Prognostic Impact of Mechanical Activation Delay by Cross Correlation Analysis in Heart Failure Patients with narrow QRS treated with Cardiac Resynchronization Therapy: an Echocardiography Guided Cardiac Resynchronization Therapy (EchoCRT) Trial Sub-study

Short Title: Association of activation delay by tissue Doppler imaging with outcomes after CRT.

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Abstract

Background: Cross Correlation Analysis (CCA) using tissue Doppler imaging (TDI) shown to be associated with outcome after cardiac resynchronization therapy (CRT) in heart failure (HF) patients with wide QRS. However, its significance in narrow QRS patients treated with CRT is unknown.

Objectives: The aim of the current study was to investigate the association of mechanical activation delay by CCA with study outcome in HF patients enrolled in the EchoCRT trial.

Methods: Baseline CCA could be performed from TDI in the apical views in 807 of 809 (99.7%) enrolled patients while 6-months follow-up could be performed in 610 of 635 (96%) patients with available echocardiograms. Patients with a pre-specified maximal activation delay $\geq$ 35 ms were considered to have significant delay. The study outcome was HF hospitalization or death.

Results: Out of 807, 375 (46%) patients did not have delayed mechanical activation at baseline by CCA. Patients without delayed mechanical activation randomized to CRT-On had an increased risk of poor outcome (HR 1.70, 95% CI 1.13-2.55, P=0.01) in comparison to those with CRT-Off with a significant interaction term (P=0.04) between delayed mechanical activation and device randomization for the endpoint. Among patients with paired baseline and follow-up data with no events before 6-months follow-up (n=541), new-onset delayed mechanical activation in the CRT-On group showed significant increase in unfavorable events (HR 3.73, 95% CI 1.15-12.14, P=0.03).

Conclusions: In the EchoCRT population, absence of delayed mechanical activation by CCA was significantly associated with poor outcomes possibly due to the onset of new delayed mechanical activation with CRT pacing. (Echocardiography Guided Cardiac Resynchronization Therapy [EchoCRT] Trial; NCT00683696)

Key words: heart failure, cardiac resynchronization therapy, echocardiography, dyssynchrony, tissue Doppler imaging.

Condensed Abstract

In the current study we applied cross correlation analysis method (CCA) to assess mechanical activation delay in the population of echocardiography guided cardiac resynchronization therapy (EchoCRT) trial in which CRT was implanted in patients with narrow QRS (<130ms). CRT was fatal to patients with no activation delay at baseline which was possibly due to the pacemaker induced new activation delay.

Abbreviation List

CRT = cardiac resynchronization therapy

ECG = electrocardiographic

HF = heart failure

LVEF = left ventricular ejection fraction

TDI = tissue Doppler imaging

Several studies in the past have demonstrated that the assessment of mechanical dyssynchrony by echocardiography can supplement current electrocardiographic (ECG) criteria (wide QRS ≥ 120 ms) in selection of CRT candidates leading to an overall reduction in the non-responders rate.(1-3) However, conventional methods of identifying dyssynchrony based on segmental time-to-peak measurements have failed when applied in randomized trials for selecting patients for CRT with narrow QRS (<130ms).(4,5)

The largest CRT trial conducted on narrow QRS (<130 ms) patients - echocardiography guided cardiac resynchronization therapy (EchoCRT) - demonstrated that HF patients with narrow QRS (<130 ms) do not respond to CRT despite the presence of baseline mechanical dyssynchrony by time-to-peak methods by either tissue Doppler longitudinal velocity or speckle tracking radial strain.(4) In fact, an increased incidence of mortality was observed in patients randomized to CRT-On in comparison to the control group and the trial was stopped due to futility without achieving its complete target population. Another trial - The Resynchronization therapy in narrow QRS (RethinQ) - performed before EchoCRT with similar design where mechanical dyssynchrony was one of the selection criteria, also showed no benefit of CRT in HF patients with narrow QRS.(5)

More recently, it was shown that peak-to-peak measures of mechanical dyssynchrony may be influenced by contractile heterogeneity or scar not responsive to CRT.(6) Patterns of myocardial mechanics that have been shown to reflect electrical delay have shown very promising results and seem to better identify a true substrate for CRT response.(6-8) These newer methods seem superior to the conventional time-to-peak methods.(7,9) Among these, one approach is assessment of mechanical activation delay by cross correlation analysis (CCA) using tissue Doppler Imaging (TDI).(7,10) Presence of a delayed mechanical activation by CCA in the

wide QRS patients is associated with improved prognosis as well as response after CRT.(7,10,11) However, its significance is unknown in HF patients with narrow QRS (<130 ms) treated with CRT. Accordingly, the objective of the current study was to assess the association of delayed mechanical activation by the CCA method both at baseline and follow-up after randomization to clinical outcomes in patients enrolled in the EchoCRT trial.

Methods

Study Population

The current study is a pre-specified sub-study of the EchoCRT trial. All the patients included in the EchoCRT trial had left ventricular ejection fraction (LVEF) ≤ 35%, QRS duration of ≤ 130 ms, severe symptomatic HF with New York HF Association (NYHA) class III-IV symptoms, LV end diastolic diameter ≥ 55 mm, and echocardiographic evidence of mechanical dyssynchrony by time-to-peak methods. Methods used to identify dyssynchrony in this study were presence of TDI based opposing wall delay of ≥ 80 ms in the apical 4-chamber or 3-chamber view, and radial strain delay ≥ 130 ms between the septum and the posterior walls in the LV mid-segment short axis view. All the patients included in the trial were older than 18 years and provided informed consent for inclusion in the trial. It was a multicenter randomized trial in which patients were included between a period of 2008 to 2013 and involved 112 centers from 22 different countries. Patients with bradycardia pacing or atrial fibrillation with in the past few months were excluded. The main study results along with a detailed study protocol have been published.(4) All the patients included received a CRT device with defibrillator capacity (CRT-D) (Biotronik Lumax, Berlin, Germany) and randomized in 1:1 fashion to CRT-On and CRT-Off after a successful implantation of the device. For the current sub-study, 807 (99.7%) of

809 were included with the baseline data and 610 (96%) of 635 patients were included with paired data at both baseline and 6-months follow-up.

Cross correlation analysis

All the echocardiograms were performed using a single vendor ultrasound system GE Vivid 7 or E9, Horton, Norway. To reduce variability the offline TDI based analysis was performed on a single GE EchoPAC system (version BT 11, Horton, Norway) by a single observer blinded to the patient data. CCA has been illustrated in detail in our previous publications (Figure 1).(7,10,11) Briefly, regions of interest (7 x 15 mm) were placed on the base segments of the opposing walls in all three apical views and the resulting velocity data were imported on an automated excel sheet with a pre-written algorithm to perform CCA analysis. Subsequently, velocity data were converted to acceleration data by using time differentiation. A baseline correlation coefficient was calculated between the acceleration curves from two opposing walls during systole in each of the three apical views without time-shift. These acceleration curves were then time-shifted against each other frame-by-frame to maximum of 15 frames in both directions to calculate a correlation coefficient again. The time-shift resulting in the maximum correlation between the opposing walls was termed as maximum activation-delay (AD-max). Patients were classified as having significant activation delay if the AD-max was ≥35ms in any of the three apical views based on our previous work.(7,10) Systole was identified by calculating the aortic valve opening and closure timings from a pulse Doppler signal in the APLAX view. Activation delay by CCA was measured at both baseline and 6-months. For the analysis of the patients with paired CCA data, patients were divided into the following four groups based on the presence or absence of mechanical activation at baseline and follow-up:

1. No activation delay: no activation delay at both baseline and at follow-up.

2. Improved activation delay: activation delay at baseline but not at follow-up
3. Persistent activation delay: activation delay at baseline and at follow-up
4. New activation delay: no activation delay at baseline but activation delay at follow-up.

Study outcome

The outcome variable of this study was the primary end-point of all-cause death or first HF hospitalization within a period of 3.5 years.

Statistics

All the statistical analyses were performed by an independent Statistical Centre at the Robertson Centre for Biostatistics, University of Glasgow. Baseline characteristics were compared with the use of analysis of variance tests or chi-square tests for continuous and categorical variables respectively. Hazard ratios for CRT-On and CRT-Off with 95% confidence intervals were calculated with the Cox proportional hazards models for treatment effect and country of recruitment as a covariate. The interaction between delay subgroup and randomized treatment group was tested in a Cox model that included delay subgroup and treatment main effect and interaction terms. Time-to-event curves were estimated using the method of Kaplan and Meier.

Results

Among the 807 patients with baseline CCA analysis data, they were equally distributed with 404 (50.1%) patients in the CRT-Off group and 403 (49.9%) in the CRT-On group. Of these 807 patients, time-to-peak dyssynchrony data was available in 806 patients. Among these, 420 (52%) patients had dyssynchrony by both radial strain and TDI opposing wall delay, 201

(25%) had dyssynchrony by lone TDI, and rest 185 (23%) patients had dyssynchrony by lone radial strain. A significant mechanical activation delay by CCA was observed in 223 (55%) patients among the CRT-Off patients and in 209 (52%) among the CRT-On patients. The baseline characteristics of the patients in the CRT-Off and CRT-On based on activation delay are summarized in Table 1. No significant differences were observed between the groups for the baseline characteristics.

Association of baseline mechanical activation delay by CCA to long-term outcome

The trial was stopped due to futility on advice of the independent data and monitoring board. The median follow-up period was 1.15 years (interquartile range 0.48 to 2.05 years). HF hospitalizations and all-cause death were observed in 216 (27%) patients by the time the trial was stopped. Separately, there were 187 HF hospitalizations and 29 deaths in the follow-up interval of 3.5 years. On dividing the patients into four groups, it was observed that patients with no mechanical activation delay by CCA in the CRT-On group suffered the highest number (32%) of events (Figure 2). Among patients with no mechanical activation delay, patients randomized to CRT-On group had an increased risk of an unfavorable outcome in comparison to those with CRT-Off with a HR 1.7 (95% CI 1.13-2.55, P=0.01; Figure 3). However, among patients with presence of activation delay, no significant difference was observed for events among the two CRT randomization groups (HR 0.96, 95% CI 0.66-1.40, P=0.84). Importantly, there was a significant interaction term between activation delay by CCA and randomization to CRT device for the outcome events (P=0.04).

Changes in mechanical activation delay associated with outcome

At 6-months follow-up, echocardiographic data for the CCA was available in 610 (96%) patients out of 635 patients with follow-up echocardiograms. After excluding patients who had

already suffered HF hospitalization before the 6 months follow-up analysis, a final number of 541 patients were available for follow-up analysis. Among these, 274 (51%) had CRT-Off and 267 (49%) were from the CRT-On group. The distribution of the four groups based on mechanical activation delay at baseline and follow-up among patients with CRT-Off vs CRT-On was similar: no activation delay (31% vs. 30%), improved activation delay (27% vs. 31%), persistent activation delay (27% vs. 23%), and onset of new activation delay (15% vs.16%).

A total of 102 patients suffered either HF hospitalization or death from 6 months until completed follow-up excluding events that occurred in the first 6 months. The event rate was significantly higher among patients with a new mechanical activation delay observed on the 6 months echocardiogram in the CRT-On group in comparison to the CRT-Off group (30% vs 12%; HR 3.73, 95% CI 1.15-12.14, P=0.03; Figure 4). No significant difference was observed for the outcome events between the other three groups based on randomization.

Discussion

This pre-specified sub-study of the EchoCRT trial of HF patients with narrow QRS width shows that the absence of mechanical activation delay by CCA at baseline and new onset activation delay observed in follow-up in patients treated with CRT was significantly associated with poor clinical outcomes. These results support the notion that delayed activation by CCA is measuring a different mechanical phenomenon than time-to-peak dyssynchrony. These observations may provide new insight in the interpretation of EchoCRT trial and mechanistic working of CRT in general.

The EchoCRT trial used the best documented methods for dyssynchrony for selection of patients at the time of study design, i.e. both longitudinal TDI velocity and 2D STE radial strain time to peak assessment. In HF patients with wide QRS, these methods have been demonstrated

to be of additive prognostic value.(1,2,12) Moreover, single center studies using these methods have shown that narrow QRS HF patients having echocardiographic dyssynchrony treated by CRT device have improvement in HF symptoms and LV reverse remodeling comparable to patients with wide QRS.(13,14) Meanwhile, questions have been raised regarding the specificity of these methods.(4-6,10) Time to peak measurements alone do not provide any information on the nature of the wall deformation such as whether differences are due to scarring or activation timing differences.(6) Although time-to-peak differences due to abnormalities in the myocardial tissue is demonstrated to have prognostic significance in various types of cardiomyopathies,(15,16) it is not correctable by CRT specifically in the absence of concomitant electrical dyssynchrony.(4,5) Our results of the current analysis strengthen the view that peak-to-peak methods are relatively nonspecific for detecting true dyssynchrony responsive to CRT, as only one-half of the patients included in EchoCRT trial had significant mechanical activation delay by CCA. Mechanical activation delay by CCA may be less susceptible to differences in mechanical motion patterns not caused by delayed activation.(7,10) CCA analysis in wide QRS complex patients undergoing CRT have proven beneficial in identifying responders having both wide and intermediate QRS durations and has been demonstrated to be able to evaluate resynchronization efficacy to obtain maximum CRT benefit.(7,10,11)

Unlike CCA method which is more of a quantitative approach, other methods which are qualitative in nature for the assessment of dyssynchrony, such as identification of typical contraction pattern (9) and apical rocking (17) are proposed to identify the true left bundle branch block (LBBB) patients with activation delay. Both these methods have shown excellent additional value in identifying potential responders to CRT in patients with left bundle branch block (LBBB) which is principally due to exclusion of patients who are misdiagnosed as LBBB

by ECG. However, this unique contraction pattern of the opposing walls described by Risum et al (9) is specific to patients with true LBBB and would be physiologically implausible in other kinds of cardiomyopathy. On the other hand, dyssynchrony by CCA quantifies the activation delay between two opposing walls rather than relying on a specific contraction pattern and thus could be applicable in patients other than LBBB. It has not only demonstrated to be superior to TDI time-to-peak in wide QRS patients in predicting survival after CRT but has also shown promising results in the intermediate QRS (120-149 ms) patients.(7)

It seems, however, that even when selecting patients with the stricter CCA-criteria for mechanical activation delay, there is no convincing positive effect of CRT in HF patients with narrow QRS. One possible explanation could be that mechanical activation delay in the setting of narrow QRS needs not represent a substrate amenable to CRT. The follow-up CCA-analysis agrees with this interpretation, as CRT was inefficient in correcting mechanical activation delay in a large group of patients. Even though CCA is less susceptible to other motion differences between LV walls, it is likely that mechanical activation can be delayed for other reasons than delays in electrical activation, such as differences in electro-mechanical coupling. It should also be considered that the study sample size was reduced by premature termination of the trial, and there are relatively wide confidence limits to these subgroup estimates of treatment effect.

The strongest signal of our analysis is the suggestion of a harmful effect of CRT isolated to patients with no activation delay at baseline by CCA. This is an important finding given the higher mortality observed in the CRT-On group in EchoCRT. Follow-up evaluation confirmed that especially patients without activation delay randomized to CRT-On who developed new activation delay had a significantly worse outcome, with an almost 4-fold increased risk of adverse events. Similar observation have been made regarding new or worsened activation delay

during CRT in patients with a wide QRS.(11,18-20) This finding of potential harm from CRT in patients without baseline mechanical activation delay also fits well with a previous study of CCA in intermediate to wide QRS HF patients treated with CRT, where lack of baseline activation delay was associated with a poor long-term outcome.(7)

There are several interesting perspectives in the present analysis. Firstly, when considering HF patients with narrow QRS ≤ 130 ms, it seems the prevalence of potential responders to CRT is quite low, and will be hard to identify, even with advanced methods such as CCA. Secondly, in HF patients with intermediate QRS 130-149 ms, the prevalence of potential responders is probably higher, and as the effect of CRT overall in this group is less well established, there could be a role for methods such as CCA to select patients for CRT in future trials. Thirdly, in HF patients with intermediate or broad QRS > 150 ms, CCA seems an attractive method for detecting patients that are potentially harmed by CRT. This sets the stage for potential trials in the future of deferral of CRT in patients without mechanical activation delay, or trials of turning off CRT in patients where new-onset mechanical activation delay cannot be corrected by optimization.

Limitations

The current study is a post-hoc study. Although it was a pre-specified sub-study which was approved before the study commenced, the method applied in the study was not a part of the patient selection process for the trial. Another limitation of the study was the lack of 6-months follow-up echocardiograms in many patients, 610 patients had 6-months follow echocardiograms for the CCA resulting into a loss of about 24% patients for the follow-up analysis. This was mostly due to the premature closure of the study.

Conclusions

In conclusion, the effect of CRT in HF patients with narrow QRS (≤ 130ms) in terms of HF hospitalization and death depends on left ventricular mechanical activation delay determined by echocardiographic CCA. CRT specifically resulted in poor outcome in HF patients with narrow QRS and no activation delay by CCA at baseline which is most probably caused by the pacing-induced development of new activation delay. This study provides new mechanistic insight into effects of CRT pacing in HF patients which is of clinical significance.

Perspectives

Competency In Medical Knowledge: This study demonstrates the limitation of the time-to-peak based dyssynchrony measures which are applied in the routine clinical practice. Nearly, 45% patients did not have significant activation delay by cross correlation analysis (CCA) when applied on the patients selected in the EchoCRT trial who were included based on the dyssynchrony by time-to-peak based methods. CRT was particularly fatal to patients with narrow QRS who lacked activation delay at baseline by CCA due to the risk of pacemaker induced new activation delay.

Translational Outlook: Further randomized studies applying this method specifically in patients with intermediate QRS duration (120-140 ms) where the guidelines are unclear about CRT implantation would be beneficial.

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Figure Legends

Central illustration: Cross correlation analysis by Tissue Doppler Imaging and outcome in narrow QRS patients treated with cardiac resynchronization therapy

Left panel shows increased hospitalization due to HF and mortality in patients with no activation delay at baseline and implanted with CRT with a significant interaction between device randomization and activation delay for the end-points. Right Panel shows that patients with new activation delay after CRT in comparison to those with no CRT had poor outcome indicating the role of device induced activation delay in the poor prognosis.

Figure 1: Examples comparing dyssynchrony by time-ot-peak and activation delay by cross correlation analysis

Two examples from the trial showing dyssynchrony by time-to-peak (≥ 80 ms) opposing wall delay using the tissue Doppler imaging. However, only the patient in the upper panel has a significant activation delay (≥ 35 ms) on cross correlation analysis (CCA). The patient in the lower panel has nearly no activation delay (6 ms). This can be visually appreciated when we compare the acceleration curves of the septum and lateral walls (third column) of the two panels.

Figure 2: Baseline activation delay and Outcome

Bar diagram showing the incidence of events of heart failure hospitalization or death among the two CRT device randomization groups based on the activation delay.

Figure 3: Baseline activation delay and time to events

Kaplan Meier curve showing the time to events for the four patient groups based on the presence or absence of activation delay at baseline and CRT device randomization.

Figure 4: Change in activation delay and Outcome after 6-months of CRT implantation

Bar diagram showing the comparative incidence of outcome events between CRT-Off and CRT-On after 6-months of device implantation among the four patients groups based on the presence or absence of activation delay at baseline and 6-months follow-up. Only patients with no events in the first 6-months of device implantation were included in this analysis.

Table 1 Baseline Characteristics

Variables	CRT-Off with No AD		CRT-On with No AD		CRT-Off with AD		CRT-On with AD	
	n	Statistics	n	Statistics	n	Statistics	n	Statistics
Age (years)	181	57.4 (11.72)	194	57.0 (13.07)	223	59.2 (13.12)	209	58.1 (12.77)
Males (n)	181	127 (70.17%)	194	145 (74.74%)	223	163 (73.09%)	209	149 (71.29%)
QRS width (ms)	180	104.0 (12.04)	192	106.1 (12.43)	221	106.7 (12.00)	205	105.9 (13.65)
Walking distance (m)	175	317.5 (118.93)	192	330.7 (123.38)	219	326.9 (124.84)	204	325.7 (114.31)
Quality of life score	181	55.2 (23.63)	194	51.5 (25.07)	221	47.5 (24.14)	208	51.3 (23.67)
NYHA Classification (n)	181		194		223		209	
I		1 (0.55%)		2 (1.03%)		2 (0.90%)		0 (0.00%)
II		5 (2.76%)		4 (2.06%)		7 (3.14%)		3 (1.44%)
III		170 (94%)		184 (95%)		204 (91%)		200 (96%)
IV		5 (2.76%)		4 (2.06%)		10 (4.48%)		6 (2.87%)
BNP (pg/ml)	99	244 (89-613)	109	242 (40-493)	94	290 (126-600)	91	224 (115-564)
NT-proBNP (pg/ml)	77	1071 (462-2203)	74	1121 (414-2444)	122	923 (529-1999)	110	1378 (556-2675)
Sitting SBP (mmHg)	181	118 (16)	194	118 (22)	223	122 (21)	209	117 (18)
Sitting DBP (mmHg)	181	73 (11)	194	73 (13)	223	73 (13)	209	73 (12)
BMI (kg/m2)	181	30 (7)	194	31 (15)	223	32 (16)	209	31 (7)
Ischemic cardiomyopathy (n)	180	93 (52%)	194	99 (51%)	223	120 (54%)	209	119 (57%)
MI > 3 months ago (n)	181	71 (39%)	194	69 (36%)	223	83 (37%)	209	98(47%)
PCI > 3 months ago (n)	181	56 (31%)	194	74 (38%)	223	74 (33%)	209	98 (47%)
CABG > 3 months ago (n)	181	35 (19%)	194	35 (18%)	223	39 (17%)	209	42 (20%)
Hypertension (n)	178	119 (67%)	194	124 (64%)	223	151 (68%	205	137 (67%)
Congenital heart disease (n)	175	3 (1.7%)	192	3 (1.6%)	220	7 (3.2%)	206	3 (1.5%)
Prior ischemic stroke or TIA (n)	180	28 (16%)	193	19 (10%)	221	19 (9%)	207	30 (14%)

Diabetes (n)	181	69 (38%)	193	77 (40%)	222	84 (38%)	208	89 (43%)
Chronic lung disease (n)	180	33 (18%)	191	30 (16%)	220	45 (20%)	209	39 (19%)
Chronic kidney disease (n)	180	17 (9%)	192	30 (16%)	220	25 (11%)	209	36 (17%)
LV EF Biplane (%)	181	27.4 (5.3)	194	27.4 (5.5)	223	26.7 (5.6)	209	26.7 (5.8)
LV end diastolic diameter (mm)	181	66 (7)	194	67 (7)	223	67 (8)	209	67 (8)
ACE inhibitor or ARB (n)	181	177 (98%)	194	185 (95%)	223	206 (92%)	209	197 (94%)
Aldosterone antagonist (n)	181	105 (58%)	194	118 (61%)	223	132 (59%)	209	128 (61%)
Beta-blocker (n)	181	178 (98%)	194	183 (94%)	223	216 (97%)	209	203 (97%)
Diuretic agent (n)	181	160 (88%)	194	160 (82%)	223	191 (86%)	209	185 (88%)
MR grade (n)	180		192		221		206	
None/Trace		69 (38%)		64 (33%)		77 (35%)		69 (34%)
Mild		65 (36%)		80 (42%)		89 (40%)		83 (40%)
Moderate		25 (14%)		31 (16%)		34 (15%)		33 (16%)
Moderate/Severe		14 (8%)		11 (6%)		12 (5%)		14 (7%)
Severe		7 (4%)		6 (3%)		9 (4%)		7 (3%)
LV ESV (ml)	180	134 (47)	194	140 (49)	223	142 (54)	207	142 (49)
LV EDV (ml)	180	183 (57)	194	191 (58)	223	192 (65)	207	190 (55)
TDI (ms)	181	97 (39)	194	98 (34)	223	105 (34)	208	104 (31)
Speckle tracking (ms)	173	218 (109)	181	213 (100)	202	223 (102)	191	223 (99)

AD= activation delay; NYHA= New York Heart Association; BNP= brain natriuretic peptide; SBP= systolic blood pressure; DBP= diastolic blood pressure; BMI= body mass index, MI= myocardial infarction; PCI= percutaneous coronary interventions; CABG= coronary artery bypass surgery; TIA= transient ischemic attack; LV= left ventricular; EF= ejection fraction; ACE= angiotensin converting enzyme; ARB= angiotensin II receptor blocker; MR= mitral regurgitation; EDV= end-diastolic volume; ESV= end-systolic volume; TDI= tissue Doppler imaging

Prognostic Impact of Mechanical Activation Delay by Cross Correlation Analysis in Heart Failure Patients with narrow QRS treated with Cardiac Resynchronization Therapy: an Echocardiography Guided Cardiac Resynchronization Therapy (EchoCRT) Trial Sub-study

Short Title: Association of activation delay by tissue Doppler imaging with outcomes after CRT.

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Abstract

Background: Cross Correlation Analysis (CCA) using tissue Doppler imaging (TDI) shown to be associated with outcome after cardiac resynchronization therapy (CRT) in heart failure (HF) patients with wide QRS. However, its significance in narrow QRS patients treated with CRT is unknown.

Objectives: The aim of the current study was to investigate the association of mechanical activation delay by CCA with study outcome in HF patients enrolled in the EchoCRT trial.

Methods: Baseline CCA could be performed from TDI in the apical views in 807 of 809 (99.7%) enrolled patients while 6-months follow-up could be performed in 610 of 635 (96%) patients with available echocardiograms. Patients with a pre-specified maximal activation delay $\geq$ 35 ms were considered to have significant delay. The study outcome was HF hospitalization or death.

Results: Out of 807, 375 (46%) patients did not have delayed mechanical activation at baseline by CCA. Patients without delayed mechanical activation randomized to CRT-On had an increased risk of poor outcome (HR 1.70, 95% CI 1.13-2.55, P=0.01) in comparison to those with CRT-Off with a significant interaction term (P=0.04) between delayed mechanical activation and device randomization for the endpoint. Among patients with paired baseline and follow-up data with no events before 6-months follow-up (n=541), new-onset delayed mechanical activation in the CRT-On group showed significant increase in unfavorable events (HR 3.73, 95% CI 1.15-12.14, P=0.03).

Conclusions: In the EchoCRT population, absence of delayed mechanical activation by CCA was significantly associated with poor outcomes possibly due to the onset of new delayed mechanical activation with CRT pacing. (Echocardiography Guided Cardiac Resynchronization Therapy [EchoCRT] Trial; NCT00683696)

Key words: heart failure, cardiac resynchronization therapy, echocardiography, dyssynchrony, tissue Doppler imaging.

Condensed Abstract

In the current study we applied cross correlation analysis method (CCA) to assess mechanical activation delay in the population of echocardiography guided cardiac resynchronization therapy (EchoCRT) trial in which CRT was implanted in patients with narrow QRS (<130ms). CRT was fatal to patients with no activation delay at baseline which was possibly due to the pacemaker induced new activation delay.

Abbreviation List

CRT = cardiac resynchronization therapy

ECG = electrocardiographic

HF = heart failure

LVEF = left ventricular ejection fraction

TDI = tissue Doppler imaging

Several studies in the past have demonstrated that the assessment of mechanical dyssynchrony by echocardiography can supplement current electrocardiographic (ECG) criteria (wide QRS ≥ 120 ms) in selection of CRT candidates leading to an overall reduction in the non-responders rate.(1-3) However, conventional methods of identifying dyssynchrony based on segmental time-to-peak measurements have failed when applied in randomized trials for selecting patients for CRT with narrow QRS (<130ms).(4,5)

The largest CRT trial conducted on narrow QRS (<130 ms) patients - echocardiography guided cardiac resynchronization therapy (EchoCRT) - demonstrated that HF patients with narrow QRS (<130 ms) do not respond to CRT despite the presence of baseline mechanical dyssynchrony by time-to-peak methods by either tissue Doppler longitudinal velocity or speckle tracking radial strain.(4) In fact, an increased incidence of mortality was observed in patients randomized to CRT-On in comparison to the control group and the trial was stopped due to futility without achieving its complete target population. Another trial - The Resynchronization therapy in narrow QRS (RethinQ) - performed before EchoCRT with similar design where mechanical dyssynchrony was one of the selection criteria, also showed no benefit of CRT in HF patients with narrow QRS.(5)

More recently, it was shown that peak-to-peak measures of mechanical dyssynchrony may be influenced by contractile heterogeneity or scar not responsive to CRT.(6) Patterns of myocardial mechanics that have been shown to reflect electrical delay have shown very promising results and seem to better identify a true substrate for CRT response.(6-8) These newer methods seem superior to the conventional time-to-peak methods.(7,9) Among these, one approach is assessment of mechanical activation delay by cross correlation analysis (CCA) using tissue Doppler Imaging (TDI).(7,10) Presence of a delayed mechanical activation by CCA in the

wide QRS patients is associated with improved prognosis as well as response after CRT.(7,10,11) However, its significance is unknown in HF patients with narrow QRS (<130 ms) treated with CRT. Accordingly, the objective of the current study was to assess the association of delayed mechanical activation by the CCA method both at baseline and follow-up after randomization to clinical outcomes in patients enrolled in the EchoCRT trial.

Methods

Study Population

The current study is a pre-specified sub-study of the EchoCRT trial. All the patients included in the EchoCRT trial had left ventricular ejection fraction (LVEF) ≤ 35%, QRS duration of ≤ 130 ms, severe symptomatic HF with New York HF Association (NYHA) class III-IV symptoms, LV end diastolic diameter ≥ 55 mm, and echocardiographic evidence of mechanical dyssynchrony by time-to-peak methods. Methods used to identify dyssynchrony in this study were presence of TDI based opposing wall delay of ≥ 80 ms in the apical 4-chamber or 3-chamber view, and radial strain delay ≥ 130 ms between the septum and the posterior walls in the LV mid-segment short axis view. All the patients included in the trial were older than 18 years and provided informed consent for inclusion in the trial. It was a multicenter randomized trial in which patients were included between a period of 2008 to 2013 and involved 112 centers from 22 different countries. Patients with bradycardia pacing or atrial fibrillation with in the past few months were excluded. The main study results along with a detailed study protocol have been published.(4) All the patients included received a CRT device with defibrillator capacity (CRT-D) (Biotronik Lumax, Berlin, Germany) and randomized in 1:1 fashion to CRT-On and CRT-Off after a successful implantation of the device. For the current sub-study, 807 (99.7%) of

809 were included with the baseline data and 610 (96%) of 635 patients were included with paired data at both baseline and 6-months follow-up.

Cross correlation analysis

All the echocardiograms were performed using a single vendor ultrasound system GE Vivid 7 or E9, Horton, Norway. To reduce variability the offline TDI based analysis was performed on a single GE EchoPAC system (version BT 11, Horton, Norway) by a single observer blinded to the patient data. CCA has been illustrated in detail in our previous publications (Figure 1).(7,10,11) Briefly, regions of interest (7 x 15 mm) were placed on the base segments of the opposing walls in all three apical views and the resulting velocity data were imported on an automated excel sheet with a pre-written algorithm to perform CCA analysis. Subsequently, velocity data were converted to acceleration data by using time differentiation. A baseline correlation coefficient was calculated between the acceleration curves from two opposing walls during systole in each of the three apical views without time-shift. These acceleration curves were then time-shifted against each other frame-by-frame to maximum of 15 frames in both directions to calculate a correlation coefficient again. The time-shift resulting in the maximum correlation between the opposing walls was termed as maximum activation-delay (AD-max). Patients were classified as having significant activation delay if the AD-max was ≥35ms in any of the three apical views based on our previous work.(7,10) Systole was identified by calculating the aortic valve opening and closure timings from a pulse Doppler signal in the APLAX view. Activation delay by CCA was measured at both baseline and 6-months. For the analysis of the patients with paired CCA data, patients were divided into the following four groups based on the presence or absence of mechanical activation at baseline and follow-up:

1. No activation delay: no activation delay at both baseline and at follow-up.

2. Improved activation delay: activation delay at baseline but not at follow-up
3. Persistent activation delay: activation delay at baseline and at follow-up
4. New activation delay: no activation delay at baseline but activation delay at follow-up.

Study outcome

The outcome variable of this study was the primary end-point of all-cause death or first HF hospitalization within a period of 3.5 years.

Statistics

All the statistical analyses were performed by an independent Statistical Centre at the Robertson Centre for Biostatistics, University of Glasgow. Baseline characteristics were compared with the use of analysis of variance tests or chi-square tests for continuous and categorical variables respectively. Hazard ratios for CRT-On and CRT-Off with 95% confidence intervals were calculated with the Cox proportional hazards models for treatment effect and country of recruitment as a covariate. The interaction between delay subgroup and randomized treatment group was tested in a Cox model that included delay subgroup and treatment main effect and interaction terms. Time-to-event curves were estimated using the method of Kaplan and Meier.

Results

Among the 807 patients with baseline CCA analysis data, they were equally distributed with 404 (50.1%) patients in the CRT-Off group and 403 (49.9%) in the CRT-On group. Of these 807 patients, time-to-peak dyssynchrony data was available in 806 patients. Among these, 420 (52%) patients had dyssynchrony by both radial strain and TDI opposing wall delay, 201

(25%) had dyssynchrony by lone TDI, and rest 185 (23%) patients had dyssynchrony by lone radial strain. A significant mechanical activation delay by CCA was observed in 223 (55%) patients among the CRT-Off patients and in 209 (52%) among the CRT-On patients. The baseline characteristics of the patients in the CRT-Off and CRT-On based on activation delay are summarized in Table 1. No significant differences were observed between the groups for the baseline characteristics.

Association of baseline mechanical activation delay by CCA to long-term outcome

The trial was stopped due to futility on advice of the independent data and monitoring board. The median follow-up period was 1.15 years (interquartile range 0.48 to 2.05 years). HF hospitalizations and all-cause death were observed in 216 (27%) patients by the time the trial was stopped. Separately, there were 187 HF hospitalizations and 29 deaths in the follow-up interval of 3.5 years. On dividing the patients into four groups, it was observed that patients with no mechanical activation delay by CCA in the CRT-On group suffered the highest number (32%) of events (Figure 2). Among patients with no mechanical activation delay, patients randomized to CRT-On group had an increased risk of an unfavorable outcome in comparison to those with CRT-Off with a HR 1.7 (95% CI 1.13-2.55, P=0.01; Figure 3). However, among patients with presence of activation delay, no significant difference was observed for events among the two CRT randomization groups (HR 0.96, 95% CI 0.66-1.40, P=0.84). Importantly, there was a significant interaction term between activation delay by CCA and randomization to CRT device for the outcome events (P=0.04).

Changes in mechanical activation delay associated with outcome

At 6-months follow-up, echocardiographic data for the CCA was available in 610 (96%) patients out of 635 patients with follow-up echocardiograms. After excluding patients who had

already suffered HF hospitalization before the 6 months follow-up analysis, a final number of 541 patients were available for follow-up analysis. Among these, 274 (51%) had CRT-Off and 267 (49%) were from the CRT-On group. The distribution of the four groups based on mechanical activation delay at baseline and follow-up among patients with CRT-Off vs CRT-On was similar: no activation delay (31% vs. 30%), improved activation delay (27% vs. 31%), persistent activation delay (27% vs. 23%), and onset of new activation delay (15% vs.16%).

A total of 102 patients suffered either HF hospitalization or death from 6 months until completed follow-up excluding events that occurred in the first 6 months. The event rate was significantly higher among patients with a new mechanical activation delay observed on the 6 months echocardiogram in the CRT-On group in comparison to the CRT-Off group (30% vs 12%; HR 3.73, 95% CI 1.15-12.14, P=0.03; Figure 4). No significant difference was observed for the outcome events between the other three groups based on randomization.

Discussion

This pre-specified sub-study of the EchoCRT trial of HF patients with narrow QRS width shows that the absence of mechanical activation delay by CCA at baseline and new onset activation delay observed in follow-up in patients treated with CRT was significantly associated with poor clinical outcomes. These results support the notion that delayed activation by CCA is measuring a different mechanical phenomenon than time-to-peak dyssynchrony. These observations may provide new insight in the interpretation of EchoCRT trial and mechanistic working of CRT in general.

The EchoCRT trial used the best documented methods for dyssynchrony for selection of patients at the time of study design, i.e. both longitudinal TDI velocity and 2D STE radial strain time to peak assessment. In HF patients with wide QRS, these methods have been demonstrated

to be of additive prognostic value.(1,2,12) Moreover, single center studies using these methods have shown that narrow QRS HF patients having echocardiographic dyssynchrony treated by CRT device have improvement in HF symptoms and LV reverse remodeling comparable to patients with wide QRS.(13,14) Meanwhile, questions have been raised regarding the specificity of these methods.(4-6,10) Time to peak measurements alone do not provide any information on the nature of the wall deformation such as whether differences are due to scarring or activation timing differences.(6) Although time-to-peak differences due to abnormalities in the myocardial tissue is demonstrated to have prognostic significance in various types of cardiomyopathies,(15,16) it is not correctable by CRT specifically in the absence of concomitant electrical dyssynchrony.(4,5) Our results of the current analysis strengthen the view that peak-to-peak methods are relatively nonspecific for detecting true dyssynchrony responsive to CRT, as only one-half of the patients included in EchoCRT trial had significant mechanical activation delay by CCA. Mechanical activation delay by CCA may be less susceptible to differences in mechanical motion patterns not caused by delayed activation.(7,10) CCA analysis in wide QRS complex patients undergoing CRT have proven beneficial in identifying responders having both wide and intermediate QRS durations and has been demonstrated to be able to evaluate resynchronization efficacy to obtain maximum CRT benefit.(7,10,11)

Unlike CCA method which is more of a quantitative approach, other methods which are qualitative in nature for the assessment of dyssynchrony, such as identification of typical contraction pattern (9) and apical rocking (17) are proposed to identify the true left bundle branch block (LBBB) patients with activation delay. Both these methods have shown excellent additional value in identifying potential responders to CRT in patients with left bundle branch block (LBBB) which is principally due to exclusion of patients who are misdiagnosed as LBBB

by ECG. However, this unique contraction pattern of the opposing walls described by Risum et al (9) is specific to patients with true LBBB and would be physiologically implausible in other kinds of cardiomyopathy. On the other hand, dyssynchrony by CCA quantifies the activation delay between two opposing walls rather than relying on a specific contraction pattern and thus could be applicable in patients other than LBBB. It has not only demonstrated to be superior to TDI time-to-peak in wide QRS patients in predicting survival after CRT but has also shown promising results in the intermediate QRS (120-149 ms) patients.(7)

It seems, however, that even when selecting patients with the stricter CCA-criteria for mechanical activation delay, there is no convincing positive effect of CRT in HF patients with narrow QRS. One possible explanation could be that mechanical activation delay in the setting of narrow QRS needs not represent a substrate amenable to CRT. The follow-up CCA-analysis agrees with this interpretation, as CRT was inefficient in correcting mechanical activation delay in a large group of patients. Even though CCA is less susceptible to other motion differences between LV walls, it is likely that mechanical activation can be delayed for other reasons than delays in electrical activation, such as differences in electro-mechanical coupling. It should also be considered that the study sample size was reduced by premature termination of the trial, and there are relatively wide confidence limits to these subgroup estimates of treatment effect.

The strongest signal of our analysis is the suggestion of a harmful effect of CRT isolated to patients with no activation delay at baseline by CCA. This is an important finding given the higher mortality observed in the CRT-On group in EchoCRT. Follow-up evaluation confirmed that especially patients without activation delay randomized to CRT-On who developed new activation delay had a significantly worse outcome, with an almost 4-fold increased risk of adverse events. Similar observation have been made regarding new or worsened activation delay

during CRT in patients with a wide QRS.(11,18-20) This finding of potential harm from CRT in patients without baseline mechanical activation delay also fits well with a previous study of CCA in intermediate to wide QRS HF patients treated with CRT, where lack of baseline activation delay was associated with a poor long-term outcome.(7)

There are several interesting perspectives in the present analysis. Firstly, when considering HF patients with narrow QRS ≤ 130 ms, it seems the prevalence of potential responders to CRT is quite low, and will be hard to identify, even with advanced methods such as CCA. Secondly, in HF patients with intermediate QRS 130-149 ms, the prevalence of potential responders is probably higher, and as the effect of CRT overall in this group is less well established, there could be a role for methods such as CCA to select patients for CRT in future trials. Thirdly, in HF patients with intermediate or broad QRS > 150 ms, CCA seems an attractive method for detecting patients that are potentially harmed by CRT. This sets the stage for potential trials in the future of deferral of CRT in patients without mechanical activation delay, or trials of turning off CRT in patients where new-onset mechanical activation delay cannot be corrected by optimization.

Limitations

The current study is a post-hoc study. Although it was a pre-specified sub-study which was approved before the study commenced, the method applied in the study was not a part of the patient selection process for the trial. Another limitation of the study was the lack of 6-months follow-up echocardiograms in many patients, 610 patients had 6-months follow echocardiograms for the CCA resulting into a loss of about 24% patients for the follow-up analysis. This was mostly due to the premature closure of the study.

Conclusions

In conclusion, the effect of CRT in HF patients with narrow QRS (≤ 130ms) in terms of HF hospitalization and death depends on left ventricular mechanical activation delay determined by echocardiographic CCA. CRT specifically resulted in poor outcome in HF patients with narrow QRS and no activation delay by CCA at baseline which is most probably caused by the pacing-induced development of new activation delay. This study provides new mechanistic insight into effects of CRT pacing in HF patients which is of clinical significance.

Perspectives

Competency In Medical Knowledge: This study demonstrates the limitation of the time-to-peak based dyssynchrony measures which are applied in the routine clinical practice. Nearly, 45% patients did not have significant activation delay by cross correlation analysis (CCA) when applied on the patients selected in the EchoCRT trial who were included based on the dyssynchrony by time-to-peak based methods. CRT was particularly fatal to patients with narrow QRS who lacked activation delay at baseline by CCA due to the risk of pacemaker induced new activation delay.

Translational Outlook: Further randomized studies applying this method specifically in patients with intermediate QRS duration (120-140 ms) where the guidelines are unclear about CRT implantation would be beneficial.

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Figure Legends

Central illustration: Cross correlation analysis by Tissue Doppler Imaging and outcome in narrow QRS patients treated with cardiac resynchronization therapy

Left panel shows increased hospitalization due to HF and mortality in patients with no activation delay at baseline and implanted with CRT with a significant interaction between device randomization and activation delay for the end-points. Right Panel shows that patients with new activation delay after CRT in comparison to those with no CRT had poor outcome indicating the role of device induced activation delay in the poor prognosis.

Figure 1: Examples comparing dyssynchrony by time-ot-peak and activation delay by cross correlation analysis

Two examples from the trial showing dyssynchrony by time-to-peak (≥ 80 ms) opposing wall delay using the tissue Doppler imaging. However, only the patient in the upper panel has a significant activation delay (≥ 35 ms) on cross correlation analysis (CCA). The patient in the lower panel has nearly no activation delay (6 ms). This can be visually appreciated when we compare the acceleration curves of the septum and lateral walls (third column) of the two panels.

Figure 2: Baseline activation delay and Outcome

Bar diagram showing the incidence of events of heart failure hospitalization or death among the two CRT device randomization groups based on the activation delay.

Figure 3: Baseline activation delay and time to events

Kaplan Meier curve showing the time to events for the four patient groups based on the presence or absence of activation delay at baseline and CRT device randomization.

Figure 4: Change in activation delay and Outcome after 6-months of CRT implantation

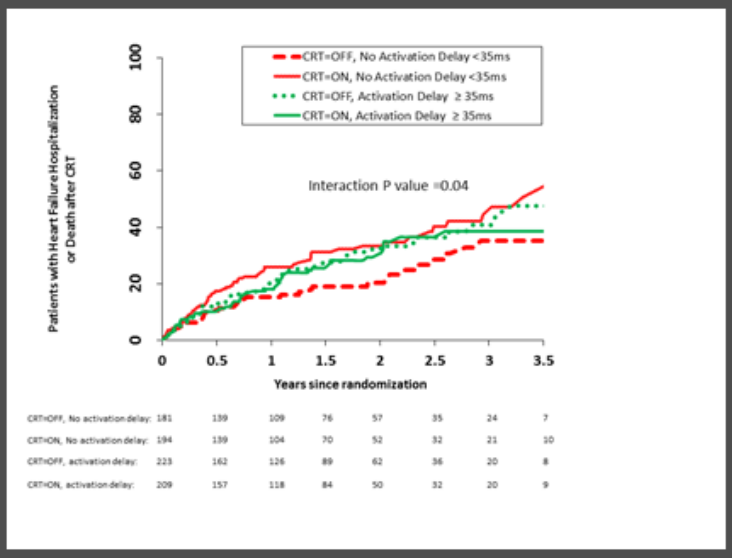
Bar diagram showing the comparative incidence of outcome events between CRT-Off and CRT-On after 6-months of device implantation among the four patients groups based on the presence or absence of activation delay at baseline and 6-months follow-up. Only patients with no events in the first 6-months of device implantation were included in this analysis.

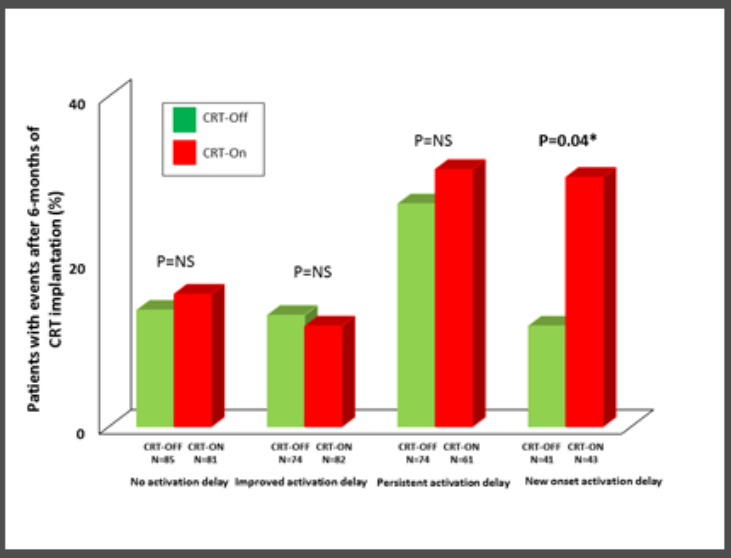
Table 1 Baseline Characteristics

Variables	CRT-Off with No AD		CRT-On with No AD		CRT-Off with AD		CRT-On with AD	
	n	Statistics	n	Statistics	n	Statistics	n	Statistics
Age (years)	181	57.4 (11.72)	194	57.0 (13.07)	223	59.2 (13.12)	209	58.1 (12.77)
Males (n)	181	127 (70.17%)	194	145 (74.74%)	223	163 (73.09%)	209	149 (71.29%)
QRS width (ms)	180	104.0 (12.04)	192	106.1 (12.43)	221	106.7 (12.00)	205	105.9 (13.65)
Walking distance (m)	175	317.5 (118.93)	192	330.7 (123.38)	219	326.9 (124.84)	204	325.7 (114.31)
Quality of life score	181	55.2 (23.63)	194	51.5 (25.07)	221	47.5 (24.14)	208	51.3 (23.67)
NYHA Classification (n)	181		194		223		209	
I		1 (0.55%)		2 (1.03%)		2 (0.90%)		0 (0.00%)
II		5 (2.76%)		4 (2.06%)		7 (3.14%)		3 (1.44%)
III		170 (94%)		184 (95%)		204 (91%)		200 (96%)
IV		5 (2.76%)		4 (2.06%)		10 (4.48%)		6 (2.87%)
BNP (pg/ml)	99	244 (89-613)	109	242 (40-493)	94	290 (126-600)	91	224 (115-564)
NT-proBNP (pg/ml)	77	1071 (462-2203)	74	1121 (414-2444)	122	923 (529-1999)	110	1378 (556-2675)
Sitting SBP (mmHg)	181	118 (16)	194	118 (22)	223	122 (21)	209	117 (18)
Sitting DBP (mmHg)	181	73 (11)	194	73 (13)	223	73 (13)	209	73 (12)
BMI (kg/m2)	181	30 (7)	194	31 (15)	223	32 (16)	209	31 (7)
Ischemic cardiomyopathy (n)	180	93 (52%)	194	99 (51%)	223	120 (54%)	209	119 (57%)
MI > 3 months ago (n)	181	71 (39%)	194	69 (36%)	223	83 (37%)	209	98(47%)
PCI > 3 months ago (n)	181	56 (31%)	194	74 (38%)	223	74 (33%)	209	98 (47%)
CABG > 3 months ago (n)	181	35 (19%)	194	35 (18%)	223	39 (17%)	209	42 (20%)
Hypertension (n)	178	119 (67%)	194	124 (64%)	223	151 (68%	205	137 (67%)
Congenital heart disease (n)	175	3 (1.7%)	192	3 (1.6%)	220	7 (3.2%)	206	3 (1.5%)
Prior ischemic stroke or TIA (n)	180	28 (16%)	193	19 (10%)	221	19 (9%)	207	30 (14%)
Diabetes (n)	181	69 (38%)	193	77 (40%)	222	84 (38%)	208	89 (43%)

Chronic lung disease (n)	180	33 (18%)	191	30 (16%)	220	45 (20%)	209	39 (19%)
Chronic kidney disease (n)	180	17 (9%)	192	30 (16%)	220	25 (11%)	209	36 (17%)
LV EF Biplane (%)	181	27.4 (5.3)	194	27.4 (5.5)	223	26.7 (5.6)	209	26.7 (5.8)
LV end diastolic diameter (mm)	181	66 (7)	194	67 (7)	223	67 (8)	209	67 (8)
ACE inhibitor or ARB (n)	181	177 (98%)	194	185 (95%)	223	206 (92%)	209	197 (94%)
Aldosterone antagonist (n)	181	105 (58%)	194	118 (61%)	223	132 (59%)	209	128 (61%)
Beta-blocker (n)	181	178 (98%)	194	183 (94%)	223	216 (97%)	209	203 (97%)
Diuretic agent (n)	181	160 (88%)	194	160 (82%)	223	191 (86%)	209	185 (88%)
MR grade (n)	180		192		221		206	
None/Trace		69 (38%)		64 (33%)		77 (35%)		69 (34%)
Mild		65 (36%)		80 (42%)		89 (40%)		83 (40%)
Moderate		25 (14%)		31 (16%)		34 (15%)		33 (16%)
Moderate/Severe		14 (8%)		11 (6%)		12 (5%)		14 (7%)
Severe		7 (4%)		6 (3%)		9 (4%)		7 (3%)
LV ESV (ml)	180	134 (47)	194	140 (49)	223	142 (54)	207	142 (49)
LV EDV (ml)	180	183 (57)	194	191 (58)	223	192 (65)	207	190 (55)
TDI (ms)	181	97 (39)	194	98 (34)	223	105 (34)	208	104 (31)
Speckle tracking (ms)	173	218 (109)	181	213 (100)	202	223 (102)	191	223 (99)

AD= activation delay; NYHA= New York Heart Association; BNP= brain natriuretic peptide; SBP= systolic blood pressure; DBP= diastolic blood pressure; BMI= body mass index, MI= myocardial infarction; PCI= percutaneous coronary interventions; CABG= coronary artery bypass surgery; TIA= transient ischemic attack; LV= left ventricular; EF= ejection fraction; ACE= angiotensin converting enzyme; ARB= angiotensin II receptor blocker; MR= mitral regurgitation; EDV= end-diastolic volume; ESV= end-systolic volume; TDI= tissue Doppler imaging


CRT=OFF, No Activation Delay <35ms
CRT=ON, No Activation Delay <35ms
CRT=OFF, Activation Delay ≥ 35ms
CRT=ON, Activation Delay ≥ 35ms
Interaction P value =0.04
Patients with Heart Failure Hospitalization or Death after CRT
0
20
40
60
80
100
0
0.5
1
1.5
2
2.5
3
3.5
Years since randomization
CRT=OFF, No activation delay: 181 139 109 76 57 35 24 7
CRT=ON, No activation delay: 194 139 104 70 52 32 21 10
CRT=OFF, activation delay: 223 162 126 89 62 36 20 8
CRT=ON, activation delay: 209 157 118 84 50 32 20 9

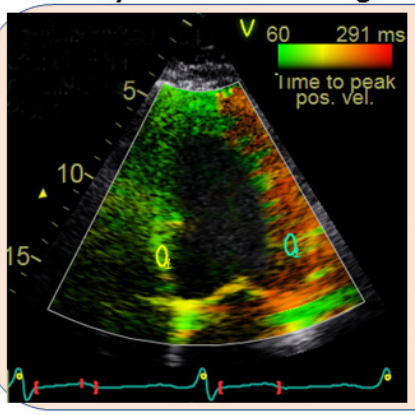

CRT-Off
CRT-On
Patients with events after 6-months of CRT implantation (%)
0
20
40
P=NS
P=NS
P=NS
P=0.04*
CRT-OFF N=85
CRT-ON N=81
CRT-OFF N=74
CRT-ON N=82
CRT-OFF N=74
CRT-ON N=61
CRT-OFF N=41
CRT-ON N=43
No activation delay
Improved activation delay
Persistent activation delay
New onset activation delay

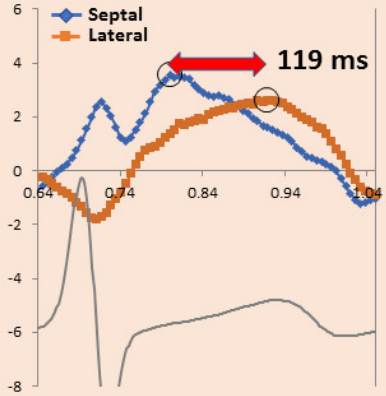
Tissue Doppler
Tissue Synchronization Images

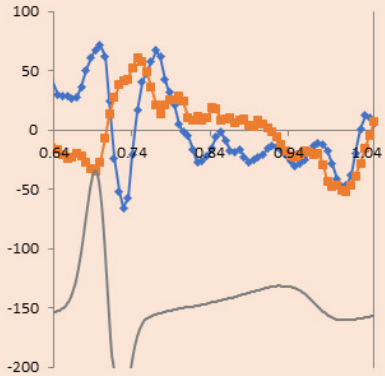
Tissue Doppler
Velocity Curves

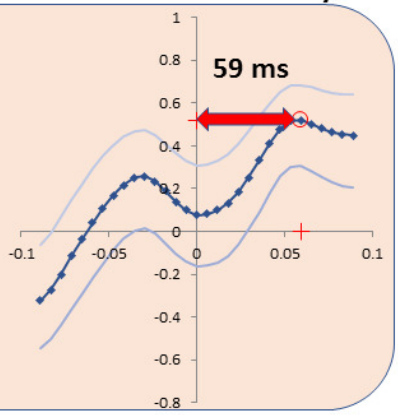
Tissue Doppler
Acceleration Curves

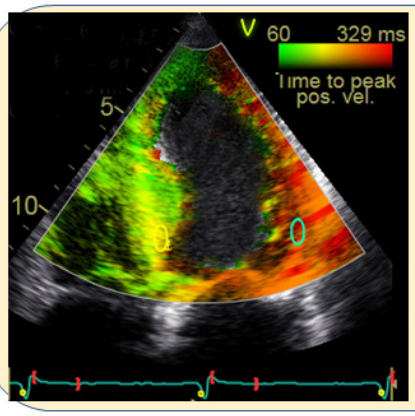
Activation Delay by
Cross Correlation Analysis

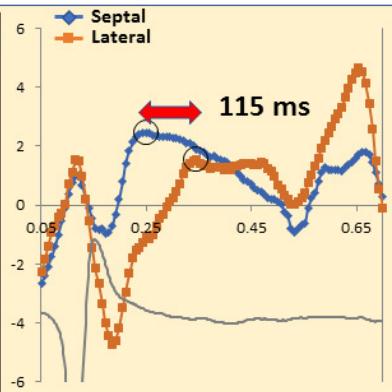


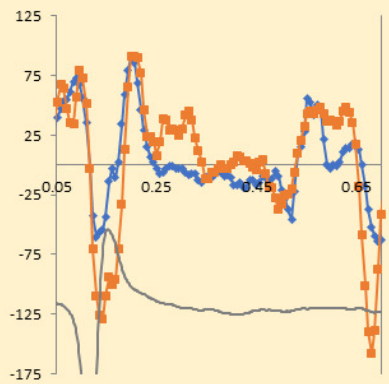


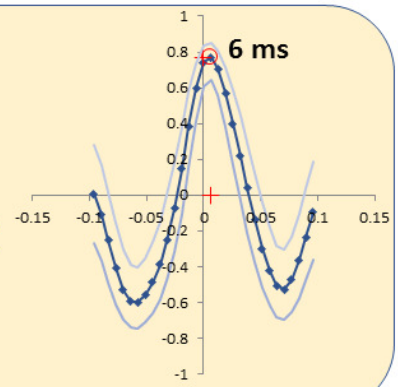


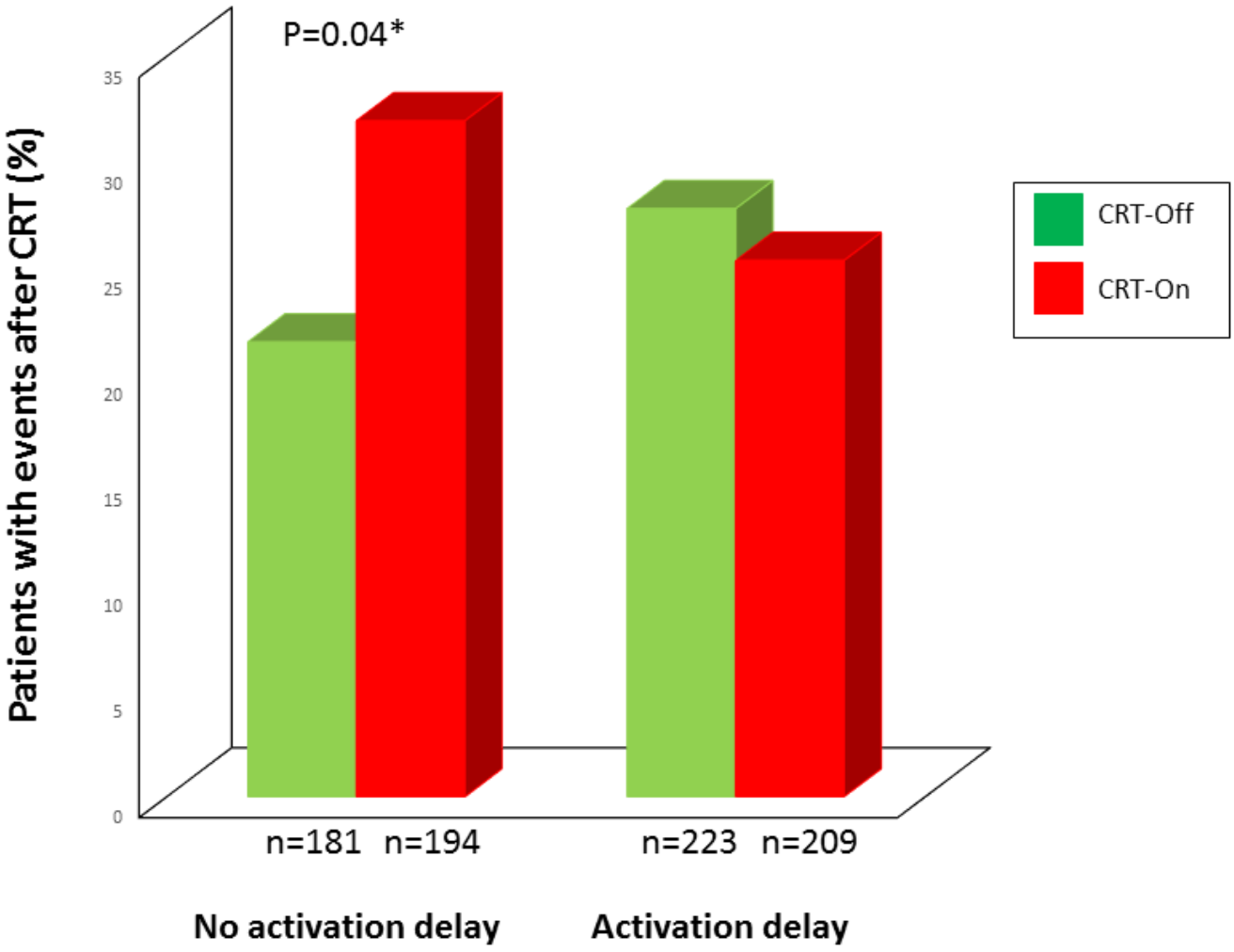


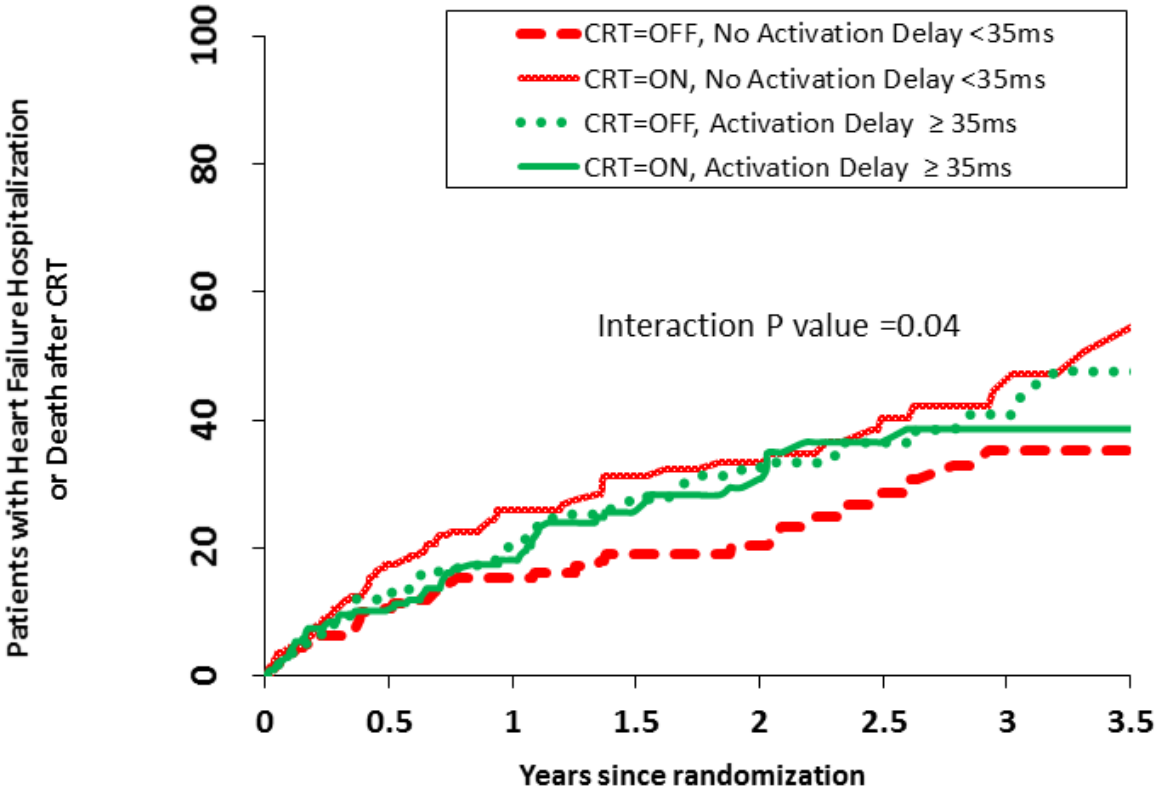




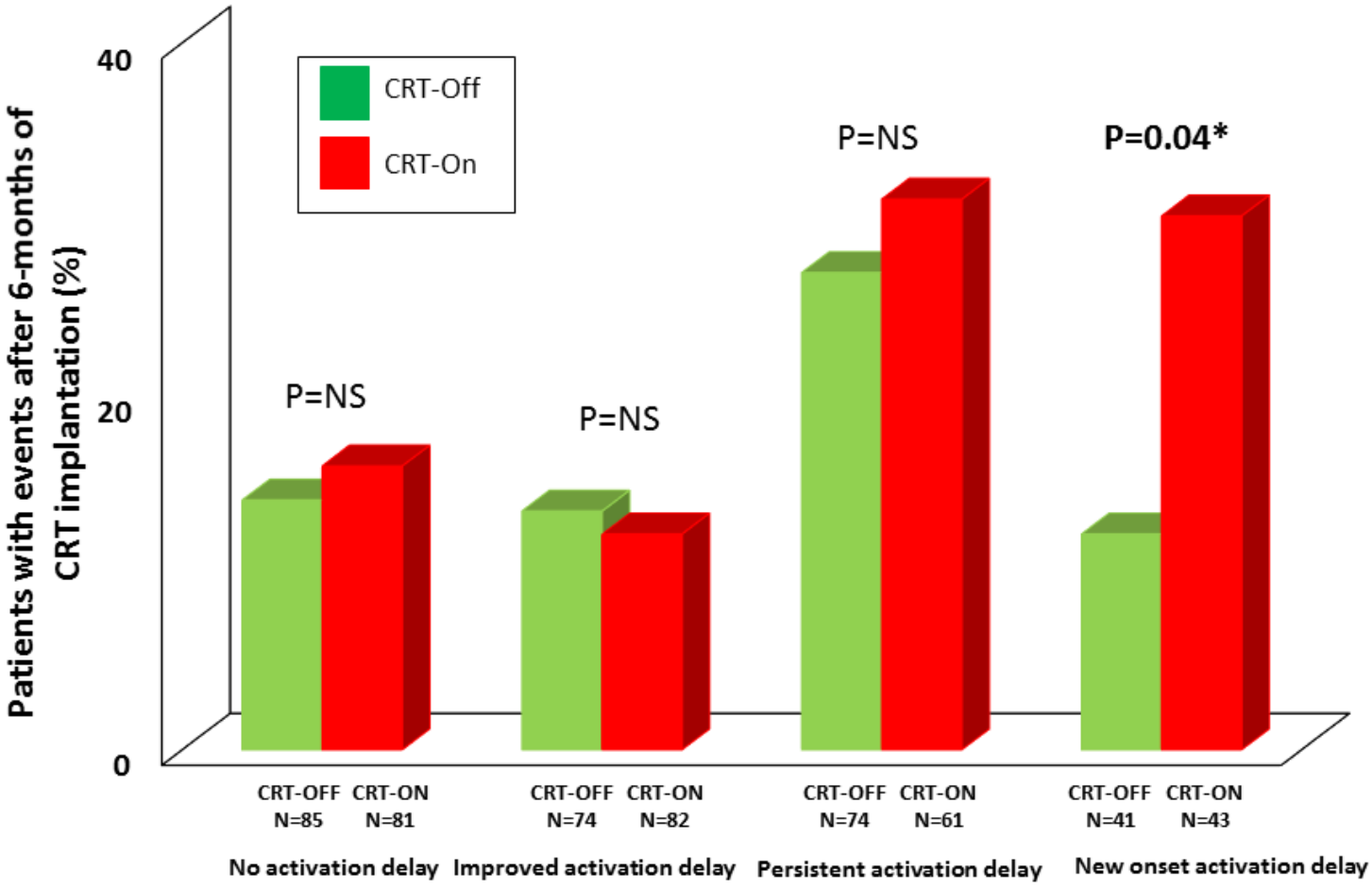





P=0.04*
Patients with events after CRT (%)
35
30
25
20
15
10
5
0
n=181
n=194
n=223
n=209
No activation delay
Activation delay
CRT-Off
CRT-On



CRT=OFF, No activation delay:	181	139	109	76	57	35	24	7
CRT=ON, No activation delay:	194	139	104	70	52	32	21	10
CRT=OFF, activation delay:	223	162	126	89	62	36	20	8
CRT=ON, activation delay:	209	157	118	84	50	32	20	9


Patients with events after 6-months of CRT implantation (%)
40
20
0
CRT-Off
CRT-On
P=NS
P=NS
P=NS
P=0.04*
CRT-OFF N=85
CRT-ON N=81
CRT-OFF N=74
CRT-ON N=82
CRT-OFF N=74
CRT-ON N=61
CRT-OFF N=41
CRT-ON N=43
No activation delay
Improved activation delay
Persistent activation delay
New onset activation delay