ORIGINAL ARTICLE

Association between reverse electrical remodeling and cardiac fibrosis markers in patients with cardiac resynchronization therapy

Kardiyak resenkronizasyon tedavisi uygulanmış hastalarda tersine elektriksel yeniden şekillenme ile kalp fibrozu belirteçleri arasındaki ilişki

Hamza Sunman, M.D.,[1] Uğur Canpolat, M.D.,[2] Hikmet Yorgun, M.D.,[2] Adem Özkan, M.D.,[3] Muhammet Ulvi Yalçın, M.D.,[2] Tülin Bayrak, M.D.,[3] Levent Şahiner, M.D.,[2] Ergün Barış Kaya, M.D.,[2] Asuman Özkara, M.D.,[3] Kudret Aytemir, M.D.,[2] Ali Oto, M.D.[2]

[1]Department of Cardiology, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey

[2]Department of Cardiology, Hacettepe University Faculty of Medicine, Ankara, Turkey

[3]Department of Biochemistry, Hacettepe University Faculty of Medicine, Ankara, Turkey

ABSTRACT

Objective: Cardiac resynchronization therapy (CRT) induces structural and electrical reverse remodeling of the failing heart. However, the association between native QRS narrowing and cardiac fibrosis markers has not been investigated in patients with an implanted CRT device.

Methods: A total of 41 symptomatic patients diagnosed with systolic heart failure who underwent CRT implantation were included in this study. Electrocardiogram findings and cardiac fibrosis marker levels [galectin-3, growth-differentiation factor-15 (GDF-15) and procollagen III N-terminal propeptide (P3TD)] were collected before and 12 months after initiation of biventricular pacing. Reverse electrical remodeling was defined as a decrease in 12-month intrinsic QRS (iQRS) duration by ≥20 milliseconds after CRT implantation.

Results: The median QRS duration decreased from 155 milliseconds (interquartile range [IQR]: 142–178 milliseconds) before CRT to 142 milliseconds (IQR: 130–161 milliseconds) (p=0.001) after 12 months of CRT. According to the predefined criteria, electrical remodeling was detected in 16 (39.0%) patients. The median galectin-3, GDF-15, and P3TD levels were significantly decreased after CRT implantation in patients with electrical remodeling [27.65 ng/mL (IQR: 24.4–35.2 ng/mL) vs 23.00 ng/mL (IQR: 16.0-36.7 ng/mL), p=0.017; 3104 pg/mL (IQR: 2923–4825 pg/mL) vs 2276 pg/mL (IQR: 1294–3209 pg/mL), p=0.002; 0.43 ng/mL (IQR: 0.23–0.64) vs 0.15 ng/mL (IQR: 0.04–0.29 ng/mL), p=0.034, respectively]. The galectin-3, GDF-15, and P3TD levels were not significantly changed in patients without electrical remodeling [26.80 ng/mL (IQR: 23.9–31.5 ng/mL) vs 28.80 ng/mL (IQR: 23.0–34.8 ng/mL), p=0.211; 4221 pg/mL (IQR: 2709–4995 pg/mL) vs 3035 pg/mL (IQR: 2038–4872 pg/mL), p=0.143; and 0.34 ng/mL (IQR: 0.11–0.68 ng/mL) vs 0.21 ng/mL (IQR: 0.09–0.37 ng/mL), p=0.112, respectively].

Conclusion: The results from the small sample used in this study indicated that electrical reverse remodeling after CRT was associated with a decrease in cardiac fibrosis.

ÖZET

Amaç: Kardiyak resenkronizasyon tedavisi (KRT) kalp yetersizliğinde yapısal ve elektriksel ters yeniden şekillenmeyi uyarmaktadır. Ancak, KRT yerleştirilmiş hastalarda QRS'teki daralma ile kalp fibrozu belirteçleri arasındaki ilişki daha önce araştırılmamıştır.

Yöntemler: Semptomlu sistolik kalp yetersizliği bulunan ve KRT yerleştirilmiş 41 hasta çalışmaya alındı. Elektrokardiyografi bulguları ve kalp fibrozu belirteç seviyeleri (galektin-3, büyüme farklılaşma faktörü-15 [GDF-15] ve prokollajen III N-terminal propeptid [P3TD]) biventriküler pacing öncesinde ve on iki ay sonrasında toplandı. Ters elektriksel yeniden şekillenme intrinsik QRS süresinin ≥20 ms azalması olarak tanımlandı.

Bulgular: QRS süresi KRT öncesi 155 ms'den ([çeyrekler arası aralık / interquartile range – IQR] 142–178) 12 aylık KRT sonrası 142 ms'ye (IQR: 130–161) düşmüştür (p=0.001). Daha önce tanımlanan ölçütlere göre elektriksel yeniden şekillenme 16 (%39.0) hastada gözlenmiştir. Galectin-3, GDF-15 ve P3TD düzeyleri KRT sonrası elektriksel yeniden şekillenmesi olan hastalarda anlamlı düzeyde azalmıştır (sırasıyla, 27.65 ng/mL'ye karşı [IQR: 24.4–35.2 ng/mL] 23.00 ng/mL [IQR: 16.0–36.7 ng/mL]; p=0.017, 3104 pg/mL'ye karşı [2923–4825 pg/mL] 2276 pg/mL [1294–3209 pg/mL]; p=0.002 ve 0.43 ng/mL'ye karşı [IQR: 0.23–0.64] 0.15 ng/mL [IQR: 0.04–0.29 ng/mL]; p=0.034). Ancak elektriksel yeniden şekillenmesi olmayan hastalarda Galectin-3, GDF-15 ve P3TD düzeylerinde anlamlı azalma olmamıştır (sırasıyla, 26.80'e karşı [IQR: 23.9–31.5 ng/mL] 28.80 ng/mL [IQR: 23.0–34.8 ng/mL]; p=0.211, 4221 pg/mL'ye karşı [IQR: 2709–4995 pg/mL] 3035 pg/mL [IQR: 2038–4872 pg/mL], p=0.143 ve 0.34 ng/mL'ye karşı [IQR: 0.012–0.880] 0.21 ng/mL [IQR: 0.09–0.37 ng/mL]; p=0.112).

Sonuç: Bu küçük çaplı çalışmada, KRT sonrası elektriksel ters yeniden şekillenmenin kalp fibrozunda azalma ile ilişkili olduğunu gösterdik.

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Correspondence: Dr. Hamza Sunman. Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Ankara, Turkey.
Tel: +90 312 - 596 29 43 e-mail: hamzasunman@gmail.com

In a failing heart, prolonged ventricular conduction time is associated with heart failure progression and a poor outcome. QRS widening causes dyssynchronous ventricular contraction due to dispersion of ventricular depolarization, resulting in intra- and interventricular mechanical dyssynchrony. Cardiac resynchronization therapy (CRT) is a valuable treatment option for patients with severe heart failure and left ventricular conduction disturbances that reduces both morbidity and mortality.[1,2] CRT reduces the heterogeneity of ventricular contraction with biventricular stimulation and causes mechanical remodeling of the ventricles. In CRT, biventricular stimulation usually results in an immediate narrowing of the paced QRS-complex and a reduction in left ventricular chamber size, as well as improvement in ejection fraction. The extent of the QRS shortening induced by biventricular pacing seems to correlate with the structural remodeling. Despite optimal management of patients, nearly 30% do not respond to CRT. In this regard, evaluation of electrical remodeling in conjunction with structural remodeling may be useful for patient selection and follow-up. As paced QRS duration is imperfect in assessing the impact on underlying electrical remodeling induced by CRT, the alteration in intrinsic QRS (iQRS) duration is a useful index for the reversal of electrical remodeling.[3] Studies have demonstrated that a shortening of the iQRS duration was associated with better clinical and echocardiographic response.[4] However, investigations of the mechanism of intrinsic electrical remodeling are limited. The aim of the present study was to evaluate the association between cardiac fibrosis and electrical remodeling in patients with a CRT device.

METHODS

Study population

Appropriate patients with a QRS duration ≥120 milliseconds, a baseline New York Heart Association (NYHA) classification of II or III, and a left ventricular ejection fraction ≤35% on optimal medical therapy were prospectively enrolled. Clinical CRT responders were defined as patients alive with a NYHA class improvement ≥1 and no hospitalization for decompensation. Patients who were pacemaker-dependent, or who had less than 90% ventricular pacing, or who had a right ventricular pacing upgraded to CRT, and/or atrial fibrillation were excluded. Patients with use of anti-arrhythmic drugs other than beta-blockers, right bundle branch block, or an intraventricular conduction disturbance were also excluded. The investigation conformed with the principles outlined in the Declaration of Helsinki and was approved by the local institutional review board; informed consent was obtained from each patient.

Abbreviations:

CRT	*Cardiac resynchronization therapy*
ECG	*Electrocardiogram*
GDF-15	*Growth-differentiation factor-15*
iQRS	*Intrinsic QRS*
LBBB	*Left bundle branch block*
LV	*Left ventricle*
NYHA	*New York Heart Association*

Electrocardiogram evaluation

A baseline intrinsic electrocardiogram (ECG) was recorded at a paper speed of 25 mm/second and a caliber of 10 mm/mV before CRT and after 12 months of pacing. In order to record intrinsic ECGs after CRT implantation, the devices were reprogrammed to VVI 40. After 1 minute of native rhythm, a surface ECG was recorded, and then the previous device settings were restored. Reverse electrical remodeling was defined as a decrease in iQRS duration of ≥20 milliseconds after CRT implantation.[4] The delta iQRS duration value between ECGs recorded at the time of implantation and 1 year afterward was used for analysis. Two independent physicians checked all ECG results manually after magnification to 200%. Any disagreement was settled by mutual consent.

Device implantation

The left ventricular lead was implanted in the coronary sinus to achieve permanent epicardial stimulation as described previously.[5] A lateral or posterolateral site was chosen as the primary area if it was accessible, pacing thresholds were sufficient, and phrenic nerve stimulation was absent. The right ventricular lead was implanted in the apex in all patients, and the right atrium lead was implanted in the right atrial appendage. The CRT devices and leads used were manufactured by Medtronic, Inc. (Minneapolis, MN, USA) and Biotronik SE & Co. KG (Berlin, Germany). The pacing mode was set as DDD, which is programmed to maximize biventricular pacing. The coronary sinus lead position, pacing mode, and programming of timing intervals were evaluated at 1, 3, 6, and 12 months after pacemaker implantation.

Echocardiography

Serial echocardiography was performed both before and after CRT implantation to assess the degree of left ventricle (LV) reverse remodeling and change in cardiac function. LV end-diastolic volume, LV end-systolic volume, and ejection fraction were assessed using Simpson's equation. Patients were classified as echocardiographic CRT responders if they were alive and showed a ≥15% decrease in LV end-systolic volume (compared with baseline) at the 12-month follow-up visit.[6]

Laboratory analysis

Blood samples were obtained from the patients after 30 minutes of bed rest both before CRT implantation and at the 12-month follow-up visit and were stored at -80°C until analysis. The biomarkers assessed were galectin-3 (BMS279/2; Bender MedSystems, Vienna, Austria), growth differentiation factor-15 (GDF-15) (RD191135200R; Biovendor Research and Diagnostic Products, Brno, Czech Republic) and procollagen III N-terminal propeptide (P3TD) (E0573Hu; USCN Life Science Inc., Wuhan, China). All blood samples were processed according to manufacturer's instructions and spectrophotometrically read on a SpectraMax M2 reader (Molecular Devices, Inc., Silicon Valley, CA, USA).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20 (IBM Corp., Armonk, NY, USA). All variables were examined with regard to distributional properties using the Shapiro-Wilk test, visual inspection, and assessment of kurtosis and skew. Normally distributed continuous variables were analyzed using Student's t-test and expressed as mean±SD. Abnormally distributed continuous variables were analyzed using the Mann-Whitney U test and expressed as median (interquartile range [IQR]). Categorical variables were presented as percentages and analyzed using Fisher's exact test or a chi-square test (with continuity correction). Time-related changes in electro-echocardiographic parameters and biomarker levels were analyzed with general linear model-repeated measures and the Bonferroni test adjustment. Spearman correlation analysis was used to assess the correlations between the time-related changes (delta) in QRS duration and biomarker levels. Furthermore, a multivariable, repeated-measure, mixed-effect regression model was used to determine the significant independent predictors of delta QRS duration (electrical response). A p value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 41 patients (28 male; mean age: 61.00±11.89 years) who were referred to the center for CRT device implantation were enrolled. A biventricular ICD was implanted in all of the study patients. Reverse electrical remodeling according to the predefined criteria was detected in 16 (39.0%) patients, and the remaining 25 (61.0%) did not have electrical remodeling. There was no significant difference between the responders and non-responders in terms of age, gender, risk factors, or echocardiographic features. All patients had sinus rhythm and left bundle branch block (LBBB); 16 (39%) had ischemic cardiomyopathy and 25 (61.0%) had non-ischemic cardiomyopathy. Baseline characteristics of the study population are listed in Table 1.

Follow-up

During the follow-up period, 29 (70.7%) patients were echocardiographic responders and 12 (29.3%) were echocardiographic non-responders. There were 30 (73.2%) patients with clinical response and 12 (29.3%) who were clinical non-responders. The distribution of clinical, echocardiographic, and electrocardiographic responses is illustrated in Figure 1.

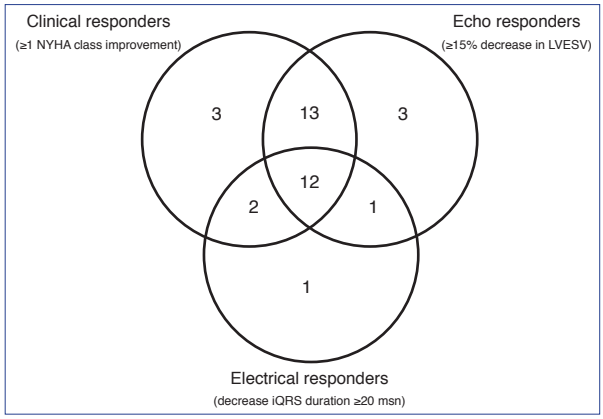

Figure 1. Distribution of clinical, echocardiographic, and electrocardiographic responders. Six patients were not clinical, electrical, or echocardiographic responders and are not included in this diagram.

iQRS: Intrinsic QRS; LVESV: Left ventricular end-systolic volume; NYHA: New York Heart Association.

Table 1. Baseline characteristics of the study participants

	All patients (n=41)	Electrical responders (n=16)	Electrical non-responders (n=25)	*p*
Age, years (mean±SD)	61.00±11.89	61.69±14.3	60.56±10.4	0.771
Gender (female), n (%)	13 (31.7)	4 (25.0)	9 (36.0)	0.693
Body mass index (kg/m^2)	27.32±2.9	26.25±2.8	28.01±2.8	0.055
Hypertension, n (%)	31 (75.6)	10 (62.5)	21 (84.0)	0.150
Diabetes mellitus, n (%)	8 (19.5)	3 (18.8)	5 (20.0)	>0.999
Heart failure etiology				0.252
Non-ischemic, n (%)	25 (61.0)	12 (75.0)	13 (52.0)	
Ischemic, n (%)	16 (39.0)	4 (25.0)	12 (48.0)	
Echocardiographic responders, n (%)	29 (70.7)	13 (81.2)	16 (64.0)	0.305
Clinical responders, n (%)	30 (73.2)	14 (87.5)	16 (64.0)	0.152
ACEi/ARB, n (%)	41 (100)	16 (100)	25 (100)	
Beta blocker, n (%)	41 (100)	16 (100)	25 (100)	
Loop diuretic, n (%)	37 (90.2)	15 (93.8)	22 (88.0)	>0.999
Spironolactone, n (%)	22 (53.0)	6 (37.5)	16 (64.0)	0.181
Digoxin, n (%)	28 (68.3)	12 (75.0)	16 (64.0)	0.693
Baseline QRS (ms)	155 (142–178)	173 (155–181)	146 (130–163)	0.002
Paced QRS (ms)	142 (130–161)	140 (128–150)	146 (130–168)	0.172
First-year intrinsic QRS (ms)	145 (134–162)	148 (130–160)	145 (138–165)	0.649
Delta QRS (ms)	3.0 (-1.5–20)	20.0 (20–23)	0.0 (-3.5–2.5)	<0.001

Data without normal distribution are presented as median (interquartile range). ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker.

Six patients did not respond clinically, electrically, or echocardiographically. Two of these 6 patients were hospitalized once as a result of decompensation. One patient was added to a heart transplant program; however, heart transplantation was not performed during the study period. During the follow-up period, no study patients underwent surgical or percutaneous revascularization. In all of the study patients, paced QRS duration just after CRT implantation was significantly shorter than QRS duration prior to CRT implantation [142 milliseconds (IQR: 130–161 milliseconds) vs. 155 milliseconds (IQR: 142–178 milliseconds); p=0.002]. The iQRS duration significantly decreased from 155 milliseconds (IQR: 142–178 milliseconds) to 145 milliseconds (IQR: 134–162 milliseconds) after 12 months of biventricular pacing (p=0.001). The paced QRS duration just after CRT implantation was significantly reduced in the group with electrical remodeling, but not in the group without [from 173 milliseconds (IQR: 155–181 milliseconds) to 140 milliseconds (IQR: 128–150 milliseconds); p<0.001 and from 146 milliseconds (IQR: 130–163 milliseconds) to 146 milliseconds (IQR: 130–168 milliseconds); p=0.372, respectively] (Table 1). The first year iQRS duration was significantly lower when compared with the baseline QRS duration [173 milliseconds (IQR: 155–181 milliseconds) to 148 milliseconds (IQR: 130–160 milliseconds); p=0.001] in patients with an electrical response. However, the baseline and first-year iQRS durations were not different [146 milliseconds (IQR: 130–163 milliseconds) to 145 milliseconds (IQR: 138–165 milliseconds); p=0.518] in patients without electrical response. The median delta iQRS was 20 milliseconds (IQR: 20–23 milliseconds) in the electrical responder group. The baseline and first-year iQRS duration was nearly the same in the electrical non-responder group. In addition, there was no significant change in the PR or QTc interval during the same follow-up period in patients with or without electrical remodeling. The LV end-diastolic volume and the LV end-systolic volume decreased from 170 mL (IQR: 145–260 mL) to 160 mL (IQR: 129–224

Table 2. Electrocardiogram, echocardiography, and laboratory findings before and after cardiac resynchronization therapy

	Electrical responders (n=16)				Electrical non-responders (n=25)				$p^{\dagger}$
	Baseline	Follow-up	Δ	p^{*}	Baseline	Follow-up	Δ	p^{*}	
Native PR (ms)	167 (150–189)	172 (160–180)	5 (0–8)	0.306	175 (150–200)	180 (166–204)	3 (0–11)	0.087	0.729
Native QRS (ms)	173 (155–181)	148 (130–160)	20 (20.0–23.7)	<0.001	146 (130–163)	145 (138–165)	0 (-3.5–2.5)	0.728	<0.001
Native QTc (ms)	450 (431–484)	445 (438–486)	2.5 (-1.5–15.7)	0.560	442 (405–455)	447 (427–463)	7.0 (-2.5–25.5)	0.084	0.552
End-diastolic volume (mL)	170.5 (125–280)	157.5 (114–227)	18.0 (2.2–35.2)	0.003	170.0 (151–260)	160.0 (131–224)	10 (4.0–32.5)	0.019	0.639
End-systolic volume (mL)	117.5 (87–191)	111.0 (72–146)	23.0 (11.0–33.3)	0.001	125.0 (113–191)	115.0 (87–166)	19.0 (7.5–27.0)	0.001	0.582
Ejection fraction (%)	28.31±5.88	34.88±9.5	6.5 (1.5–9.8)	0.004	26.32±4.2	32.12±7.3	6.0 (1.5–9.5)	<0.001	0.722
NYHA class	2.93±0.25	2.06±0.44	0.88±0.3	<0.001	2.92±0.28	2.36±0.7	0.6±0.4	<0.001	0.085
Galectin-3 (ng/mL)	27.65 (24.4–35.2)	23.00 (16.0–36.7)	2.1 (1.3–8.7)	0.030	26.80 (23.9–31.5)	28.80 (23.0–34.8)	1.5 (-0.2–1.8)	0.626	0.003
GDF-15 (pg/mL)	3104 (2923–4825)	2276 (1294–3209)	1402 (765–1918)	0.003	4221 (2709–4995)	3035 (2038–4872)	537 (-640–1383)	0.107	0.022
P3TD (ng/mL)	0.43 (0.23–0.64)	0.15 (0.04–0.29)	0.21 (0.09–0.56)	0.038	0.34 (0.11–0.68)	0.21 (0.09–0.37)	0.1 (-0.12–0.36)	0.492	0.029
BNP (pg/mL)	233.0 (99–769)	113.5 (62–272)	66 (-10–286)	0.156	289.0 (83–768)	201.0 (53–1004)	-1 (-245–171)	0.986	0.113

The data without normal distribution are presented as median (interquartile range). The data with normal distribution are presented as mean±SD. *Bonferroni adjusted p-values are for comparison of baseline and after 12 months of CRT treatment. †p-values are for comparison of changes between responders and non-responders. BNP: B-type natriuretic peptide; GDF-15: Growth differentiation factor-15; NYHA: New York Heart Association; P3TD: Procollagen III N-terminal propeptide.

mL) (p<0.001) and from 125 mL (IQR: 104–191 mL) to 115 mL (IQR: 81–158 mL) (p<0.001), respectively. The ejection fraction increased from 27.1±4.9% to 33.2±8.3% (p<0.001) after 12 months of biventricular pacing (Table 2). Resolution of LBBB was observed in 1 patient.

Laboratory analysis

Analysis of the electrical responders showed that at the 12-month follow-up visit, the level of galectin-3, GDF-15, and P3TD was significantly lower than at baseline. In the electrical non-responders, the level of these biomarkers did not change significantly at the 12-month follow-up. Detailed results are provided in Table 2. In echocardiographic responders, the level of galectin-3, GDF-15, and P3TD was significantly lower [26.90 ng/mL (IQR: 24.4–32.1 ng/mL) vs 24.00 ng/mL (IQR: 17.4–29.5 ng/mL), p=0.001; 3219.60 pg/mL (IQR: 2781.5–4875.5 pg/mL) vs 2326.00 pg/mL (IQR: 1809.8–3481.6 pg/mL), p=0.001; 0.42 ng/mL (IQR: 0.14–0.63 ng/mL) vs 0.13 ng/mL (IQR: 0.05–0.25 ng/mL), p=0.001, respectively). In echocardiographic non-responders, there was no significant change in galectin-3, GDF-15, or P3TD level [28.85 ng/mL (IQR: 23.2–34.1 ng/mL) vs 34.25 ng/mL (IQR: 30.3–38.4 ng/mL), p=0.059; 3487.95 pg/mL (IQR: 2993.9–5083.1 pg/mL) vs 4027.25 pg/mL (IQR: 2533.8–6229.4 pg/mL), p=0.986; 0.42 ng/mL (IQR: 0.11–0.84 ng/mL) vs 0.74 ng/mL (IQR: 0.21–0.83 ng/mL), p=0.905, respectively]. In order to further explore the relationships between electrical response and the investigated biomarkers, a detailed correlation analysis was performed. In the electrical responder group, the delta QRS duration correlated significantly with the delta galectin-3 level (rho=0.528; p=0.015), delta GDF-15 level (rho=0.478; p=0.021), and the delta P3TD level (rho=0.301; p=0.038). In addition, the delta QRS duration correlated significantly with the

delta end-diastolic volume (rho=0.403; p=0.024) and the delta end-systolic volume (rho=0.576; p=0.022). In the multivariable, repeated-measure, mixed-effect regression model, the delta galectin-3 level and the delta GDF-15 level were independent predictors of electrical response [beta±SE: 1.48±0.6, 95% confidence interval (CI): 0.159–2.811; p=0.031 and beta±SE: 0.41±0.2, 95% CI: 0.009–2.811; p=0.046, respectively].

DISCUSSION

The results of this study demonstrated that reverse electrical remodeling after CRT implantation was associated with decreased cardiac fibrosis. CRT emerged as an electrical therapy, and there has not been much investigation of any association between the reversal of underlying electrical dyssynchrony and cardiac fibrosis. To our knowledge, this is the first study to investigate cardiac fibrosis in patients with CRT implantation.

CRT is an effective treatment option in appropriately selected heart failure patients. The duration and waveform of the QRS complex are the most valuable predictors of CRT response. Wider QRS duration and LBBB morphology provide the appropriate background for resynchronization and are frequently associated with a favorable response to CRT.[7–9] In addition to the baseline QRS duration, several studies have indicated that QRS narrowing after initiation of biventricular pacing also predicted beneficial outcomes for CRT. Abbreviation in the QRS duration on biventricular pacing ECG was taken as a sign of rectification of electrical dyssynchrony produced directly by CRT and the amount of abbreviation in paced QRS duration has been positively associated with a therapeutic response to CRT.[10,11] There has also been increasing interest in the iQRS duration in recent years, as well as the baseline and paced QRS duration. There are various limitations to the evaluation of paced QRS duration. Namely, paced QRS is formed by the fusion of propagation originating from different ventricular pacing locations and represents the instant and direct effects of CRT. For these reasons, it has been suggested that the duration of paced QRS is not the best indicator of the underlying electrical remodeling. In contrast, alteration in the iQRS duration is far superior to paced QRS duration when assessing reversal of electrical dyssynchrony. Yang et al.[3] reported that native QRS narrowing was associated with a beneficial response and greater improvements in echocardiography. They concluded that abbreviation of the native QRS duration was an important sign for electrical remodeling imposed by CRT.

Several biomarkers are used to detect the underlying molecular pathophysiology of the disease condition. We evaluated cardiac fibrosis to investigate the underlying mechanism of electrical remodeling. P3TD is released during collagen biosynthesis and it is a useful marker of active myocardial collagen synthesis. A number of studies have demonstrated that a high level of circulating P3TD was predictive of death and hospitalization in heart failure patients.[12,13] Galectin-3 is involved in the mechanisms of fibrogenesis in a failing heart and is associated with extracellular matrix turnover. The level of galectin-3 also predicts long-term mortality in patients with heart failure.[14] As a stress-responsive cytokine, GDF-15 plays a pivotal role in the development and progression of cardiovascular diseases such as heart failure, coronary artery diseases and atrial fibrillation. It has been demonstrated that circulating GDF-15 was significantly correlated with the severity of myocardial fibrosis.[15,16] In the present study, we found that there was a significant decrease in fibrosis biomarker levels in the electrical responder group and no significant decrease in the electrical non-responder group. Although the exact mechanism of the narrowing of the native QRS duration is unclear, any abnormality in collagen metabolism may also be deleterious to cardiac function, as the resultant fibrotic changes can cause ventricular dysfunction and conduction abnormalities.[17] Conversely, mechanical remodeling with smaller chamber sizes may lead to a recovery of collagen metabolism, and result in an improvement in systolic functions and conduction properties.

One of the points to be noted is that electrical and echocardiographic remodeling may not always coexist. Patients without electrical remodeling on native ECG may exhibit improvements in echocardiography, and vice versa. Accordingly, 44.8% of responders and 25.0% of non-responders had native QRS narrowing post-CRT in our patient cohort. In addition, the B-type natriuretic peptide level did not significantly differ between the groups with and without electrical remodeling. This variation might be attributed to the differences in individual substrates, inhomogeneity

of electrical dyssynchrony, and dissociation between mechanical and electrical dyssynchrony.[18,19]

Limitations

The main limitation of our study is the small sample size, but this was the first study to evaluate cardiac fibrosis in electrical remodeling. Secondly, the current guidelines include a class I recommendation for CRT in patients with a QRS duration ≥150 milliseconds. Only two-thirds of the patients in the present study met this criterion. Thirdly, as blood samples were obtained at only 2 time points, i.e., upon entering the study and at the 12-month follow-up, it is possible that some information on the time course of these markers may have been missed. Finally, use of more rigorous methods than an enzyme-linked immunosorbent assay test will yield more accurate results.

Conclusion

Cardiac fibrosis markers decreased after 1 year of biventricular pacing in patients with electrical remodeling. These results suggest that improvement in cardiac fibrosis plays an important role in electrical remodeling in patients with CRT. The results of our study merit further research.

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REFERENCES

1. Pitzalis MV, Iacoviello M, Di Serio F, Romito R, Guida P, De Tommasi E, et al. Prognostic value of brain natriuretic peptide in the management of patients receiving cardiac resynchronization therapy. Eur J Heart Fail 2006;8:509–14. [CrossRef]
2. Karaahmet T, Tigen K, Mutlu B, Gürel E, Cevik C, Kahveci G, et al. Prognostic significance of left ventricular systolic dyssynchrony in patients with nonischemic dilated cardiomyopathy. Turk Kardiyol Dern Ars 2009;37:301–6.
3. Yang XW, Hua W, Wang J, Liu ZM, Ding LG, Chen KP, et al. Native QRS narrowing reflects electrical reversal and associates with anatomical reversal in cardiac resynchronization therapy. J Interv Card Electrophysiol 2014;41:161–8. [CrossRef]
4. Sebag FA, Martins RP, Defaye P, Hidden-Lucet F, Mabo P, Daubert JC, et al. Reverse electrical remodeling by cardiac resynchronization therapy: prevalence and clinical impact. J Cardiovasc Electrophysiol 2012;23:1219–27. [CrossRef]
5. Pitzalis MV, Iacoviello M, Romito R, Massari F, Rizzon B, Luzzi G, et al. Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. J Am Coll Cardiol 2002;40:1615–22. [CrossRef]
6. Karaca O, Omaygenc MO, Cakal B, Cakal SD, Gunes HM, Olgun E, et al. Adjusting the QRS Duration by Body Mass Index for Prediction of Response to Cardiac Resynchronization Therapy: Does One QRS Size Fit All? Ann Noninvasive Electrocardiol 2016;21:450–9. [CrossRef]
7. Gold MR, Thébault C, Linde C, Abraham WT, Gerritse B, Ghio S, et al. Effect of QRS duration and morphology on cardiac resynchronization therapy outcomes in mild heart failure: results from the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study. Circulation 2012;126:822–9. [CrossRef]
8. Stavrakis S, Lazzara R, Thadani U. The benefit of cardiac resynchronization therapy and QRS duration: a meta-analysis. J Cardiovasc Electrophysiol 2012;23:163–8. [CrossRef]
9. Birnie DH, Ha A, Higginson L, Sidhu K, Green M, Philippon F, et al. Impact of QRS morphology and duration on outcomes after cardiac resynchronization therapy: Results from the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT). Circ Heart Fail 2013;6:1190–8. [CrossRef]
10. Lecoq G, Leclercq C, Leray E, Crocq C, Alonso C, de Place C, et al. Clinical and electrocardiographic predictors of a positive response to cardiac resynchronization therapy in advanced heart failure. Eur Heart J 2005;26:1094–100. [CrossRef]
11. Rickard J, Cheng A, Spragg D, Cantillon D, Chung MK, Tang WH, et al. QRS narrowing is associated with reverse remodeling in patients with chronic right ventricular pacing upgraded to cardiac resynchronization therapy. Heart Rhythm 2013;10:55–60. [CrossRef]
12. Wang TJ, Larson MG, Benjamin EJ, Siwik DA, Safa R, Guo CY, et al. Clinical and echocardiographic correlates of plasma procollagen type III amino-terminal peptide levels in the community. Am Heart J 2007;154:291–7. [CrossRef]
13. Poulsen SH, Høst NB, Jensen SE, Egstrup K. Relationship between serum amino-terminal propeptide of type III procollagen and changes of left ventricular function after acute myocardial infarction. Circulation 2000;101:1527–32. [CrossRef]
14. Lok DJ, Lok SI, Bruggink-André de la Porte PW, Badings E, Lipsic E, van Wijngaarden J, et al. Galectin-3 is an independent marker for ventricular remodeling and mortality in patients with chronic heart failure. Clin Res Cardiol 2013;102:103–10. [CrossRef]

15. Lok SI, Winkens B, Goldschmeding R, van Geffen AJ, Nous FM, van Kuik J, et al. Circulating growth differentiation factor-15 correlates with myocardial fibrosis in patients with non-ischaemic dilated cardiomyopathy and decreases rapidly after left ventricular assist device support. Eur J Heart Fail 2012;14:1249–56. [CrossRef]
16. Adela R, Banerjee SK. GDF-15 as a Target and Biomarker for Diabetes and Cardiovascular Diseases: A Translational Prospective. J Diabetes Res 2015;2015:490842. [CrossRef]
17. Chalikias GK, Tziakas DN. Biomarkers of the extracellular matrix and of collagen fragments. Clin Chim Acta 2015;443:39–47. [CrossRef]
18. Yu CM, Chan YS, Zhang Q, Yip GW, Chan CK, Kum LC, et al. Benefits of cardiac resynchronization therapy for heart failure patients with narrow QRS complexes and coexisting systolic asynchrony by echocardiography. J Am Coll Cardiol 2006;48:2251–7. [CrossRef]
19. Varma N. Cardiac resynchronization therapy and the electrical substrate in heart failure: what does the QRS conceal? Heart Rhythm 2009;6:1059–62. [CrossRef]

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