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EDITORIAL COMMENT

Cardiac allograft vasculopathy: How can it be predicted?

Doença coronária do aloenxerto cardíaco. Como podemos prevê-la?

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Cardiac transplantation is a well-established therapy for selected cases of end-stage heart disease. In its early stages, one-year survival was only 50%,[1] the poor results being due to allograft rejection or infection. Advances in immunosuppressive therapy with more effective regimens was crucial in improving survival at one year after heart transplantation.

As short-term survival improved, cardiac allograft vasculopathy (CAV) became a major limitation of long-term survival.

Because cardiac transplant recipients do not feel the classic symptoms of myocardial ischemia, as a result of denervation of the allograft, early diagnosis is challenging, but extremely important because it enables the disease to be recognized and treated in the initial stages, preventing progression and improving prognosis. The disorder is primarily immune-mediated, but some nonimmune factors are also of importance. Once CAV is diagnosed, the International Society for Heart and Lung Transplantation (ISHLT) guidelines[2] recommend the introduction of everolimus or sirolimus, since their antiproliferative effects can delay the progression of CAV and reduce its severity, on top of statin therapy. In selected patients, coronary revascularization should be performed and in advanced CAV, retransplantation.

In the single-center study by Picão et al. published in this issue of the *Journal*,[3] patients with heart transplantation underwent routine coronary angiography at one, three, five, eight, 10 and 12 years after transplantation and additional exams if clinically justified. The prevalence of CAV (9.7% and 17.6% at five and eight years post-transplantation, respectively) was much lower than that described in the literature (29% and 40% in the 2015 ISHLT report[4]).

The diagnostic prevalence of CAV is closely linked to the method used to identify it. Coronary angiography remains the recommended screening method for CAV, but its sensitivity is low. Conventional angiography does not assess the arterial wall and the vascular remodeling associated with CAV. The pathological characteristics of CAV differ significantly from those of typical atherosclerotic coronary disease. CAV involves concentric and diffuse proliferation of the arterial intima, with thickening and pathological remodeling leading to progressive narrowing of the lumen, particularly of small and medium-sized arteries. These findings are more difficult to diagnose by conventional angiography compared to the eccentric plaque typical of atherosclerotic coronary disease. In this setting, intracoronary imaging tools such as intravascular ultrasound (IVUS) and optical coherence

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tomography (OCT) significantly improve diagnostic accuracy for coronary disease in heart transplant patients.[5,6]

An optimal screening test should be safe, easy to perform and clinically able to either rule out disease or confirm its presence and assess its severity in order to support a valid clinical decision. There is growing interest in newer non-invasive imaging techniques that can exclude CAV, such as dual imaging stress echocardiography with wall motion and Doppler-derived coronary flow reserve of the left anterior descending artery (which excludes disease with a high negative predictive value of 91.1%),[7] positron emission tomography myocardial perfusion imaging, coronary computed tomography (CT) angiography (CCTA), and cardiac magnetic resonance imaging. CCTA can provide non-invasive anatomical assessment by visualizing the coronary artery lumen and wall. New-generation multislice systems with dual-source technology improve spatial and temporal resolution, helping to overcome the limitation of high heart rates often seen in these patients. CCTA currently has excellent sensitivity, specificity and negative predictive value for the detection of CAV,[8] although it is less sensitive than IVUS; as a screening method it can be improved if associated with non-invasive physiological assessment (CCTA complemented by CT-based fractional flow reserve). These non-invasive techniques are likely to become more clinically important in the future.[9]

More accurate screening algorithms are needed for early detection of disease or for identification of patients at risk of developing CAV. In this context, identifying CAV predictors, as Picão et al.[3] did in their study, is clinically important. They identified previous ischemic heart disease and carotid artery disease in the recipient, as well as donor age, as predictors of CAV. The rising age of donors in recent decades, with more comorbidities, especially in Europe, decreases the quality of the graft, and it is thus necessary to be aware of this risk predictor.[10] In future studies, it would be useful to analyze other possible predictors of CAV development in larger multicenter study populations, such as the cause of brain death, ischemia-reperfusion injury, viral infection and metabolic disorders.

Based on these results, changes were proposed in the authors' institutional protocol, including routine coronary angiography for donors over the age of 50 years to confirm eligibility for heart transplantation, and assessment with OCT at the time of the first routine angiography for recipients deemed at higher risk for CAV according to the clinician's judgment (including patients with vascular disease), in order to improve diagnostic accuracy and to adjust immunosuppressive therapy accordingly. We agree that if the disease is to be identified early, intracoronary imaging (IVUS or OCT) will need to be used routinely in association with invasive angiography, especially in the first years after transplantation. Progressive intimal thickening in the first year post-transplantation identifies patients at high risk for future cardiovascular events.

In future, non-invasive imaging methods will certainly replace coronary angiography for CAV screening. Invasive angiography in association with IVUS or OCT will be restricted to high-risk patients, for those with inconclusive or positive results on non-invasive tests, and for those needing coronary revascularization.

Conflicts of interest

The authors have no conflicts of interest to declare.

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