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Baseline aortic pre-ejection interval predicts reverse remodeling and clinical improvement after cardiac resynchronization therapy

Hakan Aksoy, Sercan Okutucu, Kudret Aytemir, Ergun Baris Kaya, Banu Evranos, Giray Kabakci, Lale Tokgozoglu, Hilmi Ozkutlu, Ali Oto

Department of Cardiology, Hacettepe University Faculty of Medicine, Ankara, Turkey

Abstract

Background: *Cardiac resynchronization therapy (CRT) has been shown to reduce heart failure-related morbidity and mortality. However, approximately one in three patients do not respond to CRT. The aim of the current study was to determine the parameter(s) which predict reverse remodeling and clinical improvement after CRT.*

Methods: *A total of 54 patients (43 male, 11 female; mean age 61.9 ± 10.5 years) with heart failure and New York Heart Association (NYHA) class III–IV symptoms and in whom left ventricular ejection fraction (LVEF) was ≤ 35% and QRS duration was ≥ 120 ms, despite optimal medical therapy, were enrolled. An echocardiographic examination was performed before, and six months after, CRT. An echocardiographic response was defined as a reduction of end-systolic volume ≥ 10% after six months, and a clinical response was defined as a reduction ≥ 1 in the NYHA functional class score.*

Results: *An echocardiographic response was observed in 38 (70.4%) of the patients and a clinical response occurred in 41 (75.9%) of the patients. Of the dyssynchrony parameters, only the aortic pre-ejection interval (APEI) was observed to significantly predict the clinical response ($p = 0.048$) and echocardiographic response ($p = 0.037$). A 180.5 ms cut-off value for the APEI predicted the clinical response with a sensitivity of 92.3% and a specificity of 39%, and the echocardiographic response with a sensitivity of 93.0% and a specificity of 42%.*

Conclusions: *APEI derived from pulsed-wave Doppler, which is available in every echocardiography machine, is a simple and practical method that could be used to select patients for CRT.* (Cardiol J 2011; 18, 6: 639–647)

Key words: cardiac resynchronization therapy, echocardiography, dyssynchrony, heart failure

Introduction

Intraventricular conduction abnormalities concomitant with systolic dysfunction are frequently encountered in patients with heart failure (HF). Of all patients with HF, 25–50% have a QRS duration > 120 ms and 15–27% have a left bundle branch block [1]. Delayed conduction in patients with dilated cardiomyopathy leads to abnormal depolarization of the ventricles, inter- and intra-ventricular contraction and relaxation dyssynchrony, increased regional and global wall stress, as well as decreased

Address for correspondence: Sercan Okutucu MD, Department of Cardiology, Hacettepe University Faculty of Medicine, Sihhiye, Ankara, P.O. 06100, Turkey, tel: +90 312 305 17 81, fax: +90 312 311 40 58, e-mail: sercanokutucu@yahoo.com

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effective ejection time and stroke volume [2, 3]. Consequently, impaired synchronization results in poor ventricular function, remodeling of the left ventricle, and HF, which triggers a pathophysiologic process with increased morbidity and mortality.

Cardiac resynchronization therapy (CRT) improves functional capacity, left ventricular (LV) systolic, diastolic and autonomic functions, and survival, in patients with refractory HF and left bundle branch block [4–7]. Multicenter, randomized, double-blind trials such as COMPANION [8] and CARE-HF [4] have demonstrated that CRT improves symptoms and exercise capacity, while shortening hospitalization for patients who, despite optimal medical therapy, have symptoms consistent with New York Heart Association (NYHA) class III–IV, with a QRS duration of ≥ 120 ms and a decreased left ventricular ejection fraction (LVEF).

Although CRT is a positive approach in decreasing mortality and morbidity in patients with advanced stage HF, 25% of patients fail to demonstrate an improvement in symptoms following CRT. Consequently, evaluating synchronization impairment before administering CRT can be useful in determining those patients who are likely to benefit from the procedure [4–7].

The aim of the present study was to establish the optimal echocardiographic parameter(s) in patient selection and evaluation of the response to CRT.

Methods

Study population

Sixty-three patients with symptoms of NYHA class III–IV HF, a LVEF ≤ 35%, sinus rhythm, and a QRS duration ≥ 120 ms, despite optimal medical therapy, who were admitted to our department between December 2007 and May 2009, were enrolled in the study. Four of the 63 could not undergo CRT implantation owing to inappropriate coronary sinus (CS) anatomy. In addition, three patients were excluded from the study because they did not attend follow-up visits, and two patients were excluded because of poor echogenicity. The remaining 54 patients (43 males and 11 females; mean age ± SD: 61.9 ± ± 10.5 years) were evaluated in terms of age, gender, coronary artery disease (CAD) history, diabetes mellitus (DM), hyperlipidemia, hypertension (HT), and other related diseases. All patients were also examined with respect to their functional capacities. All patients underwent a complete physical examination, and their height and weight were recorded. All patients also underwent 12-lead electrocardiography. The patients underwent a detailed echocardiographic examination twice: once at baseline and again six months after CRT.

Patients were excluded if they had been admitted with acute coronary syndrome in the last three months, required continuous or intermittent intravenous inotropic drugs, had a life expectancy of < six months, had a history of pacemaker implantation, mechanical tricuspid valve, heart transplantation, or electrical storm. Informed consent was obtained from all patients and the study was approved by the Hospital Ethics Committee.

Echocardiographic evaluation

The patients underwent transthoracic echocardiography at baseline and again six months after CRT implantation. Echocardiographic examination was performed in the left lateral position using Vingmed System Five GE Ultrasound (General Electric, Horten, Norway) with a 2.5–3.5 MHz transducer from parasternal long- and short-axes, and apical two- and four-chamber views. The measurements were based on the criteria set out by the American Society of Echocardiography. The patients underwent M-mode echocardiography, two-dimensional (2D) echocardiography, pulsed wave (PW) Doppler, color Doppler, and PW and color tissue Doppler imaging. From the parasternal long axis, the left ventricular end-diastolic diameter (LVEDD) and the left ventricular end-systolic diameter (LVESD) were measured using M-mode (at the mitral chordal level perpendicular to the long axis of the ventricle). Then the LVEF was calculated. The endocardial boundaries were identified using end-diastolic and end-systolic images from the apical four-chamber view, and the left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) and LVEF were calculated with the modified Simpson's method [9]. In the parasternal short axis, the sequence between the contractions of septal and posterior walls at the level of the papillary muscle was measured as the septal-to-posterior wall motion delay (SPWMD). A sequence > 130 ms was regarded as an indicator of intraventricular dyssynchrony [10].

The intervals between the onset of QRS to the beginning of ejection at the aortic and pulmonary valve levels using PW Doppler were defined as the aortic pre-ejection interval (APEI) and the pulmonary pre-ejection interval (PPEI), respectively. An APEI value ≥ 140 ms reflects prolonged LV activation, dyssynchrony and delayed LV ejection [11]. Interventricular mechanical delay (IVMD) was defined as the difference between APEI and PPEI. An

IVMD value ≥ 40 ms is regarded as an indicator of interventricular dyssynchrony [10].

PW tissue Doppler (PWTD) (during echocardiography [real-time]) was performed at the septum distal to the point where the septal leaflet of the mitral valve was adherent to the annulus (basal septum) and at the lateral basal segments. Using PWTD, the interval between the QRS onset and the onset of peak systolic velocity (Sm) was measured by placing a sample volume of 10 mm width in the septal and lateral mitral annulus at the apical four-chamber view. A delay ≥ 60 ms between the lateral wall and the septum was regarded as intraventricular dyssynchrony [12].

Color tissue Doppler samples were recorded from the apical two- and four-chamber views, ensuring that they covered a minimum of three cardiac cycles. The recordings were performed with gray-scale 2D images at a frame rate of 150/s and a depth of 10.8 mm. The recordings were performed at the end of expiration to preclude interference from global cardiac movement. The sample volumes were placed on the basal segments of the septal and lateral walls. The time elapsed between the peak velocities of the septum and lateral wall was calculated. An interval ≥ 65 ms was regarded as intraventricular dyssynchrony [13]. EchoPAC 6.3.6 GE software was used for the calculations.

Device implantation

Following creation of the pacemaker pocket through a left pectoral incision, a left subclavian vein puncture was performed. A defibrillation electrode was placed in the apex of the right ventricle. After CS cannulation, the CS and its branches were monitored using venography. The LV electrode was placed in the posterolateral branch of the CS in 50 (92.5%) patients. It was placed in the anterolateral branch of the CS in the remaining four (7.5%) patients. The electrodes were tested for pacing and sensing characteristics. All implanted biventricular pacemakers also had the feature of working as a defibrillator. Atrioventricular delay was optimized using 2D echocardiography following implantation.

Definition of the response

A decrease of ≥ 10% in LVESV at six month follow-up was defined as echocardiographic response [14]. Clinical response was defined as a decrease by ≥ 1 in the NYHA functional class score [5, 6].

Statistical analysis

Numerical variables with a normal distribution were expressed as mean ± SD, and numerical variables without a normal distribution were expressed as the median with minimum and maximum values. Categorical variables were expressed in percentages. A Pearson χ^2 test was used to compare the two groups in the study. A significance test was performed for differences between the groups with respect to the mean values. The patients who were under or above the cut-off points were compared using Fisher's exact test. Inter-observer and intra-observer agreements were assessed with intra- and interclass correlation coefficient, and with the average difference between readings, corrected for their mean (variability). Receiver operating characteristics (ROC) curve analysis was performed to establish both the parameters that can best predict the CRT response, and the best cut-off points for those parameters. SPSS 15.0 statistical analysis software (SPSS Inc., Chicago, IL, USA) was used to evaluate variables and tests. A p value < 0.05 was considered significant.

Results

Patient characteristics

Fifty-four patients (43 males and 11 females; mean age ± SD: 61.9 ± 10.5 years) with complete baseline echocardiographic measurements, dyssynchrony analysis, and follow-up records concerning left ventricle volume and ejection fraction values, were enrolled in the study.

Of the patients, 40 (74.1%) had HT, 19 (35.2%) had DM, 39 (72.2%) had hyperlipidemia, and 38 (70.4%) had a history of CAD. Drug therapies used by the patients were similar before and after CRT. The patients' characteristics are presented in Table 1. The QRS duration, as well as LVEDD, LVESV, and LVEF, measured using the modified Simpson's method, were shown to have improved significantly at the six month follow-up (Table 2).

An echocardiographic response, defined as a decrease of ≥ 10% in LVESV, was observed in 38 (70.4%) patients. A clinical response, defined as a decrease of ≥ 1 in NYHA functional class score, was observed in 41 (75.9%) patients.

Reproducibility

For intra-observer reliability analysis, a sample of 15 patients was re-analyzed over the 5–7 days between first and second analysis. Intra-observer correlation coefficient and variability for LVESV

Table 1. Baseline clinical and demographic features of patients.

Age (years)	61.9 ± 10.5
Male	43 (79.6%)
Diabetes	19 (35.2%)
Hypertension	40 (74.1%)
Coronary artery disease	38 (70.4%)
QRS duration [ms]	146.64 ± 25.94
Left atrial diameter [cm]	4.47 ± 0.50
LV end-diastolic diameter [cm]	6.85 ± 0.76
LV end-systolic diameter [cm]	5.70 ± 0.73
LV end-diastolic volume [mL]	169.87 ± 47.11
LV end-systolic volume [mL]	128.09 ± 40.27
LV ejection fraction [%]*	24.68 ± 4.01
LV fractional shortening [%]**	12.39 ± 3.12
ACE-I or ARB use	54 (100%)
Beta-blocker use	48 (88.8%)
Diuretic use	54 (100%)
Digoxin use	42 (77.7%)
Spironolactone use	29 (53.7%)
Decline in LV end-systolic volume ≥ 10%	38 (70.4%)

Numerical variables were presented as the mean ± standard deviation and categorical variables were presented as percentages; *measured by modified Simpson's method; **measured by M-mode echocardiography; ACE-I — angiotensin converting enzyme inhibitors; ARB — angiotensin receptor blockers; LV — left ventricular

were 0.980 and 1.1%, and for LVEDV were 0.913 and 1.7%, respectively. The inter-observer correlation coefficient and variability for LVESV were 0.921 and 1.6%, and for LVEDV they were 0.876 and 2.5%.

Intra-observer correlation coefficient and variability for SPWMD were 0.891 and 3.2%; for IVMD they were 0.798 and 5.5%; for APEI they were 0.903 and 2.0%; for PW-TDI (lateral-septal delay) they were 0.878 and 3.7%; and for C-TDI (lateral-septal delay) they were 0.881 and 3.4%, respectively. The inter-observer correlation coefficient and variability for SPWMD were 0.767 and 5.8%; for IVMD were 0.732 and 7.2%, for APEI were 0.853 and 4.1%, for PW-TDI (lateral-septal delay) were 0.743 and 7.1%, for C-TDI (lateral-septal delay) were 0.798 and 5.7%, respectively.

Clinical response

A comparison between patients with and without a clinical response in terms of baseline demographic and echocardiographic values revealed that CAD had a significantly higher incidence in patients without a response (61.5 *vs* 93.3%, p = 0.020; Table 3). LVEF values, measured using the modified Simpson's method, were shown to have improved significantly (p = 0.046).

Patients with a clinical response had a longer SPWMD, IVMD and APEI than the patients without a clinical response. However, the difference was significant only with respect to the APEI (Table 4).

Of the dyssynchrony parameters, only the APEI was observed to significantly predict a clinical response (p = 0.048) in the analysis comparing patients meeting and failing to meet the cut-off values described in the literature, while the remaining parameters did not reach statistical significance (Table 5). The APEI was calculated to have a positive predictive value of 81.8% and a negative predictive value of 50%. ROC analysis revealed the area under the curve (AUC) value of the APEI in predicting clinical response to be 0.70 (p = 0.031) (Fig. 1). The APEI, with a cut-off point of 180.5 ms, was calculated to have 92.3% sensitivity and 39% specificity in predicting the clinical response.

Echocardiographic response

A comparison between the patients observed with and without an echocardiographic response revealed no significant difference in terms of base-

Table 2. Comparison of clinical and echocardiographic parameters at baseline and six months after cardiac resynchronization therapy (CRT).

	Before CRT	After CRT	P
NYHA functional capacity	2.87 ± 0.58	1.90 ± 0.70	0.004
QRS [ms]	146.64 ± 25.94	132.96 ± 21.06	< 0.001
LVEDV [mL]	169.87 ± 47.11	154.87 ± 42.68	< 0.001
LVESV [mL]	128.09 ± 40.27	109.29 ± 37.56	< 0.001
LVEF (Simpson's method) (%)	24.68 ± 4.01	30.24 ± 7.80	< 0.001

Numerical variables were presented as the mean ± standard deviation; LVEDV — left ventricular end-diastolic volume; LVESV — left ventricular end-systolic volume; LVEF — left ventricular ejection fraction

Table 3. Comparison of demographic and echocardiographic data of patients with and without clinical response or echocardiographic response to cardiac resynchronization therapy.

Parameter	Clinical response (+)	Clinical response (–)	P	Echocardio-graphic response (+)	Echocardio-graphic response (–)	P
Age (years)	61.1 ± 10.4	64.4 ± 10.8	NS	61.8 ± 10.3	62.3 ± 11.3	NS
Male	30 (76.9%)	13 (86.7%)	NS	28 (73.7%)	15 (93.8%)	NS
Diabetes mellitus	33.3%	40%	NS	36.8%	31.3%	NS
Hypertension	69.2%	86.7%	NS	76.3%	68.8%	NS
Coronary artery disease	61.5%	93.3%	0.020	63.2%	87.5%	0.048
Baseline QRS [ms]	146.04 ± 26.77	148.53 ± 24.07	NS	147.00 ± 24.75	145.81 ± 29.42	NS
QRS (follow-up) [ms]	132.12 ± 21.82	135.61 ± 19.05	NS	131.92 ± 18.43	135.43 ± 26.84	NS
LVEDV [mL]	169.78 ± 46.34	170.15 ± 51.42	NS	166.84 ± 49.55	177.06 ± 41.29	NS
LVEDV (follow-up) [mL]	153.19 ± 41.69	160.15 ± 47.01	NS	147.15 ± 42.48	173.18 ± 38.41	0.035
LVESV [mL]	127.92 ± 39.34	128.61 ± 44.73	NS	125.68 ± 42.51	133.81 ± 34.94	NS
LVESV (follow-up) [mL]	106.85 ± 37.54	117.00 ± 38.07	NS	101.18 ± 37.60	128.56 ± 30.59	0.013
LVEF (%)*	24.90 ± 3.75	24.00 ± 4.86	NS	25.07 ± 4.25	23.75 ± 3.33	NS
LVEF (follow-up) (%)*	31.26 ± 8.13	27.00 ± 5.78	0.046	32.15 ± 8.30	25.68 ± 3.75	0.004

Numerical variables were presented as the mean ± standard deviation; *measured by modified Simpson's method; LVEDV — left ventricular end--diastolic volume; LVESV — left ventricular end-systolic volume; LVEF — left ventricular ejection fraction

Table 4. Comparison of dyssynchrony parameter times in patients with respect to clinical or echocardiographic response to cardiac resynchronization therapy.

	Clinical response (+) n = 41 (75.9%)	Clinical response (–) n = 13 (24.1%)	P	Echocardio-graphic response (+) n = 38 (70.4%)	Echocardio-graphic response (–) n = 16 (29.6%)	P
SPWMD [ms]	204.35 ± 54.81	188.00 ± 65.70	0.357	209.47 ± 59.72	176.87 ± 47.28	0.040
IVMD [ms]	48.10 ± 21.39	45.93 ± 24.85	0.751	44.50 ± 20.68	54.62 ± 24.64	0.127
APEI [ms]	171.15 ± 31.58	145.20 ± 32.96	0.010	170.42 ± 32.70	148.56 ± 32.12	0.028
PW-TDI (lateral--septal delay) [ms]	77.92 ± 33.40	78.20 ± 19.26	0.976	77.55 ± 33.65	79.06 ± 19.46	0.837
C-TDI (lateral--septal delay) [ms]	82.30 ± 22.84	87.66 ± 25.60	0.459	83.55 ± 24.96	84.37 ± 20.44	0.908

Numerical variables were presented as the mean ± standard deviation; SPWMD — septal-to-posterior wall motion delay; IVMD — interventricular mechanical delay; APEI — aortic pre-ejection interval; PW-TDI — pulse-wave-tissue Doppler imaging; C-TDI — color-tissue Doppler imaging

Table 5. Comparison of dyssynchrony parameters in predicting the clinical and echocardiographic response to cardiac resynchronization therapy.

Parameter	Dyssynchrony cut-off value		Total	Decrease of ≥ 1 in NYHA class	P	Decrease of ≥ 10 in LVESV	P
SPWMD [ms]	≥ 130	+	49	38 (77.6%)	0.347	35 (71.4%)	0.468
		–	5	3 (60%)		3 (60%)	
IVMD [ms]	≥ 40	+	36	27 (75%)	0.552	23 (63.9%)	0.122
		–	18	14 (77.8%)		15 (83.8%)	
APEI [ms]	≥ 140	+	44	36 (81.8%)	0.048	34 (77.2%)	0.037
		–	10	5 (50%)		4 (40%)	
PW-TDI (lateral--septal delay) [ms]	≥ 60	+	42	30 (71.4%)	0.143	29 (69%)	0.496
		–	12	11 (91.7%)		9 (75%)	
C-TDI (lateral--septal delay) [ms]	≥ 65	+	49	38 (77.6%)	0.347	33 (63.7%)	0.159
		–	5	3 (60%)		5 (100%)	

NYHA — New York Heart Association; LVESV — left ventricular end-systolic volume; SPWMD — septal-to-posterior wall motion delay; IVMD — interventricular mechanical delay; APEI — aortic pre-ejection interval; PW-TDI — pulse-wave tissue Doppler imaging; C-TDI — color-coded tissue Doppler imaging

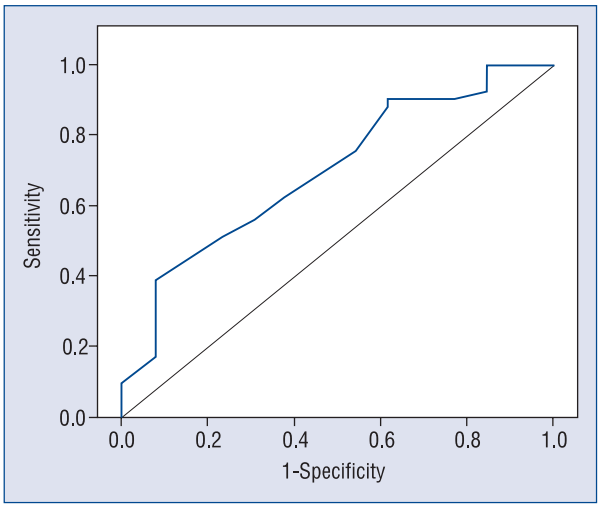

Figure 1. Receiver operating characteristics analysis for aortic pre-ejection interval in predicting clinical response.

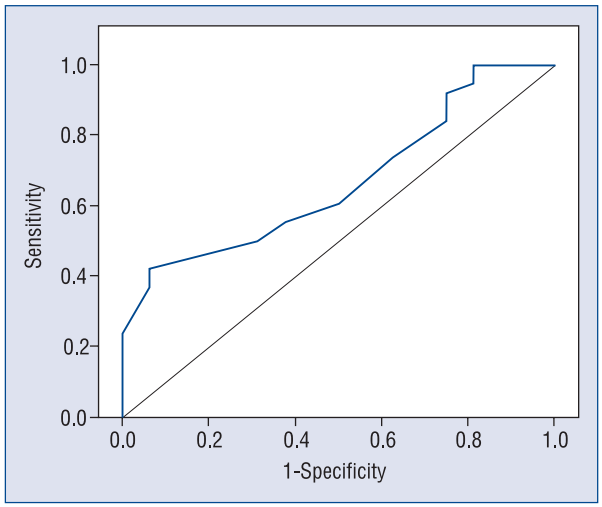

Figure 2. Receiver operating characteristics analysis for aortic pre-ejection interval in predicting echocardiographic response.

line demographic and echocardiographic data, except for the presence of CAD. While 63.2% of the patients with an echocardiographic response had CAD, 87.5% of the patients with no response had CAD ($p = 0.048$). Significant improvements were determined in the follow-up period in LVEDV, LVESV, and LVEF values measured using the modified Simpson's method (Table 3).

Comparing dyssynchrony parameters in the patients with and without an echocardiographic response demonstrated that the patients with a response had a longer SPWMD and APEI. These differences were statistically significant with respect to both parameters (Table 4).

Among the dyssynchrony parameters, only the APEI was observed to significantly predict the echocardiographic response, defined as a decrease ≥ 10% in the LVESV ($p = 0.037$) (Table 5).

ROC analysis revealed that the APEI had an AUC value of 0.668 ($p = 0.048$) in predicting the echocardiographic response (Fig. 2). The APEI, with a cut-off point of 180.5 ms, was established to have 93% sensitivity and 42% specificity in predicting the echocardiographic response.

Discussion

Echocardiography has been proposed as an effective method of selecting patients eligible for CRT [15], although opinions on this issue still differ. PROSPECT, a recently published trial, was designed to investigate the adequacy of echocardiographic parameters in determining the CRT response. It concluded that the selection of patients for CRT is not based solely on echocardiographic parameters, whereas the fundamental selection criterion in the evaluation of dyssynchrony is QRS width [10]. On the other hand, our study found that the APEI is a predictor of clinical and echocardiographic response following CRT. However, SPWMD, IVMD, PW, and color tissue Doppler parameters were observed to be inadequate in predicting the clinical and echocardiographic response.

Since the responses of patients to CRT vary, the patients were divided into two groups based on the improvements in NYHA functional classification and reverse remodeling of the LV, referred to as the 'responding' and 'non-responding' patients.

Several studies have defined the criteria for response to therapy as a decrease of ≥ 1 in NYHA functional class or a decrease of ≥ 10% in LVESV [14, 16]. Bax et al. [13] reported in their study that 31% of patients failed to achieve a clinical response. PROSPECT reported that 69% of the patients improved, 15% remained unaltered, and 16% deteriorated [10]. In our study, 41 (75.9%), of the patients were found to be responding to therapy clinically, consistent with the results of previous studies. Yu et al. [14] evaluated 141 patients undergoing CRT implantation and maintained a decrease of ≥ 10% in LVESV at six month follow-up to be the most important predictor of death for all causes and cardiovascular death.

In the present study, setting the criterion for echocardiographic therapy response as a decrease of ≥ 10% in LVESV, 38 (70.4%) patients were

judged to have responded to therapy. The higher rate observed in the present study compared to the previous studies may be attributed to the fact that the other studies defined therapeutic response as a decrease of ≥ 15% in LVESV [17, 18]. Moreover, the ideal end-point to assess the response to CRT remains unclear, and there are differences in clinical and echocardiographic response rates [19].

M-mode indices

The first to be developed, and still the simplest, echocardiographic method for evaluating dyssynchrony is SPWMD. In the study by Pitzalis et al. [20] conducted on 20 patients, it was reported that SPWMD predicted LV reverse remodeling. A more recent study by Pitzalis et al. [21] suggested that a longer SPWMD is associated with decreased risk in the progression of HF. However, both studies had high percentages of patients with non-ischemic cardiomyopathy (78%). Retrospective analysis of the 79 patients in the CONTAK-CD trial demonstrated that SPWMD failed to predict the clinical and echocardiographic responses. Of the patients in the trial, 72% had ischemic cardiomyopathy. However, the analysis performed on the patients with non-ischemic cardiomyopathy did not establish SPWMD to have any predictive value [22].

A major restriction on SPWMD measurement is the presence of regional wall motion abnormalities. The measurements are unreliable, particularly in patients in whom the anterior septum is akinetic. Consequently, the reliability of SPWMD in predicting the response to CRT is decreased.

According to the results obtained in the present study, SPWMD could not predict either echocardiographic or clinical response. One reason why SPWMD poorly predicts the CRT response may be the high ratio of CAD in our patient population (70.4%). However, we found that patients with an echocardiographic response had a longer SPWMD than non-responders. Although there are conflicting results in the literature concerning this particular parameter, it is an easily measured index of radial dyssynchrony which should be measured and carefully analyzed in all patients.

Pulse-wave Doppler indices

The APEI is a combined electromechanical index wherein higher values reflect prolonged LV activation, LV dyssynchrony and delayed ejection [11]. It is easily obtained by measuring the time interval between the beginning of the QRS complex and the onset of transaortic ejection. St John Sutton et al. [23] reported that an APEI > 160 ms was an independent predictor of the CRT response. Wiesbauer et al. [24] maintained that an APEI with a cut-off value of 140 ms predicted the clinical and echocardiographic responses. The PROSPECT trial also reported that prolonged APEI was associated with clinical and echocardiographic responses [10].

In the current study, it was determined that the baseline APEI were significantly longer in the clinical and echocardiographic responding groups compared to the non-responding group. ROC analysis showed that the APEI with a cut-off point of 180.5 ms predicted the clinical response with 92.3% sensitivity and 39% specificity, while it had 93% sensitivity and 42% specificity in predicting the echocardiographic response. Contradicting these results, a recent study by Bordachar et al. [25] could not find any statistically significant role of APEI in predicting response to CRT.

It has been reported that IVMD, with a cut-off point varying between 40–60 ms, predicts the response to CRT [26, 27]. Da Costa et al. [28] also reported IVMD values > 50 ms to be the only dyssynchrony parameter predicting a positive response to CRT. Richardson et al. [26] stated in the analysis performed for the CARE-HF trial that a cut-off value of 50 ms predicted survival. Similarly, the PROSPECT trial reported that IVMD, with a cut-off value of 40 ms, predicted the clinical and echocardiographic responses [10]. In contrast to those results, IVMD was not established to predict the clinical and echocardiographic responses in the present study. Since factors such as changes in preload and afterload, which have an impact on ventricular ejection and pulmonary and systemic hypertension, alter this particular parameter, the use of IVMD in predicting the CRT response is limited when compared to intraventricular dyssynchrony parameters [29].

Pulse-wave and color tissue Doppler indices

Bax et al. [30] reported that a delay of > 60 ms between the lateral and septal walls measured on PW tissue Doppler predicted the CRT response with 80% accuracy. Bordachar et al. [31] demonstrated a strong correlation between intraventricular dyssynchrony observed on PW tissue Doppler and hemodynamic variables. However, these variables do not reflect LV reverse remodeling, which requires long-term follow-up. Soliman et al. [32], on the other hand, concluded that PW tissue Doppler measurement of the delay between the lateral and septal walls failed to predict the clinical and echocardiographic responses. In the present study, this particular parameter was not associated with

predicting clinical and echocardiographic responses to CRT. PW tissue Doppler imaging is susceptible to angle-related mistakes, and does not allow the simultaneous viewing of a regional myocardial movement within a stroke. Furthermore, determining peak systolic velocity may be complicated in ischemic cardiomyopathy patients. Therefore, PW tissue Doppler appears inadequate in predicting CRT response. This particular approach may yield better results by increasing the number of segments analyzed [33] or by 3D analysis of the myocardial velocity and deformation [34].

A number of studies have reported color tissue Doppler to have high accuracy in predicting post-CRT clinical improvement and LV reverse remodeling [13]. Bleeker et al. [35] reported that the delay between the lateral wall and septum measured by color tissue Doppler with a cut-off value of 65 ms had 90% sensitivity and 82% specificity in predicting the response to CRT. It was established to have 52.6% sensitivity and 69.2% specificity at a cut-off value of 60 ms in predicting LV reverse remodeling in the PROSPECT trial [10]. This particular parameter was not observed to predict the clinical or echocardiographic response to CRT in the present study. However, it should be noted that intraventricular dyssynchrony was determined by using two segments of the left ventricle (the basal portions of the septum and lateral wall). Since this particular model did not evaluate the ventricle in its entirety, the longest delay between the segments might not have been determined. Studies employing models with four or 12 segments have reported higher rates of accuracy in predicting the response to CRT [13, 36].

Limitations of the study

There were a few significant limitations to our study. The number of patients enrolled was relatively small. Our data should be supported by larger studies in order to decrease the probability of randomness in the results. The follow-up period was limited to six months; long-term results are unknown. The inter-observer correlation coefficients were relatively low, and corresponding variabilities were high for indices of dyssynchrony. LV dyssynchrony is a 3D and complex issue involving ventricular electrical activation, the distribution of myocardial fibers, and the torsion forces on those fibers. Therefore, 3D echocardiography or using parameters evaluating radial and circumferential dyssynchrony may be a better approach. We could not examine those characteristics because echocardiography software including novel imaging approaches such as tissue synchronization imaging, 2D strain, and 3D echocardiography were not available.

Another limitation of the study was the presence of extensive scar tissue in ischemic patients which may have resulted in decreased clinical and echocardiographic response rates despite dyssynchrony. The use of magnetic resonance imaging along with echocardiography may be beneficial in determining the presence of scar tissue, as well as its localization and size, when selecting patients for CRT.

Conclusions

CRT has become a well-established therapeutic option for patients with HF and LV dyssynchrony. Despite recent advances in non-invasive evaluation methods, most current indices do not adequately identify responders to CRT. Prolonged APEI reflects delayed LV activation, LV dyssynchrony and ejection. Our data revealed that APEI, which can be measured in almost all patients evaluated by transthoracic echocardiography, could predict LV reverse remodeling and clinical response following CRT. The assessment of this parameter could therefore help to predict responders to CRT.

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