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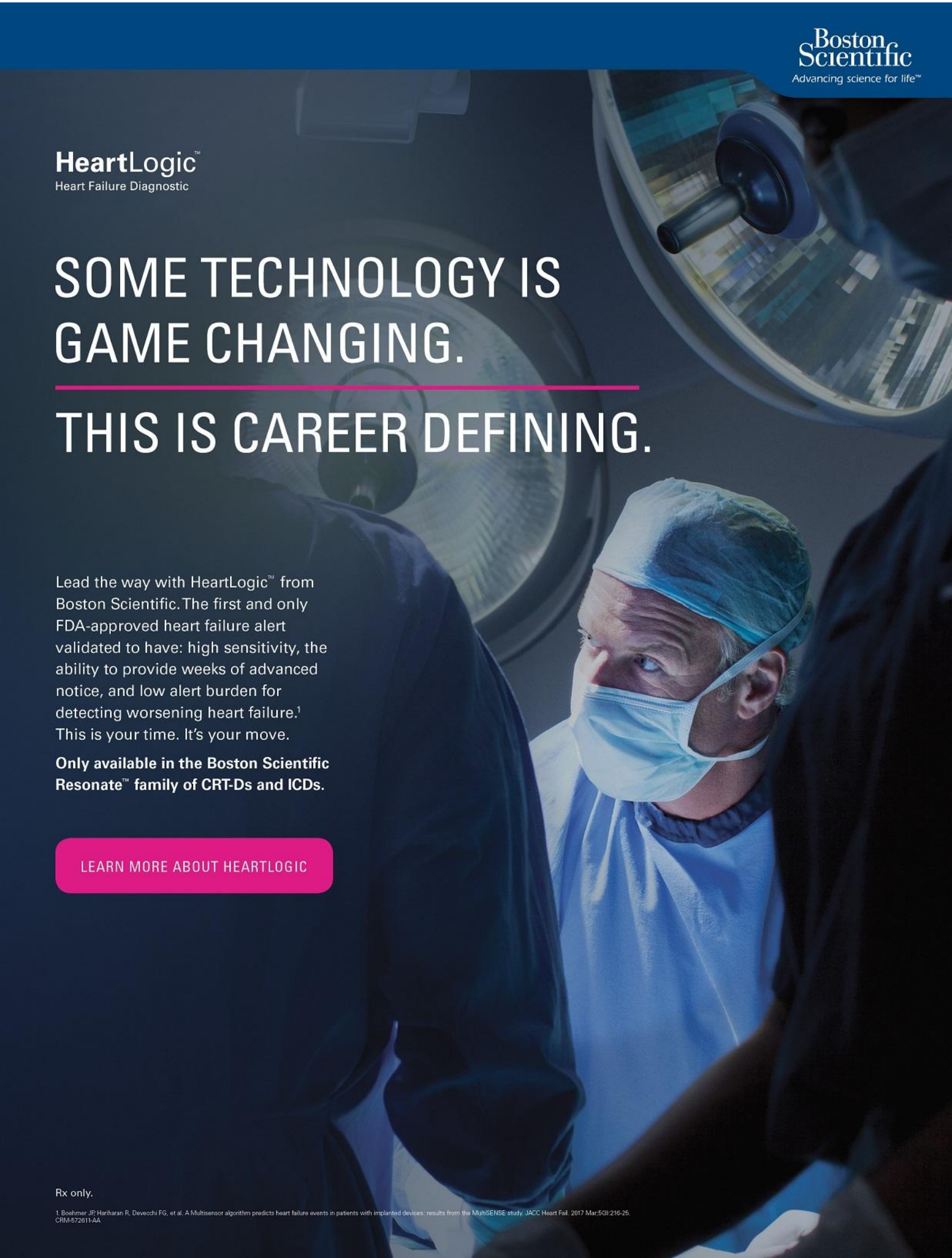
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Interlead electrical delays and scar tissue; response to cardiac resynchronization therapy in patients with ischemic cardiomyopathy

Short title: Interlead electrical delays and CRT

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Condensed abstract

Interlead electrical delays (IEDs) and left ventricular scar tissue were measured in 68 patients with ischemic cardiomyopathy and LBBB before CRT implantation. Patients with a long RV-LV-IED at implantation were most prone to respond to CRT independently of scar tissue and QRS duration. CRT did not change the duration of IEDs even among patients with LV remodeling.

What's new?

It has been questioned whether interlead electrical delays are useful markers of respond in the presence of scar tissue. In a cohort of ischemic CRT patients IEDs during implant and baseline scar tissue by MRI were measured.

- RV-LV-IED was an independent marker of response in CRT patients with ischemic cardiomyopathy even in the presence of scar tissue.

- RV-LV-IED may be particular useful in patients with QRS < 150 ms.

- CRT did not influence RV-LV-IED over time.

Abstract

Background:

The importance of interlead electrical delays (IEDs) in the presence of scar tissue for response to cardiac resynchronization therapy (CRT) in patients with ischemic cardiomyopathy is poorly described.

Methods:

Sixty-eight CRT patients with ischemic cardiomyopathy and left bundle branch block were included. IEDs, the time between sensing of native impulse at the RV-lead and LV-lead, were measured at implantation and after eight months. MRI was used for assessment of scar tissue. Echocardiographic response was defined as ≥ 15% decrease in left ventricular end-systolic volume. NYHA class, Minnesota Living with Heart Failure Questionnaire and 6-minute walk-test were used to assess clinical response.

Results

A total of 44 patients (65 %) were responders to CRT. At implantation, IEDs were significantly longer among responders compared to non-responders (RV-LV-IED: 87 ms ± 33 ms vs. 65 ms ± 47 ms, $p < 0,05$), most evident in patients with QRS < 150 ms. Responders had less myocardial scar tissue than non-responders (1 ± 0,5 vs. 1,4 ± 0,6, $p = 0,01$). However, in the multivariate model including QRS-duration and scar tissue, IEDs were

independently associated with LV remodeling after CRT: OR 3,99 [95% CI 1,02-15,7] (p = 0,04).

During the course of treatment, no changes were observed in IEDs among echocardiographic responders.

Conclusion:

RV-LV-IED was an independent marker of response in CRT patients with ischemic cardiomyopathy even in the presence of scar tissue and may be particular useful in patients with QRS < 150 ms. CRT did not influence this measurement over time.

Keywords: Cardiac resynchronization therapy, heart failure, interlead electrical delay, ischemic cardiomyopathy.

List of abbreviations:

6MWT = 6-min walking test

ACEI = angiotensin converting enzyme inhibitor

ARB = angiotensin receptor blocker

BB = beta blocker

CABG = coronary artery bypass grafting

CRT = cardiac resynchronization therapy

DCM = non-ischemic dilated cardiomyopathy

ECG = electrocardiogram

EGM = electrogram

GFR = glomerular filtration rate

HF = heart failure

ICD = implantable cardioverter defibrillator

IHD = ischemic heart disease

IED = interlead electrical delay

LBBB = left bundle branch block

LV = left ventricle

LVEF = left ventricular ejection fraction

LVESV = left ventricular end-systolic volume

MI = myocardial infarction

MLHFQ =Minnesota living with heart failure questionnaire

MRI = magnetic resonance imaging

NYHA = New York Heart Association (functional classes of heart failure)

pLV-sRV-IED = paced left ventricle to sensed right ventricle interlead electrical delay

pRV-sLV-IED = paced right ventricle to sensed left ventricle interlead electrical delay

RV-LV-IED = sensed right ventricle to left ventricle interlead electrical delay

RV-LV-IED/QRS-d = RV-LV-IED divided by surface ECG QRS-duration

STS = Scar tissue score

Introduction

Selection of patients who will respond to cardiac resynchronization therapy (CRT) can be challenging. The primary target for CRT is an electrical substrate of significant left ventricle (LV) activation delay. Any method that reliably reflects such a delay may be useful in identifying CRT-responders. (1-3) Most patients with left bundle branch block (LBBB) have a significant LV activation delay presumably amenable to CRT. However, electrophysiological mapping studies indicate that around 1/3 of patients with LBBB defined by ECG do not have a significant LV activation delay. (4, 5) ECG-changes due to hypertrophy, LV-dilatation, isolated fascicular blocks or slowed intraventricular conduction may be misinterpreted as true LBBB. (6, 7) The electrical delays measured between the right ventricle (RV) and LV may serve as markers of favorable outcome to CRT. (6, 8-10) In contrast to more comprehensive approaches such as endocardial mapping, interlead electrical delays (IEDs) can easily be obtained during CRT implantation. The electrical time distance between native impulse sensing in the RV-lead and LV-lead (RV-LV-IED) may be considered as an indirect measurement of the activation delay in the LV. Thus, a relatively long RV-LV-IED suggests a beneficial response to CRT. (6, 8, 10, 11) One pitfall using IEDs is the presence of scar tissue in the LV which may cause prolonged activation times in the absence of a well-defined substrate for CRT. Accordingly, the value of IEDs in patients with ischemic cardiomyopathy in particular has been questioned. (6, 12, 13)

The aim of this study was to investigate the prognostic utility of IEDs in CRT patients with ischemic cardiomyopathy including the importance of left ventricular scar tissue. Furthermore, we evaluated the relationship between changes in LV volumes and IEDs in the course of treatment.

Methods

Study population

Between October 2009 and July 2012 seventy consecutive patients were prospectively enrolled in the study and underwent successful implantation of a biventricular pacemaker at Gentofte University Hospital in Denmark (65 patients) and Lund University Hospital in Sweden (5 patients). Patients fulfilled the following criteria at the time of implantation: left ventricular ejection fraction (LVEF) $\leq$ 35%, sinus rhythm, left bundle branch block (LBBB), QRS interval $\geq$ 120 ms, New York Heart Association (NYHA) functional class II or III and optimal pharmacologic treatment (maximally tolerated dosages of beta-blockers, ACE-inhibitors/angiotensin-II receptor blockers and spironolactone). All patients had ischemic heart disease defined as > 70% stenosis in one or more epicardial coronary artery diagnosed by coronary catheterization or prior myocardial infarction (MI) or coronary artery bypass graft surgery (CABG). Patients were excluded if they had significant primary valve disease, chronic atrial fibrillation, dementia or mental retardation, severe claustrophobia or metal implants contraindicative of magnetic resonance scan, acute coronary syndrome within 3 months, severe kidney insufficiency (GFR < 35 ml/min/1,73m^2) and severe health condition threatening short-term survival.

Device implantation and programming

All patients were implanted with a CRT-device with defibrillator capacity (CRT-D) from St. Jude Medical (St. Paul, MN). One lead was implanted in the right atrium, a right ventricular lead was placed on the septum and the left ventricular lead was placed preferably in a lateral position. Only patients with > 92 % biventricular pacing was included.

Echocardiography

A full standard echocardiography was performed at baseline (the time for CRT-implantation) and after 8 months. All echocardiographic studies were performed on Vivid 9 ultrasound machines (GE Healthcare, Horten, Norway). All analyses were performed off-line blinded to outcome using EchoPac PC (version BT11 GE Vingmed Ultrasound). Simpson´s method of discs as an average of three measurements was used to measure left ventricular end systolic volumes (LVESV) and left ventricular ejection fraction (LVEF).

Interlead electrical delays (IEDs)

IEDs were measured at CRT implantation and after 8 months with CRT, using an automated function in the St-Jude device. Three different IEDs were measured; RV-LV-IED, pRV-sLV-IED and pLV-sRV-IED. RV-LV-IED was defined as the time interval in milliseconds between sensing of the native impulse at the RV-lead and LV-lead. pRV-sLV-IED was defined as the time interval between pacing at the RV-lead and sensing at the LV-lead, and pLV-sRV-IED was defined as the delay between pacing at the LV-lead and sensing at the RV-lead. To account for beat-to-beat variations all intervals were averaged over eight consecutive beats. RV-LV-IEDs were also adjusted to surface ECG QRS-duration to account for individual differences in myocardial size. The RV-LV-IED was divided by the QRS-duration at baseline and given as a proportion of the QRS-duration (RV-LV-IED/QRS-d).

Cardiac Magnetic Resonance Imaging scan analysis

A General Electric 1.5 Tesla CV scanner was used with 8-channel cardiac coil. For late gadolinium enhancement imaging, 0.1 mmol/kg of gadolinium was injected and imaging started after 10 minutes delay in short axis and multiple long axis views. Cardiac gated

segmented inversion-recovery prepared gradient echo pulse sequence was used with field of view 38-42 cm, matrix of 256 x 192-256, slice thickness of 7-8 mm, interslice gap of 2-3 mm, inversion time of 175-300 ms, adjusted to null normal myocardial signal. The optimal inversion time that nulls normal myocardium was determined by acquiring multiple images of the same midventricular view using different inversion times. ReportCard software (General Electric, Waukesha WI 4.2) was used to quantify scar tissue by manual tracing. The left ventricle was divided into sixteen regions. Percent scar tissue in the regions of interest (%ROI) was scored from zero to four; 0 (%ROI 0-1), 1 (≥ 1-24), 2 (≥ 15-49), 3 (≥ 50-74), 4 (≥ 75-100). Scar tissue score was defined as the mean of scar tissue scores in all 16 regions.

Clinical outcome and definition of responders

The primary outcome variable was left ventricle reverse remodeling, measured with echocardiography at baseline and after 8 months. A significant left ventricle reverse remodeling and response to CRT was defined as patients with a decrease in left ventricular end-systolic volume (LVESV) ≥ 15% after eight months. Volumes were analyzed as absolute values. Clinical response was defined as an improvement in NYHA functional class by one or more, ≥ 10 % reduction in score on the MLHFQ, or ≥ 10 % improvement in the 6MWT at eight months follow-up.

Statistical Analysis

Statistical analysis was performed using SPSS 24 for Mac. Descriptive statistics were reported as mean ± standard deviation for normally distributed continuous variables and reported as proportions for categorical variables. Normality was tested by Shapiro-Wilk test, box-plot was created to check for outliers and Levene's test was assessed to check for

homogeneity of variances. Differences between mean data were compared with independent-samples t-test and differences in proportions were compared by applying chi-square-test or Fisher's exact test. A p-value < 0,05 was considered significant for all tests. The Spearman's rank-order correlation was run to measure whether there was an association between the percentages of electrical (RV-LV-IED) and anatomical (LVESV) reverse remodeling. To determine whether there was a monotonic relationship between the variables a visual inspection of a scatterplot of the two variables was performed. Receiving operating characteristic curve analysis was used to identify the optimal cut-off value for RV-LV-IED and for RV-LV-IED/QRS-duration that could best discriminate between responders and non-responders. The value that maximized the area under the ROC curve (AUC) was used as the optimal cut-point. Candidate variables with p -values < 0,1 in univariate analysis were included in the multivariable regression model using backward selection to test the independent association with outcome.

This study complies with the Declaration of Helsinki. The research protocol was approved by the locally appointed ethics committee, and informed consent of the subjects has been obtained.

Results

Out of 70 patients, one patient was excluded due to early LV lead displacement and one patient died before CRT implantation. The study population included 19 % women and had a mean age of 69 ± 8 years. All the patients had LBBB and ischemic cardiomyopathy. The patients were mostly in NYHA functional class III (79 %), with a wide QRS-complex (160 ± 20 ms), increased LVESV (146 ± 62 ml) and impaired LVEF (27 ± 7 %). In general, the patients were medically optimized.

Response to CRT

Echocardiographic response

After eight months follow-up 44 out of 68 (65 %) patients showed significant LV reverse remodeling (LVESV from 152 ± 29 ml to 104 ± 55 ml, p < 0,001), non-responders; (LVESV from 134 ± 44 ml to 138 ± 43 ml, p = 0,296).

Clinical response

Sixty out of sixty-eight patients (88 %) had clinical effect with improvement in either NYHA functional class, MLHFQ or 6MWT distance. Improvement in NYHA functional class was seen in 38/68 patients (56 %), 46/65 (71 %) showed significant improvement on MLHFQ and 32/59 (54 %) improved significantly in 6-minute walking test distance.

Response in relation to IEDs

Baseline characteristics according to echocardiographic response are presented in **Table 1**. RV-LV-IED was significantly longer among responders compared to non-responders (87 ± 33 vs. 65 ± 47 ms, p = 0,047). Responders to CRT also had a significantly longer RV-LV-IED adjusted to surface ECG QRS-duration (RV-LV-IED/QRS-d) compared to non-responders (p = 0,026). The response rates for each quartile of RV-LV-IED/QRS-d are demonstrated in **Figure A** demonstrating the importance of a certain degree of activation delay for CRT response. With regards to the other IEDs there were no significant differences between responders and non-responders at baseline.

For patients with QRS-durations of 120-149 ms RV-LV-IED was significantly longer among responders compared to non-responders (75 ± 19 vs. 48 ± 32 ms, p = 0,035). For

patients with QRS-durations of 150 ms or more there was no significant difference in the RV-LV-IED between responders and non-responders (90 ± 36 vs. 79 ± 54 ms, p = 0,498). Using the median for RV-LV-IED, in a model with QRS-duration, IED was still independently associated with LV remodeling after CRT: OR 3,99 [95% CI 1,02-15,7] (p = 0,04).

Clinical response

Responders, assessed with improvement in 6 minutes walking distance, had a significantly longer RV-LV-IED/QRS-d compared to non-responders (p = 0,049). RV-LV-IED ≥ 50 % of the surface ECG QRS-duration showed a tendency of association to response in NYHA functional class (p = 0,064). Otherwise, no significant association between IEDs and clinical parameters were present.

Cut-off values for IEDs

The cut-off value for RV-LV-IED that best predicted LV reverse remodeling after CRT was 46 ms (sensitivity 87 %, specificity 62 %) and for RV-LV-IED/QRS-d the optimal cut-off value was 0,33 (area under the curve 0,70, 95 % CI 0,58 – 0,80; p = 0,007; sensitivity 87 %, specificity 54 %). Among patients with RV-LV-IED/QRS-d < 0,33 only 23 % were echocardiographic responders (p = 0,001).

In multivariate analysis including sex, age and scarburden an IED/QRS > 0,33 was highly associated with significant LV reverse remodeling: HR 7,3 [95% CI 2,04-26,10] (p= 0,002). IED as a continuous variable was found to be borderline significant in the multivariate model: OR 1,02 [95% CI 0,99-1,033] (p= 0,06).

However, the cut-off value was not useful for identification of clinical responders with regards to improvement in NYHA functional class, MLHFQ or 6MWT distance, see **Figure B**.

Electrical remodeling

IEDs do not change over time and are independent of LV volume changes. After eight months of CRT no significant changes in RV-LV-IED/QRS-d were observed among echocardiographic responders (from 0,54 ± 0,20 to 0,57 ± 0,22, p = 0,205) or non-responders (from 0,37 ± 0,21 to 0,39 ± 0,26, p = 0,556). The same applied for the other IEDs. Overall there was no difference in changes of the IEDs (ΔRV-LV-IED/QRS-d) over time between responders and non-responders (p = 0,386).

Accordingly, no correlation was demonstrated between changes in LVESV and RV-LV-IED/QRS-d, spearman's rho was 0,109 and the correlation coefficient was not statistically significant (p = 0,384). The same applied when continuous variables where used, spearman's rho was 0,2 and the correlation coefficient was not statistically significant (p = 0,194). Similarly, no correlation was found between decrease in LVESV and the other IEDs. The linear regression model comparing the percent change in LVESV and RV-LV-IED showed that a 10 ms increase in baseline RV-LV-IED was associated with a 1,4 % decrease in LVESV. [95% CI -0.0026-0.00056], (p= 0,04).

However, a significant decrease in the QRS-duration was observed after CRT among echocardiographic responders (from 162 ± 20 ms to 136 ± 22 ms, p < 0,001).

IEDs and scar tissue

Patients with a long RV-LV-IED/QRS-d (≥ 0,33) had more myocardial scar tissue than patients with a short RV-LV-IED/QRS-d (< 0,33) (1,0 ± 0,5 vs. 1,4 ± 0,5, p = 0,040). There were more responders among patients with long RV-LV-IED/QRS-d and a low scar tissue burden (below 1,19) than in the other patient groups, but the difference was not statistically significant (p = 0,065), see **Figure C**.

Even among patients with echocardiographic response and a low scar tissue burden no changes were observed in IEDs over time (ΔRV-LV-IED/QRS-d: from 0,53 ± 0,2 to 0,56 ± 0,04, p = 0,378).

Discussion

The importance of IEDs for response to CRT patients with ischemic cardiomyopathy is poorly described. In the present study the role for scar tissue and IEDs were investigated in a cohort of ischemic CRT patients.

The study demonstrated that

1) The IEDs (RV-LV-IED) are useful markers of response in CRT-patients with ischemic cardiomyopathy independent of scar tissue.
2) IEDs may be particularly useful among patients with QRS less than 150 ms.
3) After LV reverse remodeling no changes in IEDs can be demonstrated, and changes in IEDs and LV-volumes are not correlated.

The use of the RV-LV-IED to evaluate the LV activation delay and the association with CRT response has been investigated throughout recent years. Gold et al (14) used QLV (the time interval from the onset of QRS at surface ECG to the first peak by the LV lead at the sensed electrogram) and reported that patients with IEDs in the highest quartile had a significantly better chance of reverse remodeling response and improvement in quality of life after CRT. Later, the same group showed that long IEDs (this time measured as RV-LV duration) were also associated with improved outcome based on a composite end point of HF hospitalization or death. (15) Similarly, smaller studies have suggested that RV-LV-IED,

as used in the present study, can be related to echocardiographic response as well as symptomatic benefits. (6, 8, 10, 12, 15-18)

It has been questioned whether prolonged IEDs are useful as markers of response in the presence of scar tissue. (4, 6) Scar tissue may cause prolonged IEDs without the presence of an electrical substrate well-suited for CRT. The current study confirms the importance of IEDs for response to CRT specifically in patients with ischemic cardiomyopathy. Thus, prolonged IEDs were associated with a favorable CRT-response independent of scar tissue. Interestingly, our data further suggest that IEDs may be particularly useful in patients with QRS between 120-149 ms. Responders and non-responders in this group separated quite clearly numerically in IED values. The data suggests that some patients with QRS 120-149 ms do not have a significant activation delay in the LV despite LBBB by ECG. Short IEDs (presuming anatomical separation) support such cases.

It is well-known that patients with ischemic heart disease (IHD) benefit less from CRT than other HF patients. (19-21) Emerek et al. (6) reported that patients with IHD had significantly shorter and more heterogeneous RV-LV-IEDs likely to result in less LV reverse remodeling after CRT compared to patients with non-ischemic dilated cardiomyopathy (DCM). Our results support that a large variety in IEDs exists among CRT-patients with IHD. Patients with long IEDs were found to have slightly more scar tissue but seemingly without compromising the predictive value.

The importance of interlead electrical delays fits well with the concept of the working mechanism behind CRT. A significant activation delay of the LV must be present for CRT to have an optimal effect, and the importance of a long IED may not be surprising. The clinical implications on the other hand is still not clear. A role for IEDs may suggest a strategy of evaluating interventricular electrical delay at the time of LV lead implantation with the goal of

achieving as long an IED as possible. This may include repositioning of the LV lead or changing the pacing site in case of a quadripolar LV-lead. (15)

A national multicenter CRT study regarding IED-guided CRT (Danish-CRT) has now been initiated to elucidate questions like this.

Only few studies have looked at the impact of other IEDs on CRT response, such as the paced IEDs between the RV and LV-leads. (6, 9, 22) Emerek et al. (6) found no relation to CRT-outcome for pRV-sLV-IED or pLV-sRV-IED. In agreement, the current study did not show any association between pRV-sLV-IED or pLV-sRV-IED and CRT-outcome. RV-LV-IED depicts the actual conduction disease better than the other IEDs and therefore is superior to pRV-sLV-IED and pLV-sRV-IED in identifying significant LV activation delay such as in the presence of a true LBBB activation. The value of RV-LV-IED and RV-LV-IED/QRS-d corresponding with the highest accuracy in predicting CRT response was 46 ms and 0,33 respectively, for the current study.

The relationship between electrical and anatomical reverse remodeling was recently investigated by D'Onofrio et al. (23) in a sub-analysis of CRT-MORE. They demonstrated that LV reverse remodeling yields some decrease in RV-LV-IED after 6 months, but the variables where not found significantly correlated to each other. D'Onofrio et al proposed a different time course of the electrical and anatomical reverse remodeling as one explanation of the lack of association. The present study had an observation time of 8 months and confirmed their results. Our findings did not support the hypothesis that a reduction in LV-volume correlate to a reduction in IEDs. Although patients with a long RV-LV-IED/QRS-d showed a great potential of LV reverse remodeling, they underwent minimal electrical changes (assessed by IEDs) and this was independent of the LV scar burden. It appears

that CRT correct conduction delays, but does not improve the electrical substrate and thus IEDs will remain unchanged even in the presence of LV volume changes.

It has been proposed that the QRS-duration should be corrected by the heart size when selecting patients for CRT. Based on the present study it is not likely that the QRS-duration should be dependent on changes of heart size.

Limitations

Patients with IHD show dispersion in their electrical activation pattern, the optimal anatomical position may not correspond to the optimal electrical position and the LV-lead may not be positioned at the latest activated site in every patient. The vast majority of LV-leads were placed in a postero-lateral branch of the sinus coronaries thought to be the latest activated site in case of LBBB. Placement of the LV lead in other areas may cause misinterpretation regarding LV activation time.

The findings in this article are based on an automated feature from St. Jude to measure IEDs. This feature uses manual measurements from the intracardiac EGM. It is comparable to Q-LV measurements although individual differences are observed. Consequently, cutoff-values are not interchangeable between studies using different methods.

IEDs may be partly dependent on both RV and LV lead location. As mentioned in the method section the RV-leads were typically placed in the mid-distal septum. The LV-lead preferentially in a (postero)-lateral branch of the coronary sinus. The values for IEDs may not be comparable to other implanting centers where the RV-lead is preferably placed in the apex.

This study was performed in patients with LBBB and sinus rhythm. The results do not

necessarily apply to other CRT-patients.

In total 11 patients did not have MRI with scar assessment. This was due to poor image quality (3), claustrophobia (3), other reasons (5).

Conclusion

RV-LV-IED was an independent marker of response in CRT patients with ischemic cardiomyopathy even in the presence of scar tissue and may be particular useful in patients with QRS < 150 ms. CRT did not influence IEDs over time.

Conflict of interest

None declared.

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Table 1

Clinical characteristics of studied patients by responders and non-responders

	Responders (n = 44)	**Non-responders** (n = 24)	p -value
Characteristics			
Age (years)	69 ± 7	69 ± 9	0,947
Male, n (%)	33 (75)	22 (92)	0,117
Prior CABG, n (%)	19 (43)	13 (57)	0,318

Prior MI, n (%)	23 (52)	6 (25)	0,041*
Diabetes, n (%)	13 (30)	4 (19)	0,386
HT, n (%)	26 (59)	14 (58)	1
HC, n (%)	37 (84)	16 (67)	0,129
Creatinin (mmol/L)	102 ± 30	102 ± 39	0,992
BMI (kg/m^2)	26 ± 4	27 ± 4	0,298
NYHA III, n (%)	35 (80)	19 (80)	1
MLHFQ	42 ± 22	36 ± 16	0,233
6MWT (meters)	384 ± 109	366 ± 85	0,432
QRS-d (msec)	162 ± 20	156 ± 19	0,175
QRS-d ≥ 150, n (%)	32 (73)	11 (46)	0,037*
Scar-tissue score	1,0 ± 0,5	1,4 ± 0,6	0,006*
LVEF (%)	27 ± 8	28 ± 7	0,451
LVESV (ml)	152 ± 69	135 ± 44	0,208
RV-LV-IED (msec)	87 ± 33	65 ± 47	0,047*
RV-LV-IED/QRS-d	0,5 ± 0,2	0,4 ± 0,3	0,026*
RV-LV-IED ≥ 50% of QRS-d	24 (55)	7 (29)	0,074
pRV-sLV-IED	162 ± 22	162 ± 30	0,91
pRV-sLV-IED/QRS-d	1 ± 0,2	1 ± 0,2	0,479
pLV-sRV-IED (msec)	142 ± 32	146 ± 34	0,665
pLV-sRV-IED/QRS-d	0,9 ± 0,2	1 ± 0,2	0,217
Medications			
ACEI/ARB, n (%)	43 (98)	23 (96)	1
BB, n (%)	40 (91)	23 (96)	0,649
Diuretic, n (%)	35 (80)	19 (79)	1
Spiron, n (%)	30 (68)	15 (63)	0,789

Statin, n (%)	41 (93)	21 (88)	0,658

CABG = coronary artery bypass surgery; MI = myocardial infarction; HT = hypertension; HC = hypercholesterolemia; BMI = body mass index; NYHA = New York Heart Association function classification; MLHFQ = Minnesota living with heart failure questionnaire; 6MWT = 6 minutes walking test; QRS-d = QRS-duration; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; RV-LV-IED = sensed right ventricle to left ventricle interlead electrical delay; pRV-sLV-IED = paced right ventricle to sensed left ventricle interlead electrical delay; pLV-sRV-IED = paced left ventricle to sensed right ventricle interlead electrical delay; ACEI/ARB = angiotensin-converting enzyme inhibitorer / angiontensin receptor blocker; BB = beta-blocker; spiron = spironolacton

Figure legends

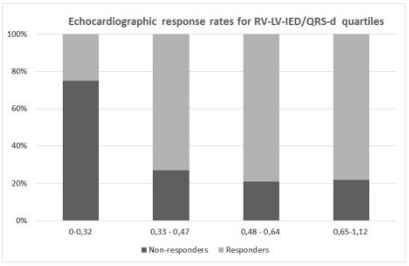

Figure A: Echocardiographic response in relation to RV-LV-IED/QRS-d quartiles.

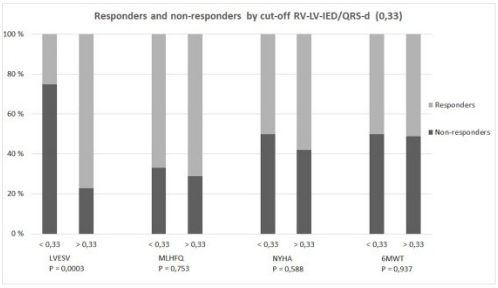

Figure B: The percentage of echocardiographic and clinical responders and non-responders in patients based on a cut-off for RV-LV-IED/QRS-d at 0,33.

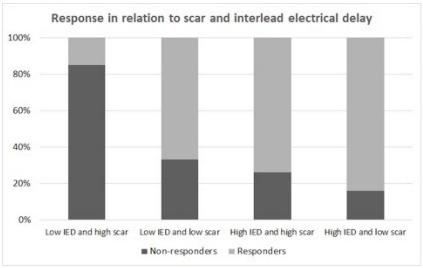

Figure C: The percentage of echocardiographic responders and non-responders divided by high or low IED (defined as RV-LV-IED/QRS-d above or below the cut-off value at 0,33) and high or low scar (defined as a scar tissue score above or below 1,19).