



ORIGINAL CLINICAL SCIENCE

Elevated immune monitoring as measured by increased adenosine triphosphate production in activated lymphocytes is associated with accelerated development of cardiac allograft vasculopathy after cardiac transplantation

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BACKGROUND: Elevated immune monitoring (IM), as measured by adenosine triphosphate (ATP) release from activated lymphocytes, has been suggested to represent an under-immunosuppressed state. Its association with the development of angiographic cardiac allograft vasculopathy (CAV) is unknown. **METHODS:** Patients transplanted between January 2007 and December 2011 with annual angiograms and at least 1 IM assay were included in the analysis. Peak IM scores were determined for each patient. Patients with peak IM in the highest quartile (Group 2) were compared with those with scores in the lower quartiles (Group 1). Mild disease was scored as Grade 1 (CAV1) and moderate or severe disease was scored as Grades 2 or 3 (CAV2/3).

RESULTS: Two hundred forty patients were included. The mean age at transplant was 54.2 ± 12.1 years. Time to peak IM assay was 105.9 ± 44.1 days and average number of assays obtained per patient was 3.1 ± 1.8 . Patients in the highest quartile (Group 2) had peak IM ≥ 446 ng ATP/ml. Mean clinical follow-up was 4.6 ± 1.7 years. CAV1 was observed in 86 of 180 (47.8%) patients in Group 1 and 39 of 60 (65.0%) in Group 2. Freedom from CAV1 was significantly lower in patients in Group 2 (log rank, $p = 0.012$). CAV2/3 occurred in 7 of 180 (3.7%) patients in Group 1 and 9 of 60 (15.0%) patients in Group 2. Freedom from CAV2/3 was significantly lower in patients in Group 2 ($p = 0.003$). In multivariate analysis elevated peak IM assay was still found to be associated with angiographic CAV (hazard ratio 1.647, confidence interval 1.020 to 2.661, $p = 0.041$).

CONCLUSION: Elevated peak IM, as measured by increased ATP production, in activated lymphocytes is associated with decreased freedom from angiographic CAV.

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Cardiac transplantation remains the most durable option for end-stage heart failure, but there is a limited donor supply.¹ Although the incidence of acute rejection has decreased with improved immunosuppression, cardiac allograft vasculopathy (CAV) persists as a major cause of

late graft failure.² Several immunologic and demographic variables have been associated with the development of CAV, but their respective contributions are not well established and no risk model exists to identify patients at increased risk of CAV.³ Moreover, in clinical practice, there are no readily available serologic assays that have been associated with CAV. Therefore, there remains an unmet need for early serologic non-invasive testing to identify patients at increased risk.

For over a decade, pravastatin and Vitamins C and E have been routinely incorporated after transplantation for primary prevention of CAV^{4,5}; however, studies in the current era continue to demonstrate that approximately 20% to 25% of patients nonetheless have accelerated coronary plaque progression on intravascular ultrasound (IVUS) after transplantation and are at increased risk for developing CAV.^{6–8} Although mammalian target-of-rapamycin (mTOR) inhibitors have shown promise in de novo cardiac transplantation, their use is limited by increased drug discontinuation due to side effects in this patient cohort.^{7,9–11} The early identification of patients at increased risk of CAV has major prognostic and therapeutic implications. Patients with increased risk of CAV may benefit from intensified CAV surveillance. In patients with detected CAV, mTOR inhibitors may be introduced for secondary prevention of CAV progression.^{12,13}

Serologic non-invasive T-cell immune monitoring (IM), as measured by adenosine triphosphate (ATP) release from activated lymphocytes, has been used to guide management of immunosuppressive therapy after solid-organ transplantation. In a recent study of adult liver recipients, patients were randomized to standard practice or tacrolimus titration based on serial IM assays (ImmuKnow; Viracor-IBT Laboratories, Lee's Summit, MO). Patients were randomized to immunosuppression modification based on the assays had decreased infections and improved survival compared with standard practice.¹⁴ In cardiac transplantation, low scores have been shown to be associated with infection,¹⁵ and high scores 2 months after transplant have been shown to be associated with rapid coronary plaque progression by IVUS.⁶ However, it is not known whether any elevated score early after cardiac transplant is associated with coronary plaque progression and development of angiographic CAV downstream. We therefore hypothesize that any elevated IM assay score in the first 6 months after cardiac transplantation will be associated with increased risk for development of angiographic CAV.

Methods

Institutional immune monitoring and screening angiography protocol

All transplanted patients with baseline and 1-year coronary angiograms and at least 1 IM assay were included for the 5-year period between January 2007 and December 2011. IM assays were routinely measured after transplantation during office visits in the first year. IM assays performed between 2 and 6 months post-transplant were selected for analysis. It has been shown previously that the association of IM assays with coronary plaque progression is inconsistent before 2 months and

becomes unassociated after the first 6 months.⁶ The peak score of IM assay scores was determined for each patient. Immunosuppressive regimens were adjusted for low IM scores of <100 ng ATP/ml, based on earlier observations of their association with occult infection.¹⁵ On the rare occasions with values of >600 ng ATP/ml, adjustments were made on an individual basis. By institutional protocol, patients also underwent routine angiographic screening for CAV. Patients with kidney insufficiency, hypersensitivity to contrast media or anti-coagulants and active infection or inadequate vascular access, and those followed at another institution after transplantation, were not routinely screened. The severity of CAV was scored as Grade 1 (CAV1) for mild disease and Grade 2 or 3 (CAV2/3) for moderate or severe disease. Scoring was based on the International Society for Heart and Lung Transplantation (ISHLT) proposed classification scheme.¹⁶

End-points and baseline characteristics

The optimal cut-off for a peak IM assay score to identify patients at increased risk for angiographic CAV has not been determined. An elevated IM score at 2 months has been associated with rapid plaque progression on IVUS,⁶ corresponding to the highest quartile of post-transplant patients, and earlier studies have identified the prevalence of patients who develop rapid progression of coronary plaque at 20% to 25% of post-transplanted hearts.^{6–8} Patients were therefore divided into 2 groups based on quartiles of their peak IM scores. Patients with peak IM scores in the lowest 3 quartiles were included in Group 1, and the patients with an elevated peak IM score in the highest quartile were included in Group 2.

Co-primary end-points were freedom from CAV1 and freedom from CAV2/3. Incidence of developing donor-specific antibodies (DSA) within the first year post-transplantation was also reported. Baseline characteristics, including recipient age and gender, hypertension, diabetes, ischemic time, high-risk cytomegalovirus (CMV) mismatch, pre-transplant peak panel-reactive antibodies (PRA), pre-transplant peak PRA $\geq 10\%$, pre-transplant peak PRA $\geq 25\%$, pre-transplant cholesterol, pre-transplant creatinine, ischemic or non-ischemic etiology, pre-transplant mechanical circulatory support, donor age and gender, HLA-DR haplotype mismatch, anti-thymocyte globulin induction therapy and immunosuppressive regimen, were compared between the 2 groups.

Statistical and multivariate analysis

Statistics were performed utilizing SPSS software (IBM, Armonk, NY). Fisher's exact test was used for categorical variables, the 2-tailed Student's *t*-test was used for continuous variables, and log-rank test was used for survival curves. Multivariate analysis was performed with Cox proportional hazards regression analysis. In addition to the IM assay score, 8 variables previously associated with angiographic CAV were pre-specified to be included in the model: donor age; pre-transplant sensitization; high-risk CMV mismatch; mTOR inhibitor use; ischemic etiology; diabetic status; ischemic time; and treated rejection. In addition, any baseline characteristics with $p < 0.10$ on univariate analysis were also included in the multivariate analysis. Hazard ratios are reported.

Results

Two hundred eighty-two patients with at least 1 IM assay were transplanted between 2007 and 2011. Forty-two patients were not included due to lack of angiographic follow-up due to follow-up at another institution (62%),

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