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EDITOR'S NOTE

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Dear Colleagues,

Greetings from the Editor's desk.

Cardiac allograft vasculopathy is the leading cause of mortality (up to 32%) at 5-10 years post heart transplantation. The pathogenesis of CAV is most likely due to a complex interplay of both immunological and non immunological factors. Dr Kishore Gupta our guest author has written a well crafted gist of this entity. The article encompasses the probable etiological factors, angiographic and functional nomenclature, clinical presentation, diagnosis and treatment.

I thank Dr Gupta on behalf of the Editorial team. I'm sure our dear readers will enjoy reading this article. Happy Reading!

Dr Manoj Durairaj
Editor "The Revival"

SUB EDITOR

Dr Talha Meeran

MBBS, MD, FACC, Consultant Cardiologist, Dept of Advanced Cardiac Sciences and Cardiac Transplant, Sir HN Reliance Foundation Hospital, Mumbai.

Dear Colleagues,

The July edition of REVIVAL features an elaborate and well rounded review on Coronary Allograft Vasculopathy (CAV) by Dr Kishore Gupta. CAV remains the Achilles heal of cardiac transplant. Despite the advances in the field, the rates of CAV and it's prognosis remain the same over the last decade. Hence it is imperative for every individual involved in cardiac transplant to be well informed on this topic.

Sincerely,
Dr Talha Meeran
Sub Editor "The Revival"

PRESIDENTIAL MESSAGE

Prof. (Dr) V. Nandakumar

Director & Chief, Division of Cardio Vascular/Thoracic Surgery & Cardiac Transplantation, Metromed International Cardiac Centre, Calicut, Kerala.

Dear Colleagues,

Greetings from the Society for Heart Failure and Transplantation

July issue of 'The Revival' presents Cardiac Allograft Vasculopathy - an article by Dr Kishore Gupta. Cardiac vasculopathy influences long term survival of heart transplant recipients. Dr Kishore has covered this topic in detail which includes various risk factors, clinical presentation, imaging techniques for diagnosis and management protocol. He has also stressed how preventive strategies help in reducing progression of this deadly complication which will otherwise finally lead to retransplantation

This will be a very useful and comprehensive article for both transplant surgeons and cardiologists.

Best wishes,
Prof. (Dr) V. Nandakumar
President

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Special thanks to Dr Kishore Gupta for authoring this month's article.

Designed by Maithili Kulkarni

CARDIAC ALLOGRAFT VASCULOPATHY

DR KISHORE GUPTA

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Following his surgical training of DNB CTVS at Fortis Healthcare Mohali under the esteemed guidance of Dr. TS Mahant, he joined as a Consultant Cardiothoracic Surgeon at Marengo CIMS and has been an important part of Cardiac surgery transplant team led by Dr. Dhiren Shah. He has authored and co-authored numerous review and research articles in reputed national and international journals. Areas of interest include heart transplantation and total arterial revascularization.

- Lifetime member IACTS
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- JIC faculty 2019-2021
- Committee member IACTS 2020 annual conference
- Delivered online lectures in various international conferences.
- Attended various national conferences.
- Lifetime member MNAMS
- Involved in regular academic activities at institute level.
- Pursuing MBA healthcare from a reputed national university.

Cardiac allograft vasculopathy (CAV), a pathologic immune-mediated remodelling of the cardiac vasculature post cardiac transplantation, presents as a diffuse and progressive thickening of the coronary arteries and remains the major cause of increased morbidity and mortality after transplant due to the development of ventricular dysfunction and life-threatening arrhythmias [1]

The prevalence of CAV increases with increased duration of graft survival, with rates of 8%, 29% and 47% at 1, 5 and 10 years following cardiac transplantation. [2] Despite the improvement in 1-year post transplant survival rates, evolution of transplant immunology and immunosuppression therapy, organ preservation methods, surgical techniques and diagnostic modalities, there has been a marginal improvement in survival beyond 1-year post transplantation over last 4 decades.

CAV remains the leading long-term cause of death and re-transplantation following heart transplantation accounting up to 32% of patient mortality at 5–10 years, surpassing the contributions of malignancies (22%) and infections (11%). [3,4]

RISK FACTORS

CAV is multifactorial in origin and is earlier considered to be a form of chronic rejection due to the crucial role played by various alloimmune and autoimmune mechanisms in the pathogenesis.[5-7] Although the precise mechanism of CAV is not completely elucidated, a complex interplay of a wide array of both immunologic and non-immunologic factors which can be donor or recipient related result in the pathogenesis of CAV. The initial endothelial insult resulting from ischemia-reperfusion injury or from host immune response to the cardiac allograft lead to activation of the endothelium. [8-12]

Various immune and non-immune factors which play the role are listed in the Table 1.

Table 1 **Risk factors for CAV**

	NON IMMUNE FACTORS	IMMUNE FACTORS
Organ donor related	• Old age • Explosive brain death • Donor derived atherosclerosis • Hypertension • Diabetes mellitus • Smoking	• Alloantibodies • Allograft endothelial cells
Recipient related risk	• Native coronary artery disease • Cytomegalovirus infection • Hypertension • Diabetes mellitus • Smoking • Obesity • Ischemic etiology for end stage heart disease • Hypercholesterolemia • Insulin resistance and pro-inflammatory state	• HLA mismatch • Non HLA mismatch • Acute cellular Rejection • Antibody mediated rejection
Procurement related	Ischemic injury Thermal injury Reperfusion injury Peri-transplant ischemia	

CAV is a morphologically and clinically heterogeneous disease with significant phenotypic variation in angiographic manifestation and clinical presentation. CAV is graded as absent (CAV0), mild (CAV1), moderate (CAV2) and severe (CAV3), accordingly.

In the year 2010, ISHLT issued a consensus statement, stating that coronary angiography in conjunction with assessment of cardiac allograft function is likely to detect CAV with high degree of confidence. [13]

Table 2 **ISHLT recommendations for CAV nomenclature**

TABLE 2 Angiographic and Functional Nomenclature of CAV*	
Grade	Description
CAV-0 (not significant)	No detectable angiographic lesion
CAV-1 (mild)	LM<50%, any primary vessel<70%, or any branch<70%
CAV-2 (moderate)	LM 50%-70%, a primary vessel≤70%, or branch≥70% in branches of 2 systems
CAV-3 (severe)	LM≥70%, 2 or more primary vessel ≥70%, or branch stenoses≥70% in all 3 systems
Functional Parameters	
Functional upgrading	Evidence of significant systolic dyfunction(EF<45%) Evidence of restrictive hemodynamics orCI <2.1 l/min/m^2

Clinical Presentation

CAV can be indolent or may lead to clinical sequelae such as myocardial infarction (MI), decreased exercise capacity, heart failure, arrhythmia, and sudden cardiac death. Clinical presentation is usually delayed as patients usually do not experience angina due to denervated status of the transplant heart and can have silent MI. These patients can be asymptomatic for some time or can have non-specific symptoms of fatigue, nausea, or abdominal discomfort. [14,15] CAV can often present as sudden death or intractable arrhythmias. Other less common presentation is severe diastolic dysfunction (normal LVEF) resulting from microvasculopathy or small vessel CAV.

Biomarkers

Brain natriuretic peptide and C-reactive protein have been suggested as biomarkers for the detection of CAV. [16-18] *Two endothelium-enriched miRNAs, miR-126-5p and miR-92a-3p,* combined with age and creatinine conferred good discrimination between patients without and with CAV. [19-20] Another miRNA, miR-628-5p was found to be significantly elevated in heart transplant recipients with CAV with a sensitivity of 72% and a specificity of 83% to predict CAV. [21]

Vascular Changes

CAV is typically described as diffuse and concentric narrowing of both large epicardial and small intramyocardial arteries. The changes include intimal fibromuscular hyperplasia, atherosclerosis, and vasculitis. Despite pathological differences, CAV and traditional coronary artery disease (CAD) do share some similarities and have some common contributing factors. However, there are numerous differentiating features between the two.

Difference between CAV and native atherosclerotic disease

Feature	CAV	CAD
Symptoms	Asymptomatic	Angina
Onset	Rapid onset	Slow onset
Pathology	Allo-immune mediated	Immune mediated
Angiography	Diffuse disease (distal pruning)	Focal proximal disease
Vessel involved	Epicardial /intramyocardial	Epicardial
Histopathology features		
Intimal proliferation	Concentric	Eccentric
Internal elastic lamina	Intact	Disrupted
Calcium deposits	Uncommon	Common

Diagnosis

Echocardiography

As a screening tool, resting echocardiography provides limited diagnostic accuracy for CAV detection, particularly in mild forms. LVEF is often at the upper limit of normal due to either graft denervation and increased levels of circulating catecholamines, and is generally preserved even in advanced forms of CAV. [22-26]

The role of dobutamine stress echocardiography (DSE) in the diagnosis of CAV is controversial, especially with regards to recognition of early CAV. In fact, DSE detects angiographically evident CAV with a sensitivity of 70–80% which is marginally lower when IVUS is performed during ICA (72–79%). [27,28]

Intravascular Ultrasound (IVUS)

IVUS utilizes ultrasound to visualize the coronary lumen and layers of the arterial wall and identifies the maximal intimal thickness. [29] IVUS also allows for virtual histology, which uses backscatter radiofrequency data to generate a tissue map that characterizes vessel wall composition (fibrous, fibro-fatty, necrotic core, and dense calcium) with 87–96% in vivo accuracy. [30-31]

***Figure 1* Classifies CAV into 4 categories on the basis of IVUS examination.**

	Class I	Class II	Class III	Class IV
Severity	Minimal	Mild	Moderated	Severe
Intimal thickness	<0.3mm	<0.3mm	0.3-0.5 mm>0.5mm,<180	>1.0mm
Extent of plaque	<180	>180	>0.5mm,<180	>0.5mm,>180

Figure1 CAV, cardiac allograft vasculopathy: IVUS, intravasular ultrasound.
Reproduced from St Goar FG *et al.* [175]

Optical coherence tomography (OCT)

OCT is a technique that uses an optical analogue of ultrasound to provide cross-sectional images with a super high resolution, 10-fold higher compared with IVUS and has been shown to be the most useful for this purpose. OCT has the ability to clearly differentiate among the wide variety of vascular wall components. It accurately represents the intima–media interface, classifying tissues as fibrous, homogeneous, fibro-calcified, poor in signal with well-defined borders, or diffuse borders, or with an abundant amount of lipids.[32]

Coronary computed tomography angiography (CTA)

CCTA provides high-quality and high-resolution coronary images. Initial evidences stated that CCTA may be used as a screening tool in HT recipients for de novo CAV or as a follow-up strategy. [33-34] Furthermore, it detects an intimal maximal thickness (IMT)>0.5 mm similar to IVUS, thus being at par sensitive with ICA (nearly 97%).

If CAV is suspected, invasive coronary angiography becomes mandatory and further iodinated contrast is required. Annual or biannual angiography is the current standard for the diagnosis of CAV (Class I, LOE C) but if it is performed for screening purpose after 4-6 weeks heart transplant it has Class IIa, LOE C indication.

Nuclear imaging

Single photon emission computed tomography (SPECT)

SPECT has a high negative predictive value but low specificity and sensitivity which may be explained by the diffuse, balanced distribution of ischemia in CAV, as it is not territory-related. Global reduction in color-contrast can lead to false negatives. Although SPECT is not a good diagnostic tool for early detection of CAV yet it provides prognostic information. [35]

Positron emission tomography

PET shows more accuracy as compared with SPECT in the diagnostic workup of non-allograft coronary artery disease. The study of myocardial blood flow (MBF) can reveal the diffuse, non-segment specific nature of CAV, with earlier identification of the disease. [36]

Cardiac magnetic resonance

Cardiac magnetic resonance imaging (CMR) allows the high-resolution visualization of the epicardial coronary arteries and does not require exposure to ionizing radiation. CMR appears to be promising and may predict outcome for microvasculopathy form of CAV.

Imaging techniques in CAV (37)

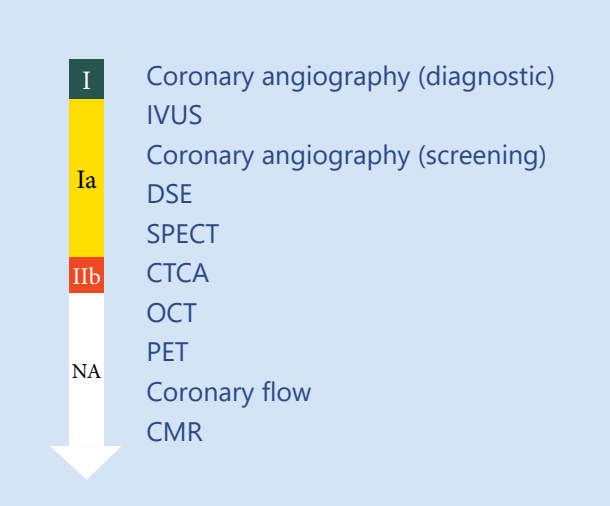

Figure 2- Showing the ISHLT recommendations [37] for various diagnostic modalities in the diagnosis of CAV

Management

There are several strategies for the prevention and treatment of CAV that might be of value to stall the pathological remodelling which include anti-thrombotic therapy, and newer immunosuppression approaches which include costimulation blockade and anti-IL6 monoclonal antibodies, and further cholesterol-lowering strategies.

Aspirin

Aspirin is the only **prophylactic** anti-platelet agent indicated for the heart transplant patients. The rate of CAV was six-fold lower in patients treated with aspirin compared with the non-treated patients (7% vs 37%). The combination of clopidogrel and everolimus has been also shown to significantly reduce the development of transplant arteriosclerosis in murine aortic allografts. [38]

Statins

Statins have lipid-lowering and immunomodulatory effects that are beneficial for preventing CAV. Statin therapy reduced the incidence of CAV and haemodynamically significant rejection and improved survival. Therefore, statins are recommended for all HT recipients and usually initiated early in the immediate post-operative period.[39-41]

Immunosupression

A randomized controlled trial comparing MPA and azathioprine showed less coronary intimal thickening on intravascular ultrasound with MPA. Additionally, mTOR inhibitors inhibit fibroblast proliferation and smooth muscle cell proliferation that are responsible for coronary intimal hyperplasia in CAV. Traditionally, calcineurin inhibitors (CNI) have formed the foundation of maintenance immunosuppression, significantly reducing rejection and improving survival.

Proliferation Signal Inhibitors

The current ISHLT guidelines recommend the introduction of a PSI in place of MMF for patients with established CAV (Class IIa, LOE B). [37]

There is 17% absolute risk reduction at 1-year for a combined clinical endpoint that included CAV, however there was no difference in mortality when two doses of everolimus were compared to azathioprine. [42] Studies also suggested that there was greater progression of CAV when everolimus was used with MMF without a CNI. [43]

Revascularisation

Percutaneous Coronary Intervention (PCI)/ Coronary Artery Bypass Grafting (CABG)

As a result of the diffuse nature of CAV, PCI has limited effectiveness to treat CAV. Trials have demonstrated that early restenosis is frequent with both balloon angioplasty (41–67%) and stenting (25–64%).[44] CABG too carries high perioperative risk (up to 40%) and one-year mortality (up to 58%).[45]

AICD

Role of AICD in preventing sudden cardiac death among patients with a depressed ejection fraction and ischemic heart disease seems a decent option but still needs to be studied.[47]

Retransplantation

Retransplantation is considered the only definitive therapy for CAV. Early results with retransplantation were poor with low one-year (54%) and median survival (less than two years). Similarly, one-year survival for retransplantation secondary to CAV (typically after one year) is 81% compared with less than 60% one-year survival when used for primary graft failure.[48]

CONCLUSION:

CAV is a leading cause of death after heart transplantation. It is likely that an invasive approach (coronary angiography) will best identify early CAV, in combination with IVUS/OCT. Non-invasive imaging modality seems to have high utility in medium- to long-term follow-up and may reduce the need for invasive testing. in future.

Treatment of CAV remains a challenge for clinicians as therapeutic options are limited. Current clinical treatment for CAV is primarily focused on preventative strategies including CMV infection prevention, rejection avoidance, vascular risk factor management, and specific pharmacotherapies, such as statins, aspirin, calcineurin inhibitors and mTOR inhibitors that halt the progression of the disease. Mycophenolic acid (MPA) and mTOR inhibitors (sirolimus and everolimus) reduce the development and progression of CAV but their optimal use and combination with other drugs and the long term results need to be established with further studies.

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