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Long-Term Mortality After Cardiac Allograft Vasculopathy

Implications of Percutaneous Intervention

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Objectives This study compared the prognosis of patients with proximal cardiac allograft vasculopathy (CAV) treated with percutaneous intervention (PCI) to the prognosis of those with severe CAV not amenable to PCI.

Background CAV is a progressive form of arterial narrowing affecting patients with orthotopic heart transplants (OHTs). PCI has been used to treat patients with focal CAV, but its efficacy remains unclear.

Methods Of 853 patients undergoing OHT and subsequent coronary angiographies at the Cleveland Clinic, all patients with at least moderate CAV (>30%) on any coronary angiogram following OHT were included. Of remaining patients with no/mild CAV, 200 patients were randomly chosen to represent the comparison group. All angiograms of the included patients were reviewed and graded according to the International Society of Heart and Lung Transplantation (ISHLT) nomenclature.

Results Of the 393 included patients, 100 patients underwent definitive intervention for CAV. Of these 100 patients, 90 patients underwent PCI only, 6 patients underwent coronary artery bypass grafting, and 4 patients underwent repeat OHT. We observed a progressive increase in long-term mortality with worsening CAV. Patients with ISHLT grade 3 CAV had the highest long-term mortality compared with other groups. In addition, there was a significant reduction in the risk for mortality at 2-year follow-up (adjusted odds ratio: 0.26; 95% confidence interval [CI]: 0.08 to 0.82) and 5-year follow-up (adjusted odds ratio: 0.28; 95% CI: 0.09 to 0.93) after PCI compared with patients diagnosed with ISHLT grade 3 CAV, who were deemed unsuitable for PCI. Furthermore, statin use was associated with a significant survival benefit in patients with CAV (hazard ratio: 0.21; 95% CI: 0.07 to 0.61).

Conclusions Worsening severity of CAV was associated with progressively worse long-term survival among heart transplant recipients. Among patients with CAV, long-term survival in those with CAV amenable to PCI was greater than that in those with severe CAV not treatable with PCI. (J Am Coll Cardiol HF 2014;2:281–8) © 2014 by the American College of Cardiology Foundation

Cardiac allograft vasculopathy (CAV) is currently one of the leading causes of death beyond the first year after orthotopic heart transplantation (OHT) (1,2). In fact, among 85,000 OHTs performed worldwide to date, CAV and late graft failure (likely due to CAV) accounted for roughly 32% of deaths at 5-year follow-up, surpassing deaths due to malignancies (23%) or infections (10%) (3).

CAV is characterized by diffuse and progressive coronary arteriopathy with concentric intimal hyperplasia, which is different from focal atherosclerotic plaques. It is believed that CAV most commonly starts in the distal small vessels and then ultimately involves the entire intramyocardial and proximal epicardial arteries of the allograft (4), although the exact pathophysiology of CAV remains poorly understood. Current etiologic hypotheses include immune-mediated phenomena, chronic inflammation along with nonimmunologic factors of ischemia-reperfusion injury, cytomegalovirus infection, and modification by classic risk factors for coronary artery disease (CAD) (e.g., hypertension, hyperlipidemia, diabetes) (4). Treatment options remain limited and include aggressive modification of CAD risk factors (5–7), use of oral antiproliferative agents such as sirolimus (8), percutaneous intervention (PCI) (2), and/or repeat OHT (9), all with unproven and suboptimal efficacy. Despite being associated with poorer outcomes, repeat OHT remains the only definitive therapy for CAV (9). In contradistinction,

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CAV = cardiac allograft vasculopathy

ISHLT = International Society for Heart and Lung Transplantation

OHT = orthotopic heart transplantation

PCI = percutaneous coronary intervention

PCI has been used as a palliative treatment in patients with focal disease (10). It remains unclear whether focal CAV amenable to PCI carries a better prognosis than does diffuse CAV. We therefore sought to compare the prognosis of patients with proximal CAV treated with PCI to the prognosis of those with severe CAV not amenable to PCI.

Methods

Study population. The study population was derived from a cohort of patients undergoing OHT after 1992, and subsequent coronary angiographies, at the Cleveland Clinic. All available angiographic reports on all patients were reviewed. Of 853 patients undergoing OHT and subsequent coronary angiographies, all patients with complete clinical information and angiographic data available for review were considered for inclusion in our study. All patients with any coronary artery stenosis $\geq$30% on any coronary angiogram were included. From the remaining patients with normal coronary arteries or mild CAV (<30%) on all available coronary angiograms, 200 patients were randomly selected for inclusion in the study (Fig. 1). The extent of CAV on each coronary angiogram was graded according to the standard nomenclature provided by the International Society for Heart and Lung Transplantation (ISHLT) (11) (Online Appendix). According to our current institutional practice, all patients with severe CAV involving a proximal vessel are treated with PCI. Because a large majority of patients with OHT do not present with typical ischemic symptoms due to denervation of the transplanted heart, most institutions, including ours, intervene on angiographically severe lesions in intervenable coronary artery segments. Coronary artery bypass grafting (CABG) was considered in patients with severe multivessel CAV in whom it was believed that PCI would deliver suboptimal and incomplete revascularization.

Study variables. The data for the study were collected from electronic and paper medical records. All angiograms were reviewed by the primary authors (S.A. and A.P.) to classify the extent of CAV according to the ISHLT nomenclature (11). The primary outcome was long-term all-cause mortality, which was determined using the U.S. Social Security Death Index (SSDI) and the electronic medical record. Cause of death was ascertained whenever possible. The principal independent variable of interest was the extent of CAV, as described previously. Other variables that were sought included demographic characteristics, clinical characteristics including immunosuppressive regimen, and PCI-related characteristics.

Statistical analysis. All statistical analyses were performed using Stata statistical software version 12.1 (StataCorp LP, College Station, Texas). Continuous variables are presented as mean $\pm$ SD, and categorical variables are presented as proportions. Comparisons of continuous and categorical variables were performed using the Student t test and the chi-square test, respectively. All statistical tests were 2-tailed, and statistical significance was set at $p < 0.05$.

Time-to-event data were collected such that each patient's follow-up duration was stratified into "bins." The first bin represented the time interval between OHT and first coronary angiography and was assumed to represent CAV grade 0. Each subsequent bin represented the time interval between 2 successive angiographies. CAV classification was determined for each subsequent bin on the basis of the ISHLT grade ascertained from the coronary angiogram performed at the beginning of each binned time interval. Because the primary independent variable of interest was a time-varying covariate, unadjusted Kaplan-Meier analyses were not performed for comparing differences in survival between the various ISHLT grades. All survival analyses and respective comparisons between the various ISHLT categories were performed using multivariate Cox proportional hazards regression modeling adjusting for age, sex, race, hypertension, diabetes, hyperlipidemia, chronic kidney disease, dialysis, body mass index, prior smoking, chronic obstructive pulmonary disease, and peripheral vascular disease. All baseline characteristics, including the independent variable (CAV severity), were entered as time-varying covariates into the multivariate regression model.

Because the current ISHLT nomenclature does not have a separate category for PCI, the binned time interval of PCI intersected with that of ISHLT grade 2 or 3 CAV. To compare the survival of patients undergoing PCI with that of those who had grade 3 CAV that was deemed to be nonintervenable, we used multivariate logistic regression analysis with mortality at various pre-determined time points. We calculated 6-month, 1-year, 2-year, and 5-year mortality in the comparison groups to be utilized as the dependent variable in the logistic regression analysis. For calculating these timed mortality rates, the initial time ($t = 0$) in the PCI group was assumed to be the date of first PCI. Similarly, the initial time ($t = 0$) in the nonintervenable ISHLT grade 3 group was assumed to be the date of coronary angiography that demonstrated the disease. For the purposes of this comparison, patients who were ultimately treated with CABG or repeat OHT were excluded.

Results

Of 853 patients undergoing OHT at the Cleveland Clinic since 1992, 393 were included in the study. Figure 1 is a flow diagram to illustrate the inclusion of patients in the study. A total of 100 patients underwent definitive intervention for CAV. Of these 100 patients, 90 underwent PCI only, 6 underwent CABG, and 4 underwent repeat OHT. Table 1 illustrates the baseline characteristics of the study population. The age in our cohort was 52.3 $\pm$ 12.3 years. The majority of patients (79.9%) were men.