of the atherosclerotic lesion. Moreover, simvastatin has been shown to have a direct influence on the gene expression of ET-1 in cultivated endothelial cells, leading to improved endothelial function and thus protecting against atherosclerosis and microvasculopathy[89]. Another direct positive effect of simvastatin in the atherogenesis process is that it reduces monocyte adhesion to endothelial cells, which is one of the initial steps in the development of atherosclerotic plaques[90].

The use of calcium channel blockers or angiotensin-converting enzyme inhibitors (ACE-Is) decrease the incidence of CAV detected by IVUS[91]. Additionally, the use of calcium channel blockers decreases angiographically detected CAV 2-years after HT[92]. ACE-Is partially improve allograft microvascular endothelial dysfunction, reduce oxidative stress, and down-regulate endothelial ET-1 release[93], and their use has been associated with plaque regression[94] and improved graft survival[30]. The combined use of an ACE-I and a calcium-antagonist is more effective than the individual use of either drug alone on CAV development. Large randomized clinical trials are warranted to evaluate the possibility of this synergistic efficacy[95].

CONCLUSION

Coronary microvascular function has an impact on long-term graft survival after HT. Microvascular vessel disease has been demonstrated by histological findings of stenotic microvasculopathy and evaluated by non-invasive CFR[41,45,96]. The potential influence of combined immunosuppressive regimens, lipid-lowering agents, or ACE-Is and/or calcium-antagonists on microvessel response is therefore of major interest. More trials are needed for microvasculopathy prevention and/or CFR preservation and to reduce the negative prognostic impact on the survival of HT recipients.

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