Usefulness of Two-Dimensional Strain Parameters to Diagnose Acute Rejection after Heart Transplantation

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Background: Acute cellular rejection (ACR) is still a relevant complication after orthotopic heart transplantation. The diagnosis of ACR is based on endomyocardial biopsy (EMB). Recent advances in two-dimensional strain imaging may allow early noninvasive detection of ACR. The objective of this study was to analyze the usefulness of conventional and new echocardiographic parameters to exclude ACR after orthotopic heart transplantation.

Methods: Thirty-four consecutive adult heart transplant recipients admitted to a single center between January 2010 and December 2012 for orthotopic heart transplantation were prospectively included. A total of 235 pairs of EMB and echocardiographic examination were performed. A median of seven studies per patient (interquartile range, six to eight studies per patient) were performed during the first year of follow-up. Classic echocardiographic parameters; speckle-tracking-derived left ventricular (LV) longitudinal, radial, and circumferential strain; and global and free wall right ventricular (RV) longitudinal strain were analyzed.

Results: ACR was detected in 26.4% of EMB samples (n = 62); 5.1% (n = 12) required specific treatment (ACR degree ≥ 2R). Lower absolute values of global LV longitudinal strain and free wall RV longitudinal strain were present in patients with ACR degree ≥ 2R compared with those without ACR (13.7 ± 2.7% vs 17.8 ± 3.4% and 16.6 ± 3.6% vs 23.3 ± 5.2%, respectively). An average LV longitudinal strain < 15.5% had 85.7% sensitivity, 81.4% specificity, 98.8% negative predictive value, 25.0% positive predictive value, and 81.7% accuracy for the presence of ACR degree ≥ 2R. Free wall RV longitudinal strain < 17% had 85.7% sensitivity, 91.1% specificity, 98.8% negative predictive value, 42.9% positive predictive value, and 90.7% accuracy for ACR degree ≥ 2R. Both variables were normal in 106 echocardiograms (57.6%); none of these patients presented with ACR degree ≥ 2R.

Conclusions: The combination of two new echocardiographic measures, global LV and RV free wall longitudinal strain, may be able to identify a group of heart transplant patients who are unlikely to have ACR. If these findings are confirmed independently, it may be possible to use LV and RV strain measures as reliable tools to exclude ACR and to reduce the burden of repeated EMB. (J Am Soc Echocardiogr 2015;■:■-■.)

Keywords: Heart transplantation, Acute rejection, Speckle-tracking, Strain

Despite the use of potent immunosuppressive agents after orthotopic heart transplantation (OHT), acute cellular rejection (ACR) remains an important complication during the first year of follow-up.[1] ACR is graded using the International Society for Heart and Lung Transplantation nomenclature.[2,3] Intensification of immunosuppressive therapy is used in patients with ACR degree ≥ 2R.

Endomyocardial biopsy (EMB) is the gold-standard method to diagnose ACR, and it is performed routinely in OHT patients because ACR episodes are commonly asymptomatic.[2] However, EMB is an invasive and expensive procedure. Potential noninvasive approaches for the detection of ACR have been investigated, mostly on the basis of echocardiography. In this setting, left ventricular (LV) size, wall thickness, LV mass, and LV ejection fraction as well as pericardial effusion have been found to be insensitive markers of ACR.[4,5] Diastolic measurements and Doppler tissue imaging (DTI) parameters have also shown conflicting results.[6-10]

The utility of myocardial strain and strain rate in the diagnosis of ACR is still under discussion. DTI-derived deformation parameters

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Abbreviations

ACR = Acute cellular rejection

DTI = Doppler tissue imaging

EMB = Endomyocardial biopsy

LV = Left ventricular

NPV = Negative predictive value

OHT = Orthotopic heart transplantation

PPV = Positive predictive value

RV = Right ventricular

have been tested in different studies, with high diversity in their cutoff points and consequently with poor reproducibility.[11-13] Experimental and human-based studies with speckle-tracking echocardiography have found a significant relationship between ACR and radial strain values and also with LV torsion.[14-17]

Our objective was to evaluate which echocardiographic parameters (classical or speckle-tracking derived) can exclude ACR more accurately by performing a prospective study in OHT patients. The ultimate goal is to achieve a safe reduction in the number of EMBs in the early post-OHT period.

METHODS

We performed a total of 235 pairs of EMB and echocardiographic examination (median, seven EMBs per patient; interquartile range, six to eight). Patients underwent echocardiographic evaluation on the same day (typically 2–3 hours after EMB). We prospectively included 34 consecutive adult recipients admitted at our center between January 2010 and December 2012 for OHT. All transplantations were performed by a single team, using a modified biatrial technique. The timetable for EMB and echocardiography during the first year of follow-up is shown in Table 1. One pathologist and two echocardiographers, blinded to the parallel results, performed the pathologic and echocardiographic evaluations, respectively. Rejection monitoring was performed by EMB, following our institutional protocol. Rejection grading was based on the 2005 International Society for Heart and Lung Transplantation recommendations.[3] If ACR degree ≥ 2R was present, the patient was admitted to the hospital to intensify immunosuppressive therapy with intravenous steroids as recommended in the OHT guidelines. Our institution's protocol also includes coronary angiography 1 year after OHT. The results of EMB were used as the gold standard for the analysis of the echocardiographic results. Our study was in compliance with the Declaration of Helsinki and was approved by our ethics committee. Written informed consent was provided by all study participants.

Data regarding patient demographics, donor characteristics, and baseline biochemistry were prospectively collected in our OHT database. All patients received immunosuppressive therapy per local protocol. Induction therapy with two doses of basiliximab was given on days 0 and 4 after OHT. Maintenance therapy included cyclosporine A or tacrolimus, mycophenolate mofetil, and prednisone.

Two-Dimensional Echocardiography

All patients underwent echocardiography using an iE33 digital ultrasound system with an S5-1 transducer (Philips Medical Systems, Best, The Netherlands). Cine loops from two standard apical views (four chamber and two chamber) and parasternal views were recorded using grayscale harmonic imaging. LV ejection fraction was assessed using the biplane Simpson method. Pulsed-wave Doppler echocardiography was performed, and diastolic parameters were evaluated from mitral inflow velocities. DTI data from the mitral and tricuspid annuli were recorded by placing a tissue Doppler sample volume at the septal and lateral annuli, and the E/E′ mitral flow ratio was calculated. Recorded images were digitally stored for offline analysis using dedicated software (X-Celera version 7.0; Philips Medical Systems). Echocardiographic analysis was performed by specialists blinded to all clinical data.

Peak systolic longitudinal strain by speckle-tracking was assessed in apical two- and four-chamber views using a 12-segment model of the left ventricle. Peak systolic longitudinal strain was assessed in six right ventricular (RV) segments in the apical four-chamber view. The endocardial borders were traced semiautomatically, and the operator manually adjusted the region of interest in segments that failed to track properly. Any segments that subsequently failed to track were excluded. Circumferential and radial strain was obtained from 12 segments in LV short-axis views at the basal and papillary muscle levels. Global longitudinal strain, circumferential strain, and radial strain were calculated as averages of peak systolic strain values obtained from all segments in the respective views. RV free wall longitudinal strain was obtained by averaging the peak longitudinal strain from the three RV lateral segments. Strain values are expressed in absolute numbers to diminish reader confusion.

Table 1 Schedule of visits, EMBs, and echocardiographic examinations during the first year after OHT

Time after OHT	Clinical follow-up	EMB	Echocardiography
10–15 d			
20 d			
1 mo			
45 d			
2 mo			
3 mo			
4 mo			
5 mo		Only if previous ACR	
6 mo			
1 y		Coronary angiography	

All procedures were scheduled except EMB at 20 and 45 days.

Table 2 Number of EMBs performed and degrees of ACR found during follow-up

Variable	Mean ± SD	Range
Number of EMBs/patient	6.9 ± 2.1	2–11
Follow-up (mo)	30.7 ± 12.1	13–49
Number of ACR episodes per patient	1.8 ± 1.8	0–6
ACR degree		
0R	73.6%(*n* = 173)	
1R	21.3%(*n* = 50)	
2R	3.8%(*n* = 9)	
3R	1.3%(*n* = 3)	