

Cardiac allograft vasculopathy: Microvascular arteriolar capillaries ("capioles") and survival

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TABLE OF CONTENTS

1. Abstract
2. Introduction
3. CAV: risk factors and pathogenesis
 - 3.1. Immunological risk factors and inflammation
 - 3.2. Non-immunological risk factors
 - 3.3. Endothelial injury/dysfunction: ischemia/reperfusion, coagulation and fibrinolysis
 - 3.4. Microvascular arterial capillaries ("capioles") and survival
4. Diagnosis and monitoring
5. New therapeutic approaches and future perspectives
6. Conclusions
7. Acknowledgement
8. References

1. ABSTRACT

Cardiac allograft vasculopathy (CAV) is a serious complication of heart transplantation in adults and children. Risk factors include human leukocyte antigen mismatches, number and duration of rejection episodes, type of immunosuppression, antibody-mediated rejection, hypertension, hyperlipidemia, obesity, smoking, diabetes, cytomegalovirus infection, mode of donor brain death, donor age and ischemia/reperfusion injury. Endothelial injury and dysfunction in CAV are characterized by changes in adhesion molecules and up-regulation of major histocompatibility class II antigens followed by endothelial activation of complement C4d. Subsequently, activation of the coagulation cascade leads to deposition of fibrin on endothelium followed by proliferation and migration of vascular smooth muscle cells. The development of a special type of microvessels with phenotypic characteristics of arterial capillaries ("capioles") seems to provide a survival advantage for patients with CAV. Novel therapies of CAV include statins, and heparin-induced extracorporeal low-density lipoprotein apheresis. Bbeta15-42 which is a fibrin peptide has been shown to improve the graft microvasculature and to reduce ischemia/reperfusion-induced damage. Despite these advances, there is a need to identify and stratify individual CAV risk factors, to develop early biomarkers of CAV, and to better decipher the events that lead to antibody-mediated rejection.

2. INTRODUCTION

Heart failure is an epidemic threat which increases in frequency in aging populations. This condition is a significant global health problem, that leads

to excessive medical expenditure and imposes a large burden on economy (1,2). Despite significant advances in cardiovascular medicine, management and surgery, heart failure-associated mortality rates remain high, with almost half of the patients dying within five years of diagnosis. As a multifactorial clinical syndrome, there is a need for deeper insights into the mechanisms of this condition and the development of innovative therapeutic strategies for its prevention and treatment.

Heart failure affects more than 6 million individuals in the United States and 5-10% of those individuals has advanced or stage D disease, that is associated with high mortality and poor quality of life (3, 4). Heart 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 (5). 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 a median survival of 11 years for all and 13 years for recipients surviving the first year (6).

One of the principal causes of morbimortality beyond the first year post-transplant is cardiac allograft vasculopathy (CAV), which is a diffuse transplant coronary artery disease unique to cardiac transplant recipients (5-13). CAV is characterized by progressive occlusion of the graft arteries and becomes a serious late complication after heart transplantation since it not only affects epicardial arteries but intramyocardial arteries

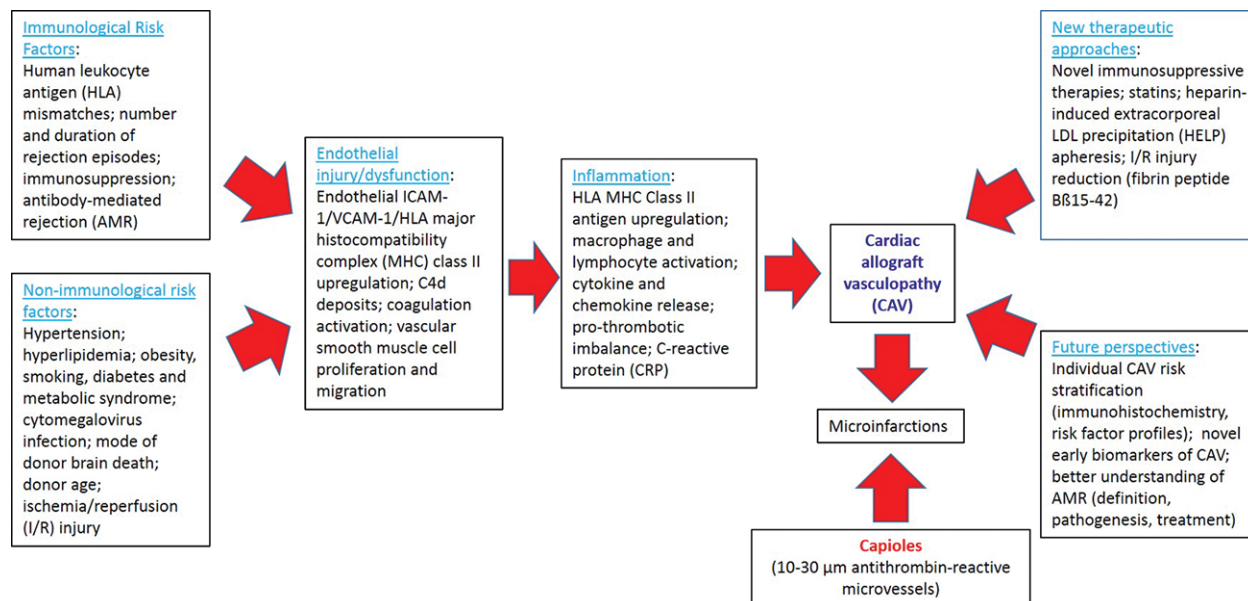


Figure 1. A block diagram of risk factors and treatment. Immunological and non-immunological risk factors, endothelial injury/dysfunction, inflammation, cardiac allograft vasculopathy (CAV), development of microinfarctions and development of capioles for survival, new therapeutic approaches and future perspectives.

and arterioles, as well as veins and capillaries, leading to restrictive cardiac allograft physiology and increasing heart failure (9, 14-17). CAV is a major complication in heart transplantation because it significantly limits long-term graft and patient survival. CAV is a principal cause of death. Near 20% of deaths 1-year post-transplant are associated with graft failure due to antibody-mediated rejection and CAV (14). The proportion of deaths confirmed to be caused by CAV is roughly 10% 1 to 3-years post-transplant, with further increases in subsequent years.

Although the overall survival from heart transplantation improved significantly over the past 30 years, primarily due to the introduction of new immunosuppressive agents, CAV continues to be a significant cause of death following the first year post-transplant. The prevalence of CAV remains high: 8% at 1 year, 30% at 5 years, and 50% at 10 years (13). CAV affects more than 30% of transplanted patients after 5 years and failure due to CAV eventually accounts for 30% of recipients' deaths following transplantation (15). CAV is less frequent in pediatric heart transplantation, and the incidence of CAV in the pediatric population was recently found to be 5% at 2 years, 15% at 5 years and 28% at 10 years following transplantation (11). Differences in freedom from CAV are identified between individual age groups: 16% of infants, 26% of 1- to 5-year-olds, 27% of 6- to 10-year-olds and 37% of 11- to 17-year-olds develop CAV by 9-years post-transplant. Graft survival by 3 years after the diagnosis of CAV varies by age with infant recipients having the worst outcomes (infants 42%, 1- to 5-year-olds 55%, 6- to 10-year-olds 69%, 11- to 17-year-olds 64%) (18).

Intravascular ultrasound detects new arteriopathy in nearly half of cardiac transplants within 1 year of transplantation (19). CAV compromises the entire graft microvasculature, leading to progressive vessel narrowing that significantly affects the graft small arteries and arterioles. CAV is irreversible, and the only alternative for patient survival after severe narrowing is re-transplantation. Most of the intimal thickening occurs during the first year after transplantation and to prevent CAV development and progression, it is essential to optimize immunosuppressive therapies and treat the CAV-related comorbidities since the moment of transplantation. Notwithstanding significant advances for improving outcomes in heart transplantation (17, 20, 21), CAV remains the major cause of late deaths, and early diagnosis is essential to reduce CAV-related deaths (21). Identification of early risk biomarkers of CAV is a major concern in heart transplantation (15) since early CAV, diagnosed within 1 year of the procedure, is an independent predictor of 5-year mortality (22).

3. CAV: RISK FACTORS AND PATHOGENESIS

3.1. Immunological risk factors and Inflammation

CAV defined by the circumferential intimal thickening of the arterial vasculature of the transplanted heart, with proliferation and migration of a heterogeneous group of cells into the intima, develops and progresses as a result of immunological and non-immunological insults (Figure 1) (12, 14, 15, 23). Endothelial damage is

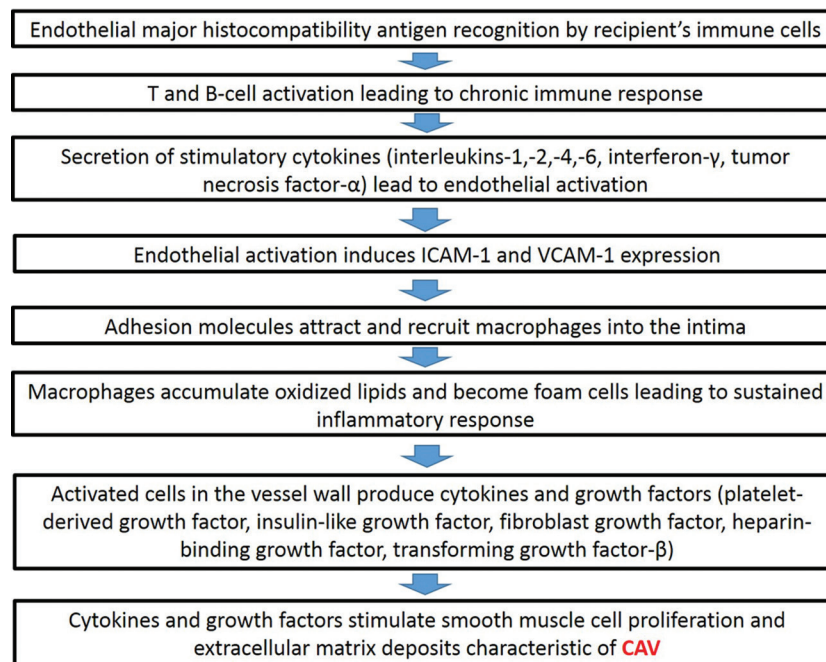


Figure 2. Sequential steps in the development and progression of cardiac allograft vasculopathy (CAV).

a leading 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. 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 (24).

The persistent activation of the immune system due to chronic allorecognition exacerbates the atherogenic diathesis of hyperlipidemia resulting in de novo cardiovascular dysfunction in organ transplant recipients (25). Human leukocyte antigen mismatch is a major determinant for CAV development (26, 27). The number of human leukocyte antigen mismatches and the number and duration of cellular rejection episodes increase the risk of CAV (28). Heart transplant recipients with donor-specific antibodies to human leukocyte antigens class II seem to be at increased risk for accelerated CAV (29). De novo donor-specific antibodies have a strong negative impact on CAV, rejection, and graft survival in pediatric recipients of heart transplants (30).

Circulating antibodies against endothelial cell antigens, like vimentin, are associated with CAV (31-33). It is possible that anti-vimentin antibodies could be involved in antibody-mediated rejection and subsequent CAV development (33). 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 (chemokine C-X-C motif ligand 12) on neointima formation after injury (34). The blockade of stromal cell-derived factor 1 Spiegelmer (olaptesed pegol, NOX-A12) lead to a significant decrease in neointima formation (34). Furthermore, treatment of primary vascular smooth muscle cells with NOX-A12 lead to a significant reduction in proliferation. Transforming growth factor-beta, tumor necrosis factor-alpha and interleukin-6 levels were significantly reduced under stromal cell-derived factor 1 inhibition, supporting the idea that reducing inflammatory mediators ameliorates atherosclerosis-like lesions. Therefore, pharmacological inhibition of stromal cell-derived factor 1 with NOX-A12 may represent a therapeutic option to mitigate CAV (34).

The development and progression of CAV can follow sequential steps (Figure 2): (1) endothelial major histocompatibility molecules are recognized by recipient immune cells; (2) T and B-cells become activated leading to a chronic immune response; (3) secretion of stimulatory cytokines (interleukins-1, -2, -4, -5, and -6, interferon-gamma, tumor necrosis factor-alpha) lead to endothelial activation; (4) endothelial activation induces expression of endothelial adhesion molecules (intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1); (5) adhesion molecules attract and recruit macrophages into the arterial intima; (6) macrophages accumulate oxidized lipids and become foam cells leading to a sustained inflammatory response; (7) activated cells in the vessel wall produce cytokines and growth factors (platelet-derived growth factor, insulin-like growth

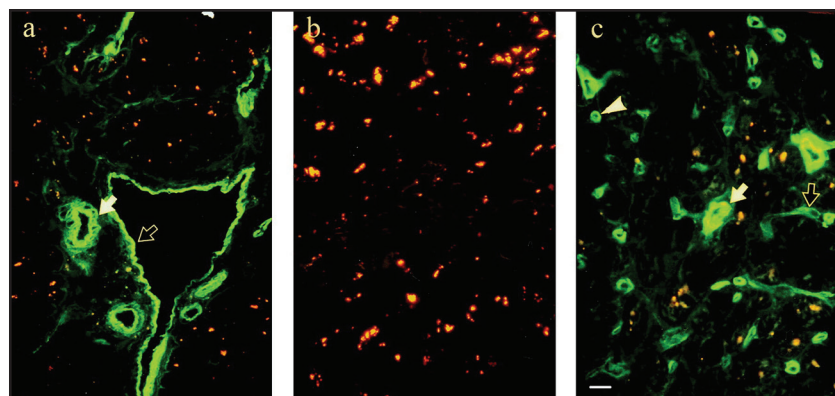


Figure 3. Antithrombin reactivity of heart biopsy specimens. Note (a) arterial (arrow) and venous (open arrow) antithrombin in normal heart, (b) absence of antithrombin detected during the first 3-months post-transplant in a heart that subsequently developed CAV 1 year after transplantation, and (c) arterial (arrow), venous (open arrow), and unusual capillary (arrowhead) antithrombin ("capioles") developed during the first 3 months after transplantation in a heart that remained free of CAV 5 years after transplantation. Scale bar in c, 50 μ m. Original magnification X 400.

factor-1, fibroblast growth factor, heparin-binding growth factor, transforming growth factor-beta); (8) cytokines and growth factors stimulate smooth muscle cell proliferation and extracellular matrix deposits characteristic of CAV (35). The sequence of events in CAV development seems to involve different histopathological phenotypes found associated with the time of transplantation and the clinical patient characteristics (36).

Antibody-mediated rejection is another factor that seems to be involved in the pathogenesis of CAV. Antibody-mediated rejection 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 graft microvessels associated with antibody-mediated rejection could contribute to endothelial damage (38). Recent studies have shown that C4d immunostaining is a significant predictor of CAV and death (39-41). Antibody-mediated rejection is present in a significant number of late failing heart transplants and is associated with severe CAV (42). Patients with allograft dysfunction and donor-specific antibodies or positive C4d on endomyocardial biopsies have increased incidence of CAV, suggesting an antibody-mediated injury (40). C4d deposition could also reflect non-antigen-dependent complement activation, however, such as that caused by ischemia/reperfusion injury (43).

3.2. Non-immunological risk factors

Risk factors for CAV include traditional risk factors like hyperlipidemia (exacerbated by calcineurin inhibitors), obesity, smoking, hypertension and diabetes (worsened by steroids), transplant-associated factors like donor age, explosive mode of donor brain death, donor intracranial hemorrhage, and other factors like cytomegalovirus infection and ischemia/reperfusion injury. Recent evidence based on virtual histology-intravascular ultrasound suggests that donor ischemic cardiomyopathy may be independently associated with

development and progression of plaques and higher cardiac events rate after transplantation which highlights the contribution of atherosclerosis to the pathogenesis of CAV. Biomarkers associated with endothelial injury like apoptotic circulating endothelial cells and apoptotic endothelial microparticles may be used to clinically predict CAV (44).

It is possible that the combination of immunological and non-immunological risk factors is associated with development and progression of CAV (45). The final effect of these factors leads to activation of allograft endothelium and generation of persistent vessel inflammation that causes intimal proliferation characteristic of CAV (35). A summary of the different risk factors for CAV, their current biomarkers, treatment strategies, therapeutic targets and treatment side effects is shown in Table 1.

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

Ischemia/reperfusion immediately following transplantation seems to play a fundamental role in short- and long-term heart transplant outcomes by inducing early microvascular damage (46). Although the normal microvascular myocardial microenvironment is thrombo-resistant, it turns pro-thrombotic following cardiac allograft injuries as a result of perioperative ischemic damage, reperfusion injury, and allograft rejection. Recipients with myocardial microvascular fibrin and myocardial cell injury (as demonstrated 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 (47). The presence of a pro-thrombotic microvasculature in human cardiac allografts (as defined by early elevation of tissue factor and fibrin and reduction of tissue plasminogen activator and antithrombin) are associated with both onset and severity of CAV and graft failure (47-51), supporting

Table 1. Risk factors, current biomarkers and therapeutic strategies (including therapeutic targets and treatment side effects) for cardiac allograft vasculopathy (CAV)

Risk factors	Current biomarkers	Treatment strategies	Therapeutic targets	Treatment side effects
Human leukocyte antigens mismatches	Anti-HLA antibodies	Immunosuppression	T- and B-cell populations	Infection, nephrotoxicity, diabetes, hyperlipidemia, malignancies
Number and duration of rejection episodes	Endomyocardial biopsies, Micro RNA profiling	Increased Immunosuppression	T- and B-cell populations	Infection, nephrotoxicity, diabetes, hyperlipidemia, malignancies
Type of immunosuppression	Personalized immunosuppression: biomarkers assessing risk of rejection (interferon-gamma, interleukin-2, T-cell surface antigens), individual response to immunosuppressants (target enzyme activity, T-cell subsets), graft dysfunction (cytokines, chemokines) (112)	Tailor immunosuppression to individual patient's needs	T- and B-cell populations	Infection, nephrotoxicity, diabetes, hyperlipidemia, malignancies
Antibody-mediated rejection	Capillary edema, macrophage infiltration and microthrombi in biopsies, microvascular C4d, capillary CD68 macrophages, microvascular fibrin, donor-specific antibodies	Corticosteroids, Plasmapheresis/ immunoadsorption with/ without intravenous immunoglobulins (IVIg), Rituximab, bortezomib, eculizumab, alemtuzumab, splenectomy	Circulating antibodies, T and B cells, complement activation, plasma cells	Corticosteroids: Dyslipidemia, hyperglycemia, osteoporosis; plasmapheresis: rebound antibodies, bleeding, hypotension, allergic reactions, pathogens transmission; IVIg: fever, myalgia, volume overload; rituximab: Thrombotic events
Hypertension (secondary to immunosuppression: calcineurin inhibitors, steroids)	Systolic/diastolic blood pressure	Antihypertensive drugs (calcium channel blockers, angiotensin converting enzyme inhibitors)	Blood pressure	Headaches, dizziness, lightheadedness, fainting, bleeding gums, nausea
Hyperlipidemia (secondary to immunosuppression)	Low-density lipoprotein cholesterol (LDL<100 mg/dl)	Diet and monitoring, statins	LDL cholesterol	Muscle pain, rhabdomyolysis, hepatotoxicity (statins)
Diabetes (secondary to immunosuppression: steroids, cyclosporine, tacrolimus)	Glucose levels	Diet and monitoring, adjust immunosuppressive treatment	Blood glucose	Immunosuppression-related side effects
Obesity (pre-transplant and immunosuppression-related)	Body mass index (BMI)	Diet, exercise	BMI<30	Immunosuppression-related side effects
Smoking	Nicotine's metabolite and expired carbon monoxide levels	Smoking cessation	Cotinine, carbon monoxide	Anti-depressants (bupropion) side effects
Cytomegalovirus infection	Cytomegalovirus (CMV)-specific T-cell monitoring	Val (Ganciclovir)	CMV DNA polymerase chain reaction analysis	Anemia, diarrhea, headache, numbness and tingling, retina detachment, fever
Mode of donor brain death (linked to impaired graft quality and immunogenicity)	Cardiac function markers, catecholamine levels, apoptosis (caspase) and necrosis (troponin I) markers, proinflammatory cytokines and adhesion molecules levels, complement and coagulation activation markers	Steroid treatment and therapeutic hypothermia (donors)	Hemodynamic, hormonal, metabolic, and inflammatory monitoring	Steroid-related side effects

(Contd...)

Table 1. (*Continued....*)

Risk factors	Current biomarkers	Treatment strategies	Therapeutic targets	Treatment side effects
Donor age (subclinical coronary artery disease)	CAV Imaging	Treatment for CAV risk factors, statins	Monitoring to minimize CAV development	Statins-related side effects, side effects associated with treatment of CAV risk factors
Ischemia/reperfusion injury	Brain natriuretic peptide, troponins T and I, caspase 3	Blockade of cytokines/chemokines, adhesion molecules, NF- κ B, specific MAP kinases, metalloproteinases, induction of protective genes, and modulation of the innate immune system, fibrin derived peptide Bbeta (15-42)	Monitoring of myocardial damage	Side effects associated with different ischemia-reperfusion treatments

the concept that an early hypercoagulable state is a biomarker of CAV.

The activation of arterial microvessels, evidenced by ICAM-1 and major histocompatibility complex class II antigen expression, also predicts CAV and graft failure (52-54). Interestingly, the recovery of microvascular antithrombin following an initial loss in patients with a pro-thrombotic phenotypic state (Figure 3), is strongly associated with a significant survival improvement (50). All previous investigations suggest that interventions aimed at promoting collateral and microvascular growth may serve as effective therapies for CAV and CAV-related complications (55). CAV also limits the lifespan of pediatric heart transplant recipients. Recent investigations directed to identify blood markers of inflammation, endothelial dysfunction and transplant-associated vascular damage in children after heart transplantation suggest that subclinical inflammation and natural anticoagulant/thrombomodulin activity are important after transplantation (56).

Microvascular thrombosis and the loss of activators of fibrinolysis, as well as enhanced activation of the microvascular endothelium (Figure 4), are detectable very early, within the first few days after transplantation, suggesting that ischemia/reperfusion injury participates in long-term outcome. Massive ICAM-1-mediated microvascular fibrinogen deposition and platelet adhesion have been shown to occur as early as 10 minutes after reperfusion (57). Interestingly, Rose (33) has demonstrated that anti-vimentin antibodies could participate in the development and progression of a pro-thrombotic microvascular state since the interaction between anti-vimentin antibodies, neutrophils and platelets contributes to the pro-thrombotic phenotype leading to CAV. Ischemia/reperfusion facilitates endothelial dysfunction and CAV by triggering platelet adhesion, leading to release of growth factors,

upregulation of major histocompatibility class I and II antigens, stimulation of the release of donor antigens, and promotion of adhesion molecule expression and smooth muscle cell proliferation (58, 59).

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 late development of CAV and graft loss. When the information obtained from all markers is combined to identify the best single composite marker, however, loss of tissue plasminogen activator is the dominant and often, the only predictor of long-term risk (46). Microvascular fibrin following ischemia/reperfusion detected in the first post-transplant biopsy obtained at a median 9 days after transplantation (60) would normally be removed by the activation of the fibrinolytic system. Fibrin remains if there is early loss of tissue plasminogen activator, however, which may partially explain why depletion of tissue plasminogen activator 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 higher risk of developing the disease (61). 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.

Supporting the role of a dysfunctional allograft microvasculature in CAV development and progression, it has been demonstrated that coronary microvascular dysfunction is associated with new onset of CAV in heart transplant patients with normal coronary angiography (62); the microvascular changes

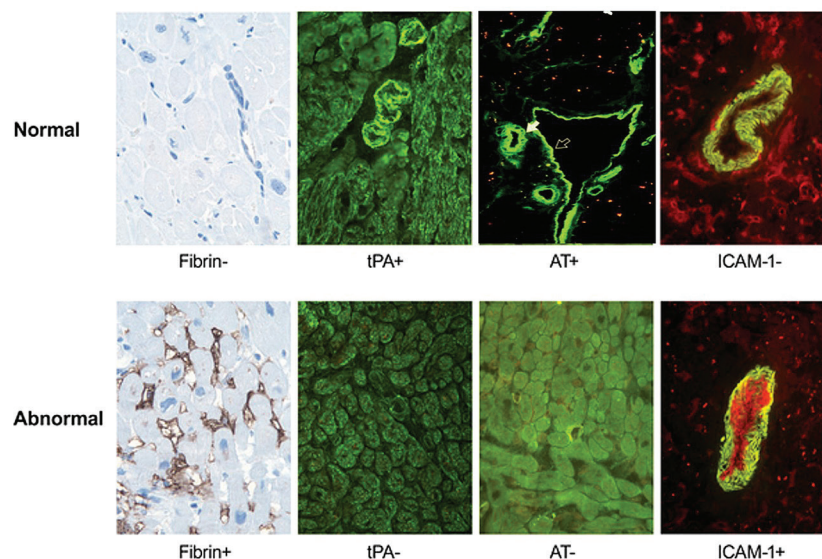


Figure 4. Microvascular phenotypes of normal and abnormal hearts. A normal heart (top row) shows absence of microvascular fibrin (fibrin-), presence of tissue plasminogen activator (tPA+) in arteries and arterioles, presence of antithrombin (AT+) in arteries and veins but not capillaries and absence of arterial and arteriolar endothelial intercellular adhesion molecule-1 (ICAM-1). An abnormal heart shows presence of microvascular fibrin (fibrin+), loss of tissue plasminogen activator in arteries and arterioles (tPA-), loss of microvascular antithrombin (AT-) and strong expression on intercellular adhesion molecule-1 (ICAM-1) in arteries and arterioles. Original magnification 640X.

are associated with hypertrophic remodeling of coronary arterioles (63); and everolimus appears to prevent such microvascular remodeling and preserves coronary flow reserve (63). The identification of a high-risk patient subgroup so early after transplantation (in some cases, within days post-transplant) suggests again that very early events, like tissue reperfusion injury, may have long-term consequences for these patients. Since systemic inflammation may be associated with CAV, several investigators have evaluated plasma levels of C-reactive protein for their association with CAV and heart transplant survival. Pethig *et al* (64) suggested that progressive CAV is accompanied by elevated C-reactive protein levels. Labarrere and colleagues (52) demonstrated that early increases in C-reactive protein are associated with elevation of cardiac ICAM-1 expression and increased soluble ICAM-1 levels, and these findings are predictive of the development of more aggressive CAV and graft failure. Hognestad *et al* (65) not only suggested a link between C-reactive protein and CAV but also correlated statin therapy with a reduction of C-reactive protein levels, providing further evidence for the role of inflammation in CAV (66). It has been recently demonstrated that the prediction of CAV and graft failure due to CAV improves when inflammatory markers are added to a previously validated atherothrombotic model (67). Early inflammatory status, measured by the 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 (67). Recent studies have

shown the potential usefulness of employing plasma protein biosignatures for CAV detection (68).

3.4. Microvascular arterial capillaries (“capioles”) and survival

We hypothesize that the development of antithrombin-reactive microvessels after heart transplantation is evidence of growing coronary collateral vessels that confer a favorable prognosis in patients with CAV. Collaterals are specialized endogenous bypass vessels that are present in most tissues and provide protection against ischemic injury caused by ischemic stroke, coronary atherosclerosis, peripheral artery disease, and other conditions and diseases (69). These are naturally occurring artery-to-artery or arteriole-to-arteriole anastomoses present in healthy tissues that increase their vascular diameter in obstructive diseases. Studies in animals and humans suggest that individual variability exists in the number of native collateral arteries and this variability renders some individuals more prone to ischemic diseases than others (70, 71).

The antithrombin-reactive microvessels (Figure 5) have particular phenotypic characteristics that differ from normal arteries, capillaries and veins. The capillaries that bind antithrombin are generally larger than normal capillaries (estimated range: 10-30 μ m), and unlike normal capillaries (< 10 μ m), they react with antibodies to smooth-muscle-specific α actin (72,73) and the Pathologische Anatomie Leiden-Endothelium (PAL-E) antigen (72, 73): an antigen normally found only in venules (74, 75), small to medium-size veins (74, 75),

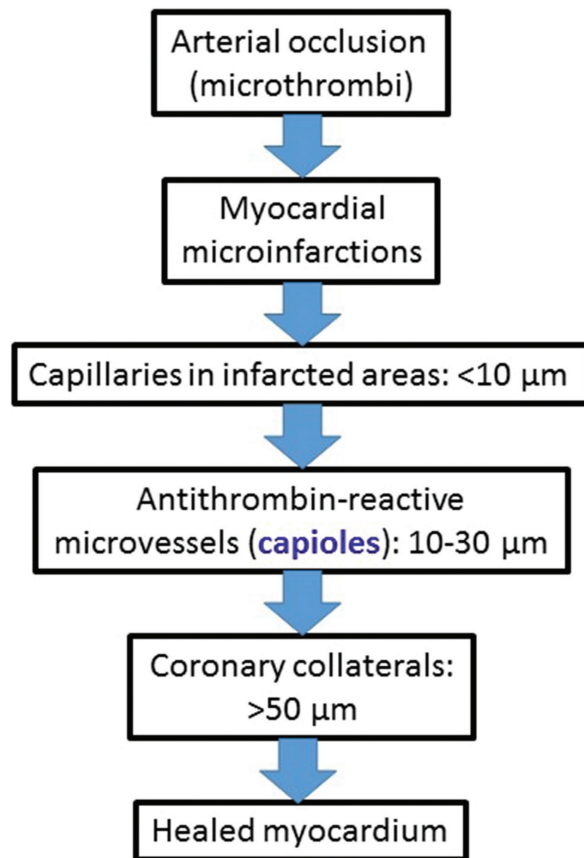


Figure 5. Capiole development in areas of microinfarction associate with myocardial healing.

and capillaries with the altered vascular permeability observed in angiogenesis (74). 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 (72, 73). These capillary-like vessels may be participating in the generation of new arterioles from capillary structures (capillary arterialization (76-78)) in response to ischemic injury through which they undergo diameter increase and recruit smooth muscle actin-positive mural cells to become new arterioles. The increased capillary arterialization in the presence of thrombin supports this hypothesis (71).

Although their size and abundance would more likely classify these vessels as capillary-like structures, it is evident these capillaries may in fact be undergoing some transition or vascular remodeling involving smooth-muscle-specific α -actin-reactive pericytes or smooth muscle cells, which are not commonly associated with quiescent capillaries. Based on their vascular phenotypic characteristics, it is tempting to suggest that these are capillaries with altered permeability and some features of very small arterioles ("capioles") (75). Capioles that react

with antibodies to antithrombin, smooth muscle α -actin and PAL-E, seem to have an activated endothelium expressing ICAM-1 and human leukocyte antigen DR.

It is possible that capioles are microvessels involved in the process of arteriogenesis, collateral capillaries undergoing arterialization (71), since arteriogenesis has been attributed to enlargement of a pre-existing collateral network or de novo formation of new arterial vessels by means of capillary arterialization (79, 80). Angiographic studies performed in patients with capioles showed always the presence of small vessel disease with a blush pattern (81). Although the artery-to-artery or arteriole to arteriole connection cannot be completely demonstrated by histology or immunopathology studies, the extraordinary phenotypic similarity between capioles and the collateral capillary arterialization following arteriolar ligation found in mice (78); and the presence of small vessel disease with a blush pattern found in transplanted hearts with capioles strongly suggest these particular vessels are involved in collateral arterial/arteriolar formation.

The formation of new (collateral) arteries from capioles could occur in response to occlusion of arterial trunks in areas of microinfarction (as depicted in Figures 1 and 5), characterized by extensive fibrin deposits in and around damaged cardiomyocytes (72, 73, 75). Indeed, capioles are predominantly identified next to areas of microinfarction in transplanted hearts with severe lesions of cardiac allograft vasculopathy (72, 73, 75). Quiescent capillaries found in normal hearts and hearts without microvascular fibrin deposits never express antithrombin reactivity compared to the antithrombin-reactive capioles (75). Interestingly, metarterioles (arterial capillaries) which are short vessels that link arterioles and venules in the mesentery microcirculation and apparently not in any other organ (82) have similar characteristics to the capioles. Each metarteriole forms a precapillary sphincter that encircles the entrance to the respective capillary bed, and the constriction of these sphincters reduces or shuts off blood flow through their respective capillary beds. This allows the blood to be shunted to venous system in the mesentery microcirculation. Capioles, however, are most probably capillaries becoming arterialized with outstanding anticoagulant properties.

The presence of capioles (capillary-sized vessels α -actin, PAL-E and antithrombin-reactive) in heart transplants with microvascular fibrin deposits and CAV is associated with a significant increase in the expression of vascular endothelial growth factor (83), also known as vascular permeability factor, and placental growth factor (84) in cardiac myocytes, suggesting that these potent angiogenic factors participate in the generation of myocardial capioles. This hypothesis is supported by the recent finding that arteriogenesis seems to be associated with higher exposure to vascular endothelial growth factor (80).

4. DIAGNOSIS AND MONITORING

Diagnosis and monitoring of CAV depend mostly on the use of invasive techniques, such as coronary angiography and intravascular ultrasound. Coronary angiography is less invasive than intravascular ultrasound but is only moderately sensitive in detecting early CAV (23). Patients with only mild CAV detected angiographically 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 (11).

On the other hand, intravascular ultrasound has been found to be valuable in the prediction of both CAV and other cardiovascular end points (23) 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. In these patients, it is essential 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 (85). 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 (86). 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 after transplantation (86), (calculated as Δ vessel volume/ Δ 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.

Intravascular ultrasound only detects changes in epicardial arteries, however, and cannot detect changes that occur in intramyocardial arteries and other microvascular vessels within the transplanted heart (87). 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 microvascular involvement even in the presence of a normal angiogram (88). The inability to directly visualize the arterial wall with conventional angiographic techniques leads to the 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 (89). Non-invasive methods that directly determine structural and functional alterations of the coronary microcirculation are needed in severe CAV (90). 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 have been recently described (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 microvasculopathy 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 microvessels of the transplanted heart. The challenge is developing effective therapies that can prevent or reverse early features of microvascular disease (94). In the ongoing effort to find early biomarkers for CAV, 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).

5. NEW THERAPEUTIC APPROACHES AND FUTURE PERSPECTIVES

Given the relatively poor prognosis of CAV, prevention remains an important strategy. The use of proliferation inhibitors (sirolimus and everolimus) has been shown to alter the course of the disease (96, 97) and may decrease the rate of CAV progression (98). Conversion to everolimus from mycophenolate mofetil in maintenance periods after heart transplantation may decrease the rate of CAV progression based on intravascular ultrasound indices (98). 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 (99) and although percutaneous intervention improves survival in patients with severe CAV, the outcomes still are not ideal (97). 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 (100). 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 (100). 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 (101). Everolimus seems to improve the allograft microvasculature since it appears to prevent such microvascular remodeling and preserve coronary flow reserve (63).

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 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 transplant and the relative risks and benefits are unknown (102).

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 (66). 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 (103). This further suggests that improving the status of the microvessels in transplanted hearts with severe CAV may be considered as a novel therapy to increase survival. Understanding the physiopathology of endothelial and microvascular dysfunction in CAV plays a crucial role in the development of new therapies (104).

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 (105) and superoxide dismutase-mimetics (106) 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 (107, 108).

Revascularization by interventional cardiology or cardiothoracic surgical approaches has been attempted to correct discrete stenosis along the coronary arteries (17). Placement of coronary stents is associated with rapid restenosis and sirolimus-coated drug-eluting stents did not show significant CAV improvement compared with placement of bare metal stents (109). Furthermore, the use of stent placement is of temporary and short-term utility 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 (17). 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 experiencing retransplantation (12). Retransplantation may be a consideration for selected patients.

6. CONCLUSIONS

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 (35). The combination of non-immunological and immunological risk factors facilitates a more rapid development of severe disease. Inflammation with the up-regulation of adhesion molecules and major histocompatibility class II antigens in endothelium and inflammatory cells, the activation of macrophages and lymphocytes in the vessel wall with cytokine and chemokine release, the pro-thrombotic imbalance in endothelium and inflammatory cells, and the presence of pro-inflammatory molecules like C-reactive protein

sustain a persistent vascular inflammation leading to development of CAV and CAV progression.

The main reason why CAV is so detrimental for the long-term outcome of the transplanted hearts is the panvascular compromise of the disease affecting from arteries having different types of lesions (110) to veins including capillaries. 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 (111).

7. ACKNOWLEDGEMENT

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Abbreviations: CAV: cardiac allograft vasculopathy; C4d: complement split product 4d; ICAM-1: intercellular adhesion molecule-1; HELP: Heparin-mediated Extracorporeal LDL/fibrinogen Precipitation

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