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Cardiac allograft vasculopathy after heart transplantation: current prevention and treatment strategies

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Abstract. – OBJECTIVE: Cardiac allograft vasculopathy (CAV) is a leading cause of mortality in heart transplantation patients. Despite optimal immunosuppression therapy, the rate of CAV post-transplantation remains high. In this review, we gathered all recent studies as well as experimental evidence focusing on the prevention and treatment strategies regarding CAV after heart transplantation.

MATERIALS AND METHODS: A complete literature survey was performed using the PubMed database search to gather available information regarding prevention and treatment strategies of CAV after heart transplantation.

RESULTS: Several non-immune and immune factors have been linked to CAV such as ischemic reperfusion injury, metabolic disorders, cytomegalovirus infection, coronary endothelial dysfunction, injury and inflammation respectively. Serial coronary angiography combined with intravascular ultrasound is currently the method of choice for detecting early disease. Biomarkers and noninvasive imaging can also assist in the early identification of CAV. Treatment strategies such as mammalian target of rapamycin inhibitors proceed to grow, but prevention remains the objective.

CONCLUSIONS: Early detection is the key to therapy management. It enables early identification and diagnosis of patients with CAV, who would gain the most from prompt treatment. Further investigation is needed to elucidate the multifactorial pathophysiological process of CAV, develop detection methods and find treatments that prevent or slow disease progression.

Key Words:
Cardiac allograft vasculopathy, Graft dysfunction, Heart transplantation, Immunosuppression, Coronary.

Abbreviations

CAV = cardiac allograft vasculopathy; CFR = coronary flow reserve; CMR = cardiac magnetic resonance; CMV = cytomegalovirus; CNI = calcineurin inhibitors CTCA = coronary computed tomography angiography; DSE = dobutamine stress echocardiography; FFR = fractional flow reserve; HLA = human leukocyte antigens; IMR = index of microcirculatory resistance; IVUS = intravascular ultrasound; MPI = myocardial perfusion imaging; mTOR = mammalian target of rapamycin inhibitors; OCT = optical coherence tomography; PCI = percutaneous coronary intervention; RNA = ribonucleic acid.

Introduction

Heart transplantation has become a mainstay treatment choice for end-stage heart failure[1,2]. Cardiac allograft vasculopathy (CAV) has been a critical drawback to strong long-term results and a leading cause of morbidity and mortality post-transplantation[3,4]. Despite advancements in immunosuppression therapy, CAV still affects 50% of heart transplant recipients[1-4]. Several immune and non-immune factors have been associated with CAV[3,4]. Hypertension, diabetes mellitus, hyperlipidemia, cytomegalovirus (CMV) and donor brain death are key factors in the development of CAV[4]. The denervated transplanted heart prevents recipients from experiencing pain. Therefore, the early detection of CAV is of utmost importance. Biomarkers and different imaging modalities (dobutamine stress echocardiography, computed tomography angiography, cardiac magnetic resonance) have been proposed, but serial

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coronary angiography and intravascular ultrasound remain the best option[4,5]. The introduction of statins and mammalian target of rapamycin inhibitors (mTOR) in clinical practice changed the course of the history of CAV[1]. In this review, we present current clinical and experimental studies regarding prevention and treatment strategies of CAV after heart transplantation.

Materials and Methods

We have gathered all experimental and clinical studies focused on current prevention and treatment strategies regarding CAV after heart transplantation. The MEDLINE/PubMed database was searched for publications with the medical subject heading "transplantation" and keywords "vasculopathy", "coronary" or "endothelial". We restricted our search to the English literature.

Pathophysiology

CAV is a fibroproliferative disorder involving the vasculature (epicardial and intramural) of the transplanted heart[6]. Intimal proliferation, inflammation and lipid accumulation lead to circumferential intimal thickening[6]. CAV is a diffuse, multifactorial and complex disease initiated by different factors, that ultimately cause inflammation and endothelial injury[6,7]. The endothelium regulates the vessel tone, inhibits platelet activation, thrombosis, leukocyte adhesion and vascular smooth muscle cell proliferation. As a result, endothelial damage commences a cascade of an extensional cell healing process that leads to vascular cell proliferation, fibrosis and remodeling[6,7]. Intravascular ultrasound has demonstrated that this intimal thickening occurs during the first year after heart transplantation, showing a biphasic response of early expansion and late constriction[6].

Immune Factors

The interaction of "foreign" human leukocyte antigens (HLA) of the allograft endothelial cells with the T-lymphocytes of the recipient initiates endothelial cell activation and accumulation of inflammatory cells[8]. This leads to cytokines secretion (interleukins 2, 4, 5, and 6; interferon-gamma; tumor necrosis factor-alpha), proliferation and up-regulation of endothelial adhesion molecules[8]. Activated macrophages accumulate to the intima and secrete cytokines (interleukin 1 and 6, tumor necrosis factor-alpha) and growth factors[8]. As a result, this causes smooth muscle cell to shift to the intima, proliferation and extracellular matrix deposition[8]. High-class I HLA antibodies promote endothelial and smooth muscle cell proliferation through the activation of the mammalian target of rapamycin (mTOR) pathway and the induction of intracellular fibroblast growth factor receptor expression[9,10]. HLA antibodies have been linked to poor allograft results and development of vasculopathy[11].

Non-Immune Factors

Non-immune factors that have been correlated with CAV are old age (both donors and recipients), male sex, obesity, diabetes mellitus, dyslipidemia, coronary artery disease, brain donor death, organ preservation and ischemia-reperfusion injury[2]. Cytomegalovirus (CMV) infection is linked to the increased incidence of CAV[12]. CMV contributes to endothelial dysfunction[13] and impairs the nitric oxide synthase pathway through the elevated generation of the nitric oxide synthase inhibitor asymmetric dimethylarginine[14]. Furthermore, a molecular mimicry of endothelial cell surface molecules has been associated with endothelial damage[15]. Table I summarizes the risk factors for cardiac allograft vasculopathy after heart transplantation.

Table I. Summary of the risk factors for cardiac allograft vasculopathy after heart transplantation.

Classical risk factors	Transplant-related risk factors
Hypertension	Cytomegalovirus infection
Diabetes mellitus	Brain donor death
Dyslipidemia	Organ preservation
Old age (both donors and recipients)	Ischemia-reperfusion injury
Smoking	HLA mismatch
Male sex	Cellular rejection
Obesity	Immunosuppression
Coronary artery disease	Number of rejection episodes

Diagnosis and Surveillance

Detection is crucial for early CAV diagnosis because the denervated transplanted heart prevents recipients from experiencing pain[1,2]. As a result, there is no typical symptomatology of ischemic disease due to denervation, and recipients usually manifest atypical symptomatology or late after the presence of CAV with reduced ejection fraction, arrhythmia or sudden cardiac arrest[1,2]. Different noninvasive and invasive imaging modalities are utilized for CAV diagnosis. Noninvasive modalities include stress echocardiography, cardiac magnetic resonance, myocardial perfusion imaging, computed tomography coronary angiography and invasive are coronary angiogram, intravascular ultrasound and optical coherence tomography, fractional flow reserve and index of microcirculatory resistance[1,2,16].

Noninvasive

Stress Echocardiography

Dobutamine stress echocardiography (DSE) can identify patients at risk and facilitates surveillance of CAV[17]. Stress echocardiography has a high (92 to 100%) negative predictive value for subsequent cardiovascular episodes, and a prognostic value comparable to that of coronary angiography and intravascular ultrasound[17,18]. However, a recent study of 1.243 heart transplantation patients who underwent DSE at a nine-year post-transplantation period showed a very small number of positive DSE and a poor sensitivity for early detection of CAV[19]. Sade et al[20], in a total of 90 studies of DSE combined with coronary flow reserve (CFR), reported that CFR increased the diagnostic accuracy of DSE. Tona et al[21] validated these results, showing that a CFR $\leq$ 2.5 was independently associated with a higher probability of new-onset CAV and a higher probability of death.

Myocardial Perfusion Imaging

Myocardial perfusion imaging (MPI) has prognostic value but moderate diagnostic accuracy[22,23]. Manrique et al[23] showed that a normal gated single photon emission computed tomography is associated with a low risk of cardiac events and can alleviate the necessity for coronary angiography. Positron emission tomography MPI has superior diagnostic precision in comparison to single photon emission computed tomography for the detection of ischemic heart disease[24,25]. Murthy et al[26] in a study of 2783 patients concluded that quantitative assessment of coronary vasodilator function with positron emission tomography is an independent predictor of mortality in patients with known or suspected ischemic heart disease and provides incremental risk stratification over clinical and gated MPI. Flow quantification assessment is the best tool for early CAV diagnosis because it can detect homogenous declines in flow that are compatible with diffuse disorder[26]. Two surveys of nineteen and twenty-seven heart transplant recipients respectively have reported a poor inverse association between positron emission tomography flow reserve and intravascular ultrasound findings of CAV[27,28]. Mc Ardle et al[29] also showed that abnormalities in rubidium-82 positron emission tomography are predictors of adverse episodes in heart transplantation patients.

Cardiac Magnetic Resonance

Muehling et al[30] showed a good association between magnetic perfusion imaging reserve and CFR, and also an increased precision for screening CAV. In a single-center survey of 47 patients, cardiac magnetic resonance (CMR) was an independent prognosticator of CAV with increased diagnostic accuracy[31]. Braggion-Santos et al[32] evaluated late gadolinium enhancement patterns in 132 heart transplantation patients. Late gadolinium enhancement was useful to detect myocardial scar related to early CAV in a great number of heart transplantation patients[32]. CMR has certain limitations in these patients, such as increased resting heart rates, contraindicated implantable devices, risk of renal insuffiency[30,31].

Coronary Computed Tomography Angiography (CTCA)

Late-model multi-slice multi-detectors and dual-source high tech have enhanced the spatial and temporal resolution of CTCA[33,34]. An analysis of thirteen studies investigating 615 patients showed that CCTA using currently available technology is a reliable noninvasive imaging alternative to coronary angiography with excellent sensitivity, specificity, and negative predictive value for the screening of CAV[33]. Poor visualization of the distal coronary vessels and increased resting heart rates are the main limitations of this method[33,34].

Invasive

Coronary Angiography

Current guidelines for the care of heart transplantation patients recommend coronary angiogram as the method of choice for CAV detection in accordance with clinical availability and prognostic significance[16]. Constanzo et al[35] in a large study of 5963 heart transplantation patients found that the coronary artery disease occurred in almost 42% of the patients by 5 years. Severe angiographic allograft coronary artery disease occurred in 7% of the patients at 5 years (left main stenosis > 70% or 2 or more primary vessels stenoses > 70% or branch stenoses > 70% in all 3 vessels)[35]. The diffuse nature of CAV disease, however, leads to the absence or late luminal occlusions[1,2]. Consequently, coronary angiography as a method to screen CAV is inadequate because it can only visualize the arterial lumen and large epicardial vessels[1,2,35].

Intravascular Ultrasound (IVUS)

The use of IVUS regarding CAV screening, as its prognostic value, is well established in the literature, providing exceptional imaging of the lumen and vessel wall[36-38]. A multi-center study by Koshigawa et al[37] concluded that progression of intimal thickening ≥ 0.5 mm in the first year after heart transplantation seems to be a reliable surrogate marker for mortality, and nonfatal major adverse cardiac episodes. Furthermore, the authors reported that the development of CAV after five years from heart transplantation is correlated with a 50% probability of death or re-transplantation after 5-years[16,37]. Rickenbacher et al[38] demonstrated that patients with maximal intimal thickness > 0.3 mm at one-year after transplantation were at high-risk of CAV development and poor 4-year survival. Potena et al[39] recently reported that an increase in maximal intimal thickness ≥ 0.35 mm was associated with an increase in major adverse cardiovascular events. Okada et al[40] in a study of 100 heart transplantation patients found that remodeling of the proximal left anterior descending artery segment at 1 year was the primary element of long-term mortality or re-transplantation.

Optical Coherence Tomography (OCT)

OCT has a ten-times better resolution in comparison to IVUS and as a result is an ideal imaging tool for the assessment of the vessel intima and plaque morphology[41]. Ichibori et al[42] found that increased microchannels identified by OCT in patients more than a year post-transplantation were associated with intimal volume and coronary risk. Dong et al[43] also showed that high-grade cellular rejection was correlated with intimal volume and macrophage accumulation. OCT, however, is not a cost-effective method with contrast necessities, and lower tissue penetration that bounds the estimate of deep plaque characteristics[41].

Fractional Flow Reserve (FFR) and Index of Microcirculatory Resistance (IMR)

CAV is a disease of diffuse nature with complex changes in coronary physiology[1,2]. FFR and IMR provide an independent assessment of the epicardial arteries and microvasculature respectively[44,45]. Epicardial vessels and microvasculature are involved in CAV, and alterations in one could change the estimate in the other[44-47]. Endothelial dysregulation, as evaluated by decreased CFR, enhanced IMR or irregular vasoconstrictor response to acetylcholine is associated with intimal thickening and CAV[46,47].

Biomarkers

Current literature does not support the use of biomarkers for CAV detection[48]. MicroRNAs are small RNA molecules that negatively regulate gene expression and are measurable in peripheral blood[48]. Neumann et al[48] recently found that microRNA 628-5p was able to predict CAV with a specificity of 83% and a sensitivity of 72%, suggesting a potential role for biomarkers in CAV screening.

Prevention and Treatment

Drug Therapy

Increased platelet aggregation is a known factor for sudden cardiac death and myocardial infarction in heart transplantation recipients[49]. Consequently, aspirin is used in the daily clinical practice in these patients[49]. Statins are known lipid-lowering, anti-inflammatory agents, that inhibit the natural killer cell cytotoxicity[50]. In a landmark study by Kobashigawa et al[51] pravastatin pretreatment improved cholesterol levels and reduced CAV, rejection, and mortality. Wenke et al[52] found the same beneficial results using simvastatin. A meta-analysis of three randomized controlled studies demonstrated the beneficial effects of statins in reducing rejection episodes

and improving survival[53]. Based on the fact that endothelial dysfunction is associated with CAV, Fang et al[54] investigated supplementation with antioxidants such as vitamins C and E. The authors reported that antioxidant therapy hindered an early progression of transplant-related coronary arteriosclerosis[54]. Small trials of calcium-channel blockers and angiotensin-converting enzyme inhibitors showed enhanced microvascular function and prevented the onset of CAV[55,56]. Schroeder et al[55] administered diltiazem two to four weeks after transplantation and observed a decline in CAV. Erinc et al[56] used a combination of an angiotensin-converting enzyme inhibitor and a calcium-channel blocker and found that this simultaneous approach was better than either drug only for diminishing the development of CAV. The mTOR sirolimus and everolimus hinder vascular smooth muscle and fibroblast proliferation[57]. mTOR changed the course of history for heart transplantation showing reduced CAV prevalence and progression[57-59]. Calcineurin inhibitors (CNI) have been traditionally the treatment of choice for maintenance immunosuppression[59]. A multi-center Scandinavian trial randomized 115 heart transplantation patients to everolimus without calcineurin inhibitor 7-11 weeks after the procedure or standard cyclosporine immunosuppression therapy[59]. The everolimus alone group demonstrated significantly reduced CAV progression[59]. Eisen et al[60] also compared everolimus with azathioprine. Everolimus was more efficient than azathioprine in reducing the severity and incidence of CAV[60]. Several studies compared sirolimus with current immunosuppression therapy, highlighting the antiproliferative and antimigratory effects of sirolimus to hinder CAV progression[61-63]. To muddy the waters, a randomized trial by Arora et al[64] showed no effect on CAV progression in patients that received late everolimus than standard immunosuppression therapy. Matsuo et al[65] validated this theory also using sirolimus. On the evidence of these trials, prompt switch to mTOR needs to be taken into consideration in the presence of CAV[64,65].

Revascularization

Surgical intervention is associated with increased mortality[1,2]. Percutaneous coronary intervention is also an enigma due to the diffuse nature of the disease, and there is no sufficient evidence for any survival benefit over medical therapy[66,67]. Lee et al[66] investigated 105 patients who underwent percutaneous coronary intervention (PCI) with bare-metal stents or drug-eluting stents. A high in-stent restenosis rate was associated with poorer outcomes at 7 years follow-up[66]. Dasari et al[67] showed that drug-eluting stents lowered the long-term risk of in-stent restenosis in comparison to bare-metal stents without affecting survival.

Re-transplantation

Current guidelines recommend re-transplantation for certain patients with progressive CAV[16,68,69]. Re-transplantation is associated with lower survival and increased CAV incidence[16,69].

Conclusions

CAV is a major cause of death post-transplantation and involves over 50% of the recipients within 10 years after the procedure. For patients with severe 3-vessel CAV disease, the one-year mortality could be as high as 90%. Initial intimal thickening shows the progress of the angiographic disorder, the adverse cardiovascular results and the reduced survival. Detection of early CAV is the key to treatment management. Prevention strategies should be initiated promptly, and diagnosing methods focusing on surveillance of early disorder are crucial. Several non-invasive modalities have been proposed to evaluate CAV, but coronary angiography combined with IVUS or OCT remains the accepted standard of care. The combination enables precise visualization of the arterial wall, plaque characterization, and estimate of coronary macrovasculature and microvasculature. The investigation in non-invasive imaging is promising and could assist in medium and long-term follow-up. The current treatment management is based on prevention strategies modifying immune and non-immune targets. The mTOR has been a vital step towards regression of CAV, but their optimal utilization requires further randomized trials.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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