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The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

Dobutamine stress echocardiography during follow-up surveillance in heart transplant patients: Diagnostic accuracy and predictors of outcomes

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KEYWORDS:
cardiac allograft vasculopathy;
dobutamine stress echocardiography;
heart transplantation;
accuracy;
outcomes

BACKGROUND: Cardiac allograft vasculopathy (CAV), a major cause of graft failure and mortality at >3 years after orthotopic heart transplantation (OHT), is commonly evaluated using dobutamine stress echocardiography (DSE). We sought to study: (a) the incidence of positive results and diagnostic accuracy of DSE; and (b) the predictors of adverse outcomes in OHT patients.

METHODS: We studied 497 consecutive patients (63 ± 10 years, 78% men) with OHT who had undergone DSE as part of routine surveillance at our center between 1998 and 2013. Every DSE and coronary angiogram performed during follow-up was reviewed. CAV was regraded according to the 2010 recommendations of the International Society for Heart and Lung Transplantation. Composite events (death, coronary revascularization, myocardial infarction and retransplantation) were recorded.

RESULTS: There were 1,243 DSE studies performed during a median of 8.7 (6.2 to 11.9) years after transplantation. Only 22 studies (1.8%) were positive, 978 (78.7%) were negative and 243 (19.5%) were non-diagnostic (sub-maximal heart rate response) for ischemia. Among 497 patients, only 20 (4%) had at least one positive DSE study. There were 310 diagnostic DSEs with coronary angiograms performed within 1 year of one another other. In this subgroup, the sensitivity, specificity, positive predictive value and negative predictive value of DSE were 7%, 98%, 82% and 41%, respectively, to detect any CAV, and 28%, 98%, 71% and 89% to detect CAV Grades 2 or 3, respectively. There were no deaths during DSE. At 5.6 ± 3.6 years after DSE, there were 201 (40%) events. Degree of CAV (and not DSE-based ischemia, $p = 0.3$) independently predicted outcomes ($p < 0.001$).

CONCLUSIONS: The incidence of a positive result is very low in OHT patients undergoing surveillance DSE. DSE is insufficiently sensitive for detection of early CAV. Degree of CAV and not DSE-based ischemia independently predicted outcomes.

J Heart Lung Transplant 2015;34:710–717

Orthotopic heart transplantation (OHT) is the definitive treatment for patients with end-stage heart failure. In the current era, with contemporary immunosuppressive regimens, patient selection and pre- and post-transplant care, the median survival of heart transplant recipients exceeds 10 years.[1] However, despite these advances,

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1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2014.11.019

transplant recipients continue to have a relatively high mortality and morbidity, driven mainly by cardiac allograft vasculopathy (CAV), malignancy and renal failure at ≥3 years post-OHT.[1]

Among transplant survivors, CAV affects approximately 8% by Year 1, 30% by Year 5 and 50% by Year 10, and is one of the leading causes of graft failure and mortality after the third year of OHT.[1] Patients tend to present with silent myocardial infarction, allograft dysfunction, heart failure and sudden cardiac death.[2,3] Hence, it is important to pre-emptively diagnose hemodynamically significant stenosis caused by CAV. In addition, there are emerging data showing that modification of medications (particularly immunosuppression) may delay the progression or even allow regression of CAV.[4–7] However, diagnosing CAV is quite challenging because patients are usually asymptomatic or have an atypical presentation due to cardiac allograft denervation.[3] As a result, many institutions have adopted the practice of annual invasive coronary angiography (ICA) as a routine screening tool to detect CAV in transplant recipients. However, the diffuse nature, and vascular remodeling commonly seen in CAV may limit the ability of ICA to document the burden of CAV when only vessel lumens are visualized.[8] The limited ability of conventional angiography to detect early-stage CAV, the invasive nature of the procedure and the high prevalence of renal impairment after OHT have together resulted in many institutions utilizing alternative non-invasive stress testing to decrease the need of ICA. At our institution, we routinely perform ICA annually in the first 5 years after OHT and every 1 to 2 years thereafter.

Dobutamine stress echocardiography (DSE) is used as part of routine surveillance in OHT recipients, typically alternating with ICA, especially beyond the first 5 years post-OHT. This is based on its ability to detect ischemia, founded on hemodynamically significant coronary stenosis caused by CAV, with a reasonable sensitivity and negative predictive value and high specificity.[9–13] However, most of these studies were conducted 10 to 20 years ago and had small sample sizes and, importantly, used different angiographic definitions for diagnosis of CAV. Therefore, we conducted this study to determine: (a) incidence of positive DSE in contemporary OHT patients; (b) its diagnostic accuracy in a subset of the study population also having ICA within 1 year of DSE; and (c) predictors of adverse outcomes.

Methods

Patient population

Our study was an observational, retrospective analysis of OHT patients from a single center. A total of 1,250 DSE examinations were performed as part of routine surveillance in 503 OHT patients between 1998 and 2013. Of these, data from 7 patients were excluded due to poor image quality ($n = 4$), dynamic intracavitary obstruction of the left ventricle at rest ($n = 1$) or severe hypertension at baseline ($n = 2$). The final study population consisted of 497 OHT recipients who underwent a total of 1,243 DSEs. The electronic medical records were queried to extract the clinical and demographic data temporally closest to DSE. Every DSE and ICA performed during follow-up was systematically reviewed. DSE and ICA reviews were performed blinded to each other and the clinical data. The decision to obtain DSE or ICA was driven by our institutional protocol, yet approved by the treating transplant cardiologist at the time of patient evaluation. Patients who had an abnormal DSE had an ICA performed, out of routine protocol, at the recommendation of the treating transplant cardiologist at the time. The study was approved by the institutional review board.

Resting echocardiography and DSE

Standard echocardiographic machines (Philips Medical Systems, General Electric and Siemens Medical Systems) were utilized. Before initiation of DSE, a comprehensive resting echocardiogram was performed, according to American Society of Echocardiography (ASE) guidelines.[14] Diastolic function was not routinely reported because of the presence of "transplanted atria" anastomosed to the native atria, resulting in dilated atria. Standard valvular assessment (for stenosis and regurgitation) was performed using ASE guidelines.[15] Subsequently, DSE was performed by dedicated, experienced personnel, under the supervision of the interpreting physician.[16] Prior to initiating dobutamine infusion, standard resting echocardiographic images of the left ventricle were also obtained in short-axis and 2-, 3- and 4-chamber views, to assess for wall motion abnormalities. Resting electrocardiogram (ECG), heart rate and blood pressure were recorded. Subsequently, dobutamine was infused continuously, starting at 10 μg/kg/min for 3 minutes and progressively increasing to 20, 30 and 40 μg/kg/min, until the patients achieved 85% of the maximum predicted heart rate (220 – age). If the target heart rate was not achieved, atropine was given up to a total dose of 1 mg. Every 3 minutes, ECG, rhythm strip, heart rate and blood pressure were recorded, along with symptoms. Also, at every stage, echocardiographic images of the left ventricle were obtained in the aforementioned views. Similar echocardiographic data were obtained at peak dobutamine infusion when the target heart rate was reached. Subsequently, ECG, rhythm strips, heart rate and blood pressure were monitored during recovery for at least 6 minutes. All echocardiographic images were digitally stored and DSE was interpreted by experienced cardiologists according to standard recommendations of the ASE.[16] An ischemic response during DSE was defined by new or worsening abnormalities of wall motion from baseline indicative of ischemia, whereas the absence of these findings was classified as a negative study. The studies where patients did not achieve the target heart rate were defined as non-diagnostic.

Coronary angiography and grading of cardiac allograft vasculopathy

Standard coronary angiography was performed in 483 of 497 patients (97%). All angiographic reports were reviewed and re-graded (in a post hoc manner) for severity of CAV, according to a standardized nomenclature for CAV, as recommended by the International Society for Heart and Lung Transplantation (ISHLT).[17] ISHLT CAV Grade 0 was defined by no detectable angiographic lesions. ISHLT CAV Grade 1 (mild) was defined by angiographic left main (LM) <50% stenosis or primary/branch vessel with a maximum lesion of <70% stenosis (including diffuse narrowing); Grade 2 (moderate) was angiographic LM <50% stenosis, a single primary vessel ≥70% stenosis or isolated branch stenosis ≥70% in branches of two systems; and Grade 3 (severe) was angiographic LM ≥50% stenosis, two or more primary