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Reduction in the QRS area after cardiac resynchronization therapy is associated with survival and echocardiographic response

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Abstract

Introduction: Recent studies have shown that the baseline QRS area is associated with the clinical response after cardiac resynchronization therapy (CRT). In this study, we investigated the association of QRS area reduction (ΔQRS area) after CRT with the outcome. We hypothesize that a larger ΔQRS area is associated with a better survival and echocardiographic response.

Methods and Results: Electrocardiograms (ECG) obtained before and 2–12 months after CRT from 1299 patients in a multi-center CRT-registry were analyzed. The QRS area was calculated from vectorcardiograms that were synthesized from 12-lead ECGs. The primary endpoint was a combination of all-cause mortality, heart transplantation, and left ventricular (LV) assist device implantation. The secondary endpoint was the echocardiographic response, defined as LV end-systolic volume reduction ≥ of 15%. Patients with ΔQRS area above the optimal cut-off value (62 μVs) had a lower risk of reaching the primary endpoint (hazard ratio: 0.43; confidence interval [CI] 0.33–0.56, $p < .001$), and a higher chance of echocardiographic response (odds ratio [OR] 3.3;CI 2.4–4.6, $p < .0001$). In multivariable analysis, ΔQRS area was independently associated with both endpoints. In patients with baseline QRS area ≥109 μVs, survival, and echocardiographic response were better when the ΔQRS area was ≥62 μVs ($p < .0001$). Logistic regression showed that in patients with baseline QRS area ≥109 μVs, ΔQRS area was the only significant predictor of survival (OR: 0.981; CI: 0.967–0.994, $p = .006$).

Conclusion: ΔQRS area is an independent determinant of CRT response, especially in patients with a large baseline QRS area. Failure to achieve a large QRS area reduction with CRT is associated with a poor clinical outcome.

KEYWORDS
cardiac resynchronization therapy, echocardiographic response, heart failure, QRS area, QRS area reduction, survival

1 | INTRODUCTION

Cardiac resynchronization therapy (CRT) has become the cornerstone of treatment in patients with heart failure that is associated with ventricular conduction abnormalities. Patients suitable for CRT are thought to be those with cardiomyopathy (CMP) and an electrical substrate. This electrical substrate is considered as the presence of delayed electrical activation of the left ventricular (LV) lateral wall, resulting in a discoordinate ventricular contraction with less effective systolic function, contributing to the development of heart failure.[1] This delayed LV lateral wall activation is more often present in patients with a wide QRS and left bundle branch block (LBBB) than in patients without LBBB, which arguably explains why heart failure patients with LBBB have better outcomes after CRT.[1,2]

In recent years, the QRS area from vectorcardiography (VCG) has emerged as a new and potentially better marker than QRS duration and QRS morphology in predicting outcome after CRT. Small studies have indicated that a large QRS area strongly correlates with delayed LV lateral wall activation, independent of QRS morphology,[2] and that it is inversely correlated with myocardial scar size.[3] In addition, the QRS area has been shown to have a strong association with clinical outcome and echocardiographic response.[4,5] These findings suggest that the QRS area reflects the CRT-treatable electrical substrate and that it could be used to select heart failure patients suitable for CRT.[2,4]

The present study investigates whether the reduction in QRS area (ΔQRS area) after CRT, presumably indicating correction of the electrical substrate, is associated with a better long-term response to CRT. It was the aim of the present study to investigate whether QRS area reduction after CRT is associated with CRT outcome and to investigate whether it is independent of baseline QRS area. The study was performed in a large cohort, using both clinical and echocardiographic endpoints.

2 | METHODS

We conducted a retrospective analysis on the Maastricht–Utrecht–Groningen (MUG) registry.[4] The MUG-registry consists of all patients from three university hospitals in the Netherlands, implanted with a CRT-device between January 2001 and January 2015. No formal inclusion or exclusion criteria existed for this registry.

2.1 | Patient population

Patients were eligible for the current analysis when they underwent a de novo CRT-device implantation, and a 12-lead ECG at baseline, and a paced 12-lead ECG between 2 and 12 months (median: 3 months, 25–75 percentile: 2–5 months) after implantation were available. Selection of patients, implantation of the device, and follow-up of device and patient were all according to local protocols prevailing at the time of enrollment.

Local hospital patient information systems were used for baseline data collection. From patients' history and referral letters, information was collected on heart failure etiology, comorbidities, and medication. The etiology of heart failure was classified as ischemic when evidence of myocardial infarction, coronary artery disease presumably explaining cardiomyopathy, or CABG was present in the medical history. At the time of this study, the Dutch Central Committee on Human-related Research (CCMO) allowed the use of anonymous data without prior approval of an Institutional Review Board provided that the data was acquired for routine patient care. All data used were handled anonymously. All study procedures were performed in compliance with the Declaration of Helsinki.

2.2 | Study endpoints

The primary endpoint was a combination of all-cause mortality, heart transplantation (HTx), and left ventricular assist device (LVAD) implantation. Data were obtained from hospital records linked to municipal registries for mortality data.

Secondary endpoints were the relative left ventricular end-systolic volume (LVESV) reduction and echocardiographic response defined as LVESV reduction ≥15% after 6–12 months. Left ventricular ejection fraction (LVEF) and dimensions were calculated using Simpson's modified biplane method.

2.3 | Electrocardiographic data

ECGs from both baseline and after CRT-device implantation were digitally stored (MUSE Cardiology, GE Medical System) for QRS area calculation, as well as QRS duration and morphology analysis. The conversion from ECG to VCG was automated, but the start and end of the QRS complex were indicated manually using the superimposed

X, *Y*, and *Z*-leads of the VCG. QRS morphology was defined based on ESC criteria.[1] For the QRS area calculation, the 12-lead ECG signals were extracted from the digitally stored PDF files and subsequently converted into the three orthogonal VCG (*X*-, *Y*-, and *Z*-) leads using the Kors conversion matrix in the custom made Matlab software (MathWorks Inc.) QRS area was calculated as $(X_{area}^2 + Y_{area}^2 + Z_{area}^2)^{½}$ (Figure 1).[6]

Changes in QRS area (ΔQRS area) and change in QRS duration (ΔQRS duration) were calculated. ΔQRS area and ΔQRS duration were defined as their respective changes from baseline, that is BiV-paced values were subtracted from their baseline values. This means that a positive value represents a *reduction* in QRS area and duration (Figure 1).

2.4 | Statistical analysis

Statistical analysis was carried out using the IBM SPSS package, version 26 (SPSS Inc.) Continuous and categorical variables are reported as mean ± *SD* and counts (percentages), respectively. Continuous variables were compared using independent *t*-test analysis. Dichotomous variables were analyzed using Pearson's χ^2 test. An analysis of the whole study population was made on the relation of baseline and ΔQRS area and QRS duration with the primary and secondary endpoints. The total study cohort was divided into two groups based on an optimal cut-off point of ΔQRS area and ΔQRS duration, achieving the highest sensitivity and specificity for prediction of the primary endpoint, using the Youden index. Subsequently, the study cohort was divided into three groups, based on the combination of the cut-off point for ΔQRS area, and median baseline QRS area used previously.[4] Similarly, the cohort was divided using a cutoff of 150 ms for baseline QRS duration and the optimal cut-off point for ΔQRS duration.

Kaplan–Meier survival analyses were used to evaluate the different groups in relation to the primary endpoint. A Log-rank test was performed to determine the significance of survival differences between the groups. Cox and logistic regression analyses were performed to analyze the uni- and multivariable-adjusted effect of group characteristics on primary and secondary outcomes, respectively. Hazard ratios (HR) and odds ratios (OR) were reported for primary and secondary endpoints, respectively. Multivariable regression analyses included VCG, ECG, and clinical variables known to affect outcomes after CRT. Eventually, a multivariable prediction model with QRS area, ΔQRS area, and the interaction term of both variables, was investigated in relation to survival within the entire cohort and in the groups with baseline QRS area ≥109 and <109 μVs. Statistical significance was considered when the two-sided *p* value was <.05.

3 | RESULTS

3.1 | Baseline characteristics

The total MUG cohort consists of 1946 patients. For this study, 340 patients (17%) with right ventricular (RV)-pacing and 114 patients (6%) with a narrow QRS (<120 ms) were excluded. Another 193 patients (10%) who did not have an ECG available between 2 months and 1 year after implantation were excluded (Figure 2).

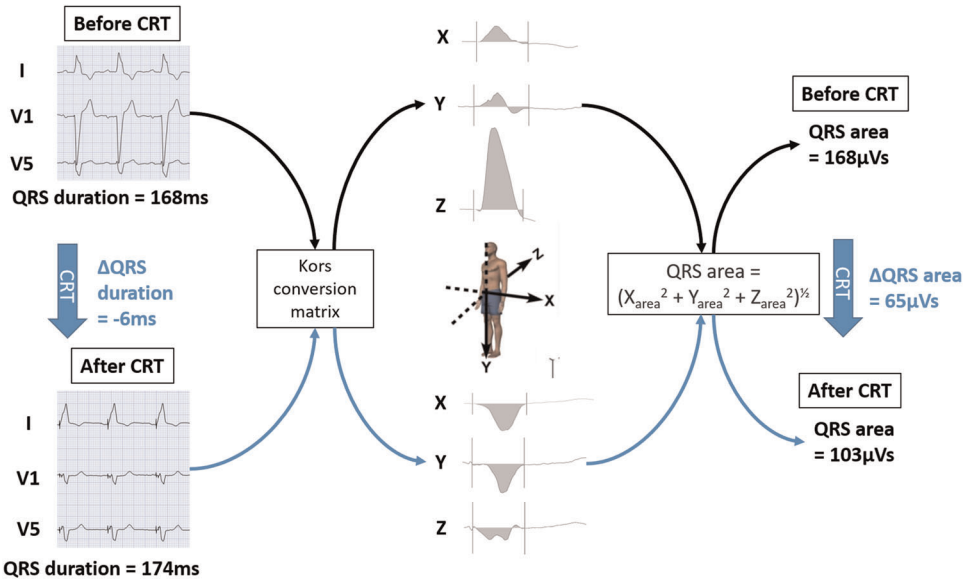

FIGURE 1 Transformation of ECG to vectorcardiograph (VCG) and calculation of ΔQRS area. 12-lead ECGs are mathematically converted into VCGs with the three orthogonal X, Y, and Z leads using the Kors matrix. The *X*-, *Y*-, and *Z* leads of a patient before and during CRT are shown. QRS area is then calculated from these three orthogonal leads using the formula presented. Note that in this patient (who was a responder) QRS area decreased considerably whereas the QRS duration slightly increased. CRT, cardiac resynchronization therapy; ECG, electrocardiogram

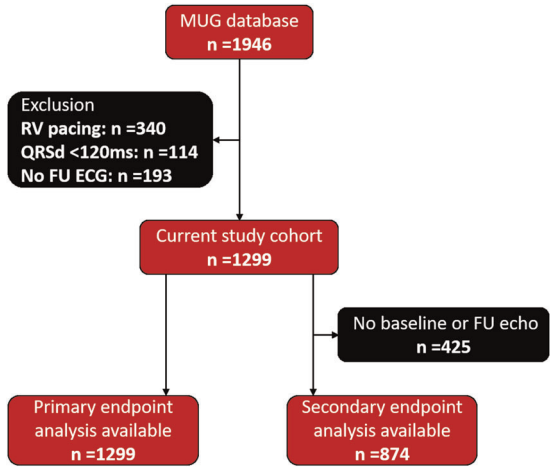

FIGURE 2 Flowchart of the study population. A total number of patients in MUG-database, excluded patients, and availability for primary- and secondary-endpoint analyses are shown. FU, follow-up; HTx, heart transplantation; LVAD, left ventricular assist device; LVESV, left ventricular end-systolic volume; MUG, Maastricht Utrecht Groningen; RV, right ventricular

This cohort ($n = 1299$) represents a general CRT population (Table 1) with an age of 67 ± 11 years, 71% male, 50% had an ischemic etiology, and 15% had atrial fibrillation. Patients were predominantly in New York Heart Association functional Class II and III (93%). The baseline QRS area was 118 ± 54 μVs and QRS duration was 161 ± 21 ms. An LBBB QRS morphology was present in 78%.

3.2 | Lead location

The final LV-lead position was inferolateral in 571 patients, lateral in 435 patients, anterolateral in 122 patients, inferior in 106 patients, and anterior in 8 patients. The QRS area reductions were 30 ± 53 μVs, 46 ± 50 μVs, 46 ± 55 μVs, 19 ± 54 μVs, and 14 ± 85 μVs, respectively (Supporting Information Appendix). A one-way analysis of variance (ANOVA) showed that a final lateral and anterolateral LV-lead location achieved a significantly higher reduction in QRS area compared to a final inferolateral and inferior LV-lead position ($p < .0001$, Supporting Information Appendix).

3.3 | Primary endpoint

The follow-up of the patients in this study cohort was 3.9 ± 2.4 years. Information on the primary endpoint was available in all 1299 patients. A total of 408 patients (31%) reached the primary endpoint.

CRT reduced the QRS area by 35 ± 53 μVs. The reduction in QRS area was significantly smaller in patients who reached the primary endpoint as compared to those who did not (24 ± 51 μVs vs. 41 ± 53 μVs, $p < .001$).

The highest sensitivity and specificity for predicting the primary endpoint was at a cut-off value of the reduction in QRS area of 62μVs. When patients were divided into those with ΔQRS area above and below 62 μVs, the primary endpoint was reached significantly less frequently in patients with large (≥62 μVs) versus small (<62 μVs) ΔQRS area (18% vs. 37%, respectively, $p < .001$). The Kaplan–Meier survival curves show a significantly better outcome in patients with a ΔQRS area ≥62 μVs (log-rank < 0.0001, Figure 3), with a relative risk reduction of 57% (HR: 0.43; CI: 0.33–0.56, $p < .0001$).

A significantly larger percentage of patients with ΔQRS area ≥62 μVs were females and had LBBB, while a significantly lower percentage had atrial fibrillation, ischemic cardiomyopathy, and diabetes mellitus (Table 1). Furthermore, patients with ΔQRS area ≥62 μVs had a higher average baseline QRS area and QRS duration.

3.4 | Secondary endpoint

Echocardiographic data for the secondary endpoint analyses were available in 878 patients (Figure 1). In this cohort, CRT reduced LVESV by 19 ± 31%, and 492 patients (56%) were echocardiographic responders.

Patients with ΔQRS area ≥62 μVs had a significantly larger reduction in LVESV as compared to patients with ΔQRS area <62 μVs (33 ± 30% vs. 13 ± 30%, respectively; $p < .0001$). Consequently, patients with ΔQRS area ≥62 μVs were more often echocardiographic responders than patients with ΔQRS area <62 μVs (75% vs. 48%, respectively; OR: 3.3; CI: 2.4–4.6, $p < .0001$).

3.5 | Uni- and multivariable analysis in relation to the primary and secondary endpoint

Univariable regression analysis showed that baseline QRS area and ΔQRS area (≥109 μVs and ≥62 μVs, respectively), as well as baseline QRS duration and ΔQRS duration (≥150 and −11 ms, respectively) as factors significantly associated with primary and secondary outcomes, as were sex, QRS morphology, heart failure etiology, and atrial fibrillation (Table 2). Multivariable regression analysis showed that only ΔQRS area, baseline QRS area, and sex were independently associated with the primary and secondary endpoints (Table 2). ΔQRS area ≥62 μVs had the strongest association with the primary endpoint (HR: 0.61; CI: 0.44–0.86, $p = .004$), as well as with the secondary endpoint (OR: 1.8; CI: 1.2–2.6, $p = .005$; Table 2).

Additionally, a multiple logistic regression analysis on the entire cohort showed that ΔQRS area, corrected for baseline QRS area, was independently associated with survival (OR: 0.993; CI: 0.987–0.999, $p = .016$). In the group with baseline QRS area ≥109 μVs, ΔQRS area remained significantly associated with survival (OR: 0.981; CI: 0.967–0.994; $p = .006$) (Table 3).

TABLE 1 Baseline characteristics and *p* values for statistical difference between different ΔQRS area groups

	All patients (*n* = 1299)	ΔQRS area ≥62μVs (*n* = 365)	ΔQRS area < 62 μVs (*n* = 915)	*p*-value high vs. low ΔQRS area
Mean age (years)	67 ± 11	65 ± 11	67 ± 11	**.002**
Women (%)	29	35	27	**.01**
Ischemic CMP (%)	50	34	57	**<.001**
Atrial fibrillation (%)	15	7	16	**<.001**
BMI (kg/m^2)	27.0 ± 5	26.6 ± 5	27.3 ± 5	**.02**
Diabetes Mellitus (%)	24	22	26	**.004**
Hypertension (%)	43	40	44	.21
LVEF (%)	25 ± 9	25 ± 9	25 ± 9	.85
LVEDV (ml)	217 ± 88	219 ± 85	217 ± 88	.79
LVESV (ml)	167 ± 78	169 ± 78	165 ± 77	.45
NYHA I (%)	2	4	1	**.002**
NYHA II (%)	39	41	38	
NYHA III (%)	54	50	56	
NYHA IV %	5	5	5	
NT proBNP (pmol/L)	316 ± 526	310 ± 642	318 ± 481	.87
MDRD ml/min)	71 ± 32	76 ± 34	70 ± 32	**.003**
Beta-blocker (%)	82	84	82	.40
ACEi/ARB (%)	90	90	90	.95
MRA (%)	45	41	47	.10
CRT-D (%)	94	93	94	.50
QRS duration (ms)	161 ± 21	170 ± 18	157 ± 20	**<.001**
QRS area (μVs)	117 ± 52	170 ± 42	96 ± 40	**<.001**
LBBB morphology[a](%)	78	92	73	**<.001**

Note: p value was calculated using χ^2 test. Bold values represent a statistical significant result, i.e. a *p*-value below the alfa of .05.

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CMP, cardiomyopathy; CRT-D, cardiac resynchronization therapy with defibrillation function; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MDRD, modification of diet in renal disease; MRA, mineral corticoid receptor antagonist; NT proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association.

[a]According to ESC guidelines.

3.6 | Combination of baseline QRS area and ΔQRS area

Based on the combination of baseline QRS area (≥ and <109 μVs) and ΔQRS area (≥ and <62 μVs) the patients were divided into four groups. Only 12 patients showed the combination of baseline QRS area <109 μVs and ΔQRS area ≥62 μVs and were merged with the other baseline QRS area <109 μVs groups. This resulted in three groups: Group 1 with baseline QRS area ≥109 μVs and ΔQRS area ≥62 μVs, Group 2 with baseline ≥109 μVs and ΔQRS area <62 μVs, and group 3 including all patients with baseline QRS area <109 μVs (Table 4).

Primary endpoint analysis showed a significant difference between the three groups (log-rank < 0.0001, Figure 4A). There was a 41% lower incidence of the primary endpoint in Group 1 compared to Group 2, and a 37% lower incidence of the primary endpoint in Group 2 compared to Group 3.

Relative reductions of LVESV for Group 1, 2, and 3 were 33 ± 30%, 20 ± 33%, and 10 ± 27%, respectively (Figure 4B). The percentages of echocardiographic responders in Group 1, 2, and 3 were 77%, 60%, and 41%, respectively (Figure 4B). The differences between the groups were all statistically significant ($p < .0001$).

There was no significant difference in baseline characteristics between Group 1 and 2, except for the baseline QRS area, while in

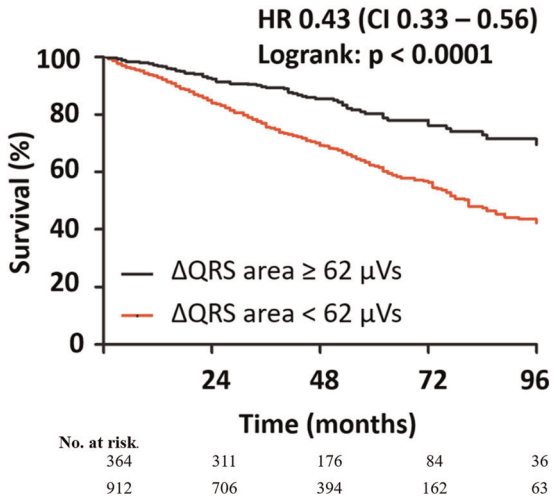

FIGURE 3 Kaplan–Meier survival curves and hazard-ratio for ΔQRS area ≥ and <62 μVs. CI, confidence interval; HR, hazard ratio; Survival, survival free from the primary endpoint

Group 3 there was a significantly lower percentage of women and of patients with LBBB, and a higher percentage of patients with ischemic CMP and atrial fibrillation (Table 4).

4 | DISCUSSION

In this large retrospective cohort study, the change in the QRS area after CRT was found to be independently associated with both the primary clinical and secondary echocardiographic outcomes. A larger ΔQRS area, with an optimal cut off at 62 μVs is associated with significantly better outcomes in CRT treated patients. Moreover, this association seems to be of added value to the baseline QRS area.

4.1 | Value of assessing the degree of resynchronization to predict CRT response

Recent evidence strongly suggests that baseline QRS area is a stronger predictor for CRT response than baseline QRS morphology or QRS duration.[4,7,8] The current findings that the ΔQRS area is independently associated with all-cause mortality and echocardiographic response after CRT strongly supports our hypothesis that the change in the QRS area reflects modification of the electrical substrate. The independent association of a large ΔQRS area next to a large baseline QRS area suggests that the level of resynchronization that is achieved influences outcomes in these patients. Thus, aiming at a larger reduction in QRS area after CRT may additionally benefit patients.

As mentioned above, the ΔQRS area seems to determine outcome independent from the baseline QRS area. This could be interpreted as electrical substrate modification by CRT being an independent factor from electrical substrate presence. The finding of electrical substrate modification being an independent factor aids the previous findings that LV-paced conduction times by CRT are unrelated to baseline QRS morphology and that a poor correlation exists between intrinsic activation delay (qLV) and LV-paced conduction time.[9] Also, another study reported that ΔQRS area was associated with event-free survival independently from QRS morphology.[10] As for ΔQRS area's value in relation to endpoints, the findings of the present analysis are in agreement with a study that showed a correlation of acute hemodynamic CRT-benefit with QRS area decrease.[11] Furthermore, Okafor et al. found that the combination of the change in QRS duration and QRS area was significantly associated with long-term cardiac- and total mortality, major adverse cardiac events, and ventricular arrhythmias.[7] However, in contrast to our findings, their multivariable analysis did not show an independent association of ΔQRS area with outcomes, but this discrepancy may be explained by the difference in cohort size (380 vs. 1299) and the inclusion of patients with an upgrade from RV pacing in the Okafor study.

4.2 | Comparison of change in the QRS area versus changes in QRS duration and QRS morphology

This study is the first to show that ΔQRS area is better associated with CRT-benefit than ΔQRS duration. Interestingly, baseline QRS duration and ΔQRS duration were not independently associated with both the primary and secondary endpoints. Previous studies showed mixed results in this respect, with a substudy of the PROSPECT trial showing association of QRS duration reduction with the combined endpoint of echocardiographic response and clinical improvement,[12] while in the REVERSE trial, such an association was not observed.[13]

These inconsistent results regarding QRS duration may be caused by differences in patient populations and choice of the cut-off value for ΔQRS duration, but also variability in measurement of QRS duration in BiV-paced ECGs may play a role. A study by de Pooter et al. showed that in paced QRS complexes inter and intra-observer variability of QRS duration nominal values amounted to around 20 ms and that the technique used for measurement of QRS duration even influences the association with CRT-response.[14,15] In contrast, variability in the QRS area was less than half of that of QRS duration.[14] Besides its more robust measurement, the advantage of ΔQRS area is that it combines elements of QRS duration and morphology into one objective measurement. The importance of changes in QRS morphology has, for example, been demonstrated by Sweeney et al. in a multivariable prediction model, in which biventricular QRS fusion patterns and a decrease in QRS duration ≥25 ms were associated with echocardiographic CRT-response.[16]

4.3 | Clinical implications

The results from the present study show that a larger benefit from resynchronization may be obtained when there is a larger reduction

TABLE 2 Uni- and multivariable regression analyses for VCG-, ECG-, and clinical parameters in relation to primary outcomes (mortality/LVAD/Htx) and secondary outcomes (echocardiographic response)

	Univariable regression		Mulitvariable regression	
All-cause mortality, heart transplantation, LVAD				
Variable	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**
BL QRS area ≥ 109 μVs	**<.001**	0.49 (0.40–0.60)	**.024**	0.72 (0.55–0.96)
BL QRS duration > 150 ms	**.003**	0.73 (0.60–0.90)	.30	1.1 (0.89–1.49)
ΔQRS area ≥ 62 μVs	**<.001**	0.43 (0.33–0.56)	**.004**	0.61 (0.44–.86)
ΔQRS duration ≥ −11 ms	**<.001**	0.51 (0.41–0.65)	**.006**	0.67 (0.50–0.89)
Age	**<.001**	1.02 (1.01–1.03)	.08	0.99 (0.98–1.00)
Male sex	**<.001**	1.7 (1.3–.1)	**<.001**	1.6 (1.2–2.1)
LBBB*	**<.001**	0.60 (0.48–0.73)	.05	0.78 (0.61–1.00)
Atrial fibrillation	**<.001**	1.6 (1.2–2.1)	.62	1.08 (0.80–1.45)
iCMP	**<.001**	1.5 (1.3–1.9)	.53	0.93 (0.73–1.18)
MDRD	**<.001**	0.984 (0.980–0.988)	**<.001**	0.981 (0.976–0.986)
Diabetes mellitus	.41	1.1 (0.877–1.380)		
Echocardiographic response (ΔLVESV ≥15%)				
Variable	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**
BL QRS area ≥109 μVs	**<.001**	3.3 (2.5–4.4)	**.003**	1.7 (1.2–2.5)
BL QRS duration >150 ms	**<.001**	2.1 (1.6–2.8)	.07	1.4 (0.97–2.0)
ΔQRS area ≥62 μVs	**<.001**	3.3 (2.4–4.6)	**.005**	1.8 (1.2–2.6)
ΔQRS duration ≥ −11 ms	**<.001**	2.3 (1.5–3.3)	.68	1.1 (0.7–1.7)
Age	.14	0.99 (0.98–1.00)		
Male sex	**<.001**	0.54 (0.40–0.72)	**.007**	0.63 (0.45–0.88)
LBBB*	**<.001**	2.9 (2.1–4.2)	**.002**	1.8 (1.2–2.7)
Atrial fibrillation	**.001**	0.51 (0.34–0.75)	.11	0.70 (0.46–1.08)
iCMP	**<.001**	0.53 (0.40–0.69)	.11	0.78 (0.57–1.06)
MDRD	.07	1.004 (1.000–1.009)		
Diabetes mellitus	.51	0.90 (0.65–1.24)		

Note: Bold values represent a statistical significant result, i.e. a *p*-value below the alfa of .05.
Abbreviations: BL, baseline; ECG, electrocardiogram; HTx, heart transplantation; iCMP, ischemic cardiomyopathy; LBBB, left bundle branch block; LVAD, left ventricular assist device; LVESV, left ventricular end-systolic volume; MDRD, modification of diet in renal disease; VCG, vectorcardiography.
*According to ESC criteria.

in the QRS area after CRT. This may imply that CRT can be optimized by aiming for the largest possible reduction in the QRS area. This optimization could be achieved by choosing the best LV-lead position, and optimizing AV- and/or VV-delay.[17,18] Importantly, we found that patients with an anterolateral or lateral final lead position resulted in the highest ΔQRS area, while interestingly most patients had a final inferolateral lead. This finding may imply that QRS area measurement during implantation may guide LV lead positioning. Future studies should focus on the difference in QRS area reduction at different LV lead positions in the same patient, and its possible role in the optimization of LV lead positioning.

In a study by Engels et al.[19] AV-delay programming influenced QRS area reduction. Additionally, small studies found that, during LV fusion pacing, the AV-delay providing the largest acute hemodynamic benefit coincides with the AV-delay providing the largest reduction in the QRS area.[11,20] Furthermore, it was demonstrated that QRS area reduction could be used to identify favorable LV-lead configuration resulting in the best acute hemodynamic response.[11] The QRS area is currently not readily available on conventional ECG equipment. However, it is easy to obtain its values using the method used in this study and similar methods used by other centers.[11–13] Thus, the ΔQRS area is a promising marker that potentially could be used to

TABLE 3 Logistic regression analysis on entire cohort and on subgroups with baseline QRS area ≥109μVs and <109 μVs

Parameters	All patients (*n* = 1279)	Baseline QRS area < 109μVs (*n* = 649)	Baseline QRS area ≥ 109μVs (*n* = 630)
Baseline QRS area	**OR: 0.994**	OR: 0.997	OR: 0.995
	(CI: 0.991–0.998)	(CI: 0.988–1.005)	(CI: 0.985–1.004)
	***p* = .005**	*p* = .443	*p* = .249
ΔQRS area	**OR: 0.993**	OR: 1.017	**OR: 0.981**
	(CI: 0.987–0.999)	(CI: 0.999–1.034)	**(CI: 0.967–0.994)**
	***p* = .016**	*p* = .063	***p* = .006**
Baseline*ΔQRS area	*p* = .104	***p* = .033**	***p* = .021**

Note: Bold values represent a statistical significant result, i.e. a *p*-value below the alfa of .05.
Abbreviations: CI, 95% confidence interval; OR, odds ratios for the probability of primary endpoint occurrence for every 1 μVs increase in QRS area; *p*= *p* value after performing the Wald-test for significance.
*According to ESC criteria.

TABLE 4 Baseline characteristics and p-values for statistical difference between different groups when combining high baseline QRS area with either high ΔQRS area and low ΔQRS area

Baseline	Group 1 (*n* = 352)	Group 2 (*n* = 297)	Group 3 (*n* = 630)	*p* value Group 1 vs. Group 2	*p* value Group 2 vs. Group 3
QRS area (μVs)	172 ± 40	142 ± 28	75 ± 22	**<.001**	**<.001**
ΔQRS area (μVs)	102 ± 32	28 ± 28	3 ± 35	**<.001**	**<.001**
%Women	34	34	25	.99	**.004**
%LBBB*	92	89	66	.13	**<.001**
%AF	7	11	19	.13	**.003**
%iCMP	33	41	65	.05	**<.001**
%NYHA I-II-III-IV	4-41-50-5	1-43-52-4	1-36-57-5	.13	.27
% DM	22	23	27	.14	.12
Age (years)	65 ± 11	66 ± 11	67 ± 10	.05	**<.001**
MDRD (ml/min)	76 ± 34	72 ± 34	69 ± 31	.15	.19

Note: Bold values represent a statistical significant result, i.e. a *p*-value below the alfa of .05.
Abbreviations: AF, atrial fibrillation; DM, diabetes mellitus; iCMP, ischemic cardiomyopathy; LBBB, left bundle branch block; MDRD, modification of renal disease; NYHA, New York Heart Association.
*According to ESC criteria.

optimize CRT during and after implantation, especially in patients with a high baseline QRS area.

4.4 | Limitations

The present study has all the limitations of an observational, retrospective cohort, with no control group for the clinical endpoint. Therefore, the association between ΔQRS area and the primary endpoint cannot be directly interpreted as CRT benefit in the individual patient. However, for echocardiographic outcomes, each patient is their own control. The similarity in results for the primary clinical and secondary echocardiographic endpoints strongly supports the idea that a combination of baseline and ΔQRS area could be predictive for CRT benefit.

Furthermore, it should be noted that for the present study the current ΔQRS area measurements are based on the difference between the ECGs recorded before and 2–12 months after CRT, while optimization is preferably performed within a few days after CRT device implantation. This time difference must be taken into account. For the QRS area, a change over time during CRT is not known, but a small study showed that in patients receiving CRT, QRS duration remains unchanged over a 6-month period.[21] Another note of caution is that the currently observed association between ΔQRS area and CRT benefit is based on differences between patients, whereas the

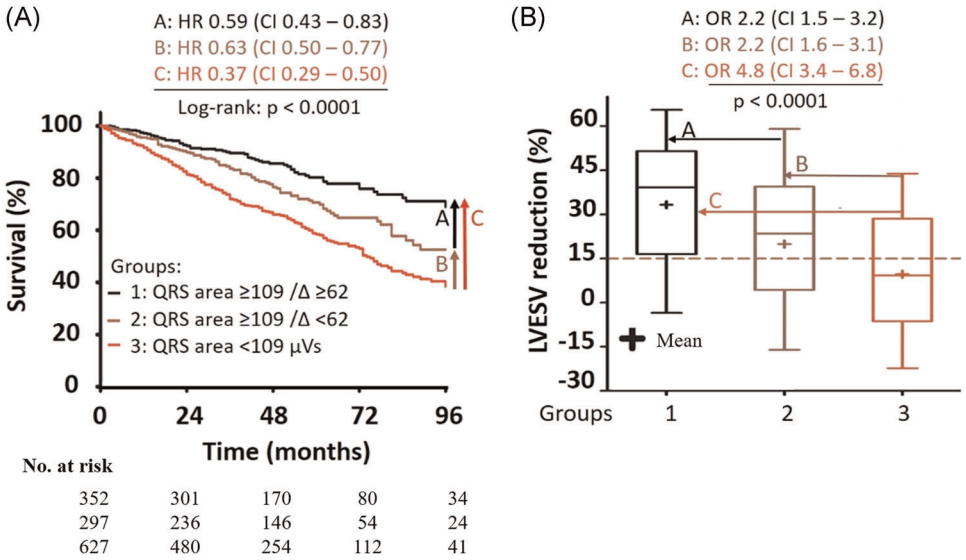

FIGURE 4 (A) Kaplan–Meier survival curves and hazard ratios for groups combining high baseline QRS area with either high or low ΔQRS area. Survival, free from primary endpoint; HR, hazard ratio for Group 1 (=upper black line) compared with Group 2 (=middle brown line) (A), Group 2 compared with Group 3 (=lower red line) (B), and Group 1 compared to Group 3 (C); CI, confidence interval. panel B. Boxplot and odds ratios for groups combining high baseline QRS area with either high or low ΔQRS area. Whiskers range from 10th to 90th percentile. BL, baseline; OR, odds ratio for a percentage of echocardiographic responders of Group 1 compared with Group 2 (A), Group 2 compared to Group 3 (B), and Group 1 compared to Group 3 (C); CI, confidence intervals. $p < .0001$ indicates statistical significance for differences in mean LVESV reduction between all groups

aforementioned purpose would be to find the optimum within the individual patient.

Although baseline QRS area was consistently higher in the groups with higher ΔQRS area, we believe that baseline QRS area is not the *only* factor influencing ΔQRS area, and that CRT-device implantation and -programming are also of significant importance. Therefore, future prospective studies are needed to demonstrate that CRT optimization using ΔQRS area improves outcomes.

5 | CONCLUSION

Reduction in QRS area after CRT is independently associated with survival and reverse remodeling in patients with heart failure, particularly in patients with a large baseline QRS area. Such an association was not observed for the change in QRS duration after CRT. Further studies are needed to investigate whether the reduction in QRS area can be used for CRT optimization in the individual patient.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author (M.G.). The data are not publicly available due to their containing information that could compromise the privacy of research participants.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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