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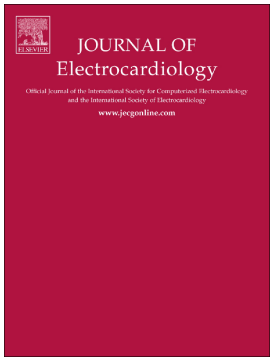

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Left axis deviation in patients with left bundle branch block is a marker of myocardial disease associated with poor response to Cardiac Resynchronization Therapy

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Abstract

Aims:

Patients with left axis deviation (LAD) and left bundle branch block (LBBB) show less benefit from cardiac resynchronization therapy (CRT) compared to other LBBB-patients. This study investigates the reasons for this.

Methods:

Sixty-eight patients eligible for CRT were included. Patients were divided into groups according to QRS-axis; normal axis (NA), left axis deviation (LAD) and right axis deviation (RAD). Before CRT implantation CMR imaging was performed to evaluate scar tissue. Echocardiography was performed before and after implantation. The electrical substrate was assessed by measuring interlead electrical delays. Response was evaluated after 8 months by left ventricular (LV) remodelling and clinical response.

Results:

Forty-four (65 %) patients were responders in terms of LV remodelling. The presence of LAD was found to be independently associated with a poor LV remodeling non-response OR 0.21 [95% CI 0.06 - 0.77] (p= 0.02). Patients with axis deviation had more myocardial scar tissue (1.3 ± 0.6 vs. 0.9 ± 0.6, P = 0.04), more severe LV hypertrophy (14 (64 %) and 6 (60 %) vs. 7 (29%), P = 0.05) and tended to have a shorter interlead electrical delay than patients with NA (79 ± 40ms vs. 92 ±

48ms, P = 0.07). A high scar tissue burden was more pronounced in non-responders (1.4 ± 0.6 vs. 1.0 ± 0.5, P = 0.01).

Conclusions:

LAD in the presence of LBBB is a predictor of poor outcome after CRT. Patients with LBBB and LAD have more scar tissue, hypertrophy and less activation delay.

Keywords: cardiac resynchronization therapy, heart failure, left bundle branch block, QRS axis deviation

Highlights

- LAD among CRT-patients is a marker of poor response to CRT both in terms of left ventricular remodeling and functional response

- Patients with LAD in the presence of LBBB are characterized by structural myocardial changes with more hypertrophy and scar tissue compared to non-LAD patients as well as less pronounced LV activation delay.

List of Abbreviations

6MWT = 6-minute walk test
ACEI = angiotensin converting enzyme inhibitor
ARB = angiotensin receptor blocker
BB = beta blocker
BSA = body surface area
CABG = coronary artery bypass grafting
CRT = cardiac resyncronization therapy
ECG = electrocardiogram
EF = ejection fraction (of left ventricle)
GFR = glomerular filtration rate
HF = heart failure
ICD = implantable cardioverter defibrillator
IHD = ischemic heart disease
IVSd = interventricular septal thickness at end-diastole (mm)
LAD = left axis deviation
RAD = right axis deviation
NA = normal axis
LBBB = left bundle branch block
LV = left ventricle
LVEDD = left ventricular end-diastolic dimension (mm)
LVEF = left ventricular ejection fraction
LVESV = left ventricular end-systolic volume
MI = myocardial infarction
MLHFQ = Minnesota Living with Heart Failure Questionnaire
NYHA = New York Heart Association (functional classes of heart failure)
PWd = posterior wall thickness at end-diastole (mm)
RBBB = right bundle branch block ROI = region of interest
SD = standard deviation
STS = scar tissue score

1. Introduction

Cardiac Resynchronization Therapy (CRT) is an established treatment for a subgroup of patients with heart failure (HF), but more than one third of CRT-recipients demonstrate suboptimal response. [1, 2] In addition, recent landmark clinical trials have demonstrated that CRT may cause harm in some patients. [3, 4] This emphasizes the importance of identifying predictors of CRT response to further refine current selection criteria and adjust outcome expectations.

Patients with left bundle branch block (LBBB) have the most favorable response to CRT [2, 5] but for unclear reasons the QRS-axis holds additional prognostic information. Studies indicate that patients with an abnormal QRS-axis may benefit less from CRT compared to patients with a normal QRS-axis, although the importance of an abnormal QRS axis is still debatable. [6-8] It may be that an abnormal QRS-axis in the presence of LBBB reflects more advanced underlying structural disease compared to patients with LBBB and a normal axis. [9-10] Another explanation may be that these patients have different activation sequences less amenable to CRT.

The aim of this study was to investigate the pathophysiology behind QRS-axis deviation in LBBB and its impact on CRT by 1) characterizing structural and electrical differences within subgroups of left, right and normal axis, and 2) to relate these findings to response after CRT.

2. Material and methods

2.1. Study population

Seventy consecutive patients with heart failure and ischemic heart disease (IHD) referred for CRT-implantation between October 2009 and July 2012 at Gentofte University Hospital in Denmark (63 patients) and Lund University hospital in Sweden (5 patients) were prospectively included in this study. All patients fulfilled the following criteria at the time of implantation: left ventricular ejection fraction (LVEF) ≤ 35 %, New York heart association (NYHA) functional class II and III, despite optimal medical treatment and LBBB defined as QRS duration > 120ms, broad notched or slurred R wave in leads I, aVL, V5, and V6, absent q waves in leads I, V5, and V6 and R peak time greater than 60 ms in leads V5 and V6 and normal in leads V1, V2, and V3. IHD was defined as either prior coronary artery bypass grafting (CABG), prior myocardial infarction (MI) or > 70 % stenosis in one or more major epicardial coronary artery diagnosed on coronary artery catheterization. Patients with significant primary valve disease, atrial fibrillation, acute coronary syndrome and/or revascularization within three months of the baseline echocardiography were excluded. As were pregnant patients, patients with dementia or mental retardation, severe health condition threatening short-term survival, severe kidney insufficiency defined as glomerular filtration rate (GFR) < 35 mL /min/1.73 m^2, severe claustrophobia or metal implants contraindicative of magnetic resonance scan.

2.2. 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 high right atrium, a right ventricular lead was placed on the septum and the LV lead was placed preferably in a posterolateral position. Only patients with > 92 % biventricular pacing were included.

2.3. ECG-analysis

Patients were divided into three groups according to QRS-axis; 1) Normal axis (NA: -30° to 90°), 2) Left axis deviation (LAD: < -30° to -90°) and 3) Right axis deviation and far right axis deviation (RAD: < -90 to > 90°). To determine the QRS-axis it was decided if the axis was normal, right-sided or left-sided by looking at lead II and I. Then, by assessing the lead with the most isoelectric QRS-complex, and finding the perpendicular direction to the lead fitting into the previous determined axis, the approximate axis was found. The assessed axis was crosschecked with the axis automatically calculated by the ECG-machine. If mismatch occurred, the manual assessment was used.

2.4. Echocardiography

Echocardiographic studies were performed on Vivid 9 ultrasound machines (GE Healthcare, Horten, Norway) and analyses were performed using Echopac PC (version BT11 GE Vingmed Ultrasound). All analyses were performed off-line blinded to outcome and ECG information. Simpson´s method of discs was used to measure left ventricular end systolic volumes (LVESV) and left ventricular ejection fraction

(LVEF). LV mass was quantified using Devereux' formula (0.8{1.04(((LVEDD + IVSd + PWd)^3 - LVEDD^3))} + 0.6), and indexed to body surface area (BSA) calculated by the Mosteller formula ($\sqrt{\frac{height\ x\ weight}{3600}}$). LV mass was divided into mildly, moderately and severely abnormal according to sex and reference ranges for LV mass indexed to BSA**.** [11]

2.5. 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 × 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, see **Figure 1**. Percent scar tissue in the regions of interest (%ROI) was scored from zero to four; 0 (%ROI 0-1), 1 (≥ 1 – 24), 2 (≥ 25 – 49), 3 (≥ 50 – 74), 4 (≥ 75 – 100). Scar tissue score was defined as the mean of scar tissue scores in all 16 regions.

2.6. Interlead electrical delays (IEDs)

IEDs were measured the day after CRT implantation, using an automated function in the St-Jude device. RV-LV-IED was defined as the time interval in milliseconds between sensing at the right ventricle (RV)-lead and left ventricle (LV)-lead. To account for beat-to-beat variations all intervals were averaged over eight consecutive beats. [12]

2.7. Follow-up and outcomes

The primary end-point was LV reverse remodelling, measured as LVESV. Responders were defined as patients with ≥ 15 % decrease in LVESV after eight months. Clinical response, the secondary end-point, was defined as an improvement in NYHA functional class by one or ≥ 10 % reduction in score on the Minnesota living with heart failure questionnaire (MLFHQ) or a ≥ 10 % increase in walking distance on the six-minute walk test (6MWT) after eight months.

2.8. Statistical Analysis

Statistical analysis was performed using SPSS. P-values < 0.05 were considered statistically significant. Box-plot was created to check for outliers and normality was tested by Shapiro-Wilk-test. Levene's test of equality of variances was used to test for homogeneity. Characteristics of patients separated by responders/non-responders were compared with Chi-square-test, independent-samples t-test or one-way Anova as appropriate. Multivariate analysis was performed using logistic regression. Candidate variables with *P*-values of < 0.1 in univariate

analysis were included in the multivariable model using backward selection. Continuous variables are reported as mean ± standard deviation (SD), non-normally distributed data are presented as median and IQR and categorical variables are reported in percentages. 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 1975 Declaration of Helsinki. The research protocol was approved by the locally appointed ethics committee, and informed consent of the subjects has been obtained.

3. Results

Out of 70 patients, one patient had a displaced LV-lead within the first month and one patient died 3 days before CRT-implantation. Accordingly, both were excluded from any further analysis. In 2 patients the first implant attempt failed (both due to coronary dissection) but was successful at a later second attempt. Sixty-one patients (90%) had the LV lead placed in a posterior or lateral site.

The study group had a mean age of 69 ± 8 years and 55 patients (81 %) were male. Most patients (79 %) were classified in NYHA class III, the rest in NYHA class II. In general, the patients were on optimal medical therapy.

3.1. QRS-axis and myocardial structural changes

LAD was identified in 29 patients (43 %), 10 (15 %) patients had RAD and 29 (43 %) had NA. The mean QRS-axis was - 4°± 66°; - 50° ± 13° for LAD, 73° ± 115° for RAD and 16° ± 35° for NA. The baseline characteristics according to axis deviation are presented in **Table 1.**

In patients with axis deviation structural myocardial changes were more common when compared to patients with NA. Thus, patients with axis deviation had more scar tissue (1.3 ± 0.6 vs. 0.9 ± 0.5, P = 0.04) compared to patients with NA, for LAD vs NA (1.25 ± 0.6 vs. 0.9 ± 0.5, P = 0.05). Furthermore significant LV hypertrophy was more frequently observed with axis deviation compared to normal axis (20 (63 %) vs. 7 (29 %) for NA, P = 0.01), for LAD vs NA (14 (64 %) vs. 7 (29 %), P = 0.04). The scar tissue was distributed mainly apically and anteroseptally in patients with LAD, see **Figure 1**, while the distribution in patients with NA appeared

more uniform. Patients with LAD had a shorter RV-LV-IED than patients with NA (72 ± 28 ms vs. 92 ± 48ms, P = 0.05) despite similar QRS-duration.

3.2. Response to CRT in relation to QRS axis

LV remodelling

During the follow up period of eight months LVESV was reduced from 146 ± 62 mL to 117 ± 53 mL (P = < 0.005) and LVEF was increased from 27 ± 7 % to 36 ± 10 % (P = < 0.005) for the overall population. Forty-four patients (65 %) were responders in terms of LVESV reduction of > 15%. Baseline characteristics of patients according to volumetric response are presented in **Table 2.** There were significantly fewer responders among patients with LAD compared to patients without LAD (14 (48 %) vs. 30 (77 %) P = 0.01), LAD compared to NA; (14 (48 %) vs. 23 (80 %) P = 0.03) Responders were characterized by having less scar tissue in the LV (1 ± 0.5 vs. 1.4 ± 0.6, P = 0.01) and longer native activation delay, assessed by RV-LV-IED from the CRT-device, than non-responders (87 ± 3 vs. 65 ± 47, P = 0.03). Fifty-two percent of responders had a history of myocardial infarction and 73 % had QRS-duration over 150 ms on ECG. In a multivariate regression model for the overall group (including gender, age, scar burden and QRS-duration) the presence of LAD was found to be independently associated with a poor LV remodeling non-response OR 0.21 [95% CI 0.06 - 0.77] (p= 0.02). QRS-width < 150 ms, OR 0.22 [95% CI 0.06 - 0.79] (p= 0.02) and high scar burden (above median) OR 0.37 [95% CI 0.08 – 1.02] (p= 0.06) were also independently associated with a poor remodeling response.

Clinical response

Sixty patients (88 %) responded clinically to CRT treatment, either by reduced NYHA class or improved MLHFQ or 6MWT. Eighteen (30 %) patients responded in all clinical categories. In terms of NYHA class reduction in particular, there were fewer responders among patients with LAD compared to non-LAD patients (11 (40 %) vs. 27 (71 %), P = 0.01), see **Figure 2.** No differences were observed between groups with respect to 6MWT and MLHFQ.

4. Discussion

Previous studies have shown that the presence of QRS axis deviation is a predictor of unfavorable outcome after CRT. [6-7] However, reasons for this association are not well described. The current study demonstrates that the presence of LAD in CRT candidates with LBBB frequently reflects underlying structural myocardial disease such as hypertrophy and higher amount of scar tissue. Furthermore, patients with LAD have a tendency to a shorter activation delay, evaluated by interlead electrical delays. Scar tissue was a main determinant of outcome and is likely to explain the prognostic importance of LAD.

The presence of LAD in a LBBB patient is important because it indicates a less favorable outcome after CRT compared to other patients. In the current study patients with LAD were less likely to respond to CRT than patients with non-LAD both clinically (NYHA functional class) and with regards to reverse remodelling. Other studies have reported a reduced response among patients with axis deviation. Brenyo et al. [6] found that patients with LAD had less reduction in LVESV and dyssynchrony as well as a higher risk of subsequent HF-hospitalizations and death compared to patients with non-LAD. Perrotta et al. [7] found that both left and right axis deviation was associated with worse survival rate and higher risk of HF-hospitalizations compared to NA.

The current study explored potential reasons for a suboptimal response to CRT among patients with LBBB and concomitant LAD. Patients with LAD were characterized by more severe myocardial disease such as scar tissue and LV hypertrophy. While hypertrophy was not related to LV remodelling after CRT, scar tissue demonstrated an independent association with response.

The amount of myocardial scar tissue as well as positioning of the LV lead in a scar tissue region has proven to be predictive of less benefit from CRT. [13-16] Patients with scar tissue might be less likely to experience favorable reverse remodelling and localized areas of scar tissue might interfere with the myocardial activation resulting in an inefficient activation sequence and thereby less response. Studies have shown that transmural scarring and localized postero-lateral scarring in particular are associated with unfavorable outcome. [17, 18] In this study the scar tissue was distributed mainly apically and anteroseptally in patients with LAD. In patients with LBBB activation it seems plausible that scarring of the apical and anteroseptal regions would skew the axis towards a more left directed axis. Thus, this pattern seems to fit our findings.These results could imply a possible benefit of a pre-implantation CMR to target placement of the LV-lead in a segment free of scar tissue.

Prior studies regarding the importance of LV-hypertrophy for CRT response are lacking, but in general LV hypertrophy is associated with multiple different conditions including hypertension, aortic valve disease and genetic disorders, and a hypertrophied LV can represent severe cardiomyopathy. [19-20] These matters were not further explored in the current study. Of note, none of our patients had hypertrophic cardiomyopathy as the primary diagnosis.

Patients with LAD had a tendency to a shorter RV-LV-IED than patients with NA. RV-LV-IED may be considered as an indirect measure of the activation delay in the LV and a longer delay has been associated with a favorable outcome in several studies. [12] The difference in IED could imply that some of the patients with LAD do not have a true LBBB and a wide QRS may to a higher degree be caused by scar tissue and hypertrophy. [21]

5. Study limitations

This study is limited by a relatively small number of patients. Larger studies are warranted to establish the role for LAD as a clinically useful criterion for selection of CRT candidates. Due to the limited number of patients, patients with right axis deviation were less focused on in the current study. Patients with LAD tended to have a smaller LVESV at baseline, making it less likely that they became responders only through regression to the mean bias. The possible role of LV lead location in modulating the differential outcome in the three subgroups of patients has not been addressed. LV lead positioning was preferably placed in the posterolateral wall. This may affect the measurement of interlead electrical delays. The presumption that the difference in interlead electrical delay could imply that some of the patients with LAD do not have a true LBBB, requires that leads are positioned in similar positions. Acute QRS narrowing has shown to predict favorable prognosis in patients with LBBB. [22] This parameter might contribute to explain differences in outcome between subgroups, but was not addressed in the study.

6. Conclusions

LAD is independently associated with a poor remodelling response to CRT. The presence of LAD in LBBB reflects underlying structural myocardial disease in patients with IHD treated with CRT, in particular scar tissue. In addition LAD patients show a trend to a less pronounced LV activation delay. These findings are likely the explanation for a suboptimal response to CRT in patients with LAD.

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Tables

Table 1: Baseline Characteristics of Patients by QRS axis

Characteristic	Total (n = 68)	NA (n = 29)	LAD (n = 29)	RAD (n =10)	P Value
Age (years)	69 ± 8	69 ± 8	68 ± 9	72 ± 6	0,47
Male, n (%)	55 (81)	25 (86)	22 (76)	8 (80)	0,6
HT, n (%)	40 (59)	19 (66)	15 (52)	6 (60)	0,56
HC, n (%)	53 (78)	24 (83)	21 (72)	8 (80)	0,63
Diabetes, n (%)	17 (27)	7 (41)	7 (41)	3 (30)	0,95
BMI (kg/m2)	27 ± 4	27 ± 4	27 ± 4	25 ± 4	0,6
Prior CABG, n (%)	32 (48)	15 (52)	12 (43)	5 (50)	0,79
Prior MI, n (%)	27 (41)	10 (37)	13 (48)	4 (40)	0,58
Creatinine (µmol/L)	102 ± 33	101 ± 32	102 ± 37	102 ± 25	0,99
NYHA III, n (%)	54 (79)	25 (86)	20 (69)	9 (90)	0,18
MLHFQ	67 ± 40	43 ± 22	38 ± 20	36 ± 18	0,61
6MWT (m)	378 ± 100	392 ± 82	363 ± 104	383 ± 138	0,58
QRS-d (msec)	160 ± 20	161 ± 23	163 ± 18	149 ± 16	0,14
QRS-d >150, n (%)	43 (63)	20 (69)	19 (66)	4 (40)	0,25
Scar-tissue score	1,1 ± 06	0,9 ± 0,6	1,3 ± 0,6	1,3 ± 0,6	**0,04***
LVEF (%)	27 ± 7	27 ± 9	28 ± 7	26 ± 4	0,71
LVESV (mL)	146 ± 62	151 ± 71	137 ± 52	157 ± 62	0,6
LVIDd (cm)	6,1 ± 1,0	6,0 ± 1,1	6,1 ± 0,8	6,1 ± 1,1	0,97
LV-htphy, n (%)	27 (48)	7 (29)	14 (64)	6 (60)	**0,05***
RV-LV-IED (msec)	79 ± 40	92 ± 48	72 ± 28	63 ± 36	0,1
pRV-sLV-IED (msec)	162 ± 25	166 ± 23	164 ± 23	145 ± 33	0,07
Medications					
ACE/ARB, n (%)	66 (97)	29 (100)	27 (93)	19 (100)	0,25
BB, n (%)	63 (93)	26 (90)	28 (97)	9 (90)	0,57
Diuretic, n (%)	54 (80)	24 (83)	24 (83)	8 (80)	0,81
Spiron, n (%)	45 (66)	19 (66)	21 (72)	5 (50)	0,43
Statin, n (%)	62 (91)	27 (93)	26 (90)	9 (90)	0,89

HT = hypertension; HC= hypercholesterolemia; BMI = body mass index;
CABG = coronary artery bypass surgery; MI = myocardial infarction;
NYHA = New York Heart Association fuctional classification;
MLFHQ = Minnesota Living with Heart Failure Questionnaire;
6MWT = 6-minute walk test; QRS-d = qrs-duration;
LVEF = left ventricular ejection fraction;
LVESV = left ventricular end-systolic volume;
LV-htphy = moderately or severely abnormal left ventricular mass;
RV-LV-IED = time interval between sensing at the RV-lead and LV-lead
pRV-sLV-IED = paced right ventricle to sensed left ventricle interlead electrical delay;
ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blockers;
BB = beta-blockers; spiron = spironolactone.

Table 2: Baseline Characteristics of Patients by Response to CRT

	Responders	**Non-responders**	
Characteristic	(n = 44)	(n = 24)	P Value
LAD, n (%)	14 (32))	15 (63)	**0,01***
Age (years)	69 ± 7	69 ± 10	0,94
Male, n (%)	33 (75)	22 (92)	0,12
HT, n (%)	26 (59)	14 (35)	0,95
HC, n (%)	37 (84)	16 (67)	0,1
Diabetes, n (%)	13 (30)	4 (19)	0,34
BMI (kg/m2)	26 ± 4	27 ± 4	0,23
Prior CABG, n (%)	19 (43)	13 (57)	0,3
Prior MI, n (%)	23 (52)	4 (18)	**0,01***
Creatinine (µmol/L)	102 ± 30	102 ± 38	0,99
NYHA III, n (%)	35 (80)	19 (79)	0,6
MLHFQ	42 ± 22	36 ± 16	0,28
6MWT (m)	385 ± 109	366 ± 85	0,5
QRS-d (msec)	163 ± 20	156 ± 19	0,18
QRS-d >150, n (%)	32 (73)	11 (46)	**0,03***
Scar-tissue score	1 ± 0,5	1,4 ± 0,6	**0,01***
LVEF (%)	27 ± 8	28 ± 7	0,46
LVESV (mL)	152 ± 69	136 ± 44	0,27
LVIDd (cm)	6 ± 0,9	6 ± 1	0,3
LV-htphy, n (%)	20 (51)	7 (41)	0,49
RV-LV-IED (msec)	87 ± 33	65 ± 47	**0,03***
pRV-sLV-IED (msec)	162 ± 22	162 ± 30	0,91
Medications			
ACE/ARB, n (%)	43 (98)	23 (96)	0,59
BB, n (%)	40 (91)	23 (96)	0,42
Diuretic, n (%)	35 (80)	19 (79)	0,6
Spiron, n (%)	30 (68)	15 (63)	0,42
Statin, n (%)	21 (88)	41 (93)	0,36

HT = hypertension; HC= hypercholesterolemia;
BMI = body mass index; CABG = coronary artery bypass surgery; MI = myocardial infarction;
NYHA = New York Heart Association fuctional classification;
MLFHQ = Minnesota Living with Heart Failure Questionnaire;
6MWT = 6-minute walk test; QRS-d = qrs-duration;
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Figure legends

Figure 1: Scar Tissue Score and Distribution in Left Ventricle according to QRS-axis

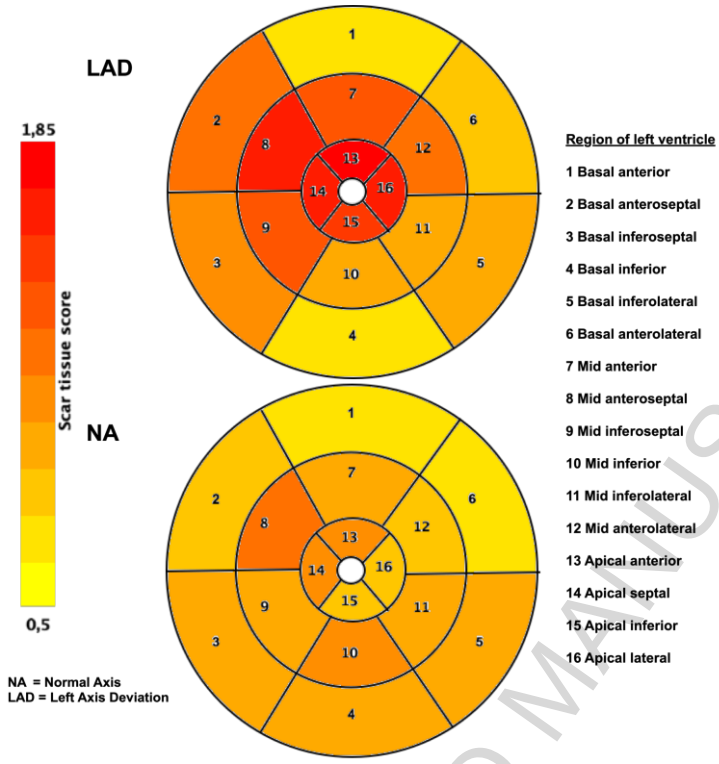
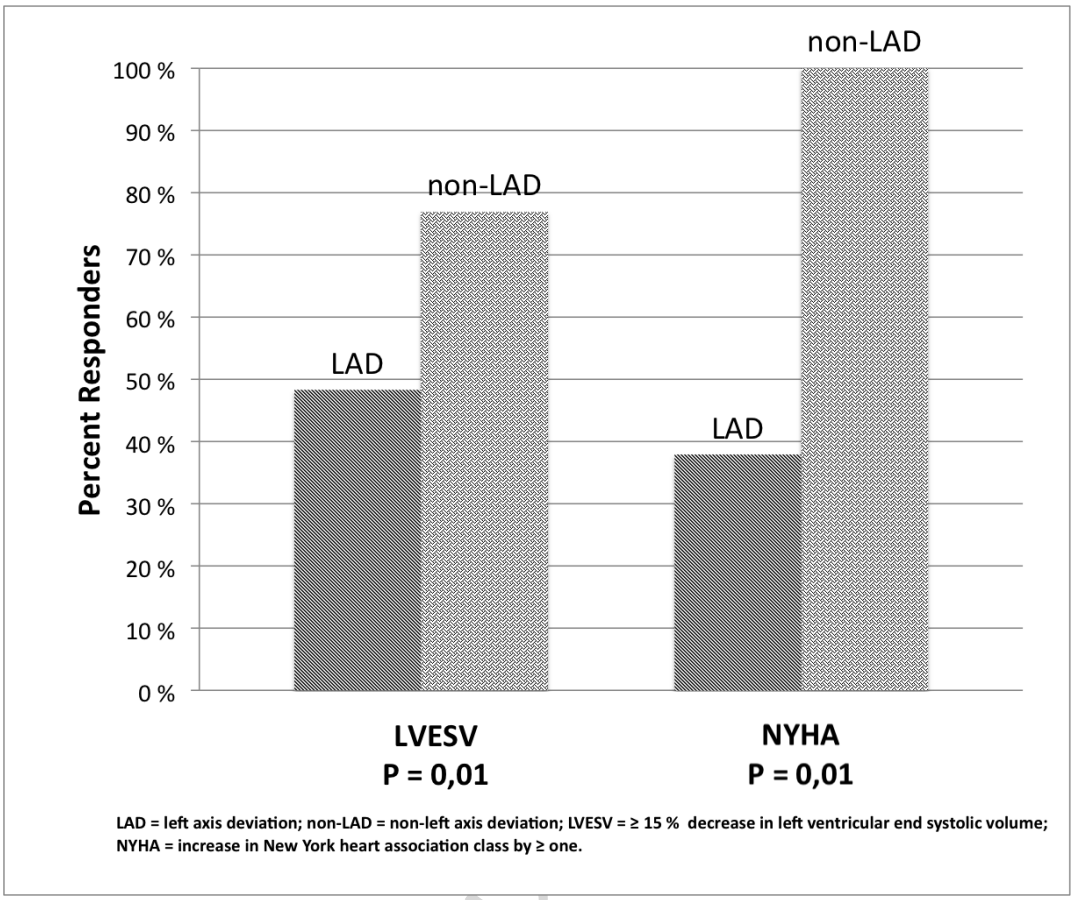
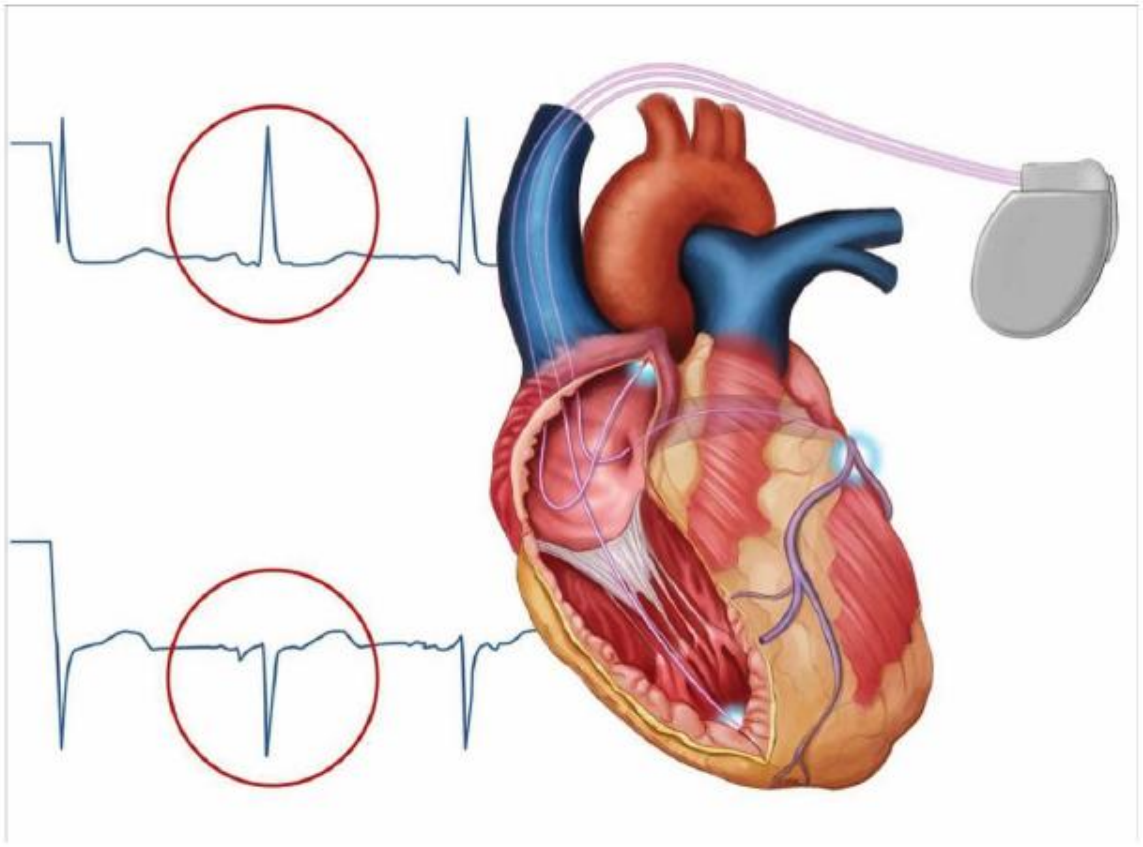


Figure 2: Percent Responders in terms of LVESV and NYHA by Left Axis Deviation (LAD) and Normal Axis (NA)



LAD = left axis deviation; non-LAD = non-left axis deviation; LVESV = ≥ 15 % decrease in left ventricular end systolic volume; NYHA = increase in New York heart association class by ≥ one.



Graphical abstract

Highlights

- LAD among CRT-patients is a marker of poor response to CRT both in terms of left ventricular remodelling and functional response

- Patients with LAD in the presence of LBBB are characterized by structural myocardial changes with more hypertrophy and scar tissue compared to non-LAD patients as well as less pronounced LV activation delay.