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Interplay of coronary angiography and intravascular ultrasound in predicting long-term outcomes after heart transplantation

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BACKGROUND: Cardiac allograft vasculopathy (CAV) remains the major cause of late graft-related death after heart transplantation (HT). Identification of patients at risk of cardiovascular events has relevant implications in appropriately guiding resources and intensity of follow-up. In this context, the prognostic relevance of serial coronary imaging long-term after HT is unexplored.

METHODS: Recipients with intravascular ultrasound (IVUS) and coronary angiography performed 1 and 5 years after HT were monitored for subsequent 1 to 10 years to analyze the association of serial coronary imaging with cardiovascular death and major cardiovascular events (MACEs).

RESULTS: Included were 131 patients. The MACE incidence was 31.8 per 1,000 patient-years, and cardiovascular mortality was 17.4 per 1,000 patient-years. Progression of coronary lesions detected by angiography and changes in IVUS-defined parameters, including an increase in maximal intimal thickness (MIT) $\geq$0.35 mm and vascular remodeling, predicted MACE occurrence. However, only MIT change $\geq$0.35 mm also predicted cardiovascular mortality. Among patients with normal or stable angiography, an MIT change $\geq$0.35 mm identified those with a significantly higher MACE rate (80 vs 13 events/1,000 patient-years). Worsening metabolic parameters appeared associated with the increasing severity of CAV development.

CONCLUSIONS: Combined imaging analysis of progression of angiographic lesions and IVUS-detected MIT between 1 and 5 years post-HT allows discriminating patients at high, intermediate, and low risk for adverse long-term cardiovascular outcomes. The metabolic syndrome milieu is confirmed as a key risk factor for long-term CAV progression and adverse prognosis.

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Cardiac allograft vasculopathy (CAV) remains the major cause of late graft dysfunction and death after heart transplantation (HT).[1] Its prevalence steadily increases during post-HT follow-up, with at least 50% of patients affected within 10 years after HT.[1] Nevertheless, according to international registry data, more than 50% of long-term mortality related to graft failure is not ascribed to CAV. It can be reasonably speculated that a consistent fraction of those deaths may be related to underestimated CAV, underlining the need for improving CAV diagnosis long-term after transplant.

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Typical CAV features[2,3] reduce the diagnostic sensitivity of coronary angiography[4]; however, current guidelines indicate angiography, coupled with the assessment of graft function, as the imaging procedure of choice for CAV diagnosis and classification and to predict long-term prognosis.[5] Although intravascular ultrasound (IVUS) imaging allows detection of angiographically silent early CAV, not enough data support this technique for routine CAV diagnosis, in particular in the long-term follow-up.[5] An IVUS-detected increase in intimal thickness during the first year post-HT is a marker for CAV development and predicts cardiovascular (CV) prognosis, but whether IVUS performed subsequently to Year 1 after HT bears any additional prognostic information is unknown.[6,7] Moreover, therapeutic interventions designed to reduce CAV development have traditionally focused on the first year after HT, using IVUS findings as surrogate end point,[8–10] thus leaving unexplored the effect of therapies and management of risk factors on late progression of IVUS and angiographic lesions.

The scopes of this study were to (1) analyze the role of serial coronary imaging in improving the stratification of CV prognosis late after transplantation, focusing angiography classification on the grades proposed by current International Society for Heart and Lung Transplantation (ISHLT) guidelines[5] and (2) explore the hypothesis that IVUS imaging performed later than the first year of follow-up may provide further information to serial coronary angiography in predicting long term prognosis.

Methods

This study was approved by local Ethical Committee and was in compliance with local laws and regulations.

Study design

This was a single-center observational analysis of the effect of coronary imaging on the long-term outcome of recipients surviving at least 5 years after transplant. The sole inclusion criteria comprised availability of IVUS performed at 1 (study baseline) and 5 years after transplant, done as part of our standard CAV surveillance protocol, since 1998.[11] Severe comorbidities, moderate to severe renal dysfunction, and unwillingness to undergo invasive procedures were the main reasons to withdraw IVUS and angiography performance in our routine clinical practice. Patient demographic variables, therapies, and clinical events were retrieved from a prospectively filed Web-based secured database including all transplant recipients ever followed up at our center since 1985 and from the hospital electronic repository.

Coronary angiography and IVUS

Coronary angiography was performed with standard techniques. At least 2 planes for the right coronary artery and 3 for the left coronary artery were examined and digitally recorded for off-line analysis. The angiograms were reviewed and classified according to ISHLT guidelines[5] and graded (from CAV 0 to CAV 3) blinded to clinical events and IVUS findings. Angiographic progression was evaluated by comparing Year 1 and Year 5 angiograms and was identified as ISHLT grade progression or as any worsening of disease severity within the same grade; for example, a change from mild single-vessel disease to mild multiple-vessel disease is a progression of CAV extension, although in both cases remaining at ISHLT Grade 1.

The IVUS procedure was performed on the left anterior descending (LAD) artery, after excluding stenoses $\geq 70\%$, as detailed previously.[12] Analyzed vascular segments from Year 1 and Year 5 studies were accurately matched, using side-by-side longitudinal reconstruction of the LAD and left main arteries.[13] Our Institutional IVUS Core Laboratory performed 2-dimensional and 3-dimensional IVUS analysis by a semi-automated method using Qivus Clinical Edition software (Medis Medical Imaging Systems BV, Leiden, Netherlands). Changes in maximal intimal thickness (MIT) and in intimal, lumen, and whole vessel volumes were evaluated to describe variability in coronary geometry potentially associated to clinical outcomes. To minimize variability in the measurements,[14] only 1 individual (V.P.), blinded to the patients' outcome, performed the software-assisted measurements reported in this study.

Study end points

Study outcome was the occurrence of the composite end point of fatal and non-fatal major CV events (MACEs), including myocardial infarction, myocardial revascularization, and admission for acute heart failure. Sudden death, in the absence of known potentially fatal non-CV morbidities, was considered of CV etiology. For descriptive purposes, we additionally analyzed separately the occurrence of CV death, but the limited number of this event prevented multivariate analyses. Patient follow-up was recorded up to 10 years after Year 5 coronary imaging (i.e., 15 years after transplantation).

Data analysis

Continuous variables are expressed as means $\pm$ standard deviation or as medians (25th–75th percentile) if skewed distribution. Differences among groups were assessed by analysis of variance and chi-square tests, as appropriate. The receiver operating characteristic (ROC) curve was used to identify the cutoff in IVUS measurements best predictive of study outcomes. Person-time and incidence rates were calculated, and 95% confidence intervals (CIs) were reported. Composite MACE and CV death-free survivals were estimated with the Kaplan-Meier method, and differences between groups were assessed with the log-rank test. Contribution of clinical and laboratory data to outcomes was identified by Cox univariate and multivariate regression analysis. The goodness of fit of multivariate Cox regression models, including clinical and imaging data, was compared by the likelihood ratio test. A value of $p < 0.05$ was considered significant.

Results

Study population and events

The study included 131 HT recipients between July 1998 and October 2007. A study flow chart is depicted in Supplementary Figure 1 (available on the www.jhltonline.