Classification Model of Heart Transplant Outcomes Based on Features of Left Ventricular Functional Geometry.

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Abstract

The function of the transplanted heart will be affected by acute allograft rejection, chronic rejection, high blood pressure and so on. All these factors may induce the remodeling of the left ventricle (LV) that will significantly affect the prognosis of heart transplantation (HT). The LV configuration changes from end diastole to end systole (LV functional geometry) are an important factor of the heart pump function optimization. The objective of this study was the assessment of HT outcomes using parameters of LV functional geometry.

We used linear discriminant analysis (LDA) to build classification model which was based on LV function geometry indexes and LV longitudinal strain. The training set consisted of three groups of patients with different degrees of LV systolic dysfunction: 1) 24 healthy volunteers with normal systolic function; 2) 52 patients suffering from ischemic heart disease with preserved LV systolic function; 3) 35 patients with dilatational cardiomyopathy with significant LV systolic dysfunction.

We examined 31 patients after orthotopic HT who had postoperative period from 1 to 9 years. Group of HT patients were stratificated of our LDA model. Our LDA model with parameters of LV functional geometry can facilitate the diagnosis and reveal deterioration of the allograft condition.

1. Introduction

Heart transplantation (HT) is still the only possible life-saving treatment for end-stage heart failure, the critical epilogue of several cardiac diseases.

Rejection, especially when associated with hemodynamic compromise, chronic rejection and coronary artery vasculopathy (CAV) remain leading causes of morbidity and graft loss [1]. Therefore, improved detection of functional changes in the graft that could signify the presence of early acute graft rejection and CAV is critical for improved outcomes experienced by this challenging group of patients [1,2].

Currently the ‘‘gold standard’’ for the diagnosis of allograft rejection and CAV is cardiac catheterization with endomyocardial biopsy and selective coronary angiography, respectively. This procedure is invasive, carries inherent risk, and may underestimate the presence of graft pathology. Patients can be evaluated less invasively with echocardiography and clinical examination. The search for noninvasive techniques to assess cardiac allograft function remains a high priority objective for HT professionals [2,3].

Dynamic changes in the left ventricular (LV) configuration from end diastole to end systole contribute essentially to the heart pump function optimization [4]. These changes could be described by the term LV “functional geometry” [5]. It was demonstrated that the coordination of spatio-temporal movements of LV wall segments may be significantly affected by cardiac diseases and by molecular and cellular myocardial remodeling [6].

The aim of this study was to test the hypothesis that changes in functional geometry parameters by echocardiography would be detected earlier than changes in traditional measures of cardiac function in those patients who develop allograft dysfunction. And construct classification model of prognoses of allograft state on base of different systolic dysfunction patterns.

2. Material and methods

2.1. Study population

We retrospectively examined 31 patients after orthotopic HT who had postoperative period from 1 to 9 years. 20 patients who had postoperative period less than

Table 1. Indexes of LV

Indexes	NSD	MSD	SSD	HT(< 2years)		HT (> 2years)		
				Non rejection	Rejection	II class	Start progressive CHF	III and IV class
EF, %	70±2	65±4	25±2 *§	49±1	43±1	61±4	60±3	34±2 *§
EDV, ml	94±2	100±3	220±14 *§	91±3	100±3	100±4	99±3	190±15 *§
ESV, ml	31±2	41±3	170±12 *§	48±2	61±2 *§	43±3	42±3	150±11 *§
SWTd, mm	9±0.2	9±0.2	7±0.3 *	11±0.3	12±0.3	9±0.2	9±0.2	8±0.3 *
PWTd, mm	10±0.2	10±0.2	8±0.3 *	12±0.3	13±0.3	10±0.2	10±0.2	8±0.3 *
GLS (%)	-21±2	-18±2	-8±3 *§	-15±2 *	-13±2 *	-18±2	-17±2	-10±3 *§
CV REF, %	13±1	22±1 *	46± 3 *§	35±1 *§	43± 3 *§	25±1 *	41± 3 *§	47± 3 *§
CV AI, %	12±1	18±1 *	37± 2 *§	18±1 *	26± 2 *§	23±1 *	27± 2 *§	38± 2 *§
SI ED	0.55±0.01	0.54±0.0	0.64±0.02 *§	0.49±0.0 *	0.49±0.02 *	0.49±0.0	0.54±0.02	0.64±0.02 *§
SI ES	0.47±0.01 $^{\#}$	0.43±0.0 $^{\#}$	0.62±0.02 $^{\#*\S}$	0.41±0.0 $^{\#}$	0.43±0.02 $^{\#*}$	0.41±0.0 $^{\#}$	0.51±0.02 $^{\#*\S}$	0.61±0.02 $^{\#*\S}$
Δ SI, %	15±2	18±2	3±1 *§	16±2	13±1	15±2	3±1 *§	3±1 *§
GI ED	0.74±0.01	0.72±0.0	0.75±0.01	0.68±0.0 *	0.75±0.01	0.74±0.0	0.75±0.01	0.75±0.01
GI ES	0.68±0.01 $^{\#}$	0.65±0.0 $^{\#}$	0.75±0.01 *§	0.62±0.0 $^{\#*}$	0.75±0.01 *§	0.66±0.0 $^{\#}$	0.71±0.01 *§	0.74±0.01 *§
Δ GI, %	8±0.1	9±0.1	1±0.01 *§	9±0.1	1±0.01 *§†	8±0.1	3±0.01 *§	1±0.01 *§
ACI ED	0.41±0.004	0.43±0.0	0.39±0.01 *§	0.41±0.0	0.39±0.01 *§	0.41±0.0	0.40±0.01	0.39±0.01 *§
ACI ES	0.44±0.001 $^{\#}$	0.45±0.0 $^{\#}$	0.39±0.01 *§	0.43±0.0 $^{\#}$	0.38±0.01 *§	0.45±0.0 $^{\#}$	0.39±0.01 *§	0.39±0.01 *§
Δ ACI, %	4±0.5	4±0.5	0±0.2 *§	4±0.5	0±0.2 *§†	4±0.5	1±0.2 *§	0±0.2 *§
FSPI ED	0.19±0.02	0.24±0.0 *	0.15±0.01 *§	0.25±0.0 *	0.15±0.01 *§	0.26±0.0 *	0.25±0.01 *§	0.15±0.01 *§
FSPI ES	0.32±0.02 $^{\#}$	0.37±0.0 $^{\#*}$	0.19±0.02 *§	0.41±0.0 $^{\#*}$	0.18±0.02 *§	0.39±0.0 $^{\#*}$	0.29±0.02 *§	0.19±0.02 *§
Δ FSPI, %	37±3	34±3	17±6 *§	32±3	16±5 *§	33±3	15±4 *§	16±6 *§

EF- LV ejection fraction, EDV and ESV - end diastolic and end systolic volume, SWT - septum wall thickness, PWT - CV REF - coefficient of variation of individual regional ejection fraction, CV AI - coefficient of variation of individual asinchrony index, SI - shericity index, ED - end diastole, ES- end systole, Δ - relative change of index between ED and ES, GI - Gibson index, ACI - apical conicity index, FSPI - Fourier shape-power index, (# p<0.05 between ED and ES, * - p<0.05 between pathology and NSD, § - p<0.05 between SSD and MSD).

2 years were reviewed for development of acute rejection. The diagnosis of acute rejection was based on the International Society for Heart and Lung Transplantation criteria (ISHLT). Biopsy specimens with ISHLT grade 2R rejection or higher were considered as the rejection group and grade 0R or 1R were classified as the non-rejection group. There were total 105 cases (in average 4 cases per patients) and 38 cases from them with acute rejection. Biopsy was accompanied by echocardiographic evaluation performed within 1 week before or 1 day after the date of the biopsy.

17 patients had postoperative period more than 2 years (total 67 cases). This subgroup of patients was investigated for progressive chronic heart failure (CHF). In addition to standard clinical procedures for assessing the patient's condition, echocardiography was performed. For 27 cases, class II CHF was identified according to the New York classification, for 25 cases III grade of CHF. And 15 cases, when echocardiogram characteristics were received within a month to the apparent deterioration (progression of CHF) of the patient's condition. Three patients were diagnosed with CAV confirmed by angiography echocardiography was performed for 2 weeks before angiography.

The training set of classification model consisted of three groups of patients with different degrees of LV systolic dysfunction. The first: control group consisted of 24 healthy volunteers without signs of cardiovascular diseases and with normal systolic function (non systolic dysfunction - NSD). The second group with mild systolic dysfunction (MSD) with preserved LV systolic function (ejection fraction >50%) consisted of 52 patients suffering from ischemic heart disease. And the third group with significant LV systolic dysfunction (SSD) consisted of 25 patients with dilatational cardiomyopathy (ejection fraction < 35%). The study was approved by ethics comities of Yekaterinburg Regional Clinical Hospital # 1. All subjects provided written informed consent.

2.2. Echocardiography

Ultrasound LV images in classical 2D apical four-chamber view were recorded during the entire cardiac cycle simultaneously with ECG recording by ultrasound system Philips IE33. The systolic function was evaluated by Simpson's method. Echocardiography standard protocol involved such parameters as: LV ejection fraction, LV end-diastolic and end-systolic volumes, thicknesses of septum and of the posterior LV wall. In addition, the endocardial and epicardial borders were obtained semiautomatic by using QLab (Philips). These borders were visually inspected throughout the cardiac cycle and manually adjusted if necessary. Peak systolic longitudinal strain was obtained in 7 LV segments from an apical 4-chamber view by using QLab. Global longitudinal strain (GLS) was calculated as the average of strain values obtained from the 7 segments.

For evaluation of functional geometry parameters all echocardographic images with myocardial borders were digitized and analyzed off-line with using custom made software [5]. The contribution of different LV wall regions in global ejection fraction was evaluated by the computerized automatic analysis of the LV wall segmental kinetics. Internal LV sectors were obtained by segmental division of the LV image along the endocardial contour. The regional ejection fractions have been calculated as the maximal changes in sector areas during the cycle. Asynchrony of regional contractions was assessed by the fraction of the time to approach the minimal sector area (local systole) during the cycle in the duration of global systole. The coefficients of variation in the individual regional ejection fractions and in the asynchrony data for a patient were used as individual indexes of spatial and temporal heterogeneity in the LV wall regional function [5]. We assessed also several LV shape indexes: 1) conventional sphericity index; 2) Gibson index, which also characterizes a degree of shape circularity; 3) apical conicity index which shows the degree of conical shape of the apical zone; 4) Fourier shape-power index showing the complexity of the LV shape as compared to the circle [5,6].

2.3. Classification model

We used linear discriminant analysis (LDA) to build classification models for evaluating state of transplant allograft. The first model was based on parameters from standard protocol (Table 1). The second model included standard echocardiography parameters and GLS. The third classification model was based on LV function geometry indexes (Table 1).

Statistical analysis was performed by SPSS 22.0. All shown data are expressed as Means ± Standard Deviation for the entire group of subjects. A P value of < 0.05 was considered statistically significant.

3. Results

In the previous work [5] we investigated the differences in the parameters of functional geometry for groups of patients with different degrees of LV systolic dysfunction. The ranges of the change in the characteristics of the functional geometry for these groups were obtained (Tab. 1)

Indexes of spatial and temporal heterogeneity of regional function were significantly higher in all patient groups than in the control (Table 1). The decrease in systolic function in patients correlated with the increase in regional heterogeneity. Significant negative correlation between the spatial heterogeneity index and global ejection fraction was demonstrated in all groups. The following correlation coefficients were found: r=-0.56 (p<0.01) in NSD; r=-0.57 (p<0.01) in MSD; and r=-0.58 (p<0.01) in SSD. ROC-analysis showed that the index of LV spatial heterogeneity of higher than 17% (reference value 13 ± 1%) and the index of LV temporal heterogeneity of higher than 15% (reference value 12 ± 1%) are indicative for pathology and have significant diagnostic power.

The dynamics of LV shape indexes during cardiac cycle was not qualitatively different in the MSD in comparison with NSD. Gibson and conicity indexes were statistically not different in the NSD and MSD. However, Fourier index in MSD was higher than in NSD in all phases of cardiac cycle. The increase of this index higher threshold value (0.33) showed the high diagnostic significance as followed from the ROC-analysis.

ROC-analysis showed high discriminatory power between SSD and NSD in terms of sphericity, Gibson and Fourier indexes at the end systole. Gibson index was significantly higher, while conicity and Fourier indexes were significantly lower in SSD than in NSD. It means that in SSD patients, LV shape was more spherical during both phases of contraction and relaxation. ROC-analysis demonstrated high diagnostic significance of all LV shape indexes for discrimination between SSD and NSD, MSD.

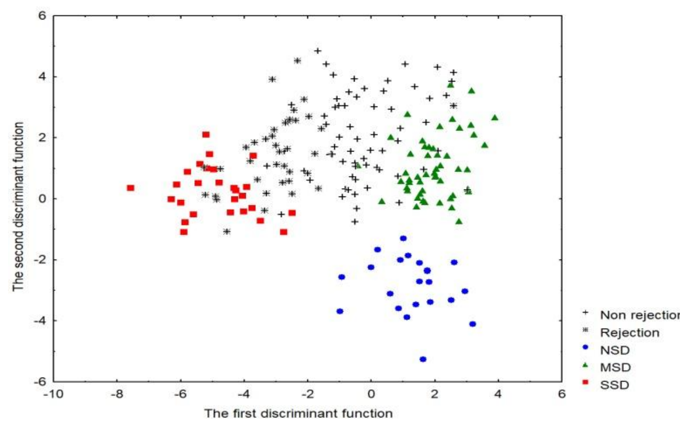

Figure 1. Classification model based on functional geometry parameters. Scatterplot of canonical scores in HT patients with postoperative period less than 2 years.

Using LDA, we built three classification models. The first model contained the characteristics of the standard protocol, the classification accuracy of the NSD-13%, MSD - 96%, and SSD - 100%. When the GLS parameter was added, the quality of the classification was significantly improved, so NSD-45%, MSD-90% and SSD-100% were correctly defined. The classification model, constructed according to the characteristics of functional geometry, divided all the groups with an accuracy of 100% (Fig. 1).

Classification of HT patients.

For HT patients with postoperative period less than 2 years the possibility of classification of the acute allograft rejection state was studied, the model constructed according to the standard protocol and the model with the characteristics of the standard protocol and the GLS were able to determine only 21% and 24% of cases of acute rejection, identifying them in the SSD group, the rest cases were classified in the MSD group (Table 2). A model constructed from the characteristics of functional geometry accounted for 90% of cases of acute rejection in the SSD group (Table 2, Fig. 1).

Table 2. Classification of HT patients (postoperative period < 2 years). The percentage of correct classification is shown.

Model	Non rejection (67 cases)	Rejection (38 cases)
Standard protocol	94% (63 cases)	21% (8 cases)
Standard protocol + GLS	94% (63 cases)	24% (9 cases)
Function geometry	82% (55 cases)	90% (34 cases)

For patients with a postoperative period of more than 2 years, the possibility of classifying the prognosis for the progression of CHF was investigated. For this purpose, the characteristics of the LV were considered for a month before the apparent deterioration of the patient's condition. Models with standard characteristics and GLS were able to classify only 6% of such cases in the SSD group, while the model constructed according to the characteristics of functional geometry is 93% (Table 3).

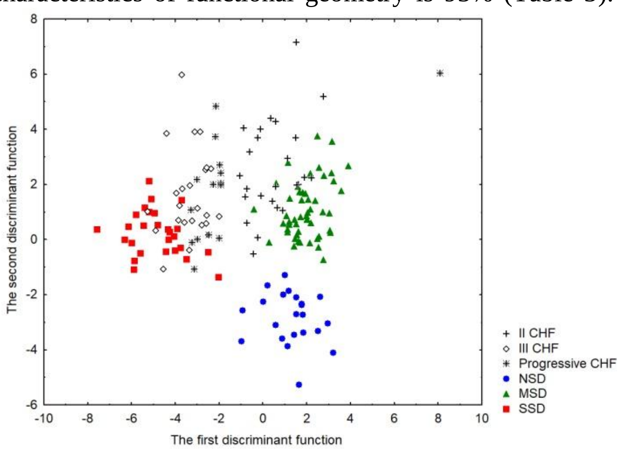

Figure 2. Scatterplot of canonical scores in HT patients with postoperative period more than 2 years.

Three patients had CAV diagnosed by angiography. A about month before the diagnosis of CAV in all three patients the probability of selection in the SSD group increased by more than 20% although the classification model referred them to the MSD group.

Table 3. Classification of HT patients (postoperative period > 2 years). The percentage of correct classification is shown.

Model	II class CHF (27 cases)	Progressive CHF (15 cases)	III and IV class CHF (25 cases)
Standard protocol	96% (26 cases)	6% (1 case)	96% (24 cases)
Standard protocol + GLS	93% (25 cases)	6% (1 case)	93% (23 cases)
Function geometry	100% (27 cases)	93% (14 cases)	100% (25 cases)

4. Conclusion

Our LDA model with parameters of LV functional geometry can facilitate the diagnosis and reveal deterioration of the allograft condition.

Acknowledgements

This work was supported by RF Government Act #211 of March 16, 2013 (agreement 02.A03.21.0006). The work was carried out within the framework of the IIF UrB RAS theme No AAAA-A18-118020590031-8.

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