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ORIGINAL PAPER

Does mechanical dyssynchrony in addition to QRS area ensure sustained response to cardiac resynchronization therapy?

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Aims Judicious patient selection for cardiac resynchronization therapy (CRT) may further enhance treatment response. Progress has been made by using improved markers of electrical dyssynchrony and mechanical discoordination, using $QRS_{AREA,}$ and systolic rebound stretch of the septum (SRSsept) or systolic stretch index (SSI), respectively. To date, the relation between these measurements has not yet been investigated.

Methods and results A total of 240 CRT patients were prospectively enrolled from six centres. Patients underwent standard 12-lead electrocardiography, and echocardiography, at baseline, 6-month, and 12-month follow-up. QRS_{AREA} was derived using vectorcardiography, and SRSsept and SSI were measured using strain-analysis. Reverse remodelling was measured as the relative decrease in left ventricular end-systolic volume, indexed to body surface area (ΔLVESVi). Sustained response was defined as ≥15% decrease in LVESVi, at both 6- and 12-month follow-up. QRS_{AREA} and SRSsept were both strong, multivariable adjusted, variables associated with reverse remodelling. SRSsept was associated with response, but only in patients with $QRS_{AREA} \geq 120$ µVs (AUC = 0.727 vs. 0.443). Combined presence of SRSsept ≥ 2.5% and $QRS_{AREA} \geq 120$ µVs significantly increased reverse remodelling compared with high QRS_{AREA} alone (ΔLVESVi 38 ± 21% vs. 22 ± 21%). As a result, 92% of left bundle branch block (LBBB)-patients with combined electrical and mechanical dysfunction were 'sustained' volumetric responders, as opposed to 51% with high QRS_{AREA} alone.

Conclusion Parameters of mechanical dyssynchrony are better associated with response in the presence of a clear underlying electrical substrate. Combined presence of high SRSsept and QRS_{AREA}, but not high QRS_{AREA} alone, ensures a sustained response after CRT in LBBB patients.

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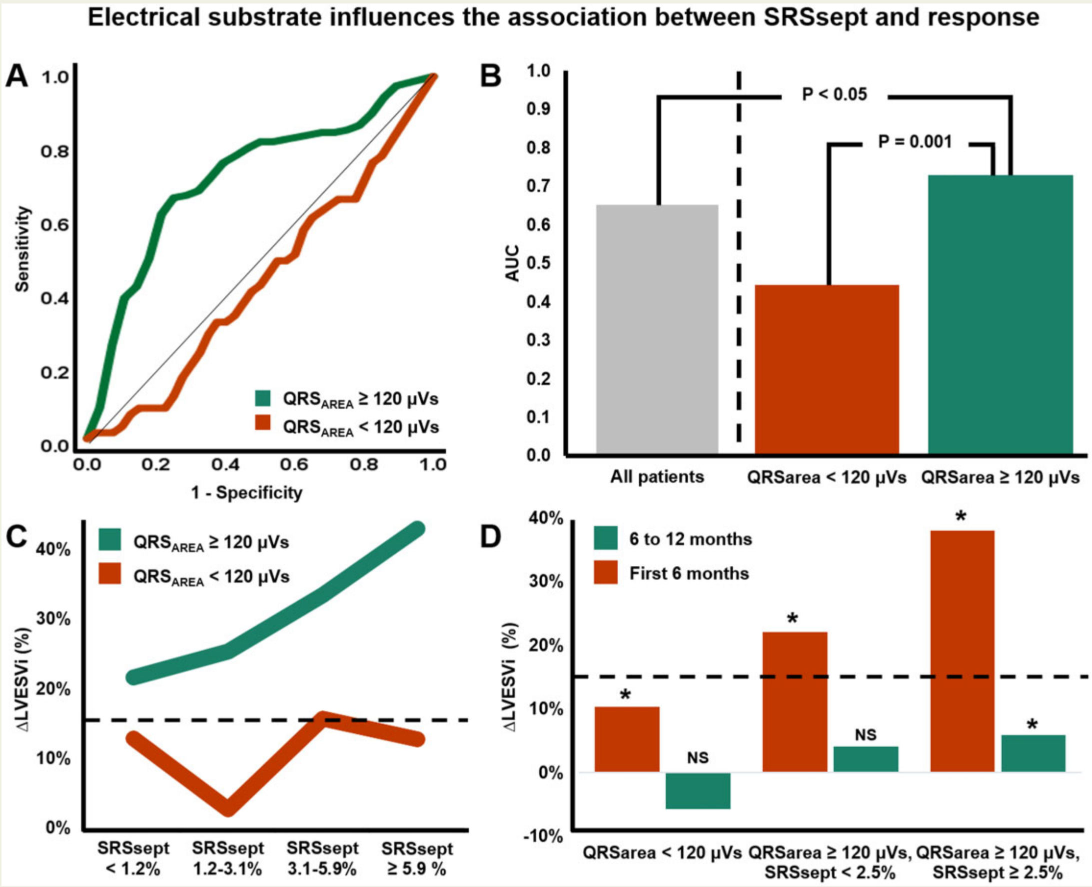
Graphical Abstract



Combined assessment of SRSsept and high QRS_{AREA} significantly improves the association with 6-month response, when compared with SRSsept alone (*A, B*). The amount of SRSsept is positively associated with response after 6 months, but only in patients with high QRS_{AREA} (*C*). Simultaneous presence of both high QRS_{AREA} and SRSsept, indicative of coupled electrical and mechanical delay, greatly enhances the extent of reverse remodelling after CRT (*D*). *$P < 0.05$.

Keywords cardiac resynchronization therapy • echocardiography • heart failure • strain imaging • QRS area

Introduction

Cardiac resynchronization therapy (CRT) alleviates symptoms and greatly reduces morbidity and mortality in patients with dyssynchronous heart failure. Although CRT in general is highly effective, response is variable, and some patients experience no clinical benefit or sometimes even deleterious effects of CRT outcome.[1] It is therefore that judicious selection of patients is of great importance.

Patient selection criteria dictate that heart failure patients are deemed eligible for CRT based on the presence of sufficient electrical substrate, characterized by left bundle branch block (LBBB) QRS-morphology and a prolonged QRS-duration.[2] Unfortunately, various definitions of LBBB morphology exist, and defining QRS-morphology is hampered by significant inter-observer disagreement.[3] Improvements have been made using QRS_{AREA}, which has a stronger association with survival and volumetric response after CRT, independently of QRS morphology.[4,5] Since QRS_{AREA} can be easily retrieved from a standard ECG, it is readily implementable in everyday practice.

Because, by itself, an electrical substrate does not 'necessarily' contribute to significant deterioration of left ventricular (LV) function, measuring mechanical discoordination can be beneficial as well.[6] The extent of mechanical impairment can be reflected by the amount of stretching that occurs during systole [i.e. systolic rebound stretch of the septum (SRSsept)], also referred to as 'wasted work'[7–9] (*Figure 1*). Strain-imaging can therefore be used as a tool to quantify the severity of LV systolic impairment that can be attributed to the underlying electrical conduction delay, and by extent determine ones probability to respond to CRT.

Although the importance of QRS_{AREA} and SRSsept has been demonstrated separately, both have yet to be integrated into a single model.[5,10] It is presently unknown whether measuring mechanical

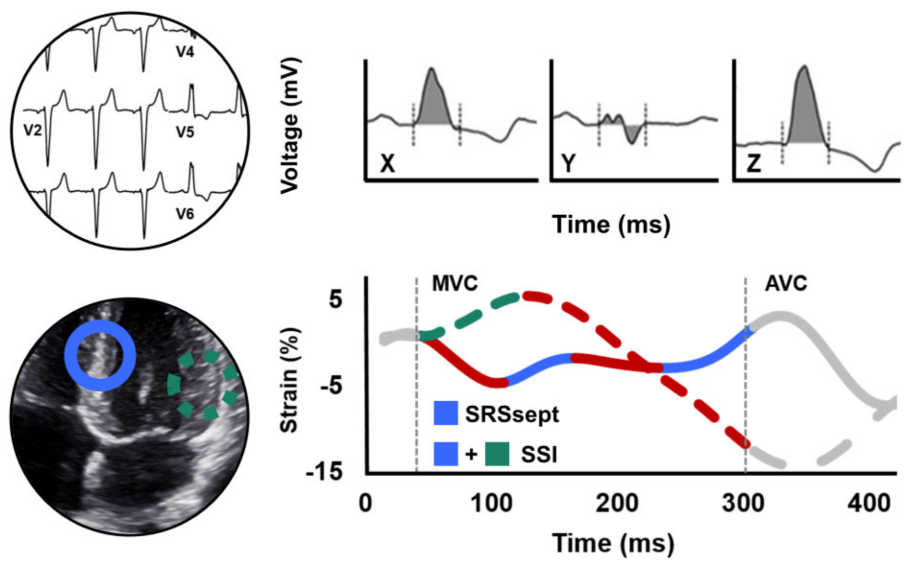


Figure 1 QRS_{AREA} was derived using vectorcardiograms, recoded from the conventional 12-lead ECG (upper panel). Indices of discoordination were determined using speckle tracking echocardiography (lower panel). AVC, aortic valve closure, MVC, mitral valve closure; SRSsept, systolic rebound stretch of the septum; SSI, systolic stretch index.

discoordination is still of added value in patients with a clear electrical substrate when defined by QRS_{AREA}.[4] In addition, research often solely focuses on response after 6 months, without evaluating whether CRT-induced reverse remodelling, and by extent clinical benefit, is sustained. To this purpose, this study set out to investigate whether the presence of high QRS_{AREA} with accompanying LV discoordination results in more pronounced 6- and 12-month LV reverse remodelling, when compared with high QRS_{AREA} alone. We hypothesize that the presence of 'combined' electrical and mechanical dysfunction are of added benefit, especially in predicting a lasting CRT-response.

Methods

Study design

This study reports a predefined subanalysis of the prospective multicentre Markers and Predictors of Response (MARC) study, which reported 6-month outcome only.[5] The MARC study was primarily designed to investigate various markers for response in patients with *de novo* implantation of a CRT device (clinicaltrials.gov: NCT01519908). The study was initiated and executed by six centres within the framework of the Center for Translational Molecular Medicine (CTMM), project COHFAR (grant 01C-203). All ECGs and echocardiograms were analysed by a core laboratory, blinded to both clinical patient history and volumetric response (University Medical Center of Utrecht, The Netherlands). Data underlying this article are under management of the statistical core laboratory (University Medical Center of Groningen, The Netherlands). This study complied with the Declaration of Helsinki and was approved by the review boards of all participating centres. All patients provided written informed consent.

Study participants

Patients were deemed eligible upon adhering to European and American guideline criteria for CRT at the time of inclusion (February 2012 to November 2013). Patients in sinus rhythm, LV ejection fraction (LVEF) < 35%, and LBBB ≥ 130 ms or non-LBBB ≥ 150 ms were included. In addition, patients had New York Heart Association (NYHA) class II or III heart failure symptoms, despite receiving optimal medical therapy. Exclusion criteria included renal insufficiency (<30 mL/min/1.73 m^2), previous resynchronization or anti-bradycardia pacing therapy, right bundle branch block, recent myocardial infarction, permanent atrial fibrillation or flutter, and permanent second or third degree atrioventricular block.

Study protocol

Each patient received a CRT device, programmed at implant to DDD-mode with sensed atrioventricular delay 90 ms, paced atrioventricular delay 130 ms; and interventricular delay 0 ms. Optimization of AV and/or VV delay was performed according to local protocols. A 12-lead digital ECG and echocardiograms were obtained, at baseline, 6- and 12-month follow-up. LVEF and cardiac dimensions were calculated using Simpson's modified biplane method.[11] The primary study endpoint was LV end-systolic volume reduction, indexed to body surface area using the Du Bois formula (ΔLVESVi).[12] Since body size is associated with reverse remodelling, indexation was performed to allow for superior, standardized, and inter-individual comparison.[11] Echocardiographic response was defined as follows: non-response, LVESVi < 15%; response, LVESVi ≥15%; super-response, LVESVi ≥ 30%. Sustained remodelling was defined as LVESVi ≥ 15% at both 6- and 12-month follow-up, relative to baseline.

Electrocardiographic data

Standard 12-lead ECGs were analysed by the ECG core laboratory in order to calculate QRS_{AREA}, QRS duration, and define LBBB morphology. ECGs were semi-automatically recoded into vectorcardiograms, each consisting of three orthogonal leads (*X*, *Y*, and *Z*), using the Kors conversion matrix in custom made Matlab software (MathWorks Inc.) (*Figure 1*).

The three orthogonal leads from the vectorcardiogram together form a 3D-vector loop, from which QRS_{AREA} was calculated as $(X_{area}{}^2 + Y_{area}{}^2 + Z_{area}{}^2)^{1/2}$. Presence of LBBB was determined retrospectively according to morphological features from to the European Society of Cardiology (ESC) and the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS).

Mechanical dyssynchrony and discoordination

Speckle-tracking echocardiography was performed on GE and Philips equipment. A focused view of the septum and conventional apical 4-chamber view were acquired. Onset of QRS-complex and closure time of the aortic valve, using Pulsed-wave Doppler images of the LV outflow tract, were used to define systole. Images were traced alongside the endocardial border of the septum and LV lateral wall (LVlw), excluding the apex. Analysis was performed on vendor-independent software (TomTec Cardiac Performance Analysis, TomTec Imaging Systems GmbH, Unterschleissheim, Germany). SRSsept and systolic stretch index (SSI) were calculated as indices of mechanical discoordination. For SRSsept, tracings in the 'focused' septal view were used whenever possible (61% of patients).

SRSsept was defined as the sum of stretch that occurred in the septum following prematurely terminated shortening, during systole (*Figure 1*).[7] SSI was subsequently calculated by adding the amount of prestretch that occurred in the LVlw to SRSsept.[13] Contemporary, timing-based, markers of inter- and intraventricular were assessed as well. Interventricular mechanical delay (IVMD) was measured as the difference between left and right ventricular pre-ejection intervals, using pulsed wave Doppler. Apical rocking and septal flash were assessed visually, defined as a short rocking motion of the apex and rapid short inward motion of the septum, respectively.[14]

Statistical analysis

Statistical tests were performed in SPSS version 25 (IBM, Armonk, NY, USA). Continuous data were expressed using mean ± standard deviation (normally distributed variables) or as median, inter-quartile range (non-normally distributed variables). Categorical data were described by an absolute number of occurrences and associated frequency (%). Data of two subgroups were compared using a *t*-test or Mann–Whitney *U* test, dependent on normality of the data. In the case of multiple subgroups, a one-way ANOVA was used with Bonferroni *post hoc* test where applicable. Fisher's χ^2 test was used for categorical data.

To test the association between discoordination and QRS_{AREA} at baseline and LVESVi-reduction at follow-up, univariate and multivariate adjusted linear regression analyses were performed with correction for potential confounders. Confounders were selected based on parameters that showed an association with ΔLVESVi in univariate analysis with $P < 0.1$. Variables that were added to the final model using backward selection were sex, age, ischaemic cardiomyopathy, LBBB morphology, QRS duration, QRS_{AREA}, apical rocking, septal flash, IVMD, SRSsept, and SSI. Assumptions of multivariable linear regression were checked for the existence of non-linearity, heteroskedasticity, and multicollinearity by graphical analyses and correlations tests. Normality of residuals was tested by a Q–Q plot.

Based on the presence of sufficient baseline electrical substrate (i.e. high QRS_{AREA}) and/or concomitant discoordination (i.e. high SRSsept), the study population was divided into subgroups. To this end, optimal cut-off values were determined on the basis off highest sensitivity and specificity for discrimination of responders (≥15% LVESVi-reduction) from non-responders, using the Youden index.

Results

A total of 240 patients were prospectively included, of whom paired LVESVi measurements at both 6 and 12 months were available in 200. Participants were predominantly male (62%) with a mean age of 66 and an average QRS duration of about 180 ms (Supplementary data online, *Table S1*). The majority of patients was NYHA II (63%), with ischaemic cardiomyopathy (ICM) in 42% of cases. Overall, $LVESV_i$ decreased by 22 ± 24% (75 ± 31 mL/m^2 vs. 58 ± 31 mL/m^2), with 61% of patients being a volumetric responder.

Sustained vs. non-sustained remodelling

A total of 114 patients (57%) demonstrated sustained remodelling. Following initial non-response at 6 months, 19 patients demonstrated delayed reverse remodelling after 12 months (ΔLVESVi 23 ± 13%; $P < 0.001$) (*Figure 2*). Conversely, 12 delayed non-responders demonstrated initial reverse remodelling, which was not sustained at 12-month follow-up (ΔLVESVi -30 ± 22%; $P < 0.001$). Reliability of LVESV measurements was excellent, with intra- and interclass correlation coefficients of 0.994 and 0.988, respectively ($P < 0.001$).

Mechanical discoordination and reverse remodelling

Differences in various baseline characteristics on the basis of low QRS_{AREA} and high $QRS_{AREA,}$ with and without concomitant mechanical discoordination, are summarized in Supplementary data online, *Table S2*. A total of 11 variables were selected for univariate linear regression analysis (*Table 1*). Significant multivariable adjusted associations with ΔLVESVi, after both 6 and 12 months, were revealed for QRS_{AREA} (β = 0.283 and β = 0.473) and SRSsept (β = 0.177 and β = 0.211), respectively. Other echocardiographic predictors were only significant at either 6 months (IVMD; β = 0.180) or 12 months (apical rocking; β = 0.189). When comparing SSI and SRSsept, only the latter proved to be associated with reverse remodelling after multivariate adjustment. Intra-observer reliability for SRSsept was high with an intraclass correlation coefficient of 0.89 ($P < 0.001$).[10]

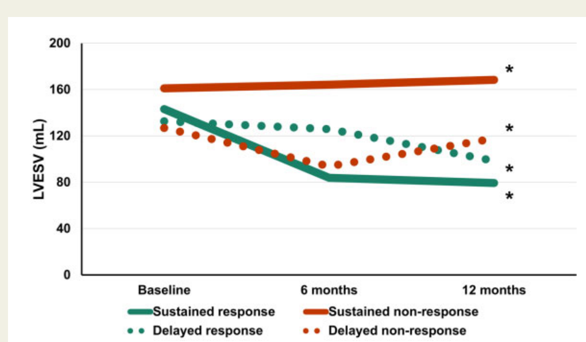


Figure 2 Changes in left ventricular end-systolic volume over the course of 6- and 12-month follow-up periods. *$P < 0.05$ between 6 and 12 months.

Table 1 Univariate and multivariate analysis for 6- and 12-month reduction in LVESVi

	Univariate, 6M		Multivariate, 6M		Multivariate, 12M	
	β	*P*-value	B	*P*-value	β	*P*-value
Male sex, *n* (%)	-0.168	0.014				
Age (years)	-0.169	0.013	-0.150	0.022	-0.225	0.001
ICM, *n* (%)	-0.320	<0.001				
LBBB, *n* (%) (ESC)	0.250	<0.001	0.137	0.069		
QRS duration (ms)	0.128	0.072	-0.177	0.031	-0.225	0.008
QRS_{AREA} (µVs)	0.437	<0.001	0.283	0.002	0.473	<0.001
Apical rocking, *n* (%)	0.313	<0.001	0.125	0.081	0.189	0.007
Septal flash, *n* (%)	0.233	0.001				
IVMD (ms)	0.369	<0.001	0.180	0.020		
SRSsept (%)	0.372	<0.001	0.177	0.014	0.211	0.003
SSI (%)	0.394	<0.001				

β, standardized regression coefficient (represents the number of standard deviations that the outcome will change as a result of one standard deviation change in the predictor); 6M, 6-month follow-up; 12M, 12-month follow-up; ICM, ischaemic cardiomyopathy; LBBB, left bundle branch block; IVMD, interventricular mechanical delay; SRSsept, systolic rebound stretch of the septum; SSI, systolic stretch index.

Disagreement between electrical substrate and mechanical dyssynchrony

The optimal cut-off value for QRS_{AREA} (AUC = 0.674; $P < 0.001$) and SRSsept (AUC = 0.652; $P = 0.001$) were 120 µVs and 2.5%, respectively (Supplementary data online, *Figure S1A*). However, baseline QRS_{AREA} and SRSsept were poorly related to each other ($R = 0.358$; *P*-value < 0.001) (Supplementary data online, *Figure S1B*). Of all patients, 9% had isolated high SRSsept, whereas high QRS_{AREA} without concomitant SRSsept was found in 26% of cases (Cohen's kappa = 0.318). When combining these two cut-off values with age and apical rocking,[10] multivariate logistic regression analysis demonstrated good associations with 6-month response (AUC = 0.757; $P < 0.001$) and sustained response (AUC = 0.774; $P < 0.001$) (Supplementary data online, *Table S3*).

The importance of combined electromechanical dysfunction

Baseline SRSsept was increasingly associated with ΔLVESVi, but only in patients with $QRS_{AREA} \geq 120$ µVs (AUC = 0.727 vs. 0.443; *P*-between = 0.001) (*Graphical Abstract A –C*; Supplementary data online, *Table S4*). Assesment of QRS_{AREA} in addition to SRSsept significantly improved the association with 6-month response, when compared with assesment of SRSsept alone (AUC = 0.727 vs. AUC = 0. 652; $P < 0.05$) (*Graphical Abstract B*). This assocation was near-identical for patient with and without ICM (ΔAUC = 0.008; NS). In patients with high QRS_{AREA}, simultaneous presence of high SRSsept resulted in significantly more 6-month reverse remodelling than in patients with $QRS_{AREA} \geq 120$ µVs alone (ΔLVESVi 38 ± 21% vs. 22 ± 21%; $P = 0.001$) (*Graphical Abstract D*).

Only in patients with both high QRS_{AREA} and SRSsept, reverse remodelling was continued significantly between 6- and 12-month follow-up (ΔLVESVi 6 ± 23%; $P = 0.028$) (*Graphical Abstract D*). The presence of SRSsept consistently enhanced response in patients with $QRS_{AREA} \geq 120$ µVs, even in patients with very high baseline QRS_{AREA} (≥ 155 µVs) (*Figure 3*). Moreover, 90% of patients with both high QRS_{AREA} and SRSsept ($n = 59$) were volumetric responders, as opposed to only 54% of patients with only $QRS_{AREA} \geq 120$ µVs ($n = 48$). Lastly, 68% of patients with both elevated QRS_{AREA} and SRSsept were classified as super-responder, as opposed to 40% of patients with high QRS_{AREA} alone.

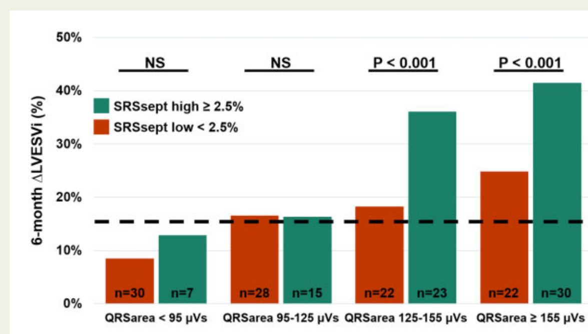


Figure 3 Influence of either the presence (green) or the absence (red) of high SRSsept for various quartiles of baseline electrical dyssynchrony.

Sustained remodelling and varying pattern of dyssynchrony

Using the ESC or AHA criteria for LBBB, 31% and 69% of patients were classified as non-LBBB, respectively. The additive benefit of SRSsept in non-LBBB was significant only when using strict AHA criteria (*Figure 4*). In LBBB patients however, simultaneous presence of high SRSsept ensured sustained remodelling when compared with high QRS_{AREA} alone, both according to ESC ($n = 49$ vs. $n = 39$) and AHA ($n = 23$ vs. $n = 19$) criteria.

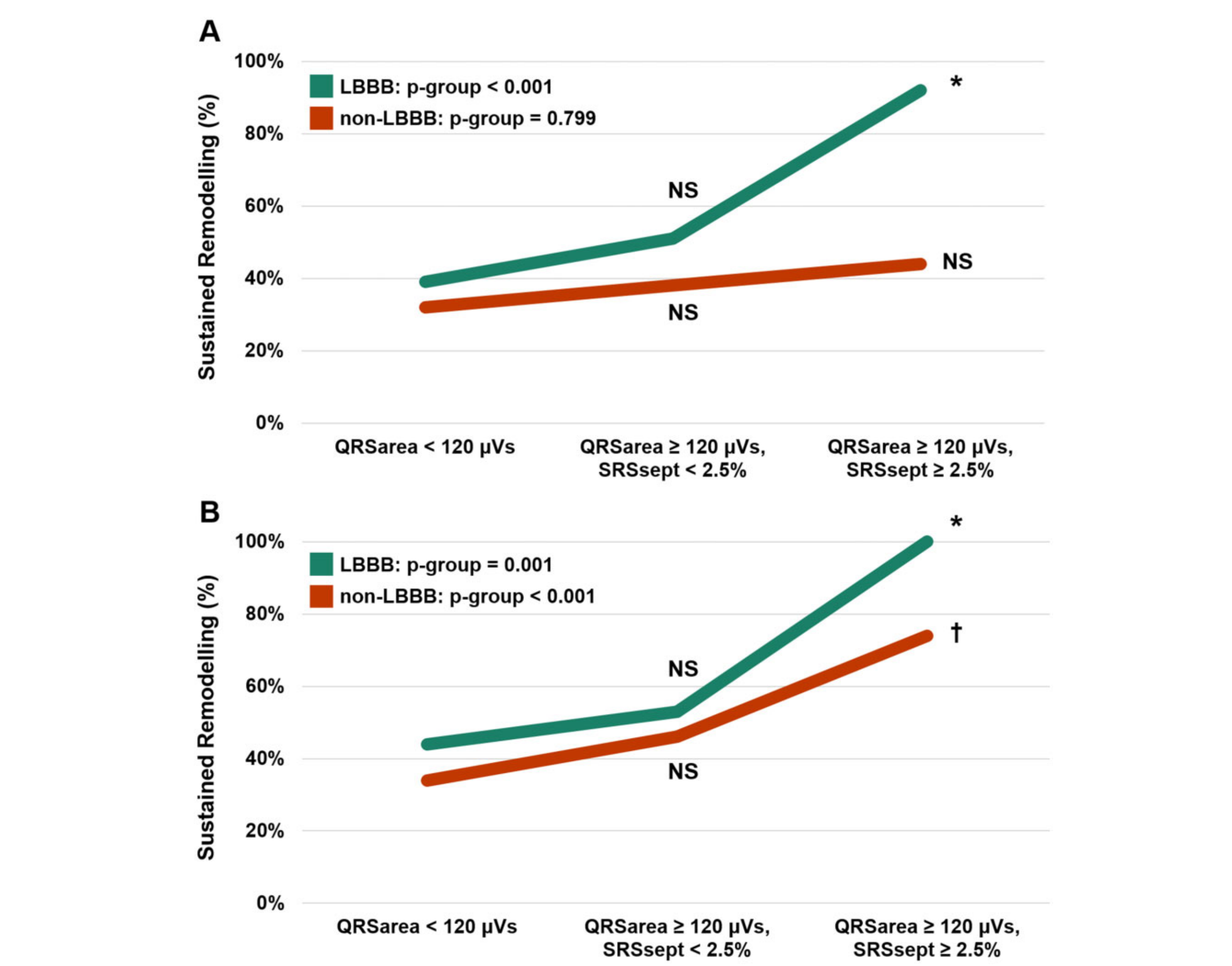


Figure 4 The presence of mechanical discoordination in patients with high QRS_{AREA} ensures sustained reverse remodelling in patients with LBBB (green) according to ESC (upper panel) or AHA (lower panel) criteria. *$P < 0.001$ compared with both categories; $^{\dagger}P = 0.001$ compared with $QRS_{AREA} < 120$ µVs. .

Discussion

The most pertinent finding of the present prospective multicentre study is that both SRSsept and QRS_{AREA} are associated with sustained reverse remodelling after multivariable adjustment. More specifically, the identification of SRSsept ≥ 2.5%, rather than QRS_{AREA} alone, appears to be especially of added value in achieving 'sustained' remodelling in LBBB patients with high QRS_{AREA}.

Enhanced identification of electrical substrate using QRS_{AREA}

Despite an average QRS-duration of 180 ms, 39% of patients were non-responders. As such, current guideline criteria for an electrical substrate are incapable of ensuring a volumetric response. QRS_{AREA} is derived objectively from the ECG, reflects LV activation delay, and is inversely associated with scar.[15,16] QRS_{AREA} may as such be preferred above the more subjective QRS morphology.[3] The subjectivity of LBBB morphology is further underscored by our results, since the added benefit of SRSsept in non-LBBB patients was dependent on the definition used. Also, reduction of QRS_{AREA} more strongly predicts response to CRT than QRS duration or LBBB morphology.[4] In particular, QRS_{AREA} was independently associated with both all-cause mortality and echocardiographic response.[4] QRS_{AREA} therefore better reflects the electrical substrate amenable to resynchronization than its traditional counterparts, especially in patients with non-LBBB morphology, who would otherwise be deemed less suitable candidates for CRT.[4,17] It is currently unknown to which degree high levels of QRS_{AREA} can be found in patients with QRS duration <130 ms, and whether these patients are likely to respond to CRT.

Indices of mechanical discoordination in CRT

Although apical rocking is an easy visual assessment, it is no quantifiable measure, subjectively assessed, and has limited inter-observer reproducibility.[18] In contrast to both IVMD and apical rocking, SRSsept was consistently of added value to elevated QRS_{AREA}, both at 6- and 12-month follow-up. Since a 'reduction' of SRSsept, but not IVMD, is associated with reverse remodelling, SRSsept is also more likely to reflect the amenable mechanical substrate to CRT.[19]

Discoordination-imaging in CRT patients aims to capture the contradictory contraction pattern that occurs during systole, and thereby quantify the extent by which LBBB causes LV dysfunction.[19] Because regional septal dysfunction is a major contributor to deteriorated LV function in CRT patients, SRSsept indirectly reflects LV discoordination as a whole.[20] Using a concept similar to our approach,[7,10,19] myocardial work elegantly combines strain-imaging with a single non-invasive estimate of LV pressure.[20,21] Wasted myocardial work thereby essentially represents a measure of paradoxical systolic stretching, 'indexed' to blood pressure.

Aalen *et al.*[18] demonstrated higher predictive power of septal-to-LVlw work difference when compared with SSI in predicting reverse remodelling (AUC = 0.77 vs. 0.73). In contrast to our work, simultaneous assessment of MRI-derived septal viability was used instead of QRS_{AREA}. Importantly however, MRI-derived septal viability was incorporated only into the analysis of myocardial work, whereas this was neglected with respect to SSI. In another recent study from Gorcsan *et al.*,[13] similar or superior outcomes were reported using SSI in ~500 patients, when compared with myocardial work.[18] To date, no direct comparison between either methods has been conducted investigating clinical endpoints. Regardless, SRSsept has previously been thoroughly investigated and should be considered a robust parameter with good intra-observer reliability.[7,8,10] Future studies, integrating electrical substrate assessment with both, septal dysfunction and septal viability, may demonstrate further improvement in response prediction.

Combined electrical and mechanical dysfunction ensures CRT response

Previous work already emphasized that no parameter, aimed at characterizing LV mechanical inefficacy, should be interpreted on its own, without also evaluating the underlying electrical substrate. In particular, lack of sufficient electrical dyssynchrony (i.e. QRS-duration < 130 ms) generally precludes benefit from CRT, regardless of the presence of mechanical dyssynchrony.[22] Conversely, also in patients with QRS-duration ≥ 130 ms, non-electrical substrates such as (septal) scarring and myocardial stiffness may affect mechanical dysynchrony, which is unlikely to be corrected by CRT.[9,18]

Our findings are therefore in agreement with this work, since we were unable to demonstrate additional benefit of SRSsept in patients with relatively low levels of baseline electrical dyssynchrony. However, over two-thirds of all patients with both elevated QRS_{AREA} and SRSsept were classified as super-responders, with only one in ten patients becoming volumetric non-responders. In addition, over 90% of LBBB patients were sustained remodellers.

Clinical implications for strain-analysis

The identification of potential super-responders and sustained remodellers, as a surrogate marker of stable disease remission and subsequent sustained prognostic benefits,[12] may be useful in the process of deciding which patients are eligible to receive CRT without an implantable cardioverter-defibrillator.[23] More appropriate discrimination between CRT with and without implantable cardioverter-defibrillator is especially valuable in low-to-middle income countries who maintain lower cost-effectiveness thresholds, thereby increasing referral and implant rates.

Unfortunately, because of previously conflicting results, echocardiographic analysis of mechanical dyssynchrony still holds no place in contemporary practice revolving patient selection for CRT.[24] Strain-based parameters of discoordination are however much more promising than timing-based indices, and should be further investigated in randomized trials.[7,8,10,19] New studies, prospectively investigating discoordination-indices, are therefore highly awaited. Especially given that the negative results from PROSPECT, which was a non-randomized study, were published well over a decade ago.[24]

Study limitations

Our findings should be interpreted in the context of limitations inherent to its non-randomized design. However, our results were derived prospectively from a relatively large sample size in a multicentre setting of unselected patients, were reproducible at multiple time points, and therefore robust. Moreover, core laboratory analysis minimized measurement variability for echo and QRS_{AREA}. For SRSsept, optimal image quality of the septum was ensured by acquiring focused septal views with high framerate in only 61% of cases. Also, although various vendors were used for image-acquisition, our use of vendor-independent software limited its influence on our results.[25] Conversely, with varying image-quality and different vendors, our study also reflects a real-world situation, and at the same time underscores how the quality of SRSsept may be improved even further. Because no focused LVlw views were acquired for calculation of SSI, no definite conclusions can be drawn with respect to potential non-inferiority of SRSsept, relative to SSI.

Conclusion

Our work demonstrates, for the first time, the importance and practicability of the combined assessment of QRS_{AREA} and SRSsept in a real-world setting.

Mechanical discoordination, in the presence of an underlying electrical substrate, ensures responsiveness to CRT with high certainty in the majority of patients. Discoordination-imaging may therefore be particularly useful in identifying super-responders and patients who will show sustained disease remission.

Supplementary data

Supplementary data are available at *European Heart Journal—Cardiovascular Imaging* online.

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and The Dutch Heart Foundation. All other authors have reported that they have no relationships relevant to the contents of this article to disclose.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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