HEART FAILURE AND TRANSPLANTATION

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REVIEW:

An update on CAV imaging: Time for individualized therapy?

Introduction

Despite an overall improved survival following heart transplantation (HTx) during the last decades, the slope of the survival curve beyond the first postoperative year has not improved substantially [1]. While pre- and post-operative management and patient selection have improved, along with immunosuppression, the decay in survival following the first post-transplant year has not changed in 30 years.

Cardiac allograft vasculopathy (CAV) remains a leading impediment to long-term survival. CAV is traditionally considered as a chronic rejection causing diffuse accelerated fibroproliferative intimal thickening involving epicardial coronary vessels, the microvascular system, and the cardiac veins [2]. The pathogenesis of CAV is complex and involves immune reactions, vascular inflammation, and endothelial injury and dysfunction [3]. The condition is even more complex since not all vascular compartments seems affected simultaneously in all patients [4]. Myocardial function [5] and perfusion may improve during the first postoperative year, whereas the macrovascular CAV tends to worsen. Furthermore, the discrimination between CAV and donor transmitted coronary artery disease and later between CAV and development of traditional coronary artery disease (CAD) is challenging. Several pharmacological approaches has been suggested to prevent or postpone CAV development, such as statins [6], calcium channel blockers [7], angiotensin-converting enzyme inhibitors [8], platelet inhibitors [9] and proliferation signal inhibitors [10]. Despite these advances in CAV preventive medications, the CAV incidence has shown minimal reduction based on International Society for Heart and Lung Transplantation (ISHLT) statistics [11]. Furthermore, no medication has been shown to improve outcomes once CAV is established. Therefore, we speculate if our understanding and treatment of CAV as a uniform condition should be reformed and how to determine the CAV phenotype and severity most efficiently.

Several imaging modalities have been employed for CAV imaging [12], and all possess advantages and disadvantages which must be considered. In this review, we focus on the evaluation of macrovascular and microvascular CAV.

Evaluation of macrovascular function

Anatomical imaging:
Coronary angiography (CAG) is the most widely accepted imaging modality for CAV surveillance and is the recommended modality in the guidelines. Thus, CAV is currently classified primarily based on prevalence and severity of angiographic lesions [13]. This CAV classification is known to possess prognostic value. Furthermore, percutaneous intervention (PCI) can be performed *ad hoc* during the procedure. It is well known, that PCI of certain coronary lesions has a positive prognostic value in ischemic heart disease. However, it remains unknown if PCI is superior to optimal medical therapy in providing prognostic value in HTx patients. CAG often underestimates the CAV burden, especially in the early phase where the coronaries tend to undergo expansive vascular remodelling without lumen narrowing [14]. Interestingly, CAG combined with fractional flow reserve (FFR) assessment links the anatomical CAV assessment to a functional CAV assessment [15]. Additionally, CAG combined with intracoronary imaging for early CAV signs has shown to provide prognostic value both in the early [16] and late phase [17] following HTx. Intravascular ultrasound (IVUS) with measurement of maximal intima thickness (MIT) and intima/media ratio is performed in many centers both for clinical and research purposes. Approx. 50% of angiographic normal vessels in long-term HTx patients have intima thickening indicating CAV [18]. Thus, IVUS is considered the gold standard for CAV assessment. However, IVUS is used to dichotomize the patients into those with and those without CAV, and there is no CAV severity classification based on IVUS. Furthermore, IVUS is expensive and time consuming and no medication has been shown to postpone the CAV process when diagnosed by IVUS.
Optical coherence tomography (OCT) has become the state-of-the-art high-resolution intravascular imaging modality for assessment of coronary microstructure. IVUS and OCT detect CAV equally when traditional IVUS parameters are considered [19,20], i.e. MIT and the intima/media ratio. The main advantage of OCT over IVUS is that OCT provides a 10 times greater spatial resolution than IVUS. This enables a more detailed evaluation of the vessel wall microstructure. Even though only a few small studies investigated CAV in HTx patients by OCT [19-23], the data clearly shows that the old notion of CAV being a single disease of diffuse intimal proliferation is incorrect. The in-vivo characterization allows differentiation of CAV into patients with typical CAD, patients with a thrombo-fibrotic phenotype, and patients with a mixed phenotype. Similarly, different CAV phenotypes has been described in autopsy studies [24]. Thus, the medical therapy of HTx patients may be individualized and optimized by phenotype characterization. Furthermore, detailed evaluation of coronary microstructure by OCT may prove beneficial as surrogate endpoint in future randomized trials in HTx populations.
The challenges with both IVUS and OCT are the cost of the catheters and intracoronary wires as well as the need for staff with interventional experience. In addition, OCT requires contrast injection during image acquisition which adds to the contrast required from angiography alone. In addition, OCT can be challenging to interpret without significant experience. Some findings such as microtubules may be subtle and therefore expertise in heart transplant OCT has been confined to selected experienced centers thusfar.

Computed tomography (CT) has not been recommended for routine use in HTx patients. The elevated heart rate due to heart denervation limits the image quality. Yet, the improved CT scanner quality now provides a high negative predictive value for epicardial stenosis, and CT detects increased wall thickness in 50% more coronary segments than conventional CAG [25,26].

Microvascular function

Non-invasive myocardial perfusion imaging

Myocardial perfusion imaging links the evaluation of both microvascular and macrovascular function as the myocardial perfusion is highly dependent on both vascular compartments. Cardiovascular magnetic resonance (CMR) is a potentially attractive CAV screening modality owing to the lack of ionizing radiation and the ability to assess ventricular function, myocardial perfusion, and myocardial scarring at a single examination. Myocardial perfusion is strongly correlated to both microvascular function, in term of index of microvascular resistance (IMR) and to IVUS detected epicardial CAV [27,28]. In a similar manner, both positron emission tomography (PET) and echocardiographic Doppler detected coronary flow reserve (CFR) are strongly related to epicardial CAV and provides prognostic value [29-32].

Myocardial function imaging

In patients with sufficient acoustic windows, both dobutamine stress echocardiography and exercise stress echocardiography can been employed as surrogate CAV severity markers. Recently, exercise stress global longitudinal strain (GLS) assessment by speckle tracking echocardiography has been suggested to improve the echocardiographic graft function surveillance [30]. Myocardial deformation is highly dependent on myocardial perfusion. Thus, exercise stress GLS reflects the function of both vascular compartments. Furthermore, information of physical exercise capacity may also be beneficial in the surveillance of HTx patients. However, the sensitivity and specificity to detect macrovascular CAV by stress echocardiography is moderate. Yet, it remains unknown if a “false negative patient” who has undetected CAD/CAD would benefit from PCI.

Invasive microvascular function

The IMR is a specific invasive assessment of microvascular function describing the ratio between coronary pressure and flow [33]. During the first postoperative year following HTx, the IMR seems to improve whereas the epicardial CAV worsens. IMR measurement one year following HTx is a strong survival predictor [34] and is related to subclinical graft dysfunction [33,35].

Perspectives

This review emphasizes that CAV is a heterogeneous disorder and that no single imaging modality provides information of all CAV aspects in all patients. Furthermore, CAV development over time with early expansive and later inward remodelling of the epicardial coronary vessels suggests that different imaging modalities may be beneficial in the early and late phases following HTx.

Especially in the early phase, CAG and non-invasive testing falls short in CAV detection [36]. Therefore, intracoronary imaging may be beneficial in this phase. If CAV doesn’t develop during the early period after HTx, it is a good prognostic factor, and these patients may be able to undergo less frequent invasive CAV screening. However, patients with evidence of early CAV may need more aggressive medical therapy and more frequent coronary surveillance. Moreover, the macrovascular phenotype

detected by OCT could be an important factor. Thus, patients with typical CAV may prove benefit from high-dose statins and proliferation signal inhibitors. However, the driving forces for coronary lesions in the late phase are more similar to traditional CAD. Furthermore, typical CAD may co-exist with CAV, which reinforces the importance of risk factor modification.
A comprehensive CAV severity characterization in both the early and late phase following HTx should evaluate both macrovascular and microvascular compartments, as both possess independent prognostic value. The early changes in microvascular vessels may be noted by some observers on routine biopsies, whereas evaluation of IMR or non-invasive myocardial perfusion or function imaging can be considered after the first postoperative period. In order to employ the non-invasive testing for routine surveillance, it seems crucial to obtain a baseline value in a stable phase typically 3 to 6 months post-transplant. Patients with normal GLS [37]and patients with preserved CFR [29] seem to have a low risk of CAV development. The risk-stratification based on non-invasive imaging modalities may be improved by analysing cardiac biomarkers such as Troponin-T, NT-proBNP, and circulating donor specific antibodies. The combination of non-invasive imaging and biomarkers may someday be used as indicators for invasive CAV evaluation.

To move the field forward, we first need to find a treatment that will change the natural history of patients with CAV or traditional CAD post heart transplant and then prove that imaging guided therapy is associated with better outcomes. In the interim, without such data, we should focus on risk factors reduction and statin therapy much like a traditional non-transplant cardiac patient. As imaging becomes more widespread, we will hopefully understand the complex processes affecting post-transplant patients better, and derive focused treatments which may ultimately improve the long term survival of heart transplant recipients worldwide.

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