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New Developments for the Detection and Treatment of Cardiac Vasculopathy

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Abstract

Purpose of Review—Cardiac allograft vasculopathy (CAV) is a major limitation to long term survival after heart transplantation. Innovative new techniques to diagnose CAV have been applied to detect disease. This review will examine the current diagnostic and treatment options available to clinicians for CAV.

Recent Findings—Diagnostic modalities addressing the pathophysiology underlying CAV (arterial wall thickening and decreased coronary blood flow) improve diagnostic sensitivity when compared to traditional (angiography and dobutamine stress echocardiography) techniques.

Summary—Limited options are available to prevent and treat CAV; however progress has been made in making an earlier and more accurate diagnosis. Future research is needed to identify the optimal time to modify immunosuppression and investigate novel treatments for CAV.

Keywords

Cardiac allograft vasculopathy; screening; intracoronary imaging; coronary blood flow; proliferation signal inhibitors

Introduction

Heart transplantation (HT) remains the gold-standard for treatment of Stage D heart failure, resulting in improved quality of life, exercise capacity, and survival. While post-transplant survival has improved from a median of 8 years in the 1980s to over 12 years in 2016, this gain is primarily attributable to improved first year survival.¹ Following the first year,

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Figure 2B is adapted from: Mehra MR, Crespo-Leiro MG, Dipchand A, et al. International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy-2010. *The Journal of heart and lung transplantation* : the official publication of the International Society for Heart Transplantation 2010;29:717–27.

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cardiac allograft vasculopathy (CAV) is the third most common cause of death after HT. Graft failure is listed as distinct cause of death but most cases of graft failure are from CAV. If graft failure is included then CAV is the most common cause of long term mortality.¹ CAV is observed in 30–45% of HT recipients by 5 years post-transplant and 50–65% by 10 years.^{1, 2}

CAV is a distinct form of vascular disease unique to the coronary arteries of HT recipients. It is characterized by diffuse epicardial neointimal hyperplasia³, concentric medial microvascular disease⁴, and impaired coronary blood flow.⁵ Findings of coronary artery luminal narrowing are attributable to restrictive remodeling from external elastic lamina constriction.⁶ (Figure 1) The causes of CAV are multifactorial: *non-immunologic damage* (organ preservation, ischemia reperfusion injury, donor brain death, infection [CMV], and donor hypertension, age, and gender match), *immune-mediated injury* (donor-specific antibodies, antibody mediated and cellular rejection, inflammatory cytokines), and *atherosclerotic* (diabetes, hypertension, dyslipidemia).

Invasive Testing

Coronary Angiography

The original Gao angiographic criteria for CAV⁷ to describe anatomic lesions (Type A, B1, B2, and C lesions) was replaced in 2010 with the current International Society for Heart and Lung Transplantation (ISHLT) nomenclature (Figure 2). Annual or biannual angiography is the current standard for the diagnosis of CAV (Class I, LOE C).⁸ Screening may also be performed 4–6 weeks post-HT to evaluate for donor disease (Class IIa, LOE C).⁸ Angiography is prognostic of outcomes. Compared to those without CAV, patients with mild forms (ISHLT CAV1) have a two-fold risk of death, while patients with severe CAV (ISHLT CAV3) have a 15 times higher mortality.² Nevertheless, angiography is limited in its ability to detect CAV because it provides only a “lumengram”, failing to provide information about arterial wall thickening and coronary blood flow. Furthermore, there is significant inter-observer variation in angiographic grading.⁹ Newer modalities that enhance the detection of CAV will now be discussed.

Intravascular Ultrasound (IVUS)

IVUS utilizes ultrasound to visualize the coronary lumen and layers of the arterial wall. (Figure 3) IVUS performed 4–6 weeks after transplantation identifies donor disease if maximal intimal thickness (MIT) exceeds 0.5 mm. When compared to IVUS, the sensitivity of angiography to detect CAV ranges from 43–44%.^{10, 11} IVUS also provides important prognostic information, as a MIT ≥ 0.5 mm or an increase from baseline to one-year post-HT of ≥ 0.5 mm have both been linked to future angiographic CAV, death, graft loss, and myocardial infarction.^{12–15} 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.¹⁶ Using this technique, plaques identified as inflammatory (necrotic core and dense calcium >30%) have been shown to predict CAV progression.¹⁷ Limitations of widespread IVUS use have been cost, operator experience, and potential risk. IVUS is safe with reversible arterial

spasm being the most common complication (up to 2.9%, but less with nitroglycerin pretreatment) and rare acute complications (0.4% risk of occlusion, embolism, dissection, or thrombus).^{18, 19}

Optical Coherence Tomography (OCT)

OCT is a light based technology that allows for intracoronary imaging with 10 times the spatial resolution of IVUS (10–20 μm), providing clear delineation of the arterial intima and media. (Figure 4) This increased resolution permits in-vivo vessel histological analysis²⁰, detecting atherosclerotic plaque characteristics (calcification, lipid pools & necrosis), high-risk features (macrophages [inflammation], thin-cap fibroatheromas, microchannels), and complex plaques (layered, intimal laceration, intraluminal thrombus). Compared to IVUS and angiography, OCT has superior interobserver correlation²¹ and has been successfully used to screen for CAV.^{22–24} While OCT derived MIT presumably has the same prognostic significance as IVUS measured MIT, outcomes data is lacking at this time. A commonly cited drawback for OCT has been the need for additional contrast media (8–10 mL); however both dextran and saline may be used rather than contrast.²⁵

Coronary Flow

Impaired myocardial blood flow is a consequence of both epicardial and microvascular CAV.^{26, 27} By placing a pressure wire in the coronary artery, blood flow throughout the coronary vasculature can be quantified. Specific measurements include: fractional flow reserve (FFR) for the epicardial arteries, index of microcirculatory resistance (IMR) for the microvasculature, and total coronary flow with the coronary flow reserve (CFR). (Figure 5) Among non-transplant patients, a decreased FFR^{28, 29}, decreased CFR^{30, 31}, and increased IMR³² have all been associated with an increased risk of adverse cardiovascular events. Intracoronary flow measures are not as well studied for CAV, but are promising granted the pathophysiology of CAV. In one study a CFR <2.0 had a sensitivity of 79% and negative predictive value of 93% to predict angiographic CAV (>50% stenosis) or cardiac death.³³ However this finding has not been replicated.³⁴ Abnormal microvascular function one year post-HT, defined as an IMR ≥ 20 , portends a 250% increased risk of death, graft failure, or CAV at 5 years after transplant.³⁵ Further, at one year post-HT a FFR<0.90 leads to a 37% absolute increase in mortality and an IMR ≥ 20 leads to a 30% absolute increase in death or re-transplantation at five years. While additional studies are needed to confirm these findings and to define implications of abnormal coronary flow parameters later after HT, this is a diagnostic technique with great potential.

Non-Invasive Testing

Stress Echocardiography

Exercise stress echocardiography is hindered by the impaired heart rate response of heart transplant recipients, resulting in a sensitivity of only 15–33%^{36, 37} to diagnose angiographic CAV. Dobutamine stress echocardiography (DSE) is the most commonly employed non-invasive test screening for CAV (Figure 6). Early studies (the largest included 109 patients) compared DSE to coronary angiography and demonstrated sensitivities and negative predictive values (NPV) ranging from 65% to 95% and 71% to 92% respectively.^{38–43}

Subsequent studies comparing DSE to IVUS diagnosed CAV again showed adequate sensitivity (72–79%) and NPV (62–71%).^{40, 42} A positive DSE has also previously been associated with increased risk of cardiac events and death.⁴⁴ Recently, two independent studies including over 500 patients questioned the adequacy of DSE to detect angiographic CAV, finding that in clinical practice the sensitivity of DSE was only 6.5% in ISHLT CAV1, 27% in ISHLT CAV2, and 24% in ISHLT CAV3.^{45, 46}

Contrast-enhanced transthoracic echocardiography (CETE)

CETE with CFR has been employed to screen for CAV. In a study of 22 patients six years after HT, CFR was inversely related to MIT and a CFR cutoff of 2.9 had good sensitivity (80%) and specificity (100%) to diagnose IVUS confirmed CAV.⁴⁷ Similarly CETE with CFR may diagnose angiographic CAV (82% sensitive, 87% specific)⁴⁸ and decreased CFR by this technique has been associated with an increased risk of MACE.⁴⁹ This modality requires excellent echocardiographic images and may be limited in HT patients with poor acoustic windows and has limited reproducibility.

Coronary Computed Tomography Angiography (CCTA)

CCTA was called “promising” in the most recent ISHLT Guidelines (Class IIb recommendation) to diagnose CAV.⁸ A 2013 meta-analysis⁵⁰ found CCTA to be on par with coronary angiography to diagnose any CAV, with a sensitivity of 97% and negative predictive value (NPV) of 88%. However, an analysis comparing CCTA to IVUS demonstrated the limitations of both CCTA and angiography, as the sensitivity and NPV of CCTA were 81% and 50% respectively. Limitations of this technique include a limited ability to detect small vessel disease, need for heart rates <65 (unless a dual source scanner is used), radiation exposure (~8–12 mSv), and contrast exposure (60–120 mL).

Myocardial Perfusion Imaging (MPI)

Single-photon emission computed tomography (SPECT)—Similar to stress echocardiography, exercise SPECT MPI is limited to diagnose CAV. Pharmacologic stressors improve the ability of SPECT to diagnose CAV, as dobutamine SPECT has a sensitivity and NPV of 89–90% and 79–96% respectively.^{51, 52} Reports vary regarding the ability of dipyridamole SPECT to detect stenosis 50%, with sensitivity and specificity ranging from 21%–92% and 86–92% respectively^{53–55}, and may miss luminal disease (sensitivity 56%).⁵³ Negative studies are prognostic as the NPV for dobutamine SPECT is 95–98% for adverse cardiac events over the next 12 months^{51, 56} and is 78% over six years for dipyridamole SPECT.⁵³ The main limitation of this technique is radiation, which can range from 4–24 mSv.⁵⁷ Additionally, given the diffuse nature of CAV, balanced ischemia may be missed.

Positron Emission Tomography (PET)—Cardiac PET stress testing provides superior perfusion information compared to SPECT, and PET also quantifies myocardial blood flow. Measurement of CFR by PET allows for detection of microvascular disease and/or diffuse balanced ischemia. (Figure 7) Among non-transplant patients a decreased CFR measured by PET is associated with increased mortality with up to ten years of follow-up.^{30, 31, 58} Two single center studies of PET to screen for CAV found an association with future adverse

cardiac events.^{59, 60} And while this technique also exposes the patient radiation, it is significantly less (~2 mSv).^{57, 61}

Cardiac Magnetic Resonance Imaging (CMR)—CMR is not widely used to diagnose CAV. A small study demonstrated CMR coronary angiography had a modest ability to detect any angiographic CAV in vessels greater than 1.5 mm (Sensitivity 60% and Specificity 100%).⁶² Similar to PET, CMR can quantify coronary blood flow and adenosine stress CMR derived myocardial blood flow has been shown to be able to identify both epicardial and microvascular CAV in three small studies.^{63–65} Limitations of CMR include the need for lower heart rates, the risk of nephrogenic systemic fibrosis due to gadolinium administration in patients with impaired renal function, and implanted or retained non-MRI compatible devices.

Biomarkers

Currently no biomarker capable of diagnosing CAV has been identified. Several biomarkers have been associated with an increased risk of developing CAV including donor specific anti-HLA antibodies^{66–69}, persistent troponin elevation after the first month⁷⁰, elevated von Willebrand factor⁷¹, and a combination of an elevated N-terminal pro brain natriuretic peptide (NT-proBNP) and C-reactive protein (CRP)⁷².

Prevention

Statins

Since the initial trial demonstrating the benefits of pravastatin⁷³, statin therapy has become standard of care following HT (Class I, LOE A).⁸ That study found that pravastatin initiated two weeks after HT not only lowered cholesterol, but also reduced hemodynamically significant rejection, improved one-year survival, and decreased the incidence of CAV (and persisted to 10 years).⁸ Subsequent studies have found similar benefits with other statins^{74–77} and a meta-analysis of nine studies found statins decreased the odds of death by 76%, CAV by 67%, hemodynamically significant/fatal rejection by 63%, and terminal cancer by 70%.⁷⁸

Aspirin

HT recipients have been shown to have increased ADP induced platelet aggregation⁷⁹ and increased platelet aggregation has been associated with CAV.⁸⁰ However, the use of aspirin in HT recipients is empirical as there is no evidence demonstrating improved outcomes with its use.

Diltiazem

A study before the use of statins found diltiazem was associated with preservation of coronary artery diameter and improved post-transplant survival.⁸¹ However, this finding was not confirmed with concomitant statin use.⁸²

Mycophenolate Mofetil (MMF)

Following transplantation use of MMF or a PSI carries a Class IIa, LOE B recommendation to reduce the onset and progression of CAV.⁸ In 660 de-novo HT recipients, when compared to azathioprine MMF at 1500 mg twice a day resulted in a 7% absolute decrease in death or retransplantation and also decreased MIT progression as measured by IVUS.⁸³

Proliferation Signal Inhibitors (PSI)

The Class IIa recommendation⁸ for PSIs is principally based on studies that introduced PSIs at the time of transplantation or soon after.^{83–86} The first study supporting PSI use studied 634 de-novo heart transplant recipients comparing two doses of everolimus (1.5 mg/day and 3.0 mg/day) to azathioprine. This study found a 17% absolute risk reduction at one year for a combined clinical endpoint that included CAV, however there was no difference in mortality.⁸⁴ Subsequently, this trial was repeated using MMF as a comparator and again everolimus was found to be superior to MMF (14% absolute risk reduction) for the prevention of CAV, but only non-inferior for mortality at one year.^{85, 86}

Treatment

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).⁸ In a trial of 46 patients with established CAV rapamycin was found to decrease a combined endpoint of death, worsening CAV, or need for coronary intervention.⁸⁷ However, the widespread adoption of rapamycin has been limited by tolerability. A sub-study of the NOCTET trial included 111 patients that completed IVUS examination at a median of 5.8 years after transplantation who were treated with everolimus (and low dose CNI) or regular immunosuppression. Over half (52%) had CAV (defined at MIT >0.5 mm) and disappointingly there was no difference in progression of CAV between each arm after one year of follow-up. A more troubling finding was the suggestion that there was greater progression of CAV when everolimus was used with MMF (without a CNI).⁸⁸ And again, there was no evidence of a mortality benefit with PSI use.

Revascularization

Percutaneous Coronary Intervention (PCI)—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%)^{89, 90}, and that any early success with bare metal stenting is mitigated by 5 years when restenosis rates reach 69%.⁸⁹ The use of DES may reduce the risk of restenosis⁹¹, but have not been shown to improve survival.⁹² In a single center study, patients with ISHLT CAV 3 that was amenable to PCI and who underwent PCI had a decreased odds of death at two (OR 0.26, 95% CI 0.08–0.82) and five years (OR 0.28, 95% CI 0.09–0.93) compared to patients with ISHLT CAV 3 not amenable to PCI.⁹³ Thus it is reasonable to perform PCI for CAV that is amenable to PCI as a palliative treatment.

Coronary Artery Bypass Grafting (CABG)—CABG should be used with caution as it carries both a high perioperative (up to 40%) and one-year mortality (up to 58%).^{94–96}

Implantable Cardioverter Defibrillator (ICD)

Sudden cardiac death is one of the modes of mortality for patients with CAV. ICD has been shown to decrease the risk of sudden cardiac death among patients with a depressed ejection fraction and ischemic heart disease, however is not well studied among HT recipients. The most common indications for ICD use in HT recipients are low ejection fraction, ISHLT CAV 3, unexplained syncope, survived cardiac arrest, and ventricular arrhythmias.^{97, 98} In one study 10 of 36 patients received shocks and 80% received appropriate shocks.⁹⁸ However, there has been no evidence to support that ICDs improve survival in those with CAV and ICD implantation in the setting of immunosuppression is not without risk.

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). Subsequently it was found that the timing of retransplantation matters; when performed within the first year following primary transplantation post-retransplant one-year survival is 53%, while retransplantation after one year has significantly improved one-year survival (78–81%). 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.⁹⁹ Furthermore, while still inferior to primary transplant, median survival is now 10 years.⁹⁹ Biventricular mechanical circulatory support as a bridge to retransplantation has been reported to have good pre- and post-retransplant outcomes¹⁰⁰, however the use of ECMO should be avoided.¹⁰¹

Conclusion

CAV is prevalent following transplantation and has a high associated mortality. The currently recommended diagnostic techniques (coronary angiography, DSE) lack the sensitivity of techniques that measure coronary arterial wall thickening and coronary blood flow. Treatment of CAV remains a challenge for clinicians as therapeutic options are limited. Future research is needed to determine novel treatments for CAV and the optimal time to institute currently available treatment.

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Key Points

- CAV is a major limitation to long term post-transplant survival
- Traditional diagnostic techniques (angiography & dobutamine stress echocardiography) are limited to diagnose CAV
- Diagnostic techniques focusing on imaging coronary arterial wall thickening and coronary blood flow have shown increased sensitivity to diagnose CAV
- Treatments for established CAV remain limited

Figure 1. Pathologic images of coronary atherosclerosis: **(A)** Native coronary atherosclerosis characterized by lipidic plaque (*) **(B)** Cardiac allograft vasculopathy characterized by circumferential intimal thickening (arrowheads) in the absence of lipid.

Reproduced from Gao, S.Z., Alderman, E.L., Schroeder, J.S. et al. Accelerated coronary vascular disease in the heart transplant patient: coronary arteriographic findings. *J Am Coll Cardiol.* 1988; 12: 334–340

B.

ISHLT CAV0 (Not significant)	No angiographic lesion
ISHLT CAV1 (Mild)	Left main <50%, 1° vessel <70% with normal LV function
ISHLT CAV2 (Moderate)	Left main ≥50%; single 1° vessel vessel ≥70%, or isolated branch stenosis ≥70% in 2 systems; normal LV function
ISHLT CAV3 (Severe)	Left main ≥50%, 2 or more 1° vessel ≥70%, or branch stenosis ≥70% in all 3 systems. Or if ISHLT CAV1 or CAV2 with LVEF ≤45% Or restrictive physiology (E/A>2, IVRT <60 msec, RA>12 mmHg, PCWP>25 mmHg, CI<2 L/min/m ²)
<u>Primary Vessel:</u> Proximal and Mid LAD, LCx, ramus, or dominant/co-dominant RCA	
<u>Branch Vessel:</u> Distal 1° vessel, any segment within a large septal, diagonal, and/or OM branch; any portion of a non-dominant RCA	

Adapted from: Mehra MR, Crespo-Leiro MG, Dipchand A, et al. International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy-2010. *The Journal of Heart and Lung Transplantation.* 2010;29:717-27.

Figure 2.

Nomenclature for CAV: **(A)** Anatomic Gao Classification **(B)** 2010 ISHLT CAV recommended nomenclature

A. **B.**

Figure 3.
Intravascular Ultrasound Images: **(A)** IVUS of a normal coronary artery **(B)** IVUS demonstrating CAV with a MIT of 0.6 mm (green arrows)

Figure 4. Optical Coherence Tomography Images: (A) OCT of normal coronary artery (B) CAV with marked intimal thickening on OCT (C) OCT demonstrating CAV with macrophage accumulation (green arrow) within fibrous intimal thickening

Figure 5.
Coronary physiology measurements including FFR, CFR and IMR

Figure 6.
Dobutamine stress echocardiography of a transplant recipient: A negative study demonstrating normal wall motion and augmentation of contractility

Figure 7. Cardiac stress PET with CFR. Rest and stress perfusion images are on the left side of the figure (yellow arrows). Measurements of rest flow, stress flow, and CFR for each major vessel and for the total heart is present on right side of the figure (green arrows)