

Echocardiographic prediction of outcome after cardiac resynchronization therapy: conventional methods and recent developments

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Abstract Echocardiography plays an important role in patient assessment before cardiac resynchronization therapy (CRT) and can monitor many of its mechanical effects in heart failure patients. Encouraged by the highly variable individual response observed in the major CRT trials, echocardiography-based measurements of mechanical dyssynchrony have been extensively investigated with the aim of improving response prediction and CRT delivery. Despite recent setbacks, these techniques have continued to develop in order to overcome some of their initial flaws and limitations. This review discusses the concepts and rationale of the available echocardiographic techniques, highlighting newer quantification methods and discussing some of the unsolved issues that need to be addressed.

Keywords Heart failure · Cardiac resynchronization therapy · Echocardiography · Mechanical dyssynchrony

Introduction

Cardiac resynchronization therapy (CRT) has been developed along with experimental data indicating a direct effect of conduction disturbances on mechanical coordination, with subsequent deleterious effects on cardiac function, efficiency, structure, and regional gene expression [1–5]. In the clinical setting, large prospective multicenter trials

have established CRT to induce reverse remodeling and improve exercise capacity, left ventricular (LV) function and survival in patients with advanced (NYHA III-IV), medication resistant heart failure and ventricular conduction disturbances (the vast majority having left bundle branch block [LBBB]) [6–8]. More recently, CRT has also proven its mechanical and clinical effectiveness in earlier disease stages [9, 10]. Encouraged by the highly variable response in individual patients observed in major trials [6, 10], echocardiography-based measurements of dyssynchrony have been extensively investigated with the aim of improving response prediction and CRT delivery [11–16]. After initial results in single center studies were met by enthusiasm, disillusion and criticism followed because in multicenter trials echocardiography hardly improved the prediction of response to CRT [17, 18]. While for many a reason to abandon the idea of echocardiography-guided prediction and application of CRT [19], it has compelled many others to reconsider the physiologic rationale and technical limitations of echocardiographic approaches and improve them accordingly. In this paper, we critically review the available echocardiographic techniques, their rationale, methods of quantification (time intervals, regional delays, and discoordination) and some of the unsolved issues that need to be addressed before echocardiography can be considered as a reliable tool to predict outcome after CRT.

Echo-physiological principles and rationale

In the normal heart, electrical and mechanical anatomy and function are closely tuned to each other in a way that ensures a carefully sequenced concatenation of mechanical events, eventually leading to an efficient biventricular filling, contraction and pump function. A “classic”

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conduction disturbance with a LBBB-sequence induces an abnormal and delayed right-to-left transeptal activation and pressure gradient (“interventricular dyssynchrony”) and provokes an additional delay in the onset of force development in the posterolateral LV wall compared to the relatively early activated septum (“intraventricular dyssynchrony”). The relative delay in overall LV activation may also cause a prolonged left-sided atrioventricular (AV) delay (“atrioventricular dyssynchrony”). As discussed by Prinzen et al. in this issue of the journal [104], the ensuing imbalances in mechanical forces give rise to inefficient back-and-forth mechanical interactions between and within the ventricles, from now on referred to as “discoordination”. This discoordination impairs the pressure and stroke work ability of the heart [2] causes or worsens mitral insufficiency [20] delays and prolongs LV isovolumic events [21] and impairs diastolic filling [21] (Fig. 1). In addition, features of mechanical discoordination such as abnormal wall stretch also entail secondary energetic and molecular effects that play a role in the further disease manifestations [105]. Notwithstanding that electrical dyssynchrony may be the initiator of the unfavorable mechanics, the magnitude of such mechanical interaction ultimately depends on more than electrical dyssynchrony

alone (e.g. influence of local loading, contractility, etc.). Accordingly, both experimental as well as clinical studies suggest that mechanical rather than electrical dis- and re-coordination predict and ensure effective CRT, respectively [11, 22–25]. As illustrated in Fig. 1 and discussed throughout this paper, many of the abovementioned mechanical events and consequences can be evaluated by echocardiography. Being non-invasive and applicable after CRT, echocardiography can also help us to understand the actual mechanism of CRT. The basic rationale for echocardiographic quantification and monitoring of mechanical dyssynchrony remains therefore valid. In fact, by defining echocardiographically determined LV ejection fraction (LVEF) and dimensions as inclusion and outcome criteria in the major CRT trials, echocardiography has always been an essential and inseparable part of adequate selection and monitoring of this therapy.

Left ventricular time intervals and atrioventricular dyssynchrony

Conventional Doppler-based quantification of the LV pre-ejection period (LVPEP), total isovolumic time, and total

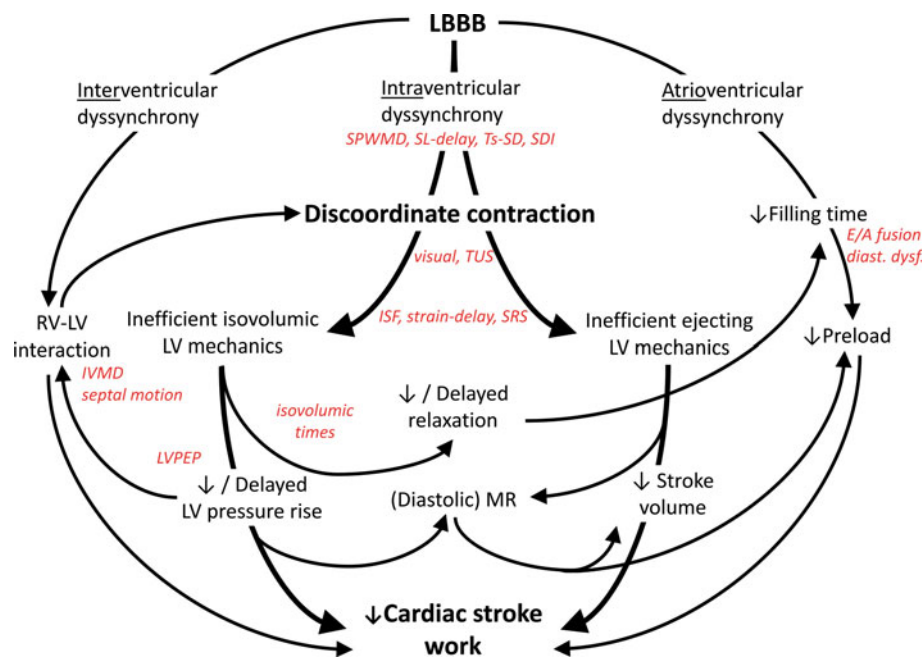


Fig. 1 Mechanical dyssynchrony in left bundle branch block. Schematic representation of the mechanism by which electrical dyssynchrony can cause inefficient (bi-)ventricular filling, contraction, and pump function. Parameters assessable by echocardiography are highlighted in red italics. Of note: intrinsic (local) contractility, elasticity, and loading make that not all delays (=dyssynchrony) necessarily lead to similar mechanical interactions and discoordination. The effects of so-called atrio-, inter- and intraventricular dyssynchrony partially overlap and closely interact, with

discoordination induced by intraventricular delays playing a central and determining role at all levels. *ISF* internal stretch fraction, *IVMD* interventricular mechanical delay, *LV* left ventricle, *LVPEP* left ventricle pre-ejection period, *MR* mitral regurgitation, *RV* right ventricle, *SDI* three-dimensional dyssynchrony index, *SL-delay* septal-to-lateral delay, *SPWMD* septal-to-posterior wall motion delay, *SRS* systolic rebound stretch, *Ts-SD* tissue-Doppler velocity standard deviation, *TUS* temporal uniformity of strain

filling time belong to the most straightforward and established techniques to screen for dyssynchrony. As a consequence of intra- (and inter)ventricular discoordination, isovolumic contraction and relaxation are delayed and prolonged at the expense of both ejection and filling [21]. Additionally, the relatively delayed activation and contraction of the LV may induce a functional first degree AV-block and diastolic mitral regurgitation, further aggravating disturbances in LV filling and effective preload (Figs. 1, 2). Inversely, CRT has been shown to immediately optimize preload and filling, to reduce isovolumic periods, and increase stroke volume [8, 26–29]. Besides relating to dyssynchrony at multiple levels, cardiac time intervals are confounded by their sensitivity to altered loading, contractility, and most importantly changes in heart rate. Indexed for RR-interval, filling time and total isovolumic time have been shown to predict response to CRT with roughly the same accuracy as local temporal dyssynchrony measurements, while profiting from an excellent feasibility (>95%) and reproducibility (variability \approx 5%) unmatched by any of the latter [17, 28, 30]. Of note, in a typical CRT population, the frequency and relevance of a compromised filling explained by isolated AV dyssynchrony only remains debated. Parsai et al. [31] found compromised filling without evident intraventricular dyssynchrony in 23% of their population but also found less reverse remodeling in these patients, whereas Lafitte et al. [32] demonstrated compromised filling in about 30% of their total population. In addition, although routinely performed in the major trials and advised by the American society of echocardiography [33] also the benefits of AV-optimization have not conclusively been shown [34] let alone to be independent of concomitant inter- and intraventricular recoordination as well [26, 35].

Interventricular dyssynchrony

The interventricular mechanical delay (IVMD) estimates the mechanical dyssynchrony between the right ventricle (RV) and the left ventricle (LV). Since right ventricular mechanical events in LBBB occur rather timely, in practice IVMD will to a large extent be driven by the delay in effective LV contraction (e.g. measured by LVPEP), ensuing the right-to-left transseptal pressure gradient in early systole [36, 37]. The former can however also be influenced by circumstances where the associated pressure gradient is modified by significant alterations in right and/or left ventricular loading [38, 39]. The resulting systolic and diastolic phase differences between RV and LV pressure can be effectively corrected by CRT and are paralleled by acute hemodynamic improvement [37, 38, 40]. The conventional echocardiographic method to quantify IVMD

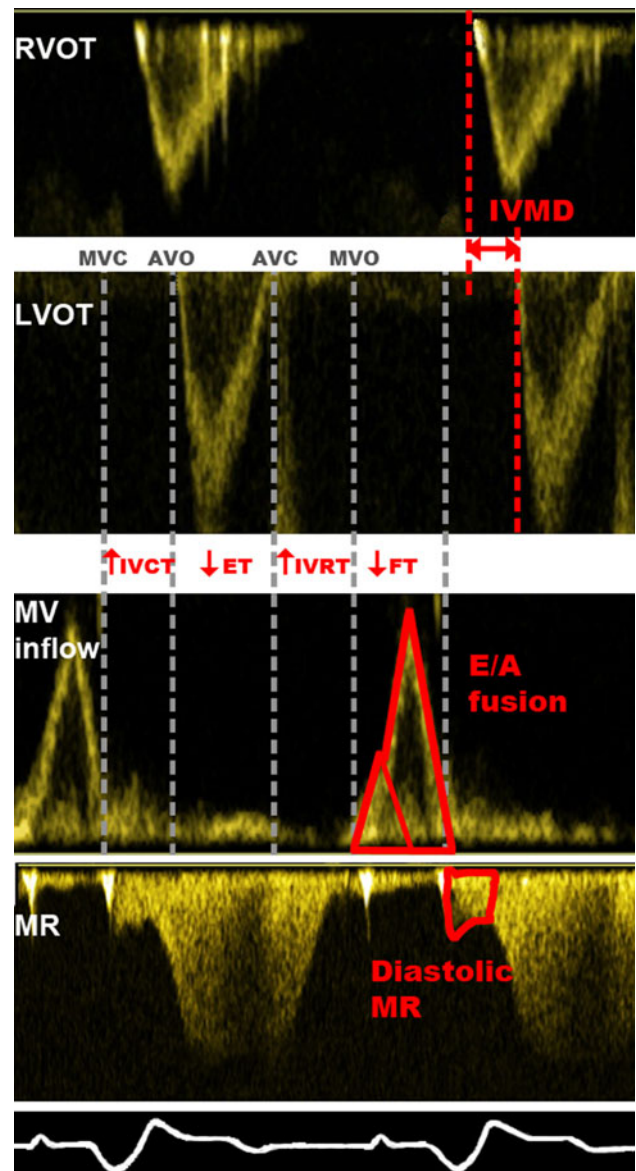


Fig. 2 Global time intervals. The effect of dyssynchrony on global time intervals is illustrated by Doppler registrations over the right- and left ventricular outflow tract (RVOT resp. LVOT) and the mitral valve (MV). Isovolumic contraction (IVCT) and relaxation (IVRT) are delayed and prolonged at the expense of both ejection (ET) and filling (FT). Delayed ejection and pressure rise causes diastolic mitral regurgitation (MR). The impaired ventricular filling causes fusion of the early relaxation phase of the ventricle with the atrial contraction leading to E/A fusion. AVC aortic valve closure, AVO aortic valve opening, MVC mitral valve closure, MVO mitral valve opening

evaluates the systolic phase shift by measuring the delay between the onset of RV and LV ejection as derived from pulsed wave Doppler in the RV and LV outflow tract, respectively (Fig. 2). Feasibility and reproducibility of this parameter are very good. Higher IVMD values have consistently been reported to be associated with more reverse remodeling in several large clinical studies [17, 22, 41, 42]

with cut-offs mostly around 40–49 ms. In the CARE-HF trial, an IVMD of >40 ms was one of the inclusion criteria for patients with QRS between 120 and 150 ms [7]. Within this trial, patients with IVMD >49 ms derived statistically more survival benefit from CRT than those with lower values, making it the only marker to date with proven impact on the prognostic success of CRT. Inversely the RethinQ-trial has demonstrated very low IVMD values in patients with narrow QRS and accordingly poor response [18].

Alternative methods to quantify interventricular dyssynchrony based on tissue Doppler delays between the RV and LV free walls have been used [12, 43]. The incremental value of such locally derived markers over the conventional method, and of local inter- over intraventricular temporal delays, remains disputed [17, 18, 28, 30, 43].

Measurements of regional intraventricular dyssynchrony

Whereas LV time intervals and IVMD are measurements of global dyssynchrony, regional dyssynchrony measurements inherently relate to delays in distinct events between various specific regions. Over the last decade, several techniques and approaches have been proposed that differ in three respects: (1) they are based on timing of either motion, velocity of motion, or myocardial deformation, (2) either peak or onset events are measured, and (3) the amount of dyssynchrony is assessed by standard deviation of peaks, maximal delay, maximal opposing wall delay or

by selective wall delay (e.g. septal-to-lateral wall delay) (Table 1).

Quantification based on tissue motion or tissue velocity delays

Nearly all commonly proposed measurements of regional dyssynchrony are based on the timing of myocardial longitudinal or radial motion or its velocity. To date, motion- and velocity-based methods are also the only regional dyssynchrony markers tested and evaluated in multicenter trials [17, 18, 44].

One-dimensional techniques assessing motion delay

The septal-to-posterior wall motion delay (SPWMD) selectively measures the delay between the peak inward motion of the septum and that of the posterior wall on parasternal M-mode images at the midventricular level (Fig. 3, panel a). A cut-off of ≥ 130 ms has initially been proposed to predict both volumetric response as well as clinical outcome after CRT [14, 45]. The method can be applied on all echocardiographic systems without the need for specialized software. Limitations specific to the method consist of problems in achieving an alignment perpendicular to the walls in patients with low parasternal windows (partially amenable by using anatomical M-mode), and measurement difficulties in the presence of severe hypo- or akinesia due to previous infarction or severely compromised radial motion in advanced heart failure. The frequency with which these shortcomings are encountered in the target population for CRT (16–28%) poses important

Table 1 Measurements of regional delay to predict CRT response

Author (Ref.)	Parameter	N	Population	Ischemic etiology (%)	Follow-up (months)	Response	Cut-off	Sensitivity (%) / specificity (%)
Pitzalis [14]	SPWMD	20	NYHA III, QRS ≥ 140 ms, LVEF $\leq 35\%$, SR, LBBB	20	1	LVESV $\geq 15\%$	130 ms	100/63
Soliman [50]	3D-SDI	90	NYHA \geq III, QRS ≥ 120 ms, LVEF $\leq 35\%$, SR	51	12	LVESV $\geq 15\%$	>10%	96/88
Bax [12]	Ts-4	80	NYHA \geq III, QRS ≥ 120 ms, LVEF $\leq 35\%$, SR, LBBB	55	6	LVESV $\geq 15\%$ NYHA ≥ 1	65 ms 65 ms	92/92 80/80
Yu [56]	Ts-SD12	30	NYHA III, QRS ≥ 140 ms, LVEF $\leq 40\%$	40	3	LVESV $\geq 15\%$	32.6 ms	100/100
Yu [16]	TSI-Ts-SD12	56	NYHA \geq III, QRS ≥ 120 ms, LVEF $\leq 40\%$	50	3	LVESV $\geq 15\%$	34.4 ms	87/81
Suffoletto [15]	2D-RS	50	NYHA \geq III, QRS ≥ 120 ms, LVEF $\leq 35\%$, SR	62	8 \pm 5	LVEF $\geq 15\%$	130 ms	89/83

2D-RS speckle tracking radial strain, 3D-SDI standard deviation of 16 time-volume peaks, LBBB left bundle branch block, LVEF left ventricle ejection fraction, LVESV left ventricle end-systolic volume, NYHA New York Heart Association class, SPWMD M-mode septal to posterior wall motion delay, SR sinus rhythm, Ts-4 maximal velocity delay between 4 basal segments, TSI tissue synchronization imaging, Ts-SD12 standard deviation of velocity peaks in 12 basal and midventricular segments

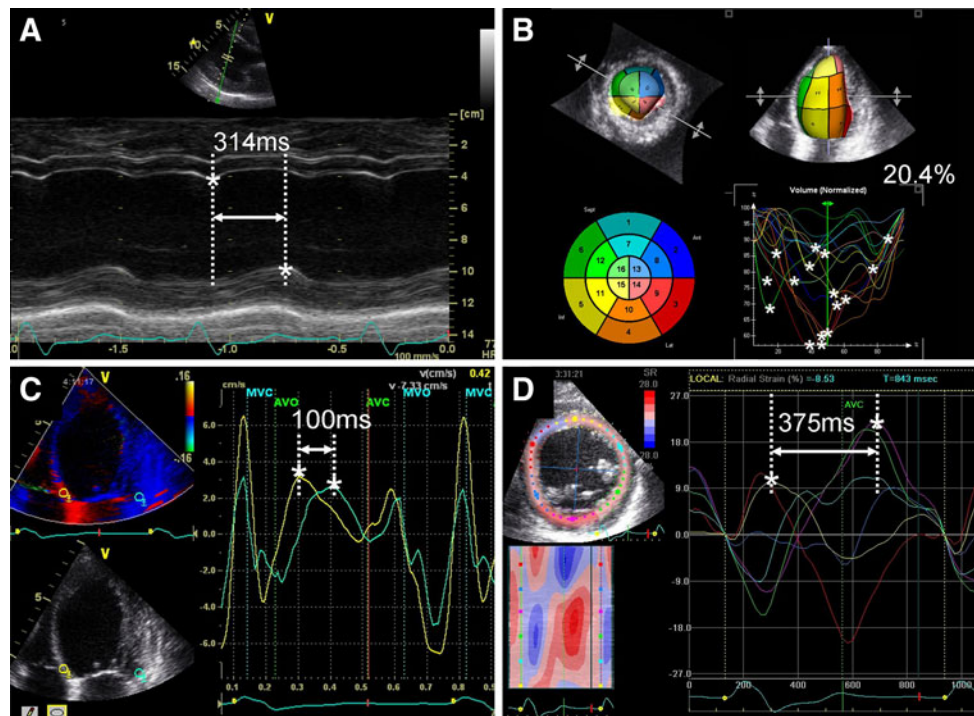


Fig. 3 Approaches to assess regional intraventricular dyssynchrony. Four of the most often applied measurements of regional dyssynchrony are displayed. Asterisks indicate peak measurements. Panel a septal-to-posterior wall motion delay by parasternal M-Mode, panel

b three-dimensional dyssynchrony index derived from three-dimensional echocardiography, panel c tissue Doppler derived septal-to-lateral peak systolic velocity delay, panel d speckle-tracking derived anteroseptal-to-posterior peak radial strain delay

difficulties and may explain the negative results in most subsequent studies [17, 44, 46].

Tissue tracking measures the longitudinal displacement of the myocardium with respect to the ultrasound transducer by temporal integration of the tissue Doppler velocity profiles. Dyssynchrony is assessed by determining the location and the number of wall segments with delayed longitudinal displacement (i.e. after aortic valve closure), and by measuring the magnitude of the time delay for each segment [17, 47].

Three-dimensional motion delays

The novel three-dimensional echocardiography technology allows to measure endocardial wall motion with reference to a ventricular center point. An LV volume is obtained by computerized reconstruction of multiple subvolumes acquired in 4–7 consecutive, ECG-triggered cardiac cycles. Tracking of the LV endocardial border is computer assisted, with only the definition of end-diastolic and end-systolic position of the mitral annulus and apex being operator dependent in recent software packages. Regional time-volume curves in 16 LV subvolumes are reconstructed with reference to the ventricular center point, thereby describing ventricular dyssynchrony in terms of regional delays in peak volume displacement throughout

the ventricle. The three-dimensional dyssynchrony index (3D-SDI) quantifies dyssynchrony as the standard deviation of the time to minimum systolic volume as a percentage of cardiac cycle length (Fig. 3, panel b). Most published reports indicate that 3D-SDI adequately predicts reverse remodeling and the acute systolic improvement after CRT [48–50]. An additional advantage of the approach lies in the fact that it integrates dyssynchrony quantification of the whole ventricle within the most accurate and reproducible echocardiographic assessment of LV volumes and ejection fraction used to monitor response. Limitations are the need for a good image quality and a stable heart rhythm [51].

Tissue velocity delays

Tissue Doppler Imaging (TDI) determines the longitudinal velocity of the tissue with reference to the ultrasound probe from an apical view, either by conventional pulsed-wave TDI or by offline analysis of color-coded TDI images. The time to onset or peak systolic velocity in the investigated segments is measured with reference to the QRS, and the relative delays between these segments are employed as a measure of mechanical dyssynchrony. Whereas timing of onset velocities and the use of pulsed wave velocities have been applied by several investigators [43, 52] measuring the delay between peak velocities within a single high

frame-rate color-coded TDI image has the advantage of being the more practical and more extensively investigated approach [12, 16, 53–58]. Accordingly, the American society of echocardiography recommends using peak measurements determined by color-coded TDI and restricting the identification of velocity peaks to the ejection period (i.e. between aortic valve opening and closure as determined by Doppler in the LVOT) [33]. Of the many indices that have been proposed, the delay between the (antero-)septum and the opposite (postero-)lateral wall (Fig. 3, panel c, cut-off 60–65 ms) [12, 53] and the standard deviation of 12 basal and midventricular velocity peaks derived from the 3 standard apical views (Ts-SD12, cut-off 32 ms) [56] have been best evaluated in single center studies as well as in the multicenter setting [17]. A practical way to derive tissue velocities is tissue synchronization imaging (TSI). After manual definition of the regions of interest in two-dimensional or triplane TDI images, this approach automatically detects peak velocities and displays the results in numeric data and color-coded parametric plots [16, 53, 55]. The approach has shown a good correlation with the manual TDI-approach and a similar predictive accuracy [16]. Limitations specific to the TDI-methodology consist of an unclear physiologic correlate for peak velocity timing, and the angle dependency of the method requiring optimal alignment of the tissue with the ultrasound beam. In angulated basal segments therefore, velocity tracings and thus the timing of their peak can change considerably by small changes in the position of the sample volume [59].

General limitations of motion- and velocity-based techniques

On the assumption that timing of systolic motion and/or velocity in the investigated segment reflects the mechanical activity of the underlying myocardium, TDI and other motion-based methods have not only been proposed to investigate the presence of dyssynchrony but also to detect the site of latest activation or to screen for dyssynchrony in failing hearts with narrow QRS [18, 60]. This core assumption itself, however, is subject to several limitations, most important the inability to differentiate active from passive motion caused by tethering of adjacent segments [61]. This can lead both to apparently inversed activation delays (free wall preceding the septum, e.g. by apical rocking) despite classical LBBB as well as to apparent or excessive delays even without underlying conduction delays (e.g. by including postsystolic motion in ischemic or infarcted segments) [59, 62, 63]. In particular when acquisitions or measurements are delayed by referencing them to QRS-triggering instead of QRS-onset (as for automated measurements like 3D-SDI), the early and brief

lived septal motion typically associated with LBBB is often missed or disregarded and the postsystolic, passive recoil motion is erroneously measured instead. These confounders at least partially explain the high incidence of dyssynchrony in failing hearts without conduction delays reported by these techniques, and the disappointing predictive performance in a number of more recent large studies [17, 18, 48, 59, 64, 65].

Quantification based on tissue deformation delays

When compared to motion and velocity-based techniques, measurements of myocardial deformation (strain) provide a superior ability to discriminate active contraction from passive translational motion, and thereby theoretically overcome the most important limitation of the former techniques. Strain can be derived either by postprocessing and temporal integration of color-TDI-derived velocity data or by speckle tracking [66]. TDI-derived strain however suffers from the same angle dependency as the fundamental velocity data from which it is derived, and additionally requires significant expertise to obtain reliable results. In line with these limitations, variable results have been obtained regarding the identification of mechanical dyssynchrony and prediction of CRT outcome [30, 58, 64]. Speckle tracking two-dimensional strain (2DS) relies on the automated tracking of unique speckle patterns generated by the acoustic backscatter interference during standard grey-scale imaging, rendering the technique largely angle independent. Moreover, it is applicable on 2- as well as 3-dimensional datasets and profits from a considerably automated analysis which speeds up analysis time, and improves measurement reproducibility for less experienced operators [66, 67]. Compared to the traditional gold standard to measure myocardial deformation by magnetic resonance tagging, it has the advantage of providing trigger-independent information throughout systole as well as diastole. Myocardial deformation by 2DS can provide quantification of longitudinal shortening, circumferential shortening, and radial thickening. Suffoletto et al. used radial 2DS to quantify the delay between peak strain of the antero-septal and posterior wall (Fig. 3, panel d). A cut-off of 130 ms (as published previously for SPWMD) was found to be predictive for acute increase in stroke volume and longer-term increase in LVEF [15]. The same cut-off was applied in combination with the previously proposed TDI septal-to-lateral delay of ≥ 60 ms in a subsequent study, demonstrating the superiority of a combined assessment over the single use of any of the two [54]. In analogy with the approaches used for TDI-derived velocities, the standard deviation between multiple segments and analysis of strain in the circumferential and longitudinal

direction were attempted, but neither proved superior to the radial anteroseptal-to-posterior approach [68].

Considerations and limitations regarding regional temporal dyssynchrony

Regardless of the technique used to derive the fundamental data, the concept and measurement of regional temporal dyssynchrony in itself has some important limitations. First, as opposed to the normal heart, the dyssynchronous and failing heart is characterized by complex and multiphasic mechanical behavior rendering the definition of onsets and peaks much more complex, increasing the measurement variability inherent to echocardiography [17, 30, 59]. As opposed to assessment of global dyssynchrony by cardiac time intervals, echocardiographic indices of regional temporal dyssynchrony suffer from a lower feasibility and a larger variability (>20% in large studies) [17, 30]. Second, as far as the peak of the chosen mechanical event has any intrinsic physiological or functional relevance in the first place, considering only its timing ignores the importance of its extent (amplitude) and overall mechanical impact. Therefore, equal delays in segments with different contractility will result in the same dyssynchrony index, while it is unlikely that they have an equally important mechanical impact. Finally, also the spatial organization of dyssynchrony (random versus clustered) determines how the disturbance translates into an inefficient LV performance, and whether pacing from two opposite sites can be expected to be successful.

Assessment of mechanical dyssynchronization and inefficiency

Whereas dyssynchrony refers merely to delays in onset- or peak mechanical events, dyssynchronization assesses the severity (amplitude) and/or distribution of counteractive mechanical behavior caused by imbalanced forces.

Qualitative appraisal of dyssynchronization-related motion features

The easiest and most readily available method to assess mechanical dyssynchronization is by visual identification of characteristic motion abnormalities associated with LBBB. Both an early and abruptly interrupted or multiphasic contraction of the interventricular septum as well as an abnormal systolic septal-to-lateral shuffling motion of the LV apex have been recognized as motion features associated with LBBB [69, 70]. Both abnormalities can be ascribed to the transmission of contractile force from the early activated and contracting RV and interventricular septum to the still

quiescent LV free wall, with reversal of the sequence later in systole. Jansen et al. [71] used both motion abnormalities to predict reverse remodeling with high sensitivity and specificity (Table 2). More recently, a semi-quantitative assessment of abnormal septal motion as part of a multiparametric approach yielded moderate predictive results as a single parameter, but the combination with AV and interventricular dyssynchrony parameters resulted in adequate prediction of response to CRT [31]. More quantitative approaches to identify subtle forms of LBBB motion abnormalities have recently been applied [70].

Quantification of mechanical dyssynchronization and inefficiency

Quantitative measurements of dyssynchronization introduce phase and (mostly) amplitude information by taking the entire time course of the mechanical process into account, thereby obviating some of the problems inherent to measurements of regional dyssynchrony. Conceptually, these indices express mechanical inefficiency and as argued by Leclercq et al. [23] and Kirn et al. [24] are particularly sensitive to spatially clustered simultaneous shortening and stretching. Several of these indices have first been implemented using magnetic resonance (MR) tagging [23, 24, 72, 106]. The methods applicable to echocardiography include phase analysis of myocardial motion or deformation, assessment of stretch relative to shortening, and selective quantification of inefficient deformation (Table 2; Fig. 4).

Phase analysis of myocardial motion or deformation

By submitting motion or deformation throughout the ventricle to Fourier analysis, relative (systolic and diastolic) cyclic phase relations between myocardial segments or walls can be assessed. These methods therefore by excellence express the spatial organization of out of phase mechanical behavior without providing information on the amplitude of motion or deformation. Breithardt et al. [73] thus analyzed septal and lateral inward motion, demonstrating a larger out of phase motion to be predictive of acute hemodynamic response to CRT. Extending these findings, Buss et al. [74] demonstrated potential for prediction of reverse remodeling but could not outperform measurements of regional delay. In analogy, the circumferential uniformity ratio estimate (CURE) or temporal uniformity of strain (TUS) implements phase analysis based on deformation, initially implemented on MR-tagging images [23, 75, 76]. In its first application in humans, TUS was able to identify clinical responders with perfect sensitivity [72]. Applied to echocardiographic speckle tracking data and using very strict response criteria ($\geq 15\%$ volume reduction and $\geq 25\%$ LVEF improvement), Bertola et al.

Table 2 Measurements of mechanical discoordination and inefficiency

Author (Ref.)	Parameter	N	Population	Ischemic etiology (%)	Follow-up (months)	Response	Cut-off	Sensitivity (%) / specificity (%)	Other results
<i>Visual appraisal</i>									
Jansen [71]	Shuffle and septal motion	53	NYHA \geq III, QRS \geq 120 ms, LVEF \leq 35%, SR, LBBB	49	3	LVESV \geq 10%	NA	91/76	
<i>Phase analysis</i>									
Buss [74]	EPI	42	NYHA \geq III, QRS \geq 130 ms, LVEF \leq 35%	43	6–8	LVESV \geq 15% LVEF \geq 8%	59%	88/75 95/67	Ts-SD performed similar
Bitchick ^a [72]	TUScirc	20 CRT 27 heterogeneous 9 control	CRT: NYHA III, clinical recommendation for CRT	40	6	NYHA \geq I	0.75	100/71	TDI septal-to-lateral delay indicated dyssynchrony in 44% of controls whereas TUS was normal
Bertola [77]	TUScirc	68	Heart failure, QRS \geq 120 ms, LVEF \leq 35%	43	3–6	LVESV \geq 15% and LVEF \geq 25%	0.52	56/63	TUS improved after CRT, 2DS-SD did not change
Ascione [78]	RGDI	62 CRT 15 control	CRT: NYHA \geq III, QRS \geq 120 ms, LVEF \leq 35%, SR	44	6	LVESV \geq 15%	47%	87/74	Ts-SD had more overlap between responders and non-responders, RGDI and LGDI were lower in controls
<i>Stretch relative to shortening</i>									
Kim ^a [24]	ISF	19 CRT 9 control	–	47	3	LVESV \geq 15%	–	–	Only baseline ISF differed between responders and non-responders, baseline onset or peak variance was different from controls but did not differentiate responders
Wang [79]	ISF	30 CRT 40 narrow QRS HF 20 control	CRT: NYHA \geq III, QRS \geq 120 ms, LVEF \leq 35% HF: LVEF \leq 35%	CRT: 40 HF: 50	0 and 6	LVESV \geq 15%	40%	94/67	Acute ISF reduction provided the best prediction of CRT response compared to acute improvement in temporal parameters and baseline ISF
<i>Selective quantification of inefficient deformation</i>									
De Boeck [80]	SRSsept	62	NYHA \geq III, QRS \geq 120 ms, LVEF \leq 35%	44	6.5 \pm 2.3	LVESV \geq 15%	4.7%	81/81	SRS conversion into additional shortening correlated with improvements in LVEF
Lim [85]	Strain-delay	100	NYHA \geq III, QRS \geq 120 ms, LVEF \leq 35%	35	3	LVESV \geq 15%	25%	82/92	Temporal velocity indices did not differentiate responders, temporal 2DS indices did not correlate with reverse remodeling in patients with ischemic etiology of HF

Table 2 continued

Author (Ref.)	Parameter	N	Population	Ischemic etiology (%)	Follow-up (months)	Response	Cut-off	Sensitivity (%) / specificity (%)	Other results
Abe [86]	FIC	9 CRT 31 non-CRT HF 20 control	CRT: NYHA \geq III, QRS \geq 120 ms, LVEF \leq 35%, SR HF: LVEF \leq 35%, SR	CRT: 33 HF: 48	NA	–	–	–	FIC was larger in CRT compared to non-CRT candidates, 2DS-SD did not differ between those groups

^a MR-tagging study. 2DS-SD standard deviation of speckle tracking peak strain times, CRT cardiac resynchronization therapy, EPI echocardiographic phase imaging, FIC fractional inefficient contraction, HF heart failure, ISF internal stretch fraction, LGDI longitudinal global dyssynchrony index, LVEF left ventricle end-systolic volume, NYHA New York Heart Association class, RGGDI radial global dyssynchrony index, SRSsept systolic rebound stretch in the septum, TDI tissue Doppler imaging, Ts-SD standard deviation of tissue velocity peak times, TUScirc temporal uniformity of circumferential strain

[77] obtained only moderate prediction. A simplified approach, omitting Fourier processing, was presented by Ascione et al. [78] who measured the absolute time duration that basal septal and lateral wall were out of phase (one shortened and the other stretched).

Assessment of stretch relative to shortening

Also initially designed for and implemented by MR-tagging studies, the internal stretch fraction (ISF) expresses the relative burden of paradoxical stretch during systolic shortening. This requires time differentiation and integration of all myocardial deformation (strain rate data) to obtain an averaged shortening and lengthening signal respectively. In contrast to the previous methods, it therefore incorporates amplitude information. Shortening amplitude thus quantifies the impact of mechanical discoordination on the overall mechanical (dys)function, whereas stretch amplitude (being dependent on local elasticity as well as remote contractile force) indirectly incorporates information on viability and contractility [24]. The superiority of ISF over regional delay measurements was demonstrated by direct comparison of both methods on the same MR-tagging data [24]. Whereas both methods accurately discriminated CRT recipients from healthy controls, only ISF was able to differentiate responders from non-responders. A recent echocardiographic study further extended these findings by demonstrating that acute recoordination (defined as radial ISF decrease) after CRT predicted reverse remodeling after 6 months better than acute resynchronization (defined as radial standard deviation of peak strains). In this latter study, of the baseline variables only ISF was able to predict reverse remodeling [79].

Selective quantification of inefficient deformation

Whereas phase analysis and ISF assess the ratio of the inefficient component (i.e. reciprocal stretch or out of phase motion) and the efficient component (i.e. systolic shortening or in phase motion), the subsequently discussed methods express and quantify the inefficient component in absolute terms. They thus represent the absolute gain in shortening that would theoretically occur if (peak) shortening was perfectly timed on aortic valve closure.

Systolic rebound stretch (SRS) measurement is in several regards a continuation and specification of the concepts of ISF. It specifically measures only the absolute stretching that occurs after initial shortening and disregards the early stretching associated with delayed and postsystolic shortening. Whereas prestretch and postsystolic shortening can also result from ischemia or excessive loading, early systolic shortening and SRS occur in early activated segments and are highly specific for underlying

dyssynchronous activation [80–82]. Thus, the aspecific components of discoordination that can also occur in the setting of ischemia or scarring, and that are not or only moderately related to CRT response (Fig. 5), are left out of the analyses [80, 83, 84]. SRS is consistently converted into additional segmental shortening by CRT. The central role of the septum in the pathophysiology of dyssynchrony was confirmed by revealing that the majority of SRS and functional improvements occurred in the septum. In the prediction of reverse remodeling, septal (cut-off 4.7%) and total ventricular SRS performed equally well [80].

Rather than selectively measuring systolic stretch, Lim et al. used speckle tracking longitudinal deformation to calculate the sum of the differences between absolute peak values and end-systolic values across 16 segments. By thus incorporating information on prominent diastolic deformation (i.e. diastolic exceeding systolic amplitude) and additionally discarding the information from akinetic or markedly stretched segments, the index (cut-off 25%) reached sensitivity and specificity of 82 and 92% respectively for the prediction of reverse remodeling. Especially in patients with ischemic heart failure etiology, it thereby

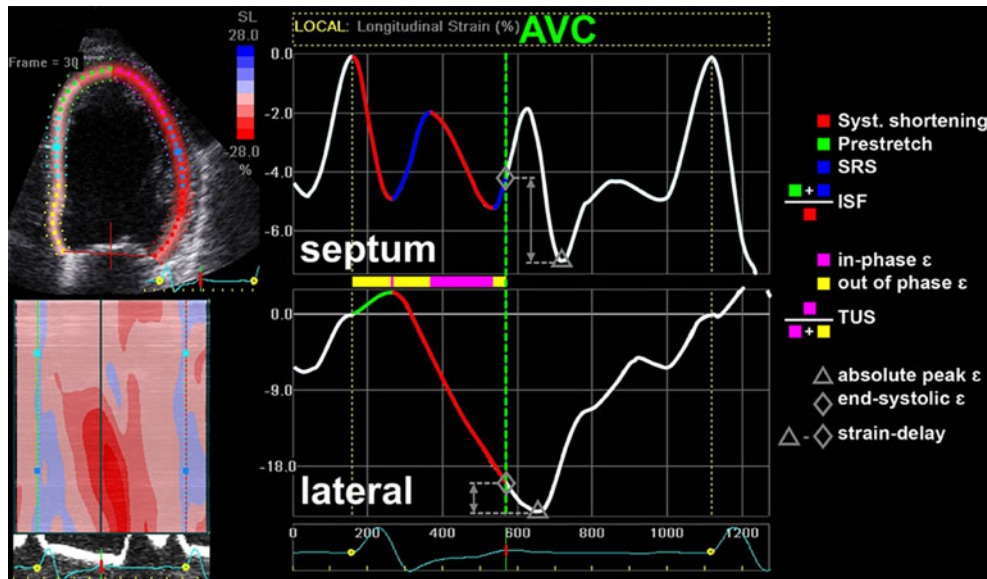


Fig. 4 Approaches to assess mechanical discoordination. Deformation traces of the septum and lateral wall are displayed as derived from speckle tracking. The green vertical dashed line indicates the end of systole as defined by aortic valve closure (AVC). Several concepts of discoordination measurements are illustrated. Notice that

assessment of TUS and ISF require either Fourier analysis or time differentiation and integration steps, respectively, that are not displayed in the current figure. ϵ strain, *ISF* internal stretch fraction, *SRS* systolic rebound stretch, *TUS* temporal uniformity of strain

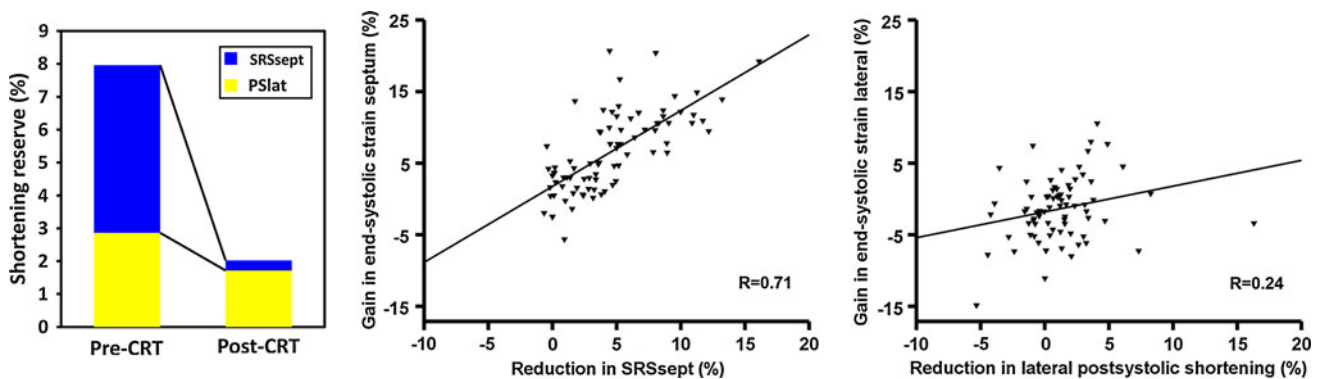


Fig. 5 Conversion of stretch and postsystolic shortening into effective shortening by CRT. Relation of septal systolic rebound stretch (*SRSsept*) and lateral postsystolic shortening (*PSlat*) with gain in function are displayed. *Left panel* shows the effect of CRT on both components of contractile inefficiency: CRT nearly eliminates

SRSsept whereas the effect on *PSlat* is less pronounced. *Middle panel* displays the relation of *SRSsept* reduction with local gain in function. *Right panel* displays the same relation for *PSlat* reduction (unpublished data)

compared favorably to the regional delay methods TDI Ts-SD12, TDI septal-to-lateral delay, and 2DS 12 segments standard deviation [85].

In an analogous approach, Abe et al. measured segmental and global time-area changes of the myocardium in a midventricular short-axis trace to calculate the fractional inefficient contraction (the fraction by which the summed regional area changes exceed the actual global area change). Their method also compared favorably to regional delay measurements in particular with regard to the blinded differentiation of patients with guideline indication for CRT from those with heart failure but not meeting the guideline criteria [86].

Considerations and limitations regarding discoordination measurements

Although discoordination measurements are designed to represent mechanical inefficiency, its shortening and stretch components are load dependent. Discoordination indices are therefore only indirect markers of (imbalanced) contractile force development and lack information on the ultimate consequences of dyssynchrony on the pressure-generating ability of the heart. Initial experimental results indicate that elevated wall stress in the setting of progressive dilatation is paralleled by increased variation in regional work and that measurements of discoordination accurately reflect this increased dissipation of work [87]. Seemingly contradictory, explorative patient data indicate that dobutamine induced pre- and afterload reduction (and increased contractility) can unmask mechanical discoordination [88] and the effects of changes in loading and contractility therefore need to be further elucidated. On the other hand, with abnormal stretch and wall stress being important determinants of secondary biological effects of dyssynchrony, the significance of stretch-based indices may reach beyond the purely hemodynamic aspects of CRT. From a practical point of view, discoordination measures are technically challenging and have not been implemented in commercially available software packages [89]. On top of inaccuracies originating from variability in strain amplitude measurement, methodologies selectively assessing dyscoordination in the systolic period are susceptible to errors in delineating and incorporating this temporal component. Feasibility is also an important issue for many of the indices that require sampling large parts of the LV (e.g. CURE, ISF), since echocardiographic approaches are frequently incapable of investigating one or more LV segments or walls. Finally, clinical experience with these indices is promising but still sparse making definite conclusions on their feasibility and value likewise premature.

Unsolved issues

In which direction to assess dyssynchrony?

The introduction of two- and three-dimensional deformation techniques and the concomitant possibility to assess dyssynchrony and discoordination in the longitudinal, circumferential, and radial direction have compelled investigators to reconsider the optimal direction for the analyses. Whereas circumferential and longitudinal deformation are elicited by shortening of (midmyocardial respectively endo- and epicardial) muscle fibers oriented in these directions, radial thickening is the result of myocardial incompressibility, and thus represents a combined effect of the former two. The superior predictive potential of radial dyssynchrony in echocardiographic studies has mainly been attributed to this combined effect, although differences in sampling location and measurement reliability might also have affected the results [15, 68, 90, 91]. From a mathematical point of view, and confirmed by MR-tagging studies, the large dynamic range of circumferential deformation renders it most sensitive to subtle changes in (dys)synchrony [75, 92]. On the other hand, when assessed by echocardiography, longitudinal deformation is of interest especially because of its favorable feasibility and reproducibility compared to the other directions [30]. Additionally, when applied to single walls instead of the (more common) complete apical view, its spatial and temporal resolutions are unmatched by any of the other approaches [80, 81].

The influence of myocardial scar and lead localization

In addition to problems in the recognition of true, amenable dyssynchrony, variability in therapy response introduced by the patients natural disease course, mechanical factors independent of dyssynchrony, and inappropriate delivery of resynchronization make that response prediction cannot be expected to be perfect. The presence of posterolateral scar as well as the total scar burden has been associated with a reduction in response to CRT [13, 93, 94]. The former most likely relates to the inability to obtain an adequate LV lead position, whereas the latter can be related to insufficient viable myocardium to be recruited by CRT [95, 96]. If advanced scarring is predictive of non-response after CRT, measurements of the amenable substrate for CRT should preferably indicate a decreasing likelihood of response with increasing amounts of myocardial scar. Parameters of mechanical discoordination seem to display this pattern, whereas measurements of QRS-width or markers of temporal dyssynchrony are relatively unaffected (Fig. 6).

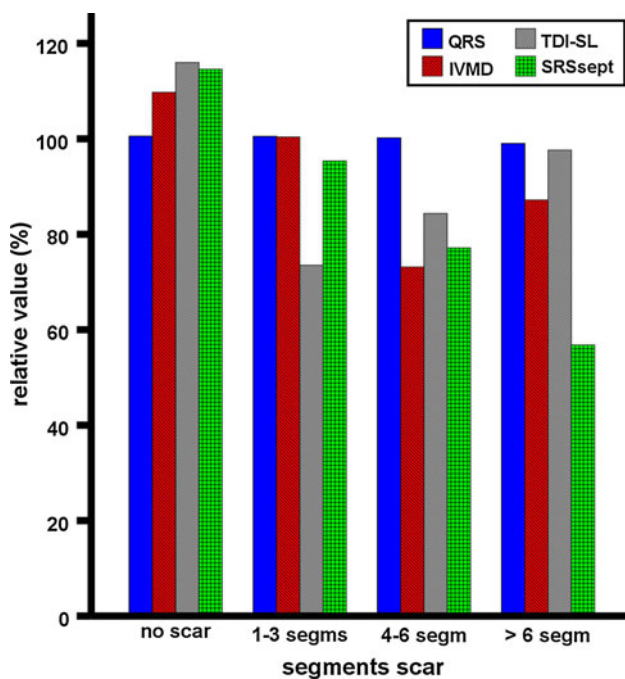


Fig. 6 Scar and dyssynchrony. Normalized baseline values for electrical and mechanical dyssynchrony and discoordination parameters for increasing amounts of scar (population mean used for reference). SRSsept is the only parameter that consistently shows a decrease in dyssynchrony with increasing amounts of scar (unpublished data). IVMD interventricular mechanical delay, SRSsept septal systolic rebound stretch, TDI-SL tissue Doppler septal-to-lateral delay

Apart from the unfavorable lead localization in the area of scar, observational studies have suggested LV lead placement to be optimal in the most mechanically delayed segment [60, 97]. This suggestion has recently been refuted by an experimental study that demonstrated optimal lead position to coincide with the site of most pronounced electrical resynchronization rather than with the site of most mechanical delay [96]. Currently, there is no role for echocardiography in determining the optimal site for LV lead placement.

Echocardiography to extend the indications for CRT

Although single center studies have suggested echocardiography as an additional screening to extend the application of CRT to patients with narrow-QRS heart failure, this could not be confirmed in a large prospective study [18, 98]. To prevent more such negative results, validation of proposed parameters in a normal control population should reduce the chance of false positives and prevent the heedless implementation of insufficiently validated parameters [64]. More recently, several investigators have accordingly incorporated normal controls in their analyses, demonstrating adequate differentiation of patients and

controls by measurements of discoordination, but not by measurements of regional delay [72].

Definition of response

One of the most important issues that requires clarification is the definition of response. The most relevant response within a heart failure population lies within the improvement of symptoms, heart failure hospitalizations, and reduction in mortality. In an attempt to circumvent the placebo effect of CRT observed in the clinical trials, many echocardiographic studies have disregarded these outcomes and used surrogate endpoints like reverse remodeling and LVEF improvement instead. This methodology has been justified by demonstrating a relation between reverse remodeling and long-term mortality benefit after CRT both in observational studies [99] as well as in recent large multicenter randomized trials [100]. Nevertheless, reverse remodeling may not be necessary for long-term response [8, 22, 101] and in the CARE-HF trial decreased neuro-hormonal activation proved to be even more closely linked to prognosis [102]. The issue is further complicated by the poor agreement among different response criteria [103] and the inability of the observational study designs to differentiate genuine response from the spontaneous course of disease [22]. It is likely that a spectrum of responses ranging from only symptom reduction to complete reverse remodeling exists and classification should preferably cover the broad spectrum of this response.

Conclusion

Echocardiography may play an important role in patient assessment before CRT and is currently one of the most commonly used non-invasive imaging modalities to provide information on its mechanical effects in heart failure patients. Despite recent negative results, echocardiographic techniques have continued to develop with new discoordination approaches benefiting from an improved ability to specifically detect only the amenable substrate for CRT. To make these techniques a valuable addition also to the clinical field, further improvements in measurement feasibility and reliability, a better understanding of the effects of loading and wall stress, and multicenter validation are required. Although the complexity of the disease and its therapy make perfect prediction unlikely, there is no doubt that the mechanical assessment of dyssynchrony will continue to provide additional insight into the disease process and help to optimize therapy delivery.

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