Cardiac allograft vasculopathy

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UNIVERSITY OF ZAGREB

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Cardiac Allograft Vasculopathy

GRADUATE THESIS



Zagreb, 2017

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List of Abbreviations

E-selectin	Endothelial selectin
FGF	Fibroblast growth factor
ICAM-1	Intracellular adhesion molecule-1
IFN-γ	Interferon-gamma
IGF-1	Insulin-like growth factor-1
IL-1	Interleukin-1
IL-6	Interleukin-6
MCP-1	Macrophage chemoattractant protein-1
PDGF	Platelet-derived growth factor
P-selectin	Platelet selectin
TGF-α	Transforming growth factor-alpha
TGF-β-1	Transforming growth factor-beta-1
TNF-α	Tumor necrosis factor-alpha
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor

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Summary

Title: Cardiac Allograft Vasculopathy

Author: Robin Hansson

Cardiac allograft vasculopathy (CAV) is a disease characterized by endothelial dysfunction, intimal thickening of coronary arteries with subsequent ischaemia and failure of the transplanted heart. CAV is one of the major determinants of longterm survival in cardiac transplant patients with an incidence of 48% at 10 years. The disease evolves from a complex interplay between both immunological and non-immunological factors, some being ”classical” atherosclerotic risk factors. Clinical diagnosis can be very difficult since these patients present with atypical symptoms of myocardial ischemia, no angina because of graft denervation, or often no symptoms at all. Instead the initial presentation is often progressive heart failure or sudden death making screening methods vital to detect the disease early. The standardized diagnostic and screening tool for the clinical practice is currently coronary angiography, although positive predictive value is only 44% when compared to intravascular ultrasound as the gold standard. Another a major disadvantage of angiography is the risk of developing contrast nephropathy since many of these patients have renal dysfunction from immunosuppressive treatment. While CAV generally is a slowly progressive disease, effective prevention and treatment methods are lacking and hence the disease carries a poor prognosis. Statins and mTOR inhibitors are key players in both prevention and treatment and are part of the standard drug regime for all patients. In addition to medical treatment, revascularization therapy is also possible in a very small subgroup of patients. However, revascularization is considered palliative and is not proven to prolong graft survival. Implantable cardioverter-defibrillator (ICD) devices are used in advanced stages but is not evidence-based for CAV in particular. Unfortunately the only definite and ultimate treatment option is retransplantation. New treatment methods are clearly needed.

Keywords: Coronary Artery Disease ■ Heart Transplantation ■ Immunology ■ Inflammation ■ Microcirculation

Sažetak

Naslov: Vaskulopatija Srčanog Presadka

Autor: Robin Hansson

Vaskulopatija srčanog presadka (VSP) je bolest karakterizirana disfunkcijom endotela, zadebljanjem intime koronarnih arterija sa posljedičnom ishemijom i zatajivanjem transplantiranog srca. VSP je jedna od glavnih determinanata dugoročnog preživljavanja u srčanih transplantiranih bolesnika sa učestalosti od 48% nakon 10 godina. Bolest se razvija iz složenih međudjelovanja između imunoloških i neimunoloških faktora, od kojih su neki "klasični" faktori aterosklerotskog rizika. Klinička dijagnoza može biti vrlo zahtjevna jer se ovi bolesnici prezentiraju sa atipičnim simptomima ishemije miokarda, bez angine zbog denervacije presadka, ili su često potpuno bez simptoma. Progresivno popuštanje presatka ili iznenadna smrt su nerijetko prve manifestacije ove bolesti, učinivši metode probira bitnima u ranom otkrivanju bolesti. Standardni alat u dijagnostici i probiru u kliničkoj praksi je trenutno koronarna angiografija, makar joj je pozitivna prediktivna vrijednost samo 44% kada se usporedi sa intravaskularnim ultrazvukom kao zlatnim standardom. Još jedna nepovoljna osobina angiografije je rizik od razvoja kontrastne nefropatije s obzirom da mnogo ovih pacijenata ima renalnu disfunkciju zbog imunosupresivne terapije. Iako je VSP generalno sporo progredirajuća bolest, nedostaju učinkovite metode prevencije i liječenja te je zbog toga bolest povezana sa lošom prognozom. Statini i inhibitori mTOR-a su za sada ključni u prevenciji i liječenju te su dio standardnog režima lijekova za sve pacijente. Uz lijekove, terapija revaskularizacijom je također moguća u relativno maloj podgrupi bolesnika. Međutim, revaskularizacija se smatra palijativnom metodom te nije dokazano da produžuje preživljavanje presadka. Implantabilni kardioverter-defibrilator (ICD) se često koristi u uznapredovalim stadijima VSP, iako bez koristi utemeljene dokazima. Nažalost, jedina preostala definitivna opcija liječenja jest ponovna transplantacija. Više je nego očito da trebamo nove i učinkovitije metode liječenja.

Ključne riječi: Bolest Koronarnih Arterija ■ Transplantacija srca ■ Imunologija ■ Upala ■ Mikrocirkulacija

1.0 Introduction

Cardiac transplantation (HTx) is the gold standard treatment of advanced heart failure refractory to medical treatment, whereof non-ischemic cardiomyopathy is the most common diagnosis of the recipient. A total number of 4746 adult and pediatric heart transplants, including 589 combined heart and lung transplants, was registered in year 2014 to the International Society of Heart and Lung Transplantation (ISHLT). However it's estimated that the total HTx number worldwide likely exceeds 5000 per year. The typical global adult recipient based on ISHLT's data have a mean age of 54 years, a median survival of 12 years and the major morbidities they are expected to suffer from are hypertension, renal dysfunction, hyperlipidaemia, diabetes mellitus and at last cardiac allograft vasculopathy.[1] At Rebro University Hospital around 20 HTx are performed annually.[2]

Cardiac allograft vasculopathy (CAV), also known as transplant coronary artery disease or cardiac transplant vasculopathy, is a disease characterized by endothelial dysfunction, intimal thickening of coronary arteries and subsequent ischaemia and failure of the transplanted heart. Incidence of CAV detected by angiography is 8% at 1 year, 29% at 5 years, 48% at 10 years. The three leading causes of death in the first post-transplant year are graft failure, non-CMV infection and multiple organ failure. After 3 years however, the leading causes of death are graft failure, malignancy, CAV and renal failure. Hence CAV is one of the major morbidities and major determinants of longterm survival.[3] In order to classify CAV uniformly worldwide a standardized nomenclature was formulated by the ISHLT in 2010 (Table 1). The nomenclature is based on visual angiographic findings together with measures of cardiac allograft function and does also have a prognostic value.[4]

Table 1. Recommended Nomenclature for Cardiac Allograft Vasculopathy

ISHLT CAV_0 (Not significant): No detectable angiographic lesion

ISHLT CAV_1 (Mild): Angiographic left main (LM) <50%, or primary vessel with maximum lesion of <70%, or any branch stenosis <70% (including diffuse narrowing) without allograft dysfunction

ISHLT CAV_2 (Moderate): Angiographic LM <50%; a single primary vessel ≥70%, or isolated branch stenosis ≥70% in branches of 2 systems, without allograft dysfunction

ISHLT CAV_3 (Severe): Angiographic LM ≥50%, or two or more primary vessels ≥70% stenosis, or isolated branch stenosis ≥70% in all 3 systems; or ISHLT CAV1 or CAV2 with allograft dysfunction (defined as LVEF ≤45% usually in the presence of regional wall motion abnormalities) or evidence of significant restrictive physiology (which is common but not specific; see text for definitions)

Definitions

a) A "Primary Vessel" denotes the proximal and Middle 33% of the left anterior descending artery, the left circumflex, the ramus and the dominant or co-dominant right coronary artery with the posterior descending and posterolateral branches.

b) A "Secondary Branch Vessel" includes the distal 33% of the primary vessels or any segment within a large septal perforator, diagonals and obtuse marginal branches or any portion of a non-dominant right coronary artery.

c) Restrictive cardiac allograft physiology is defined as symptomatic heart failure with echocardiographic E to A velocity ratio >2 (>1.5 in children), shortened isovolumetric relaxation time (<60 msec), shortened deceleration time (<150 msec), or restrictive hemodynamic values (Right Atrial Pressure >12mmHg, Pulmonary Capillary Wedge Pressure >25 mmHg, Cardiac Index <2 l/min/m2)

2.0 Pathogenesis

Endothelial dysfunction and intimal proliferation with narrowing of coronary vessels is the endpoint of CAV. It results from the complex interplay between *immunological* and *non-immunological factors* (Figure 1.). CAV has long been referred to as chronic rejection, which should be avoided since it does not take non-immunogenic factors into account. CAV has quite different pathological characteristics (Table 2) in comparison to "classical" atherosclerotic cardiovascular disease (CVD) although some non-immunogenic factors are common to both disease entities. The CAV lesions have a diffuse and concentric nature and preferentially affects small and medium sized vessel compared to proximal and eccentric lesions seen in atherosclerotic CVD. Also coronary veins and intramyocardial vessel are more frequently involved in the former.[5]

The endothelium represents a critical border between the donor's and the recipient's allogenic tissues. Much like border patrol it serves a meaningful purpose by protecting both sides from unwanted trafficking but as tension rises it becomes corrupt and adds to the problem; termed endothelial activation and/or dysfunction. Activation means increased expression of human leukocyte antigen (HLA) molecules, adhesion molecules and cytokines leading to matrix deposition and smooth muscle cell (SMC) proliferation.[6,7,8,9,10,11] This pro-inflammatory milieu and procoagulant response leads to typical vascular changes seen in CAV.

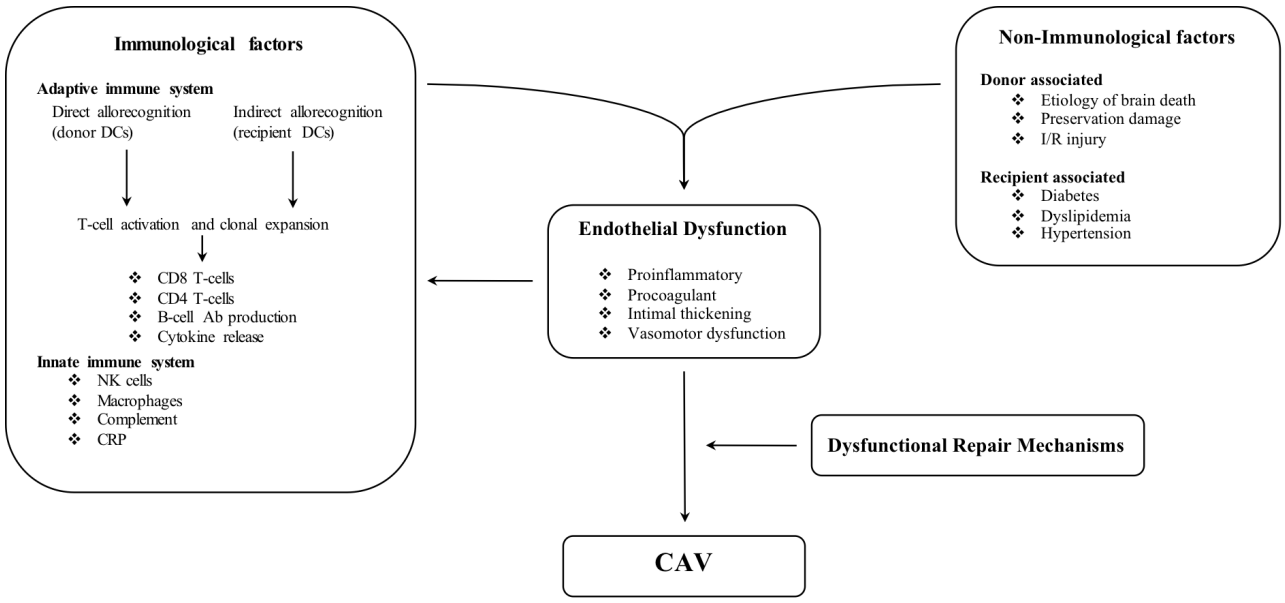


Figure 1. Pathogenesis of Cardiac Allograft Vasculopathy. *DCs, Dendritic cells. Ab, Antibody. NK, Natural killer. I/R, Ischemia/Reperfusion.

Endothelial dysfunction strictly speaking means that the vessel is unable to dilate properly and has an increased resting tone. The principal cause is reduced nitric oxide, either from decreased production or increased consumption, though increased endothelin activity is also a contributing factor.[12,13] The term dysfunction is sometimes also used to describe ”activation” simultaneously, putting all these abnormal endothelial behavior under one umbrella and this terminology will be used henceforth.

Neovascularization of heart tissue is a topic highly debated whereof replacement of endothelial cell is one subtopic, which is large enough for the sake of this discussion. Current knowledge is that replacement of endothelial cells and vasculogenesis is contributed by circulating host endothelial progenitor cell (EPCs).[14] While Medawar’s hypothesis suggests that this is a sign of graft adaptation it may however just be a sign of endothelial damage with ineffective repair mechanisms, for three reasons. First, endothelial progenitor cell (EPCs) are significantly decreased in the circulation and enriched in coronary arteries of patients with CAV.[15] Secondly, the significance of EPCs reparative contribution is not thought to be substantial.[16] And finally, inflammation suppresses EPCs survival and mobilization.[17]

Table 2. Differences between Cardiac Allograft Vasculopathy and Atherosclerotic Cardiovascular Disease

	CAV	**Atherosclerotic CVD**
Location	Distal	Proximal
Plaque type	Diffuse/Longitudinal, concentric	Focal, eccentric
Inflammation	Yes	Rarely
Vasculitis	Infrequently	Never
Internal elastic lamina	Intact	Disrupted
Calcium deposits	No	Yes

2.1 Immunological factors

Immunological events seem to be of the greatest importance, after all CAV only develops in donor's and not recipient's arteries. There are a number of ways for host immune cells to recognize the graft as foreign. Donor dendritic cells (DCs) can present foreign major histocompatibility complex (MHC) to host T-cells, called the *direct pathway*.[18] Host DCs can internalize, process and present donor peptides with their MHC, the *indirect pathway*.[19] A relatively novel discovery is that host DCs can acquire donor MHC through cell-to-cell contact, named the *semi-direct pathway.*[20] Donor endothelial cells can also present their MHC I, and later if activated MHC II as well, to host T-cells.[21] It is though that the *indirect pathway* is responsible for both cardiac allograft vasculopathy and chronic rejection.[18,22]

Whatever the starting point may be, both the cellular and humoral arm are involved, with T- and B-cell activation and differentiation to CD8+ T-cells, CD4+ T-cells and specific antibodies. Studies have shown that HLA mismatching, HLA-DR in particular, have a greater incidence in recipients who develop CAV compared to those who do not.[23] Same applies for specific antibodies towards HLA class I or class II, but also peptide-specific anti-endothelial antibodies.[24,25,26] A temporal relationship has been observed in the appearance of activated T-cells in cardiac grafts, with early predominance of cytotoxic/CD8+ T-cells and later helper/CD4+ T-cells in more advanced pathological stages. Endothelial cells, like all other nucleated cells, express their MHC class I from the very beginning and later expresses MHC class II when activated.[27]

Several factors reflect the impact of systemic inflammation and the innate immune system's involvement. The well known C-reactive protein (CRP), a marker of systemic inflammation, is an established predictor of CAV.[28] Increased gene expression of Toll-like receptor 4 (TLR-4) in circulating monocytes is associated with CAV.[29] Presence of complement component 4d (C4d) in endomyocardial biopsy is an independent risk factor.[30] Natural killer (NK) cells inflict CAV independently from T- and B-cells in concert with donor specific antibodies (DSA).[31]

A plenty of cytokines and adhesions molecules are found in CAV lesions. These include c*ytokines:* IL-1, IL-6, TNF-α, PDGF, IGF-1, MCP-1, FBGF, VEGF, TGF-α, TGF-β-1 and IFN-*γ*. *Adhesion molecules* include: ICAM-1, VCAM-1, E-selectin and P-selectin. They mediate different pathological mechanism including leukocyte and platelet adhesion, chemoattraction of leukocytes, SMCs proliferation etc.[7–11] The role of IFN-*γ* is of particular interest since deficiency of this cytokine prevents CAV in mice models.[32]

Lastly, increased frequency of moderate and severe cellular rejection episodes as well as total rejection score, correlates well with CAV suggesting that immunological events are of utmost importance in the pathogenesis of the disease.[33,34,35,36,37]

2.2 Non-immunological factors

Non-immunological factors can be classified as recipient or donor associated. The most important *recipient associated* risk factors are components of the metabolic syndrome (central obesity, hypertension, diabetes, dyslipidemia) since they are very frequent, present either prior to HTx or as a result of immunosuppressive therapy (i.e. cyclosporine & corticosteroids). Lipid abnormalities are not merely a risk factors but also seem to correlate well with CAV severity.[38,39,40] Patients with either high glucose or high insulin concentrations have higher incidence of CAV and a reduced survival.[41] Insulin resistance has a synergistic effect with elevated CRP levels which is evident from a fourfold increased risk of developing CAV when occurring together, highlighting the interplay between immunological and non-immunological events.[42]

Cytomegalovirus infection (CMV) is another risk factor. CMV activates the immune system both directly and secondarily through endothelial assault causing endothelial dysfunction.[43] It's also though that CMV infection has negative influence on vascular remodeling from observations of net lumen loss in infected patients.[44]

Older age of the recipients is a protective factor while the opposite is true for donors. Male sex and older age are *donor associated* risk factors.[45,46] Age is one of the strongest predictors for atherosclerotic CVD and indeed history of atherosclerotic CVD in the recipient or the donor are risk factors for CAV.[46,47,48] Surprisingly older donor age and/or history of CVD does not reduce survival nor freedom from ischemic events.[13,49] Other *donor associated* risk factors are: explosive brain death (e.g. head trauma and intracerebral hemorrhage)[50,51], organ preservation damage[52], ischaemia-reperfusion injury[43], DD genotype of ACE gene polymorphism[53] & hepatitis C virus seropositivity[54].

Miscellaneous risk factors are hyperhomocysteinemia[55], increased elastase activity[56], thrombospondin-1[57], expression of tissue factor and the vitronectin receptor[58]. The exact role of fibrinolysis is still under scrutiny. On one hand animal models suggest that plasminogen system contributes to CAV as mentioned earlier. In contrast, tissue-type plasminogen activator (tPA) depletion and plasminogen activator inhibitor-1 (PAI-1) expression in human cardiac grafts are much more related to CAV (78% vs 24%) and their carriers are much more likely to die or need a second HTx (30% vs. 2.5%).[59,60]

3.0 Diagnosis & Screening

Detecting CAV is truly a challenge. Foremost, clinical symptoms are often absent or atypical. When early symptoms do appear, patients seldom present with angina pectoris (because of graft denervation) or premonitory symptoms at exertion. The most common symptoms according to a study of 22 HTx patients were angina equivalents such as weakness and dyspnea that led to misdiagnosis of infection or congestive heart failure (HF) at admission.[61] Also electrocardiogram (ECG) is of limited value because of the high prevalence of electrocardiographic abnormalities in this population of patients.[62] When early symptoms are absent, the initial presentation of CAV is often progressive HF or sudden death. Therefore, effective screening methods are warranted in order to detect the disease in early stages and to improve it's outcome. The general screening schedule for a post HTx patient at Rebro University Hospital can be seen in Table 3.

3.1 IVUS

Intravascular ultrasound (IVUS) is the most sensitive method in diagnosing CAV. Hence, IVUS is used in many large multicenter studies to assess drug efficacy in treatment and prevention of CAV. It is also used in clinical practice when other diagnostic methods fail to explain the reason for graft failure. Unlike coronary angiography which only visualizes the vessel lumen, IVUS also inspects tunica intima and media of the vessel wall. Through serial observations it’s seen that the most rapid rate of intimal proliferation occurs during the first post-transplant year. Should the intimal thickening be ≥0.5mm in that period of time it’s defined as rapidly progressive, which is associated with more frequent deaths, graft loss and nonfatal major adverse cardiac events (45.8% vs. 16.8%).[63] Risks of procedure complications are low in experienced hands, with reports showing complications of 1.6% when performing multi vessel IVUS.[64] IVUS is unfortunately a very costly and time-consuming tool. So despite IVUS's high positive predictive value (PPV) and low risk of complications, it is not recommended for routine surveillance in the clinical practice.[4]

Table 3. Screening schedule for post HTx patients at Rebro University Hospital.

	Biopsy (cellular)	Biopsy (humoral)	DSA*†	Angio*	Echo*	6MWT*†	Holter†
1 mo	+	+	+	+	+	+	+
2 mo	+				+	+	+
4 mo	+				+	+	+
6 mo	+	+	+		+	+	+
9 mo	+				+		
1 year	+	+	+	+	+	+	+
16 mo	+				+		
20 mo	+				+	+	+
2 years	+	+	+		+	+	+
30 mo	+				+	+	+
3 years	+	+	+	+	+	+	+
4 years	+	+	+		+	+	+
5 years	+	+	+	+	+	+	+
7 years	+	+	+	+	+	+	+
10 years	+	+	+	+	+	+	+

*mo, months. DSA, donor specific-antibody. Angio, coronary angiography. Echo, echocardiography. 6MWT, six-minute walk test. †For scientific purposes.

3.2 Coronary angiography

Coronary angiography (Figure 2. & Figure 3.) is the standard method for surveillance and monitoring of CAV.[4] A baseline examination is performed at around 4 weeks post-transplant and then biannually, annually or every other year there after (Table 3.) depending on each center's preferences. More frequent examinations may be indicated if signs of graft failure through other diagnostic methods are present, e.g abnormal ventricular wall motion visualized on echocardiography. Coronary angiography can only assess luminal diameter and the contrast-filling time. This makes it very hard to spot CAV lesions early since the lesions are concentric, longitudinal and diffuse. Hence, the PPV of coronary angiography is only 44% compared to IVUS as the gold standard.[65] To avoid false diagnosis of CAV from vasospasm, an intracoronary vasodilator such as nitroglycerine should be administered prior to contrast. A paradoxical

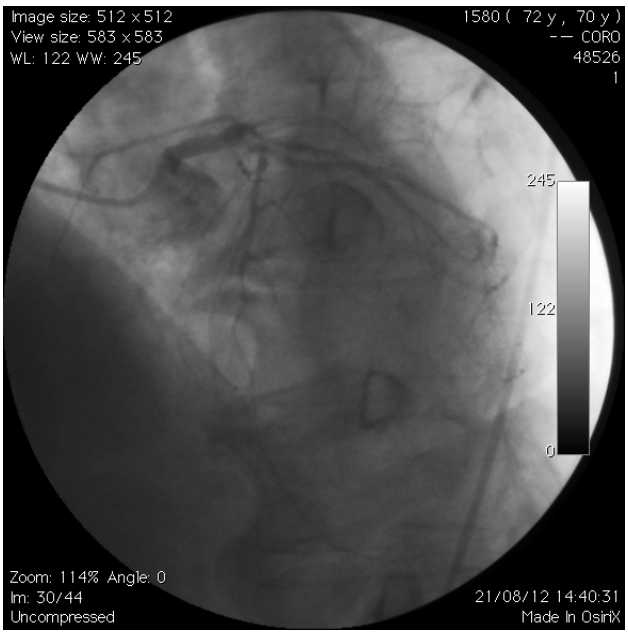


Figure 2. Coronary angiography showing diffuse stenosis of the left anterior descending artery and distal pruning of left circumflex artery in a patient with CAV.

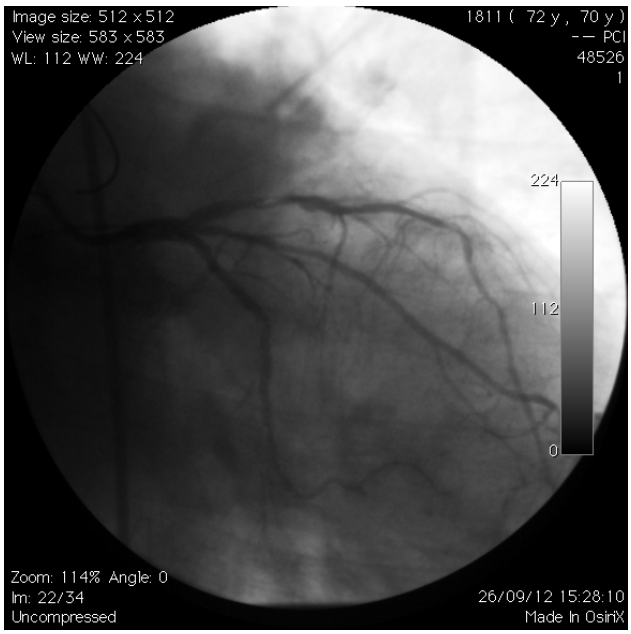


Figure 3. Coronary angiography showing severe stenosis of mid-left anterior descending artery with some diffuse irregularities on both left anterior descending and left circumflex arteries in a patient with CAV.

vasoconstrictive response towards the vasodilator signifies endothelial dysfunction and is significantly associated with higher incidence of angiographic vasculopathy at 1 year (58% vs. 13%).[66]

To attain the contrast-filling time, TIMI (thrombolysis in myocardial infarction) frame count is used. TIMI frame count is the number of cine frames required for dye to reach distal coronary landmarks during coronary angiography and it may very well correlate with CAV, though conflicting result have emerged from different studies.[67,68] Two additional measures that rely on the angiographic wire are coronary flow reserve (CFR) and optical coherence tomography. In order to measure CFR a doppler ultrasound transducer is located at the tip of the wire, thus the velocity of coronary blood flow can be measured. CFR is the increase of flow in response to a intracoronary vasodilator, and is found be reduced in patients with proven CAV.[69] Optical coherence tomography is a novel method that seems to be very sensitive in detecting early CAV but further research is needed to determine its definite its role.[70] A major drawback of angiography is the risk of contrast induced nephropathy, since HTx patients sooner or later develop renal dysfunction from immunosuppressive therapy.

3.3 Endomyocardial biopsy

Except for being part of routine allograft rejection surveillance, endomyocardial biopsy can also diagnose CAV. As stated earlier, endothelial dysfunction is the endpoint in the pathogenesis of the disease. Demonstrating endothelial dysfunction through immunohistochemistry can therefore predict CAV before angiographic changes are noticed. In a study of 121 HTx patients, specimens demonstrated presence for ICAM-1 and HLA-DR (markers of endothelial dysfunction) in 78 patients within the first 3 months post-transplant. This group had a significant higher risk and progression rate for developing angiographic CAV compared to the 43 patients with negative specimens.[71] Simple histological evaluation of microvasculopathy is not as useful in predicting CAV. While it's postulated that microvasculopathy is a prognostic factor CAV some studies are skeptical.[72,73,74] Heimann et al did however find stenotic microvasculopathy to be a risk factor for three-vessel epicardial disease and a predictor of long-term survival after HTx.[75]

A major disadvantage of endomyocardial biopsy is its low sensitivity when compared to IVUS or angiography. This is presumably because of the low probability of obtaining a sample with microvasculature.

3.4 Noninvasive investigations

Because of several disadvantages of angiography (i.e patient discomfort, radiation and use of contrast agents) other potential techniques are being explored. The best validated noninvasive technique for the moment is *dobutamine stress echocardiography*. According to a study of 109 HTx recipients the sensitivity was 85% when compared to angiography and IVUS combined as the gold standard, and the negative predict value (NPV) was excellent.[76] Although later studies have not been able to reproduce such a high sensitivity and NPV (one large study of 497 patients showing only 7% and 41% respectively)[77], stress echocardiography is still recommended as part of general CAV screening and as a substitute for a selected patient group, i.e. patients at low risk (with no signs of CAV on angiography/IVUS at five years) or/and with advanced renal disease (eGFR < 30 to 40 mL/min/1.73 m2) at risk of developing contrast nephropathy. Results however should always be interpreted with caution and coronary angiography should be performed if CAV is suspected.

Other noninvasive investigation methods are *coronary computed tomography angiography (CCTA)*, *cardiovascular magnetic resonance (CMR)*, *positron emission tomography (PET)*, *CFR by echocardiogram* and *biomarkers*.

A meta-analysis in year 2014 concluded that 64-slice CCTA is a reliable alternative to coronary angiography with sensitivity and NPV of both 97%, when compared to coronary angiography as a gold standard.[78] Unfortunately, major disadvantages keep this method from being recommended as a standard noninvasive screening tool such as high burden of radiation, increased risk of nephrotoxicity from the greater amount of contrast needed, difficulties in detection of distal and small vessel disease and the high prevalence of tachycardia in these patients.[79,80]

Finding a biomarker that could potentially replace invasive methods would surely ease diagnostics. While many biomarkers have been found to be associated with CAV none has been established for a definite use. Both higher CRP and N-terminal pro-brain natriuretic peptide (NT-pro BNP) levels are associated with higher all-cause mortality in HTx patient, but neither predicts CAV development specifically.[81] The von Willebrand factor on the other hand is predictive of the patients with increased risk of CAV.[82] A promising marker detected recently is microRNA 628-5p (miR-628-5p) that was able to detect CAV with a sensitivity of 72% and a specificity of 83% in advanced CAV patients.[83]

4.0 Prognosis

Survival of patients diagnosed with CAV seems to have increased in the transplant era of 2003–2012 compared to 1994–2002 (2014 ISHLT report).[84] Lengthened survival can however not be attributed to a substantially improved treatment strategy and prognosis is still quite dim. Although the disease generally is slowly progressive the final outcome is devastating, i.e. pump failure or malignant arrhythmia resulting in HF and death if re-transplantation is not performed. In a multicenter study of 2609 HTx patients, 7% of those with angiographic CAV either died or were re-transplanted at 5 years. And two thirds (66%) of those with severe CAV (defined as left main stenosis >70%, two or more primary vessels stenoses >70%, or branch stenoses >70% in all three systems).[85] In a smaller study of 54 patients overall survival at one, two, and five years was 67%, 44%, and 17 % respectively, when stenosis of coronary arteries was defined as ≥40%. [86]

5.0 Prevention

Given the poor prognosis and lack of effective treatment, prevention is the cornerstone of CAV management. The standard immunosuppressive management for a cardiac transplant recipient used at Rebro University Hospital can be seen in Table 4. Out of these, mammalian target of rapamycin (mTOR) inhibitors everolimus and sirolimus have shown the greatest ability to prevent and/or slow CAV development. Though, only sirolimus has role in treatment of established CAV at the moment.

Table 4. Immunosuppressive management for HTx recipient at Rebro University Hospital.

	first month	months 2–6	>6 months
Cyclosporine	target level: 200–250ng/ml	target level: 150–200ng/ml	target level: 100–150ng/ml
Tacrolimus	target level: 12–15ng/ml	target level: 10–15ng/ml	target level: 5–10ng/ml
Mycophenolate mofetil	1000–1500mg b.i.d		
Everolimus		target level: 3–8ng/ml	target level: 3–8ng/ml
Steroids	0.2mg/kg/day	0.15–0.2mg/kg/day	0.1mg/kg/day

5.1 mTOR inhibitors

mTOR inhibitors block the interleukin-2 (IL-2) transduction pathway and hence prevents T- and B-cell proliferation. Sirolimus (SRL) may also inhibit SMC proliferation that might be of particular importance. Studies shows that SRL in combination with cyclosporine and steroids reduces both CAV and grade 3a acute rejection significantly at 2 years in comparison to azathioprine combined with the aforementioned drugs.[87] Everolimus (EVL) also demonstrates the same superiority in comparison to azathioprine.[88] The downside to mTOR inhibitors is that side effects such as anemia, thrombocytopenia, hyperlipidemia, and renal dysfunction are more frequently seen. They have unwanted interaction with calcineurin inhibitors (CNI) in such a way that renal function is worsened. Additionally, SRL needs to be avoided in the early post-transplant period because its impairment of wound healing.

Other studies have compared EVL to mycophenolate mofetil (MMF) and cyclosporine. In the one trial, a multicenter 24-month study of 721 de novo cardiac transplant recipients, patients where randomly assigned to EVL with reduced cyclosporine (to reduce renal dysfunction) or MMF with standard-dose cyclosporine. While the EVL regime did reduce CAV incidence it also had higher mortality rates at 3 months and at 1 year, leading to suspension of this study arm by the data safety monitoring board.[89] EVL is therefore not recommended for early use after HTx according to the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration (FDA). A Scandinavian study tried an alternative approach by replacing cyclosporine with EVL either completely or partly (EVL only or EVL with low dose cyclosporine, both in combination with MMF and corticosteroids). Findings proved that EVL prevents CAV independently without

cyclosporine and that renal dysfunction can be avoided. Unfortunately, patient with CNI-free therapy experienced almost twice the incidence of biopsy-proven cardiac allograft rejection >grade 2R compared to those who remained on cyclosporine (10.2% vs. 5.9 percent).[90] Hence, CNI-free therapy with EVL should be used cautiously and delayed until adequate rejection control is obtained.

5.2 Statins

Statins, or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are part of standard care of HTx patients even before dyslipidemia develops. Besides improvement of the lipid profile statins also lower CRP levels, improve endothelial function, reduced inflammation at the site of the coronary plaques, inhibit platelet aggregation, and show anticoagulant effects.[91,92] All of which are very beneficial in CAV prevention, supposedly. Statins improve survival, reduce incidence and severity of CAV, and reduce incidence of allograft rejection.[93] For optimal care it's vital that statin therapy is initiated early. This was demonstrated in a study through adding statin therapy to the control arm at 4 years and later reevaluating any potential difference. At 8 years the group randomly assigned to the statin group at the very start showed increased survival (89% vs. 60%) as well as increased vascular benefits.[94] The main adverse affect of statins is myopathy and there is particularly concern since both cyclosporine and tacrolimus inhibit the enzyme, CYP3A4, responsible for metabolizing most statins. Fortunately pravastatin and fluvastatin have other metabolic pathways and are safer options for HTx recipients.[95]

5.3 Miscellaneous

Since oxidative stress appears to play a role in CAV pathogenesis is was postulated that *antioxidant therapy* could prevent progression. This was later confirmed by Fang et al, who randomly assigned patients to take vitamin C (500 mg twice daily) and E (400 IU twice daily) during the first two (0–2) post-transplant years. Intimal index had increased by 8% for the placebo group versus 0.8% in the treatment group at 1 year.[96] Another study also found L-arginine therapy to be beneficial. It is though that HTx patient use an excess of endogenous NO to buffer increased vascular oxidant stress, and that L-arginine supplementation corrects the NO deficit.[97]

Cytomegalovirus prophylaxis, compared to a preemptive approach, is associated with delayed onset of CMV infection, lower viral burden, reduced CMV disease/syndrome and less intimal thickening at 1 year.[98]

Diltiazem showed promising results in the early 90's. While the average coronary diameter fell in the control group from 2.41 mm at baseline to 2.19 and 2.22 at 1 and 2 years, respectively, it remained unchanged for the treatment group.[99] Limitations to these finding are that this study preceded the statin era and that IVUS wasn't used to confirm the results. A later multicenter retrospective study of 719 patients also refuted the benefits of diltiazem and consequently its use is not indicated today.[100]

Although the coagulation response of endothelial cells is altered in CAV patients there is no evidence that *aspirin* therapy is beneficial. The high platelet reactivity seen in these patients may explain the aspirin resistance.[101]

6.0 Treatment

Once a patient has established CAV very little can be done to prevent progression or cause regression. Options are adjusting the immunosuppressive treatment, revascularization therapy such as percutaneous intervention (PCI) and coronary artery bypass grafting (CABG), prevention of sudden cardiac death with prophylactic implantable cardiac defibrillator (ICD), and ultimately retransplantation. Moreover, heart failure should of course be treated with with conventional HF medication.

6.1 Adjusting immunosuppression

Immunosuppression can be adjusted in two ways in the treatment of CAV. First, because of the observed correlation between acute allograft rejection and CAV it's thought that augmentation might be possible. In a study of 76 patients, 22 episodes of vasculopathy was treated with a three day methylprednisolone pulse and antithymocyte globulin. Regression was noted in 15 (68%) and incidence of regression was 92% if instituted within the first year (versus 40% if instituted after the first year).[102] Despite positive results, augmentation therapy is not routinely used because of the increased risk of infections and malignancy that follows.

Secondly, sirolimus (SRL) has been evaluated in two reports for treatment of established CAV. One of the trials simply added SRL to the regime while the second replaced the CNI (tacrolimus or cyclosporine) with SRL. Combined findings from both trials where that SRL has less need for PCI & CABG, lower incidence of MI, smaller increase in catheterization score, lower death rate, and less increase in mean coronary plaque volume and plaque index.[103,104] The only and very major concern with a CNI-free regime, again, is the potential increased risk of acute rejection. Heart Save the Nephron (STN) trial experienced this first hand when they had to terminate their study

prematurely, since 4 out of 7 patient randomized to SRL developed a grade IIIA rejection episode. These patient were given a CNI-free regime already 12 weeks post-transplant, and risk of rejection might be lower as the time from transplant increases. Consensus is that SRL is beneficial in treatment of established CAV however questions like ”when to initiate treatment” and ”if to replace CNI or not” remain.

6.2 Revascularization

Revascularization therapy is considered palliative and is only used in highly selective patients, because of the diffuse and distal nature of CAV lesions. PCI has been used in patients with lesions limited to only one artery in several studies, yet it remains unproven if the intervention improves graft survival. The immediate success rate is very high regardless of type of PCI used, though restenosis rate differ significantly. Ballon angioplasty shows an immediate success rate of 92–94% and restenosis rate of 20–55% at six to 15 months after the procedure.[105,106,107,108,109] Bare metal stents (BMS) has a slightly better immediate success rate but a significantly lower restenosis rate compared to angioplasty (7% vs 39% at three months as well as 34% vs 71% at eight months, respectively).[110,111] However, after 5 years differences seem to abate with reports showing nearly identical restenosis rates for both methods.[112] Although drug eluting stents (DES) are generally recommended over BMS, current studies show conflicting results.[113,114,115,116,117] Risk of in stent restenosis (ISR) is diminished by higher dosage of antiproliferative agents (azathioprine ≥1 mg/kg per day or mycophenolate ≥3 g/day) and increased by the presence of anti-HLA antibodies.[118,119]

On a final note, CABG is also possible. Though, in a report of 12 patients undergoing the procedure as much as four patients died perioperatively, raising concerns about high mortality.[120]

6.3 Other treatment modalities

Retransplantation is the last resort when all other options have failed and the only definite treatment. With such scarce resources of grafts, patient eligible for a retransplant are part of a highly selective and small subgroup (about 3% of all recipients). These patients, typically of young age, have an expected survival of 70% and 38% at 1 and 10 years respectively, which is inferior to primary transplant recipients. The two most important prognostic factors are etiology of graft failure and intertransplant interval between the first and second transplant. Interestingly, CAV has the best prognosis while primary graft failure has the worst. Patients with an interval of ≤2 years have a survival rate of 60% at 1 year compared to 75% for patient with an interval >2 years.[121,122]

Implantable cardioverter-defibrillator (ICD), is recommended as primary prevention in patients at risk of sudden cardiac death due to ventricular fibrillation (VF) and ventricular tachycardia (VT). Despite recommendations to use ICD in advanced CAV patients, with or without left ventricular dysfunction, there is paucity of data to settle its definite role.[123]

New strategies are needed to prevent, treat and prolong survival of cardiac transplant patients who suffer from CAV. But with such a complex pathogenesis it is difficult to find a target that can modulate the vast number of influential factors. A few studies have evaluated high-intensity interval training (HIIT) as a preventive factor and found promising results, not only as a protective factor but also because its potential to lower burden of anxiety.[124,125] Experiments on mice and rat models have found new potential drugs such as Rho-kinase inhibitor[126], VEGF inhibitor[127], complement inhibition[128], anti-OX40L monoclonal antibody[129] and JAK inhibitor[130]. A lot of research is ongoing and perhaps one of these new experimental drugs will change the grim outcome of CAV that we know today, only time will tell…

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Biography

The author was born in south of Sweden in the year of 1990. During his teenage years he tried to pursue a career in racing but when funding ran out he shifted his attention to science. After one year of chemical engineering in Stockholm he decided to move to Croatia and give medicine a try. He now resides in Sundsvall, a city in north of Sweden, with his girlfriend to finish his internship and become a licensed physician.

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