Geometric Morphometrics Features of Left Ventricle Can Classify Responders and Non-responders to Cardiac Resynchronization Therapy

Roman Rokeakh[1,2], Tatiana Chumarnaya[1], Stepan Zubarev[1,3], Lev Malishevskii[1], Olga Solovyova[1,2]

[1] Institute of Immunology and Physiology UrB RAS, Yekaterinburg, Russia
[2] Ural Federal University, Yekaterinburg, Russia
[3] Almazov National Medical Research Centre, St Petersburg, Russia

Abstract

The aim of this study was to assess the shape and deformation of the left ventricle (LV) throughout the cardiac cycle in patients with chronic heart failure (CHF) using geometric morphometrics. Geometric morphometrics (GM) is the shape analysis approach based on landmark coordinates. Based on 2D echocardiographic images, characteristics of the shape and deformation of the LV during the cardiac cycle were obtained in patients with CHF referred for cardiac resynchronization therapy (CRT). The characteristics were compared in patients who responded or did not respond to CRT. Prognostic features of LV deformation in end-systole and diastole were identified that discriminated responders from non-responders to CRT with 88.5% accuracy.

1. Introduction

Despite significant advances in the treatment of chronic heart failure (CHF), it remains a major medical and social problem associated with high morbidity and mortality worldwide [1]. Cardiac resynchronization therapy (CRT) is the standard of care for heart failure with reduced left ventricular (LV) ejection fraction. Multicenter trials have shown a significant reduction in heart failure symptoms and mortality with CRT [2]. However, a significant proportion of patients (approximately 30-40%) do not respond adequately to CRT, challenging the search for effective predictors of CRT response.

Assessment of changes in the LV shape during the cardiac cycle is thought to facilitate early diagnosis and treatment. In the clinic, the LV shape is conventionally characterised at certain fixed points in time (e.g. end-systole and end-diastole), or using peak values of LV deformation (e.g. global longitudinal strain). At the same time, more information can be obtained using a generalised analysis that includes complete information about changes in LV shape during the cardiac cycle [3, 4]. Geometric morphometrics (GM) is a mathematical approach that analyses shapes using landmark coordinates. GM has found numerous applications in various fields [5]. We have previously shown how GM can be used to discriminate CHF patients from healthy volunteers [6]. In this study, we for the first time evaluate the possibility of predicting CHF patients response to CRT with GM characteristics.

2. Methods

2.1. Clinical data

In this retrospective non-randomized single-center observational study we enrolled 26 CHF patients who underwent CRT device implantation. Inclusion criteria were: CHF functional class (FC) II-IV according to the New York Heart classification at the time of outpatient treatment; LV ejection fraction (EF) less than 35%; QRS duration greater than 120 ms; sinus rhythm, left bundle branch block; optimal drug therapy. Patients were evaluated before CRT device implantation and during the 6-month follow-up period after implantation. Patients were examined according to the standard EchoCG protocol, and 2-3 cardiac cycles were recorded in the apical 4-chamber position of the heart. Participants signed informed consent forms. The study protocol was approved by the institutional ethics committee. Patient data were annotated into responder (n = 13) and non-responder (n = 13) groups according to LVEF improvement of more than 5% and LV ESV reduction of more than 15% at 6 months compared to the preoperative values. Baseline clinical data for the patient cohort are presented in Table 1.

2.2. Segmentation

Starting from the manually processed end-diastolic frame we tracked the positions of 49 landmarks along the LV endocardial contour (points 0 and 48 - mitral, point 24 - apex, all the 49 points are equidistant in the end-diastolic frame) using previously developed software (landmarks

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Table 1. Baseline clinical data

Variable	NRSP (n=13)	RSP (n=13)	P
Gender (male)	10(77%)	7 (54%)	0.216
Ischemic etiology	7 (54%)	4 (31%)	0.214
FC			
II	2 (15%)	5 (38%)	0.385
III	10 (77%)	8 (62%)	0.674
IV	1 (8%)	0 (0%)	0.851
History of AF	5 (39%)	4 (31%)	0.681
Age, year	62±8	58±16	0.404
BMI	31±6	27±4	0.069
QRS,ms	196±27	181±23	0.128
EDD, mm	68±9	65±11	0.547
ESD, mm	59±9	55±12	0.363
IVS, mm	11±3	10±2	0.525
PLV, mm	9±1	9±1	0.265
EDV, ml	267±92	255±101	0.764
ESV, ml	195±74	185±80	0.734
EF, %	28±4	29±5	0.619
GLS, %	-7±3	-8±4	0.417
Time SD for LS, ms	123±42	114±35	0.561
GCS, %	-7±4	-9±5	0.177
Time SD for CS, ms	151±47	128±54	0.270

NRSP - non-responders; RSP - responders; FC - functional class; AF - atrial fibrillation; BMI - body mass index; EDD - end diastolic dimension; ESD - end systolic dimension; IVS - thickness of the interventricular septum; PLV - thickness of the posterior wall of the left ventricle; EDV - end diastolic volume; ESV - end systolic volume; EF - ejection fraction; GLS - global longitudinal strain; SD - standard deviation; GCS - global circumferential strain.

are shown in Fig. 1). Then we performed piecewise linear time warping, making each time series 85 frames long (the largest number of frames in the cardiac cycle observed in the data), with frames 0 and 84 corresponding to the end-diastole and frame 29 to the end-systole. Time warping was followed by 10-harmonic Fourier series approximation to ensure the continuity and the periodicity of the signals. For more details on segmentation and signal processing we refer to our previous work [6].

2.3. Geometric morphometrics

In basic GM analyses the geometric information about the objects is encoded by key points called landmarks. In our study, the LV endocardial contour was encoded by 49 landmarks resulting in (49×2) configuration matrices X for each contour. Shape is defined as all the geometric information remaining in the configuration after removing the information about location, scale and rotation. We removed location from the data by subtracting from each configuration matrix its centroid location

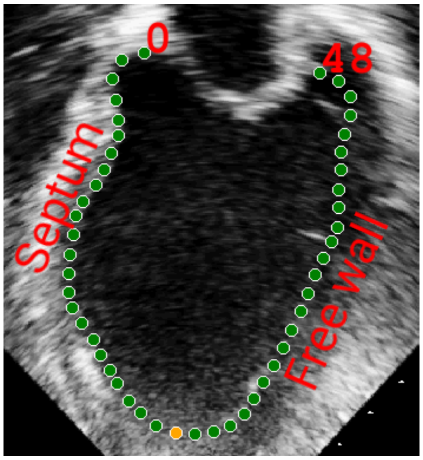

Figure 1. Landmarks along the LV endocardial contour in the EchoCG image.

$$\bar{X} = \frac{\sum_{i=0}^{48} (X)_i}{49}.$$

Scale was removed by dividing the configuration by its centroid size defined as

$$\mathrm{CS}(X) = \sqrt{\sum_{i=0}^{48} ||(X)_i - \bar{X}||}.$$

The rotations are usually factored out by the Generalized Procrustes Analysis (GPA) algorithm, which iteratively finds the sample mean shape for the set of configurations and rotates all the configurations toward that mean shape. GPA can also be used to factor out the scale, however here we only use it for rotations, utilizing the partial Procrustes distance [7]. It should also be noted, that we apply GPA to all LVs at all time frames independently. Alternative approaches can be considered. For example, we can identify the transformations for all LVs at the ED frame and apply these transformations to the subsequent time frames for each LV, thus retaining the data on LV rotation throughout the cardiac cycle. We prefer to disregard all rotational information in order to avoid accounting for breathing and other EchoCG artifacts. After removing translation, scale, and rotation, the resulting aligned configurations lie in the corresponding shape space (SS) where each shape is described by a point with (49×2) coordinates.

Since we have not only the individual LV shapes but sequences of shapes representing cardiac cycles, we wanted to consider comparing the relative frame-to-frame shape changes between patients rather than the absolute differences between the heart shapes of different patients. These two variabilities are confounded in the SS described above.

To eliminate the absolute individual differences between patients, parallel transport was proposed, together with the practically more feasible linear shift (LS) algorithm [4]. Practically the algorithm consists of selecting a common template in the shape space and transporting all shape sequences to this common template. Here we use GPA on all LVs at the ED frame to find the average ED shape and use it as the common template. After LS, we obtain a different set of shape space coordinates, which we will refer to as shape space after linear shift (SSLS). We have previously described the application of the LS algorithm to the similar dataset [6].

Next, we extracted uncorrelated and presumably informative shape features separately for SS and SSLS by performing Principal Components Analysis and keeping the first few principal components. The Deterministic Parallel Analysis and Deflated Deterministic Parallel Analysis+ methods [8] were used to select the number of principal components to keep.

2.4. Statistics

Detailed analysis was performed using the IBM SPSS Statistics 27.0.0.0 software package (Armonk, NY, USA). For qualitative data, frequencies and percentages of the total number of patients in the cohort were calculated. Quantitative data are presented as median [25th–75th] interquartile range or mean ± standard deviation if criteria for normal distribution were met. The Shapiro-Wilk test for normality was used. Comparison between two independent groups (non-responders vs. responders) was performed using T-test for normal distribution or Mann-Whitney test for non-normal distribution for quantitative data and Pearson's chi-squared test for qualitative data. Feature dependence was assessed using the Pearson correlation test for normal distribution and the Spearman rank correlation test for non-normal distribution. The critical level of statistical significance was set at 0.05.

Logistic regression with stepwise forward feature selection was used in SPSS to build the classifier.

3. Results

3.1. LV shapes and shape change in the cardiac cycle

In PCA on SS coordinates, the first 7 eigenvalues, which account for 88% of the variability in the data, were statistically significantly different from random noise.

The first five components were found to be significantly different from random noise in the SSLS space. Together they describe 68% of the variability in the data. The first 2 principal components of the SSLS space are shown in Figure 2.

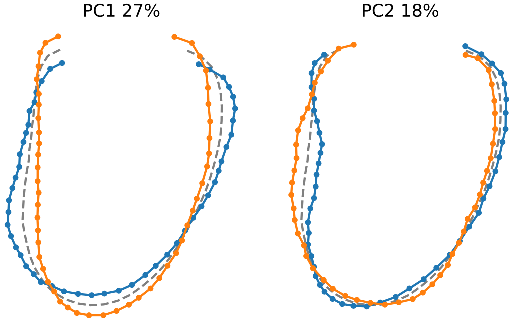

Figure 2. First two principal components in SSLS represented by LV contours. Gray dashed contour is the mean population shape. Blue and orange contours correspond to the mean - 4 sd and the mean + 4 sd of the i-th PC scores (sd - standard deviation).

The first SSLS component (27% of the variability) characterizes the LV deformation aimed at lengthening/shortening along the long axis. According to PC2 (18% of the variability), deformation of the middle part of the LV IVS occurs to a large extent. According to PC3 (11% of the variability), deformation occurs to a greater extent in the basal and apical parts of the IVS. Along PC4 and PC5 (12% of the variability together) there are small deformations that are difficult to formalize.

3.2. Comparison of CRT responders and non-responders

The SS and SSLS components during the cardiac cycle were compared between CRT responders and non-responders (Fig. 3). Significant differences were observed for the SS PC4 in the diastolic phase of the cycle. In the SSLS space, PC1 was significantly different between responders and non-responders in the mesadiastole, and PC2 was significantly different in the systolic phase of the cycle (Fig. 3). The remaining components did not show significant differences between the groups studied.

3.3. Predicting CRT response

To build a classifier predicting CRT response, we used GM features that were significantly different in univariate analysis between responders and non-responders: the SS PC4 in the systolic phase, the SSLS PC1 in the diastolic phase, and SSLS PC2 in the systolic phase. The times at which the greatest difference between groups was observed were chosen for the classifier. The final classifier included two features - SSLS PC1 and PC2. The classifier had an accuracy of 92% (with cross-validation 88.5%) in distinguishing responders from non-responders.

We then compared the performance of the classifier we

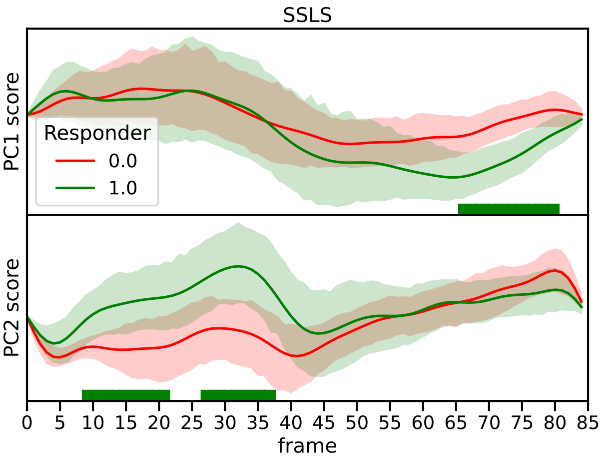

Figure 3. SSLS PC scores of responders and non-responders throughout the cardiac cycle. Mean PC scores are plotted along with bootstrapped 95% confidence intervals. Thick solid lines on the x-axis highlight the frames where there is a statistically significant difference between responder and non-responder scores.

built using the GM features with a classifier developed by Feeny et al. [9] based on conventional clinical features (Table reftab:classifier). Compared to our classifier on GM features, the Feeny's classifier showed lower accuracy for our patient group, with significantly fewer both true negative predictions (25% vs. 92%, $p < 0.001$) and true positive predictions (79% vs. 93%, $p = 0.032$).

Table 2. Comparison of a classifier built on GM features and the classifier by Feeny et al. [9]

Classifier	Accuracy	Precision	Recall	F1
GM	0.92	0.93	0.93	0.93
By Feeny	0.54	0.55	0.79	0.65

GM - geometric morphometrics

4. Conclusions

We used GM to extract features of dynamic LV shape change during the cardiac cycle in CHF patients from echocardiographic data. This is the first time that GM has been used to analyze LV shape in CHF patients.

The extracted GM features were compared between CRT responders and non-responders. Specific features of deformation in the systolic and diastolic phases of the cardiac cycle were found to be able to distinguish responders from non-responders with an accuracy of 88.5%. We compared the developed classifier with the classifier from Feeny et al [9] based on clinical data. The accuracy of the GM classifier in classifying responders and non-responders was significantly higher.

Acknowledgments

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Address for correspondence:

Roman Rokeakh
Pervomayskaya street 106, Yekaterinburg, 620049, Russian Federation
roman.rokeakh@yandex.ru