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Role of speckle tracking echocardiography in predicting Cardiac Resynchronization Therapy response

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) is a well-established treatment in selected patients with drug-refractory heart failure. In order to improve the response rate of patients treated with CRT, imaging can provide information on mechanical dyssynchrony, viability, and cardiac venous anatomy. Two-dimensional speckle tracking imaging is a new echocardiographic method could be useful in assessing dyssynchrony and regional contractility.
Aim of the work: The aim of the present study was to evaluate the ability of longitudinal strain and strain rate imaging by two-dimensional speckle tracking to predict echocardiographic response for CRT.
Subjects and Methods: We studied 28 consecutive CRT patients with class II-IV heart failure, ejection fraction (EF) ≤35%, with LBBB and QRS width ≥120 ms or non LBBB with QRS width ≥150 ms. whereas in addition to standard clinical and echocardiographic assessment baseline dyssynchrony was evaluated by speckle tracking longitudinal strain.
Results: Our patients were divided into responders (19 patients) and non-responders(8 patients) according to reduction of left ventricular end systolic volume(LVESV) by ≥15% after 3 months of pacing .There was statistically significant difference between responders and non-responders for their baseline speckle-tracking (P value <0.001). By using receiver operating characteristics (ROC) curve longitudinal dyssynchrony predicted CRT as Basal septal-Basal lateral with cutoff value 135 ms and Mid septal-Mid lateral with cutoff value 125 ms showed high sensitivity and specificity 95% and 100 % respectively for both but Basal anterior –Basal inferior with cutoff value 135 ms showed lower sensitivity and specificity 85 % and 87.5 % respectively
Conclusion: The LV dyssynchrony assessed by speckle tracking using longitudinal strain was predictive to CRT response.

Kew word: Malnutrition - Students - Correction - Prevalence – diet

INTRODUCTION

Heart Failure (HF) is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. Because some patients present without signs or symptoms of volume overload, the term "heart failure" is preferred over "congestive heart failure."

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There is no single diagnostic test for HF because it is largely a clinical diagnosis based on a careful history and physical examination.[1]

Carefully selected patients who continue to deteriorate clinically in spite of optimization of medical therapy may be considered for advanced treatment strategies. In the effort to develop novel therapies for HF, cardiac resynchronization therapy (CRT) has proved to be particularly successful. Multiple clinical trials have demonstrated that CRT can improve symptoms, exercise tolerance, and LV function in patients with depressed systolic function and intra-ventricular conduction delays. Furthermore, other studies have demonstrated a mortality benefit from CRT.[2]

At present, the effort to benefit patients with HF and left ventricular dyssynchrony using cardiac CRT fails in more than 30% of patients, a serious limitation for this invasive and expensive treatment.

Various methods have been used to predict response of CRT, including standard and Tissue Doppler Imaging (TDI) echocardiogram techniques, invasive haemodynamic monitoring, and radionuclide imaging.[2]

One of these novel technologies is 2-dimensional strain imaging or speckle-tracking echocardiography. Unlike TDI-derived strain, speckle-tracking strain imaging enables angle-independent multidirectional analysis of myocardial deformation. Several studies have demonstrated the value of this novel technique in predicting response to CRT. The utility of 2D speckle tracking echocardiography for assessing LV synchrony and thereby improving patient selection for CRT is increasingly apparent.[3-5]

Aim of the study:

The aim of the present study was to evaluate the ability of longitudinal strain and strain rate imaging by two-dimensional speckle tracking to predict echocardiographic response for CRT.

PATIENTS AND METHODS

A total of 28 Patients with sinus rhythm class II, III and ambulatory IV heart failure, ejection fraction (EF) ≤35% with LBBB and QRS wdith ≥120 ms or non LBBB with QRS width ≥150 ms were subjected to CRT implantation. Patients with significant valvular heart disease, severe pulmonary hypertension and atrial fibrillation were excluded. All patients are subjected to clinical evaluation and NYHA class assessment in addition to 6 MWT, quality of life questionnaire and Two-dimensional echocardiography where the following measurements were assessed:

LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV).

LV ejection fraction (LVEF) was calculated using the (modified Simpson's rule).

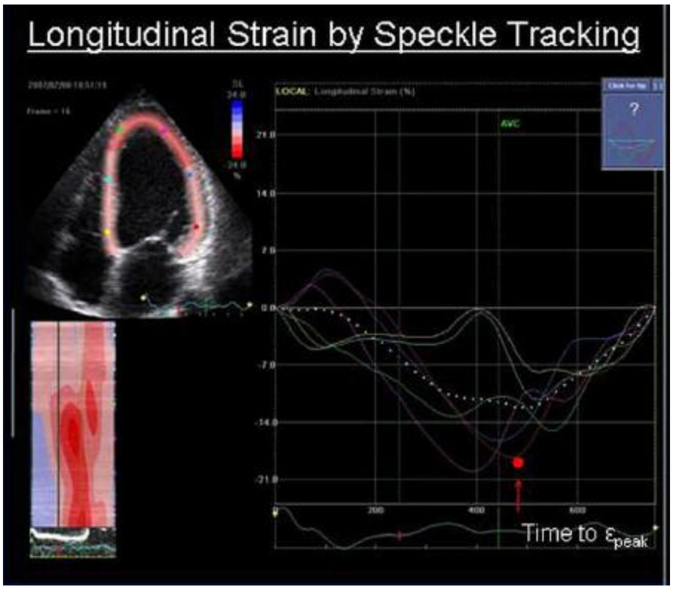
LV end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD).

Pulmonary artery systolic pressure (PASP)

Speckle tracking echocardiography for estimating LV longitudinal strain and strain rate***:***

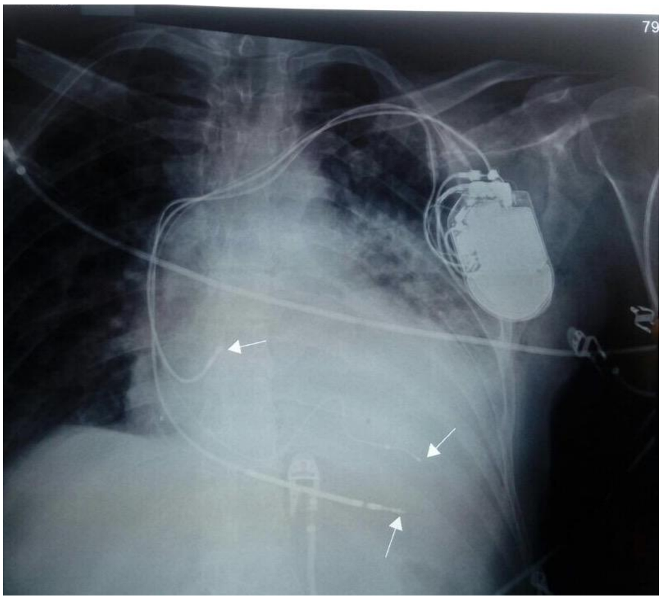
Longitudinal dyssynchrony (Figure-1) will be assessed from basal and mid-levels in apical four-chamber and two chamber. longitudinal dyssynchrony will be also assessed by a region of interest will trace the endocardium counterclockwise direction on the endocardium starting from the right-hand mitral annulus at end- diastole in each three apical view using a point-and-click approach. A second larger region of interest will be then generated and manually adjusted near the epicardium. Special care will be taken to fine-tune the region of interest, using visual assessment during cineloop playback to ensure that segments will be tracked appropriately. Apical images will be divided into six standard segments (at basal, mid, and apical levels) and six corresponding time–strain curves will be generated. Longitudinal dyssynchrony will be defined as maximum opposing wall delay in time-to-peak strain among the two apical views from basal and mid-levels using a pre-defined cut-off ≥130 ms considered as significant dyssynchrony.[6]

Figure-1. Longitudinal speckle tracking



All the patients had the CRT-Pacemaker or CRT-Defibrillator device implanted, where 3 leads were implanted; one in the right atrium, one in the right ventricle and the left ventricular lead was implanted via coronary sinus targeting the lateral wall of the LV (figure-2).

Figure-2. X-ray of one of our patient with implanted CRT-D (the 3 arrows locate the 3 leads)



All patients will be programmed at standard parameters with AV delay 110-120 ms and V-V delay 0 ms

All the patients will be re-evaluated after **3** months from initiation of CRT and the study population was divided into two groups according to CRT response stated as reduction in left ventricular end-systolic volume (LVESV) at least 15 % (reverse remodeling); responders: it included 19 patients and non-responders: it included 8 patients. One patient died before he completed 3 months follow up evaluation.

Statistical analysis

All group data were presented as mean + SD and were compared with the two-tailed Student's t-test for unpaired data. Proportional differences were evaluated with Fisher's exact test. Or the Chi-square test. ROC were constructed for each dyssynchrony parameter individually to test predefined cut-offs and to determine sensitivities and specificities.[7]

RESULTS

Patients charachterstics: (table-1)

Our study was conducted on twenty eight patients having heart failure and indicated for cardiac resynchronization therapy.

Table-1. General characteristics for all studied patients

All patients	
Age (years)	58.1±8.6 years
Gender (female)	8 (28.6%)
(male)	20 (71.4%)
Smoking	17(60.1%)
Diabetes	10 (35.7%)
HTN	16(57.1%)
CAD	11(39.3%)

Comparison between baseline & 3 months follow-up parameters for all studied patients:

Clinical assessment:

There was significant improvement of NYHA class after CRT implantation when compared with baseline one (3.1 ±0.4 Vs 2.2 ±0.9 respectively) with p value 0.003.

ECG:

Comparison between initial and follow up ECG QRS complex duration revealed no statistically significant difference (table-2).

Table-2. Comparison between initial and follow up QRS duration in all patients

	Initial	Follow up	*p* value
QRS duration (msec)	152.1±26.9	125.3±26.7	NS

NS=non significant

Echocardiographic data:

Comparison between pre- and post-implantation transthoracic Echocardiographic examination (TTE) revealed significant changes in LV diameters, volumes and contractility (table-3).

Table-3. Comparison between pre- and post-implantation echocardiography.

All patients	Pre Mean±SD	Post Mean±SD	*p* value
Echo-LVEDD(cm)	6.5±0.7	5.9±0.9	0.8
Echo-LVESD(cm)	5.8±0.9	5±0.9	0.048
LVEDV (ml)	189±90	184±81	0.400
LVESV (ml)	143.5±16.4	118.5±20.8	0.001
Echo-EF%	29±5.1	37.3±8.3	0.001

6 MWT and QOL questionnaire:

There was significant difference between the mean initial and the mean follow up 6 MWT distances and QOL questionnaire means of sums of score in all studied patients .(table 4 and 5).

Table-4. Comparison between the mean initial and the mean follow up 6 MWT in all studied patients.

6MWT	Initial	Follow up	*p* value
6MWT (m)	192.5±76.5	251.9±129.3	0.005

Table (5) Comparison between initial and follow up QOLQ in all studied patients

QOL questionnaire	Initial mean	Follow up mean	*p* value
QOL questionnaire	71.7±12.2	64±14.5	0.003

Comparison between baseline & follow –up parameters for responders and non-responder:

There was no statistically significant difference between responders and non-responders for their baseline risk factors or demographics data (table-6).

Table-6. Comparison for general characteristics between responders and non-responders.

All patients	**Responders (No. = 19)**	**Non-responders (No. = 8)**	***p* value***
Age (years)	59.7±5.5	66.4±9.3	NS
Gender (female)	7 (36.8%)	1 (12.5%)	NS
Diabetes	8.0 (42.1%)	2.0 (25%)	NS
Smoking	14.0 (73.7%)	3.0 (37.5%)	NS
Hypertension	10.0 (52.6%)	6.0 (75%)	NS
CAD	9.0 (47.4%)	2.0 (25%)	NS

NS=non significant

Clinical assessment:

There was no significant difference between responders and non-responders regarding their initial NYHA class (3.15 ±0.4 for responders versus 3.25±0.5 for non-responders).

ECG:

Baseline ECG QRS complex duration comparison between responder and non –responders revealed no statistically significant difference (table-7).

Table-7. Comparison between responders and non-responders in their initial QRS duration

QRS duration	**Responders**	**Non-responders**	***p* value**
Pre-CRT implantation (msec)	155.8±31.1	143.8±13	NS

NS=non significant

Pre implantation Echocardiographic data:

There was no statistically significant difference between responders and non-responders for their baseline Echocardiographic examination data (table-8).

Table-8. Comparison between responders and non-responders in Pre-implantation echocardiographic examination.

Pre-implantation echocardiography	Responders	Non-responders	*p* value
	Mean±SD	*Mean±SD*	
LVEDD(cm)	7.1±2.4	6.8±0.6	NS
LVESD(cm)	5.8±1	5.8±0.6	NS
LVEDV (ml)	180±65	188±70	NS
LVESV (ml)	141.7±18	148.8±12.8	NS
LVEF%	29.5±4.8	28.6±6.4	NS
PASP(mmHg)	31.3±7.9	35.6±6.7	NS

NS=non significant

Pre implantation speckle tracking:

Baseline speckle tracking results showed a statistically significant longer delay in opposing walls in responder than non-responders . (table 9 & figue-3).

Pre implantation 6 MWT and QOLQ:

There was no significant difference between responders and non-responders regarding their initial mean of distances performed in 6 MWT or baseline QOL questionnaire mean of sums of score (table 10 and 11).

Table-9. Comparison between responders and non-responders in Pre-implantation speckle tracking.

Pre-implantation speckle tracking	Responders	Non-responders	*p value*
	Mean±SD	*Mean±SD*	
B_s-B_l (ms)	182.6±32.1	117.5±31.2	< 0.001
B_a-B_i (ms)	165.8±26.9	105±26.7	< 0.001
M_s-M_l (ms)	166.1±26.4	116.3±25	< 0.001
M_a-M_i (ms)	161.1±18.2	102.5±27.1	< 0.001
SD 12	170.3±26.2	114.4±29.9	< 0.001

Bs-Bl : basal septal to basal lateral delay, Ba-Bi: basal anterior to basal inferior, Ms-Ml: mid septal to mid lateral, Ma-Mi: mid anterior to mid inferior and SD 12: standard deviation of time to peak of 12 segments.

Figure-3. comparison of speckle tracking between responder and non-responder

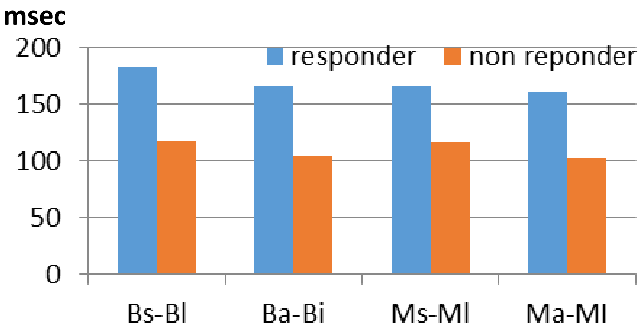


Table-10. Comparison between responders and non-responders in Pre-implantation 6MWT.

6MWT	Responders	Non-responders	*p* value
6MWT (m)	192.5±76.5	187.7±60	NS

NS=non significant

Table-11. Comparison between responders and non-responders in Pre-implantation QOLQ.

	Responders	Non-responders	*p* value
	Mean+SD	*Mean+SD*	
QOL questionaire	71.7+12.2	81.1+10.1	NS

NS=non significant

Follow-up data comparison between responders and non-responders:

Clinical assessment:

There was significant difference between responders and non-responders regarding their follow-up NYHA class, (1.75±0.6 for responders versus 3.25±0.7 for non-responders, *p* value 0.003).

ECG:

Follow- up mean of ECG QRS width duration comparison between responder and non-responders revealed no statistically significant difference *(*table-12*).*

Table-12. Comparison between responders and non-responders in Post-implantation QRS duration.

QRS duration	Responders	Non-responders	p value
Post-CRT implantation (msec)	123.2±30.4	128.1±18.1	NS

NS=non significant

Post-implantation Echocardiographic data:

There was a statistically significant difference between responders and non-responders for their mean follow-up LV EF and LVESV.(table-13).

Table-13. Comparison between responders and non-responders in Post-implantation Echocardiographic examination.

Post-implantation echocardiography	Responders	Non-responders	p value
	Mean+SD	*Mean+SD*	
LVEDD cm	5.8+0.8	6.5+1.3	NS
LVESD cm	5.2+1.2	5.7+0.6	NS
LVEDV (ml)	182+55	188+65	NS
LVESV(ml)	108.1+11.7	143.4+15.9	<0.001
LVEF%	40.4+6.5	30.1+7.8	0.003
LVEF difference%	10.9+6.4	1.5+2.9	<0.001
LVEF relative difference %	38.79+28.39	4.72+8.53	<0.001

NS=non significant
LVEF difference = post implantation LVEF - pre implantation LVEF.
LVEF relative difference is the relative increase in LVEF from pre to post implant

Post- implantation 6 MWT:

There was a statistically significant difference between responders and non-responders for their mean follow-up distances performed in 6 MWT as all responder group showed improved results of 6MWT while 50% of non-responder group also showed improved 6 MWT (table 14 & 15)

Table-14. Comparison of post implantation 6MWT between responder and non-responder.

Post-implantation 6 MWT	Responders	Non-responders	*p* value
	Mean+SD	***Mean+SD***	
Post 6 MWT (m)	314.7+89.7	102.6+72.4	<0.001
6 MWT change (m)	+73.3+45.5	+ 14.1+23.5	<0.001

6 MWT change (m) = post implantation distance -pre implantation distance

Table-15. Comparison of improved 6MWT between responder and non-responder

	Responder	Non responder	p value
Improved 6 MWT	19 (100%)	4 (50%)	0.004
Non improved 6 MWT	0	4 (50%)	

Post- implantation QOL questionnaire

There was a statistically significant difference between responders and non-responders for their mean sums of follow-up QOL questionnaire score. (Table 16 & 17)

Table-16. Comparison of post implantation QOL questionnaire between responder and non-responder

Post-implantation QOL questionnaire	Responders *Mean±SD*	Non-responders *Mean±SD*	*p value*
Post QOL questionnaire	58.5±11.2	77.1±13.5	0.001
QOL questionnaire change	17.76±12.56	5.08±9.94	0.019

Table-17. Comparison of improved QOL questionnaire between responder and non-responder

	Responder	Non responder	p value
Improved QOL *questionnaire*	15 (78.9%)	2 (25%)	0.014
Non improved QOL *questionnaire*	4 (21.1%)	6 (75%)	

Reciever Operating Characteristics Curve (ROC) to predict cardiac resynchronization therapy (CRT) response:

Baseline speckle-tracking longitudinal dyssynchrony predicted a significant reduction in LVESV by more than 15% (reverse remodeling) as Bs-Bl with cutoff value 135 ms and Ms-Ml with cutoff value 125 ms showed high sensitivity and specificity 95% and 100 % respectively for both respectively but Ba-Bi with cutoff value 135 ms showed lower sensitivity and specificity 85 % and 87.5 % respectively.(table 18 and figure 4)

Table-18. Sensitivity and specificity of different strains for predication of response

	AUC	Cut-off	Sensitivity	Specificity
Bs-BI	**96.6%**	**135**	**95.0%**	**100.0%**
Ms-MI	**96.9%**	**125**	**95.0%**	**100.0%**
Ma-Mi	**90.9%**	**135**	**95.0%**	**87.5%**
Ba-Bi	**94.4%**	**135**	**85.0%**	**87.5%**

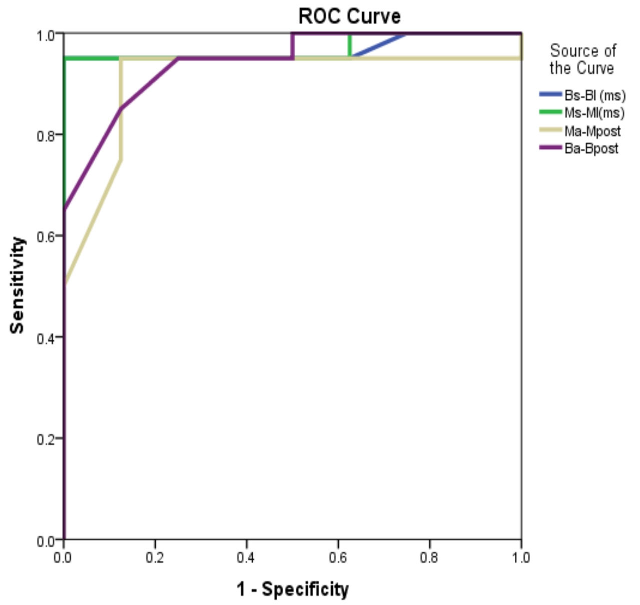


Figure-4. Receiver operating characteristics curve analysis of speckle-tracking strain approaches to dyssynchrony for predicting outcome after cardiac resynchronization therapy

DISCUSSION

Cardiac resynchronization therapy (CRT) is a well-established treatment in selected patients with drug-refractory heart failure.

However in clinical trials, 30–40% of patients do not respond to cardiac resynchronization therapy (CRT).[8] In order to improve the response rate of patients who treated with CRT, imaging can provide information on mechanical dyssynchrony, viability, and cardiac venous anatomy[9]. Implementation of these parameters may improve patient response.

Various echocardiography methods have been proposed to quantify intra-ventricular dyssynchrony, including M-mode echocardiography and tissue Doppler imaging (TDI), however in a prospective, multicenter setting, the Predictors of Response to CRT (PROSPECT) study tested the performance of these parameters to predict CRT response and concluded that no single echocardiographic measure of dyssynchrony may be recommended to improve patient selection for CRT[10]

Two-dimensional speckle tracking imaging, a new echocardiographic method could be useful in assessing dyssynchrony and regional contractility. Therefore, the aim of the present study was to evaluate the ability of longitudinal strain and strain rate imaging by two-dimensional speckle tracking to predict echocardiographic response under CRT.

Our study was conducted on twenty eight cardiomyopathy patients meeting the clinical, ECG and echocardiography criteria for CRT[11] .

Like other studies used speckle tracking in predicting CRT response[6,12-14] We used a firm definition of CRT response which is relative reduction of LVESV (reverse remodeling) by ≥15% after 3 months of pacing derived and according to this definition sixty eight percent of our patients responded to CRT therapy .

In our study no baseline measure whether clinical or echocardiographic predicted CRT response ,even the intial QRS width similar to **Dreger *et al .in 2010*** and Gasparini et al, 2014[15,16] failed to predict CRT response.

In our study baseline speckle-tracking longitudinal dyssynchrony predicted CRT response according to significant reduction in LVESV (reverse remodeling) as Bs-BI with cutoff value 135 ms and Ms-MI with cutoff value 125 ms showed high sensitivity and specificity 95% and 100 % respectively for both but Ba-Bi with cutoff value 135 ms showed lower sensitivity and specificity 85 % and 87.5 % respectively also many other studies with different speckle tracking techniques favor the potential benefits of speckle tracking for predication of response in context with our study[3-5,17-19,20-23]

In context with our study **Lim, et al. in 2009**[17] found that the 12 standard deviation of time to peak systolic velocity and the opposing septal-lateral wall delay by TDI failed to predict response to CRT, whereas the 12 segment standard deviation of time to peak strain by longitudinal speckle tracking correlated to end-systolic volume reduction ($r = -0.39$, $P < .001$).

In the most recent study in 2016 done by Ghani, et al.[19] who studied 138 patients with standard CRT indication and he found that the extent of LV dyssynchrony as measured by speckle tracking after CRT are independently associated with response to CRT .

Also in a recent study Seo, et al, 2016 (START study) in his study on 171 pts using radial , longitudinal and circumferential and he found that speckle tracking echocardiography (STE) had an incremental value to predict CRT responders.[5, 25]

CRT non-responders are an important and unresolved issue, in this study we demonstrated that speckle tracking analysis one of the methods to predict response to CRT, and can be further helpful for better predication of response in CRT.

Regarding potential future applications, the effects of CRT in patients with narrow QRS duration <120 ms and speckle-tracking dyssynchrony are presently unknown. The only randomized CRT trial in patients with narrow QRS width, known as RethinQ (Resynchronization Therapy in Patients with Narrow QRS), primarily measured dyssynchrony by tissue Doppler imaging which failed to add benefit to this group of patients.[24]

Follow-up speckle tracking can be helpful in recognizing of 'non-responders' who require possible more intensive monitoring. Moreover, the effect of AV/VV delay optimization in non-responders can be evaluated by speckle tracking analysis to see whether the extent of LV dyssynchrony decreases after CRT optimization.

Speckle tracking has also the potential to be used during the implantation to guide the location of left ventricular lead in order to measure the acute response for CRT. This simultaneous speckle tracking analyzing may minimize the non-responders rate in CRT patients. However, this needs to be investigated in prospective studies.

CONCLUSION

The LV dyssynchrony assessed by speckle tracking using longitudinal strain was predictive to CRT response.

Conflict of Interests

Authors declare that there is no conflict of interests regarding the publication of this paper.

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