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ORIGINAL CLINICAL SCIENCE

Uric acid is an independent predictor of cardiac allograft vasculopathy after heart transplantation

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BACKGROUND: Cardiac allograft vasculopathy (CAV) is a major complication after heart transplantation (HT). Uric acid (UA) may play a role in CAV due to its role in stimulating T-cell–mediated immunity. Sirolimus is associated with CAV attenuation through a number of mechanisms, including immune-mediated effects. We aimed to determine whether UA is an independent predictor of CAV and whether conversion to sirolimus as primary immunosuppression modulates UA levels.

METHODS: We retrospectively analyzed a cohort of 224 patients who underwent HT between 2004 and 2015 and had serial coronary intravascular ultrasound (IVUS) studies. Serum UA levels were measured at baseline and last follow-up IVUS in all participants. CAV progression was assessed by measuring the change in plaque volume (ΔPV) and plaque index (ratio of plaque volume to vessel volume [ΔPI]) between last follow-up and baseline IVUS after correction for time of follow-up.

RESULTS: Patients with high (≥7 mg/dl) compared with low (<7 mg/dl) UA had increased median ΔPV (0.33 [interquartile range 0.08 to 0.93] vs 0.07 [–0.17 to 0.38] mm^3/mm/year; $p < 0.001$) and ΔPI (2.0% [0.31% to 3.9%] vs 0.33% [–1.2% to 2.0%]; $p < 0.001$). Elevated UA levels were associated with a significantly increased risk of developing significant CAV progression (ΔPV >0.50 mm^3/mm) (hazard ratio 2.2, 95% confidence interval 1.1 to 4.6; $p = 0.037$). Sirolimus resulted in decreased UA levels (5.8 ± 1.4 vs 5.2 ± 1.5; $p = 0.002$) and patients converted to sirolimus and had low UA levels had the least CAV progression ($p < 0.001$). After adjustment for potential confounders, change in UA level was also an independent predictor of CAV progression.

CONCLUSIONS: UA is an independent predictor of CAV after HT. Sirolimus is associated with decreased UA levels and may explain one of the mechanisms by which sirolimus attenuates CAV progression.

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Cardiac allograft vasculopathy (CAV) is the most prominent cause of late graft failure and long-term mortality, accounting for up to 1 in 8 deaths beyond 1 year after heart transplantation (HT).[1,2] Despite recent advances in post-transplant management, incidence of CAV has been only modestly reduced, and thus is still associated with

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significant morbidity and mortality. Approximately 40% of patients develop CAV at 5 years after HT and up to 7% of these patients develop significant left main or triple-vessel disease.[3,4] Identifying modifiable risk factors for CAV early post-HT may play a key role in reducing CAV progression and improving late outcomes in this population.

CAV is a fibroproliferative disease that develops secondary to a complex interplay between immune and non-immune factors, causing sustained coronary endothelial inflammation, injury, and dysfunction.[5] Endothelial injury, in turn, initiates and drives a cascade of pathways that result in diffuse myointimal proliferation, accumulation of inflammatory cells, lipid deposition, and fibrosis, ultimately leading to diffuse concentric luminal narrowing of epicardial and intramural vessels.[5,6] Alloreactive T-cell lymphocytes and humoral responses play a substantial role, whereas hyperlipidemia, cytomegalovirus (CMV) infection, donor age, and ischemia/reperfusion injury are the major non-immune factors that contribute to the development and progression of CAV.[6,7]

Uric acid (UA) is a major predictor of atherosclerosis and cardiovascular disease in the non-transplant population.[8–10] Elevated UA levels are also associated with increased oxidative stress, chronic inflammation, impaired endothelial function, and induction of T-cell–mediated immune responses, all of which can be involved in the development and progression of CAV.[8,11–14] Among HT recipients, the role of UA in CAV progression is unclear. Moreover, conversion to sirolimus (SRL) from a calcineurin inhibitor (CNI) has been associated with attenuated plaque progression,[15] improved coronary vasomotor function, and reduced epicardial endothelial dysfunction,[16,17] but the mechanisms of this benefit have yet to be fully elucidated.

The current study has 2 primary aims. First, we aimed to determine whether increased UA levels are independently associated with increased CAV incidence and progression, as measured by plaque volumetric measurements with serial IVUS examinations. Second, we aimed to determine whether conversion to SRL, with complete withdrawal of CNI therapy, modulates UA levels. We hypothesized that increased serum UA is associated with increased CAV progression, and that patients converted to SRL have lower UA levels, thus adding another beneficial effect of SRL on CAV progression.

Methods

Study design

This study was a single-center, non-randomized longitudinal cohort investigation. Our study protocol was approved by the institutional review board of the Mayo Clinic and research consent was obtained from all patients participating in the investigation. We retrospectively analyzed 224 adult patients who underwent HT at the Mayo Clinic, Rochester, Minnesota, from January 2004 to July 2015. Patients were included in the study if they had at least 2 sequential coronary IVUS examinations for volumetric assessment of CAV progression during follow-up after HT. We excluded patients who did not have follow-up IVUS or had poor quality IVUS images, those who converted back to a CNI before completion of follow-up IVUS, and those who were treated with both SRL and CNI due to history of severe allograft rejection.

Demographic and laboratory data

Baseline characteristics and laboratory measurements were obtained at baseline and a database was prospectively constructed. Serum UA levels were collected at baseline; around 3 months post-HT and before the first IVUS, as well as at time of the last follow-up IVUS study, according to standard laboratory protocols at the Mayo Clinic. Immunosuppressive agents were reviewed and recorded at each outpatient visit post-HT and conversion from CNI to SRL therapy was performed according to our standard institutional protocol.[15,18] Briefly, the reasons for conversion to SRL varied according to the period of conversion. Until July 2006, patients were converted to SRL due to intolerance of CNI therapy, largely manifested as CNI-induced nephrotoxicity. Since July 2006, a routine conversion protocol from CNI to SRL was introduced in most patients when tolerable at least 6-months post-HT. The dose of secondary immunosuppression, mycophenolate mofetil (MMF) or azathioprine, as well as the dose of prednisone, remained unchanged during the conversion process. Biopsy was generally repeated 2 weeks after conversion and a reduced dose of CNI was reintroduced if biopsy was positive for rejection with a second attempt to withdraw CNI therapy later if rejection subsided. Trough levels of cyclosporine, tacrolimus, and SRL were measured by high-performance liquid chromatography with tandem mass spectroscopy (API 4000; Applied Biosystems, Foster City, CA) and adjusted according to the institutional protocols. The estimated glomerular filtration rate (eGFR) was calculated by the CKD-EPI (Chronic Kidney Disease—Epidemiology Collaboration) equation.

Coronary angiography and IVUS measurements

All patients underwent annual coronary angiography according to the standard protocol as well as 3-dimensional virtual histology coronary IVUS of the left anterior descending coronary artery, according to our institution's standard transplant protocol.[15,18] CAV was also graded using coronary angiography according to ISHLT criteria.[19]

IVUS images were obtained during routine coronary angiography after intracoronary administration of 100 to 200 μg nitroglycerin with a phased-array 20-MHz 3.2F IVUS imaging catheter (Eagle Eye Gold; Volcano Therapeutics, Inc., Rancho Cordova, CA). The catheter was placed distally in the left anterior descending artery (LAD) and a motorized pull-back at 0.5 mm/s back to the LAD ostium was used. The electrocardiographic (ECG)-gated gray-scale IVUS images were acquired and radiofrequency data were captured at the top of the R wave. Volumetric reconstruction was performed using pcVH (version 2.2) or Volcano Image Analysis software (version 3.1; Volcano Corp.) by 2 blinded observers. Multiple coronary segments of the LAD were assessed from baseline images and follow-up studies based on branch location. Proximal and middle-left anterior descending coronary artery regions were defined for the interrogated artery. Starting with the first complete vascular ring distal to the bifurcation with the left circumflex artery lumen, plaque volume (PV) and vessel volume (VV) were analyzed. Each measured volume was normalized to the examined segment length (SL, in square millimeters per millimeter [mm^3/mm]) to compensate for differences in examined vessel SL and adjusted for time of follow-up between the first and last follow-up exams. Plaque index