Impact of Inter-ventricular Lead Distance on Cardiac Resynchronization Therapy Outcomes

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Abstract

Cardiac resynchronization therapy (CRT) has been shown as an essential treatment of patients with heart failure, leading to improvements in symptoms, left ventricular (LV) function, and survival. However, up to 30% of appropriately selected patients remain non-responders to CRT.

The aim of our study was to test a hypothesis on the impact of lead positioning in the ventricular walls on CRT response in patients with advanced chronic heart failure with and without pre-operative inter and intra-ventricular myocardial dyssynchrony.

We examined 53 guideline-selected CRT candidates. Response to CRT was defined in 6 months after implantation of CRT devices. All patients underwent standard and Doppler echocardiography for assessment of LV function and mechanical dyssynchrony. Individual right ventricular (RV) and LV lead tip position, inter-lead distance, and the horizontal and vertical components were measured on the radiograph images with using an automated custom made software

Our results showed that the RLV inter-lead distance is an essential parameter correlated with the CRT outcomes. A logistic model comprising the RLV inter-lead distance with parameters of dyssynchrony demonstrated a high predictive power for odds of CRT success.

1. Introduction

Cardiac resynchronization therapy (CRT) has been among the most important advances for the treatment of patients with heart failure (HF). However, about 30% to 50% of patients may not show left ventricular (LV) reverse remodeling and clinical improvement [1], despite fulfilling treatment recommendations [2]. Complex mechanical alterations in a dyssynchronous ventricle is probably one of the reasons for the lack of response to CRT. After targeted patient selection, proper LV lead positioning may enhance patient response and improve prognosis [3].

There is clinical evidence that better response to CRT is demonstrated by patients with LV electrode tip located closer to the zone of latest electrical activation examined at a natural unstimulated ventricular activation [4]. The role of mechanical asynchrony in the response to CRT has also been suggested. The presence of intra-ventricular dyssynchrony before CRT implantation was shown to lead to the better hemodynamic response and survival at long-term follow-up [5]. There was shown that zones of maximal intra-ventricular myocardial dyssynchrony could also target the location of the CRT electrode tips improving the hemodynamic parameters in patients.

Suggesting that electrophysiological distance (activation timing) and following timing of regional contraction in ventricles are somehow proportional to the spatial distance between the regions we hypothesized that the distance between the right ventricular (RV) and the LV lead tips (RLV inter-lead distance) could correlate with the CRT response providing for better electrical synchronization of the ventricles. Here, we tested this hypothesis in patients with advanced chronic heart failure with and without initial inter- and intra-ventricular myocardial dyssynchrony.

2. Methods

2.1. Population

We analyzed data from 53 heart failure patients treated

 ISSN: 2325-887X DOI:10.22489/CinC.2017.290-106

with CRT between December 2007 and October 2014, retrospectively collected from National Almazov Medical Research Centre. Inclusion criteria were LV ejection fraction (EF) ≤ 35%, sinus rhythm, left bundle branch block, QRS duration of ≥120 ms, NYHA functional class III–IV and optimal pharmacotherapy at least 3 months before CRT. Response to CRT was defined in 6 months after operation as: a decrease in the LV end-systolic volume ≥ 15%, a relative increase in the LV EF > 10%, a decrease in the functional class of chronic heart failure (NYHA) by 1 or higher. All patients were classified as responders [n= 28 (53%)] or non-responders [n =25 (47%)] accordingly.

2.2. RLV inter-lead distance

The anatomic distance between the RV and LV lead tips was determined with using patient chest radiographs recorded in the antero-posterior (AP), 30° left anterior oblique (LAO) and 30° right anterior oblique (RAO) positions. Individual RV and LV lead tip position, inter-lead distance, and the horizontal and vertical components of the distance were measured on the images with using an automated custom made software (see Fig. 1, and Anatomic, Horizontal and Vertical Component means in the Table 2). Based on data from all three of the 2D plane radiographs we reconstructed a 3D distance between the RV and LV lead tips using a custom software. All individual measurements for a patient were normalized by the LV end-diastolic diameter to take into account differences in the heart size between patients.

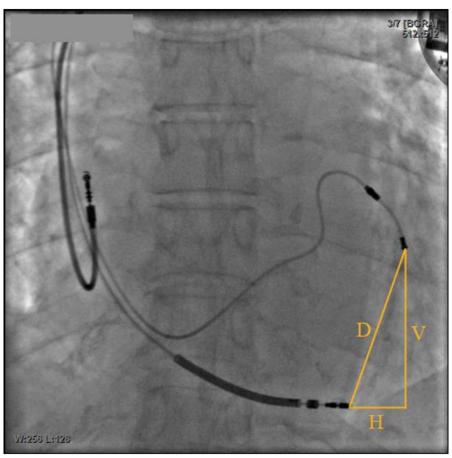

Figure 1. Inter-lead anatomic distance (D), the horizontal (H) and vertical (V) components

2.3. Echocardiography

The LV end-diastolic diameter was derived from the M-mode images of the parasternal long-axis view. The LV end-diastolic and end-systolic volumes were measured from the apical 2- and 4-chamber views, and the LV ejection fraction was calculated using the Simpson rule [6].

Mechanical dyssynchrony was determined by color-coded Tissue Doppler Imaging, using Echopac 6.1.3, General Electric Vivid 7w. We evaluated the aortic pre-ejection time, inter-ventricular mechanical delay, intra-ventricular LV dyssynchrony and the 12-segment standard deviation in the regional time to peak strain (SD12) in the LV. An inter-ventricular mechanical delay > 40 ms was considered as indicative of inter-ventricular dyssynchrony [7]. Intra-ventricular LV delay was calculated as the maximum time delay between regional peak-systolic velocities in basal septal, lateral, anterior, and inferior LV segments [8]. A mechanical delay > 100 ms was considered as indicative of intra-ventricular dyssynchrony [7].

2.4. Statistics

A comparison between the groups was made with using SPSS 22.0 software packages. The data are presented as Mean ± Standard Deviation for the entire group of subjects. The ROC (receiver operating characteristics) analysis was used to assess diagnostic significance of the parameters by evaluation of the area under the ROC-curves (AUC, see Table 1). The logistic regression was used to find the best fitting model to describe the relationship between the characteristics of interest.

3. Results

Initial clinical data are demonstrated in Table 1. We found no significant differences in the clinical data between the responder and non-responder patient groups.

Table 1. Clinical data in responder/non-responder groups before CRT

Characteristic	Responders (n=28)	Non-responders (n=25)	P (t-test)
QRS, ms	171±27	150±39	0.141
EF, %	27±8	27±7	0.769
EDV, ml	254±54	292±90	0.094
ESV, ml	189±49	217±80	0.170
EDD, mm	70±9	74±10	0.140
IVD, N (%)	20 (73%)	18 (71%)	
IVD, ms	71±27	58±28	0.219
ILVD, N (%)	17 (60%)	13 (53%)	
ILVD, ms	82±29	81±31	0.959
SD12, ms	28±11	31±17	0.570

EDD – the LV end-diastolic diameter, IVD – inter-ventricular mechanical delay, ILVD – intra-ventricular LV dyssynchrony

T-test and ROC-analysis did not find significant differences between inter-lead distances in either of separate AP, LAO and RAO positions in the groups of responders and non-responders (Table 2).

At the same time, the 3D distance between the RV and LV lead tips reconstructed from all the plane radiographs, did show a significantly higher mean for the responders against non-responders. In addition, ROC-analysis demonstrated a low but significant diagnostic level for this characteristic (Table 2).

Table 2. Inter-ventricular lead distance in responder/non-responder groups*.

Characteristic	Responder	Non responder	P (t-test)	AUC
LAO Anatomic	1.07±0.41	1.19±0.26	0.128	0.566
LAO Horizontal	0.88±0.46	1.03±0.33	0.104	0.533
LAO Vertical	0.37±0.24	0.47±0.30	0.073	0.588
RAO Anatomic	0.88±0.40	0.66±0.20	0.057	0.639
RAO Horizontal	0.44±0.25	0.59±0.33	0.120	0.627
RAO Vertical	0.53±0.32	0.38±0.24	0.199	0.588
AP Anatomic	0.81±0.40	0.71±0.26	0.389	0.538
AP Horizontal	0.54±0.38	0.50±0.27	0.661	0.515
AP Vertical	0.48±0.38	0.43±0.27	0.658	0.515
3D Distance	**1.6±0.49**	**1.2±0.47**	**0.009**	**0.698**

*Normalized by the LV end-diastolic diameter.

We used a logistic regression to analyze the influence of 3D inter-lead distance on the CRT outcome. This model allows one to assess the probability of CRT success based on the observed characteristics. A model built on the only 3D distance had low classification accuracy (60%), but the regression coefficient was statistically significant.

Then, we accounted for the mechanical dyssynchrony characteristics and built a model comprising data on the 3D distance, the intra- and inter-ventricular dyssynchrony (categorical variables with 0 or 1 for the absence or presence of the dyssynchrony) and SD12 (Table 3). Logistical regression model equation is

In (P/1-P)= -3.24+3.063DR-0.98IVD +1.36LVD-0.4SD12,

where P - probability of CRT success.

The improved model gave a higher prediction accuracy of 81%. The prediction was justified for 77% of non-responders and 85% of respondents.

Table 3. Logistical regression model

Variables	B	S.E.	Sig.	OR
3D Distance	3.06	1.35	0.02	21.39
Intra-ventricular dyssynchrony	-0.98	1.32	0.45	0.37
Inter-ventricular dyssynchrony	1.36	1.56	0.38	3.19
SD12	-0.4	0.05	0.42	0.96
Constant	-3.24			

B - regression coefficient, S.E. - Standard error, Sig. - significance, OR - odds ratio

In the model, the 3D distance was shown to be the most significant variable with the odds ratio much greater than 1. ROC-analysis predicted cut-off value of 1.349 for the 3D distance with sensitivity of 82%, and specificity of 64%. The model predicts that if a patient has the 3D distance larger than the cut-off, his odds for a positive CRT outcome would be 10 times higher than if the 3D distance is less than the cut-off.

While the regression coefficients for the inter- and intra-ventricular dissynchrony were not statistical significant, accounting for these variables significantly improved an accuracy of the logistic regression model. The odds ratio for the inter-ventricular dissynchrony was much greater than 1. Thus, the presence of inter-ventricular dyssynchrony in our group of patients increased the chance for successful CRT outcome by 3 times (Table 3). This is essential, that the presence of intra-ventricular dyssynchrony and SD12 (as a quantitative measure for the dyssinchrony) have negative coefficients in the logistic model. The factors may reflect dis-coordinations in the LV contractile performance which is hardly possible to recover by the only inter-ventricular resynchronization.

4. Conclusions

Our results showed that the RLV inter-lead distance is an essential parameter correlated with the CRT outcome. The data outline the importance of the proper lead tip positioning within the ventricles. However, the only RLV inter-lead distance is not sufficient to predict the treatment outcome and needs to be combined with other functional characteristics of the myocardium. We showed that a logistic model based on the 3D distance in combination with the intra- and inter-ventricular dyssynchrony has much higher power in assessment of the odds for CRT success.

In this study, we used postoperative data on the location of pacing lead tips in patients. But, it is important to examine possibilities for LV lead position, to assess corresponding inter-lead distances and to predict the optimal possible position in the pre-operative patient evaluation. This raises a challenging task for computational analysis of individual anatomical data (CT, MRI, echocardiography, radiography, coronarography) in combination with cardiac personalized computing modeling.

Acknowledgements

Research was supported by Act 211 Government of the Russian Federation, agreement № 02.A03.21.0006 and Program of the RAS Presidium #I.33П.

References

[1] Ypenburg C, Van De Veire N, Westenberg JJ, Bleeker GB, Marsan NA, Henneman MM, Van Der Wall EE, Schalij MJ, Abraham TP, Barold SS, Bax JJ. Noninvasive imaging in cardiac resynchronization therapy — Part 2: Follow-up and optimization of settings. Pacing Clin Electrophysiol. 2008; 31(12): 1628-39.

[2] Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J 2013;34:2281–329.

[3] Heist EK, Fan D, Mela T, Arzola-Castaner D, Reddy VY, Mansour M, Picard MH, Ruskin JN, Singh JP. Radiographic left ventricular-right ventricular interlead distance predicts the acute hemodynamic response to cardiac resynchronization therapy. Am J Cardiol. 2005; 96(5):685- 690.

[4] Gorcsan J 3rd. Is the magnet a better crystal ball for predicting response to cardiac resynchronization therapy? JACC Cardiovasc Imaging. 2008 Sep;1(5):569-571.

[5] Stankovic I, Aarones M, Smith HJ, Vörös G, Kongsgaard E, Neskovic AN, Willems R, Aakhus S, Voigt JU. Dynamic relationship of left-ventricular dyssynchrony and contractile reserve in patients undergoing cardiac resynchronization therapy. EurHeart J. 2014; 35(1):48-55.

[6] Lang R. M. et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging //European Heart Journal-Cardiovascular Imaging. – 2015. – Т. 16. – №. 3. – С. 233-271.

[7] Yu CM, Bax JJ, Gorcsan J 3rd. Critical appraisal of methods to assess mechanical dyssynchrony. Curr Opin Cardiol. 2009; 24(1):18-28.

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