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Myocardial Perfusion Reserve and Strain-Encoded CMR for Evaluation of Cardiac Allograft Microvasculopathy

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ABSTRACT

OBJECTIVES This study sought to evaluate myocardial perfusion reserve index (MPRI) and diastolic strain rate, both assessed by cardiac magnetic resonance (CMR) as a noninvasive tool for the detection of microvasculopathy.

BACKGROUND Long-term survival of cardiac allograft recipients is limited primarily by cancer and cardiac allograft vasculopathy (CAV). Besides epicardial CAV, diagnosed by coronary angiography, stenotic microvasculopathy was found to be an additional independent risk factor for survival after heart transplantation.

METHODS Sixty-three consecutive heart transplant recipients who underwent CMR, coronary angiography, and myocardial biopsy were enrolled. Stenotic vasculopathy in microvessels was considered in myocardial biopsies by immunohistochemistry and CAV was graded during coronary angiography according to International Society of Heart and Lung Transplantation criteria. In addition, by CMR microvasculopathy was assessed by myocardial perfusion reserve during pharmacologic hyperemia with adenosine and strain-encoded magnetic resonance using a modified spatial modulation of magnetization tagging pulse sequence in all patients.

RESULTS Decreasing MPRI and diastolic strain rates were observed in patients with decreasing microvessel luminal radius to wall thickness ratio and decreasing capillary density ($r = 0.45$ and $r = 0.61$ for MPRI and $r = 0.50$ and $r = 0.38$ for diastolic strain rate, respectively; $p < 0.005$ for all). Using multivariable analysis, both MPRI and diastolic strain rate were robust predictors of stenotic microvasculopathy, independent of age, organ age, and CAV by International Society of Heart and Lung Transplantation criteria (hazard ratio: 0.07, $p = 0.006$ for MPRI; hazard ratio: 0.91, $p = 0.002$ for diastolic strain rate). Patients without stenotic microvasculopathy in the presence of no or mild CAV ($n = 36$) exhibited significantly higher median survival free of events, compared with patients with stenotic microvasculopathy in the presence of no or mild CAV ($n = 18$; $p = 0.04$ by log rank).

CONCLUSIONS CMR represents a valuable noninvasive diagnostic tool, which may be used for the early detection of transplant microvasculopathy before the manifestation of CAV during surveillance coronary angiographic procedures. (J Am Coll Cardiol Img 2016;9:255–66) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CAV = cardiac allograft vasculopathy

CMR = cardiac magnetic resonance

HTx = heart transplant

ISHLT = International Society of Heart and Lung Transplantation

IVUS = intravascular ultrasound

LV = left ventricle

MR = magnetic resonance

MPRI = myocardial perfusion reserve index

ROC = receiver operating characteristic

SENC = strain-encoded MR

SI = signal intensity

Long-term graft survival after heart transplantation is still limited by cardiac allograft vasculopathy (CAV) (1). Every second heart transplant (HTx) recipient develops CAV within 10 years after transplantation, regardless of age.

CAV affects epicardial blood vessels and microvasculature in cardiac allograft recipients, but the pathophysiology of the 2 vascular regions is different. CAV causes concentric intimal hyperplasia in epicardial coronary arteries (2,3), whereas medial thickening is seen in intramyocardial blood vessels (4).

Microvasculopathy can occur in parallel with epicardial coronary artery stenosis, but most cardiac allograft recipients with a microvascular dysfunction have no evidence of impaired epicardial physiology (5). Both microvasculopathy and macrovasculopathy result in reduced myocardial perfusion and function, which leads to increased morbidity and mortality rates (6). More importantly, the prognostic impact for long-term survival of transplanted patients with microvasculopathy is independent of that of macrovasculopathy (4). Thus, early detection of CAV is an important clinical goal in this context. Although CAV of epicardial blood vessels is a common part of the post-transplant routine follow-up visits, screening for microvasculopathy is still missing in a routine setting.

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In the present study, we sought to investigate whether myocardial perfusion reserve index (MPRI) and myocardial strain, both assessed by cardiac magnetic resonance (CMR), are related to histological parameters of microvascular integrity, including capillary density and luminal radius to wall thickness in 10- to 20-μm diameter microvessels, assessed by myocardial biopsy.

METHODS

STUDY POPULATION AND SEPARATION INTO PATIENT SUBGROUPS. Sixty-three consecutive HTx recipients underwent routine coronary angiography, myocardial biopsy, and CMR within 4 weeks from cardiac catheterization. The International Society of Heart and Lung Transplantation (ISHLT) criteria for acute cellular rejection were applied for each endomyocardial biopsy. At the time of the study, all HTx recipients were in stable condition, without clinical signs of heart failure (New York Heart Association functional class >II, ejection fraction <40%), unstable angina, or acute/ongoing rejection, diagnosed by histology (ISHLT class >IA) (2). Patients received a standard double immunosuppressive therapy (mycophenolate mofetil and a calcineurin inhibitor-cyclosporine A or tacrolimus) (7). Thirty-six patients (57% of the present cohort) were included in previous reports, where the ability of angiographic myocardial blush grade was investigated to predict cardiac outcomes in transplant recipients (8). According to the results of myocardial biopsy and coronary angiography, patients were separated as follows: Group A, including patients with no or mild CAV by angiography and without stenotic microvasculopathy; Group B, including patients with no or mild CAV by angiography but evidence of stenotic microvasculopathy; and Group C, including patients with both manifest stenotic macrovasculopathy and microvasculopathy, which were subsequently excluded for correlative and receiver operating characteristic (ROC) analysis.

All procedures complied with the Declaration of Helsinki and were approved by our local ethics committee, and all patients gave written informed consent.

CMR EXAMINATION. HTx recipients were examined in a clinical 1.5-T whole-body magnetic resonance (MR) scanner Achieva system (Philips Medical Systems, Best, the Netherlands). This is part of our institutional post-transplant protocol performed in HTx recipients. Patients were asked to refrain from caffeine intake 12 h before testing. A standardized imaging protocol was used, aiming at the assessment of baseline parameters of left ventricle (LV), such as LV diameters, septal and lateral wall thickness, and ejection fraction using cine imaging. Myocardial perfusion reserve was assessed during pharmacologic hyperemia with adenosine in all patients.

MYOCARDIAL PERFUSION IMAGING. A 3-slice turbo field echo-echo-planar imaging sequence was used as described previously (9). Stress perfusion imaging was performed using a continuous intravenous infusion of 140 μg/kg/min adenosine. Three heartbeats after initiation of the sequence a bolus of 0.04 mmol/kg bodyweight gadolinium-DTPA (Magnevist, Berlex, New Jersey) was injected over an antecubital vein at a rate of 5 ml/s flushed with 20 ml 0.9% sodium chloride.

Semiquantification of myocardial perfusion was conducted in 3 LV short-axis slices using View Forum software (Philips Medical Systems). Manual contouring of endomyocardial and epimyocardial borders was assessed on the image with the brightest contrast enhancement in LV and an automated algorithm was used to match contours in the remaining images of the slice. The myocardium was divided into 6