Evaluation of the Graft Mechanical Function Using Speckle-Tracking Echocardiography During the First Year After Orthotropic Heart Transplantation

Authors' Contribution:
Study Design **A**
Data Collection **B**
Statistical Analysis **C**
Data Interpretation **D**
Manuscript Preparation **E**
Literature Search **F**
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Background: Recent advances in ultrasound strain imaging facilitate more precise monitoring of subtle myocardial changes and thus may allow for more appropriate assessment of myocardium after orthotopic heart transplantation (OHT). This study aimed to explore longitudinal left ventricular (LV) and right ventricular (RV) function by speckle-tracking echocardiography (STE) during a 12-month follow-up period in relation to acute cellular rejection (ACR) degree ≥2R and the response to intense immunosuppressive therapy with intravenous steroids.

Material/Methods: Forty-five adult heart transplant recipients were prospectively assessed at a single center from January 2016 until June 2017. Echocardiography was performed serially at baseline and together with routine biopsies at 2 weeks and 1, 2, 3, 6, 9, and 12 months after OHT. Changes in graft function were evaluated using STE before and during ACR and in the resolving period of ACR.

Results: A total of 220 pairs of biopsy specimens and strain recordings were analyzed. Moderate ACR was seen in 30 biopsies (13.6%). In the serial assessment, longitudinal strain parameters of the LV (global and 4-, 2-, 3-chamber longitudinal strain) and RV (global and free wall longitudinal strain) were decreased at baseline and improved significantly ($P<0.001$) within 12 months after OHT. The degree of improvement was not influenced by ACR. There were no significant differences in circumferential, radial, or longitudinal strain rate, or mechanical dyssynchrony. Reduced LV and RV longitudinal strain was related to ACR degree 2R and increased significantly ($P<0.0005$) during 3 days of intravenous methylprednisolone therapy.

Conclusions: Using the STE technique, we have documented an acute improvement in mechanical myocardial function following ACR steroid therapy and a progressive recovery of LV and RV longitudinal function during the first year after OHT.

MeSH Keywords: Echocardiography • Graft Rejection • Heart Transplantation • Ventricular Function

Abbreviations: **ACR** – acute cellular rejection; **CS** – circumferential strain; **EMB** – endomyocardial biopsy; **GLS** – global longitudinal strain; **ISHLT** – International Society for Heart and Lung Transplantation; **LV** – left ventricular; **LVEF** – left ventricular ejection fraction; **OHT** – orthotopic heart transplantation; **RS** – radial strain; **RV** – right ventricular; **RV FW** – RV free wall longitudinal strain; **RV LS** – RV longitudinal strain; **SD** – standard deviation; **SR** – strain rate; **STE** – speckle-tracking echocardiography; **SD-TPS** – standard deviation of time to peak strain; **TAPSE – tricuspid annular plane systolic excursion; TDI** – tissue Doppler imaging; **2CH LS** – 2-chamber longitudinal strain; **3CH LS** – 3-chamber longitudinal strain; **4CH LS** – 4-chamber longitudinal strain

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Background

The cohort of survivors post orthotopic heart transplantation is constantly increasing, and the assessment of heart transplant recipients requires specific graft surveillance protocols in the immediate post-operative period, as well as in long-term follow-up, to monitor the function of the transplanted heart, specific pathologies that affect the donor heart, and complications of invasive endomyocardial biopsies (EMBs) that are routinely performed to detect acute cellular rejection (ACR) [1–4]. Echocardiography, which is the first-line noninvasive imaging tool for assessing orthotopic heart transplantation (OHT) patients, is the part of the serial functional and morphological evaluation during follow-up, especially after the recent introduction of strain imaging by speckle-tracking echocardiography for myocardial deformation analysis [5]. Early stages of rejection-related myocardial edema or fibrosis frequently affect the subendocardial muscle fibers, resulting in the deterioration of longitudinal graft function [6]. Therefore, speckle-tracking echocardiography (STE) analysis including longitudinal deformation analysis may identify minor, subtle myocardial dysfunction not detectable by standard echocardiography. Furthermore, echocardiographic examination is usually used in cases of suspected ACR despite negative histological findings due to sampling errors in part related to the nonhomogeneous nature of rejection [7,8]; it is also used to monitor cardiac function during biopsy-proven ACR episodes [9,10]. In a more recent meta-analysis, no single conventional echo-parameter, including left ventricular ejection fraction (LVEF) or tissue Doppler imaging (TDI)-derived measurements, could be recommended as an alternative to EMB for acute rejection diagnosis [11]. Monitoring of myocardial deformation with the measurement of LV global longitudinal strain (GLS) is known to be a more sensitive tool for diagnosing early subclinical graft dysfunction, regardless of etiology, and its evaluation may be useful when combined with EMB [12]. Previous studies found that GLS was reduced in patients with ACR requiring treatment [13,14], but little is known about the strain alterations due to the response to intense immunosuppressive therapy with intravenous steroids. However, the GLS of a transplanted heart with preserved LVEF has been reported to be lower in absolute value than that of those in the general population [15,16]. Therefore, "normal" transplanted cardiac mechanics are unknown due to the lack of appropriate cut-off values for STE parameters to detect allograft dysfunction. The existing data are currently insufficient to define the actual serial changes in LV and right ventricular (RV) strain parameters within the first year of follow-up [17], the time interval in which the risk for rejection is the highest, and to schedule repeated EMBs as the standard of care.

Thus, the aim of our study was to evaluate the alterations in LV and RV myocardial deformation during the first 12 months after heart transplantation in the context of the long-term influence of ACR episodes and to ascertain the impact of intense therapy with intravenous steroids in cases requiring ACR treatment.

Material and Methods

Study population

This prospective study consisted of 50 consecutive adult heart transplant recipients admitted at the Silesian Center for Heart Diseases between January 2016 and June 2017. All the heart transplantations were performed using a bicaval technique. We excluded 5 patients (10%) who had insufficient post-transplantation imaging quality for strain analysis or an inadequate acoustic window. Consequently, our analysis cohort included 45 OHT patients.

Study protocol

The patients were consecutively followed with comprehensive echocardiographic examination at baseline (within the first week), 2 weeks, and 1, 2, 3, 6, 9, and 12 months after heart transplantation. They underwent echocardiographic evaluation typically 2–3 hours before or after surveillance biopsy. As per institution policy, rejection was monitored by serial EMBs performed weekly in the first month, every 2 weeks up to the second month, at the third month and every 3 months until the end of the first year. ACR was graded using the classification of the International Society of Heart and Lung Transplantation (1R–3R). One cardiac pathologist and 1 echocardiographer who were blinded to the parallel findings performed the histopathologic and echocardiographic assessment, respectively. The patients received transplant immunosuppressive therapy according to the local protocol. Induction therapy with basiliximab was given to patients with raised pre-transplantation panel reactive anti-body levels and patients at risk of post-transplantation renal dysfunction. Maintenance therapy included tacrolimus, mycophenolate mofetil, and prednisone. In standard clinical practice, all rejections classified as grade ≥2R were treated with intravenous methylprednisolone (1 g for 3 days). To assess serial changes in strain parameters over the first year after OHT, we divided the transplanted patients into 2 groups: those with no ACRs requiring treatment (ACR-free group) and those with at least 1 episode of ACR grade ≥2R during follow-up (ACR group). Among the biopsy specimens with ACR grade ≥2R, we identified those that underwent echocardiography before the episode of rejection, at the time of pathologic diagnosis, and during therapeutic intervention with 3 days of receiving intravenous steroids. Complete strain data in the ACR group were collected for 15 patients for all 3 time points. The echocardiographic studies were performed using a Vivid E9 ultrasound system (GE Healthcare, Horten, Norway). The images

were acquired using standard parasternal and apical views. The frame rate for STE was adjusted to 60–90 frames/sec. Strain and strain rate values were analyzed offline by dedicated software (EchoPAC system). The LV endocardial border was manually traced in the apical 4-chamber (4CH LS), 3-chamber (3CH LS), and 2-chamber (2CH LS) views for the calculation of longitudinal strain and strain rate. The peak values of the 6 segments in each view were averaged to provide a measurement of GLS. Longitudinal strain of RV was obtained in 6 segments in the apical 4-chamber view (RVLS) and as RV free wall longitudinal strain (RV FW) by averaging the peak longitudinal strain from 3 lateral segments. Circumferential strain and radial strain were analyzed from 6 LV segments in a short-axis view at the level of the papillary muscles. In addition, LV mechanical dyssynchrony was assessed in the longitudinal direction as the standard deviation of the time-to-peak strain (SD-TPS) of the LV lateral wall segments and the interventricular septum. Strain values are expressed as absolute numbers. The ejection fraction was calculated with the biplane Simpson's rule. The study was in compliance with the Declaration of Helsinki and approved by our ethics committee. Written informed consent was obtained from all involved patients.

Statistical analysis

Continuous data are presented as the mean ± standard deviation (SD). We used one-way analysis of variance (ANOVA) for parametric comparisons of strain measures obtained at baseline, 2 weeks, and 1, 2, 3, 6, 9, and 12 months after OHT. Echocardiographic indices were compared between groups with or without histories of rejection at 12 months by independent samples Student's *t*-test. This test was also used to compare continuous variables at different time periods: before versus during ACR grade ≥2R and rejection time versus intravenous steroid treatment of ACR. A 2-tailed *P*<0.05 indicated statistical significance. We used a standard statistical software package (Statistica 12, Statsoft Inc.).

Results

In the analysis cohort, we included 45 heart transplantation patients from January 2016 until June 2017. Baseline patient characteristics are shown in Table 1. A total of 220 endomyocardial biopsy specimens and echocardiograms performed 10±4 months after OHT were evaluated. Among these biopsies, treatment-requiring ACR grade 2R was detected in 30 specimens (13.6%), and 190 specimens (86.4%) showed grade 0–1R. No patients had severe (3R) rejection. Twenty-three patients (51%) had at least 1 episode of moderate ACR during follow-up, and all these episodes were asymptomatic, with LVEF remaining in the normal range. Forty patients (89%) survived the 12-month period. There were 5 deaths (11%) mainly because of severe infections, and no patient died due to rejection.

Table 1. Baseline patient characteristics for all patients (n=45).

Characteristic	Value	
Age at transplantation, years	49.5±11.5	
Male gender, n	36	(80%)
Reason for transplantation		
Ischemic heart disease, n	21	(47%)
Dilated cardiomyopathy, n	16	(35%)
Hypertrophic cardiomyopathy, n	3	(7%)
Non-compaction cardiomyopathy, n	3	(7%)
Other, n	2	(4%)
Pre-transplant circulatory assist device		
HeartWare, n	2	(4%)
HeartMate II, n	1	(2%)
POLCAS RELIGA, n	1	(2%)
Number of rejectors grade ≥2R, n	23	(51%)

Data are expressed as the mean ±SD or as the number (percentage).

Table 2 displays changes in the myocardial strain parameters during the first year after OHT. Serial assessment of the graft mechanical function using STE shows that all LV and RV strain values were markedly attenuated immediately postoperatively in heart transplanted patients in comparison with healthy individuals [18]. GLS was impaired at baseline, remained stable but low in the first 4 weeks and improved significantly afterwards (*P*<0.001). We observed the same pattern in longitudinal strain values of all 3 apical views, whereas a gradual significant improvement of RV strain values, including RV LS and RV FW, appeared within the first month after OHT and lasted until the end of the first year (*P*<0.001), as shown in Figure 1. There were no significant differences in longitudinal systolic and diastolic strain rates between the measurements at baseline and those over time after heart transplantation. Similarly, we found that circumferential strain and radial strain did not increase significantly during follow-up. The SD-TPS did not differ significantly in serial assessments (*P*=0.173). In addition, there were no significant differences in strain measurements and in LV ejection fraction obtained 12 months after transplantation in t2 groups of patients: those with no treatment-requiring ACRs (ACR-free group) and those with at least 1 episode of ACR grade ≥2R (ACR group) during follow-up.

As expected, the cases of biopsy-proven ACR grade 2R were associated with marked reductions in GLS, 4-chamber longitudinal strain, systolic strain rate and RV free wall longitudinal strain (Table 3). LV mechanical dyssynchrony was quantified

Table 2. Timing changes in myocardial strain parameters obtained within the first 12 months after heart transplantation in all strain recordings (n=220).

	Baseline	2 weeks	1 month	2 months	3 months	6 months	9 months	12 months	P
GLS (%)	12.8±3.0	12.8±2.1	14.6±2.2	14.9±2.0	16.1±2.5	16.1±1.8	17.2±2.8	17.8±1.8	<0.001
4CH LS (%)	12.9±2.9	12.7±2.6	14.1±3.0	14.1±2.6	15.2±3.1	15.3±2.1	16.8±2.9	17.8±2.8	<0.001
2CH LS (%)	12.5±3.3	13.2±2.7	14.0±2.3	15.1±2.5	15.7±2.8	16.4±2.2	17.4±3.3	18.6±2.6	<0.001
3CH LS (%)	13.4±3.5	13.1±2.7	15.3±3.1	15.4±3.0	17.1±3.0	16.7±2.2	17.4±3.2	16.8±1.7	<0.001
Systolic SR (s^{-1})	0.9±0.2	0.9±0.1	0.9±0.2	0.9±0.1	1.0±0.2	0.9±0.2	1.0±0.2	1.1±0.2	0.11
Diastolic SR (s^{-1})	1.2±0.3	1.2±0.4	1.2±0.3	1.3±0.4	1.3±0.3	1.4±0.4	1.5±0.4	1.5±0.4	0.076
RV FW (%)	17.3±4.1	18.2±3.8	19.4±3.9	19.9±3.9	21.2±4.6	21.8±3.4	24.3±5.8	23.7±3.8	<0.001
RV LS (%)	14.3±3.7	15.1±2.5	17.2±3.1	16.4±2.5	17.2±3.6	17.8±3.6	19.0±3.5	19.5±3.4	<0.001
SD-TPS (ms)	54.2±19.6	54.9±22.1	51.7±17.6	54.1±21.8	50.7±23.1	43.7±15.2	45.2±22.9	41.0±17.9	0.173
RS (%)	30.5±14.2	31.3±11.3	31.1±12.3	34.9±10.2	33.0±12.5	35.7±10.2	36.2±9.7	33.0±7.1	0.477
CS (%)	12.6±4.5	12.8±3.3	14.3±4.6	14.0±5.2	14.1±4.7	14.4±4.9	16.6±3.7	15.6±4.2	0.076

CS – circumferential strain; GLS – global longitudinal strain; RS – radial strain; RV FW – RV free wall longitudinal strain; RV LS – RV longitudinal strain; SR – strain rate; SD-TPS – standard deviation of time to peak strain; 2CH LS – 2-chamber longitudinal strain; 3CH LS – 3-chamber longitudinal strain; 4CH LS – 4-chamber longitudinal strain. Data are expressed as the mean ±SD.
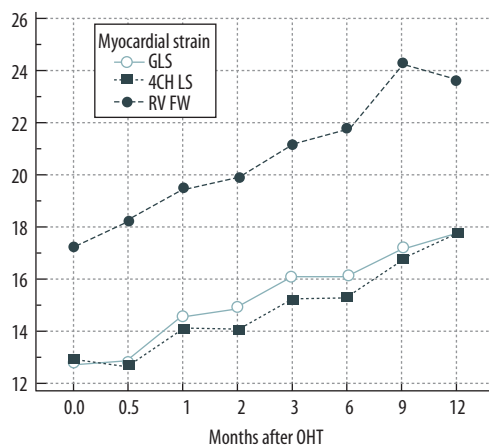

Figure 1. Evolution of global longitudinal strain (GLS), 4-chamber longitudinal strain (4CH LS), and RV free wall longitudinal strain (RV FW) values within the first 12 months after orthotopic heart transplantation (OHT).

using SD-TPS, which increased from 44.8±8.7% before rejection to 61.5±17.9% at the time of ACR grade 2R (*P*=0.023). This finding showed that prolonged TPS indicates global impairment of contractile function induced by treatment-requiring ACR. Table 4 demonstrates an acute improvement of all LV and RV longitudinal strain parameters in reaction to appropriate immunosuppressive therapy for ACR in addition to no significant regression of LV mechanical dispersion. Finally, the

marked differences in GLS, 4CH LS, and RV FW between the 3 time points are presented in Figure 2.

Discussion

Our study aimed to explore the natural history of cardiac mechanics over time and in the relation to ACR in transplanted hearts using noninvasive ultrasound-derived parameters. The major findings in the analyzed population of recipients is that LV and RV longitudinal function in the ACR-free group and the ACR group was severely reduced at baseline and increased during the first year after OHT to reach the normal range of healthy individuals at the end of the follow-up period. Moreover, the occurrence of rejection grade 2R did not lead to an impairment of myocardial deformation measured after 12 months. However, our data emphasize the need to recognize the development of substantial LV and RV longitudinal dysfunction in otherwise stable patients during the first year after OHT, which evolves depending on treatment-requiring rejection.

STE parameters have been extensively investigated during recent years. Little is known, however, about the spectrum of changes in mechanical function of a transplanted heart after the transplantation procedure. A few studies reported that strain and strain rate parameters are abnormal in many clinical settings with preserved LVEF [15,16]. The study by Eleid et al. [17] suggested that failure to improve GLS at 3 months

Table 3. Myocardial strain parameters before and during moderate acute cellular rejection in the ACR group (n=15).

	Before rejection 2R	Rejection 2R	Difference	P
GLS (%)	15.7±2.9	13.3±2.3	2.4	0.046
4CH LS (%)	14.6±2.7	12.3±1.4	2.3	0.014
2CH LS (%)	15.6±3.7	13.8±2.6	1.7	0.20
3CH LS (%)	16.9±3.2	14.1±3.2	2.7	0.06
Systolic SR (s^{-1})	1.0±0.1	0.8±0.1	0.2	0.0002
Diastolic SR (s^{-1})	1.2±0.3	1.2±0.2	0.07	0.51
RV FW (%)	21.9±5.8	16.0±4.0	5.9	0.009
RV LS (%)	17.1±3.6	15.0±2.8	2.1	0.14
SD-TPS (ms)	44.8±8.7	61.5±17.9	16.6	0.023
RS (%)	34.4±13.2	35.9±13.3	1.5	0.80
CS (%)	14.6±4.5	14.1±4.3	0.5	0.79

CS – circumferential strain; GLS – global longitudinal strain; RS – radial strain; RV FW – RV free wall longitudinal strain; RV LS – RV longitudinal strain; SR – strain rate; SD-TPS – standard deviation of time to peak strain; 2CH LS – 2-chamber longitudinal strain; 3CH LS – 3-chamber longitudinal strain; 4CH LS – 4-chamber longitudinal strain. Data are expressed as the mean ±SD.

Table 4. Myocardial strain parameters during moderate acute cellular rejection and treatment with appropriate steroid therapy in the ACR group (n=15).

	Before rejection 2R	Rejection 2R	Difference	P
GLS (%)	13.3±2.3	17.0±2.5	3.6	0.0004
4CH LS (%)	12.3±1.4	16.4±2.8	4.1	<0.0001
2CH LS (%)	13.8±2.6	16.8±3.0	3.0	0.008
3CH LS (%)	14.1±3.2	17.7±3.0	3.6	0.004
Systolic SR (s^{-1})	0.8±0.1	1.0±0.2	0.2	0.004
Diastolic SR (s^{-1})	1.2±0.2	1.4±0.4	0.2	0.05
RV FW (%)	16.0±4.0	23.3±3.8	7.3	<0.0001
RV LS (%)	15.0±2.8	19.4±2.7	4.3	0.0002
SD-TPS (ms)	61.5±17.9	50.1±20.4	11.4	0.11
RS (%)	35.9±13.3	36.7±13.9	0.9	0.86
CS (%)	14.1±4.3	15.8±4.8	1.7	0.31

CS – circumferential strain; GLS – global longitudinal strain; RS – radial strain; RV FW – RV free wall longitudinal strain; RV LS – RV longitudinal strain; SR – strain rate; SD-TPS – standard deviation of time to peak strain; 2CH LS – 2-chamber longitudinal strain; 3CH LS – 3-chamber longitudinal strain; 4CH LS – 4-chamber longitudinal strain. Data are expressed as the mean ±SD

after transplantation is associated with a higher incidence of cardiac events or death. The burden of LV dysfunction in heart transplant recipients was independent of biopsy-detected ACR. In parallel to our results, Clemmensen et al. [19,20] described a severely reduced GLS at baseline despite normal LVEF, where the degree of longitudinal function improvement 12 months after OHT was significantly affected by the occurrence of rejection episodes. Unfortunately, the investigators did not analyze RV strain; they analyzed only RV function via TAPSE (tricuspid annular plane systolic excursion). Nevertheless, our study confirmed that all patients had lower longitudinal strain values of LV and RV immediately after OHT, indicating that these represent normal values in this population. Thereafter, longitudinal strain improves gradually over the first year, and therefore, a reduction over time in such parameters must be interpreted as pathological. In the early post-transplantation period, the
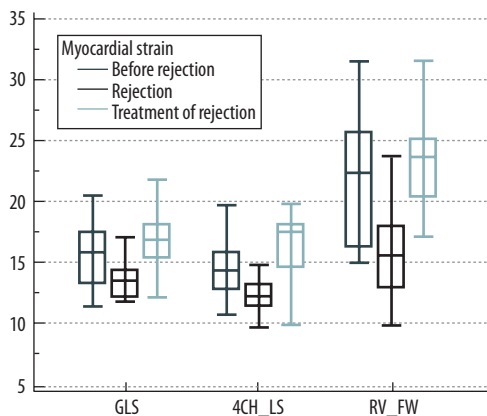
Figure 2. Box plots shows the differences in longitudinal strain values before and during acute cellular rejection (ACR) grade 2R and in the reaction to steroid therapy in the ACR group.

longitudinal deformation is influenced by surgical procedure, time of ischemia, reperfusion damage, denervation, and donor factors such as age, gender mismatch, and LV hypertrophy [1]. The radial and circumferential function remained unchanged during follow-up; however, a nonsignificant trend of an increase after transplantation was observed. This finding indicates that there is a cardiac remodeling after transplantation, which is an expansive process involving longitudinal myocardial layers of both ventricles. Recent studies showed a reduction in RV performance by TAPSE and tissue Doppler [21]; however, to the best of our knowledge, our study is the first to explore the evolution of RV longitudinal function in OHT patients as measured using strain parameters. We additionally examined the changes in the SD-TPS and there were no significant differences after 12 months post-transplantation.

A deterioration in longitudinal myocardial strain values in transplanted hearts may certainly be caused by several variables, such as diabetes mellitus, hypertension, renal failure, infections, cardiac allograft vasculopathy, and episodes of rejection. In this study, we found that strain decreases in both ventricles were significantly associated with treatment-requiring ACR, and we also monitored strain value changes during the process of augmented steroid therapy by serial STE studies. We observed absolute differences of 3.6% in GLS, 4.1% in 4CH LS, 7.3% in RV FW, and 4.3% in RV LS between the moderate rejection and treatment period. This finding is helpful for

asymptomatic patients but requires confirmation of the possible risk of ACR when withdrawing or changing steroid therapy, especially in cases of post-transplantation infections. Our results support other studies that found reduced LV longitudinal function [13–17,19,20], but only 1 study revealed a significant increase in GLS in the resolving period of moderate rejection [22]. The results for circumferential and radial strains in our study are in accordance with most previously published data [14,17,19,20] showing no relation to rejection episodes. This finding indicates that early stages of edema or fibrosis involve subendocardial myocardial muscle fibers, which leads to attenuation of longitudinal myocardial function only. Moreover, we observed dyssynchrony of LV contraction revealed by septal and lateral segments, thus suggesting the presence of significant ACR. Monitoring of both LV and RV myocardial function may be used to identify heart transplantation patients in whom the risk for treatment-requiring rejection is high, and thus, endomyocardial biopsy may be required to confirm cases with a high degree of ACR suspicion.

Limitations

We acknowledge several limitations of this study. Data were obtained from a transplantation program at a single center with a relatively small cohort of heart recipients. As a result of modern immunosuppressive therapy, there were few grade ≥2R ACR events (30 out of 220 cases). We did not evaluate the presence of humoral rejection, microvascular perfusion, or cardiac fibrosis, which could have important influences on our results. Due to the risk of sternal instability, the early postoperative echo examinations were performed in patients laying on their back, while most of the late follow-up echo studies were performed in left decubitus position. This might cause some discrepancies in the reproducibility of cross-sectional segmental visualization, thus altering strain calculation.

Conclusions

All LV and RV longitudinal myocardial strain parameters showed a gradual recovery during the first 12 months after transplantation. However, the degree of improvement measured at 12 months of follow-up was not affected by the incidence of rejection episodes. Measurements of LV and RV longitudinal strain are promising tools for the noninvasive assessment of ACR within the first year after OHT to guide the pharmacological treatment of rejection.

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