Decrease in longitudinal strain in heart transplant recipients is associated with rejection

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Background. Around 20-40% of heart transplant patients experience moderate to severe rejection within the first year after heart transplantation. Endomyocardial biopsy (EMB) is a gold standard for diagnosing heart transplant rejection. There is a need for non-invasive alternatives that allow for early, safe and reliable diagnosis of acute graft rejection prior to the onset of clinical symptoms.
Aims. Our aim was to investigate the potential of speckle tracking derived strain analysis in the diagnosis of acute graft rejection.
Methods. Patients indicated for EMB consented to a trans-thoracic echocardiography examination (TTE) within 2 hours of the EMB. Of this cohort, those with at least 2 EMBs separated ≥ 1 week, and whose TTE could be analyzed for strain, were included. The relationship between strain and EMB results was evaluated.
Results. Of the 43 patients included (mean age 51.33±1.79, 67% male), 23 had findings of rejection identified on at least one EMB and at least one EMB without rejection for comparison. A significant deterioration in the longitudinal strain during rejection compared to non-rejection was found on apical 4-chamber views (-11.51±0.91 vs -13.48±0.96, *P*=0.025) and apical 2-chamber views (-11.84±0.78 vs -14.43±0.83, *P*=0.002). In the patients in whom no rejection was identified on either EBM, there was no significant change in longitudinal strain values at two different time points.
Conclusion. Worsening of longitudinal strain was associated with acute cellular rejection. Routine TTE-based strain analysis could help in early detection of cardiac rejection and timing of EMB.

Key words: echocardiography, heart transplantation, graft rejection

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INTRODUCTION

In the first year after heart transplantation, approximately 20% to 40% of patients experience moderate to severe, acute cellular rejection which remains one of the leading causes of death[1]. Endomyocardial biopsy (EMB) serves as a gold standard in diagnosing graft rejection, but its invasive nature makes it prone to associated complications[2,3,4]. Therefore, there is a need for a non-invasive diagnostic tool, which would allow early, safe and reliable diagnosis of acute graft rejection prior to onset of clinical symptoms.

Echocardiography has been tested as a promising non-invasive technique for detection of acute cellular graft rejection in early stages, but none of the conventional parameters were found reliable enough to replace regular EMB (ref.[5]). Left ventricular (LV) ejection fraction (LV EF) is a traditionally used marker of systolic performance based on volume analyses and thus may not reveal subtle changes in contractility. Strain analysis is designed to quantify ventricular deformation in longitudinal, circumferential and radial directions on both segmental and global levels. Strain has shown to be more sensitive to early LV changes than LV EF in various pathologies[6], and it has proven superior in prognosis prediction[7,8]. In the field of heart transplantation, the speckle tracking derived strain has been recently applied, normal values for clinically stable heart transplant recipients were established[9], and an association between impaired strain and acute rejection was demonstrated in both animal[10,11] and human studies[12-14].

The aim of our study was to investigate the utility of speckle tracking derived strain analysis in the diagnosis of acute graft rejection in heart transplant recipients with preserved ejection fraction, and in detecting early subclinical phases of acute rejection.

METHODS

Study population

Study was designed as a single center prospective study. All consecutive heart transplant patients referred to our center for routine EMB between August 2008

and September 2010 were eligible for recruitment to this study. Exclusion criteria were: 1) LV EF <55%; 2) moderate or higher grade valvular pathology; 3) clinically significant pericardial effusion; 4) inadequate acoustic window; 5) moderate or higher grade cardiac allograft vasculopathy[15] assessed by routine coronary angiography (performed one month and one year after the heart transplantation); 6) unwillingness of the patient to participate in this study; 7) unavailability of study personnel.

Study protocol

Our standard protocol post heart transplantation indicates EMB to be performed weekly during the first month after heart transplantation, every two weeks during the second and third months after heart transplantation, monthly during the fourth to sixth months, every three months until the end of the first year, and annually after that. The patients included in this study were thus examined at different time points after heart transplantation. Based on the EMB results they were divided into two groups: The "Rejection Group" consisted of patients who had at least one EMB diagnosed as rejection (grade 1B and worse), and at least one EMB diagnosed as no rejection" (grade 0 or 1A). These biopsies had to be temporally separated by ≥ 1 week. The "Control Group" included those patients who did not have rejection on any of their EMB (patients with EMB results of grade 0 or 1A) during the study period. In case there was more than one EMB available with identical rejection grade in one individual, the examination with the best image quality was chosen for the analysis.

All patients involved in the study gave written informed consent. The study was in compliance with the declaration of Helsinki and was approved by institutional ethics committee.

Endomyocardial biopsy

EMB from different regions of right ventricle was performed using a jugular or trans-femoral approach. Biopsy findings were evaluated according to The International Society for Heart and Lung Transplantation guidelines from 1990 (ref.[16]) which were being routinely used in our institution at the time of the study.

Echocardiography examination

All patients underwent echocardiography within 2 hours of the EMB. Echocardiography images were obtained with ultrasound machine VIVID 7 (GE, Milwaukee, WI, USA). Routine echocardiography examination including chamber quantification was performed and evaluated according to the current guidelines[17]. The ejection fraction was calculated with the biplane Simpson's rule. Trans-aortic flow was recorded by pulsed wave Doppler. 2D loops of parasternal short axis view on the level of papillary muscles and apical four- and two-chamber views were digitally stored. For this purpose we used the highest possible frame rates (between 55 and 90 frames/s). Global circumferential and longitudinal strain and strain rate values were determined offline (Echo Pac system, General Electric, Inc.).

Strain analysis

Detailed description of strain analysis has been published previously[18]. Loops with visually assessed suboptimal tracking quality or loops, where the speckle tracking could not be obtained for at least 4 of the 6 segments were not included in the analysis. The strain was analyzed by an investigator blinded to the biopsy results. Strain was assessed in three consecutive heart cycles and an average of these values was used for analysis. The assessed strain parameters were longitudinal peak systolic strain and strain rate in apical 2- and 4-chamber view and circumferential peak systolic strain and strain rate.

The reproducibility of strain and strain rate measurements were assessed in 10 randomly chosen patients. For intra-observer reproducibility the second analysis was performed three months after the first one. Inter-observer variability was evaluated by two independent observers H. P. and M. O.

Statistical analysis

All continuous data were expressed as mean and standard error of the mean, if not stated otherwise. The categorical data was shown as number and percentage. Most

Table 1. Baseline characteristics of both groups, patients who experienced rejection episode and patients who were free from rejection – controls.

	Patients with rejection episode during follow up (n=23)	Patients without rejection episode during follow up- controls (n=20)	*P*
Male gender	16 (70%)	13 (65%)	0.750
Recipient age	53.78±1.83	48.50±3.16	0.364
Donor age	36.91±2.51	38.50±3.26	0.709
BMI (kg/m^2)	25.69±0.53	25.35±1.06	0.914
Diabetes mellitus	16 (70%)	11 (55%)	0.324
Hypertension	16 (70%)	7 (35%)	0.023
Hyperlipidaemia	17 (74%)	14 (70%)	0.775
Ischemic time (min)	161.87±52.84	142.95±48.30	0.697

BMI= body mass index of the recipient in the time of transplantation
Data are displayed as either number and percentage in categorical variables or mean ± standard error of the mean in continuous variables.

variables did not present normal distribution, therefore non-parametric tests were applied. The difference between two continuous variables for paired data was analyzed using Wilcoxon Matched Pairs test for dependent samples. For independent samples Mann-Whitney U test was used. To compare the differences in categorical variables, the χ^2 test was applied. If a number smaller than 5 occurred in a cell of a contingency table, the Yates correction for χ^2 test was used. All analyses were carried out using a statistical program Statistica, StatSoft. Inc.

RESULTS

Clinical data

Forty-three patients after heart transplantation were enrolled in the study. All included patients were in sinus rhythm without cardiac pacing. Heart transplantation in all patients was performed in a bi-atrial approach. All patients received standard immunosuppressive therapy per local protocol (either a combination of cyclosporin, mycophenolate mofetil and prednisone, or tacrolimus, mycophenolate mofetil and prednisone). Patients who presented both with and without rejection during the course of the study (n=23) were included in the Rejection Group. Of the patients without rejection, 20 were included in the Control group and underwent complete analysis. Baseline characteristics of the two groups are shown in Table 1. All included patients were Caucasian, and the most frequent cause of heart failure leading to heart transplantation was dilated cardiomyopathy. All included patients were in the range between 11 days to 4 years after heart transplantation. In the Rejection Group, most patients presented with rejection grade 1B; there were only 7 patients in rejection grade 2 and one in 3A and one in 3B. Coronary angiography performed one month after heart transplantation revealed mild cardiac allograft vasculopathy[15] in three patients, all of whom were in the rejection group. The rest of the patients were free from cardiac allograft vasculopathy.

Echocardiographic data

The analyses of echocardiography data are presented in detail in Table 2 and Fig. 1-3. The paired data analysis revealed statistically significant deterioration of longitudinal strain in both apical 4-and 2 - chamber view as well as worsening of longitudinal systolic strain rate in apical 2 - chamber view during rejection compared to non-rejection. Neither the change in circumferential strain and strain rate, nor the change in longitudinal strain rate in apical 4- chamber view had any statistically significant relationship to the presence of rejection. Due to the small number of rejection grades 2, 3A and 3B, it was not possible to find a significant correlation between the magnitude of

Table 2. Global strain and strain rate values and echocardiography characteristics of both the Rejection group and the Control group.

	Rejection group (n=23)		*P*	Control group (n=20)		*P*
	AR-	AR+		T1	T2	
Longitudinal strain 2-chamber view (%)	-14.43 ±0.83	-11.84±0.78	**0.002**	-14.41±1.72	-14.06±1.78	0.508
Longitudinal peak systolic strain rate 2-chamber view (s^{-1})	-0.99±0.07	-0.80±0.06	**0.006**	-0.87±0.13	-0.60±0.32	0.114
Longitudinal strain 4- chamber view (%)	-13.48 ±0.96	-11.51±0.91	**0.025**	-14.76±1.24	-14.06±1.02	0.730
Longitudinal peak systolic strain rate 4-chamber view (s^{-1})	-0.78±0.05	-0.77±0.05	0.422	-0.86±0.05	-0.88±0.05	0.850
Circumferential strain (%)	-18.83 ±1.33	-18.11±1.30	0.619	-20.46±1.92	-18.67±2.29	**0.004**
Circumferential peak systolic strain rate (s^{-1})	-1.39 ±0.10	-1.33±0.08	0.619	-1.34±0.12	-1.40±0.20	**0.048**
LV mass	213.83±14.17	226.97±12.55	0.330	209.10±13.25	213.85±12.62	0.627
LV mass index[a]	109.81±7.20	116.79±6.39	0.303	107.54±5.39	110.25±5.53	0.709
End-diastolic volume	89.22±6.15	98.22±7.28	0.088	97.85±5.63	98.55±6.99	0.970
End-diastolic volume index[a]	45.47±2.82	50.17±3.55	0.094	50.43±2.46	50.53±2.82	0.940
End-systolic volume	34.22±2.56	39.22±3.17	0.064	38.50±2.68	37.95±3.06	0.852
End-systolic volume index[a]	17.46±1.22	20.06±1.60	0.077	19.82±1.20	19.46±1.29	0.823
LVEF	61.70±1.10	60.39±0.85	0.202	60.90±1.14	61.75±0.91	0.401
Septal thickness	13.52±0.62	13.39±0.60	0.629	13.85±0.61	13.60±0.63	0.551
Posterior wall thickness	12.74±0.48	12.96±0.42	0.570	12,15±0.41	11.30±0.40	0.083
Time after heart transplantation (days)	351±86	385±93	0.401	88±22	253±54	

[a] indexed to body surface area of the recipient

The data from the patient in Rejection group were acquired at different clinical scenarios; as either no-rejection values (AR-) or values in the same patient in rejection (AR+). The data from the patients in Control group (subjects who did not experience rejection) were acquired at different time points T1 and T2. Values are presented as mean ± standard error of the mean. *P*-values are displayed for Wilcoxon matched-pairs test, *P*-values lower than 0.05 are highlighted.

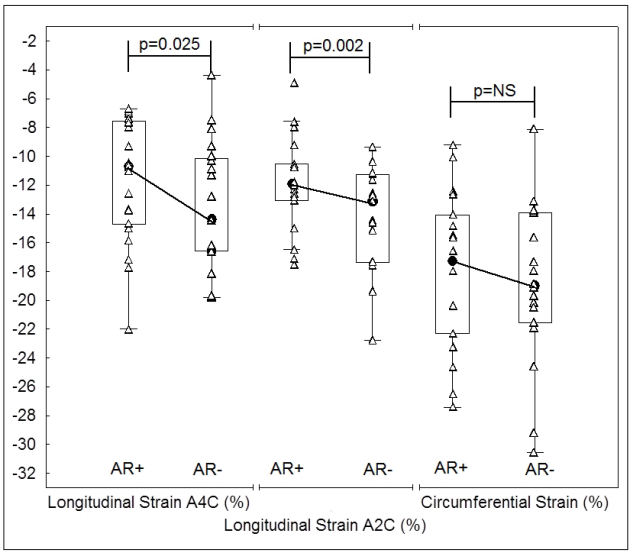

Fig. 1. Boxplots of individual strains of patients in the Rejection Group, where the triangles stand for the raw data, the connecting line points to the median, box stands for quartiles and the whiskers for non –outlier range. Graphs show the differences in individual strains in the time of rejection (AR+) to the time when patients were rejection free (AR–). Even though these are paired data, and *P*-values show the result of paired data analysis, boxplots were used to provide a better overview.

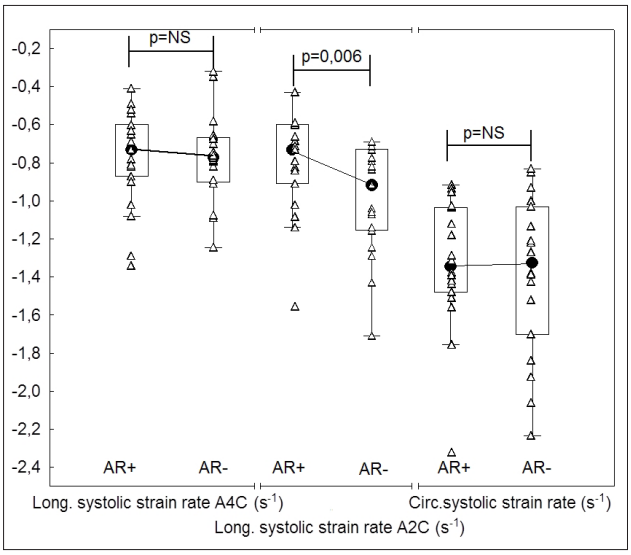

Fig. 2. Boxplots of individual strain rates with the same details as described in fig. 1.

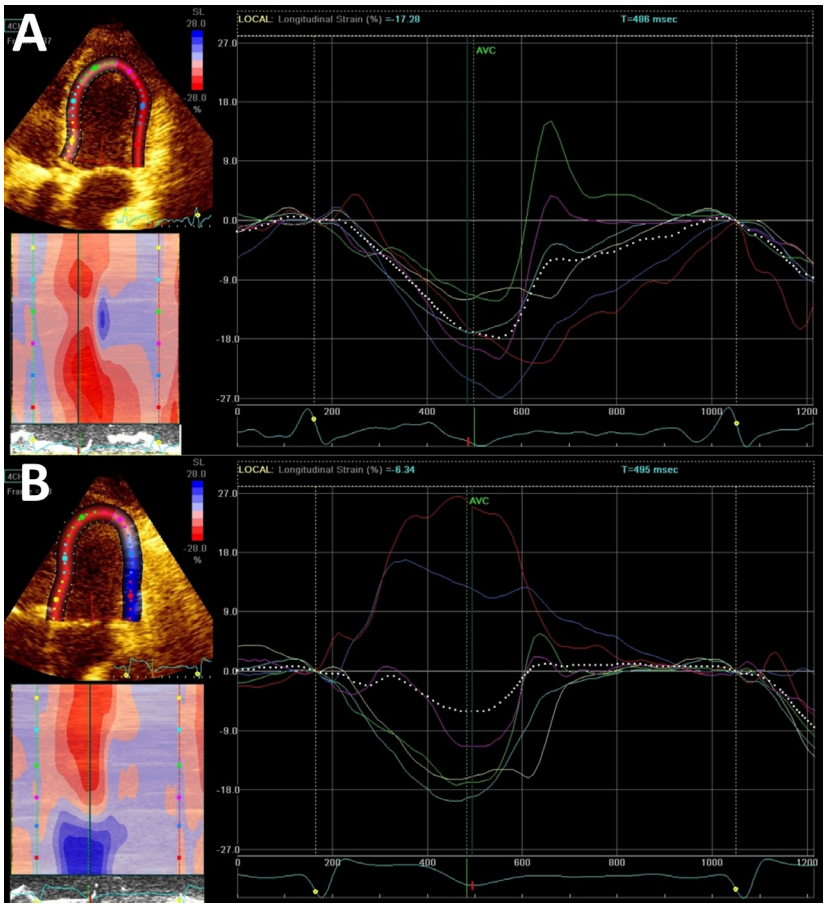

Fig. 3A. Speckle tracking derived longitudinal strain curve in heart transplant patient when free from rejection. The colored curves represent strains of individual segments and the white dotted line stands for global strain, i.e. mean for all segments.
Fig. 3B. Shows the same patient as in figure 3A, this time in rejection. Obvious decrease in absolute values of global systolic strain can be attributed to local dyssynchrony in lateral segments in this patient. Nevertheless, no regularity was observed in the rejection strain pattern.

strain deterioration and severity of rejection. No statistically significant changes in longitudinal strain or strain rate were found in the control group. However, there was a significant worsening in circumferential strain and strain rate over time in the control group.

Intra-observer variation for peak systolic strain and peak systolic strain rate were 2.26 ±1.9% and 0.97 ±3.0% respectively. The relative difference in inter-observer measurements for peak systolic strain and peak systolic strain rate were 4.4 ±2.4 % and 3.35 ±3.1 % respectively.

There was no statistically significant difference between the groups of patients with and without rejection episode during follow up in terms of LV mass index, LV end-diastolic volume index, LV end-systolic volume index, LV ejection fraction, septal or posterior wall thickness or E/e'. Similarly, there was no significant change in these variables in the paired data analyses either in the group of patients with or without rejection episode during follow up (Table 2). No significant progression of LV hypertrophy was observed in either group.

DISCUSSION

In this prospective, single-center study, we found evidence of rejection on EMB to be related to the worsening of longitudinal strain in both apical 2- and 4-chamber. This is the first clinical study showing the utility of speckle tracking to evaluate acute cellular rejection in patients after heart transplantation in a paired data setting and where the echocardiography was performed within 2 hours after the EMB.

Acute rejection was considered as 1B or worse according to the older classification from 1990 (ref.[16]). This older classification, compared to the new one[19], allows us to differentiate between mild grades of rejection, which was appropriate in our study given our goal to evaluate the sub-clinical early stages of rejection.

Our findings are in concordance with most of previously published animal[10,11] and human[12,13] data. The heart graft rejection is characterized by immune cell infiltration, edema and myocyte damage, which results in impaired mechanical LV function, and decrease in strain. Additionally, global longitudinal strain seems to be parameter sensitive enough to reveal a chronic low degree rejection often undetectable by biopsy, which may be responsible for poor prognosis in heart transplant recipients[20,21].

The circumferential strain in our study showed no relation to rejection episodes, however a trend toward decrease over time after heart transplantation was observed.

Our baseline (non-rejection) systolic longitudinal strain values are in agreement with those previously published[22,23,9]. In all above mentioned studies, as well as in our study, the same software was used with a 16 segmental model of the LV making data comparison between studies reasonable.

In animal studies, very good correlations of strain values to rejection grades have been found. Additionally, strain improved in reaction to immunosuppression treatment.[10] Nevertheless, there are a few distinctions between animal and human studies. The rats in heart transplantation studies received no immunosuppressive treatment at all, so all of them soon developed high rejection grades. The baseline values were acquired from isografts, where the transplanted heart is genetically identical to the recipient. In these studies, often a heterotopic transplant model of a non – working heart was applied[10], where the transplanted heart lacks physiological loading. This may also influence contractility and immune cell infiltration in the heart.

Strain decrease is a non-specific finding, which limits its potential clinical application. Besides the rejection and cardiac allograft vasculopathy[23], there are other factors potentially influencing the LV contractility, such as hypertension, diabetes mellitus, hyperhomocysteinaemia, pulmonary hypertension, LV preload, LV hypertrophy, renal failure, advancing age and post-transplantation infections. In early post-transplantation period, the LV strain is influenced by time of ischemia during operation, reperfusion injury and denervation. Donor variables that may also influence LV performance, are donor age, LV hypertrophy, and gender mismatch[1]. A potential clinical application of strain measurements, rather than diagnosing rejection as such, could be an improvement in timing of the EMB. Deterioration of the baseline values acquired in non-rejection would be an indication to perform EMB. Thus, we could reduce the number of biopsies, if this approach was approved in future multi-center studies with unified methodology.

There are several limitations to this study. The small number of patients who presented both with and without acute rejection (rejection group) was expected and is a common feature of the majority of studies in the transplantation field. A potential limitation to our study is higher number of patients with hypertension in the group of patients with rejection episode in the follow up comparing to controls. The higher prevalence of hypertension could have contributed to impaired strain in this group. The different timing of rejection episodes after heart transplantation is another limitation. Some patients experienced rejection before and some after baseline (non-rejection) data acquisition. If longitudinal strain values were changing over time, this might have affected the results. However, there are studies showing, that longitudinal strain values in clinically stable heart transplant recipients remain attenuated at all time points compared to healthy population and do not change even in a two[20] or three year follow up[23]. Thus, different timing of episodes should not significantly bias our data.

CONCLUSION

Using paired-data analyses, we showed that worsening of longitudinal systolic strain in heart transplant patients may be associated with acute cellular rejection, revealing milder, sub-clinical grades. This could be of major clinical relevance if these findings are confirmed in a larger study. Due to small number of higher rejection grades in this study, we could not assess the correlation between strain values and individual rejection grades.

ABBREVIATIONS

A2C, Apical two-chamber view; A4C, Apical four-chamber view; AR, Episodes without rejection; AR+, Episodes with rejection; BMI, Body mass index; EMB, Endomyocardial biopsy; LV, Left ventricle; LVEF, Left ventricle ejection fraction.

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