JACC: HEART FAILURE
VOL. 3, NO. 12, 2015

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jchf.2015.07.013

Paradoxical Vessel Remodeling of the Proximal Segment of the Left Anterior Descending Artery Predicts Long-Term Mortality After Heart Transplantation

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ABSTRACT

OBJECTIVES This study investigated the association between arterial remodeling and geographic distribution of cardiac allograft vasculopathy (CAV), and outcomes after heart transplantation.

BACKGROUND CAV is characterized by a combination of coronary intimal thickening and pathological vessel remodeling, which varies at different locations in coronary arteries.

METHODS In 100 transplant recipients, serial volumetric intravascular ultrasonography (IVUS) was performed at baseline and 1 year post-transplantation in the first 50 mm of the left anterior descending artery (LAD). IVUS indices were evaluated in the entire segment and 3 equally divided LAD segments. Paradoxical vessel remodeling was defined as [Δvessel volume/Δintimal volume <0].

RESULTS After 1 year, death or re-transplantation occurred in 20 patients over a median follow-up period of 4.7 years. Paradoxical vessel remodeling was observed in 57%, 41%, 50%, and 40% for the entire vessel, proximal, middle, and distal LAD segments, respectively. Kaplan-Meier analysis revealed a significantly lower event-free rate of survival in patients with paradoxical vessel remodeling involving the proximal LAD segment, which was not present when involving the entire LAD or mid and distal LAD segments. In multivariate analysis, paradoxical vessel remodeling of the proximal LAD segment was independently associated with death or re-transplantation (hazard ratio [HR]: 11.18; 95% confidence interval [CI]: 2.39 to 83.23; $p = 0.0015$).

CONCLUSIONS Despite the diffuse nature of CAV, paradoxical vessel remodeling of the proximal LAD segment at 1 year was the primary determinant of long-term mortality or re-transplantation. Assessment of arterial remodeling combined with coronary intimal thickening may enhance identification of high-risk patients who may benefit from closer follow-up and targeted medical therapies. (J Am Coll Cardiol HF 2015;3:942–52) © 2015 by the American College of Cardiology Foundation.

From the Division of Cardiovascular Medicine, Stanford Cardiovascular Institute, Stanford University Medical Center, Palo Alto, California. This study was supported by National Institutes of Health Heart, Lung and Blood Institute grants R01 HL093475-01A1 to Dr. Fearon and 1 PO1-AI50153 to Dr. Valantine. Dr. Kobayashi has received honoraria from Volcano. Dr. Fearon has received research grants from Medtronic and St. Jude; and speakers fees from Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received May 27, 2015; revised manuscript received July 13, 2015, accepted July 17, 2015.

Cardiac allograft vasculopathy (CAV) remains a leading cause of mortality and morbidity after heart transplantation (1). Although early heart transplantation studies focused primarily on coronary intimal thickening to assess the severity of CAV (2,3), vessel remodeling has been recognized as another important measure in recent investigations (4,5). Compared with contrast angiography, intravascular ultrasonography (IVUS) can directly visualize the arterial wall structure, offering a more sensitive method to detect intimal thickening and vessel remodeling (6).

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Previous IVUS studies of CAV have reported controversial results with respect to arterial response early after heart transplantation, demonstrating variable degrees of coronary intimal thickening and vessel size alteration in opposite directions (negative vs. positive vessel remodeling) (4,5,7–9). The discrepancies in these studies are likely explained by the use of 2-dimensional (2D) IVUS analysis and/or cross-sectional study design using heterogeneous patient populations as opposed to longitudinal investigations of the same patients. The pathology of CAV, characterized by a combination of coronary intimal thickening and pathological vessel remodeling, also appears to vary at different locations in the coronary arteries (10,11). Hence, we hypothesized that comprehensive 3D volumetric IVUS analysis might measure the nature and severity of CAV more accurately than conventional 2D planar IVUS indices. The aims of this study, therefore, were to characterize the early arterial responses, particularly pathological vessel remodeling, and anatomic distribution of CAV as measured by 3D IVUS and to investigate their association with clinical outcomes after heart transplantation.

METHODS

STUDY POPULATION. Between January 2002 and January 2013, heart transplantation recipients in stable condition with preserved renal function (serum creatinine concentration of ≤2.0 mg/dl at baseline), who successfully survived at least 1 year after heart transplantation and underwent scheduled serial IVUS imaging at baseline (within approximately 6 weeks) and at 1 year post-transplantation were eligible for enrollment in this retrospective study. Hospitalized or patients in unstable condition at 1 year were excluded. All recipients received standard immunosuppressive therapy, including induction therapy with daclizumab or rabbit antithymocyte globulin, corticosteroids, an antiproliferative agent (rapamycin or mycophenolate mofetil), and a calcineurin inhibitor (cyclosporine or tacrolimus). Patients were monitored for acute cellular rejection using right ventricular endomyocardial biopsy at scheduled intervals post-transplant: weekly during the first month, biweekly until the third month, monthly until the sixth month, and then at 9 and 12 months. Biopsy results were graded according to the International Society for Heart and Lung Transplantation (ISHLT) 2004 revised grading scale, and significant acute cellular rejection was defined as one or more episode(s) of a grade ≥2R during the first year post-transplant (12,13). Lipid parameters (total cholesterol and triglycerides) and left ventricular ejection fraction (LVEF), as measured by echocardiography, were also evaluated at 1 year post-transplantation. Patients were followed beyond the first year post-transplantation, and the primary endpoint of this study was major adverse events, defined as all-cause death or re-transplantation. The study protocol was approved by the Institutional Review Board at Stanford University, and every patient provided written informed consent.

ABBREVIATIONS AND ACRONYMS

CAV = cardiac allograft vasculopathy

IVUS = intravascular ultrasonography

LAD = left anterior descending artery

LVEF = left ventricular ejection fraction

MIT = maximal intimal thickness

IVUS IMAGING PROTOCOL. After diagnostic coronary angiography was performed, 3,000 to 5,000 units of heparin were administered intravenously, and 200 μg of intracoronary nitroglycerin were administered through a 6-F guide catheter in the left coronary artery. A 0.014-inch guide wire was advanced to the mid to distal left anterior descending artery (LAD). IVUS imaging was performed using a mechanical IVUS system with a 40-MHz imaging catheter (Galaxy with Atlantis SR Pro or OptiCross with iLab; Boston Scientific Corp., Marlborough, Massachusetts). The catheter was advanced to the mid to distal LAD, and an automated pullback was performed at 0.5 mm/s. Images of the first 50 mm of the LAD were recorded and analyzed offline (4,12,13).

IVUS ANALYSIS. IVUS analysis was performed with a validated quantitative IVUS analysis system (echoPlaque, Indec Systems, Santa Clara, California) at the Stanford University Cardiovascular Core Analysis Laboratory, blinded to clinical and angiographic information (4). Vessel, lumen, and intimal areas (calculated as: vessel minus lumen) were manually traced at 1-mm intervals throughout the first 50 mm of each LAD, and the interpolated measurements of the remaining frames were automatically generated. Vessel, lumen, and intimal volumes were calculated using the Simpson method and standardized as volume index (defined as: volume / analyzed length, mm^3/mm) (4). To represent pathological arterial response over time, paradoxical vessel remodeling was defined