HEART FAILURE AND TRANSPLANTATION
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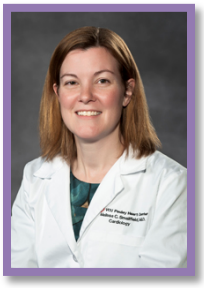

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REVIEWS:

Chirakarnjanakorn S, et al. Dobutamine stress echocardiography during follow-up surveillance in heart transplant patients: Diagnostic accuracy and predictors of outcome. *J Heart Lung Transplant* 2015;34:710-717.

In the most recent registry of the ISHLT, the median survival after orthotopic heart transplantation (OHT) is 11 years and 14 years for those patients who survive the first year after surgery. Cardiac allograft vasculopathy (CAV) remains one of the top three causes of morbidity and mortality (along with malignancy and renal failure) in patients who are 3-5 years post-transplant and beyond. CAV can affect up to 50% of transplant survivors by year 10.[1] The presentation of CAV may be varied given that patients may be asymptomatic or present with atypical symptoms due to allograft denervation. Patients may present with silent myocardial infarctions, symptoms of heart failure and allograft dysfunction or even sudden death.[2]

Currently the gold standard for detection of CAV remains invasive coronary angiography (ICA). The ISHLT standardized the grading of CAV in 2010 to include 4 stages of disease graded 0 to 3 that describe a continuum from absence of disease to severe stenosis.[3] Despite these measures, there are limitations to ICA. Use of routine ICA in CAV surveillance has not been shown to improve outcomes in OHT patients.[2] CAV is diffuse in nature involving the intimal layers of the vasculature and the microvasculature. Due to the eccentric stenosis and distal vessel pruning, angiography may not be sufficient to fully assess the burden of disease. The addition of intravascular ultrasound (IVUS) has increased sensitivity but is more invasive and expensive. Kobashigawa et al. found that progression of intimal thickening > 0.5mm in the first year was a reliable surrogate for the development of CAV by year 5.[4] Although CAV increases in incidence in the post-transplant period, abnormal renal function may limit these investigations. While ICA measures anatomical narrowing, non-invasive imaging that assesses functional significance of a given lesion has been of interest. One of these, dobutamine stress echocardiography (DSE) has been used as part of routine surveillance of CAV in OHT patients, especially after the first 5 years.

In the May issue of the *Journal of Heart and Lung Transplantion*, Chirakarnjanakorn et al. discuss the accuracy of DSE in surveillance of CAV. They performed an observational, retrospective analysis of OHT patients from 1998 to 2003 at a single center. They studied 1,243 DSEs in 497 OHT patients. The median time from OHT to DSE was 8.7 years with 78% of the studies performed between 5 and 15 years. Only 22 studies (1.8%) were read as positive for ischemia whereas 243 (19.5%) studies were non-diagnostic due to inability to reach the target heart rate and 978 (78.7%) studies were negative for ischemia. In comparison, 2,973 ICAs were performed in the same 497 OHT patients; most (78%) were performed within the first 10 years after OHT with 51% performed within the first 5 years. They identified a subset of patients in whom both DSE and ICA were performed within 1 year of each other to evaluate a total of 310 studies. There were 122 ICAs (39%) with ISHLT CAV grade 0, 145 (47%) with ISHLT CAV grade 1, 26 (8%) with ISHLT CAV grade 2, and 17 (6%) with

ISHLT CAV grade 3. In evaluating the use of DSE to determine significant CAV lesions (ISHLT grades 2 and 3), the sensitivity was 28%, specificity 98%, positive predictive value 71% and negative predictive value 89%. During a follow-up time of 5.6±3.6 years, there were 201 (40%) events. In multivariate analysis, the degree of CAV on ICA and not DSE-based ischemia predicted outcome.

In conclusion, the authors stated that although safe and associated with a high (89%) negative predicative value, DSE was not sensitive enough (sensitivity 28%) to detect early CAV. It was the degree of CAV on ICA that provided prognostic information on these patients and not the interpretation of ischemia on DSE. Due to the functional nature of DSE where abnormal wall motion results from inadequate myocardial blood supply during stress, this imaging modality may not be helpful in early CAV where there is no significant stenosis. Other noninvasive imaging modalities like contrast-enhanced coronary CTA were discussed but also have limitations with large contrast bolus in patients with baseline renal insufficiency and compromised image quality at high resting heart rates.

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In the modern era of heart transplantation, cardiac rejection remains a major cause of morbidity and mortality leading to graft dysfunction and poor outcomes. Rejection can occur in up to 20-50% of heart transplant patients at least once within the first year.[1] Currently, endomyocardial biopsy (EMB) is the gold standard for rejection surveillance. There are several possible complications with EMB including the invasive nature of the procedure, tricuspid regurgitation, arrhythmias, and right ventricular perforation.[2] Once an EMB has been performed, there are multiple reports discussing sampling error and inter-pathologist variability and reproducibility leading to inconsistent results.[3] There is also the entity of "biopsy-negative rejection" defined by negative EMB and signs of hemodynamic compromise (an absolute LVEF ≤ 40%, or a drop in LVEF>25%). The rejection episode seems to respond to immunosuppressive therapy.[4] In these cases, an EMB is not helpful and may delay therapy if the appropriate diagnosis is not made.

Due to these issues, several non-invasive methods, including echocardiography, cardiac magnetic resonance imaging (CMRI), molecular imaging, peripheral blood analysis, and electrophysiological markers have been suggested as alternatives in the rejection surveillance. One benefit of CMRI is the ability to evaluate the entire myocardium as opposed to a small area captured by EMB. CMRI findings of inflammation have been correlated with myocardial chamber size, wall thickness, and ventricular function (systolic and diastolic).[5,6]

CMRI is also a non-radiating imaging modality, so it can be safely repeated without risk of malignancy. Gadolinium can be associated with nephrogenic systemic sclerosis in patients with renal insufficiency, but these patients can undergo the same screening with a non-contrast CMRI.

In the May issue of the *Journal of Heart and Lung Transplantation*, Butler et al. compared the use of EMB to CMRI for the diagnosis of heart transplant rejection. They recruited 60 patients from a single center that were transplanted between 2006 and 2011. Patients were referred for EMB as either part of routine screening or for clinical suspicion of rejection. All patients received a CMRI within 24 hours of their EMB and before any medications were changed or added to treat acute rejection. Many parameters were evaluated with CMRI including ventricular size and function, quantitative T2 relaxation times to evaluate myocardial edema, diastolic performance and myocardial scar. EMB were evaluated for grade of acute cellular rejection (ACR) and presence of immunofluorescence staining for C4d. Positive specimens were defined as ACR with ISHLT grade ≥ 2R or antibody mediated rejection (AMR) with microvascular C4d deposition. Clinical rejection was defined as an up-titration of immunosuppression medications for the purpose of treating a suspected episode of ACR or AMR.

There were a total of 73 comparisons of EMB and CMRI included in this study. The participants were mostly male (75%) with an average age 51 ± 14 years, and a median time of 41 ± 47 months since heart transplantation. There were 15 positive EMB with 12 cases of ACR and 6 cases of AMR with 3 cases showing mixed ACR and AMR. In patients with a positive EMB there was CMRI evidence of larger RV and LV volumes, lower RV and LV ejection fraction, and increased myocardial T2 time indicating myocardial edema. By multivariable logistic regression, T2 relaxation time (> 59 msec; odds ratio 11; 95% confidence interval 2-56; p = 0.005) and RV end diastolic volume index (89 ml/m^2; odds ratio 1.1; 95% confidence interval 1.0-1.1; p = 0.01) were independently associated with a positive EMB. A CMRI line test was then generated by using a combination of cut off values for T2 relaxation time and RV end diastolic volume index (RVEDVI). This line test showed a sensitivity of 93% and specificity of 78% to predict a positive EMB. The line test negative predictive value was 98% with a positive predictive value of 52%. The overall agreement between the CMRI line test and EMB was 81%.

Clinical rejection was diagnosed in 24 patients including 10 with EMB negative rejection. In EMB negative rejection, CMRI measurements were similar to EMB positive rejection with the exception of a smaller RV size. For the diagnosis of clinical rejection, EMB had a sensitivity of 58% and specificity of 98%. In comparison, the CMRI line test had a sensitivity of 67% and a specificity of 78% for the diagnosis of clinical rejection.

In conclusion, Butler et al. found that CMRI effectively predicted the risk of histological and clinical rejection. Measures of RV volume and myocardial edema were found to be independent predictors of rejection. Using these two measurements with RVEDVI and T2 relaxation time, CMRI predicted EMB rejection with a high sensitivity and negative predictive value. There were several limitations to the study including a small sample size. There were a low number of AMR episodes making it difficult to determine if CMRI would be a good modality for detecting AMR. Most patients had only one CMRI scan, and the impact of changes in RVEDVI and T2 relaxation time could not be evaluated. As discussed in the editorial commentary by Dr. Kobashigawa, the investigators did not use the most up to date T2 mapping sequence which has been more widely adopted with more data. Despite this, Butler et al. suggested that CMRI could serve as a preliminary screening test for routine surveillance of moderate or severe rejection.

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ADDITIONAL ARTICLES OF INTEREST:

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