Mechanistic Evaluation of Echocardiographic Dyssynchrony Indices

Patient Data Combined With Multiscale Computer Simulations

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Background—The power of echocardiographic dyssynchrony indices to predict response to cardiac resynchronization therapy (CRT) appears to vary between indices and between studies. We investigated whether the variability of predictive power between the dyssynchrony indices can be explained by differences in their operational definitions.

Methods and Results—In 132 CRT-candidates (left ventricular [LV] ejection fraction, 19±6%; QRS width, 170±22 ms), 4 mechanical dyssynchrony indices (septal systolic rebound stretch [SRSsept], interventricular mechanical dyssynchrony [IVMD], septal-to-lateral peak shortening delay [Strain-SL], and septal-to-posterior wall motion delay [SPWMD]) were quantified at baseline. CRT response was quantified as 6-month percent change of LV end-systolic volume. Multiscale computer simulations of cardiac mechanics and hemodynamics were used to assess the relationships between dyssynchrony indices and CRT response within wide ranges of dyssynchrony of LV activation and reduced contractility. In patients, SRSsept showed best correlation with CRT response followed by IVMD, Strain-SL, and SPWMD (R=−0.56, −0.50, −0.48, and −0.39, respectively; all P<0.01). In patients and simulations, SRSsept and IVMD showed a continuous linear relationship with CRT response, whereas Strain-SL and SPWMD showed discontinuous relationships characterized by data clusters. Model simulations revealed that this data clustering originated from the complex multipeak pattern of septal strain and motion. In patients and simulations with (simulated) LV scar, SRSsept and IVMD retained their linear relationship with CRT response, whereas Strain-SL and SPWMD did not.

Conclusions—The power to predict CRT response differs between indices of mechanical dyssynchrony. SRSsept and IVMD better represent LV dyssynchrony amenable to CRT and better predict CRT response than the indices assessing time-to-peak deformation or motion. **(*Circ Cardiovasc Imaging*. 2012;5:491-499.)**

Key Words: echocardiography ■ heart failure ■ strain ■ computer model ■ asynchrony

Cardiac resynchronization therapy (CRT) has become an established treatment for patients with chronic heart failure, wide QRS complex, and decreased left ventricular (LV) ejection fraction (LVEF <35%).[1,2] Despite the demonstrated beneficial effects of CRT on symptoms, myocardial function, hospitalizations, and survival, a significant response cannot be established in up to 50% of patients depending on the definition of response used.[1,3,4]

Clinical Perspective on p 499

In attempts to better select patients for CRT and hence to improve outcome, indices of mechanical dyssynchrony (DYS) have been extensively explored. Although initial single-center studies were promising,[5–8] subsequent multicenter studies failed to reproduce the results.[3,4] These negative results have been attributed to poor measurement reproducibility and feasibility, technical limitations, lack of a central core laboratory, and shortcomings in study design.[4,9] While all of these reasons may contribute to the failure of DYS indices to predict CRT response, it is still unknown to what extent DYS indices comply with the elementary condition that they should reflect the substrate of dyssynchrony that is actually amenable to CRT.

In this study, we hypothesized that differences between echocardiographic DYS indices to predict CRT response originate from the different characteristics they extract from

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myocardial deformation and motion signals during various degrees of dyssynchrony. To test this hypothesis, we assessed the prediction of CRT response by 4 previously published echocardiographic DYS indices in a cohort of CRT-candidates. These patient data were combined with multiscale computer simulations of cardiovascular mechanics and hemodynamics within a wide range of (patho)physiological circumstances. The goal of the simulations was to quantify each parameter's dependence on dyssynchrony of ventricular activation in absence of measurement variability and other sources of noise. Furthermore, simulations assessed each parameter's sensitivity to global and regional differences in LV myocardial contractility.

Methods

Patient Study

Patient Population and Study Protocol

The study population constituted a consecutive cohort of patients scheduled for CRT and prospectively enrolled between August 2005 and April 2009. Indications for CRT were severe medication refractory heart failure (New York Heart Association class [NYHA] III-IV and LVEF <35%) and evidence of conduction disturbances (QRS width [mtequ]120 ms), with a left bundle-branch block[en] like morphology on the surface ECG. Echocardiographic and clinical characteristics were prospectively assessed in all patients at baseline and after a 6-month follow-up period. The execution of the study conformed to the principles outlined in the Declaration of Helsinki on research in human subjects. The study protocol was approved by the Medical Ethics Committee of the University Medical Center Utrecht.

Echocardiographi.c Protocol

Our echocardiographic protocol has been described in detail elsewhere.[10] In brief, all echocardiographic data were obtained on a Vivid 7 ultrasound machine (General Electric, Milwaukee, WI), using a broad band M3S transducer for Doppler and 2D imaging. LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), and LVEF were measured using the biplane Simpson method. Response was quantified as percent change of LV end-systolic volume (ΔLVESV) from baseline to 6-month follow-up. The LV was divided into 16 segments according to the recommendations of the American Society of Echocardiography.[11] Segments were scored scarred when they displayed akinesis or dyskinesis in combination with a disproportionate local wall thinning and hyperreflectivity in comparison to adjacent contractile segments. The patient population was subdivided into 2 groups: 1 group with <2 scarred segments (NOSCAR) and 1 group with ≥2 scarred segments (SCAR). For deformation imaging, additional single wall images of the septum and lateral wall were prospectively acquired from the apical 4-chamber view at 51 to 109 frames per second. Timing of mitral, aortic, and pulmonary valve opening and closure were derived from Doppler flow patterns and defined cardiac event timing. LV systole was defined as the period from mitral valve closure to aortic valve closure.

Deformation Analysis

Speckle-tracking software (Echopac version 6.0.1, General Electric) was used to quantify septal and LV lateral wall deformation from the single wall recordings as described previously.[10,12,13] Deformation events were temporally aligned through the ECG-traces, using the onset of the QRS complex as zero strain reference. Global longitudinal strain was used for further analyses. Peak systolic shortening was defined as maximum negative amplitude of longitudinal strain during systole.

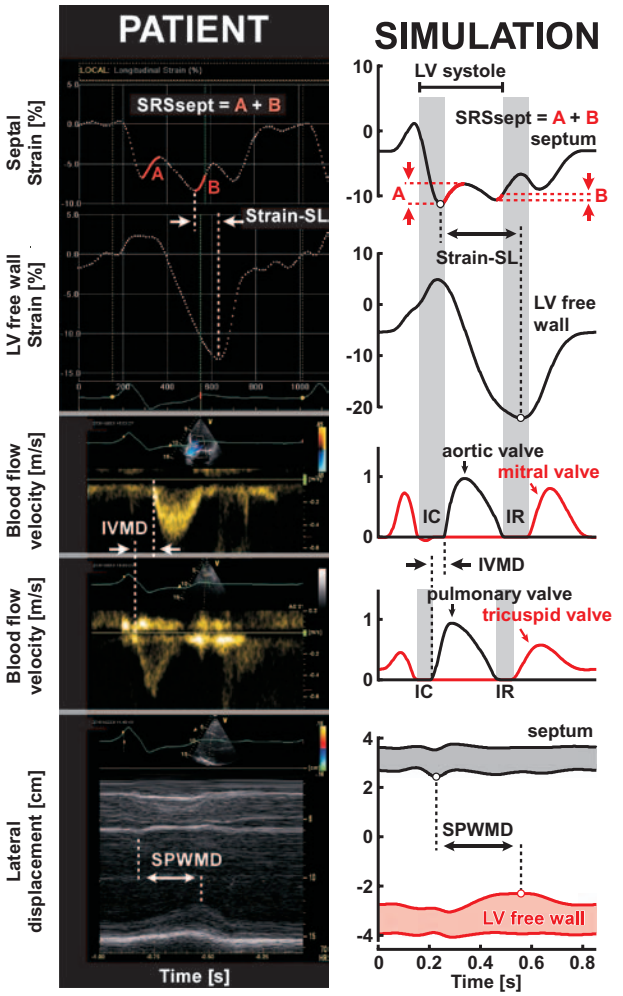


Figure 1. Definitions of DYS indices. Time courses of left ventricular (LV) strain, blood flow velocities, and wall motion as measured in a heart failure patient with left bundle-branch block (**left column**) and as derived from a DYSSYNCHRONY simulation with 50-ms delay of LV free wall with respect to septal activation (**right column**). Septal systolic rebound stretch (SRSsept) was defined as the total amount of rebound stretch (ie, stretch occurring after initial shortening) of the interventricular septum during LV systole, defined as the period between mitral and aortic valve closure. In this example, SRSsept is the sum of a midsystolic (**A**) and an end-systolic (**B**) amount of septal stretch. Septal-to-lateral peak shortening delay (Strain-SL) was defined as the time difference between maximal systolic septal and LV free wall shortening, interventricular mechanical dyssynchrony (IVMD) as the time difference between pulmonary and aortic valve opening, and septal-to-posterior wall motion delay (SPWMD) as the time difference between maximal inward displacement of the septum and of the LV free wall. **Gray bars** indicate isovolumic contraction (IC) and isovolumic relaxation (IR) phases.

Assessment of Echocardiographic Dyssynchrony Indices in Patients

As depicted in the left column of Figure 1, 4 mechanical dyssynchrony indices were assessed using their previously published operational definitions: mechanical discoordination was evaluated by quantifying the amount of systolic rebound stretch (ie, all systolic stretch occurring after initial shortening) in the septum (SRSsept)[10]; interventricular mechanical delay (IVMD) determined from the time difference between pulmonary and aortic valve opening[14]; septal-to-lateral delay (Strain-SL) calculated as the time difference between moments of peak septal and lateral wall shortening[12,15]; and the delay

between maximal inward motion of the septal and LV posterior wall (septal-to-posterior wall motion delay, SPWMD) obtained from standard M-mode recordings.[16]

CRT Device Implantation

Devices were implanted by a single left pectoral incision with transvenous LV lead insertion into a coronary sinus tributary vein (n=130) or epicardially positioned on the LV free wall by video assisted thoracoscopy (n=2). The LV lead was placed lateral or posterolateral in 110 patients (83%), anterolateral in 8 (6%), and posterior in 14 (11%). Right ventricular and atrial leads were placed conventionally.

Computer Simulations

A multiscale computer model of the cardiovascular system (CircAdapt model)[17,18] was used to quantify the dependencies of all 4 DYS indices on dyssynchrony of ventricular activation and regional variations of LV contractility.

Model Design

The CircAdapt model has been described in detail elsewhere.[17,18] In brief, it consists of modules representing myocardial walls, cardiac valves, large blood vessels, and peripheral resistances. It enables realistic beat-to-beat simulation of cardiovascular mechanics and hemodynamics under a wide variety of (patho-)physiological circumstances, including ventricular mechanical dyssynchrony.[13,18–20] Three thick-walled segments representing the LV free wall (LVFW), the interventricular septum (SEPT), and the RV free wall are mechanically coupled in a junction and ventricular mechanical interaction is incorporated by the equilibrium of tensile forces in the junction. In each cardiac wall, the myofiber stress-strain relation is determined by a 3-element muscle model describing active and passive cardiac myofiber mechanics.[18] Global left and right ventricular pump mechanics are related to myofiber mechanics in the three ventricular walls, using the principle of conservation of energy.

Simulations

Normal cardiovascular mechanics and hemodynamics were simulated as published previously.[18] This NORMAL simulation represented a healthy cardiovascular system under baseline resting conditions (cardiac output=5.1 L/min, heart rate=70 bpm, and mean arterial pressure=92 mmHg) with synchronous onset of mechanical activation of the 3 ventricular walls. The NORMAL simulation has been used as point of departure for all other simulations with abnormal LV activation and contractility. During all simulations, systemic peripheral resistance and total blood volume are adjusted so that mean arterial pressure and cardiac output are maintained at their resting values.

To assess the isolated effect of dyssynchronous mechanical activation of the ventricular walls on DYS indices, onset times of septal and LVFW mechanical activation were delayed with respect to that of the RV free wall (0–50 ms for septum and 0–100 ms for LVFW in steps of 10 ms). The LVFW was either activated simultaneously with or later than the septum (resulting in 50 DYSSYNCHRONY simulations, online-only Data Supplement Table I). Each acute change of LV activation was followed by simulation of maximally 50 cardiac cycles to reach a new steady-state mechanical equilibrium with changed LVESV.

CRT was simulated by restoring synchronous mechanical activation of the three ventricular walls, followed by the 50-cycle stabilization sequence. CRT response was quantified as ΔLVESV between the steady-state dyssynchronous and synchronous simulations.

Variations of Myocardial Contractility

In the NORMAL and DYSSYNCHRONY simulations, regional variations of LV myocardial contractility were applied to assess their isolated effect on DYS indices and on CRT response. Changes of myocardial contractility (−30% and −60%) were accomplished by decreasing the ability of active myofiber components (cross-bridges and actin) to generate stress.[18] These changes of contractility were applied regionally (SEPT or LVFW separately) as well as globally (SEPT and LVFW together).

Table 1. Baseline Patient Characteristics

n	132
Age, y	65±10
Male sex	93 (70%)
NYHA functional class IV	19 (14%)
Ischemic etiology	69 (52%)
Atrial fibrillation	27 (20%)
Heart rate, bpm	69±14
LV ejection fraction, %	19±6

NYHA indicates New York Heart Association; LV, left ventricular.

Assessment of Dyssynchrony Indices

In the simulations, DYS indices were calculated in the same way as in the patients (right column of Figure 1). Zero strain reference was set at onset of RV activation, which was 130 ms after right atrial activation, and was assumed to correspond best to the zero-strain reference used in the patients (onset QRS complex).

Statistical Analysis

Statistical analysis was performed using the SPSS statistical software package version 17.0 (SPSS Inc, Chicago, IL). A probability value <0.05 was considered statistically significant for all analyses. Values are presented as mean and standard deviation (SD) for continuous variables and as numbers and percentages for categorical variables. A paired, 2-tailed *t* test was used to test whether volumetric response parameters after 6 months of CRT were significantly different from their baseline values, whereas an unpaired, 2-tailed *t* test was used to compare the NOSCAR patient group with the SCAR group. The ability of DYS indices to predict CRT response was evaluated using scatterplots and linear regression analysis.

Results

Patients

Overall, 132 patients were enrolled. Baseline characteristics are outlined in Table 1. All patients were on stable, maximally tolerated heart failure medication with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in 89%, ß-blockers in 78%, and diuretics in 95%. In total, 8 patients died and 3 received an LV assist device implantation or heart transplantation before the 6-month follow-up visit, 5 patients were lost to follow-up, and in 9 patients LV volumes could not be quantified. Consequently, the group of patients available for testing predictive capacity of the different dyssynchrony measures constituted 107 patients. SRSsept, IVMD, and Strain-SL could be assessed in 100%, 96%, and 96% of the patients, respectively, whereas SPWMD assessment was possible in 86%.

CRT Response Versus Baseline Mechanical Dyssynchrony

Overall, LVEDV (252±78 to 225±94 mL) and LVESV (205±73 to 172±88 mL) were reduced and LVEF was increased (19±6% to 26±10%) after 6 months of CRT (all $P<0.001$). Furthermore, NYHA class was improved [mtequ]1 class in 68% of the patients, whereas it did not change in the remaining 32%. All 4 DYS indices correlated significantly with ΔLVESV (Figure 2A and Table 2), whereas none of them correlated significantly with baseline LVESV. SRSsept and IVMD showed a continuous linear relation with volumetric response, whereas Strain-SL and SPWMD showed 2 clusters of data points (Figure 2A).

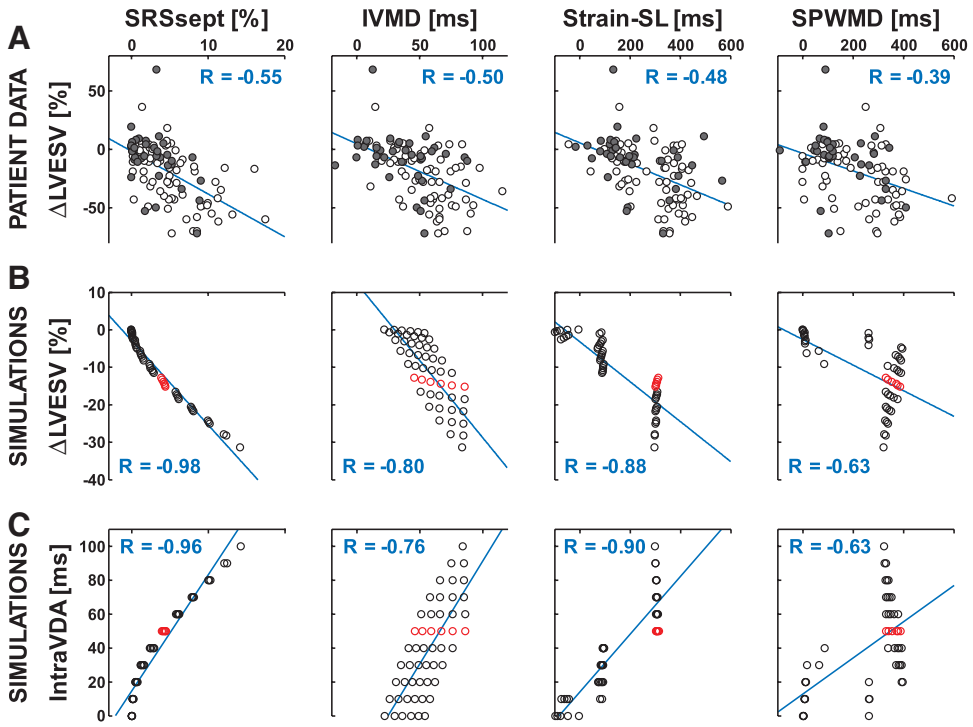


Figure 2. Cardiac resynchronization therapy (CRT) response and intraventricular dyssynchrony of left ventricular (LV) activation versus mechanical dyssynchrony (DYS) indices: Patient data (**A**) and simulations (**B** and **C**). The upper panel row (**A**) shows correlations between baseline echocardiographic DYS indices and relative change of LV end-systolic volume after 6 months CRT (ΔLVESV) as measured in the patients (<2 scarred segments: **open circles;** ≥2 scarred segments: **filled circles**). All correlations were significant (P<0.001). **B**, Similar correlation plots obtained from the DYSSYNCHRONY simulations. **C**, Correlations between intraventricular dyssynchrony of LV activation (IntraVDA), defined as SEPT-to-LVFW delay of mechanical activation, and DYS indices. **Red circles** indicate 6 simulations with constant IntraVDA of 50 ms and increasing interventricular delay.

Volumetric response and all 4 dyssynchrony indices were significantly lower in the SCAR group than in the NOSCAR group, whereas QRS width was not significantly different (Table 3). In NOSCAR patients, all 4 dyssynchrony indices showed a statistically significant correlation with ΔLVESV (Table 2). In the SCAR group, however, only SRSsept, IVMD, and Strain-SL showed statistically significant correlations with ΔLVESV.

Table 2. CRT Response Versus Baseline DYS Indices in Patients

	DYS Versus ΔLVESV		
	All Patients *R* Value	NOSCAR *R* Value	SCAR *R* Value
SRSsept	−0.56†	−0.54†	−0.44†
IVMD	−0.50†	−0.51†	−0.34*
Strain-SL	−0.48†	−0.49†	−0.35*
SPWMD	−0.39†	−0.35†	−0.33

CRT indicates cardiac resynchronization therapy; DYS, mechanical dyssynchrony; NOSCAR, group with <2 scarred segments; SCAR, group with ≥2 scarred segments; LVESV, left ventricular end-systolic volume; SRSsept, septal systolic rebound stretch; IVMD, interventricular mechanical delay; Strain-SL, septal-to-lateral peak shortening delay; and SPWMD, septal-to-posterior wall motion delay.

R indicates Pearson correlation coefficient.

*P<0.05 significant Pearson correlation.

†P<0.01 significant Pearson correlation.

Simulations

CRT Response Versus Baseline Mechanical Dyssynchrony

Figure 2B and 2C show relations of DYS indices to ΔLVESV and to intraventricular dyssynchrony of LV activation (delay of LVFW activation with respect to SEPT activation; IntraVDA), respectively, as obtained from the DYSSYNCHRONY simulations. These simulation data showed similar relations between

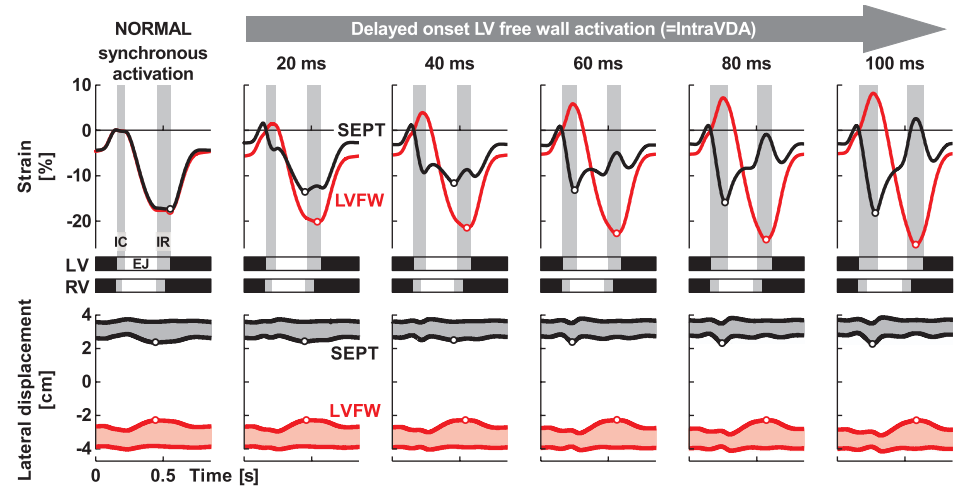
Table 3. CRT Response and Baseline DYS Indices in Patients

	All Patients (n=132)	NOSCAR (n=81)	SCAR (n=51)
CRT response			
ΔLV end-systolic volume, %	−18±25	−24±24	−8±23*
ΔLV ejection fraction, % point	7±8	9±9	3±6†
DYS indices			
SRSsept, %	4.1±3.5	5.0±3.8	2.8±2.5†
IVMD, ms	45±25	51±25	34±23†
Strain-SL, ms	249±136	277±126	203±140*
SPWMD, ms	191±131	218±132	146±118*
QRS width, ms	170±22	172±21	167±24

CRT indicates cardiac resynchronization therapy; DYS, mechanical dyssynchrony; NOSCAR, group with <2 scarred segments; SCAR, group with ≥2 scarred segments; LV, left ventricular; SRSsept, septal systolic rebound stretch; IVMD, interventricular mechanical delay; Strain-SL, septal-to-lateral peak shortening delay; and SPWMD, septal-to-posterior wall motion delay.

*P<0.005 versus NOSCAR.

†P<0.0005 versus NOSCAR.



CRT-response:						
ΔLVESV [%]	0	-3	-9	-17	-24	-31
DYS indices:						
SRSsept [%]	0	0.5	2.4	5.8	10.0	14.2
IVMD [ms]	22	31	41	51	66	84
Strain-SL [ms]	-4	92	96	310	304	298
SPWMD [ms]	0	12	86	330	328	322

Figure 3. Effect of asynchronous ventricular activation on mechanical dyssynchrony (DYS) indices. Starting from the NORMAL simulation with synchronous ventricular activation, 5 simulations with increasing delays of left ventricular free wall (LVFW) activation illustrate the effect of dyssynchronous activation on (1) septal (SEPT) and LVFW strain curves; (2) timing of LV and RV isovolumic contraction (IC), ejection (EJ), and isovolumic relaxation (IR); (3) lateral LVFW and SEPT displacement; and (4) corresponding cardiac resynchronization therapy (CRT) response and DYS indices. Systolic LVFW and SEPT shortening and inward motion peaks are indicated by open circles. IntraVDA indicates intraventricular dyssynchrony of LV activation.

DYS indices and CRT response as observed in the patients. SRSsept and IVMD gradually increased with decrease of ΔLVESV, whereas Strain-SL and SPWMD exhibited data clustering and discontinuous relations with ΔLVESV (Figure 2B). The relations between DYS indices and IntraVDA featured similar characteristics (Figure 2C). In addition, the simulations showed that IVMD strongly depended on interventricular activation delay (ie, delay of SEPT and LVFW activation with respect to RV free wall activation), whereas all other DYS indices and also ΔLVESV were relatively independent of interventricular delay.

Effect of Dyssynchronous Ventricular Activation on DYS Indices

As depicted in Figure 3, uniformity of SEPT and LVFW mechanics during synchronous ventricular activation in the NORMAL simulation disappeared with increase of IntraVDA. In the LVFW, a progressive amount of preejection stretch occurred, whereas timing of peak shortening was relatively unaffected and remained within the isovolumic relaxation phase. In contrast, the septum showed a progressive amount of shortening before onset of LV ejection. This resulted in the gradual development of an early systolic shortening peak and a progressive amount of septal systolic rebound stretch followed by a late systolic shortening peak. This second shortening peak decreased in amplitude and even disappeared at larger IntraVDA (80–100 ms). Consequently, the value of Strain-SL abruptly increased from 96 ms at 40 ms IntraVDA to 310 ms at 60 ms delay. Patterns of inward wall motion and, hence, SPWMD behaved in a similar way as wall strain and Strain-SL, respectively. In contrast, SRSsept increased gradually with IntraVDA. Increase of IntraVDA prolonged the LV isovolumic contraction phase, resulting in delayed LV ejection, whereas it hardly affected timing of RV isovolumic contraction and ejection. As a result, IVMD also increased linearly with IntraVDA. Potential volumetric CRT response in these simulations increased linearly to a maximum of 31% reduction of LVESV at 100 ms of IntraVDA.

Effect of Myocardial Contractility Variations on DYS Indices

Figure 4 shows the effects of global (Figure 4A) and regional (Figure 4B and 4C) reduction in LV myocardial contractility on volumetric CRT response and its relationship with DYS indices and IntraVDA. Reduction of either global or regional LV contractility resulted in lower values of ΔLVESV, SRSsept, and IVMD but did not disturb linearity of the relationship between SRSsept and IVMD, and ΔLVESV, except for 60% reduction in septal contractility. In contrast, Strain-SL and SPWMD either retained a clustered relationship with ΔLVESV or became relatively constant (around 160 ms, with 60% decrease of LVFW contractility) and, hence, independent of ΔLVESV and IntraVDA. In all simulations (with normal and reduced LV contractility), SRSsept and IVMD followed IntraVDA in its relationship with CRT response, whereas Strain-SL and SPWMD did show different relationships with CRT response.

Discussion

In this study, we demonstrate that the ability of echocardiographic dyssynchrony indices to predict CRT response is largely determined by the information that the indices extract from the patterns of wall motion, deformation, and ventricular ejection. Both in patients and simulations, SRSsept and

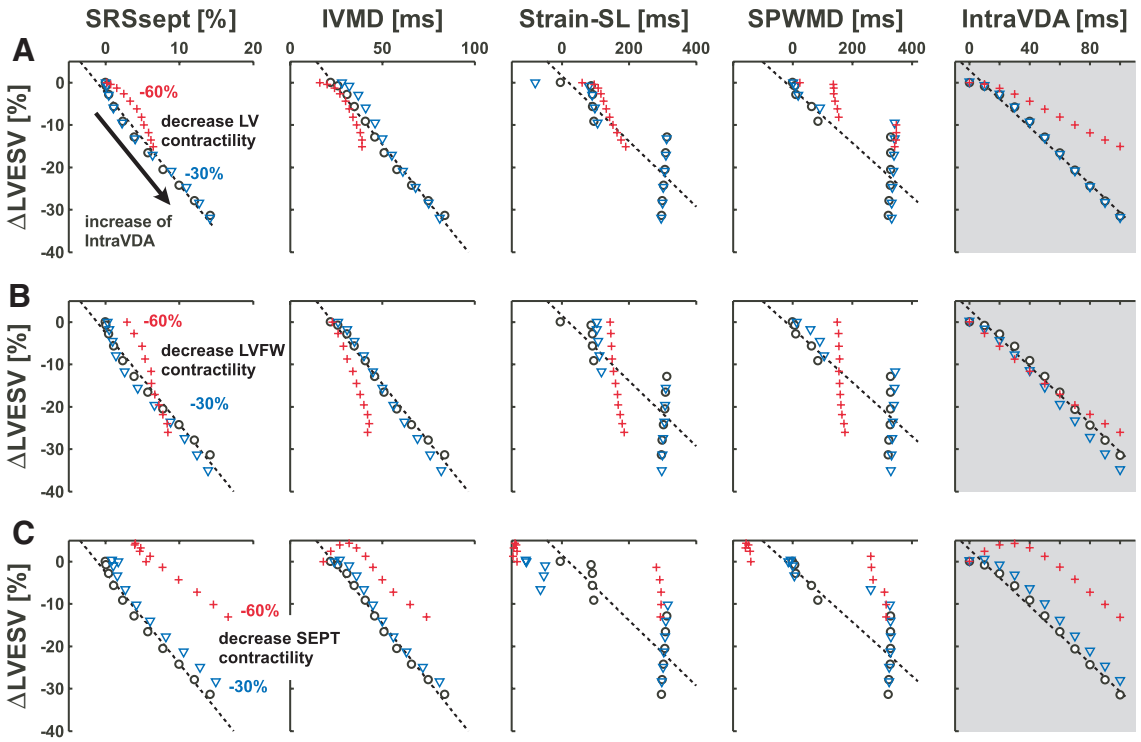


Figure 4. Effect of global (**A**), left ventricular free wall (LVFW) (**B**), and septal (SEPT) (**C**) decrease of contractility on mechanical dyssynchrony (DYS) indices and cardiac resynchronization therapy (CRT) response. The NORMAL simulation (IntraVDA=0 ms) and 10 DYSSYNCHRONY simulations (IntraVDA=10–100 ms: upper row of online-only Data Supplement Table I) are used to illustrate the isolated effects of global decrease of LV contractility (**upper panel row**) and regional decreases of LVFW (**middle panel row**) and SEPT (**bottom panel row**) contractility on volumetric CRT response and its relationship with the 4 DYS indices and IntraVDA. **Open black circles** and **dashed regression lines** correspond to the simulations with normal LV contractility; **red crosses** and **blue triangles** represent simulations with similar levels of dyssynchrony but with 30% and 60% reduction of myofiber contractility, respectively. Note that the grey panels show the effects of global and regional contractility decreases on the relationship between the intraventricular dyssynchrony of LV activation (IntraVDA) as imposed to the model and the resulting change of LV end-systolic volume (ΔLVESV). IntraVDA indicates intraventricular dyssynchrony of LV activation.

IVMD showed a continuous linear relationship with volumetric response to CRT, whereas SPWMD and Strain-SL showed an unfavorable discontinuous relationship characterized by data clusters. Patient and simulation data also agree on the fact that the linear relationships of SRSsept and IVMD with CRT response were largely preserved in the presence of scar, although correlations slightly deteriorated.

Do Echocardiographic Mechanical Dyssynchrony Indices Assess Dyssynchrony of Ventricular Activation?

The working mechanism of CRT is complex and still not completely understood. Part of this complexity comes from the fact that CRT is primarily designed for correction of an electric substrate (originating from conduction disorders) but exerts its effects mainly through correction of mechanical inefficiency.[21] To specifically target patients with a substantial electric substrate amenable to CRT, QRS width has been incorporated as a selection criterion in the guidelines. Because of the heterogeneous overall response in accordingly selected patients, mechanical dyssynchrony has been proposed as an alternative or additive selection criterion.[13,16,18–21] In turn, the problem with mechanical dyssynchrony indices derived from wall motion, deformation, or ventricular ejection signals is that they can also be evoked or influenced by local tissue abnormalities such as myocardial infarction, scar, or ischemia.[22,23] As pointed out by Kass,[24] it is most likely that only mechanical dyssynchrony originating from an electric substrate is amenable to CRT. To improve prediction of a patient's response to CRT, indices of mechanical dyssynchrony should therefore selectively identify and quantify the mechanical dyssynchrony that is evoked by an underlying electric substrate.

Although a few experimental studies investigated the relation between "true" electric activation, derived from mapping studies, and onset of shortening,[25,26] no experimental studies are known investigating to what extent the more frequently used indices assessing time-to-peak deformation or motion relate to "true" dyssynchrony of activation. Obviously, studying this in patients is virtually impossible. Therefore, we combined patient data evaluating the ability of 4 echocardiographic indices of mechanical dyssynchrony to predict CRT response with computer simulations assessing the isolated effects of dyssynchrony of LV activation and decreased contractility on each index of dyssynchrony. The simulations demonstrate that SRSsept and IVMD closely reflect the imposed dyssynchrony of LV activation, even in the presence of scar. Strikingly, time-to-peak indices poorly reflect imposed dyssynchrony, because septal motion and strain patterns consist of 2 systolic peaks, which change in

amplitude rather than in timing. Since Strain-SL and SPWMD measure the septal-to-lateral time delay of systolic peak shortening and motion, both indices increase abruptly from a low value (when the late-systolic septal shortening peak is larger than the early-systolic peak) to a large value (when the early-systolic shortening peak is larger than the late-systolic peak), whereas the imposed septal-to-lateral activation delay is gradually increased.

Predictive Performance of Echocardiographic Dyssynchrony Indices

An important aspect of our analysis is that we used volumetric response as a continuous rather than as a dichotomous variable. This approach allowed demonstrating that the relation of each of the four echocardiographic dyssynchrony indices with volumetric response was qualitatively identical in the patients and the simulations. The fact that the linear relations and characteristic discontinuous distributions in the patient cohort were overall weaker is not unexpected, since, in patients, intrinsic relations are obscured by a number of (poorly controllable) factors such as heterogeneity in natural disease course, differences in application of treatment, measurement variability, and the fact that each data point originates from a different patient rather than that several data points are obtained after modulating dyssynchrony within an individual, as is done in the simulations.

Both analyses also showed superior prediction of CRT response by SRSsept and IVMD, which is in agreement with their linear relationship with dyssynchrony of LV activation. In contrast, the discontinuous clustered relation between dyssynchrony of LV activation and time-to-peak indices (Strain-SL and SPWMD) transferred into a similarly clustered dataset for prediction of CRT response by these parameters. Because mechanical dyssynchrony evoked by primary electric dyssynchrony constitutes the amenable substrate for CRT, this typical behavior of time-to-peak indices explains their limited ability to predict CRT response. These results are supported by previous studies demonstrating septal-to-lateral delays of time-to-peak motion, deformation, or velocity to be relatively poor predictors of CRT response.[3,4,12,27] Studies treating dyssynchrony and CRT response as dichotomous variables did show predictive value of time-to-peak strain,[15,28] with dyssynchrony defined as ≥130 ms septal-to-lateral wall delay of peak wall deformation (radial, circumferential, or longitudinal). This finding is not in conflict with our data, because from Figure 2 (B and C) it can be appreciated that, even with clustered behavior of Strain-SL, values above 130 ms would predict significant delay between septal and LVFW activation and CRT response, albeit in a more qualitative manner.

Left ventricular scarring is a common feature in heart failure patients scheduled for CRT and can lead to mechanical dyssynchrony in the absence of an electric substrate. Because of its independent effects on the successful delivery of CRT, LV scarring has been incorporated into prediction models of CRT response.[29,30] The results of the current study demonstrate that LV scarring can reduce response to CRT and can affect the relationship between dyssynchrony indices and dyssynchrony of LV activation. Therefore, LV scarring can disturb the prediction of CRT response. This effect originates mainly from the fact that LV scarring directly influences the pattern of septal deformation[13] and thereby also affects the value of time-to-peak indices in a stepwise manner. In contrast, SRSsept is the only index that is linearly related to CRT response under all conditions tested.

Our study also confirmed the good predictive performance of the relatively simple index of IVMD. In the patients, IVMD predicted CRT response nearly as good as SRSsept. From the model simulations (Figure 3), it can be deduced that the LV preejection period lengthens linearly with intraventricular activation delay, whereas the RV preejection period remains unchanged. Most probably, this prolongation of the LV preejection period reflects the increasing degree of systolic mechanical discoordination, for example, myocardial preejection shortening and systolic rebound stretching, which leads to delayed LV pressure development and consequently delayed opening of the aortic valve. IVMD may therefore be considered a more global measure of LV mechanical inefficiency that is sensitive to both interventricular and intraventricular activation delay. Moreover, IVMD is the only parameter that has consistently been demonstrated to predict CRT response, also in large, multicenter trials.[3,4,31] In a recent study with a patient population comparable to ours, Miyazaki et al[4] showed that conventional Doppler-derived indices assessing timing of valve opening and closure outclassed more complicated dyssynchrony indices, partly due to their low measurement variability. In another study by the same institute, Wang et al[32] found mechanical discoordination rather than dyssynchrony to be predictive for CRT response at 6-month follow-up and for long-term survival. The latter 2 studies are in close agreement with our finding that SRSsept and IVMD, being direct and indirect indices of mechanical discoordination, respectively, better predict CRT response than time-to-peak indices of mechanical dyssynchrony such as Strain-SL and SPWMD.

Clinical Implications

The current study reveals that SRSsept and IVMD most adequately represent the dyssynchrony of LV activation and predict CRT response. Based on their intrinsic behavior, these indices should therefore be preferred over indices measuring time-to-peak deformation or motion. The presence of disturbing factors such as regional scarring should be considered when interpreting the results of the different dyssynchrony indices. In this respect, SRSsept and IVMD might prove more feasible measurements than Strain-SL and SPWMD, considering the preservation of their linear relation with ΔLVESV in the presence of LV scar. In a previous study by our laboratory, we showed that intraobserver and interobserver coefficients of variation of SRSsept were 16.3% and 19.5%,[10] respectively. Despite its relatively complicated and variability-prone derivation from the septal strain signal and timing of aortic valve closure,[12] these values on reproducibility of SRSsept are within the same range of previously published data on other DYS indices.[3,4,10] It is likely that the potential for large-scale clinical use of SRSsept as a predictor of CRT response can be further increased by the development of a simpler methodology of measurement. In this regard,

computer simulation methods as used in the present study may prove helpful.

Study Limitations

In the computer model, CRT was simulated as complete resynchronization of ventricular activation. In patients, however, CRT does not lead to complete resynchronization of ventricular activation. The position of the pacing electrodes and thus the degree of resynchronization may vary between patients. Although this may have led to overestimation of CRT response by our simulations, qualitative effects on indices of mechanical dyssynchrony were in good agreement with our observations in patients.

Left bundle-branch block was simulated as an acute delay of LVFW and SEPT mechanical activation. Analogously, simulated CRT response was defined as the "acute" change of LVESV after restoration of synchronous ventricular activation and subsequent simulation of 50 cardiac cycles, allowing hemodynamic stabilization. In this approach, dyssynchrony-induced structural and contractile remodeling as well as resynchronization-induced reverse remodeling[33–35] have not been taken into account.

Many DYS indices have been described in the literature. In the present study, we compared only 4, each representing either indices of time-to-peak deformation and motion (Strain-SL and SPWMD), timing indices of valve opening (IVMD), or indices of mechanical discoordination (SRSsept). Further studies may reveal whether other indices or combinations of indices may provide better predictions than the ones assessed in the present study.

Conclusions

The power to predict CRT response differs between echocardiographic indices of mechanical dyssynchrony. SRSsept and IVMD are better representatives of dyssynchrony of LV activation and, hence, better predictors of CRT response than indices derived from time to septal peak shortening or motion.

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CLINICAL PERSPECTIVE

Single-center studies have reported the ability of echocardiographic mechanical dyssynchrony indices to predict cardiac resynchronization therapy (CRT) response. The failure of multicenter studies to reproduce these results has been mainly attributed to poor measurement reproducibility, technical limitations, and shortcomings in study design. In the present study, we showed that the poor predictive performance of dyssynchrony indices assessing time-to-peak deformation or motion can be explained by their failure to adequately reflect the functional substrate of dyssynchrony that is amenable to CRT. Direct and indirect indices of mechanical discoordination assessing abnormal myocardial stretch during systole (septal systolic rebound stretch [SRSsept]) and prolonged or delayed left ventricular isovolumic contraction (interventricular mechanical delay [IVMD]), respectively, better predicted CRT response than time-to-peak indices of mechanical dyssynchrony (ie, septal-to-lateral peak strain delay [Strain-SL] and septal-to-posterior wall motion delay [SPWMD]). Our simulation results, showing both SRSsept and IVMD to be linearly related to the electric substrate amenable to CRT even in the presence of myocardial scar, suggest that mechanical discoordination rather than dyssynchrony should be assessed for prediction of CRT response. Future studies should focus on improving ease of measurement of mechanical discoordination to establish widespread clinical application in the diagnostic workup of CRT candidates. In the future, a deliberate selection of mechanical discoordination indices may serve as input for an integrative patient-specific computer model to improve patient selection and effectiveness of CRT.