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Association between electrical and mechanical remodeling after cardiac resynchronization therapy: systematic review and meta-analysis of observational studies

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Abstract

Cardiac resynchronization therapy (CRT) may improve not only impaired left ventricular contractility but can also induce reverse remodeling of native conduction system. Measurement of intrinsic QRS complex width during follow-up is the simplest method to assess reverse electrical remodeling (RER). We aimed to provide a literature review and meta-analysis on incidence and impact of RER and its association with mechanical remodeling. A systematic review and random-effect meta-analysis of studies reporting data on RER was performed. A total of 16 studies were included in this meta-analysis with 930 patients undergoing CRT (mean age 64.0 years, 64.1% males). The weighted mean incidence of RER was 42%. Reverse mechanical remodeling assessed by echocardiography was more frequently observed in patients with RER compared to patients without RER (75.7% vs. 46.6%; odds ratio [OR] 3.7, 95% confidence interval [CI] 2.24–6.09, $p<0.01$). Mechanical responders had a mean iQRS shortening of 7.7 ms, while mechanical non-responders experienced a mean widening of iQRS by 5.2 ms ($p<0.01$). Clinical improvement was more frequent in patients with RER vs. patients without RER (82.9% vs. 49.0%; OR 5.26; 95% CI 2.92–9.48; $p<0.01$). No significant difference in all-cause mortality between patients with and without RER was found. Mean difference between baseline intrinsic QRS and post-implantation paced QRS was significant in patients with later RER (21.2 ms, 95% CI 9.4–32.9, $p<0.01$), but not in patients without RER (6.6 ms, 95% CI -2.2–15.4, $p=0.14$). Gender, initial left bundle block morphology and heart failure etiology were found not to be predictive for RER. Our meta-analysis demonstrates that shortening of iQRS duration is a common finding during follow-up of patients undergoing CRT and is associated with mechanical reverse remodeling and clinical improvement. Clinical Trial Registration: Prospero Database-CRD42021253336.

Keywords Cardiac resynchronization therapy · Electrical remodeling · Mechanical remodeling · QRS duration, QRS shortening

Introduction

About one third of patients with heart failure have a prolonged QRS duration (> 120 ms), which is an independent risk factor for all-cause mortality [1]. It has been also shown that incremental increase in QRS duration is common in heart failure and also predicts worse outcome [2]. Cardiac resynchronization therapy (CRT) plays a key role in the treatment of patients with chronic heart failure and wide QRS complex [3, 4]. A large number of randomized controlled trials demonstrated beneficial effects on morbidity and mortality in heart failure patients, however about 30% of patients do not respond to CRT as assessed clinically or echocardiographically [5]. The main goal of CRT is the restoration of atrioventricular, interventricular and

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intraventricular synchrony of the dilated, asynchronously contracting heart. Reduction of left ventricular dimensions and improvement in left ventricular ejection fraction (LVEF) are the most frequently used measurable parameters of reverse mechanical remodeling in CRT recipients. In addition, CRT can also lead to reverse remodeling of the native conduction system (i.e., electrical remodeling), which can most simply be assessed by shortening of intrinsic QRS duration (iQRS) [6, 7]. There is limited evidence about the prevalence and clinical impact of this finding, mainly because changes in iQRS during CRT were not investigated in large randomized controlled trials.

We aimed to describe the incidence and extent of electrical response to CRT (i.e., shortening of iQRS) and its correlation with echocardiographic and clinical response by performing a systematic review and meta-analysis of published studies related to this topic.

Methods

Study selection

This meta-analysis was performed according to the Guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and was registered at Internal Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42021253336).

A systematic search in PubMed and Cochrane Library databases was performed without any limitations using the following key terms: "electrical remodeling" OR "electrical remodelling" OR "QRS duration" AND "cardiac resynchronization therapy." We evaluated the title and abstract of all records applying the following inclusion criteria to identify eligible studies for the meta-analysis:

1. prospective or retrospective observational studies (a) including patients with indication for CRT according to current guidelines and providing data on (b) incidence of reverse electrical remodeling (RER) defined as shortening of intrinsic QRS duration during follow-up or (c) studies providing data on any association between RER and mechanical and/or clinical response to CRT.
2. only full-text, English language, human studies, published in peer-reviewed journals were considered.

We excluded studies where RER was not measured by conventional 12-lead electrocardiogram and papers including patients with CRT upgrade. Regarding mechanical response we accepted various definitions of echocardiographic remodeling which are listed in Table 1. Studies were considered eligible irrespective of both baseline QRS morphology and heart failure etiology of the included patients.

Reference lists of selected manuscripts were manually checked for additional eligible publications. Two reviewers (D.P. and M.V.) conducted independently the systematic search and any disagreement was subsequently resolved by consensus. Data were extracted using a predefined form. Data extraction included information about publication details, baseline demographic and clinical parameters of patients, definition of electrical and mechanical response and proportion of patients in each group, detailed data on iQRS changes in different subgroups, duration of follow-up and mortality if available.

Endpoints of interest

The main outcome of the meta-analysis was the incidence and extent of RER and its association with mechanical response to CRT assessed by echocardiography. Furthermore, we investigated association of RER with clinical response and all-cause mortality. Conventional predictors of CRT-response such as female sex, left bundle branch block (LBBB) and non-ischaemic cardiomyopathy (NICMP) and theirs association with RER were also analyzed. Moreover, the impact of acute narrowing of paced QRS (defined as baseline iQRS-paced QRS) on later RER was investigated.

Statistical analysis

This meta-analysis was performed using a random effect model with the help of Review Manager (RevMan 5.4.1, Cochrane Collaboration, Nordic Cochrane Center, and Copenhagen, Denmark). Comprehensive Meta-Analysis (version 3, Biostat, Englewood, USA) software was used for assessment of publication bias. Categorical variables were pooled as an odds ratio (OR) with 95% confidence interval (CI). For the continuous variable, mean difference was calculated with corresponding 95% confidence intervals. All-cause mortality was calculated by pooled risk ratio (RR). The p-value < 0.05 (two tailed) was considered statistically significant. Study heterogeneity was evaluated by Cochrane's Q and I^2 index. In a minority of the studies, mean values and standard deviation of continuous variables were not available; in this case, they were replaced by values for median with interquartile range. Since there was significant heterogeneity in the design and patient characteristics of the included studies, it was assumed that the true effect size varies from one study to the other, and hence the random-effect model was applied. Methodological quality of studies was assessed using the methodological index for non-randomized studies (MINORS)[8]. Only one study contained a comparator

Table 1 Characteristics of the studies included in the meta-analysis

First author	Year	Country	Study type	Time of ECG follow-up (months ± SD)	QRS measuring method	Definition for echocardiographic response	Definition for clinical response	Definition for electrical response	Quality assessment (MINORS)
Henrikson	2007	USA	P	14	mean of 12 standard leads	increase in LVEF	NA	reduction in iQRS > 0 ms	low
Stockburger	2008	Germany	P	21 ± 14	50 mm/s, automated measurement	decrease in LVEDD	NA	reduction in iQRS > 0 ms	low
Tereschenko	2010	USA	P	13 ± 7	lead II	decrease in LVESV ≥ 15%	NA	reduction in iQRS ≥ 10 ms	moderate
Mischke	2011	Germany	P	6, 12	50 mm/s	relative increase in LVEF of > 25%	≥ 1 decrease in NYHA	NA	high
Sebag	2012	France	P	12	25 mm/s, widest complex	decrease in LVESV ≥ 15% and/or absolute increase in LVEF ≥ 10%	≥ 1 decrease in NYHA, no HF hospitalization	reduction in iQRS ≥ 20 ms	high
Yang	2014	China	R	13 (range 6–36)	25 mm/s, widest QRS, 200% magnitude	absolute increase in LVEF ≥ 10%	NA	reduction in iQRS > 0 ms	moderate
Diab*	2014	Egypt	P	15 ± 6	25 mm/s	decrease in LVESV ≥ 15% and/or absolute increase in LVEF ≥ 10% and ≥ 1 decrease in NYHA		reduction in iQRS ≥ 20 ms	moderate
Aslani	2015	Iran	P	at least 14	50 mm/s, widest QRS	decrease in LVESV ≥ 15% or increase in LVEF ≥ 10%	NA	reduction in iQRS > 0 ms	high
Zhang	2015	China	P	24	50 mm/s, lead II	decrease in LVEDD > 5 mm	NA	NA	high
Cvijic	2016	Slovenia	P	1 (3, 6, 9, 12)	25 mm/s, lead V2, 400% magnification	decrease in LVESV ≥ 15%	NA	reduction in iQRS ≥ 10 ms	high
Karaca	2016	Turkey	P	6	50 mm/s, widest QRS	decrease in LVESV ≥ 15%	≥ 1 decrease in NYHA	reduction in iQRS > 0 ms	moderate
Cheng	2017	Taiwan	P	> 6	25 mm/s, widest QRS	improvement in LVEF ≥ 25%	NA	reduction in iQRS ≥ 10 ms	high
Sunman	2018	Egypt	P	12	25 mm/s	decrease in LVESV ≥ 15%	≥ 1 decrease in NYHA and no HF hospitalization	reduction in iQRS ≥ 20 ms	high
Suszko	2019	Canada	P	6	25 mm/s, from earliest onset to latest offset	improvement in LVEF ≥ 5%	NA	NA	high
Kwon	2020	China	P	33 ± 18	25 mm/s	decrease in LVESV ≥ 15%	NA	NA	high
Li	2020	China	R	40 ± 25	25 mm/s, widest QRS	LVEF ≥ 50% (super-response)	NA	reduction in iQRS > 0 ms	moderate

P prospective; *R* retrospective; *LVEF* left ventricular ejection fraction; *LVEDD* left ventricular end-diastolic diameter; *LVESV* left ventricular end-systolic volume; *HF* heart failure; *NYHA* New York Heart Association class; iQRS: intrinsic QRS

*In the study of Diab et al. CRT-responders fulfilled both echocardiographic and clinical criteria group [9], all other studies were non-comparative. For these studies only items 1 to 8 of MINORS score (maximal point of 16) were applied. A study was defined as "high quality" if the MINORS score was ≥ 12 out of 16 or ≥ 18 out of 24, respectively (Supplementary Table 1). Publication bias was assessed using the funnel plot, the trim and fill method of Duval and Tweedie [10], and an adjusted rank correlation test according to Begg and Mazumdar [11].

Results

Studies included in the meta-analysis

Figure 1 shows the PRISMA flowchart on the literature search and study selection for the present meta-analysis. After completion of screening, a total of 16 studies fulfilling the aforementioned selection criteria were included. These studies included 930 heart failure patients (range of included patients per study 17–110, 64.1% male) who all underwent CRT. The weighted mean age was 64.0 ± 11.2 years. 35.7% of patients had ischaemic cardiomyopathy (ICMP), the baseline ECG showed LBBB morphology in 748 (80.4%) patients. Non-LBBB morphology at baseline was an exclusion criterion in eight studies. From the 16 included studies three studies provided data only on incidence of RER and these studies could not be included in the further meta-analytic calculations [9, 12, 13]. Up to two retrospective studies [13, 14], all other studies were prospective observational trials. The vaste majority of studies were single-center observations with the exception of one dual-center [13] and one multicenter study [7]. Tables 1–2 provide further details on each study included in the meta-analysis. Intrinsic QRS duration was measured by conventional 12-lead electrocardiogram before implantation and during follow-up by temporary inhibition of ventricular pacing. The mean timepoint of follow-up echocardiogram and ECG was between 6 and 15 months in most of the included studies.

Incidence and extent of reverse electrical remodeling

Incidence of RER was reported in 12 studies [6, 7, 9, 12–20]. Of note, there was no universal definition used for RER in these studies. A cut-off value for iQRS shortening of > 0 ms, ≥ 10 ms or ≥ 20 ms were applied in six, three and three studies, respectively (Table 1). Incidence of RER sorted by the used cut-off value of iQRS shortening is depicted in Fig. 2. The mean,

Fig. 1 Flowchart of the literature search and study selection

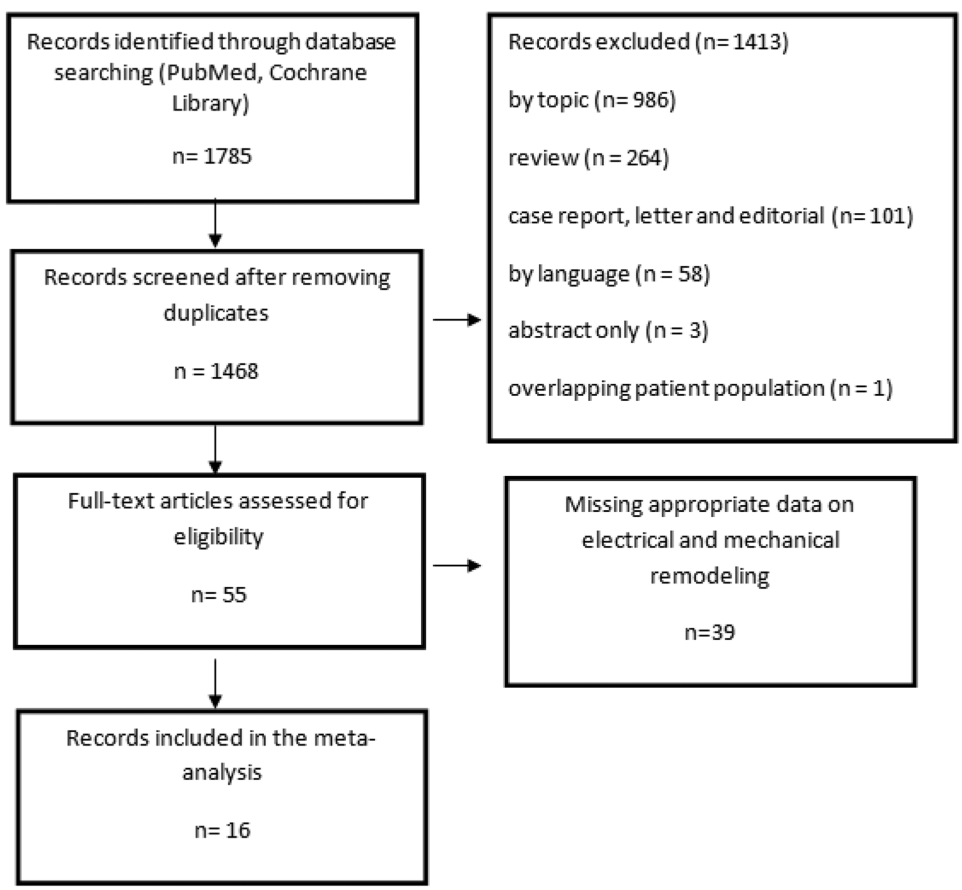

Table 2 Baseline patient characteristics and follow-up data of the studies included in the meta-analysis

First author	Number of patients	Mean age (years ± SD)	Males (%)	LBBB (%)	AF (%)	ICMP (%)	Mean LVEF (%)	Mean NYHA	Baseline iQRS (ms)	Paced QRS width (ms)	Echo responders (%)	Electrical responders (%)
Henrikson	25*	NA	16 (64)	16 (64)	0	8 (32)	19 ± 6	3 ± 0.5	155 ± 29	NA	10 (67)	10 (67)
Stockburger	21**	65 ± 9	17 (81)	21 (100)	NA	8 (38)	23 ± 7	NA	165 ± 22	NA	17 (81)	11 (52)
Tereschenko	69	66 ± 13	50 (72)	41 (59)	39 (57)	37 (54)	24 ± 9	3 ± 0	150 ± 26	166 ± 40	36 (46)	22 (32)
Mischke	38	66 ± 8	26 (68)	38 (100)	NA	18 (47)	26 ± 7	3.2 ± 0.4	175 ± 30	161 ± 25	22 (58)	NA
Sebag	85	65 ± 11	61 (72)	85 (100)	10 (12)	32 (38)	27 ± 8	2.9 ± 0.4	168 ± 20	NA	45 (53)	43 (51)
Yang	74	61 ± 9	48 (65)	35 (47)	0	17 (23)	26 ± 6	3.0 ± 0.7	163 ± 24	160 ± 18	47 (64)	30 (41)
Diab	30	55 ± 7	21 (70)	NA	0	15 (50)	29 ± 3	3.3 ± 0.4	146 ± 16	NA	23 (77)	16 (53)
Aslani	48	NA	NA	48 (100)	0	16 (34)	NA	NA	150 ± 14	NA	32 (66)	0
Zhang	80	59 ± 12	57 (71)	69 (86)	9 (11)	15 (19)	29 ± 3	2.8 ± 0.6	165 ± 27	135 ± 20	52 (65)	NA
Cvijic	62	66 ± 10	50 (81)	40 (65)	0	25 (40)	27 (24-31)	2.8 ± 0.4	185 (175-194)	169 ± 20	31 (50)	24 (39)
Karaca	110	66 (61-75)	70 (64)	94 (85)	30 (27)	47 (43)	27 ± 6	2.9 ± 0.6	161 ± 21	156 ± 25	71 (65)	48 (44)
Cheng	83	67 ± 12	54 (65)	83 (100)	12 (14)	32 (39)	22 ± 6	3.3 ± 0.5	175 ± 24	144 ± 22	49 (59)	38 (46)
Sunman	41	61 ± 12	28 (68)	41 (100)	0	16 (39)	27 ± 5	2.9 ± 0.3	155 (142-178)	142 (130-161)	29 (71)	16 (39)
Suszko	47	62 ± 14	30 (64)	41 (87)	8 (17)	16 (34)	23 ± 7	2.6 ± 0.6	173 ± 32	NA	28 (60)	NA
Kwon	100	66 ± 12	57 (57)	80 (80)	0	30 (30)	24 ± 6	NA	166 ± 36	134 ± 21	71 (71)	NA
Li	17	63 ± 11	11 (65)	16 (94)	0	0	33 ± 5	3.3 ± 0.5	175 ± 12	136 (17)	17 (100)	14 (82)

Mean LVEF and NYHA represent baseline pre-implantation values. Continuous variables are expressed as mean ± standard deviation (SD) or median and interquartile range

LBBB left bundle branch block; *AF* atrial fibrillation; *ICMP* ischemic cardiomyopathy; *LVEF* left ventricular ejection fraction; *NYHA* New York Heart Association classification

* Complete echocardiographic and ECG data only for 15 patients available

** Only patient characteristics of patients receiving CRT are given

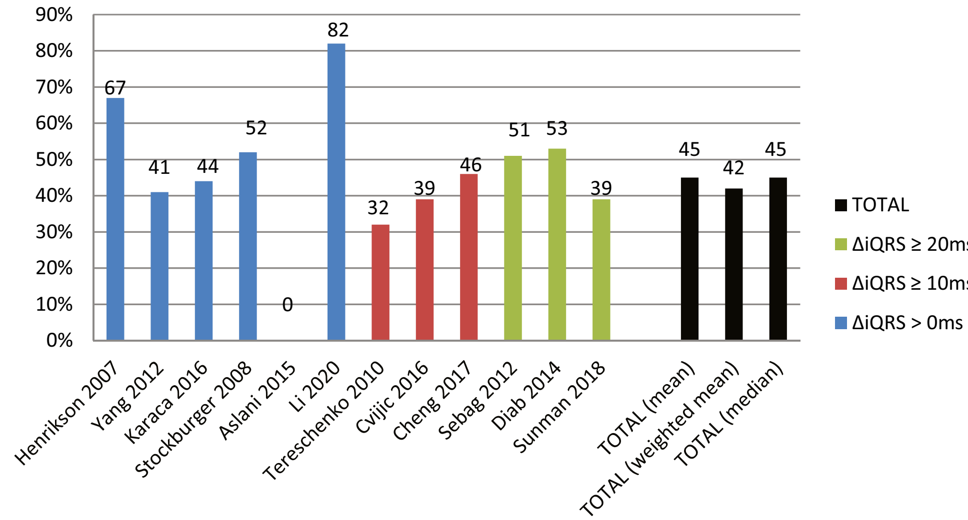

Fig. 2 Incidence of RER sorted by degree of iQRS shortening defined by each study. ΔiQRS = change in intrinsic QRS duration

weighted mean, and median overall incidence of RER in CRT recipients were 45%, 42%, and 45% (range 0–82%). The baseline QRS duration was similar in patients with and without RER (169 ± 25 ms vs. 166 ± 25 ms). Mean baseline and follow-up iQRS duration was reported in four studies including 294 participants. Patients with RER had a mean iQRS narrowing of 12.2 ms, whereas iQRS became broader by 4.6 ms in patients without RER ($p < 0.01$).

Association between electrical and mechanical response

Nine studies reported detailed echocardiographic data on mechanical response in patient groups with and without RER (Table 1) [6, 7, 14–20]. Mechanical response was more frequently observed in patients with RER (75.7%) compared to patients without RER (46.6%) and this difference was statistically significant (OR 3.7; 95% CI 2.24–6.09, $p < 0.01$, $I^2 = 37\%$, Fig. 3). A subgroup analysis including only studies with identical definition for mechanical response (i.e., ≥ 15% decrease in end-systolic volume) brought similar results (Supplementary Fig. 1). In addition, we compared extent of iQRS duration change in patients with mechanical response versus without mechanical response. Data were extracted from six studies with 356 participants, of whom 231 (64.9%) were defined as mechanical responders [14, 19, 21–24]. We found that while mechanical responders had a mean of iQRS shortening of 7.7 ms, mechanical non-responders experienced widening of iQRS by mean of 5.2 ms (Supplementary Fig. 2). Sensitivity analysis including studies only with high quality showed similar results (Supplementary Fig. 3).

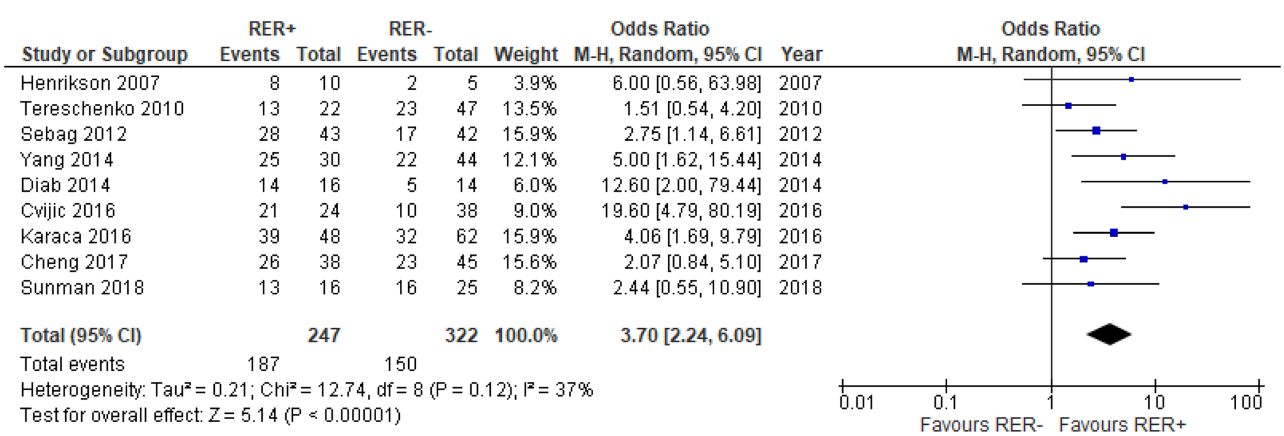

Fig. 3 Reverse electrical remodeling (RER) and mechanical response

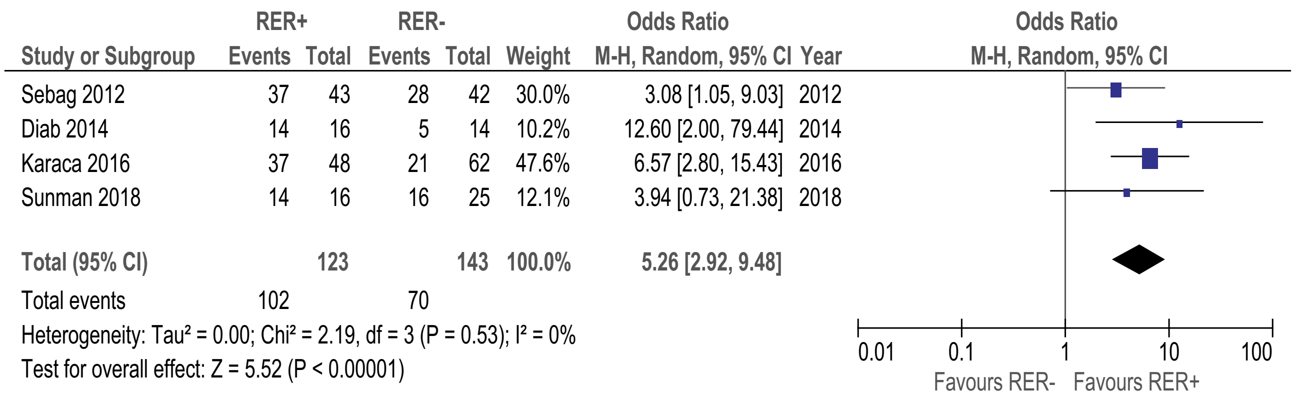

Fig. 4 Reverse electrical remodeling and clinical response

Clinical response and mortality

Regarding the clinical response we analyzed four studies (266 patients) [7, 17, 19, 20]. Clinical response was defined as ≥ 1 decrease in NYHA functional class and in two studies an additional criterion of absence of HF hospitalization was determined. The pooled analysis demonstrated that clinical improvement was more frequent in patients with RER vs. patients without RER (82.9% vs. 49.0%; OR 5.26; 95% CI 2.92–9.48; $p<0.001$; $I^2=0\%$, Fig. 4).

Regarding all-cause mortality we analyzed 5 studies including 409 participants [6, 7, 16–18]. In one study no death occurred during follow-up [7]. Three studies reported significantly reduced mortality in patients with RER [6, 16, 17], whereas one study [14] showed no association/neutral results. In a pooled analysis we found no significant difference in all-cause mortality between patients with and without RER (6.3 vs. 9.8%, RR 0.47; 95% CI 0.18–1.21; $p=0.12$; $I^2=38\%$, Fig. 5). Sensitivity analysis including only high-quality studies showed similar results for both clinical response and mortality (Supplementary Figs. 4–5).

Predictors of reverse electrical remodeling

Analysis of association between RER and gender, QRS morphology and heart failure etiology was applicable in seven ($n=225$), four ($n=124$), and seven ($n=221$) studies, respectively (Supplementary Figs. 6a-c). Proportion of RER was not significantly different between males and females (44.9% vs. 36.2%; OR 1.52; 95% CI 0.88–2.62; $p=0.08$; $I^2=46\%$) [6, 7, 14, 16–18, 20]. RER was more frequent if the baseline QRS showed LBBB morphology, but the difference was not significant (44.8% vs. 31.4%; OR 2.00; 95% CI 0.95–4.24; $p=0.07$; $I^2=49\%$) [6, 14, 16, 17]. Regarding heart failure etiology no significant association was found between underlying heart disease (ICMP vs. NICMP) and RER (OR 1.36; 95% CI 0.91–2.04; $p=0.13$; $I^2=14\%$) [6, 7, 14, 16–18, 20].

Appropriate data on acute narrowing of paced QRS (defined as baseline iQRS – post-implantation paced QRS) were reported in seven studies with overall 524 participants [6, 7, 14, 16–18, 20]. Patients who developed RER during follow-up exhibited significant acute narrowing of paced QRS by 21.2 ms (95% CI 9.4–32.9, $p<0.01$), while narrowing of paced QRS was not significant in patients without RER (6.6 ms, 95% CI -2.2–15.4, $p=0.14$, Fig. 6).

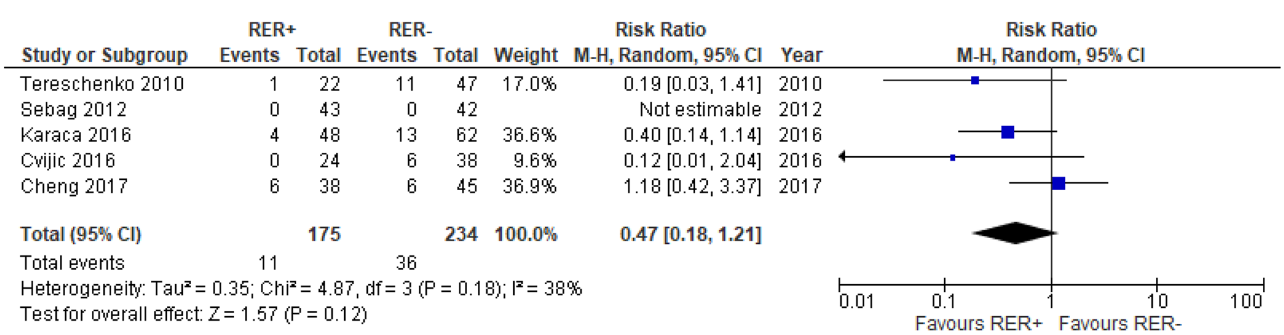

Fig. 5 Reverse electrical remodeling and all-cause mortality

Study or Subgroup	Intrinsic QRS Mean	Intrinsic QRS SD	Intrinsic QRS Total	Paced QRS Mean	Paced QRS SD	Paced QRS Total	Weight	Mean Difference IV, Random, 95% CI	Year
4.1.1 RER+									
Tereschenko 2010 RER+	147	24	22	158	35	22	5.9%	-11.00 [-28.73, 6.73]	2010
Sebag 2012 RER+	172	21	43	141	20	43	7.7%	31.00 [22.33, 39.67]	2012
Yang 2014 RER+	160	25	30	155	18	30	7.2%	5.00 [-6.02, 16.02]	2014
Karaca 2016 RER+	163	20	48	149	20	48	7.8%	14.00 [6.00, 22.00]	2016
Cvijic 2016 RER+	190	17	24	162	17	24	7.5%	28.00 [18.38, 37.62]	2016
Cheng 2017 RER+	180	27	38	136	22	38	7.2%	44.00 [32.93, 55.07]	2017
Sunman 2018 RER+	173	25	16	140	22	16	6.2%	33.00 [16.68, 49.32]	2018
Subtotal (95% CI)			**221**			**221**	**49.5%**	**21.16 [9.42, 32.90]**	
Heterogeneity: Tau² = 213.93; Chi² = 48.75, df = 6 (P < 0.00001); I² = 88%									
Test for overall effect: Z = 3.53 (P = 0.0004)									
4.1.2 RER-									
Tereschenko 2010 RER-	158	30	47	170	41	47	6.6%	-12.00 [-26.52, 2.52]	2010
Sebag 2012 RER-	164	18	42	141	22	42	7.7%	23.00 [14.40, 31.60]	2012
Yang 2014 RER-	168	23	44	163	18	44	7.7%	5.00 [-3.63, 13.63]	2014
Cvijic 2016 RER-	180	17	38	174	20	38	7.7%	6.00 [-2.35, 14.35]	2016
Karaca 2016 RER-	159	22	62	161	27	62	7.7%	-2.00 [-10.67, 6.67]	2016
Cheng 2017 RER-	171	20	45	152	20	45	7.7%	19.00 [10.74, 27.26]	2017
Sunman 2018 RER-	146	33	25	146	38	25	5.5%	0.00 [-19.73, 19.73]	2018
Subtotal (95% CI)			**303**			**303**	**50.5%**	**6.55 [-2.15, 15.24]**	
Heterogeneity: Tau² = 106.77; Chi² = 32.10, df = 6 (P < 0.0001); I² = 81 %									
Test for overall effect: Z = 1.48 (P = 0.14)									
Total (95% CI)			**524**			**524**	**100.0%**	**13.64 [5.76, 21.51]**	
Heterogeneity: Tau² = 191.27; Chi² = 106.72, df = 13 (P < 0.00001); I² = 88%									
Test for overall effect: Z = 3.39 (P = 0.0007)									
Test for subgroup differences: Chi² = 3.84, df = 1 (P = 0.05), I² = 74.0%									

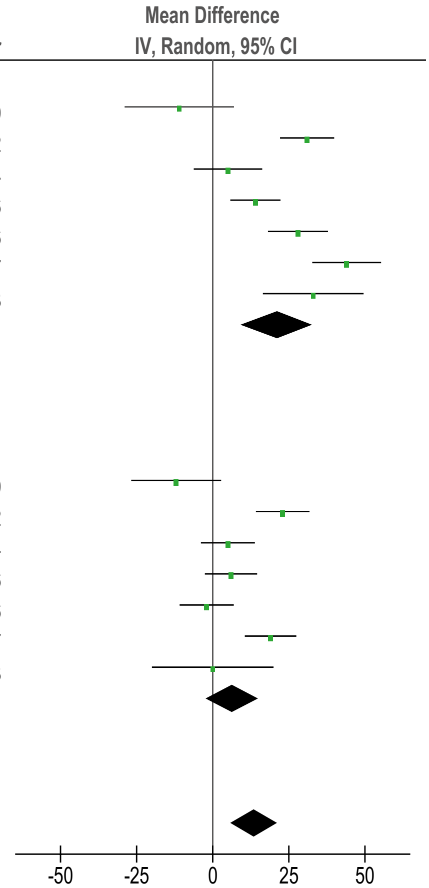

Fig. 6 Postimplantation narrowing of QRS width by pacing in patients with and without later RER

The mean difference in narrowing of paced QRS was also significant between the two groups ($p=0.05$). Similar results were found if only high-quality studies were included (Supplementary Fig. 7).

Publication bias

According to the rank correlation test of Begg and Mazumdar, there was no evidence of significant publication bias in any of the meta-analyses (association between electrical and mechanical response: $\tau=0.306$, $p=0.252$; clinical response: $\tau=0.167$ $p=0.734$; all-cause mortality: $\tau=-0.500$ $p=0.308$; gender: $\tau=0.476$, $p=0.133$; QRS morphology: $\tau=0{,}00$, $p=1.0$; HF etiology: $\tau=0.381$, $p=0.230$).

Furthermore, corresponding to the Duval and Tweedie's trim and fill input method, there was no evidence that publication bias would significantly impact on the overall effect sizes observed (Supplementary Figs. 8–13).

Discussion

Main findings

To the best of our knowledge, this is the first meta-analysis evaluating the incidence and association of reverse electrical remodeling with echocardiographic and clinical response in heart failure patients undergoing CRT. The incidence of RER in the included studies was 42%. Moreover, a significant association between RER and echocardiographic and clinical response rate to CRT was observed.

Prolonged QRS complex is an independent risk factor of mortality in heart failure patients [1]. QRS duration shows a progressive prolongation during progression of the disease in many patients, which also correlates with increased mortality [25]. The fact that in our analysis mechanical responders experienced a significant iQRS shortening while mechanical non-responders developed a widening of iQRS correlates with these findings. Shortening of iQRS could be therefore a prognostic marker; however, reverse remodeling of conduction system during chronic biventricular pacing has not been studied as intensively as echocardiographic response.

We found that RER could be detected in about 45% of patients, however a relatively large variance in incidence of RER between different studies was observed. This can be explained by the different definition of RER and the different inclusion criteria of the included studies (e.g., in the study of Li et al. only super-responders were included). Furthermore, there were differences in the utilized method of QRS measurement between the studies, which may also have influenced the proportion of patients with RER.

Mechanism of reverse electrical remodeling

The mechanism of RER in not entirely clear. The association of RER and mechanical response suggests that RER is caused by reduction of left ventricular volumes. On the other hand, improvement of the impaired intramyocardial impulse transmission and conduction velocity may also play a role [26]. Beside shortening of QRS duration, morphological changes of QRS complex may also occur during CRT, but these are not always apparent on 12-lead electrocardiogram. Major morphological changes in native QRS or complete resolution of LBBB after CRT are rarely observed and occurred only in few cases in the included studies [13, 26]. Although, minor morphological changes may occur, as described by Suszko et al. [23]. They assessed the number of leads with fragmented QRS before CRT and during follow-up with high resolution ECG and found that that reduction of leads with fragmented QRS was strongly associated with mechanical response.

Known predictors of CRT response and RER

Gender

Based on international registry data, only approximately one quarter of CRT recipients are women [27], but women obtain greater clinical and mortality benefit from CRT that men, as shown in multiple trials [28]. Several pivotal trials also indicated that women experience a greater degree of echocardiographic reverse remodeling than men [29, 30], some other studies found no difference [31, 32]. The present meta-analysis found no significant association between gender and occurrence of RER. A previous meta-analysis indicated that gender differences become apparent only during follow-up periods longer than one year [33]. This might explain different results thus mean follow-up period was between 6 and 13 months in included studies.

Baseline QRS morphology and duration

Baseline QRS morphology is a strong predictor of CRT response: while patients with LBBB have the highest chance to benefit from biventricular pacing, positive effects are markedly lower in right bundle branch block or intraventricular conduction delay [34]. Perrin et al. investigated changes of iQRS duration in different QRS morphologies during biventricular pacing. Shortening of iQRS was significantly more pronounced in complete LBBB than in case of residual left bundle conduction or non-specific intraventricular conduction delay and patients with complete LBBB had also a greater reduction in LVEF [35]. In the current meta-analysis, three of four studies showed a higher occurrence of RER in patients with baseline LBBB [14, 16, 17], but the meta-analytic calculation showed no significant difference ($p = 0.07$). Due to the limited number of studies further prospective data are needed to clarify this issue.

Duration of native QRS is also strongly associated with later response to CRT and therefore plays a crucial role in patient selection for CRT. The REVERSE trial demonstrated greater extent of mechanical remodeling and greater clinical benefit with increasing baseline QRS duration [36, 37]. In two studies including only patients with LBBB, patients with electrical response during follow-up had a significant broader baseline QRS duration that patients without RER [7, 20]. Other included studies of the meta-analysis showed no significant difference in baseline QRS duration between patients with and without RER. Further studies are needed to clarify association of baseline QRS duration with RER.

Heart failure etiology

There is a clear evidence that patients with NICMP benefit more likely from CRT [38]. Two studies showed that patients with NICMP develop greater reduction of iQRS than patients with ICMP [21, 39]. We found numerically higher occurrence of RER in patients with NICMP compared to patients suffering from heart failure of ischaemic etiology, however the difference was not significant, possibly due to low patient number.

Paced QRS duration

It has been shown that shorter paced QRS and greater acute reduction of paced QRS could be associated with later clinical and echocardiographic CRT response [40]. Our results complement these findings, since patients with later RER had a greater acute reduction of paced QRS duration. Reverse electrical remodeling can be also detectable in shortening of paced QRS duration during chronic CRT. Yang et al. assessed changes of paced QRS during long-time follow-up and found that narrowing of paced QRS was significant in responders after 6 month of biventricular pacing and super-responders (defined as LVEF ≥ 50%) had a further reduction of paced QRS duration measured at time of generator replacement [41].

Unanswered questions and further perspectives

There is very limited data about the time course of reverse electrical remodeling. *Cvijic* et al. found that shortening of iQRS precedes mechanical remodeling and can be detected already 1 month after implantation [16]. This suggests that RER may be an early marker of CRT-response.

Measurement of intracardiac conduction delays with help of quadripolar leads may be a novel and easy measurable method to assess RER [42]. Toner et al. found a greater reduction of intrinsic activation time (measured between right ventricular and left ventricular lead) in CRT-responders than in non-responders [43]. An ongoing trial should further clarify the correlation between changes in interelectrode conduction times, surface electrocardiogram, and echocardiographic response [44].

Finally, a recent, relatively small cohort study showed that about half of patients without CRT treated with sacubitril-valsartan experienced shortening of QRS complex duration which strongly correlated with the improvement in LVEF and reduction of left ventricular volume [45]. This observation suggests that medical treatment may play an important role in RER necessitating further prospective large cohort trials.

Limitations

The present meta-analysis shows all potential limitations of this kind of analysis. First, the patient number was low in most studies. Secondly, there may be a methodological bias, such as the difference in definition of RER (> 0 ms, ≥ 10 ms or ≥ 20 ms shortening of intrinsic QRS), the difference in definition of echocardiographic response, and minor differences in measuring the intrinsic QRS duration (Table 1). Thirdly, data included in this meta-analysis were collected from published papers, no individual patient data were accessed. Finally, RER could be measured only in patients who were not pacemaker-dependent, therefore the results cannot be applied to the entire CRT patient population.

Conclusions

Our systematic review and meta-analysis of currently available studies reports that reverse remodeling of the native conduction system measured by shortening of intrinsic QRS in patients undergoing CRT is associated with better echocardiographic and clinical response. Our results suggest that RER may be considered as part of the definition of response to CRT and may be used as a predictor for clinical outcomes. Measurement of iQRS by 12-lead electrocardiogram is a simple, time-saving and cost-effective method, but further prospective studies are needed to clarify the exact role of iQRS measurement in follow-up of patients undergoing CRT.

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Author contribution D.P. designed the study, performed data collection and statistical analysis and drafted the manuscript. M.V. participated on study conceptualization, data collection and statistical analysis, and revised the manuscript. G.Z.D, D.E., C.W.I and J.W.E. contributed to data interpretation and revised the manuscript for important intellectual content.

Data availability The manuscript includes supplementary tables and figures.

Declarations

Conflict of interest D.P. and D.E. have no conflict of interest. G. Z. D. reports consulting/lecture fees and/or nonfinancial support from Abbott, Biotronik, Daiichi Sankyo, Medtronic, MSD, Replant, Richter, Pfizer, and Sanofi. C. W. I. reports consulting/lecture fees and/or nonfinancial support from Abbott, Biotronik, Boston-Scientific, Medtronic, MicroPort/Sorin. J. W. E. reports receiving consultant fees, travel support and lecture fees from ZOLL Medical, travel grants from Bayer Vital, St. Jude Medical/Abbott, Novartis and lecture fees from Servier, Pfizer and Bayer and was a fellow of the Boston Scientific heart rhythm fellowship program. M.V. reports consulting fees and/or nonfinancial support from Biotronik, Medtronic, Minimal Invasive Technology Ltd. and Pfizer, outside the submitted work.

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