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ABSTRACT

BACKGROUND Cross correlation analysis (CCA) using tissue Doppler imaging has been shown to be associated with outcome after cardiac resynchronization therapy (CRT) in patients with heart failure (HF) with wide QRS. However, its significance in patients with narrow QRS 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 patients with HF enrolled in the EchoCRT trial.

METHODS Baseline CCA could be performed from tissue Doppler imaging in the apical views in 807 of 809 (99.7%) enrolled patients, and 6-month follow-up could be performed in 610 of 635 (96%) patients with available echocardiograms. Patients with a pre-specified maximal activation delay ≥35 ms were considered to have significant delay. The study outcome was HF hospitalization or death.

RESULTS Of 807 patients, 375 (46%) did not have delayed mechanical activation at baseline by CCA. Patients without delayed mechanical activation who were randomized to CRT-On compared with CRT-Off had an increased risk of poor outcome (hazard ratio: 1.70; 95% confidence interval: 1.13 to 2.55; $p = 0.01$) 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-month follow-up ($n = 541$), new-onset delayed mechanical activation in the CRT-On group showed a significant increase in unfavorable events (hazard ratio: 3.73; 95% confidence interval: 1.15 to 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)
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ABBREVIATIONS AND ACRONYMS

CRT = cardiac resynchronization therapy

HF = heart failure

LV = left ventricular/ventricle

TDI = tissue Doppler imaging

Several studies in the past have demonstrated that the assessment of mechanical dyssynchrony by echocardiography can supplement current electrocardiographic criteria (wide QRS ≥120 ms) in selecting cardiac resynchronization therapy (CRT) candidates, leading to an overall reduction in the nonresponders 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 (<130 ms) (4,5).

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The largest CRT trial conducted on patients with narrow QRS (<130 ms)—EchoCRT (Echocardiography Guided Cardiac Resynchronization Therapy)—demonstrated that patients with heart failure (HF) 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 compared with the control group, and the trial was stopped due to futility without achieving its complete target population. Another trial—RethinQ (Resynchronization Therapy in Narrow QRS)—which was performed before EchoCRT, with a similar design where mechanical dyssynchrony was 1 of the selection criteria, also showed no benefit of CRT in patients with HF 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 the assessment of mechanical activation delay by cross correlation analysis (CCA) using tissue Doppler imaging (TDI) (7,10). The presence of a delayed mechanical activation by CCA in patients with wide QRS is associated with improved prognosis as well as response after CRT (7,10,11). However, its significance is unknown in patients with HF with narrow QRS (<130 ms) treated with CRT. Accordingly, the objective of the current study was to assess the association of delayed mechanical activation using 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 was a prespecified substudy of the EchoCRT trial. All patients included in the EchoCRT trial had left ventricular (LV) ejection fraction ≤35%, QRS duration of ≤130 ms, severe symptomatic HF with New York Heart Association functional class III to IV symptoms, LV end-diastolic diameter ≥55 mm, and echocardiographic evidence of mechanical dyssynchrony by time-to-peak methods. In this study, dyssynchrony was identified by the presence of TDI-based opposing wall delay of ≥80 ms in the apical 4- or 3-chamber view, and radial strain delay ≥130 ms between the septum and the posterior walls in the LV midsegment short-axis view. All patients included in the trial were older than 18 years and provided informed consent. It was a multicenter randomized trial, in which patients were enrolled from 2008 to 2013 in 112 centers from 22

Biotronik, Boston Scientific, Sorin Group, Medtronic, and St. Jude Medical; personal fees from CardioInsight Inc.; has served as a consultant for Medtronic, Sorin, Boston Scientific, Abbott, Respicardia Inc., and Impulse Dynamics; and has received research grants from St. Jude Medical and LivaNova. Dr. Abraham has received grant support and personal fees from Biotronik, Medtronic, and St. Jude Medical; and was a member of the executive committee, which was supported by Biotronik, during the conduct of this study. Dr. Borer has received personal fees from Biotronik, Servier Laboratories, Amgen, Takeda USA, Pfizer, Cardiorentis, Novartis, ARMGO, and Celladon; has served on the clinical events committee for Takeda USA and AstraZeneca; has served on the data safety monitoring board for GlaxoSmithKline; has served as a consultant for Janssen, Novartis, Servier, Amgen, and Gilead; and is a stockholder in BioMarin and ARMGO. Dr. Dickstein has received personal fees from Biotronik, Medtronic, Sorin, and Boston Scientific. Dr. Gras has received personal fees from Medtronic, St. Jude Medical, Boston Scientific, and Biotronik. Dr. Krum has received personal fees from Biotronik. Dr. Brugada has received personal fees and other support from Biotronik. Dr. Ford has received grant support from Biotronik; grant support and personal fees from Servier and Medtronic; and personal fees from RESMED. Dr. Holzmeister has received grant support from St. Jude Medical; grant support and personal fees from Biotronik; and other support from Cardiorentis. Dr. Ruschitzka has received grants and personal fees from St. Jude Medical; and personal fees from Servier, Zoll, AstraZeneca, Sanofi, Cardiorentis, Novartis, Amgen, Bristol-Myers Squibb, Pfizer, Fresenius, Vifor, Roche, Bayer, and Abbott. Dr. Sogaard has received consultant fees from Biotronik and AstraZeneca; speaker fees from GE Healthcare; research grants from Biotronik, GE Healthcare, Bayer, and EBR systems; and has a relationship with AstraZeneca. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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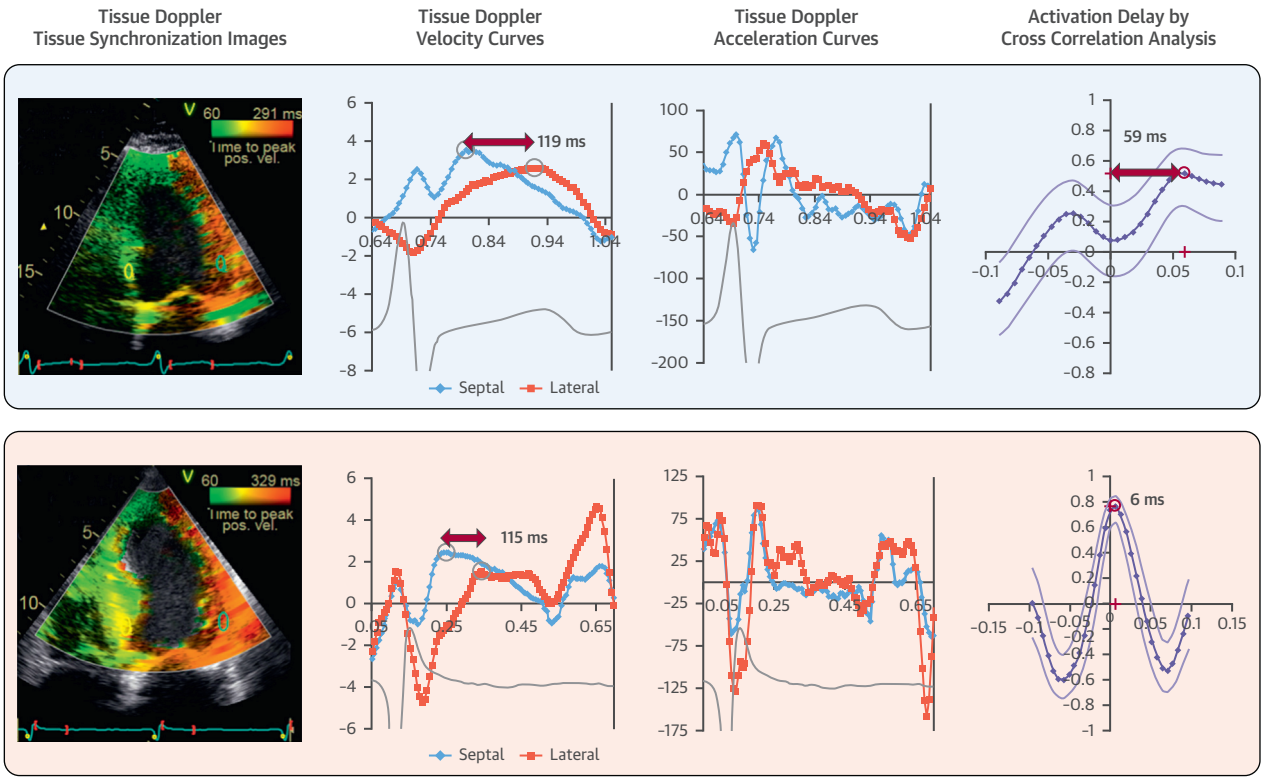
FIGURE 1 Examples Comparing Dyssynchrony by Time-to-Peak and Activation Delay by CCA



Two examples from the trial showing dyssynchrony by time-to-peak (≥80 ms) opposing wall delay using tissue Doppler imaging. However, only the patient in the **top row** has a significant activation delay (≥35 ms) on cross correlation analysis (CCA). The patient in the **bottom row** 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 2 panels.

different countries. Patients with bradycardia pacing or atrial fibrillation within the past few months were excluded. The main study results along with a detailed study protocol have been published (4). All study patients received a CRT device with defibrillator capacity (CRT-D) (Biotronik Lumax, Berlin, Germany) and were randomized 1:1 to CRT-On or -Off after a successful implantation of the device. For the current substudy, 807 (99.7%) of 809 patients were included with the baseline data and 610 (96%) of 635 patients were included with paired data at both baseline and 6-month follow-up.

CROSS CORRELATION ANALYSIS. All 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) by a single observer (B.T.) 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 × 15 mm) were placed on the base segments of the opposing walls in all 3 apical views, and the resulting velocity data were imported on an automated Excel sheet (Microsoft, Redmond, Washington) 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 2 opposing walls during systole in each of the 3 apical views without time-shift. These acceleration curves were then time-shifted against each other frame-by-frame to a 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 ≥35 ms in any of the 3 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

TABLE 1 Baseline Characteristics

	CRT-Off With No AD		CRT-On With No AD		CRT-Off With AD		CRT-On With AD	
	Total	Statistics	Total	Statistics	Total	Statistics	Total	Statistics
Age, yrs	181	57.4 ± 11.72	194	57.0 ± 13.07	223	59.2 ± 13.12	209	58.1 ± 12.77
Male	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 functional class	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	1,071 (462-2,203)	74	1,121 (414-2,444)	122	923 (529-1,999)	110	1,378 (556-2,675)
Sitting SBP, mm Hg	181	118 ± 16	194	118 ± 22	223	122 ± 21	209	117 ± 18
Sitting DBP, mm Hg	181	73 ± 11	194	73 ± 13	223	73 ± 13	209	73 ± 12
BMI, kg/m^2	181	30 ± 7	194	31 ± 15	223	32 ± 16	209	31 ± 7
Ischemic cardiomyopathy	180	93 (52)	194	99 (51)	223	120 (54)	209	119 (57)
MI >3 months ago	181	71 (39)	194	69 (36)	223	83 (37)	209	98 (47)
PCI >3 months ago	181	56 (31)	194	74 (38)	223	74 (33)	209	98 (47)
CABG >3 months ago	181	35 (19)	194	35 (18)	223	39 (17)	209	42 (20)
Hypertension	178	119 (67)	194	124 (64)	223	151 (68)	205	137 (67)
Congenital heart disease	175	3 (1.7)	192	3 (1.6)	220	7 (3.2)	206	3 (1.5)
Prior ischemic stroke or TIA	180	28 (16)	193	19 (10)	221	19 (9)	207	30 (14)
Diabetes	181	69 (38)	193	77 (40)	222	84 (38)	208	89 (43)
Chronic lung disease	180	33 (18)	191	30 (16)	220	45 (20)	209	39 (19)
Chronic kidney disease	180	17 (9)	192	30 (16)	220	25 (11)	209	36 (17)
LVEF 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	181	177 (98)	194	185 (95)	223	206 (92)	209	197 (94)
Aldosterone antagonist	181	105 (58)	194	118 (61)	223	132 (59)	209	128 (61)
Beta-blocker	181	178 (98)	194	183 (94)	223	216 (97)	209	203 (97)
Diuretic agent	181	160 (88)	194	160 (82)	223	191 (86)	209	185 (88)
MR grade	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)
LVESV, ml	180	134 ± 47	194	140 ± 49	223	142 ± 54	207	142 ± 49
LVEDV, 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
Radial strain delay, ms	173	218 ± 109	181	213 ± 100	202	223 ± 102	191	223 ± 99

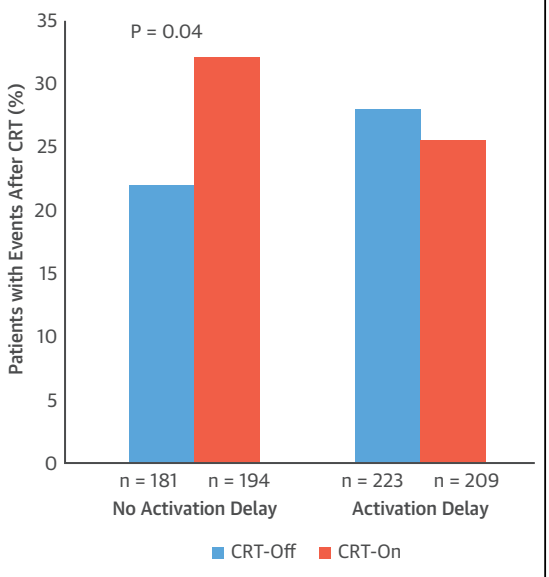
Values are n, mean ± SD, n (%), or median (interquartile range).

ACE = angiotensin-converting enzyme; AD = activation delay; ARB = angiotensin II receptor blocker; BMI = body mass index; BNP = brain natriuretic peptide; CABG = coronary artery bypass surgery; CRT = cardiac resynchronization therapy; DBP = diastolic blood pressure; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MI = myocardial infarction; MR = mitral regurgitation; NT-proBNP = N-terminal pro-b natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; TDI = tissue Doppler imaging; TIA = transient ischemic attack.

baseline and 6 months. For the analysis of patients with paired CCA data, patients were divided into the following 4 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.

FIGURE 2 Baseline Activation Delay and Outcome



Bar diagram showing the incidence of events of heart failure hospitalization or death among the 2 cardiac resynchronization therapy (CRT) device randomization groups based on the activation delay.

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

STATISTICAL ANALYSIS. All 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 (HRs) for CRT-On and -Off with 95% confidence intervals (CIs) 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 Kaplan-Meier method.

RESULTS

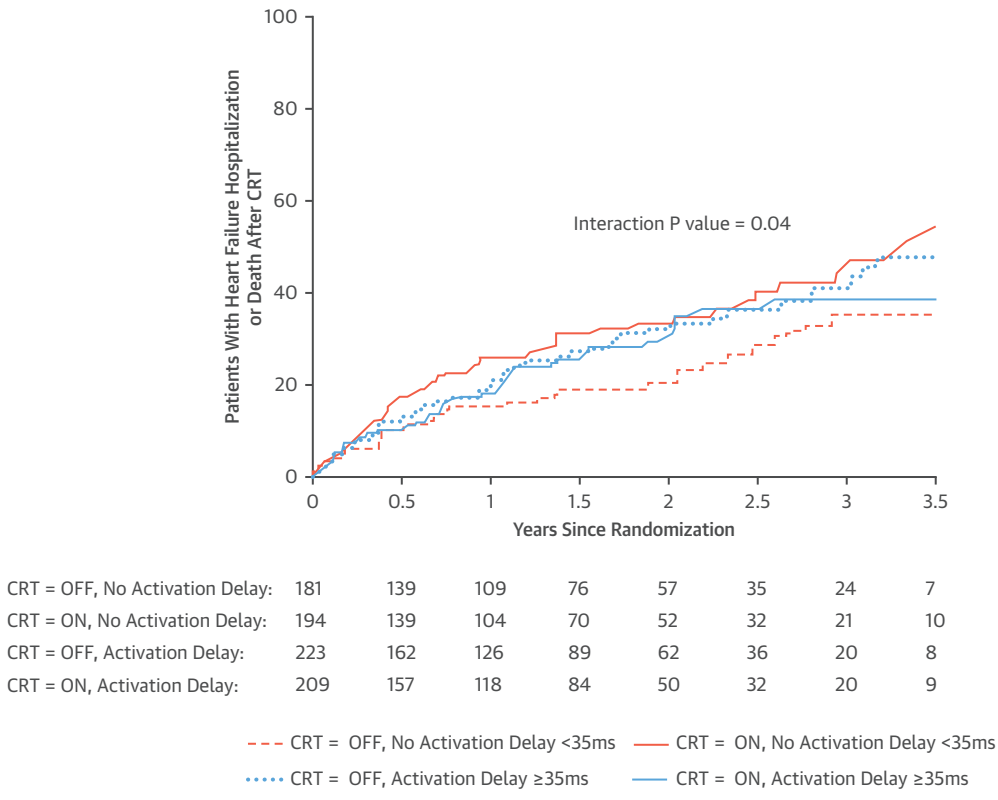
The 807 patients with baseline CCA analysis data were equally distributed, with 404 (50.1%) patients in the CRT-Off group and 403 (49.9%) in the CRT-On group. Of these 807 patients, time-to-peak dyssynchrony data was available in 806 patients: 420 (52%) patients had dyssynchrony by both radial strain and TDI opposing wall delay, 201 (25%) had dyssynchrony by lone TDI, and the remaining 185 (23%) patients had dyssynchrony by lone radial strain. A significant mechanical activation delay by CCA was observed in 223 (55%) of the CRT-Off patients and in 209 (52%) CRT-On patients. The baseline characteristics of the patients in the CRT-Off and -On groups based on activation delay are summarized in **Table 1**. No significant differences in baseline characteristics were observed between the groups.

ASSOCIATION OF BASELINE MECHANICAL ACTIVATION DELAY BY CCA WITH LONG-TERM OUTCOME. The trial was stopped due to futility by 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 4 groups, it was observed that patients with no mechanical activation delay by CCA in the CRT-On group experienced the highest number of events (32%) (**Figure 2**). Among patients with no mechanical activation delay, patients randomized to CRT-On group had an increased risk of an unfavorable outcome compared with those with CRT-Off: HR: 1.7 (95% CI: 1.13 to 2.55; $p = 0.01$) (**Figure 3**). However, among patients with presence of activation delay, no significant difference was observed for events among the 2 CRT randomization groups (HR: 0.96 [95% CI: 0.66 to 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-month follow-up, echocardiographic data for the CCA was available in 610 (96%) of 635 patients with follow-up echocardiograms. After excluding patients who were hospitalized for HF before the 6-month follow-up analysis, a final number of 541 patients were available for follow-up analysis. Among these, 274 (51%) were from CRT-Off and 267 (49%) were from the CRT-On group. The distribution of the 4 groups based on mechanical activation delay at baseline and follow-up among patients with CRT-Off and -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 experienced either HF hospitalization or death from 6 months until complete follow-up time, excluding events that occurred in the

FIGURE 3 Baseline Activation Delay and Time to Events



Kaplan-Meier curve showing the time to events for the 4 patient groups based on the presence or absence of activation delay at baseline and cardiac resynchronization therapy (CRT) device randomization.

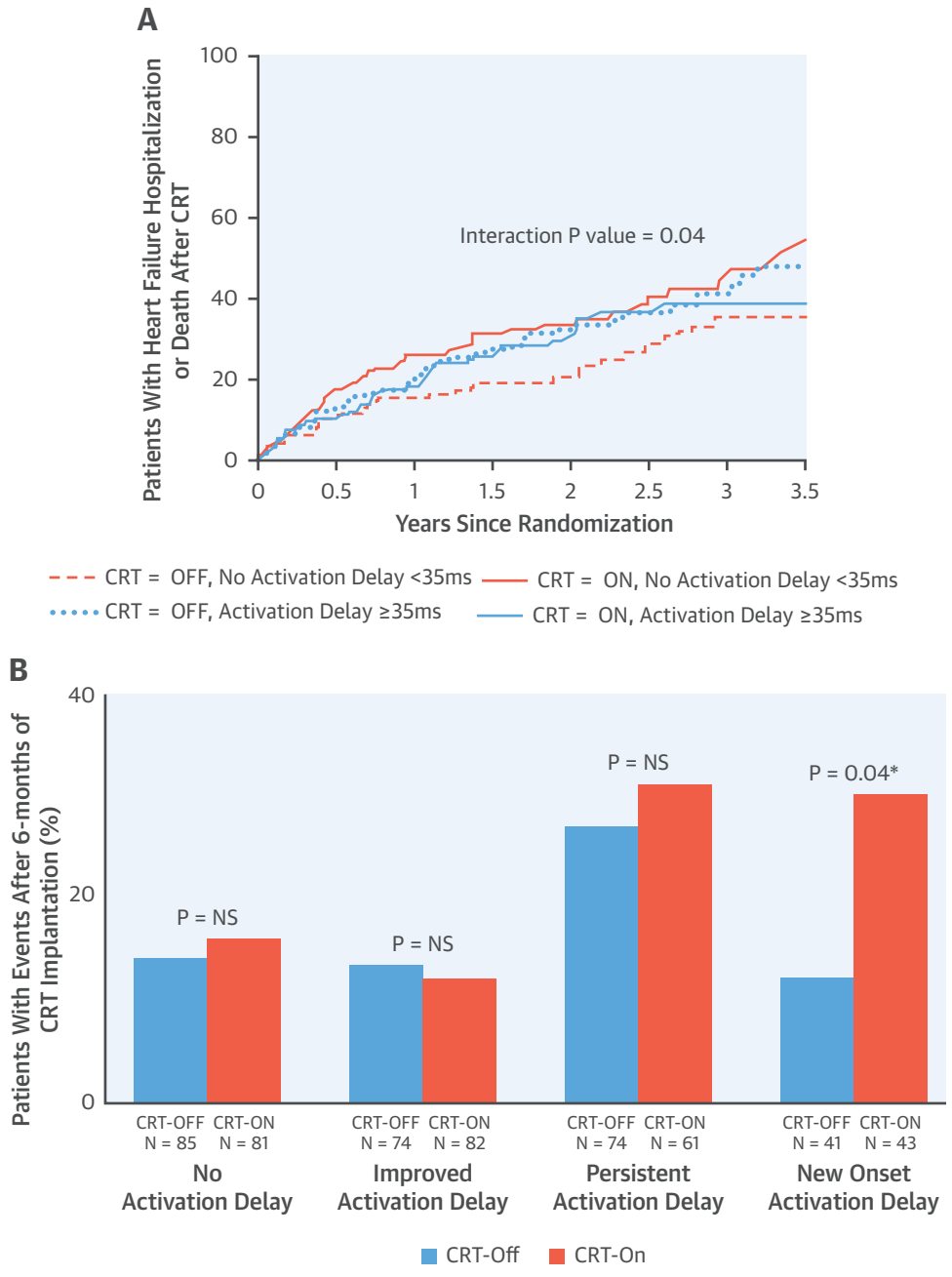
first 6 months. The event rate was significantly higher among patients with a new mechanical activation delay observed on the 6-month echocardiogram in the CRT-On group compared with the CRT-Off group (30% vs. 12%; HR: 3.73; 95% CI: 1.15 to 12.14; p = 0.03) (**Central Illustration**). No significant difference was observed for the outcome events between the other 3 groups based on randomization.

DISCUSSION

This pre-specified substudy of the EchoCRT trial of patients with HF 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 (**Central Illustration**). 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 into the interpretation of the EchoCRT trial and the mechanistic workings of CRT in general.

The EchoCRT trial used the best documented methods for dyssynchrony for selection of patients at the time of study design, that is, both longitudinal TDI velocity and 2-dimensional speckle tracking radial strain time-to-peak assessment. In patients with HF with wide QRS, these methods have demonstrated additive prognostic value (1,2,12). Moreover, single-center studies using these methods have shown improved HF symptoms and LV reverse remodeling in patients with narrow QRS HF with echocardiographic dyssynchrony treated by a CRT device, 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

CENTRAL ILLUSTRATION **Cross Correlation Analysis by Tissue Doppler Imaging and Outcome in Patients With Narrow QRS Treated With CRT**



Tayal, B. et al. J Am Coll Cardiol. 2018;71(12):1325–33.

(A) Increased hospitalization due to heart failure and mortality in patients with no activation delay at baseline and implanted with cardiac resynchronization therapy (CRT) with a significant interaction between device randomization and activation delay for the endpoints. **(B)** Patients with new activation delay after CRT compared with those with no CRT had poor outcome, indicating the role of device-induced activation delay in the poor prognosis.

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 are 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). The 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 the 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 patients with wide QRS complex undergoing CRT has proven beneficial in identifying responders with both wide and intermediate QRS durations, and has evaluated resynchronization efficacy to obtain maximum CRT benefit (7,10,11).

Unlike the CCA method, which is more of a quantitative approach, other qualitative methods for the assessment of dyssynchrony, such as identification of typical contraction pattern (9) and apical rocking (8), are proposed to identify the true patients with left bundle branch block (LBBB) with activation delay. Both of these methods have shown excellent additional value in identifying potential responders to CRT in patients with LBBB, which is principally due to exclusion of patients who are misdiagnosed as LBBB by electrocardiography. The 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 2 opposing walls rather than relying on a specific contraction pattern, and thus could be applicable in patients other than LBBB also. It has not only demonstrated to be superior to TDI time-to-peak in patients with wide QRS in predicting survival after CRT, but has also shown promising results in the intermediate QRS (120 to 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 patients with HF 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 the EchoCRT trial. Follow-up evaluation confirmed that particularly 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 observations have been made regarding new or worsened activation delay during CRT in patients with a wide QRS (11,17–19). This finding of potential harm from CRT in patients without baseline mechanical activation delay also fits well with a previous study of CCA in patients with intermediate to wide QRS HF 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. First, 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. Second, in patients with HF with intermediate QRS 130 to 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. Third, in patients with HF 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.

STUDY LIMITATIONS. The current study is a post hoc study. Although it was a pre-specified substudy that was approved before the EchoCRT trial 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-month follow-up echocardiograms in many patients: 610 patients had 6-month follow-up echocardiograms for CCA, resulting in a loss of about 24% of patients for the follow-up analysis. This was mostly due to the premature closure of the study.

CONCLUSIONS

The effect of CRT in patients with HF with narrow QRS (≤130 ms) in terms of HF hospitalization and death depends on LV mechanical activation delay determined by echocardiographic CCA. CRT specifically resulted in poor outcomes in patients with HF 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 insights into the effects of CRT pacing in patients with HF, which is of clinical significance.

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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, one-half of patients did not have significant activation delay by CCA when applied on patients having 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: Randomized studies are needed to assess the utility of CCA for selection of patients with intermediate QRS duration (120 to 140 ms) for CRT.

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