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Regional Left Ventricular Electrical Activation and Peak Contraction Are Closely Related in Candidates for Cardiac Resynchronization Therapy

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ABSTRACT

OBJECTIVES This study determined the relationship between the timing of left ventricular (LV) electrical activation and peak contraction at potential LV pacing locations in candidates for cardiac resynchronization therapy (CRT).

BACKGROUND Targeting the LV lead to the region of latest electrical activation or the segment of latest peak contraction has both been shown to improve CRT response. Whether these regions correspond within CRT patients is uncertain.

METHODS Twenty-eight consecutive CRT candidates underwent intraprocedural coronary venous electroanatomic mapping using EnSite NavX. Peak contraction time of the mapped LV regions was determined using longitudinal strain derived from speckle tracking echocardiography. Electrical activation and peak contraction times were correlated on a per patient basis, and the regions of latest electrical activation and latest peak contraction were compared.

RESULTS Successful measurements by both techniques allowed analysis in 23 of 28 patients. There was a strong positive correlation between electrical activation and peak contraction times within each patient ($R^2 = 0.85 \pm 0.09$). However, the magnitude of the electrical activation–peak contraction relationship varied greatly among patients (slope of regression line: 4.05 ± 3.23). The regions of latest electrical activation and latest peak contraction corresponded in 19 of 23 (83%) patients and were adjacent in 4 patients.

CONCLUSIONS There is a close relationship between the timing of LV electrical activation and peak contraction in CRT candidates. This finding suggests that a strategy of determining the latest activated LV region based on speckle tracking echocardiography corresponds to that based on intracardiac measurements of electrical activation. (J Am Coll Cardiol EP 2017;3:854–62) © 2017 by the American College of Cardiology Foundation.

Cardiac resynchronization therapy (CRT) has become an important treatment for heart failure patients with left ventricular (LV) systolic dysfunction and evidence of LV conduction delay. CRT aims to resynchronize the electrical ventricular activation by paced pre-excitation of the delayed LV lateral wall. CRT restores coordinated ventricular contraction, improves LV systolic function, and reverses ventricular remodeling (1). The position of the LV lead with respect to the region of

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latest activation has been shown to be an important determinant of CRT response. Studies that focus on electrical activation have demonstrated that a greater delay in time from onset of the QRS complex to the locally sensed LV lead electrogram is associated with a greater likelihood of benefit from CRT (2). Other studies have used speckle tracking–based strain measures of mechanical activation and have suggested better CRT outcome when the LV lead position coincides with the segment of latest peak contraction (3). Whether the region of latest electrical activation corresponds with the segment of latest peak contraction is uncertain. On the one hand, pre-clinical studies in nonfailing canine hearts have previously shown that electrical and mechanical activation of the heart are closely coupled (4–6). On the other hand, the results of 2 recent small-scale studies on this subject in CRT patients have been conflicting (7,8). Therefore, it remains unclear whether the pre-clinical results can be extrapolated to the dyssynchronous failing human heart. The purpose of the present study was to perform a within-patient comparison of the timing of LV electrical activation and peak contraction at potential LV pacing locations that are accessible via the coronary veins in patients undergoing CRT.

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METHODS

STUDY POPULATION. This study was conducted in 28 consecutive patients enrolled for CRT with LV ejection fractions of <35%, who were in New York Heart Association functional classes II, III, or ambulatory IV, and who had left bundle branch block (LBBB) according to specific criteria (9) or non-LBBB with a QRS duration of >150 ms. The study protocol was approved by the Maastricht University Medical Center (MUMC) Institutional Review Board.

CORONARY VENOUS ELECTROANATOMIC MAPPING. All patients underwent intraprocedural coronary venous electroanatomic mapping (EAM) at the MUMC as described previously (10). In brief, before LV lead placement, a 0.014-inch guidewire (Vision Wire, Biotronik SE&Co. KG, Berlin, Germany), which permits unipolar sensing and pacing, was inserted into the coronary sinus (CS) and connected to EnSite NavX (St Jude Medical, St. Paul, Minnesota). The guidewire was manipulated to various CS branches, creating an anatomic map, along with determining local electrical activation time during intrinsic ventricular activation. The coronary venous anatomy was classified using the segmental approach (11) by detailed evaluation of biplane coronary venograms. In the left anterior oblique (LAO) image, the CS was divided into anterior, lateral, and posterior areas, and the distribution of the branches was described similarly. The right anterior oblique (RAO) image was used to divide CS branches into basal, mid-ventricular, and apical segments. In each patient, the electrical activation time of a myocardial segment was calculated as the average of all electrical activation times measured within that segment during mapping. After the mapping procedure, the LV lead was positioned in a lateral or posterolateral vein according to routine clinical practice.

ABBREVIATIONS AND ACRONYMS

CRT = cardiac resynchronization therapy

CS = coronary sinus

EAM = electroanatomic mapping

LAO = left anterior oblique

LBBB = left bundle branch block

LV = left ventricular

MUMC = Maastricht University Medical Center

RAO = right anterior oblique

ECHOCARDIOGRAPHY. Standard 2-dimensional echocardiography was performed within 2 weeks before CRT implantation at the MUMC using a commercial machine (Philips IE 33, Philips Medical Systems, Andover, Massachusetts). Routine gray-scale cine loop images were acquired in standard apical views with a frame rate of at least 50 Hz and digitally stored for post-processing offline (Xcelera software R3.3L1; Philips, Eindhoven, the Netherlands). LV end-diastolic volume, LV end-systolic volume, and LV ejection fraction were calculated using Simpson's biplane method. Speckle tracking 2-dimensional longitudinal strain analysis was performed at the University Medical Center Utrecht by an experienced observer blinded to the electrical data using Cardiac Performance Analysis software version 1.2 (Tomtec Imaging Systems, Unterschleissheim, Germany). The endocardial border was manually traced in end systole. Subsequently, the speckle tracking software automatically analyzed frame-by-frame movement of the stable patterns of acoustic markers (speckles) to generate time–strain curves over the cardiac cycle of the myocardial segments. Because the area of the LV that can be approached for EAM via the CS is limited to the LV free wall, the assessment of segmental time-to-peak contraction was also limited to the LV free wall segments. The time-to-peak contraction of each mapped myocardial segment was measured in milliseconds from QRS onset to peak longitudinal strain. If segmental time–strain curves showed >1 peak, the first peak was assessed. Echocardiographic images that were of insufficient quality for speckle tracking strain analysis and myocardial segments with likely scar (low amplitude longitudinal strain curves <5.3%, thin wall ≤0.5 cm, abnormal increase in acoustic reflectance, and akinetic wall motion) (12,13) were handled as missing data.

COMPARISON OF ELECTRICAL ACTIVATION AND PEAK CONTRACTION TIMES. For each patient, the

TABLE 1 Patient Characteristics of the 23 Patients Included in the Analysis

Age (yrs)	69 ± 10
Male	15 (65)
Ischemic heart disease	8 (35)
NYHA functional class	
II	9 (39)
III	14 (61)
Echocardiography characteristics	
LV ejection fraction (%)	28 ± 5
LV end-diastolic diameter (mm)	62 ± 7
LV end-systolic diameter (mm)	53 ± 8
LV end-diastolic volume (ml)	172 ± 54
LV end-systolic volume (ml)	125 ± 41
ECG characteristics	
QRS duration (ms)	151 ± 14
LBBB	13 (57)
IVCD	10 (43)
Intrinsic rhythm	
Sinus rhythm	20 (87)
Atrial fibrillation	3 (13)
Treatment	
Diuretics	15 (65)
ACE-I/ARB	22 (96)
Beta-blockers	20 (87)
Spironolactone	13 (57)
Digoxin	1 (4)
Amiodarone	2 (9)

Values are mean ± SD or n (%).

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ECG = electrocardiographic; IVCD = nonspecific intraventricular conduction delay; LBBB = left bundle branch block; LV = left ventricular; NYHA = New York Heart Association.

electrical activation and peak contraction times of each myocardial segment were compared separately. Pearson's correlation coefficient was computed between the electrical activation and peak contraction times observed for each patient. The segments of latest electrical activation and latest peak contraction were determined in each patient.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD. Categorical values are expressed as observed number and percentage values. Within-patient correlation between electrical activation and peak contraction times was calculated using Pearson's correlation coefficient. Statistical analysis was performed using SPSS version 20.0 (IBM, Armonk, New York).

RESULTS

PATIENT CHARACTERISTICS. Twenty-eight consecutive patients enrolled for CRT were included in the study. Five patients were excluded from further analysis due to reasons described in the following. The patient characteristics of the 23 included patients are described in Table 1.

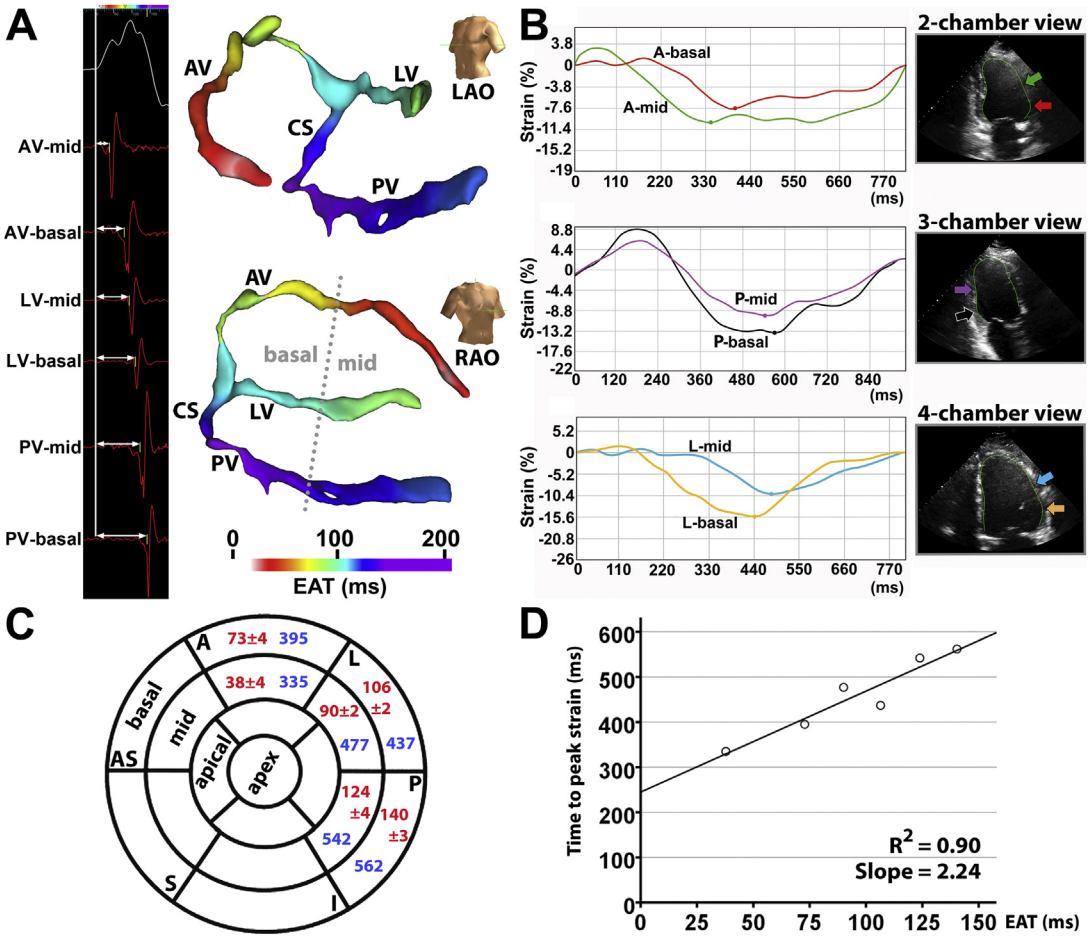
CORONARY VENOUS EAM AND SPECKLE TRACKING STRAIN ANALYSIS. Intraprocedural coronary venous EAM was accomplished in all 28 patients without complications. Coronary venous angiography in the 28 patients revealed a total of 96 coronary venous branches, of which 83 (86%) could be mapped. Three-dimensional electrical activation maps were generated from 62 ± 25 unique anatomic points. Mapping time was 19 ± 7 min, and fluoroscopy time during the entire procedure was 21 ± 4 min.

Speckle tracking strain analysis was accomplished in 23 of 28 patients. In the other 5 patients, this was hampered by insufficient quality of the acquired echocardiographic images (n = 4) and frequent premature ventricular beats (n = 1). These 5 patients were excluded from further analysis. Excluded and included patients did not differ in terms of baseline characteristics. Myocardial segments with likely scar on echocardiography, which were handled as missing data, were encountered in only 2 of 23 patients, and consisted of only 2% of all segments analyzed for time-to-peak strain.

The hemodynamic parameters of the patients were similar during both studies. The intrinsic heart rhythm during both studies was unchanged for all patients. The mean heart rate was 69 ± 14 beats/min during echocardiography and 71 ± 11 beats/min during EAM (p = 0.33). The mean QRS duration was 156 ± 16 ms during echocardiography and 154 ± 15 ms during EAM (p = 0.17).

RELATIONSHIP BETWEEN LV ELECTRICAL ACTIVATION AND PEAK CONTRACTION. Successful measurements by both coronary venous EAM and speckle tracking echocardiography allowed analysis of the electrical activation-peak contraction relationship in 23 of 28 patients. An example of the analysis in 1 patient is shown in Figure 1. In this patient, the CS and 3 side branches situated on the basal and mid-anterior, lateral, and posterior walls were mapped (Figure 1A). Earliest electrical activation was found in the mid-segment of the anterior interventricular vein, and the latest electrical activation was found in the basal segment of the posterior vein. Figure 1B shows the corresponding time–strain curves of the mapped myocardial segments obtained by speckle tracking echocardiography. In Figure 1C, the average electrical activation times and corresponding peak contraction times of the mapped myocardial segments of this patient are displayed on a bullseye of the heart. Figure 1D shows the regression line between the electrical activation and peak contraction times for

FIGURE 1 Analysis of Electrical Activation–Peak Contraction Relationship in 1 Patient

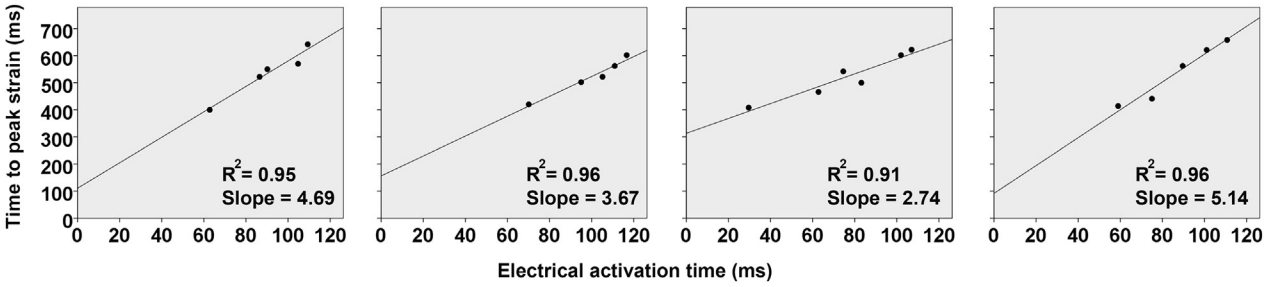


(A) Coronary venous electroanatomical map (EAM). The coronary sinus (CS) and 3 side branches (basal and mid segments) were mapped. Earliest activation is represented in **white and red** and latest activation in **blue and purple**. Representative QRS-electrogram interval recordings from each mapped segment are shown to the left of the EAM. **(B)** Corresponding time strain curves of the mapped myocardial segments. **(C)** Electrical activation times (mean ± SD) **(red numbers)** and corresponding peak contraction times **(blue numbers)** of the mapped myocardial segments of this patient displayed on a 17-segment bullseye of the heart. **(D)** Correlation between electrical activation and peak contraction times in this patient. A = anterior; AS = anteroseptal; AV = anterior interventricular vein; EAT = electrical activation time; I = inferior; L = lateral; LAO = left anterior oblique view; LV = lateral marginal vein; P = posterior; PV = posterior vein; RAO = right anterior oblique view; S = septal.

this patient. There was a strong correlation between electrical activation and peak contraction times within this patient ($R^2 = 0.90$), and the segment of latest electrical activation corresponded with the segment of latest peak contraction.

A strong linear relationship between electrical activation and peak contraction times, as observed in Figure 1, was found in all patients ($R^2 = 0.85 \pm 0.09$). The slope of the regression line between electrical activation and peak contraction times was positive in all patients, which indicated that as electrical activation time increased, the peak contraction time increased as well. This implied that the sequence of peak contraction was similar to the electrical activation sequence and also for the nonlatest segments. However, the slope, and thus, the magnitude of this relationship varied greatly among patients (slope of regression line: 4.05 ± 3.23) (Figure 2). Also, the slope of the regression line was above unity in all but 1 patient, which indicated that regional differences in timing of peak contraction were generally greater than those of electrical activation. Subgroup analysis showed no difference in the strength of the electromechanical relationship among patients with

FIGURE 2 Interindividual Variability in Electrical Activation-Peak Contraction Relationship



The regression lines between electrical activation and peak contraction times and the points by which these were created are shown for 4 representative patients. Each point was determined from measuring the electrical activation and peak contraction time of a myocardial segment within a patient. The electrical activation and peak contraction times of 5 myocardial segments (resulting in 5 points) were assessed in 3 of these patients and those of 6 myocardial segments (resulting in 6 points) were assessed in 1 patient. All regression lines exhibited high and positive correlation values. However, the slope, and thus, the magnitude of the electrical activation–peak contraction relationship varied greatly from patient to patient.

ischemic LV dysfunction versus patients with non-ischemic LV dysfunction, patients with LBBB versus patients with intraventricular conduction delay (IVCD), or patients with sinus rhythm versus patients with atrial fibrillation (Table 2).

Figure 3 shows the spatial distribution of the electrically latest activated and latest contracting segments in all patients. The segment of latest electrical activation was located anteriorly in 11 patients (basal, n = 10; mid, n = 1), laterally in 8 patients (basal, n = 5; mid, n = 3), and posteriorly in 4 patients (all basal). The segment of latest peak contraction was located anteriorly in 11 patients (all basal), laterally in 8 patients (basal, n = 5; mid, n = 3), and posteriorly in 4 patients (all basal). The myocardial segment with the largest electrical activation time also had the largest peak contraction time in 19 of 23 patients (83%). In the other 4 patients, the myocardial segments of latest electrical activation and latest peak contraction were adjacent, which was defined as located directly next to each other on either the apical–basal axis (RAO view) or the short-axis projection (LAO view), including touching diagonally.

TABLE 2 Subgroup Analysis of the Strength of the Electromechanical Relationship

Patient Subgroups	R^2	p Value
Ischemic (n = 8) vs. non-ischemic (n = 15) LV dysfunction	0.88 ± 0.09 vs. 0.84 ± 0.09	0.29
LBBB (n = 13) vs. IVCD (n = 10)	0.86 ± 0.10 vs. 0.84 ± 0.08	0.69
SR (n = 20) vs. AF (n = 3)	0.87 ± 0.05 vs. 0.85 ± 0.09	0.70

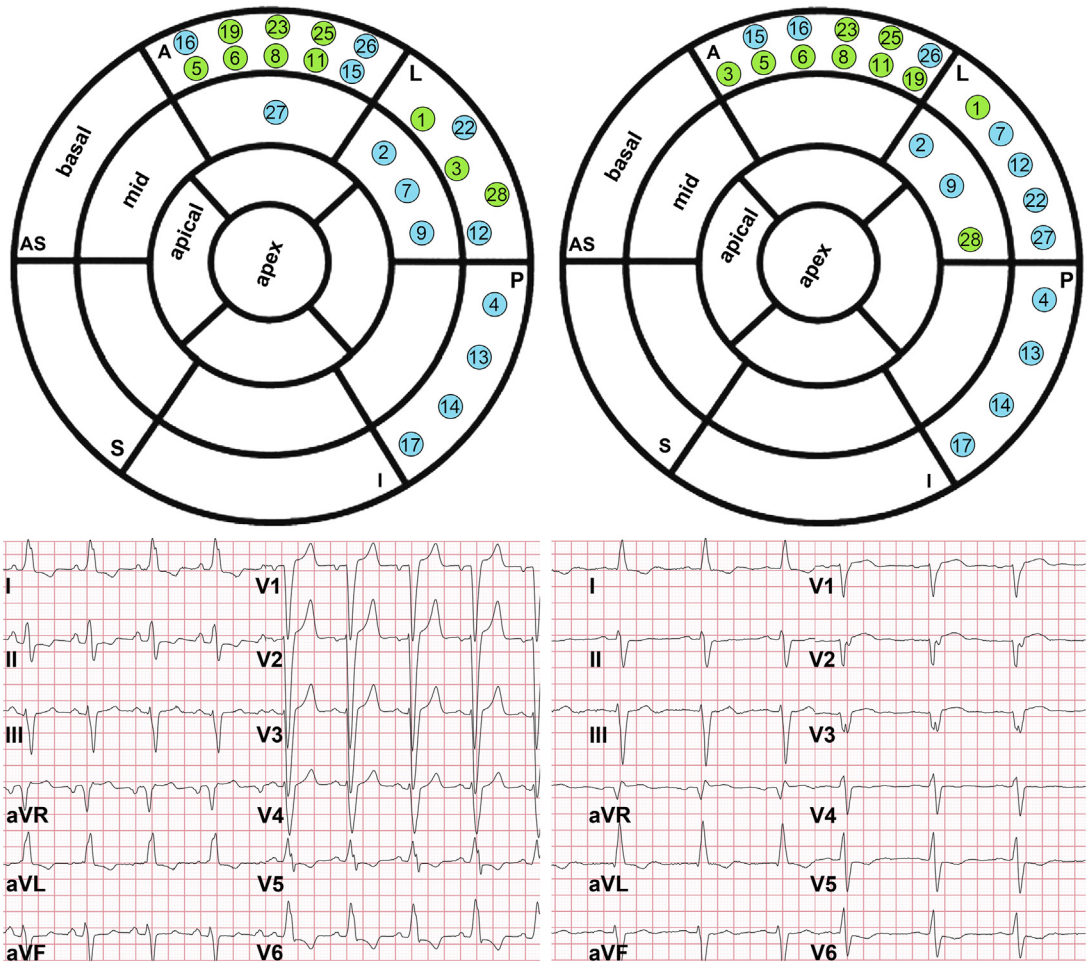
Values are mean ± SD.
AF = atrial fibrillation; SR = sinus rhythm; other abbreviations as in Table 1.

DISCUSSION

In the present study, we investigated the relationship between the timing of regional LV electrical activation and peak contraction in dyssynchronous heart failure patients who underwent CRT implantation. We demonstrated a strong positive correlation between electrical activation and peak contraction times measured at potential LV pacing regions accessible via the coronary veins in all patients. However, the magnitude of the relationship between electrical activation and peak contraction times varied greatly among patients. The myocardial segments of latest electrical activation and latest peak contraction corresponded in 83% of patients. Our data suggest that a strategy of determining the latest activated LV region based on speckle tracking strain patterns corresponds to that based on intracardiac measurements of electrical activation.

RELATIONSHIP BETWEEN TIMING OF ELECTRICAL ACTIVATION AND PEAK CONTRACTION. A number of animal studies previously studied the relation between the sequence of LV electrical activation and contraction using a combination of electrical mapping techniques and strain measurements. These studies were conducted in healthy spontaneously activated or paced canine hearts and focused on the relation between timing of electrical activation and time-to-onset of contraction, rather than peak contraction. A strong linear relation between timing of electrical activation and onset of contraction was found in these studies. In addition, mechanical delay was shown to be larger than electrical delay (4,6,14,15). Although time-to-onset of contraction might be a better surrogate for mechanical activation than

FIGURE 3 Spatial Distribution of the Electrically Latest Activated and Latest Contracting Segments in the 23 Patients Included in the Analysis



Spatial distribution of the electrically latest activated **(upper left panel)** and latest contracting segments **(upper right panel)** in the 23 patients with successful measurements by both coronary venous EAM and speckle tracking echocardiography. Each **circled number** represents a patient, with LBBB patients represented in **blue** and interventricular conduction delay (IVCD) patients represented in **green**. The segment with the largest electrical activation time also had the largest peak contraction time in 19 of 23 patients (83%). In 4 patients (#3, 7, 27, and 28), the segments of latest electrical activation and latest peak contraction were adjacent. **(Lower left and right panels)** Electrocardiograms of patient with LBBB (#6) and IVCD (n#2), respectively. Abbreviations as in Figure 1.

time-to-peak contraction, in practice, the identification of the first subtle onset of contraction can be cumbersome. Therefore, most clinical studies used time-to-peak contraction (3,16).

The findings of the present study are consistent with the results of a recent study by Suever et al. (8), who investigated the relation between electrical and mechanical delay times measured at potential pacing locations within the coronary veins. In this study, the mechanical contraction times were computed using cross correlation of radial displacement curves from high temporal resolution cine cardiac magnetic resonance images, whereas electrical activation times were derived from intraprocedural local electrograms obtained using the LV lead. Similar to our findings, they found a strong correlation between electrical and mechanical delay times within each patient. In addition, the electrically latest activated region corresponded with the latest contracting region in 91% of patients.

Our results are also in line with a recent study by Kroon et al. (17), who used NOGA mapping (Johnson & Johnson, Irwindale, California)–derived electrograms and local strain derived from the motion of the NOGA

catheter to investigate the relation between the timing of LV electrical activation and peak shortening in 10 CRT candidates. In this study, an excellent correlation was found between local electrical activation and peak shortening times in 8 of 10 patients.

Our findings are in contrast to the results of a previous study that had a similar design as ours. In the study by Fujiwara et al. (7), the electrically latest activated region, as determined by coronary venous EAM, matched with the latest contracting region, as determined by speckle tracking radial strain analysis, in only 18% of patients (7), whereas we found that the regions of latest electrical activation and latest peak contraction corresponded in 83% of patients. An important methodological difference between our study and the study by Fujiwara et al. was the use of different types of strain measurements (longitudinal strain vs. radial strain, respectively). Time-to-peak radial strain measures were also used in the larger and randomized TARGET (Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy) and STARTER (Speckle Tracking Assisted Resynchronization Therapy for Electrode Region) studies, which showed marked clinical benefit with targeted LV lead placement to mechanically late contracting segments. The reason for using time-to-peak longitudinal strain measures in the present study was because these measures were shown to be more feasible and reproducible, and were less subject to out-of-plane motion than radial strain measures (18,19). Also, in contrast to Fujiwara et al., we only measured peak contraction times of LV regions accessible via the coronary veins. In doing so, we neglected the data on mechanical activation of the septum, because this part of the LV wall is not accessible from the CS, and most importantly, is unlikely to be activated late in LBBB-like conduction abnormalities. It was previously shown in computer simulations that septum strain patterns can be complicated and multiphasic, and can sometimes show a relatively late peak in systole, even in LBBB (20), which leads to a mismatch between the determined electrical and mechanical timing.

In the present study, the latest activated region was located on the anterior wall in 11 of 23 patients. This observation could be explained by the fact that 7 of these patients did not have a typical LBBB morphology on electrocardiography, and that the remaining 4 patients had an ischemic etiology of heart failure with myocardial scarring. In patients with nonischemic LV dysfunction and LBBB, the latest activated region is typically located on the lateral or posterolateral wall (21). In contrast, the LV activation pattern in patients with non-LBBB QRS morphology or patients with ischemic LV dysfunction is shown to be more variable (22,23).

INTERINDIVIDUAL VARIABILITY IN ELECTRICAL ACTIVATION–PEAK CONTRACTION RELATIONSHIP. In the present study, we found a strong linear relationship between timing of electrical activation and peak contraction within each patient. In addition, the relationship was positive in each patient, indicating that as electrical activation time increased, peak contraction time increased as well. However, the slope of the best fit line between electrical activation and peak contraction times was 4.06 ± 3.23, which indicated that the electrical activation-peak contraction relationship varied greatly among patients and that timing differences of myocardial contraction were greater than those of electrical activation. The differences in the electrical activation-peak contraction relation among hearts might be caused by interindividual differences in local myocardial tissue properties, such as viability, contractility, and stiffness of the myocardium (17). The "amplification" of dyssynchrony when using mechanical measures is likely explained by the fact that peak contraction occurs much later in the cardiac cycle and that early activated regions show an early peak contraction, whereas late activated regions are initially pre-stretched and subsequently show a more pronounced and prolonged contraction (4,5,20). In computer models of LBBB, the more pronounced mechanical, rather than electrical, delay was attributed to the higher mechanical load that needs to be overcome by late activated regions, which causes the onset of contraction to occur relatively late (5).

CLINICAL IMPLICATIONS. The demonstration of a close correlation between timing of electrical activation and peak contraction suggests that current LV lead targeting strategies, which are based on either direct intracardiac measurements of electrical activation or speckle tracking strain echocardiography, will most likely target the same myocardial region, and as such, can be regarded as corresponding. In this respect, the present study could be regarded as a validation of the speckle tracking approach. In clinical practice, electrical mapping of the coronary veins can extend procedure time and may be cumbersome. In contrast, speckle tracking time-to-peak contraction analysis can be performed offline before CRT implantation. This information can then be provided to the clinician during CRT implantation, who can then, after performing invasive coronary venous angiography, use the segmental approach (11) to identify and match the location of the cardiac veins to the underlying LV myocardial segments and target the LV lead to the segment of latest peak contraction to enhance cardiac synchrony.

STUDY LIMITATIONS. Although this study was conducted in consecutive patients, the small sample size might have led to patient characteristics that might not resemble the normal CRT population (43% of patients had IVCD, and only 2 patients had segments with scar on echocardiography). This limits extrapolation of the data to larger CRT populations. However, the specific activation pattern (whether or not LBBB) should not influence the relation between electrical and mechanical activation; and the larger studies that used measures of mechanical activation to target LV lead placement excluded regions with scar (3,16).

The close correlation between regions of latest electrical and mechanical activation shown in this study does not prove that pacing at these sites provides long-term clinical benefit. Neither was the clinical value of pacing at these sites proven by acute hemodynamic measurements. As mentioned previously, several studies indicated that pacing in a region of late electrical or mechanical activation improves CRT response, but it is not known whether combining electrical and mechanical information may further improve LV lead targeting. Whether such a LV lead placement strategy actually increases the likelihood of a favorable CRT response needs prospective evaluation in larger, and preferably, randomized studies.

Epicardial mapping through the coronary veins is limited by coronary venous anatomy. The electrical activation time of some LV free wall segments could therefore not be assessed because they did not contain any veins.

Speckle tracking echocardiography relies on the availability of echocardiographic images with sufficient quality for reliable assessment of strain patterns. Insufficient image quality and frequent premature ventricular beats hampered reliable assessment of segmental peak contraction times in 5 patients in this study. Therefore, in these patients, the electrical activation-peak contraction relationship could not be analyzed.

CONCLUSIONS

The present study demonstrates a close relation between the timing of LV electrical activation and peak contraction measured in the LV free wall of CRT candidates. In addition, the regions of latest electrical activation and latest peak contraction largely corresponds within CRT patients. These findings suggest that a strategy of determining the latest activated LV region based on speckle tracking echocardiography corresponds to that based on intracardiac measurements of electrical activation.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: There is a close relation between the timing of LV electrical activation and peak contraction in the LV free wall of CRT candidates. Targeting LV lead placement to the latest activated region based on either intracardiac measurements of electrical activation or speckle tracking echocardiography will thus most likely target the same myocardial region, and as such, can be regarded as corresponding strategies for tailoring LV lead placement to the individual patient.

TRANSLATIONAL OUTLOOK: Increasing evidence supports the practice of placing the LV lead in the latest activated region as a means of maximizing CRT response. However, the data obtained up to now are not conclusive. The clinical value of this LV lead placement strategy requires more evaluation in long-term prospective randomized trials.

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