RESEARCH ARTICLE

Three-dimensional echocardiography as a predictor of positive response to cardiac resynchronisation therapy

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Abstract

Objective: To assess patients with three-dimensional echocardiography before cardiac resynchronisation therapy device implantation to predict the responders, and to determine the response 3 months post-intervention.

Method: The descriptive study was conducted at Kafrelsheikh University Hospital, Egypt, from January 2020 to March 2022, and comprised patients of either gender who underwent cardiac resynchronisation therapy device implantation. The patients were assessed clinically and with three-dimensional echocardiography using 16-segment systolic dyssynchrony index as the main parameter compared at baseline and 3 months after implantation. The patients were classified as non-responders, clinical responders, and clinical and echocardiographic responders. Data was analysed using SPSS 23.

Results: Of the 40 patients, 23(57.5%) were males and 17(42.5%) were females. The overall mean age was 57.43±10.47 years, mean body weight was 81.30±11.33kg, mean height was 171.15±10.56cm), and mean body surface area was 1.93±0.17m^2. Of the total, 14(35%) patients were hypertensive, 10(25%) diabetic, 15(37.5%) ischaemic and 2(5%) patients had atrial fibrillation. There were 8(20%) non-responders, 8(20%) clinical responders, and 24(60%) clinical and echocardiographic responders to therapy. Mean systolic dyssynchrony index at baseline was a positive highly significant predictor of post-therapy response (p<0.01). A positive highly significant correlation was also found between post-therapy response and end-systolic volume, three-dimensional ejection fraction, New York Heart Association class and QRS width (p<0.01).

Conclusion: Three-dimensional 16-segment systolic dyssynchrony index was found to be a significantly effective tool to predict response to cardiac resynchronisation therapy device implantation.

Keywords: Cardiac resynchronisation therapy, Three-dimensional echocardiography, Heart failure.

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Introduction

Heart failure (HF) is a common clinical entity presented with symptoms and signs of pulmonary and/or systemic congestion.[1] The recently released European Society of Cardiology (ESC) HF guidelines has classified it into 3 main groups based on ejection fraction (EF): HF with preserved ED (HFpEF ≥50%), with reduced EF (HFrEF ≤40%), and with mildly reduced EF (HFmrEF 41-49%).[2] Generally, about 50% patients have HFrEF and the remaining have HFpEF and HFmrEF.[3] There is about 20% annual mortality, mainly in patients with New York Heart Association (NYHA) class IV disease even with the newer HF drugs.[4] Medical therapy, including Angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor/neprilysin inhibitor (ARNI), Beta Blockers (BB), Mineralocorticoid receptor antagonists (MRAs) and Sodium-Glucose Co-Transporter-2 Inhibitors (SGLT2-I), are now the 4 pillars of Heart failure with reduced ejection fraction (HFrEF) treatment.[5] Cardiac resynchronisation therapy (CRT) is a good option in some patients with EF≤35%, wide QRS ≥130 msec with Left Bundle Branch Block or non left bundle branch block (LBBB or non-LBBB) morphology and still symptomatic even after 3 months of guideline-based medical therapy.[6] CRT response is determined after following up the patients clinically and by echocardiography after 3-6 months of implantation with at least one-step improvement in NYHA class and decrease in end-systolic volume (ESV) ≥15% of its basal value.[7] Three-dimensional (3D) echocardiography is an advanced modality that can predict positive CRT response by using 3D 16-segment systolic dyssynchrony index (3D 16-SDI). It is calculated by measuring the interval between the start of the cardiac cycle and the lowest systolic volume of each segment, and then figuring out the standard deviation (SD). In order to compare patients with various heart rates, it is preferable to utilise it as a percentage of the cardiac cycle rather than in milliseconds.[8] Normally, it is <5.6% and higher values of SDI represent higher levels of dyssynchrony.[9]

Unfortunately, only about 70% of candidates are responders, which makes it important to be able to predict the responders in order to avoid unnecessary implantation. The current study was planned to assess 3D 16SDI in CRT device implantation cases to predict the responders, and

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to determine the response 3 months post-intervention.

Patients and Methods

The descriptive study was conducted at Kafrelsheikh University Hospital, Egypt, from January 2020 to March 2022. After approval from the institutional research ethics committee, the sample was raised. Those included were HFrEF patients with EF≤35% and LBBB morphology in electrocardiography (ECG) with QRS duration ≥130msec who were still symptomatic on evidence-based optimal medical therapy and underwent CRT implantation. After signing written informed consent, all patients underwent full clinical evaluation, ECG and 3D echocardiography at baseline and 3 months post-implantation.

Using X5-1 transducer (Philips Epic 7c machine), ECG-gated full-volume acquision was taken in average 4 beats and then offline analysis by (3DQ-Adv, Philips) to compute end diastolic volume (EDV), ESV, 3D EF and 3D 16-SDI at baseline and 3 months post-implantation.

The cases were classified according to response to CRT. Group 1 had non-responders (Δ NYHA class 0 and Δ ESV <15%), group 2 had clinical responders (Δ NYHA class ≥1 and Δ ESV <15%) and group 3 had clinical and echocardiographic responders (Δ NYHA class ≥1 and Δ ESV ≥15%).

Data was analysed using SPSS 23. Quantitative data was presented as mean, standard deviations and range when the variables were parametric, and as median and interquartile range (IQR) when they were non-parametric. Frequencies and percentages were used to present qualitative data. Chi-square test was used to compare qualitative data. One-way analysis of variance (ANOVA) was used to compare the means of more than two groups using quantitative data and parametric distribution. Subsequently, LSD test (Least Significant Difference Test)

was used for post-hoc analysis. Margin of error was set at 5%, while confidence interval (CI) was set at 95%. Receiving operating characteristic (ROC) curve was drawn between the responders and the non-responders. P<0.05 was considered statistically significant.

Results

Of the 40 patients, 23(57.5%) were males and 17(42.5%) were females. The overall mean age was 57.43±10.47 years, mean body weight was 81.30±11.33kg, mean height was 171.15±10.56cm), and mean body surface area (BSA) was 1.93±0.17m^2. Of the total, 14(35%) patients were hypertensive, 10(25%) diabetic, 15(37.5%) ischaemic and 2(5%) patients had atrial fibrillation (AF). There were 8(20%) non-responders in group 1, 8(20%) clinical responders in group 2, and 24(60%) clinical and echocardiographic responders in group 3 (Table 1).

Mean 3D 16-SDI value at baseline was a positive highly

Table-1: Demographic, anthropometric measures, risk factors and NYHA class of the studied groups.

		(Group -1) Non-responders No. = 8	(Group -2) Clinical responders No. = 8	(Group 3) Clinical and Echocardiographic responders No. = 24	Test value•	*p-value*	Sig.
Age (years)	Mean ± SD	53.63 ± 6.95	52.38 ± 13.30	60.38 ± 9.71	2.610•	0.087	NS
	Range	42-61	21-62	39-75			
Gender	Female	1 (12.5%)	5 (62.5%)	11 (45.8%)	4.365*	0.113	NS
	Male	7 (87.5%)	3 (37.5%)	13 (54.2%)			
Weight (kg)	Mean ± SD	86.63 ± 12.51	86.00 ± 13.26	77.96 ± 9.35	2.866•	0.070	NS
	Range	70 – 110	71 – 110	60 – 95			
Height (cm)	Mean ± SD	178.75 ± 9.21	168.88 ± 8.01	169.38 ± 10.89	2.840•	0.071	NS
	Range	162 – 190	160 – 185	150 – 188			
BSA (m2)	Mean ± SD						
	Range	2.05 ± 0.17	1.96 ± 0.18	1.89 ± 0.15	3.210•	0.052	NS
		1.79 – 2.3	1.78 – 2.33	1.55 – 2.22			
HTN	No						
	Yes	5 (62.5%)	5 (62.5%)	16 (66.7%)	0.073*	0.964	NS
		3 (37.5%)	3 (37.5%)	8 (33.3%)			
DM	No						
	Yes	5 (62.5%)	6 (75.0%)	19 (79.2%)	0.889*	0.641	NS
		3 (37.5%)	2 (25.0%)	5 (20.8%)			
Ischaemic	Non-Ischaemic	2 (25.0%)	6 (75.0%)	17 (70.8%)	6.044*	0.049	S
	Ischaemic	6 (75.0%)	2 (25.0%)	7 (29.2%)			

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Table-1: *continued from previous page*

		(Group -1) Non-responders No. = 8	(Group -2) Clinical responders No. = 8	(Group 3) Clinical and Echocardiographic responders No. = 24	Test value•	*p-value*	Sig.
AF	Sinus	7 (87.5%)	7 (87.5%)	24 (100.0%)	3.158*	0.206	NS
	AF	1 (12.5%)	1 (12.5%)	0 (0.0%)			
NYHA class	III	8 (100.0%)	8 (100.0%)	24 (100.0%)	NA	NA	NA
NYHA class FU	II	0 (0.0%)	8 (100.0%)	24 (100.0%)	40.000*	0.000	HS
	III	8 (100.0%)	0 (0.0%)	0 (0.0%)			
Δ NYHA class	0	8 (100.0%)	0 (0.0%)	0 (0.0%)	40.000*	0.000	HS
	I	0 (0.0%)	8 (100.0%)	24 (100.0%)			

***p*-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)**

***: Chi-square test; •: One Way ANOVA test**

SD: Standard deviation, BSA: Body surface area, HTN: Hypertension, DM: Diabetes mellitus, AF: Atrial fibrillation, FU: Follow up, Δ NYHA class: Change in class of New York Heart Association classification.

Table-2: ECG and echocardiographic parameters of the studied groups.

		(Group -1) Non-responders No. = 8	(Group -2) Clinical responders No. = 8	(Group 3) Clinical and Echocardiographic responders No. = 24	Test value•	*p-value*	Sig.
QRS width (msec)	Mean ± SD	133.75 ± 7.44	140.00 ± 10.69	149.17 ± 8.30	10.727•	0.000	HS
	Range	130 – 150	130 – 160	130 – 160			
QRS width FU (msec)	Mean ± SD	95.00 ± 7.56	93.75 ± 5.18	98.75 ± 3.38	4.135•	0.024	S
	Range	90 – 110	90 – 100	90 – 100			
LAVI (ml/m2)	Mean ± SD	39.35 ± 9.12	51.51 ± 14.59	41.90 ± 8.04	3.699	0.034	S
	Range	20.9 – 53	32.7 – 76.8	23.6 – 62.5			
LAVI FU (ml/m2)	Mean ± SD	38.86 ± 8.98	49.78 ± 14.74	39.81 ± 7.93	3.519	0.040	S
	Range	20.9 – 52.4	30 – 74.7	23 – 59.4			
EDV (ml)	Mean ± SD	258.78 ± 71.04	210.26 ± 43.22	183.50 ± 46.13	6.537	0.004	HS
	Range	170.2 – 392.5	137.9 – 275.8	120.5 – 311.1			
EDV FU (ml)	Mean ± SD	254.29 ± 73.76	200.35 ± 39.11	167.66 ± 44.33	9.017	0.001	HS
	Range	166.5 – 394.6	135.8 – 254.5	103.3 – 288.7			
ESV (ml)	Mean ± SD	199.91 ± 55.97	163.08 ± 32.30	137.65 ± 39.82	6.724	0.003	HS
	Range	130.5 – 309.7	107.3 – 210.6	84.3 – 238.7			
ESV FU (ml)	Mean ± SD	193.58 ± 57.24	144.09 ± 31.04	112.26 ± 33.90	13.358	0.000	HS
	Range	125.9 – 306.3	93.3 – 186.5	63.6 – 200.			
Δ ESV %	Mean ± SD	3.35 ± 2.12	10.67 ± 3.14	18.84 ± 3.70	69.409	0.000	HS
	Range	0.9 – 6.8	5.7 – 13.9	15.1 – 27.4			
3D EF (%)	Mean ± SD	22.59 ± 5.60	22.29 ± 2.20	25.46 ± 5.02	1.962	0.155	NS
	Range	15 – 30.4	19.4 – 25.9	19.3 – 34.5			
3D EF FU (%)	Mean ± SD	23.75 ± 5.26	28.31 ± 2.83	33.56 ± 4.82	14.811	0.000	HS
	Range	16.1 – 31.1	24.1 – 32.5	27.5 – 45.1			
Δ 3D EF %	Mean ± SD	1.16 ± 0.57	6.00 ± 2.41	8.10 ± 1.88	43.105	0.000	HS
	Range	0.4 – 2.3	3.1 – 9.9	5.2 – 12.4			
3D 16-SDI (%)	Mean ± SD	9.14 ± 1.71	12.49 ± 2.14	15.91 ± 2.60	26.227	0.000	HS
	Range	6.3 – 11.7	8.6 – 14.6	11 – 21.4			
3D 16-SDI FU (%)	Mean ± SD	7.34 ± 1.43	7.44 ± 2.17	7.73 ± 1.28	0.247	0.783	NS
	Range	5.8 – 9.8	4 – 10.2	4.5 – 9.6			

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)

•: One Way ANOVA test

LAVI: Left atrial volume index, FU: Follow-up, EDV: End diastolic volume, ESV: End systolic volume, Δ ESV%: Percent decrease in end systolic volume, 3D EF: Three-dimensional ejection fraction, 3D-16- SDI: Three-dimensional 16-segment systolic dyssynchrony index.

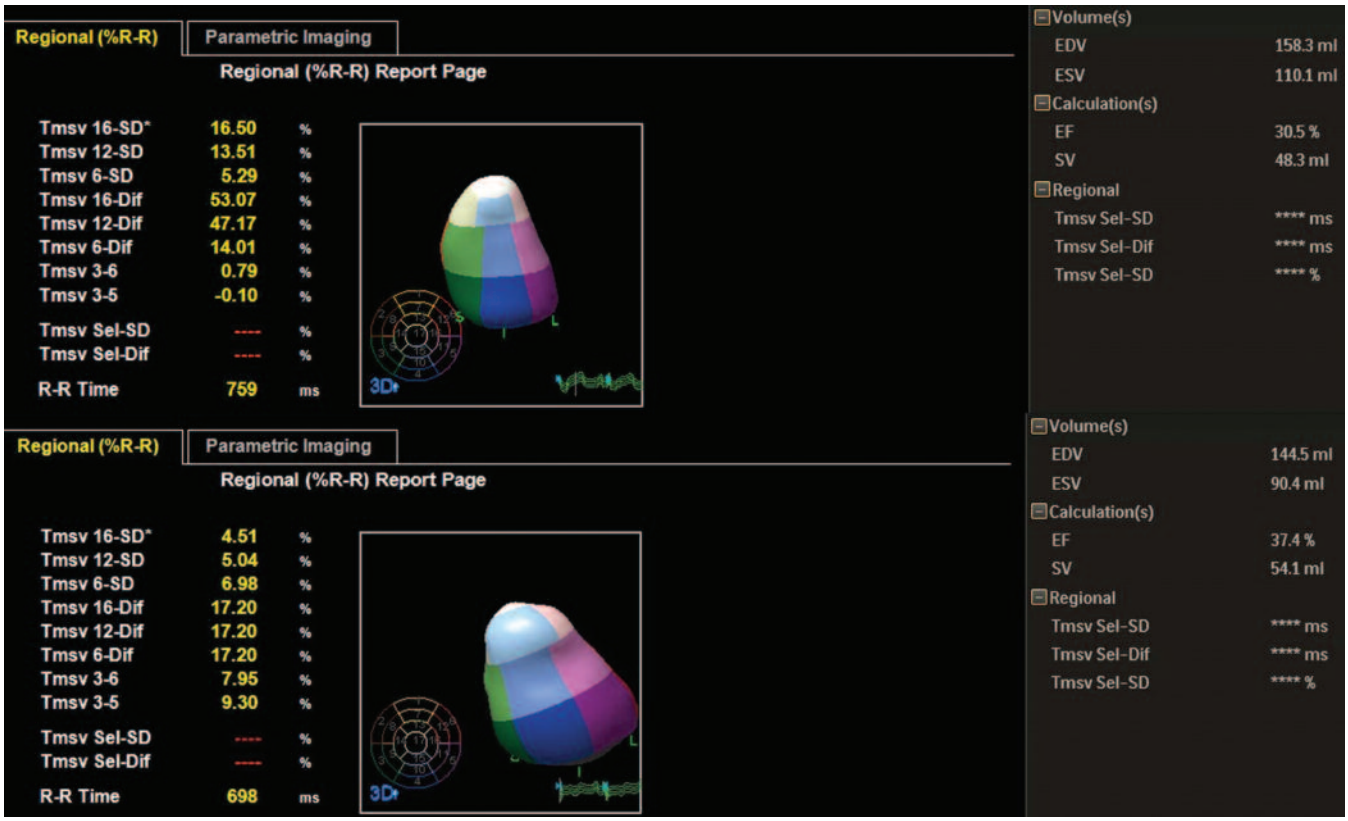

Figure: **Pre- and post-CRT 3D 16-SDI, EDV, ESV, SV and 3DEF in a patient of responder group.**
CRT: **Cardiac resynchronisation therapy, EDV: End diastolic volume, ESV: End systolic volume, SV: Stroke volume, 3D-EF: Three-dimensional ejection fraction, 3D-16-SDI: Three-dimensional 16-segment systolic dyssynchrony index, Tmsv 16-SD: standard deviation of time to minimum systolic volume in 16 segments.**

significant predictor of post-therapy response (p<0.01). A positive highly significant correlation was also found between post-therapy response and ESV, EDV, 3D EF, NYHA class, QRS width and left atrial volume index (LAVI) (p<0.01) (Table 2).

There was no significant difference among the 3 groups in terms of age, gender, height, weight, BSA, hypertension, diabetes, and AF (p>0.05). However, the difference was significant among them regarding QRS width FU, IHD and response to CRT (p<0.05).

A cut-off value of 10% for 3D 16-SDI was determined between the non-responders and the responders using the ROC curve with an excellent area under curve (AUC) of 0.957, indicating that the response will likely be positive to CRT when 3D 16-SDI ≥10 % with a sensitivity 0.996 and specificity 0.750 (Figure).

Discussion

CRT is one of the important treatment modalities that can be used in patients with HFrEF and wide QRS if they are still symptomatic after optimal medical treatment.

Actually, not all patients respond well to CRT even after applying the approved criteria for choosing the patients. Some patients are responders and the others are non-responders. The current study included 40 patients who met the inclusion criteria. There were more female responders than male (p=0.113). Demographic and anthropometric measures were also of no significant difference in relation to response to CRT (p>0.05).

Galli E et al.[10] Sugano A et al.[11] Ghani A et al.[12] Tani T et al.[13] and Van Bommel RJ et al.[14] presented findings similar to the current findings related to age and gender.

There was no significant difference between AF, diabetes and hypertension in relation to response to CRT (p>0.05) in the current study, which is line with earlier studies.[10,12,14]

In the current study, response to CRT for individuals with ischaemic and non-ischaemic cardiomyopathy was significant (p=0.049), which is in agreement with literature.[10,12,14]

Ghani A et al.[12] had 51% patients who were ischaemic compared to the current study which had 62.5% non-ischaemic patients.

The current study revealed a highly significant difference between baseline and post-CRT parameters ($p<0.01$), which is in line with literature (10,11,15) even though one these studies[11] showed no significant difference regarding QRS width.

The current study had a highly significant difference between NYHA class and CRT response. Van Bommel RJ et al.[14] reported similar findings, but it only had NYHA class IV cases. Galli E et al. (10) and Ghani A et al.[12] reported no significant difference between NYHA class and CRT response.

The current study revealed a highly significant positive association between QRS width and CRT response both at baseline and post-implantation. One study reported similar findings[12], but others[10, 14] showed no significant difference.

The relations of response to CRT with EDV, ESV, 3D EF, and 3D 16-SDI were highly significant in the current study. Literature has shown a range of results related to various parameters both at baseline and a varying phase of follow-up.[10, 15]

The current study has limitations as the sample size was not calculated and the final sample size was small. This could have a negative effect on the power of the study. It was owing to the movement restrictions as a result of the coronavirus disease-2019 (COVID-19) pandemic.

Conclusion

Candidates for CRT could be evaluated using 3D echocardiography which could predict the response by using 3D 16-SDI, and it could also be used to ensure echocardiographic criteria of responder's post-implantation.

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