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Recent advances in cardiac resynchronization therapy: echocardiographic modalities, patient selection, optimization, non-responders—all you need to know for more efficient CRT

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Abstract Cardiac Resynchronization Therapy (CRT) constitutes an established way of treatment for patients suffering from severe heart failure. However, this technologically based and expensive mode of therapy may not be effective for a substantial number of individuals. Recent research and advanced echocardiographic modalities have provided new insight on the proper patient selection, lead implantation, optimization and reasons for non-response. Based on this evidence, an overall assessment of parameters that appear to contribute significantly to the outcome of CRT in addition to electrical or mechanical dyssynchrony, seems to be a reasonable approach for more effective resynchronization therapy.

Keywords Heart failure · Dyssynchrony

Introduction

As the prevalence of heart failure sharply increases in contemporary society [1], a new mode of treatment,

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that of cardiac resynchronization, has emerged at the forefront of medical therapy, offering hope and showing significant clinical improvement in a selected patient population [2]. The rationale behind cardiac resynchronization therapy (CRT) resides on the observation that the latter can revert asynchronous mechanical events, appearing mainly in heart failure patients with wide QRS complex on surface ECG, leading to clinical improvement and lower risk of death [3]. For that reason, the current recommendations for the management of patients with heart failure have suggested CRT as an additional therapeutic modality in individuals classified as NYHA III–IV who are symptomatic despite optimal medical therapy, and who have a reduced EF (LVEF $\leq$ 35%) and QRS prolongation (QRS width $\geq$ 120 ms) [4]. However, patient selection based on electrical criterion (wide QRS) may lead to non-improvement of more than 30% of individuals after CRT [5, 6]. Moreover, recent evidence suggests that other important parameters, such as the site of pacing lead placement, the degree of scar formation, the availability of coronary venous access, the contractile reserve and A-V or V–V optimization may actually affect the final outcome of CRT and warrant particular attention when resynchronization therapy is going to be applied. In this review, echocardiographic modalities with cut-off values to assess mechanical dyssynchrony are highlighted, and an overall assessment of issues related to CRT in addition to electrical or mechanical selection criteria is demonstrated as a

reasonable approach for more effective resynchronization therapy.

Mechanical dyssynchrony: an important determinant

It is well known that prolongation of QRS (mainly LBBB) is an expression of abnormal electrical activation of the myocardium (electrical dyssynchrony) that can be translated into alteration of right and left ventricular mechanical events [7], leading to increased morbidity and higher risk of sudden cardiac death [8]. However, although mechanical dyssynchrony is present in 64% of patients with wide QRS, it also appears with relatively less prevalence (43%) in heart failure patients with narrow QRS complexes [9]. Thus, selection of candidates for CRT based only on electrical criterion (QRS duration) may actually deprive from a substantial number of patients the benefits of cardiac resynchronisation therapy. Furthermore, the evidence of electromechanical dissociation as expressed by differences in electromechanical coupling intervals between earlier and later electrically activated regions may result in various degrees of mechanical dyssynchrony in patients with similar QRS durations [10]. The above observations imply that, in fact, echocardiographic assessment of mechanical dyssynchrony may provide a better insight of the interventricular and intraventricular synchronicity than prolongation of QRS alone. This is important, as it has been shown that heart failure patients with minimal to no dyssynchrony appear to have a poor prognosis and a lower probability of CRT response [11].

Echocardiographic assessment of mechanical dyssynchrony

Mechanical asynchrony of the cardiac function has been mainly described in terms of (A) atrioventricular (A-V) dyssynchrony, (B) (V-V) interventricular dyssynchrony, and (C) intraventricular dyssynchrony. In fact, assessment of A-V dyssynchrony is currently used mainly in optimization procedures and most evidence suggests that only intraventricular dyssynchrony can effectively predict response after resynchronisation therapy [12]. However, there are studies demonstrating that each of those types of dyssynchrony may actually affect the outcome of resynchronisation

therapy and should be kept in mind when CRT assessment is carried out [13].

Atrioventricular (A-V) dyssynchrony

A-V dyssynchrony physiologically reduces the duration of left ventricular filling and thus decreases the preload, stroke volume and cardiac output. The synchronicity of atrial with ventricular mechanical events can be assessed by the evaluation of left ventricular filling time (LVFT) ratio, which is the ratio of LV filling divided by the RR interval from the surface ECG.

$$LVFT = LV\,Filling/RR(\%)$$

LV filling can be evaluated by pulsed Doppler recording of transmitral inflow (from the beginning of E to the end of A wave), with the sample volume placed at the tips of the mitral valve leaflets. A LVFT < 40% is typically observed in the presence of atrioventricular Dyssynchrony [14].

Interventricular dyssynchrony (RV-LV interaction)

Interventricular dyssynchrony occurs when there is a significant delay between RV and LV activation, which can be crudely denoted by the presence of a wide QRS on the surface electrocardiogram [15]. The LV-RV synchronicity can be assessed by two methods, as follows:

The interventricular mechanical delay (IVMD) Pulsed Doppler-derived pulmonary and aortic blood flow waves are recorded from the RV and LV outflow tracts. The time from the onset of the QRS to the start of pulmonary and aortic blood flow is measured, giving rise to RV and LV pre-ejection time intervals respectively. The subtraction of RV from LV pre-ejection intervals is an index of interventricular mechanical delay. A cut-off value of IVMD: ≥ 40 ms is regarded as an indication of interventricular dyssynchrony [15, 16].

Difference of electromechanical coupling times (RV-LV) by tissue Doppler imaging Interventricular (LV-RV) asynchrony can also be determined as the difference between electromechanical coupling times (from onset of the QRS complex up to the beginning of regional velocity of myocardial systolic

shortening), considered in the basal lateral segment of the RV and in the most delayed LV segment.

A cut-off value of 56 ms had an area under the curve (AUC) = 0.69 in order to predict functional recovery after resynchronization. This index was better than QRS duration (AUC = 0.63) in predicting CRT response, but worse than LV asynchrony (AUC = 0.77) and sum asynchrony (AUC = 0.84) [17].

IntraVentricular dyssynchrony

Several methods have been described in order to assess intraventricular dyssynchrony (Table 1), most of which are presented as follows.

M-mode-derived septal to posterior motion delay (SPWMD) Synchronicity of radial motion of the anterior septal and posterior walls can be assessed by m-mode echocardiography from the parasternal short-axis view at the mid-ventricular level. The time difference from the onset of QRS to peak of septal and posterior wall motion can be measured, and a cut-off value of SPWMD $\geq$ 130 ms is regarded as an indication of intraventricular dyssynchrony to predict CRT response [18]. However, ambiguity in septal motion measurement has been also demonstrated to be a reason for failure of prediction of CRT response [19]. As a result, LV dyssynchrony assessment was feasible in 59% of patients with M-mode echocardiography compared with 96% when colour-coded TDI was used [20].

An opposing wall delay by tissue Doppler imaging (TDI) Tissue Doppler imaging can be used to record longitudinal systolic velocities of any opposing LV wall. A 2-site (septal–lateral), 4-site (septal–lateral and anterior–inferior) and six-site method (septal–lateral and anterior–inferior and anterior septal-posterior) from the 4-, 3- and 2-chamber views have been described. The time difference from the onset of QRS to peak systolic velocity of the basal regions can be measured. The presence of significant intraventricular dyssynchrony to predict CRT response is documented when there is a time difference of opposing walls: Time to Peak Delay $\geq$ 65 ms [11] (Fig. 1).

Standard deviation of time-to-peak longitudinal systolic velocities by TDI (dyssynchrony index) Coloured-tissue Doppler has also been used for detection of LV synchronicity, taking into account the standard deviation (SD) of the average time from the onset of QRS to peak longitudinal velocity in the ejection phase (Ts), recorded from the basal and mid segments of the lateral, inf. septal, anterior, inferior, ant. septal and posterior walls in a 12-segment model. A cut-off value of dyssynchrony index $\geq$ 32.6 ms is regarded as an indication of intraventricular dyssynchrony to predict CRT response [6]. Similarly, a 6-segment model has also been used, including the six basal LV segments, with a SD cut-off $\geq$ 36.5 ms predicting response [21].

Peak velocity difference (PVD) A 6-segment model in coloured-tissue Doppler imaging can been used, measuring the time from the onset of QRS to the highest peak longitudinal velocity in either the ejection phase or post-systolic shortening of the six basal walls recorded from the 4-, 3- and 2-chamber apical views. Calculation of the maximal time difference from the above walls generates the PVD, with a cut-off value > 110 ms predicting CRT response [22]. Similarly, a maximum delay in a 12-segment model (including mid also segments) has also been used with a cut-off $\geq$ 100 ms predicting CRT response (Table 1).

Displacement mapping For displacement mapping, the velocity–time integral of tissue velocity is computed and the regional long-axis movement curve is displayed. A 6- or 12-segment model can be used, measuring the SD of time to peak displacement (Td) or the maximum delay. A cut-off $\geq$ 75 ms for the SD of Td and a cut-off $\geq$ 205 ms for the max delay of Td have been reported to predict CRT response [23].

Sum of maximal electromechanical delay RV-LV A 3-segment model has been proposed using spectral-tissue Doppler, calculating the time period from the onset of QRS to the onset of longitudinal velocity curve recorded from the basal lateral, septal and posterior walls, from the 4- and 3-chamber apical views. The time difference between the longest and shortest intervals generates the maximal electro-mechanical delay (MED). A sum of LV MED with LV-RV MED, the last calculated as the difference between electromechanical coupling times in the basal lateral segment of the RV and in the most delayed LV

Table 1 Echo modalities and intra-ventricular dyssynchrony indexes for prediction CRT response

Methodology for LV intra-ventricular dyssynchrony	Echo modality	Cut-off	Patients	Follow up period	Response	Sensitivity (%)	Specificity (%)
Septal to Posterior Motion Delay (SPWMD) [18]	M-Mode	≥130 ms	20	1 month	LVESVI ≤ 15%	100	63
Septal to Posterior Motion Delay (SPWMD) [19]	M-Mode	≥130 ms	79	6 months	LVESVI ≤ 15%	24	66
SD of time to peak longitudinal systolic (Ts) velocity of 12 LV segments (Basal &mid) (Dyssynchrony Index) [21]	Colour TDI	≥32.6 ms	55	3 months	LVESV < 15%	96	78
SD of Ts of 12 LV segments [35]	Tri plane-TDI	>33 ms	60	6 months	LVESV ≤ 15%	90	83
Septal to lateral Ts delay [24]	TSI	≥65 ms	60	6 months	LVESV ≤ 15%	81	89
Max delay inTs of 12 LV segments [32]	Colour-TDI	≥100 ms	256	6 ± 3 months	LVESV < 15%	92	68
SD of TS of 6 Basal LV segments [34]	Triplane-TDI	≥36.5 ms	49	Acute	LVESV ≤ 15%	91	81
Peak velocity difference (PVD) of 6 basal LV segments [22]	Colour-TDI	≥110 ms	49	3 months	LVESV ≤ 15%	97	55
Maximal electromechanical delay (MED) [17]	Puteed-TDI	≥102 ms	49	6 months	LVEF ≥ 25%	96	77
An opposing wall (septal-lateral-anterior-inferior) longitudinal velocity delay [11]	Colour-TDI	≥65 ms	80	6 months	NYHA ≥ 1 6 min walking distance ≥ 25%	80	80
SD of time to minimum systolic volume of 16 LV segments-systolic dyssynchrony Index (SDI) [27]	3D	SDI ≥ 5.6%	56	Acute	LVESV ≤ 15%	88	85
Radial 2D strain—anterior septal to posterior time to peak strain difference [28]	2D speckle tracking	≥130 ms	48	Acute	Stroke volume ≥ 15%	91	75
			50	>3 months	LVEF ≥ 25%	89	83
Velocity vector imaging-opposing wall peak longitudinal velocity delay of 6 basal LV segments [29]	VVI	≥75 ms	23	>3 months	LVEF ≥ 25%	85	80
Combined 2D radial strain and longitudinal velocity delay [33]	2D speckle tracking Colour-TDI	≥130 ms ≥60 ms	176	>3 months	LVEF ≥ 25%	88	80
Longitudinal strain delay index [36]	2D speckle tracking	≥25%	100	3 months	LVESVI ≤ 15%	82	92
Max delay in time to peak displacement of 12 LV segments [25]	Tissue tracking	≥205 ms	55	3 months	LVESVI ≤ 15%	62	62
SD of time to peak displacement (Td) of 12 LV segments [25]	Tissue tracking	>75 ms	55	3 months	LVESVI ≤ 15%	66	73

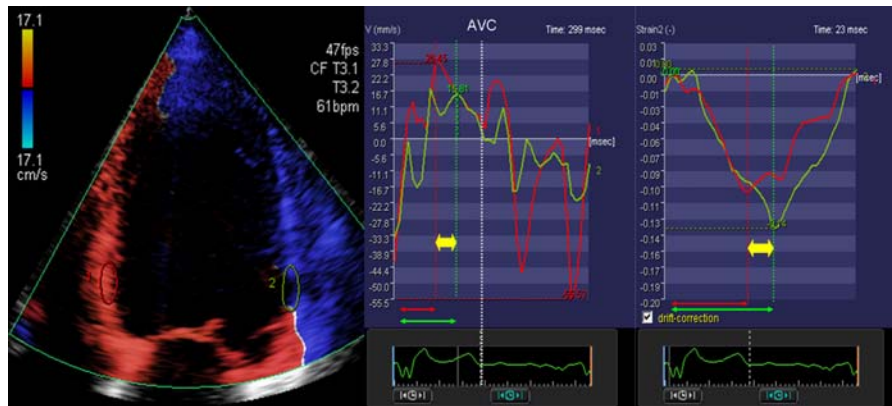Ts time from onset of QRS to peak systolic velocity, SD standard deviation

Fig. 1 Representative measurements of Dyssynchrony based on colour tissue Doppler. *Left*: Colour tissue Doppler imaging with regions of interest at the basal septal and lateral walls. *Middle*: Velocity curves are shown from the respective sites with time durations from the onset of QRS to the highest peak systolic velocity at the ejection phase (*Red* and *Green arrows*) (AVC: Aortic Valve Closure). The *yellow arrow* represents the degree of dyssynchrony between the two opposing walls. *Right*: Longitudinal strain curves from the same regions. Time durations from the onset of the QRS to the peak negative strain in the ejection or post-ejection phase are depicted. The *yellow arrow* again represents the degree of dyssynchrony between the two opposing walls

segment, have been found to predict CRT response with a cut-off ≥ 102 ms [17].

Tissue synchronization imaging (TSI) Colour-coded myocardial velocity [24, 25] based on colour-tissue Doppler imaging has also been used for qualitative assessment of LV synchronicity. The TSI algorithm automatically calculates and colour-codes the time to peak tissue velocity in every region in the image within a specified time interval with reference to the QRS signal. Event timing markers corresponding to aortic valve opening and closure can be incorporated in order to define the ejection phase. The severity of the delay for each myocardial region is depicted in a colour-coded 2D image in a sequence of green, yellow, orange or red for immediate visual identification of regional delay. Quantitative evaluation of time delay based on velocity curves can subsequently be made from the 4-, 3- or 2-chamber apical views.

Systolic dyssynchrony index by three-dimensional (3D) echocardiography Regional volume changes in respect to timing of the cardiac cycle from a 16-segment model can be provided by three-dimensional echocardiography. The time to the minimum regional volume can be calculated for each myocardial segment. As normally each segment is expected to achieve the minimum volume at almost the same point in the cardiac cycle, the degree of dispersion

of time to the minimum regional volume can reflect the severity of dyssynchrony [26]. LV dyssynchrony can be defined as the standard deviation of the average time taken to reach the minimum systolic volume for 16 LV segments (referred as the systolic dyssynchrony index, SDI). A cut-off value for SDI ≥ 5.6% has been found as evidence of intraventricular dyssynchrony predicting CRT response [27].

Septal to posterior wall delay of radial strain based on 2D speckle tracking Speckle tracking strain analysis from the short axis mid-ventricular level has also been used to assess LV dyssynchrony. Radial strain values from multiple circumferential points are calculated and data are averaged into six segmental time-strain curves. A time difference ≥130 ms of peak strain between the anterior-septal and posterior wall has been defined as a cut-off for intraventricular dyssynchrony for prediction of CRT response [28].

Opposing wall longitudinal delay by velocity vector imaging Tissue velocities are determined by the automated tracking of periodic B-mode image patterns on digital cine loops from standard apical 4-, 2- or 3-chamber views, with the user tracing the endocardial surface of the left ventricular wall from a single frame. The velocity vector images can facilitate a rapid qualitative visual assessment of LV synchronicity, but can also provide quantitative assessment. Dyssynchrony

has been determined as the greatest opposing wall peak longitudinal velocity delay at ejection or post-ejection phase from the three apical views, with a cut-off value ≥ 75 ms to predict CRT response [29].

Time-to-peak longitudinal strain standard deviation (TPS-SD) Regional longitudinal Doppler-derived strain profiles can be extracted from the basal and mid-segments of each LV wall in the standard 4-, 3- or 2-chamber apical views for a total of 12 segments. The time period from the beginning of Q on the ECG to peak negative strain can be measured for each segment and the standard deviation (SD) of the average has been used as a strain dyssynchrony index. A cut-off value TPS-SD ≥ 60 ms can identify CRT response [30]. Although some evidence suggests that strain-derived dyssynchrony index is a better measurement than the tissue velocity dyssynchrony index for monitoring changes in mechanical dyssynchrony after CRT and for predicting CRT response [31], other studies have reported contradictory results demonstrating that longitudinal strain-derived dyssynchrony analysis failed to predict CRT response compared to velocity-derived dyssynchrony indices, with the latter showing good sensitivity for the same prediction [32]. Those differences may be attributed to variability issues of the examined modes of dyssynchrony, and for that reason, further studies are needed to clarify that discrepancy.

Combined radial 2D speckle tracking and longitudinal colour-TDI dyssynchrony A combined approach has been used based on 2D speckle tracking, with a cut-off ≥130 ms between the anterior-septal and posterior wall peak radial strain delay and a 2-site (septal–lateral) systolic longitudinal velocity delay with a cut-off ≥ 60 ms. Patients having both longitudinal and radial dyssynchrony demonstrated the greatest improvement in NYHA functional class compared to those having either radial or longitudinal Dyssynchrony [33].

Triplane tissue Doppler imaging A novel three-dimensional (3-D) tissue Doppler imaging (TDI) modality [34], which permits simultaneous acquisition of TDI from all LV segments during the same heartbeat, in addition to 3-D volumes, has been used to assess intraventricular dyssynchrony. The triplane colour-coded TDI dataset can be used to analyse myocardial velocity curves from 12 LV segments and the SD of time to peak systolic velocities (Ts) is calculated as the dyssynchrony index. Data can be reported in a bulls' eye plot, and a cut-off value of Ts-SD ≥ 33 ms can predict clinical response to CRT [35]. Similarly, a 6-basal LV segment model can be used (Table 1).

Longitudinal strain delay index by speckle tracking imaging Londitudinal Strain based on 2D speckle tracking in a 16-segment model has been used in order to calculate the sum of the difference between peak and end-systolic strain defined as Strain Delay index (SDI). A cut-off of SDI ≥ 25% can predict CRT response in both ischemic and non-ischemic Cardiomyopathy [36].

Septal flash The direct mechanical consequence of dyssynchronous contraction induced by LBBB can be identified by detecting the early activation of the septum as an early septal thickening (Septal Flash) within the isovolumic contraction period. The septal flash can be visualised on the SAX or PLAX either using grey scale or tissue Doppler colour M-mode. The timing and extent of septal flash can be measured by the amplitude of early radial septal velocities. The presence of septal flash as a single parameter of intraventricular dyssynchrony appeared to have a 64% sensitivity and 55% specificity to predict CRT response [13].

Three-dimensional velocities, strain and displacement mapping based on 3D speckle tracking A novel application based on the procession of 4D data, by speckle tracking of three-dimensional cubic templates throughout the cardiac cycle, has recently evolved. This modality is able to analyse regional 3D wall motion, using components of regional displacement in different directions and subsequently calculating 3D strain and other parameters of LV function for the entire left ventricle [37]. Qualitative assessment of dyssynchrony based on parametric imaging of regional LV displacement can be obtained, using colour-coded dyssynchrony mapping of regional delays (Fig. 2). Quantitative assessment is also feasible, and cut-off values of regional velocities, displacement or 3D strain to predict CRT response are expected.

Fig. 2 Dyssynchrony imaging map by 3D speckle tracking. Parametric Imaging (*lower left*) and polar map (*centre*) displaying regional *colour* coded time delays of displacement of the entire left ventricle based on 3D speckle tracking, identifying a post systolic shortening (PSS) event located at inferior septal and inferior wall. End-systolic and end-diastolic volumes, as well as ejection fraction based on 3D measurements are also presented at the same time. Regional curves of longitudinal displacement can also be seen
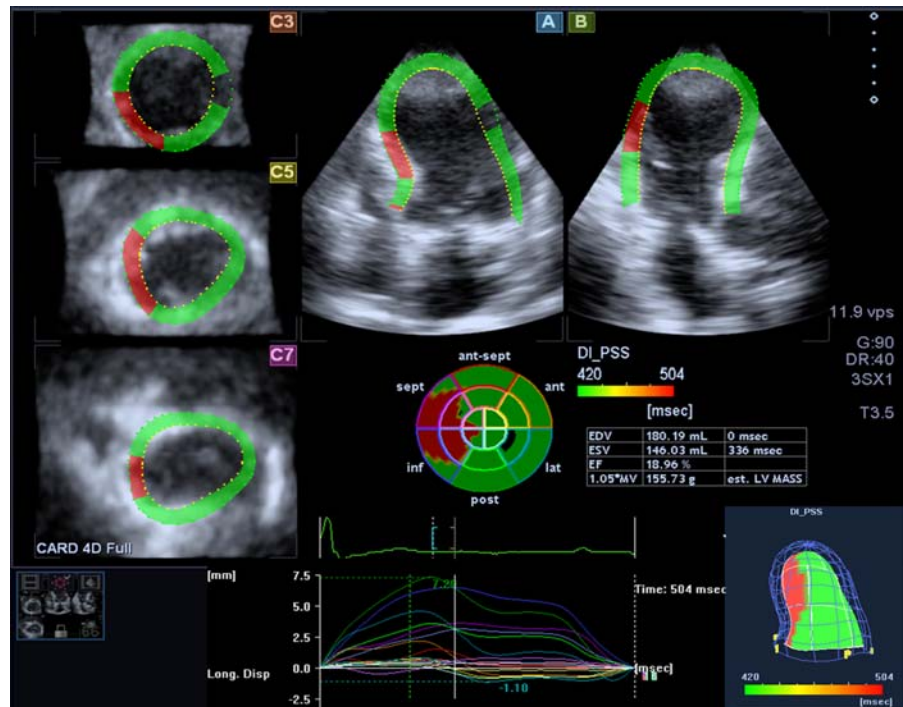
Lead implantation, scar formation and coronary venous system

The role of the exact site of implantation of the pacing lead on CRT response, has been under focus by many research groups lately. Recent evidence suggests that the site of the latest mechanical activation (most often posterolateral), identified by any of the tissue Doppler, speckle tracking Echo or 3D modalities, is the preferable pacing region, as patients appear to have better acute or long-term response and better prognosis than those with discordant lead implantation [28, 38, 39]. However, other evidence suggests that LV lead concordance to the delayed contraction segment may not be a major determining factor for favourable echocardiographic and clinical outcomes after CRT [40]. In fact, other parameters may also determine the outcome of CRT, such as the presence of scar formation at the region of lead implantation. This is of great importance in patients with ischemic heart disease, especially if this scarring is extensive. Even if the lead is implanted at the site of latest activation, the presence of extensive scarring in that region is associated with low response rates [41, 42]. For that reason, gadolinioum-enhanced cardiovascular

magnetic resonance may provide significant information for the selection process and decision making, identifying any scar formation and determining the total scar burden and its distribution [43, 44].

Another important step for the CRT process is the exploration of the coronary venous system and the correct location of the branch that will be used for lead implantation. The coronary transvenous approach through the tributaries of the coronary sinus is the usual way of LV lead placement. Subsequently, the feasibility of appropriate transvenous lead positioning should be determined exploring the anatomy of the venous system by retrograde venography or multislice computed tomography [45]. If suitable veins for pacing a particular site cannot be found, surgical LV lead positioning may be considered, using limited left-lateral thoracotomy with direct epicardial lead placement [46].

Optimization

Optimization of pacemaker settings entails adjustments in the atrio-ventricular (A-V) and right-left ventricular (V–V) synchronicity, in order to have the highest benefit from the resynchronization therapy.

A-V optimization

The aim of A-V optimization is to find the optimal A-V delay in order to have higher diastolic filling time and thus an increased stroke volume and a reduction of a probable pre-systolic MR [47]. Using transmitral pulsed-wave Doppler, diastolic filling time shown by A and E wave is recorded at different A-V delays (iterative method). In particular, starting from a long A-V delay (160–200 ms), an incremental shortening of 20 ms is applied until A-wave truncation is visualised. Then, A-V delay again is incrementally lengthened until truncation no longer exists, which normally corresponds with the longest LV filling time. The minimal AV delay that allows for adequate E and A wave separation, without A wave truncation and termination of the A wave at approximately 40–60 ms before the onset of the QRS is considered the optimal AV delay.

Aortic pulse wave Doppler may also be applied in order to assess velocity time integral (VTI), as an index of stroke volume. The highest VTI should correspond with the optimal A-V delay and the longer filling time. A simplified rule for screening A-V delay is first to check if the A-wave is absent or truncated and second if the E and A waves are merged. In the first case the A-V delay is probably too short, whereas in the second it is too long.

Although in the common clinical setting, a standard short A-V delay (100–120 ms) is usually applied, A-V optimization seems to be of great importance in cases of non-response. However, unresolved issues related to the benefit of fixed or dynamic shortening or lengthening of A-V delay remain to be further elucidated by future studies. Optimization of atrioventricular interval after CRT appears necessary during follow-up as it needs to be readjusted in up to 55% of patients [48].

V–V optimization

Accumulating evidence suggests that sequential LV-RV pacing (LV paced first) is associated with improvement of EF and exercise capacity, and reduction of mitral regurgitation in the majority of patients, compared to simultaneous or RV pre-activated biventricular pacing [49–51]. However, in other studies, simultaneous or RV pre-activation are still of benefit in a considerable cohort of patients, and equal degree of benefit among patients with LV and RV pre-activation may exist [47]. Those findings dictate the need for a patient-tailored approach for optimal V–V pacemaker settings. For that purpose, incremental change by 20 ms of V–V pacing interval, starting from −80 ms (RV first) to +80 ms (LV first) is applied. At the same time, aortic velocity time integral (VTI), as an index of stroke volume, is also measured for each V–V pacing interval. The optimal V–V offset is that of producing the greatest VTI.

CRT response and non-responders

Several clinical and echocardiographic parameters have been used in order to define acute or long-term CRT response.

The clinical/functional end points most often include changes in: (1) NYHA functional class; (2) quality-of-life score; (3) 6-min walk distance; (4) exercise capacity peak VO2; (5) heart failure hospitalizations; and (6) cardiac mortality [52–54].

The echocardiographic markers may include changes in: (1) left ventricular ejection fraction ≥ 15%; (2) reverse LV remodelling (LV end-systolic dimensions/volumes ≥ 15%); (3) degree of mitral regurgitation; (4) dp/dt; and (5) cardiac output [11, 25, 55].

Differences in the response rate can be attributed to the certain end point/marker selected (higher rates of functional response probably due to placebo effect), but also to the fact that clinical and echocardiographic response to CRT may not appear simultaneously at the same time. In fact, improvement of LV function appears to be a gradual process over time [56]. Unfortunately, there is lack of consensus for standard criteria that should be selected to define non-responders, and this may be one of the reasons of the variable rates of non-response reported in the literature. A number of other important factors though have also been described as possible reasons for non-response [57], such as: (**1**) The limitation of ECG-based selection criterion as opposed to echocardiographic-based mechanical Dyssynchrony; (**2**) Suboptimal location of the pacing lead, away from the site of the latest activation [28]; (**3**) The presence of scarring at the region of LV lead placement [41]; (**4**) Suboptimal A-V and/or V–V optimisation [47, 50]; (**5**) Unsuitable coronary venous system for appropriate

lead implantation; (**6**) Suboptimal medical therapy [58]; (**7**) Lead dislodgment; (**8**) Ischemic heart disease.

The role of myocardial contractile reserve by DSE

The role of dobutanine stress echocardiography (DSE) in patient selection for CRT has also been explored recently. A cutoff value of >7.5% increase in dobutamine-induced LVEF exhibited a sensitivity of 76% and a specificity of 86% to predict response after 6 months of CRT. In addition, contractile reserve in the region in the LV pacing lead was present only in responders (delta strain during low-dose dobutamine 6% ± 5% in responders [59]).

CRT in RBBB

Current guidelines do not discriminate LBBB from RBBB on the basis of long QRS. Furthermore, the evidence of RBBB represents an 'electrical' criterion with probably the same limitations as LBBB. Initial studies suggested that patients with RBBB may get a benefit from CRT but probably less than those with LBBB [52]. More recently, it has been demonstrated that in failing hearts, less mechanical dyssynchrony is induced by RBBB than LBBB, and the corresponding impact of CRT on the former is reduced, suggesting that right ventricular-only pacing may be equally as efficacious as biventricular CRT in hearts with pure right bundle branch conduction delay [60]. Finally, other studies again propose the 'mechanical' criterion for patient selection, dictating that among patients with RBBB, only those with LV intraventricular mechanical dyssynchrony are likely to benefit from CRT [61].

CRT in short QRS duration

CRT on patients with short QRS duration < 120 ms, remains one of the hot issues in the contemporary research and clinical arena. In this case the patient selection again is based on the controversial electrical criterion. As already mentioned, evidence suggests that patients with short QRS duration may have up to 30–50% incidence of intraventricular mechanical

Dyssynchrony [9, 62] and may benefit from CRT [63, 64]. However, the first randomised trial of CRT in patients with heart failure with narrow QRS complexes failed to show a therapeutic effect of CRT on the primary end point of peak myocardial oxygen consumption. A positive effect of CRT was observed though on the secondary end point of improvement in the NYHA functional class. In addition, subgroup analysis showed that particular patients, like those with non-ischemic disease and those with borderline QRS duration (120–130 ms), appeared to have a benefit from CRT on 6-min walk test and peak oxygen consumption, accordingly [65]. More studies are unquestionably needed to clarify the benefit of CRT on patients with short QRS duration and those are expected in the near future.

Dyssynchrony in less severe heart failure (EF > 35%)

The beneficial effect of CRT has been mainly shown in patients with severe heart failure (EF ≤ 35%) in the majority of studies. Recent evidence suggests that up to 55% of patients with less severe heart failure (EF 35–50%) may also demonstrate mechanical asynchrony based on time to peak systolic velocity (Ts) in a 12-segmental model (Ts-SD), denoting that the prevalence of mechanical systolic dyssynchrony is independent of the severity of LV systolic dysfunction [66]. This finding also underlines the potential role of cardiac resynchronization therapy for patients with moderate to mild systolic dysfunction, provided that mechanical Dyssynchrony is present. More evidence is expected from future studies.

CRT in AF

Atrial Fibrillation is common in patients with heart failure, with the prevalence of AF increasing in parallel with the severity of the disease [67]. Available data suggest that CRT is beneficial to patients with AF [68–70]; however the degree of response appears to be largely dependent on the implementation of A-V nodal ablation. As a result, CRT response has been reported to be 54% in patients with AF without nodal ablation, and 71% in those with ablation, compared to 80% in those with sinus

rhythm [71]. Furthermore, it has been shown that in patients with severe heart failure, improvement of LA function after CRT is associated with a lower incidence of AF and lower mortality [72].

The impact of CRT on longitudinal, circumferential and radial deformation and torsion

Recent findings based on 2D speckle tracking suggest that short-term improvement of global systolic function and LV reverse remodelling is primarily associated with improvement of the short-axis function (circumferential and radial strain), but not the long-axis function (longitudinal strain) or LV torsion. A favourable response was partially dependent on the relative preservation of the short-axis function, with a preserved baseline mean circumferential strain of >6.5% to be able to predict the gain in ejection fraction > 5% and LV reverse remodelling [73]. The role of radial function has also been demonstrated in another study, showing that differences in baseline LV dyssynchrony between responders and nonresponders were noted only for radial strain, whereas no differences were noted for circumferential and longitudinal strain [74]. With the advancements of 2D speckle tracking, more studies are expected to explore the role of the different components of LV function on CRT in the following years.

Ischemic versus non-ischemic cardiomyopathy

Several studies have demonstrated that CRT response is more likely in patients with non-ischemic than ischemic Cardiomyopathy [75, 76] probably due to a more heterogeneous pattern of asynchrony in the latter. However, other studies have found a comparable degree of response to CRT in those two entities [77, 78]. In a recent study, although it was found that left ventricular reverse remodelling, after CRT, occurred in similar degrees in both non-ischemic and ischemic groups, there was higher cardiovascular mortality in patients with ischemic Cardiomyopathy [79]. In another study [21], the number of segments with post-systolic shortening (PSS) appeared to be a good predictor for CRT response only in patients with

non-ischemic cardiomyopathy, but more interestingly, the predictive values of all the TDI parameters were consistently higher in the non-ischemic than the ischemic group.

For how long CRT?

This issue has not been addressed by many studies, but initial evidence suggests that despite the presence of LV reverse remodelling, interruption of CRT results in worsening of LV function and desynchronization. Therefore, continuous long-term pacing may be warranted to maintain the beneficial effects [80].

Current limitations and future perspectives

Modern echocardiography is a versatile imaging modality, but at the same time, suffers from its own limitations. As a result, those limitations may have a deleterious effect on the proposed parameters of mechanical dyssynchrony and may dominate their clinical applicability.

In particular, M-mode (motion mode) provides an excellent temporal resolution, but as the m-mode tracing represents only one anatomical dimension along a single axis established by the location of a stationary ultrasound beam, the magnitude of the spatial resolution is limited [81]. As a consequence, the proposed SPWMD index is applied only in limited areas from the SAX view, evaluating only radial motion. Furthermore, ambiguity in motion measurement, especially when there is an extensive scar formation, may also become a reason of failure in assessing dyssynchrony in certain patients.

Systolic velocities based on colour or spectral tissue Doppler imaging have been subsequently proposed to overcome the shortcomings of the limited spatial resolution of the m-mode and to provide an index of regional longitudinal dyssynchrony. Indexes such as those described above, assessing intraventricular dyssynchrony (2nd, 3rd, 4th and 6th), have been used with success in many single-centre studies. However, as velocities subdued to tethering effects and translational motion of adjacent regions, the interpretation of the mechanical properties of the heart may sometimes become uncertain. Specifically,

completely passive segments can show motion relative to the transducer due to tethering, but without any active mechanical deformation, consisting velocity and displacement information probably unreliable for the characterization of such regions [82]. In addition, all TDI data are amenable to angle dependency, and particularly for indexes based on colour tissue Doppler, high image quality is usually needed.

The theoretical advantage of deformation imaging based on TDI data, which calculates the spatial gradients in myocardial velocities and extracts regional deformation (strain) [83], gave birth to another promising index of intraventricular dyssynchrony (11th), in order to surpass the deficiencies of m-mode and velocity-based imaging. However, as the strain Doppler-derived technique is extremely vulnerable to incorporation of noise, reverberations, and artefacts, high variability consists a serious potential limitation, and contradictory publications have reduced the initial enthusiasm. For those reasons, operator experience is extremely important for calculating deformation indexes, and additional studies may be needed to clarify the value of Doppler-Strain in assessing myocardial dyssynchrony. Novel techniques based on 2D speckle tracking have also generated new intraventricular dyssynchrony indices (9th, 10th). The angle independence, the automated tracking algorithm, the lower variability, and the lesser incorporation of noise within the data, definitely give more confidence for what it is measured, however, reverberations and artefacts and more importantly the lower temporal resolution compared to TDI, remain significant shortcomings that need to be solved. Special equipment and operator experience are also significant considerations. 3D echocardiography—3D volumes, has also evolved as a promising method for the evaluation of LV dyssynchrony (8th). This modality also suffers from significant limitations, such as the low spatial and especially the low temporal resolution. Again, special equipment and operator experience are important matters.

There is also another issue that should be underlined at this point. The cut-off values published in the literature regarding the ability of certain indices to predict CRT response are in fact the optimal compromise to discriminate responders from nonresponders based on ROC analyses. For that reason, absolute devotion on the exact value for decision making is rather inappropriate and therapy should not be denied to all patients who do not fulfil precisely the described cut-offs. Furthermore, more than one index of dyssynchrony based on different echo-modality should probably be used in order to overcome the potential limitations of certain techniques and to increase the probability of accurately assessing the degree of myocardial asynchrony. As in reality, the motion of the heart is characterized by longitudinal, radial, and circumferential motion, a combination of indices also describing different spatially-oriented planes of motion will also provide a better insight into the mechanical synchronicity. Finally, in an attempt to overcome some limitations of the echo-based indices, complementary imaging modalities such as cardiac MRI, may also significantly contribute to the evaluation of myocardial dyssynchrony, as recent studies have shown [84].

Although single-centre trials have shown the benefit of evaluation of mechanical dyssynchrony in CRT, more prospective multicentre studies are definitely needed in order to verify the role of echo-based dyssynchrony indices in decision-making, and to prove that a certain combination of parameters is indeed able to discriminate responders from nonresponders. This is even more challenging because one of the first multicentre trials [85] failed to prove the need for echo-parameters of mechanical dyssynchrony, concluding that no single echocardiographic measure of dyssynchrony may be recommended to improve patient selection for CRT beyond current guidelines based on EF and QRS duration. It should be underlined though, that in the last study, a large variability in the analysis of the dyssynchrony parameters arising from technical and interpretative factors was regarded as an important reason for that failure. Certain facts should be taken into account in relation to echo-based indices of mechanical dyssynchrony, especially in a multicentre setting: (1) The quality of the measured tracings of the advanced echo parameters is probably not similar for different vendors; (2) All the indices have their own limitations based on the modality used, as mentioned before, and (3) The evolution of novel sophisticated echo parameters based on advanced technology may not have been accompanied by certified training and expertise in different centres. As a result, appropriate index selection, adequate training, and refinements in the technology of the ultrasound equipment appear to be the main challenges for the years to come.

Conclusion

From the current literature review it is clear that an overall approach of cardiac resynchronization therapy should be taken into consideration, focusing not only on electrical or mechanical dyssynchrony, but also on several other covariates that appear to contribute significantly to the outcome of that particular mode of treatment.

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