

Review Article

Cardiac Allograft Vasculopathy: Past, Present and Future!

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Abstract

Cardiac Allograft Vasculopathy (CAV) is a serious complication after heart transplantation in adults as well as children and once developed irreversibly compromises the outcome of the recipients. Human leukocyte antigen mismatches, number and duration of rejection episodes, type of immunosuppression and presence of antibody-mediated rejection are among the most relevant immunological risk factors for CAV. Hypertension, hyperlipidemia, diabetes and metabolic syndrome, cytomegalovirus infection, mode of donor brain death, donor age, obesity, smoking and ischemia/reperfusion injury are among the most important non-immunological risk factors. The combination of, non-immunological and immunological risk factors facilitates the more rapid CAV development and progression towards a severe disease. Endothelial injury/dysfunction is the first event triggering the disease process. Inflammation is the central process of CAV development and progression. In order to more effectively affect CAV outcome and prolong survival, treatment with statins is recommended, and novel approaches needed. New immunosuppressive treatments to reduce CAV like mammalian target of rapamycin inhibitors (sirolimus and everolimus) are promptly required. Therapies effective in improving the allograft microvasculature like heparin-induced extracorporeal low-density lipoprotein apheresis, or reducing the ischemia/reperfusion-related damage like fibrin peptide BB15-42 need to be introduced as possible new ways of treatment. Future perspectives for early CAV detection and prevention are: individual CAV risk stratification (immunohistochemistry, risk factor profiles), identification of novel early biomarkers, and a better understanding of antibody-mediated rejection. All unknowns need to be resolved to better and more effectively prevent CAV development and/or reduce CAV progression.

Keywords

- Cardiac allograft vasculopathy
- Ischemia/reperfusion injury
- Endothelial dysfunction
- Capioles
- Risk factors

ABBREVIATIONS

CAV: Cardiac Allograft Vasculopathy; C4d: Complement Split Product 4d; ICAM-1: Intercellular Adhesion Molecule-1; HELP: Heparin-Mediated Extracorporeal LDL/fibrinogen Precipitation

INTRODUCTION

Heart failure affects more than 6 million individuals in the United States and 5-10% of those patients have advanced or stage D disease, which is associated with a very high mortality and very poor quality of life [1,2]. Cardiac transplantation remains the most long-lasting treatment for patients with American College of Cardiology Foundation/American Heart Association stage D advanced heart failure that have exhausted other options, and it is the therapy associated with the best long-term outcomes [3]. Since the first heart transplant performed in 1967, more than 120,000 heart transplants in recipients of all ages have been registered by the International Society for Heart and Lung Transplantation through 2014, with median survival of 11 years for all and 13 years for those surviving the first year [4]. One of the major causes of morbidity and mortality beyond the first year

after transplantation is cardiac allograft vasculopathy (CAV), which is the diffuse transplant coronary artery disease unique to cardiac transplant recipients [3-11]. CAV is characterized by progressive occlusion of arteries in the allografts and becomes a serious late complication following heart transplantation since it affects intramyocardial arteries and arterioles, as well as veins and capillaries, leading to restrictive cardiac allograft physiology and increasing heart failure [7,12-15]. CAV (also known as transplant coronary atherosclerosis, cardiac allograft vasculopathy, transplant vasculopathy, allograft vasculopathy, transplant-associated coronary artery disease, transplant coronary artery disease, coronary allograft vasculopathy, cardiac transplant vasculopathy, cardiac transplant arteriosclerosis, accelerated graft atherosclerosis, transplant atherosclerosis, chronic graft arteriopathy, chronic cardiac allograft rejection or chronic rejection) is a major complication in heart transplantation because it significantly limits long-term graft and patient survival. CAV is a prominent cause of death. Approximately 20% of deaths 1 year after transplantation are due to "graft failure," and graft failure most likely results from processes such as antibody-mediated rejection and CAV [12]. The proportion of deaths confirmed to

be caused by CAV is approximately 10% between 1 and 3 years after transplantation, with further increases in subsequent years. Although the overall survival from heart transplantation has improved significantly over the last 3 decades, primarily because of improved immunosuppressive agents, CAV continues to be a significant cause of death after the first year of transplantation. The prevalence of CAV remains high: 8% at 1 year, 30% at 5 years, and 50% at 10 years after transplantation [11]. After 5 years of transplantation, CAV affects more than 30% of patients and the resulting failure due to CAV eventually accounts for 30% of recipient's deaths after transplantation [13]. CAV is less frequent in pediatric heart transplant recipients than in adults, and the conditional incidence of CAV was recently found to be 5% at 2 years post - transplant, 15% at 5 years and 28% at 10 years post - transplant [9]. Differences in freedom from CAV exist between individual age groups: 16% of infants develop CAV by 9 years post - transplant, 26% of 1- to 5-year-olds, 27% of 6- to 10-year-olds and 37% of 11- to 17-year-olds. Graft survival by 3 years after diagnosis of CAV varies by age with infant recipients faring the worst (infants 42%, 1- to 5-year-olds 55%, 6- to 10-year-olds 69%, 11- to 17-year-olds 64%) [16].

Studies using more sensitive intravascular ultrasound detect new arteriopathy in approximately half of cardiac transplants within 1 year after transplantation [17]. CAV affects the whole microvasculature of the transplanted heart, leading to progressive vessel narrowing that significantly compromises the small arteries and arterioles of the graft. It is irreversible, and the only option for patient survival after this severe narrowing is re-transplantation. Intimal thickening occurring during the first year post - transplantation is most apparent in early and aggressive presentations of CAV. However, patients with late presentations of CAV may have not displayed early pathology and instead have distinct pathological drivers of their disease (i.e., antibody - mediated rejection [18] or yet undefined entities). In order

to prevent CAV development and progression, it is imperative to optimize immunosuppression and treat the comorbidities associated with CAV progression, perhaps beginning at the time of transplantation. Notwithstanding significant advances directed to improving outcomes in the field of heart transplantation [15,19,20]. CAV remains the greatest cause of late deaths after cardiac transplantation, and early diagnosis is essential to reduce deaths from CAV because most of the damage occurs early in the disease process as noted above [20]. The identification of early biomarkers of risk for future CAV is a major concern in heart transplantation [15]. Indeed, early CAV, diagnosed within 1 year of transplantation, is an independent predictor of mortality at 5 years [21].

Immunological risk factors and inflammation

CAV, characterized by circumferential intimal thickening of the arterial tree of the transplanted heart, with proliferation and migration of a heterogeneous group of cells into the intima, is initiated and progresses as a result of both immunological and non - immunological insults (Figure 1) [10,12,13,22]. It has been proposed that endothelial damage is a primary precipitating event in the pathogenesis of CAV. T - lymphocyte responses to endothelial human leukocyte antigens or other endothelial cell antigens are potential sources for endothelial damage. Zheng et al., demonstrated that the coronary arteries of post heart - transplant patients with a prior history of high - grade cellular rejection have increasing amounts of lipid - rich plaque, suggesting that high - grade acute cellular rejection may relate to subsequent development and progression of CAV [23]. A recent study revealed that sustained activation of the immune system because of chronic allorecognition exacerbates the atherogenic diathesis of hyperlipidemia and results in *de novo* cardiovascular dysfunction in organ transplant recipients [24]. Human leukocyte antigen mismatch is a major determinant

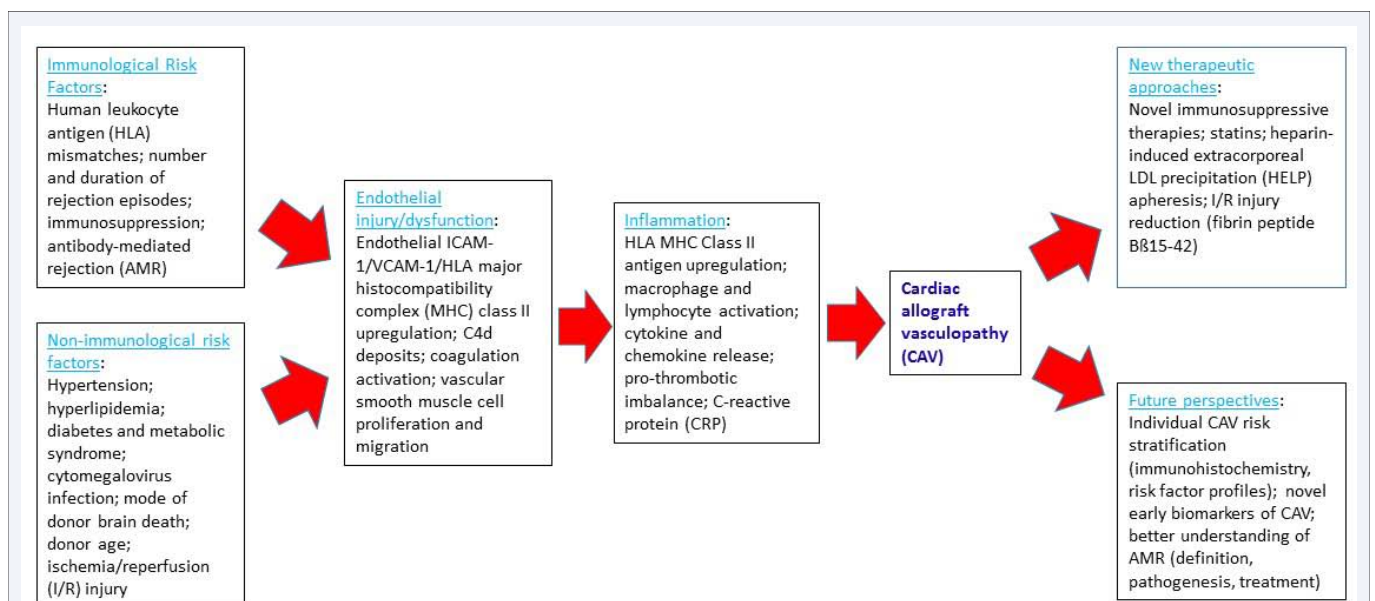


Figure 1 A block diagram of risk factors and treatment. Immunological and non - immunological risk factors, endothelial injury/dysfunction, inflammation, Cardiac Allograft Vasculopathy (CAV), new therapeutic approaches and future perspectives.

for the development of CAV [25,26]. The number of human leukocyte antigen mismatches and the number and duration of cellular rejection episodes increase the risk of CAV [27]. Heart transplant recipients with donor - specific antibodies to human leukocyte antigens class II seem to be at increased risk for accelerated CAV [28]. *De novo* donor - specific antibodies have a strong negative impact on CAV, rejection, and graft survival in pediatric recipients of heart transplants [29]. Circulating antibodies against endothelial cell antigens, such as vimentin, are associated with CAV [30,31]. Clinical studies suggest that anti - vimentin antibodies are associated with CAV in heart transplant recipients [32]. It is possible that anti - vimentin antibodies could be involved in antibody - mediated rejection and subsequent development of CAV [32]. The role of inflammation upon development of CAV is supported by recent studies suggesting a crucial role of the chemokine stromal cell - derived factor 1 also known as chemokine C-X-C motif ligand 12 on neointima formation after injury [33]. The blockade of stromal cell - derived factor 1 caused a significant decrease in neointima formation as measured by intima/media ratio potential therapeutic effect of inhibiting the stromal cell - derived factor 1 /C-X-C chemokine receptor 4/C-X-C chemokine receptor 7 axis with an anti - stromal cell - derived factor 1 Spiegelmer (olaptesedpegol, NOX-A12) on the development of chronic allograft vasculopathy [33]. *In vitro* treatment of primary vascular smooth muscle cells with NOX-A12 showed a significant reduction in proliferation. Transforming growth factor- β , tumor necrosis factor- α and interleukin-6 levels were significantly reduced under stromal cell - derived factor 1 inhibition. Therefore, pharmacological inhibition of stromal cell - derived factor 1 with NOX-A12 may represent a therapeutic option to ameliorate chronic rejection changes [33].

The sequence of events that participate in the development of CAV can be summarized as follows: (a) endothelial cell major histocompatibility molecules are recognized by recipient immune cells; (b) T and B-cells become activated leading to a chronic immune response; (c) secretion of stimulatory cytokines (interleukin-1, interleukin-2, interleukin-4, interleukin-5, interleukin-6, interferon- γ , tumor necrosis factor- α) lead to endothelial activation; (d) endothelial activation induces the expression of endothelial adhesion molecules (intercellular adhesion molecule-1 [ICAM-1], vascular cell adhesion molecule-1); (e) adhesion molecules attract and recruit macrophages into the arterial intima; (f) macrophages accumulate oxidized lipids and become foam cells leading to a sustained inflammatory response; (g) activated cells in the vessel wall produce cytokines and growth factors (platelet - derived growth factor, insulin - like growth factor-1, fibroblast growth factor, heparin - binding growth factor, transforming growth factor- β); (h) cytokines and growth factors stimulate smooth muscle cell proliferation and extracellular matrix deposits characteristic of CAV [34]. This sequence of events in the development of CAV seems to be mirrored by different histopathological phenotypes found associated to the time of transplantation and the clinical patient characteristics [35].

Antibody - mediated rejection occurs in 10-20% of patients after heart transplantation [36]. C4d immunostaining is one parameter used in its diagnosis. Antibody - mediated rejection has been identified as a risk factor for developing CAV. Indeed,

antibody - mediated rejection is another factor that seems to be involved in CAV pathogenesis which increases the incidence of CAV by 10% at 1 year and by 36% at 5 years [37]. The deposition of complement split product C4d in the graft micro vessels associated with antibody - mediated rejection could further contribute to endothelial damage [38]. Recent studies have shown that C4d immunostaining was a significant predictor of CAV and death [36,39,40]. Antibody - mediated rejection is present in a substantial fraction of late failing heart allografts and is associated with severe CAV [41]. Patients with graft dysfunction and donor - specific antibodies or positive C4d on endomyocardial biopsies show increased incidence of CAV, suggesting an antibody - mediated injury [40]. However, the deposition of C4d could reflect non-antigen-dependent complement activation, such as that caused by ischemia/reperfusion injury [42]. Late antibody - mediated rejection is frequently associated with graft dysfunction. When graft dysfunction is present in late antibody - mediated rejection there is an early and sustained increased risk of mortality and rapid development of *de-novo* CAV despite aggressive treatment [18]. Patients who had late antibody - mediated rejection with graft dysfunction had accelerated development of CAV, with 50% having *de novo* CAV within one year of antibody - mediated rejection. Prognosis after late antibody - mediated rejection is poor despite aggressive immunosuppressive therapies. Fulminant CAV is a common condition in these patients. Micro vascular inflammation is frequent in endomyocardial biopsy specimens before manifestation of symptomatic antibody - mediated rejection [43]. Current therapies in heart transplantation target both the T- and B-cell lines. Combinations that include plasmapheresis, intravenous immunoglobulin's, cyclophosphamide, and rituximab have been used in clinical studies with variable success. Two newer agents show promise, targeting both ends of the antibody - mediated spectrum: Bortezomib depletes plasma cell populations, and eculizumab blocks the terminal effects of antibody action, thus preventing myocardial cell dysfunction and death [44].

Since systemic inflammation may be associated with CAV, several investigators have evaluated plasma levels of C - reactive protein with CAV and cardiac transplant graft survival. Pethig et al. [45] suggested that progressive CAV is accompanied by elevated C - reactive protein levels. Labarrere and colleagues [46] demonstrated that early increases in C - reactive protein are associated with an increase in cardiac ICAM-1 expression and soluble ICAM-1 levels, and these findings are predictive of the development of more aggressive CAV and graft failure. Hognestad et al., [47] not only suggested a link between C - reactive protein and CAV but also correlated statin therapy with a decrease in C - reactive protein levels, providing further evidence for the role of innate immunity and inflammation in CAV [48]. It has been recently determined that the prediction of CAV and graft failure due to CAV improves when innate inflammatory markers are added to a previously validated atherothrombotic model [49]. Early inflammatory status, measured by a patient's C - reactive protein level (a non - invasive, safe and inexpensive test), independently predicts CAV and graft failure due to CAV, and adding C-reactive protein to a previously established atherothrombotic model improves its predictive power [49].

Non-Immunological risk factors

Risk factors for CAV include both traditional risk factors such as hyperlipidemia (exacerbated by calcineurin inhibitors), hypertension and diabetes mellitus (worsened by steroids), transplant - related factors such as donor factors (donor age, explosive mode of brain death, intracranial hemorrhage), and other factors like cytomegalovirus infection and ischemia/reperfusion injury [50,51]. Non - immunological risk factors include obesity and smoking [52]; factors that also affect native atherosclerotic disease. Recent evidence based on virtual histology - intravascular ultrasound suggests that ischemic etiology of cardiomyopathy prior to heart transplant may be independently associated with development and progression of plaques and higher cardiac event rate after transplant, highlighting the contribution of atherosclerosis to the pathogenesis of CAV. Biomarkers associated to endothelial injury like apoptotic circulating endothelial cells and apoptotic endothelial micro particles could be used to clinically predict CAV [53].

It is very likely that the combination of both, immunological and non - immunological risk factors is associated with development and subsequent progression of CAV [54]. The final effect of these factors culminates with the activation of the allograft endothelium and the generation of persistent vessel inflammation causing intimal proliferation characteristic of CAV [34].

Endothelial injury/dysfunction: ischemia/reperfusion, coagulation and fibrinolysis

The role of ischemia/reperfusion during the immediate post-transplant period has been emphasized as playing a fundamental role during the short-and long-term outcomes of heart transplant recipients by initially causing early micro vascular damage [55]. Although the normal micro vascular tissue microenvironment is thrombo - resistant, it turns into a pro - thrombotic microvasculature (Figure 2) after cardiac allografts injuries (as a result of perioperative ischemic damage), reperfusion injury, and the risk of allograft rejection. Indeed, patients with myocardial fibrin deposition who concomitantly demonstrate myocardial cell injury evidenced by increased levels of serum cardiac troponin I are at significantly higher risk for developing CAV during follow-up and experience greater late allograft loss [56]. The presence of a pro - thrombotic microvasculature within the graft characterized by early elevation of tissue factor and fibrin and reduction of tissue plasminogen activator and antithrombin in human cardiac allografts are associated with both onset and severity of CAV and graft failure [56-60] supporting the concept that early signs of a hypercoagulable state are relevant for subsequent outcome. Activation of arterial micro vessels (ICAM-1 and major histocompatibility complex class II expression) also predicts CAV and graft failure [61,62]. Labarrere et al., proposed that endothelial cell hypercoagulability drives CAV development and progression, and biomarkers of persistent endothelial cell injury and activation can be used as surrogate markers of CAV.

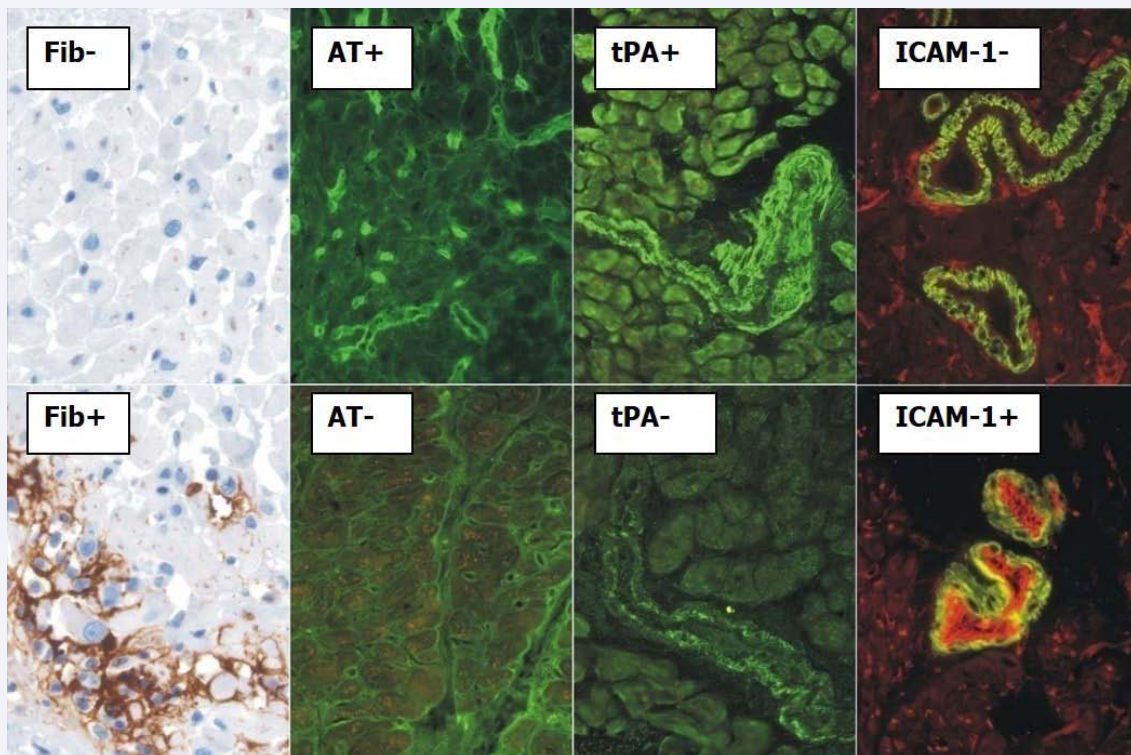
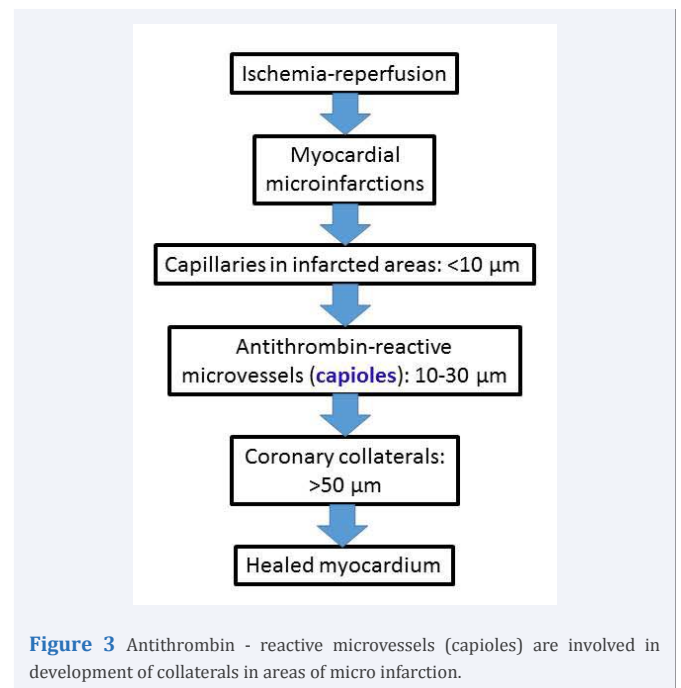


Figure 2 Immunohistochemical characteristics of a normal and a thrombotic/activated microvasculature. A normal heart (top row) shows absence of fibrin (Fib-), presence of micro vascular antithrombin (AT+) and tissue plasminogen activator (tPA+), and absence of arterial endothelial ICAM-1 (ICAM-1-). An abnormal thrombotic/activated heart (bottom row) shows presence of fibrin (Fib+), loss of micro vascular antithrombin (AT-) and tissue plasminogen activator (tPA-), and presence of arterial endothelial ICAM-1 (ICAM-1+). Original magnification X640.

Interestingly, the recovery of micro vascular antithrombin in patients with a pro - thrombotic phenotypic state, is highly associated with a significant improvement in survival [59]. Labarrere et al., [59] believe that antithrombin - reactive micro vessels are the result of development of coronary collaterals demonstrated to predict a favorable prognosis in patients with CAV. Although artery-to-artery or arteriole to arteriole connections cannot be completely demonstrated by histology or immunopathology studies, the extraordinary phenotypic similarity between antithrombin - reactive micro vessels and the collateral capillary arterializations following arteriolar ligation found in mice [63]; and the presence of small vessel disease with a blush pattern [64] found in transplanted hearts with antithrombin - reactive micro vessels strongly suggest these particular vessels are involved in collateral arterial/arteriolar formation. These neovessels have particular phenotypic characteristics. The capillaries that are able to bind antithrombin are generally larger than normal capillaries, and unlike normal capillaries, they react with antibodies to the Pathologische Anatomie Leiden -Endothelium (PAL-E) antigen [65,66] (an antigen normally found only in venules, small to medium - size veins, and capillaries with the altered vascular permeability state observed in angiogenesis [67]) and smooth-muscle-specific alpha actin [63,65,66]. It is possible that the novel capillary antithrombin - binding is associated with neovessel formation or vascular remodeling involving pericytes or smooth muscle cells and phenotypic changes on capillary endothelium [65,66]. Although their size and abundance would more likely classify these vessels as capillaries, experimentally it is evident these capillaries may in fact be undergoing some sort of transition or vascular remodeling involving smooth-muscle-specific alpha-actin-reactive pericytes or smooth muscle cells, which are not commonly associated with quiescent capillaries. It is tempting to suggest, based on their vascular phenotypic characteristics, that these are capillaries with altered permeability and some features of very small arterioles ("capioles"). These capiules with strong anticoagulant properties in areas of micro infarction can lead to the generation of collateral vessels and subsequent healing of the damaged areas (Figure 3). This suggests that interventions aimed at promoting collateral and micro vascular growth may serve as effective therapies for CAV [68].

CAV also limits the lifespan of pediatric heart transplant recipients. Recent investigations directed to identify blood markers of inflammation, endothelial dysfunction and damage to the transplanted vasculature in children after heart transplantation suggest that subclinical inflammation is present and that natural anticoagulant/thrombomodulin activity is important after transplantation [69].

Hypercoagulability and loss of fibrinolytic activation, as well as enhanced activation of the micro vascular endothelium, are detectable very early, within the first few days after transplantation in many patients, suggesting that ischemia/reperfusion injury may be a contributor to long - term outcome. Massive ICAM-1-mediated micro vascular fibrinogen deposition and platelet adhesion have been shown to occur as early as 10 minutes after reperfusion [70]. Interestingly, Rose [32] has shown that anti-vimentin antibodies could be participants in the development and progression of a pro - thrombotic micro vascular



state since the interaction between anti - vimentin antibodies, neutrophils and platelets contributes to the pro - thrombotic phenotype leading to CAV. Pathophysiologically, ischemia/reperfusion promotes endothelial dysfunction and CAV by triggering platelet adhesion, provoking release of growth factors, up regulating major histocompatibility class I and II antigens, stimulating release of donor antigens, and promoting adhesion molecule expression and smooth muscle cell proliferation [71,72]. On risk - adjusted models, measures of myocardial injury (troponin I), pro - thrombosis (myocardial fibrin, depleted arteriolar tissue plasminogen activator and vascular antithrombin), inflammation, and "immune activation" (ICAM-1, human leukocyte antigen - DR) were all independently predictive of the late development of CAV and graft loss. It was recently shown that when information from all markers is combined to produce the best single composite measure, however, loss of tissue plasminogen activator is the dominant and often, the only predictor of long - term risk [49]. Fibrin deposits after ischemia/reperfusion detected in the first post -transplant biopsy obtained at a median 9 days following the procedure [73] would normally be removed by activation of the fibrinolytic system. Fibrin deposits persist if there is early loss of tissue plasminogen activator, however, which may partially explain why tissue plasminogen activator depletion was the dominant predictor in the models. In this regard, gene polymorphisms for plasminogen activator inhibitor-1 and tissue plasminogen activator evaluated in the context of CAV development have suggested that recipients with a 2/2 plasminogen activator inhibitor-1 genotype are at a significant risk of developing the disease [74]. Of note, "absence" of early markers of atherothrombotic risk identifies a heart - transplant subgroup that "rarely" develops CAV and long - term graft failure due to CAV. In support of the role of a dysfunctional allograft microvasculature in the development and progression of CAV, it was recently shown that coronary micro vascular dysfunction correlates with the new onset of CAV in heart

transplant patients with normal coronary angiography [75] the micro vascular changes are associated with hypertrophic remodeling of coronary arterioles [76] and everolimus appears to prevent such micro vascular remodeling and preserves coronary flow reserve [76]. The fact that a high - risk patient subgroup is identifiable so early following transplantation (in some cases, within days of the transplant procedure) suggests again the possibility that very early events, such as tissue reperfusion injury related to the transplant procedure itself, may produce long - term consequences for these patients. Recent studies have shown the potential utility of using plasma protein bio signatures for detection of CAV [77].

Diagnosis and Monitoring

Diagnosis and monitoring of CAV depend mostly on invasive techniques, such as coronary angiography and intravascular ultrasound. The International Society for Heart and Lung Transplantation guidelines recommended that annual or biannual coronary angiography should be considered to assess the development of CAV [78]; and patients free of CAV at 3 to 5 years after heart transplantation, especially those with renal insufficiency, may undergo less frequent invasive evaluation. A follow - up coronary angiography is recommended at 6 months after a percutaneous coronary intervention because of high restenosis rates in heart transplant recipients. In pediatric heart transplant recipients, coronary angiography should be performed at yearly or biannual intervals. Although coronary angiography is less invasive than intravascular ultrasound is only moderately sensitive in detecting early CAV [22]. Patients with only mild angiographic CAV have significantly better outcomes than do patients with moderate or severe disease. The presence of an ejection fraction < 45%, a right atrial pressure > 12 mm Hg, or a pulmonary capillary wedge pressure > 15 mm Hg identifies children at increased risk of graft loss even in the presence of only mild angiographic vasculopathy [9]. On the other hand, intravascular ultrasound has been found to be valuable in prediction of both CAV and other cardiovascular end points [22] and is one of the best available surrogate markers for predicting outcomes from CAV. CAV progresses during the first year after heart transplantation significantly more frequently in patients with donor - transmitted atherosclerosis and maximal intimal thickness ≥ 0.5 mm. It is essential in these patients to implement an intravascular ultrasound control examination one year after transplantation. The results can lead to a change in treatment strategy to prevent further progress of the disease [79]. A recent 3D volumetric intravascular ultrasound study showed that despite the diffuse nature of CAV, paradoxical artery remodeling of the proximal left anterior descending segment at 1-year after transplantation was the primary determinant of long - term mortality or re - transplantation [80]. Paradoxical vessel remodeling was defined as increased intimal volume with negative vessel remodeling (decreased vessel volume) or decreased intimal volume with positive vessel remodeling (increased vessel volume) during the first year post - transplantation [80], calculated mathematically as: $[\Delta \text{ vessel volume} / \Delta \text{ intimal volume} < 0]$. The combined evaluation of arterial remodeling with coronary intimal thickening may enhance the prognostic value of intravascular ultrasound to identify high - risk patients who may benefit from closer follow - up and targeted medical therapies.

International Society of Heart and Lung Transplantation guidelines recommended intravascular ultrasound in conjunction with coronary angiography with a baseline study at 4 to 6 weeks and at 1 year after heart transplantation as an option to exclude donor coronary artery disease, to detect rapidly progressive CAV, and provide prognostic information [78].

Intravascular ultrasound only detects changes in epicardial arteries, however, and cannot detect changes that occur in intramyocardial arteries and other micro vascular vessels within the transplanted heart. Studies examining myocardial tissue perfusion on routine angiography suggest that microcirculatory abnormalities tend to be present across all coronary territories in cardiac transplant recipients and are associated with poor survival which supports a generalized micro vascular involvement even in the presence of a normal angiogram [81]. The inability to directly visualize the artery wall with conventional angiographic techniques has stimulated development of a number of intravascular imaging modalities. These approaches have the potential to provide a more comprehensive characterization of the burden, composition and functionality of atherosclerotic plaque, neointimal hyperplasia and allograft vasculopathy that develop within coronary arteries [82]. Non - invasive methods that directly determine structural and functional alterations of the coronary microcirculation are needed in severe CAV [83,84]. New insights to characterize plaque morphology in CAV extending far beyond the current concept of concentric and fibrosing vasculopathy into the development of atherosclerosis with vulnerable plaque and complicated coronary lesions has been recently described [85]. Optical coherence tomography provides high (10-20 μm) resolution (10-fold greater than intravascular ultrasound) intravascular imaging and it is particularly ideal for the evaluation of the arterial intima and plaque morphology [50]. Optical coherence tomography has been shown to reliably detect CAV in adult and pediatric heart transplant recipients [85-89]. Intimal thickness and plaque characteristics evaluated by optical coherence tomography have been validated against histology and intravascular ultrasound [50]. Notwithstanding, optical coherence tomography has several limitations including cost, contrast requirements, lower tissue penetration limiting evaluation of deep plaque features and like intravascular ultrasound being unable to evaluate the cardiac microvasculature. Since CAV affects both the macro (epicardial) and microcirculatory compartments, it is important to be able to evaluate both vascular compartments, and the use of invasive coronary sensor pressure and flow wires allows evaluation of both, epicardial arteries and microvasculature by measuring fractional flow reserve and index of microcirculatory resistance, respectively. Coronary flow across macro and micro vascular compartments is measured by coronary flow reserve. Chih et al., [50] reviewed that normal fractional flow reserve with reduced coronary flow reserve represented diffuse epicardial or micro vascular CAV; and for a given epicardial plaque burden, increased fractional flow reserve was found associated with deteriorated index of microcirculatory resistance. They concluded that "both scenarios reflect the reduced physiological impact of epicardial disease in the presence of micro vascular dysfunction and increased micro vascular resistance as the maximal achievable coronary flow is diminished". These data emphasize the point

that it is very important to evaluate the epicardial arteries and intramyocardial micro vasculature in CAV since this is a pan vascular disease. The graft microvasculature is affected early after transplantation and micro vascular dysfunction (reduced coronary flow reserve, increased index of microcirculatory resistance, abnormal vasoconstrictor response to acetylcholine) predicts development of CAV [50,90,91].

Noninvasive evaluation of left ventricular longitudinal myocardial deformation during exercise is feasible and strongly associated with the presence and degree of CAV. Exercise stress myocardial deformation analysis, echocardiographic coronary flow velocity reserve, or positron emission tomography coronary flow reserve may serve as a noninvasive model for the detection of CAV [92]. Cardiac magnetic resonance represents a valuable noninvasive diagnostic tool, which may be used for the early detection of transplant micro vasculopathy before the manifestation of CAV during diagnostic coronary angiographic procedures [93]. Since noninvasive tools exist to quantitatively evaluate the microvasculature, it is time to focus more on the micro vessels of the transplanted heart. The challenge is developing effective therapies that can prevent or reverse the early features of micro vascular disease [94]. In the continuous saga to find CAV early biomarkers, it has been recently shown that a significantly elevated pulmonary capillary wedge pressure at the time of the diagnosis of transplant coronary artery disease may be considered as an early marker of CAV, especially in asymptomatic heart transplant recipients [95].

New therapeutic approaches and future perspectives

Given the relatively poor prognosis of CAV, prevention remains an important strategy. Prophylaxis of CAV starts with modification of risk factors: hypertension, hyperlipemia, hyperglycemia, obesity, and smoking, as well as promotion of exercise programs [96]. Indeed, high intensity aerobic exercise reduces systolic blood pressure and improves endothelial function in heart transplant recipients. Furthermore, exercise modulates inflammation reducing C - reactive protein levels and could potentially play a significant role in prevention of CAV [97]. Accordingly, all prevention strategies have to be implemented early after transplantation, at the time of the procedure itself, and all efforts to detect early disease are essential. At present it is more likely that invasive techniques will best detect early CAV at the macro and micro vascular levels, using a combination of high - resolution studies of the arterial intima by intravascular ultrasound or optical coherence tomography and coronary physiology studies to evaluate the microvasculature [50]. Furthermore, prevention strategies are presently directed to modifiable immune and non immune factors, and mammalian target of rapamycin inhibitors have been a significant advance in reducing the progression of CAV [50]. The use of proliferation inhibitors (sirolimus and everolimus) has been shown to alter the course of the disease [98,99] and may decrease the rate of CAV progression [100]. Conversion to everolimus from mycophenolate mofetil in maintenance periods after heart transplantation may decrease the rate of CAV progression based on intravascular ultrasound indices [100]. This is a very important issue in heart transplantation in general, and CAV in particular, since greater severity of CAV is

associated with progressively worse long - term survival among heart transplant recipients [101] and although percutaneous intervention improves survival in patients with severe CAV, the outcomes still are not ideal. Everolimus is significantly more efficacious than mycophenolate mofetil in restricting progression of intimal thickening and preventing CAV as measured by intravascular ultrasound 1-year post- transplant. This finding was robustly observed in various subgroups including different lipid categories. These results appear robust irrespective of sex, age, diabetic status, donor disease, baseline low - density lipoprotein cholesterol levels, high levels of total cholesterol, low - density lipoprotein cholesterol, and triglycerides and low levels of high - density lipoprotein at month 12 post - transplant [102]. Selective use of early calcineurin inhibitor withdrawal after heart transplantation supported by everolimus, mycophenolic acid and steroids with lymphocyte - depleting induction may offer adequate immunosuppressive potency with a sustained renal advantage [103]. Everolimus seems to improve the allograft microvasculature since it appears to prevent such micro vascular remodeling and preserve coronary flow reserve [76].

Statin therapy following transplant remains the standard of care to help prevent the progression of CAV. The benefits of statin therapy following transplantation correspond to cholesterol control, anti - inflammatory (it reduces C - reactive protein levels) and immunomodulatory mechanisms as well as potentially unknown mechanisms. Despite known drug interactions with calcineurin inhibitors, the use of statins is highly recommended in the current International Society for Heart and Lung Transplantation guidelines. Limited research has been conducted on the impact of higher intensity statin therapy following heart transplantation and the relative risks and benefits are unknown [104]. Treatment of nonimmunologic factors to ameliorate CAV progression is designed to decrease hyperhomocysteinemia, hyperlipidemia, hypertension, and oxidative stress, and provide anti - cytomegalovirus therapy and diabetes control [70]. Suitable patients with advanced disease may undergo revascularization with percutaneous coronary interventions, coronary artery bypass grafting, transmyocardial laser revascularization, and Heparin - mediated Extracorporeal LDL/fibrinogen Precipitation (HELP) apheresis treatment. Interestingly, myocardial perfusion in transplanted hearts increases significantly after single HELP - apheresis treatment providing complementary evidence to clinical long-term studies showing that cholesterol reduction either with statins and/or apheresis improves heart transplant outcome. Myocardial perfusion in transplanted hearts increases significantly after reduction of low - density lipoprotein - cholesterol, lipoprotein (a), C - reactive protein and fibrinogen plasma levels following apheresis treatment in transplanted patients with severe CAV [105]. This further suggests that improving the status of the micro vessels in transplanted hearts with severe CAV may be considered as a novel therapy to increase survival. Understanding the physiopathology of endothelial and micro vascular dysfunction in CAV plays a crucial role in the development of new therapies [106].

The oxidative stress associated with ischemia/reperfusion of cardiac allografts leads to cytokine production and expression of pro - inflammatory adhesion molecules. This is one of the most important alloantigen - independent factors associated

with CAV and various strategies to ameliorate this oxidative stress have been studied. Antioxidants such as riboflavin [107] and superoxide dismutase - mimetics [108] have been found to decrease oxidative stress and reduce the incidence of CAV in murine models of cardiac transplantation. Peroxisome proliferator - activated receptors γ receptor agonists such as pioglitazone also reduce oxidative stress and have been shown to reduce CAV [109,110].

Revascularization by interventional cardiology or cardiothoracic surgical approaches has been attempted to correct discrete stenosis along the coronary arteries [15]. Placement of coronary stents is associated with rapid restenosis and sirolimus - coated drug - eluting stents didn't show significant CAV improvement compared with placement of bare metal stents [111]. Furthermore, the use of stent placement is of temporary and short-term usefulness since CAV is a diffuse disease compromising all the microvasculature and not only the major coronary arteries. Revascularization by coronary artery bypass grafting surgery for CAV post heart transplant have had high rates of periprocedural mortality and low rates of survival at 1 year post coronary artery bypass grafting [15]. Percutaneous revascularization can now be performed with new - generation drug - eluting stents (which are more effective than bare metal stents or first - generation sirolimus - coated drug - eluting stents) or with bioresorbable vascular scaffold, as recently suggested [112]. Since percutaneous coronary stent placement is likely a temporizing measure and given the poor outcomes post coronary artery bypass grafting, redo heart transplantation is an option for select patients. Annually, the rate of retransplantation is 2-4% of heart transplant recipients. These rates have remained stable for many years. CAV represents the leading cause of need for retransplantation. Survival rates after retransplantation are inferior to the survival rates after index heart transplant. Survival at 1 year after retransplantation is 70% and the 10-year survival after retransplantation is 38%. Outcomes for pediatric patients who undergo retransplantation are superior to the outcomes seen in adult patients who undergo retransplantation [12]. Retransplantation may be a consideration for selected patients.

DISCUSSION & CONCLUSION

CAV is a major complication that limits survival after heart transplantation, and a clear understanding of the underlying pathophysiological processes involved in CAV development and progression is extremely important [34]. The main reason why CAV is so detrimental for the long - term outcome of the transplanted hearts is the pan vascular compromise of the disease affecting from arteries having different types of lesions [113] to veins including capillaries and understanding the pathogenesis of these lesions will facilitate the introduction of novel and more efficacious therapies to prevent the disease. The diagnosis of CAV can be difficult but is possible with the appropriate imaging techniques. Effective treatment of CAV remains an important clinical challenge and the current immunosuppressive therapies have limited effectiveness. Although newer immunosuppressive agents have demonstrated promising results in clinical trials, agents that effectively can ameliorate or impede a rapid development and progression of CAV are still seriously needed. A pivotal issue regarding CAV development and progression is

the identification of early biomarkers that can detect patients that are prone to develop the disease. All these questions are unknowns that need to be resolved in order to better understand the disease and introduce specific targeted therapies that more effectively can impede CAV development and progression [114].

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