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Functional geometry of the left ventricle in patients after orthotopic heart transplantation in the early postoperative period

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The functional geometry of the left ventricle (LV) of heart was investigated in patients after orthotopic heart transplantation without any signs of rejection.

Typical features of LV functional geometry in heart transplant recipients with uncomplicated postoperative period were identified as compared to patients without heart disease. The authors have put forward the hypothesis about a diagnostic value of LV functional geometry parameters for a non-invasive diagnosis of graft dysfunction that would facilitate an optimum correction of treatment tactics.

Keywords: functional geometry of the left ventricle, heart transplantation.

Introduction

A high prevalence of cardiovascular diseases resulting in chronic heart failure (CHF) that is one of the most severe and prognostically unfavorable complications has become an urgent problem nowadays. The prevalence of the end-stage heart failure (III-IV functional class) in Russia has reached 2.1% accounting for 2.4 million people [1].

Heart transplantation often represents the only way to prolong the life of patients with end-stage heart failure. The average number of heart transplants performed annually in the world makes approximately 5,000 [2]. Survival of patients after heart transplantation is limited by a number of possible complications, the acute rejection being one of them [3].

A "gold standard" for the diagnosis of acute rejection is endomyocardial biopsy. This is an invasive diagnostic procedure, and, according to some authors, the related complication rate makes 6% [4]. Therefore, non-invasive diagnostic methods to identify a graft dysfunction, have been under development in recent years, including those with the use of echocardiography and various techniques of post-processing the heart images. [5]

Currently, much attention in cardiac physiology and cardiology is paid to the functional geometry of heart ventricles, i.e. ventricular shape changes at its contraction and relaxation [6]. It is known that the ventricle geometry in heart disease and the space-time coordination of functioning ventricular parts undergo significant changes alongside with molecular-cellular myocardial remodeling [7]. The data generated so far suggest an important role of the ventricular functional geometry in the regulation of cardiac contractility and pump function in normal and abnormal status [8].

The aim of our research was to make a quantitative description of the left ventricle (LV) functional geometry in patients after heart transplantation in uneventful postoperative period.

Material and Methods

The study was conducted in Sverdlovsk Regional Clinical Hospital No. 1 and included 12 patients after orthotopic heart transplantation (OHT) without rejection (WR), 5 patients with severe cellular rejection, and the control group of 24 healthy volunteers for comparison.

The LV images of the human heart in apical four-chamber position were obtained for the full contraction cycle (diastole-systole-diastole) during echocardiography (Philips IE 33 Ultrasound System) guided by simultaneous ECG recording. The LV endocardial contours in each frame were determined semi-automatically using QLAB Philips software. Post-processing of the data for each patient was performed using an original software package developed at the Institute of Immunology and Physiology, Ural Branch of the Russian Academy of Sciences (RAS), for sectoral frame-by-frame processing of LV contour images [7]. A maximum relative decrease (%) in the sector area during the cardiac cycle in relation to the end-diastolic sector area was used as the assessment of the regional ejection fraction; and the ratio of time to reach that maximum to the time of achieving the global systole was defined as an asynchrony index of regional wall motion. Coefficients of variation in patient's individual regional ejection fraction values and the regional asynchrony index were used as the indices of spatio-temporal heterogeneity of the patient's LV wall motion [7, 9]. To quantify the changes in the LV shape during a contraction cycle, the following parameters were calculated: 1) the sphericity index calculated as short-to-long LV axis ratio [10]; 2) Gibson index calculated as the ratio of the LV area bounded by endocardial contour to the area of the circle with the circle perimeter equal to the perimeter of the LV contour, reflecting the contour proximity to the circle [11]; 3) conicity index calculated as the ratio of the radius of the circle approximating the contour apical area to the LV short axis which reflects the degree of apical zone taper (conicity) [12]; 4) The Fourier shape-power index (FSPI) was generated as based on LV contour approximation to the power in all Fourier components that provided a measure of net contour deviation from a circle [13].

Statistical analysis of the obtained data and the inter-group comparisons were performed using Statistica 6.1 Software Package. The mean numerical values with a standard error are presented below. The ROC-curve (receiver operating characteristics) analysis was made using SPSS 22.0 Software Package. The diagnostic significance of the test was determined by the area under the ROC curve (AUC).

Results

Table. 1 shows the clinical data obtained in the control group and in the group of patients after OHT WR (post-OHT WR group).

Table 1. Clinical parameters in the study groups.

Parameter	Control group (N = 24)	Post-OHT WR Group (N = 12)
Age, years	31 ± 9	34 ± 7
HR, beats per min	68 ± 2	89 ± 9 [†]
EDV, ml	109 ± 6	110 ± 8

ESV, ml	36 ± 3*	58 ± 3*†
EF%	70 ± 2	47 ± 2 †
IVS, mm	10 ± 0.4	11 ± 0.5†
LVPW, mm	11 ± 0.7	11 ± 0.4
LVS(ed), mm	51 ± 1	48 ± 1†
LVS(es), mm	29 ± 1 **	30 ± 1**
FS%	33 ± 2	31 ± 1†

Note: HR, heart rate; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction up to Simpson's method; IVS, interventricular septum thickness (of the left ventricle); LVPW, left ventricle posterior wall thickness; LVS(ed), left ventricle size at the end-diastole; LVS(ed), left ventricle size at the end-systole; FS, fractional shortening.

* P <0.05 for EDV and ESV.

** P <0.05 for LVS(ed) and LVS(ed).

† P <0.05 between the OHT and control group.

The patients of the OHT WR group had significantly reduced global characteristics of the LV pump function: ejection fraction (EF) and fractional shortening (Table. 1). Alongside, we first analyzed the characteristics of the LV regional wall kinetics and found a number of differences from values obtained in the control group. Alterations in numerical values of LV functional geometry in the study groups are presented in Table. 2.

Table 2. LV functional geometry parameters in the study groups

Parameter	**Control group (N = 24)**	**Post-OHT WR Group (n = 12)**	**AUC**	**Cut-off**
EF, %	70 ± 2	47 ± 2†	0.96	56 (86%)
CV REF, %	13 ± 1	39 ± 2†	1	25 (100%)

CV AI, %	12 ± 1	29 ± 3†	0.99	16 (96%)
SI ED	0.55 ± 0.01	0.49 ± 0.03†	0.69	0.52 (70%)
SI ES	0.47 ± 0.01*	0.42 ± 0.03*†	0.7	0.45 (68%)
Δ SI, %	15 ± 2	15 ± 3		
GI ED	0.74 ± 0.01	0.68 ± 0.02 †	0.85	0.71 (80%)
GI ES	0.68 ± 0.01*	0.62 ± 0.02*†	0.8	0.66 (72%)
Δ GI, %	8 ± 0.1	8 ± 0.1		
CI ED	0.41 ± 0.004	0.41 ± 0.01		
CI ES	0.44 ± 0.001*	0.44 ± 0.03		
CI. Δ%	4 ± 0.5	4 ± 0.2		
FI CD	0.19 ± 0.02	0.26 ± 0.04†		
FI COP	0.32 ± 0.02*	0.46 ± 0.07*†	0.85	0.34 (75%)
Δ FI, %	37 ± 3	41 ± 7		

Note: EF: LV ejection fraction; GI: Gibson Index; CI: conicity index; SI: sphericity index; FI: Fourier index; CV IA, coefficient of variation in the individual asynchrony index; CV REF: coefficient of variation in individual regional ejection fraction; ED: end-diastole; ES: end-systole; Δ, relative change between the ED and the ES; AUC, area under the ROC-curve. Threshold values (cut-offs) are given only for the parameters having a diagnostic value (AUC≥ 0.7), in balanced sensitivity and specificity, the values are given in brackets.

* P <0.05 for ED and ES.

† P <0.05 between the post-OHT and the control groups.

We have established the features typical for the LV regional wall kinetics in healthy people demonstrating its significant spatial and temporal heterogeneity (Fig. 1A) [7] (Fig. 1B, C, continuous lines). In the post-OHT WR group of patients the observed reduction in the global EF occurred alongside with a significant reduction in all regional EFs (REFs) compared to their values in the control group (Fig. 1B). Although the distribution pattern of REF relationship to the segment number is similar to that in the control group, the amplitude between the peak values was significantly different from that obtained in the control group (0.21±0.02 vs. 0.13±0.01; $p<0.05$) (Fig. 1B).

The relationship of anachrony index to the segment location for the post-OHT group did not demonstrate a regular function, and the mean values scattered significantly greater than in the control group (Fig. 1D).

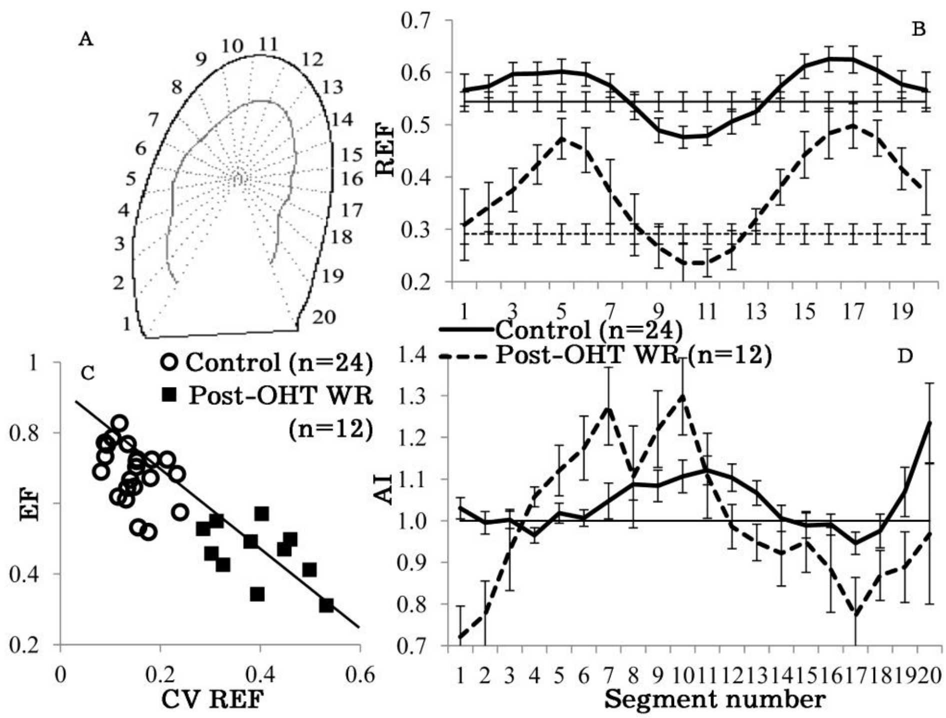


Fig. 1. A: Method of sectors. The figure demonstrates the end-diastolic and end-systolic LV contours superimposed over the mass centres; the LV inner region is divided into sectors of equal area. B: the relationship of the mean REF to the spatial position of the LV wall segment (bold lines) compared to the two-dimensional assessment of the

global EF (fine lines). C: the linear regression between the global LVEF and the coefficient of variation (CV) in REF. A statistically significant correlation (r=-0.79; r^2=0.64; p<0.01; PV=0.78-0.76; CV REF) has been found for the cumulative set of data obtained in the control group and in the post-OHT group. D: the relationship of AI in achieving the local end-systole to the segment location.

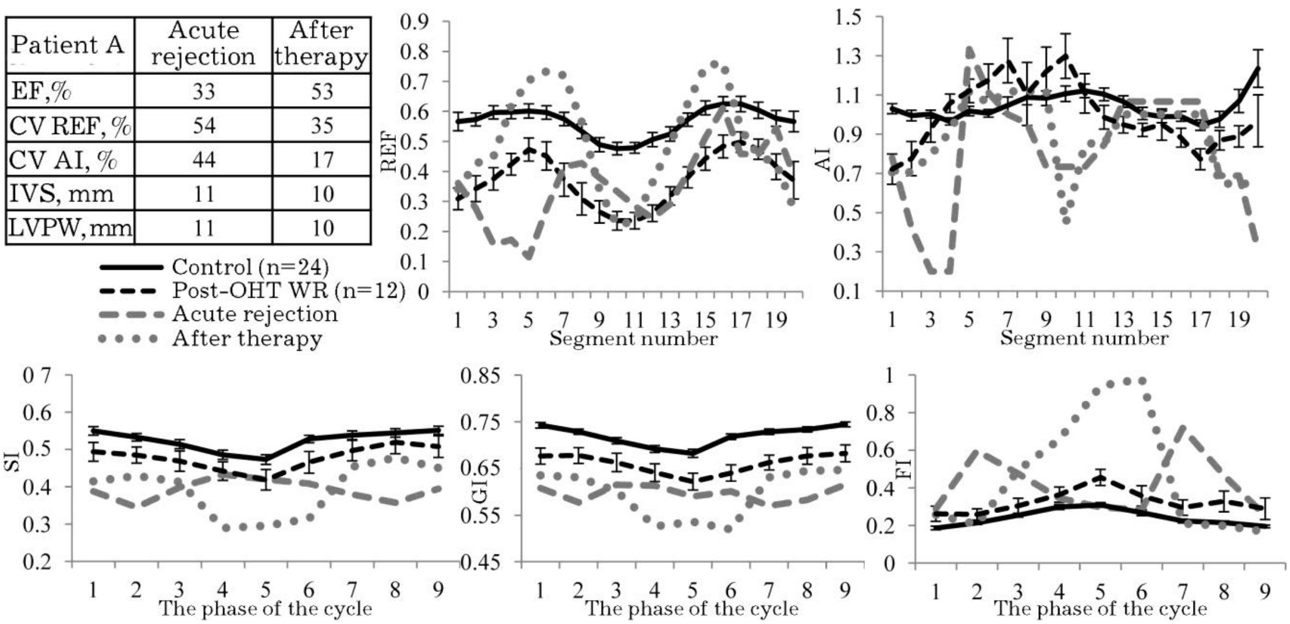
In the post-OHT group, the index of spatial heterogeneity in the regional function was significantly higher than in the control group (39±2% vs. 13±2%). In both groups, we found a negative correlation between the spatial heterogeneity index and the global EF (Fig. 1B: control group, r=0.51, p=0.01; post-OHT group, r=0.49, p=0.04), meanwhile the correlation coefficients for post-OHT patients were not significantly different from those in the control group. The "cloud" of points for the post-OHT group seen in Fig. 1B lies below and more to the right of the "cloud" of points for the control group, without overlapping it. This indicates a significant association between the increased heterogeneity of LV wall motion and the decreased ejection fraction in these patients. The observations were confirmed by the ROC analysis results that indicated a high degree of discrimination in heterogeneity index values in post-OHT patients compared to those in the control group. AUC value was equal 1, i.e. the groups could be differentiated on that basis with 100% sensitivity and specificity.

The temporal heterogeneity index was also significantly higher in the post-OHT group than in the control group (post-OHT group, 29±3%; control group, 12±1%). ROC analysis indicated a high diagnostic value of the temporary heterogeneity index (AUC=0.99; sensitivity and specificity were 96% each) (Table 2).

We have found significant differences between the post-OHT group and control group in the obtained dynamic characteristics of LV shape changes during the contraction cycle (Table. 2). For the control group, we have shown a statistically significant change in all studied shape indices from the end-diastole to the end-systole: the reduction of sphericity and Gibson indices, the increase in the conicity index and Fourier index (Table 2). These changes consistently reflect the fact of LV shape becoming less spherical during systole in the control group.

For the post-OHTgroup the shape indices displayed a less sphericity shape of the left ventricle in the end-diastole and end-systole than in the control group (Table 2). The pattern of ventricular shape changes during the contraction cycle in the post-OHT group was similar to that detected in the control group, but in all phases of the contraction cycle the LV shape remained less spherical in the patients of the post-OHT group than in the control group. ROC analysis indicated a high discrimination degree between the norm and pathology in the sphericity and |Gibson indices in the end-diastole and end-systole, and in Fourier index in the end-systole (Table. 2). The Meanwhile, relative changes in indices for the systole were not significantly different between the groups (Table. 2).

Since there have been only 5 patients with a severe rejection in our study so far, we do not present the grouped characteristics of LV functional geometry for them. Figure 2 shows an example of the individual characteristics of LV functional geometry in a patient with severe cellular rejection. All of those patients revealed significant deviations in functional geometry parameters not only from those in the control group, but also from those in the post-OHT WR group. In the rejection subgroup, all the indexes having a diagnostic value (Table. 2), exceeded the cut-off threshold; whereas in all patients without rejection, more than three diagnostic shape indices did not exceed the cut-off threshold. The endocardial biopsy performed after the pulse therapy (with methylprednisolone, 1000 mg/day for 3 days) showed an alleviation in the rejection to 1B degree that was associated with the diagnostic indices of functional geometry approaching the reference values of the control group (Fig. 2).



Patient A	Acute rejection	After therapy
EF,%	33	53
CV REF, %	54	35
CV AI, %	44	17
IVS, mm	11	10
LVPW, mm	11	10

Fig. 2. The individual characteristics of LV functional geometry in a patient with a severe cellular rejection (3B Degree): gray dashed line: acute rejection; gray dotted lines: after hormone pulse therapy (reduction in rejection severity to mild 1B degree confirmed by endomyocardial biopsy).

Conclusion

By using the original software package of ultrasound image post-processing, we revealed the specific features of LV regional wall kinetics in heart transplant recipients with uneventful course and those with acute rejection in the post-transplant period.

The clinical presentation of graft rejection confirmed by the endomyocardial biopsy results was associated with the changes in LV myocardial kinetics compared to that in the control group, the degree of deviation from the baseline was in direct correlation to the rejection severity.

The LV shape change index, i.e. the sphericity index in diastole, inversely correlated to the interventricular septum thickness (r=0.61; p=0.03) that, if increased, represents an echocardiographic sign of graft rejection.

Thus, a deviated LV functional geometry, specifically, the increased spatial and temporal heterogeneity indices if LV wall motion in heart transplant recipients can serve the basis for a non-invasive diagnosis of graft dysfunction, facilitating an optimal correction of treatment tactics. The hypothesis needs a further confirmation in the studies with increased post-OHT patient populations with uncomplicated postoperative period and with severe rejection.

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