“State of the Art Review”
CARDIAC RESYNCHRONIZATION THERAPY – Present and Future

Francesca Pizzamiglio, MD; Claudio Tondo, MD PhD*

INTRODUCTION
Approximately 2% of the adult population in developed countries has heart failure (HF) and about 400 patients per million population per year might be suitable for cardiac resynchronization therapy (CRT). Reliable estimates of heart failure in developing countries are lacking because of the absence of surveillance program to track incidence, prevalence and outcomes of HF. Nevertheless, the incidence and prevalence rates of HF should be rising due to population, epidemiological and health transitions.

The prognosis of HF is generally poor and the one-year mortality ranges from 20% in those aged <75 years to >40% if aged >75 years. However, treatment has remarkably improved the prognosis of patients with chronic HF and large randomized trials have demonstrated that CRT improves quality of life and symptoms and reduces heart failure-related hospitalizations, as well as mortality. CRT is therefore considered a cost-effective treatment.

Current indications for CRT according to 2013 ESC Guidelines are outlined in Table 1.

Cardiac resynchronization therapy improves symptoms and cardiac function in patients with New York Heart Association (NYHA) class II-IV HF. CRT improves left ventricular (LV) function thanks to its ability to increase LV filling time and ejection fraction (LVEF), to decrease LV end-diastolic- (LVEDV) and end-systolic volumes (LVESV), and to reduce functional mitral regurgitation and septal dyskinesis. Unfortunately, not all patients receiving CRT benefit from therapy; up to 30-40% of patients are considered “non-responders” in clinical practice. Definition of “non-responder”, identification of non-response predictors and development of new strategies for the optimization of the response are strongly debated.

DEFINITION OF “NON-RESPONDER”
For the definition of “non-responder” there have been a number of criteria used in studies. Clinical response measures have included the changes in NYHA functional class, exercise capacity, and heart failure quality of life score. Cardiac response to CRT has been most commonly defined as an improvement of LVEF (at least 5% from baseline) or as the reverse remodeling of LV as reflected by reduction in the LVESV. Some studies attempted to use a combination of clinical and echocardiographic parameters and others performed acute invasive hemodynamic study. Apart from choosing an appropriate parameter to define CRT response, it is also crucial to choose a suitable time point of measurement. In function of the definition and time used, the non-responder rate varies significantly (Table 2). Left ventricle reverse remodeling is probably the single most important parameter to evaluate the response to CRT 20 but its measuring has a large inter-observer variability (14.5% in the Predictors of Response to CRT - PROSPECT study26). The evaluation of LV volumes by 3-dimensional echocardiography might reduce

*List of institutions:
Cardiac Arrhythmia Research Centre, Centro Cardiologico Monzino IRCCS, Milan, Italy
Address for correspondence:
Claudio Tondo, MD PhD, Cardiac Arrhythmia Research Centre Centro Cardiologico Monzino IRCCS Via Parea 4, 20138 Milan, Italy
Tel: 0039.02.58002340 Fax: 0039.02.58002398 E-mail: claudio.tondo@ccfm.it
Randomized Clinical Evaluation (MIRACLE) study reported a mean reduction of LVESV at 6 months of 8.3% in ischemic patients and of 24.6% in non-ischemic patients’ without significant changing at one-year follow-up.

Anyway we define in detail “responders” and “non-responders”, it is challenging to identify predictors of CRT response to select ideal patients and to develop optimization tools for non-responders.

**Table 1: Current Indications for CRT according to 2013 ESC Guidelines**

<table>
<thead>
<tr>
<th>Class of Recommendation</th>
<th>Clinical Scenario</th>
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<tbody>
<tr>
<td>I</td>
<td>Patients in sinus rhythm with LBBB, QRS duration &gt;150ms and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment. (Level A) Patients in sinus rhythm with LBBB, QRS duration 120-150ms and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment. (Level B) Patients with permanent AF, chronic HF, intrinsic QRS ≥120ms and LVEF ≤35% who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment, provided that a BIV pacing as close to 100% as possible can be achieved. (Level B) Patients with permanent AF, uncontrolled heart rate and who are candidates for AV junction ablation. (Level B) Patients in sinus rhythm without LBBB but with QRS duration 120-150ms and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment. (Level B) Patients in sinus rhythm with LBBB, QRS duration &gt;150ms and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment (upgrading from conventional PM or ICD). (Level B) Patients in sinus rhythm without LBBB but with QRS duration &gt;150ms and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment. (Level B) Patients in sinus rhythm with chronic HF with QRS duration &lt;120 ms.</td>
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<tr>
<td>II a.</td>
<td>Patients in sinus rhythm without LBBB but with QRS duration &gt;150ms and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment. (Level B) Patients with permanent AF, chronic HF, intrinsic QRS ≥120ms and LVEF ≤35% who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment, provided that a BIV pacing as close to 100% as possible can be achieved. (Level B) Patients with permanent AF, uncontrolled heart rate and who are candidates for AV junction ablation. (Level B) Patients with conventional pacemaker or ICD indication, HF, reduced LVEF and expected high percentage of ventricular pacing (de novo CRT). (Level B) Patients in sinus rhythm with chronic HF with QRS duration &lt;120 ms.</td>
</tr>
<tr>
<td>II b.</td>
<td>Patients in sinus rhythm with chronic HF with QRS duration ≥120ms and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment. (Level B)</td>
</tr>
<tr>
<td>III</td>
<td>Patients in sinus rhythm with chronic HF with QRS duration &lt;120 ms.</td>
</tr>
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</table>

Class I: is recommended/indicated. Class IIa: should be considered. Class IIb: may be considered. Class III: is not recommended.

Level of evidence A: data derived from multiple randomized clinical trials or meta-analyses. Level of evidence B: Data derived from a single randomized clinical trial or large non-randomized studies. Level of evidence C: consensus opinion of the experts and/or small studies, retrospective studies, registries.

LBBB, left bundle branch block. LVEF, left ventricular ejection fraction. ICD, implantable cardiac defibrillator. PM, pace-maker. AF, atrial fibrillation. HF, heart failure. BIV, biventricular. AV, atrioventricular.


**Table 2: Recent trials reporting 'non-responder' definition and rate:**

<table>
<thead>
<tr>
<th>References</th>
<th>Patients No.</th>
<th>Parameters of response</th>
<th>Follow-up time</th>
<th>Non response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein et al.</td>
<td>1820</td>
<td>≥ 30 % reduction in LVESV</td>
<td>1 year</td>
<td>42%</td>
</tr>
<tr>
<td>Hoogslag et al.</td>
<td>170</td>
<td>Improvement by ≥ 1 NYHA classes, ≥ 15 % reduction in LVESV, ≥ 15 % decrease in NT pro BNP</td>
<td>6 months</td>
<td>34% 42% 46%</td>
</tr>
<tr>
<td>Delnoy et al.</td>
<td>199</td>
<td>Improvement by ≥ 1 NYHA classes or ≥ 10 % increase in EuroQol - Visual Analogue Scale score</td>
<td>6 months</td>
<td>39%</td>
</tr>
<tr>
<td>Khan et al.</td>
<td>220</td>
<td>≥ 15 % reduction in LVESV, improvement by ≥ 1 NYHA classes</td>
<td>6 months</td>
<td>30% 17%</td>
</tr>
<tr>
<td>Ritter et al.</td>
<td>238</td>
<td>Free from death or hospitalization and improvement by ≥ 1 NYHA classes or ≥ 10 % decrease in QOL score</td>
<td>1 year</td>
<td>37%</td>
</tr>
<tr>
<td>Gold et al.</td>
<td>426</td>
<td>≥ 15 % reduction in LVESV, &gt; 10 points decrease in QOL score</td>
<td>6 months</td>
<td>32% 28%</td>
</tr>
<tr>
<td>Khan et al.</td>
<td>131</td>
<td>≥ 15 % reduction in LVESV</td>
<td>6 months</td>
<td>42%</td>
</tr>
<tr>
<td>Leyva et al.</td>
<td>322</td>
<td>Improvement by ≥ 1 NYHA classes or ≥ 25 % increase in 6 MWT</td>
<td>1 year</td>
<td>22%</td>
</tr>
<tr>
<td>Muto et al.</td>
<td>231</td>
<td>≥ 10 % reduction in LVESV</td>
<td>6 months</td>
<td>26%</td>
</tr>
<tr>
<td>Boriani et al.</td>
<td>176</td>
<td>NYHA functional change and ≥ 5 mm decrease in LVESD or improvement in heart failure composite score or ≥ 10% decrease in LVESV</td>
<td>6 months</td>
<td>24%</td>
</tr>
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</table>

PREDICTORS OF “NON-RESPONSE”

In the MADIT - CRT trial, Goldenberg et al. reported seven predictors of echocardiographic CRT response (defined as percent reduction in LVEDV after 1 year of CRT): female sex, non-ischemic origin, LBBB, QRS > 150 ms, prior hospitalization for HF, LVEDV > 125 ml/m², and left atrium volume < 40 ml/m². The study proposed a score based on these seven factors, with a risk reduction of HF or death with CRT of up to 69% for the upper (>9 points) quartiles.

Since then, a big amount of studies have been published re-examining these predictors, substantially confirming the same findings but without really succeeding in predicting response to CRT. For this reason, in the last two years the literature focused on new pre-implant (ECG parameters, biomarkers, hemodynamic features, and combined scores) and at-implant predictors with the aim of better identifying CRT responders.

ECG parameters

Starting from the point that about 30% of patients with LBBB do not benefit from CRT, other ECG parameters have been evaluated to better identify patients who are most likely to benefit from CRT. Considering simple parameters of the basal ECG, Lee et al. showed that the presence of a normal PR interval was associated with a greater improvement in HF than the one observed in patients with first-degree atrioventricular block. These findings are in agreement with the post-hoc analysis of the CARE-HF study, showing that patients with prolonged PR interval had less improvement from CRT. In fact, a prolonged PR interval results in delayed and ineffective mitral valve closure, diastolic mitral regurgitation, and impaired hemodynamics.

Mollo et al. proposed the basal interval between the peak of R wave and the peak of S wave in lead V1 (RS-V1) as a predictor of good response. They studied 51 patients with classical indication to CRT, considering a good response when LVEF increased by ≥ 5% and NYHA class by ≥ 1 after 3 months of CRT. Among all the intervals measured with the amplified surface ECG (total QRS duration, QRS onset-R wave peak, R wave peak-S wave peak in V1 and V6, S wave peak-QRS end, and difference between QR in V6 and V1), only the basal interval RS-V1 was longer (≥ 45 ms) in responders compared with non-responders. The basal RS-V1 interval can quite reliably indicate the presence of LV dyssynchrony because R wave peak in lead V1 indicates when LV electrical activation mainly concerns the anterior wall, whereas S wave peak indicates the activation of the postero-lateral wall. Accordingly, a reduction of RS-V1 by at least 10 ms by CRT predicted a favorable clinical response to treatment.

Finally, considering the well-known duration of QRS, Sassone et al. confirmed that QRS duration is correlated with the response to CRT but showed for the first time that a basal extreme QRS widening (≥ 178 ms) was an independent predictor of non-responsiveness to CRT together with an ischemic cause. Although it was a retrospective study, it may explain at least in a measure why a non-negligible percentage of patients with LBBB receiving CRT are non-responders. Because the QRS morphology and duration represent electrical markers of the presence and extension of mechanical dyssynchrony, a basal extreme QRS widening may be expression of a severe LV dysynchrony not amenable of resynchronization or of the presence of a more extensive anatomic substrate alteration (i.e., large amount of LV fibrosis) responsible for less favorable outcome with CRT. These findings suggest that there could be a “U-shaped” distribution for the interaction between QRS duration and CRT responsiveness and that under and above the optimal values there are non-responders.

On the other hand, some authors have studied vectorcardiograms on digitized ECG and found that a larger baseline T-wave, a QRS frequency below 10 Hz, and a wider area of the QRS complex were correlated to CRT response. Vectorcardiogram is not widely used but it is a non-invasive technique that can be easily applied in daily clinical practice and that could help in identifying appropriate candidates for CRT, potentially preventing ineffective CRT device implantation.

Biomarkers

Cardiac resynchronization therapy has been associated with favorable changes in circulating levels of neurohormones and inflammatory cytokines in HF patients. The two most commonly examined neurohormones in relation to HF are B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) that are secreted by cardiomyocytes when the load on any chambers is increased. Evidence suggests a strong link between the endocrine function of the heart and the immune system. Many studies have shown that CRT induces a significant decrease in BNP but the evidence on inflammatory markers like C-reactive protein (CRP), IL-6, TNFα and soluble TNF receptors 1 and 2 (sTNFr1, sTNFr2) is inconclusive and it is not clear whether changes in the plasma levels of BNP and inflammatory markers are associated with response to CRT.

Last year Brouwers et al. re-investigated the levels of BNP and markers of inflammation in relation to CRT response and they found that echocardiographic and patient-reported CRT response was associated with lower levels of BNP and TNFα but not with other markers of inflammation. Also Rordorf et al. confirmed that circulating TNFα...
predicts the degree of LV reverse remodeling after CRT\textsuperscript{35}. By stratification of the patient cohort according to tertiles of baseline TNF\textalpha{} level, they found that patients with higher levels of TNF\textalpha{} were less likely to respond to CRT and presented a worse outcome in terms of cardiac events.

Besides BNP and inflammation markers, other authors investigated hyponatremia as a predictor for adverse events in patients receiving CRT\textsuperscript{36}. In their retrospective analysis they found that patients with post-implantation hyponatremia (either newly developed or persistent from baseline) have a poor clinical outcome and that post-CRT improvement of hyponatremia is associated with improved clinical outcomes. The neurohormonal activation observed in HF (activation of renin-angiotensin-aldosterone system, arginine vasopressin release, and upregulation of sympathetic nervous system) leads to impairment of free water excretion and contributes to the development of hyponatremia. Additionally, patients with HF receive diuretics, which may cause loss of sodium in urine and further decrease in serum sodium level. Hyponatremia is therefore a reflection of worsening HF and the improvement of hyponatremia post-CRT could be the effect of improving HF as a consequence of reversal neurohormonal changes, improvement in renal perfusion, and decrease in daily dose of diuretics. These findings come from a single-center retrospective analysis of a prospectively acquired cohort and they are therefore subject to limitations, but they could suggest that simple conventional chemistry may have added value.

As opposed to the simplicity of hyponatremia, Stolten et al. demonstrated that elevated levels of the complex biomarker galectin-3 is an independent predictor of adverse HF outcomes and that the highest galectin-3 levels are associated with a disproportionately larger benefit from CRT\textsuperscript{37} being in agreement with previous studies that investigated collagen synthesis serum markers and CRT response\textsuperscript{41,42}. Galectin-3 is a soluble beta-galactoside-binding lectin that has regulatory roles in fibrogenesis, inflammation, and tissue repair. The observation of elevated baseline levels of galectin-3 among a subset of MADIT-CRT HF subjects is consistent with the concept of persistent myofibroblast activation and proliferation that play a detrimental role in pathologic fibrosis, resulting in maladaptive cardiac remodeling, myocardial stiffness, and worsening HF. Accordingly, Marfella et al. had previously demonstrated that reverse remodeling was associated with favorable changes in microRNAs that regulate cardiac fibrosis, apoptosis, and hypertrophy\textsuperscript{43}.

While studying serum biomarkers, the BIOCRT Study investigators suggested that direct coronary sinus sampling of HF biomarkers (NT-proBNP, galectin-3, and soluble ST2) may be better than peripheral venous sampling for predicting CRT outcomes\textsuperscript{3}. In fact, they found that HF biomarkers concentrations were significantly higher in the coronary sinus than in the periphery.

All these findings may establish the basis for future genetic - based or device - based therapies for HF, thus bringing new hopes to CRT non-responders\textsuperscript{35}.

**Hemodynamic features**

Pulmonary artery hypertension is correlated with poor clinical prognosis in patients with chronic HF but there are few data concerning the impact of baseline pulmonary artery systolic pressure (PASP) on clinical outcome after CRT. Wang et al. re-evaluated the association of baseline PASP with CRT response and showed that patients with elevated PASP (>45mmHg) derive less benefit from CRT and that relatively lower PASP is predictive of better response after 6 months of CRT\textsuperscript{38,39}. Increased PASP may lead to increasing RV filling pressure and RV insufficiency. Since reversal of LV dyssynchrony through coordination of myocardial contraction is the primary aim of CRT, it may not be able to improve RV dysfunction secondary to longstanding pulmonary artery hypertension. Once pulmonary artery pressure comes to a certain level, its detrimental impact is irreversible despite CRT and adequate medications. PASP may therefore serve as a surrogate marker for severe HF, reflecting a decompensated state non responsive to CRT. CRT should be performed without delay for patients satisfying standard indications, especially before the occurrence of moderate to severe pulmonary artery hypertension.

As it is known, increased PASP may be due either to elevated left atrial pressure or to high pulmonary vascular resistance. For this reason, it has been evaluated the prognostic significance of pre- and post-capillary components of pulmonary hypertension in patients receiving CRT. Chatterjee et al. studied a population of 101 patients who underwent right heart catheterization in the 6 months before CRT and evaluated the impact of pulmonary hypertension subtype on clinical outcome. They showed that patients with the presence of a significant pre-capillary contribution to pulmonary hypertension (transpulmonary gradient >12mmHg) and baseline RV dilatation (RV end-diastolic dimension >42mm) were associated with significantly worse clinical outcome after CRT\textsuperscript{40,41}. In contrast, there was no significant difference in clinical outcome between patients without pulmonary hypertension and patients with pulmonary hypertension but normal transpulmonary gradient. Given the high prevalence of pulmonary hypertension in the CRT referral population(36% to 78%, with prevalence increasing
with severity of HF stage, this study suggests that an invasive right heart catheterization may be of value in the evaluation of patients eligible to CRT.

**Combined scores**

Given the fact that no single parameter can predict CRT response per se, many efforts have been made to find a combination of parameters able to predict such response.

In the wake of the score proposed by the MADIT-CRT trial, Yanagisawa et al. proposed a combination of consistent RV pacing, lack of prior history of ventricular arrhythmia, and smaller left atrial diameter as good predictors of greater response to biventricular pacing. Kang et al. found that the integration of TAPSE, longitudinal strain and complete LBBB can help to predict positive response to CRT51. Furthermore, Friedman et al. showed that aldosterone antagonist use, prior valve surgery, and QRS duration are multivariable predictors of progressive ventricular dysfunction after CRT implantation52.

With the aim of simplifying the evaluation of patients, some scores have been proposed. The LAnDS, scoring system considers LBBB (2 points), Age >70 years, Nonischemic origin, left ventricular end-diastolic Diameter <40mm/m2, and Septal flash (early septal thickening/thinning within the isovolumetric contraction period followed by the septal rebound stretch, 2 points). A score >5 had a high positive likelihood ratio, whereas a score <2 had a high negative likelihood ratio to have a good response after CRT.

The Simplified-SSc (Simplified-SSc, Table 3) was validated in 2013 by Wieslander et al. for the identification and quantification of myocardial scar, but it was not investigated its clinical utility to screen CRT candidates. Recently, Bani et al. evaluated for the first time the prognostic impact of this ECG score in predicting echocardiographic response to CRT at 6-month follow-up. They retrospectively evaluated 172 HF patients with true-LBBB who underwent CRT and they found that the Simplified-SSc was inversely correlated with response to CRT. The presence of myocardial scar is frequently observed in patients with symptomatic HF (either ischemic or not ischemic) and it is associated with poor response to CRT. The extent of myocardial scar is accurately detected by MRI, but in clinical practice the extensive use of cardiac MRI could present some limitations due to its costs, to the clinical expertise required, and to patient-related conditions (high burden of premature ventricular complexes, previously implanted paramagnetic devices, claustrophobia, etc.). By contrast, 12-lead ECG is feasible in every candidate for CRT and the Simplified-SSc may help in screening patients before implantation.

Besides evaluating predictors of a good response to CRT, Khatib et al. proposed the EAARN score as a predictive score for mortality in patients receiving CRT. Prospectively analyzing 608 patients treated with CRT, they found that Ejection fraction, Age, Atrial fibrillation, Renal dysfunction, and NYHA class IV (1 point each) have a significant add-on predictive effect on mortality and could be useful to stratify the prognosis of CRT patients. EAARN score can reliably identify a subgroup of patients with excellent prognosis and low mortality (EAARN 0-1) and a subgroup of patients with high mortality and poor prognosis (EAARN ≥3) in whom the benefit from CRT would be small. Patients with ≥3 risk factors may possibly have reached a point of no return, and CRT came too late to reverse such an advanced phase. Nevertheless, the score does not evaluate any potential and transient beneficial effect that may have occurred.

Finally, questions have been raised with regard to the benefit of CRT in function of race/ethnicity. Data from the IMPROVE HF were analysed without observing any significant interaction by racial/ethnic group and CRT should therefore be offered to eligible HF patients without modification based on race/ethnicity.

**Predictors at implant**

Among potential determinants of CRT response, LV lead position away from myocardial areas with substantial scar has been shown to play an important role in predicting long-term outcome. A high ventricular pacing threshold (PT) may be in some cases a manifestation of myocardial scar or simply of a more diseased myocardium. Patients with high LVPT are also at a greater risk of further increase in PT and lead dislodgment, resulting in suboptimal LV pacing. Pires et al. hypothesized that high LVPT would be associated with reduced echocardiographic and clinical response to CRT. They performed a multivariate regression analysis of the 975 patients enrolled in the CRT-D arm of the MADIT-CRT trial and they evaluated the relationship between LVPT and per cent reduction in LVEF and left atrial volume. An increasing LVPT was inversely related to per cent reduction of both.

**OPTIMIZATION OF CRT**

Optimization of CRT aims to achieve biventricular pacing as much as possible (ideally 100%), and to reduce the rate of non-responder. Placement of the LV lead to the latest site of contraction and away from the scar confers the best response to CRT, as it was already shown in the TARGET trial. In this trial, patients were randomized 1:1 to standard unguided CRT and to positioning of the LV lead at the latest site of peak contraction (TARGET group). In the TARGET group, there were a greater proportion of responders at 6 months. More recently, results from the STARTER
study (echo-guided transvenous LV lead placement vs conventional fluoroscopy approach) confirmed the superiority of the echocardiography-guided approach in terms of HF outcomes and of patient survival rate free from appropriate CRT-D therapy for ventricular arrhythmias during long-term follow-up. Since then, different imaging techniques (echocardiography, MRI, SPECT, stress echocardiography, CT and electroanatomic mapping) have been studied for the identification of the optimal site for LV lead placement.

Beyond LV lead position, optimal device programming is required to eliminate the atrioventricular (AV) and interventricular (VV) dyssynchrony. Echocardiography based methods and device-integrated methods have been studied. Furthermore, the recently proposed quadrripolar LV catheter, with two additional electrodes proximal to conventional bipolar lead electrodes seems to be of added value for the optimization and effective in improving CRT response. Finally, some authors suggested that the true multisite pacing method with a second LV lead placed in a second branch of the CS might be helpful in some cases.

**LV lead position: Echocardiography**

Echocardiography is the most used imaging technique for the identification of the latest site of contraction and of the presence and site of scars. Different standard echocardiographic parameters of global and segmental mechanical dyssynchrony have been proposed but they did not have enough predictive value. In the setting of segmental markers of dyssynchrony, radial dyssynchrony (time difference between peak shortening of septal and posterior walls) is achievable in most patients, but it could be difficult to have the optimum alignment of the M-mode cursor perpendicular to the posterior wall and the septum without interference from the basal septal segment. Furthermore, it is not easy to identify peak septal-posterior wall systolic time delay in patients with prior infarction and in patients with prolonged inward motion. Accuracy of this method remains therefore controversial in its routine application.

In view of the limitations of segmental LV dyssynchrony assessment, global LV dyssynchrony based on the analysis of the early systolic and early diastolic dyssynchrony has been proposed. The total isovolumic time (isovolumic contraction + isovolumic relaxation) seems to be the better standard echocardiographic predictor of clinical response to CRT, with a value of 15 s/min predicting good clinical response.

Tissue Doppler imaging (TDI) by pulsed-wave Doppler allows the assessment of longitudinal myocardial tissue velocity relative to the ultrasound transducer and has been widely evaluated. Indexes of dyssynchrony may be generated from differences in the peak velocity, time to peak systolic velocity, or time to onset of peak systolic velocity of the LV wall as assessed in either single or multiple views. Results of pulsed-wave TDI are controversial. Color-coded TDI and color tissue synchronization imaging provide expansion over pulsed-wave Doppler and seem to be associated with improved LVEF and reverse remodeling. In contrast of standard echocardiographic parameters, two-dimensional (2D) speckle-tracking strain proved to be a good predictor of response to CRT and an independent prognostic marker for cardiovascular events in HF patients regardless of LV global function. Recent studies confirmed its role in avoiding scar zones and predicting outcomes.

**LV lead position: MRI**

Echocardiography has inherent limitations such as sub-optimal image quality and reproducibility. Additionally, analysis methods based on echo Doppler largely look at 2D motion and this may over-simplify the complex mechanisms involved in myocardial contraction. Speckle-tracking techniques have been advocated as better methods but multi-center settings are lacking. Cardiovascular magnetic resonance can measure dyssynchrony through cine and tagged images, looking at volume change, myocardial thickening and strain and can reliably predict echocardiographic response to CRT. Last year, Sohal et al prospectively evaluated the systolic dyssynchrony index (SDI) as a predictor of response. It was defined as the standard deviation (SD) of the regional time to peak volume change, maximum muscle thickness or peak strain and it was expressed as a percentage of the cardiac cycle. They found that a SDI derived from volume change is a highly reproducible measurement that can be derived from routinely acquired cine images and that successfully predicts response to CRT. MRI is an expensive technology and it is still resource demanding, but its association with speckle-tracking radial strain can help in successfully avoiding pacing at transmural scar, especially in ischemic patients. Whether this approach can increase responders to CRT has to be investigated.

**LV lead position: SPECT**

In nuclear cardiology, 99mTc-labelled agents are widely used as myocardial perfusion imaging tracers for detecting coronary artery disease. Patients with severe resting perfusion defects have been reported not to show a positive clinical response to CRT or an objective improvement in LV volume and function.
In addition, the washout of the agent is believed to be related to the impaired mitochondrial function that coexists with myocardial damage. Shigeru et al. evaluated for the first time if the myocardial washout of $^{99m}$Tc-tetrofosmin ($^{99m}$Tc-TF) could be useful for predicting the response to CRT. They observed a significant difference between responders and non-responders for both early and delayed total defect score and washout score. Evaluation of the washout of $^{99m}$Tc-TF in addition to myocardial perfusion before CRT might therefore be useful before CRT.

Gated myocardial perfusion single photon emission computed tomography (GMPS) has been proposed for LV dyssynchrony assessment originally using phase analysis. This is a count-based method that extracts the phase from the regional LV count changes during the cardiac cycle. Phase information is related to the onset of mechanical contraction in the 3D myocardial wall and therefore provides information on the synchrony of LV contraction. In a normal heart, LV contraction is homogeneous and phase distribution is nearly uniform with a highly peaked distribution. With increasing LV dyssynchrony, phase standard deviation is expected to increase. The optimal software program for this analysis and the optimal cut-off values are still to be determined but GMPS may prove useful in the guidance of LV positioning, specifically to avoid placement of the LV lead in area of transmural scar tissue. Beside this traditional approach, SPECT myocardial perfusion imaging (MPI) and SPECT radionuclide angiography (RNA) have been the focus of recent research and development.

SPECT imaging procedures are relatively inexpensive, widely available, and highly reproducible and may be an ideal imaging modality for assessing cardiac wall motion.

**LV lead position: stress echocardiography**

Myocardial contractile reserve reflects the ability of LV wall segments that are dysfunctional in the basal state to exhibit increased contractility in response to an inotropic agent or exercise. This is related to the presence of viable myocardium. Murin et al. hypothesized that global myocardial contractile reserve determined using echocardiography during high-dose dobutamine infusion would predict LV reverse remodeling and improvement in LV function in patients indicated to CRT. They evaluated 52 consecutive patients performing stress echocardiography before CRT and they found that myocardial contractile reserve assessed with this technique can play a potentially important role in identifying responders to CRT.

**LV lead position: CT**

One of the problems of CRT is the significant anatomical variability of the coronary venous system. Inability to deliver CRT due to failure to cannulate CS or cardiac veins is about 10%. Previsualization of the coronary venous system before CRT implantation might help identify some anatomical aspects, such as the variability of CS ostium including its size and angle of entrance, the number of target coronary veins, the presence of the Thebesian of Vaeussens valves, presence of vein of Marshall, and luminal narrowing due to a crossing artery. Currently, the most common technique used to evaluate the coronary venous system is retrograde venography, obtained invasively by direct manual contrast injection. Pre-procedural three-dimensional imaging techniques such as CT may be of added value in decreasing procedural time, utilization of contrast, and fluoroscopy. Current ESC guidelines do not recommend its routinely use, but pre-procedural CT visualization of the coronary venous system may be considered in certain patients, such as patients with congenital heart disease.

**LV lead position: electroanatomic mapping**

Electroanatomic mapping systems (EAM) are widely used during electrophysiology procedures but since now they have not been applied for the evaluation of the latest site of LV activation in the context of CRT implants. In 2012 Del Greco evaluated for the first time the feasibility of a biventricular CRT-D implantation using an EAM. They performed four implantation using the EnSite NavX system and found that the use of an EAM seems to be feasible and safe, providing more detailed information and accuracy during the CS lead placement. Furthermore, the EAM was really beneficial in terms of reduction in X-ray exposure. Recently, Rad et al. re-investigated the feasibility of coronary venous EAM to guide LV lead placement in 25 consecutive patients and confirmed that coronary venous EAM contributes to the optimization of LV lead electrical delay in patients with multiple target veins. In the setting of CRT optimization and considering that conventional anatomical and imaging-guided LV lead placement strategy does not always target the vein with maximal electrical delay, the use of EAM may be taken into account trying to reduce CRT non-responders due to sub-optimal LV lead placement and X-ray exposure to patients and medical staff.

**Optimal device programming**

The optimal CRT programming is crucial in the post implantation period in order to achieve the maximum percentage of biventricular pacing. Optimization of both AV and VV timing intervals has been suggested as potential methods to improve response rates and it is recommended by current guidelines, especially in patients with ischemic heart disease or in need of atrial pacing. Echocardiography-based and device-based methods have been proposed to optimize the AV and VV delays.

The goal of AV optimization is to ensure that LV contraction does not occur before complete filling.
whereas the goal of VV optimization is to minimize LV mechanical dyssynchrony. AV optimization is achieved measuring the interval between QRS onset and closure of mitral valve with short and long AV intervals. The optimal AV delay is calculated as the longest AV delay less the difference of the time intervals of the QRS onset to mitral valve closure at short and long AV intervals. With too short AV delays the Doppler A wave is truncated, while with too long AV delays there is fusion of the E with A waves and mitral valve regurgitation.

Atrioventricular optimization is also performed with the estimation of the maximal stroke volume by measuring the velocity-time integral (VTI) of the aortic flow, or of the E and A waves with multiple AV intervals. Finally, 3D echocardiography has been proposed for CRT optimization evaluating LVEF, stroke volume and myocardial performance index.

Concerning VV optimization, the most commonly used method is to calculate the maximal aortic VTI, which is considered to be a representative index of stroke volume.

Unfortunately, results from the studies are controversial and at the moment there is no ideal echocardiographic method of AV and VV optimization. The most important issue is probably the extremely wide inter- and intra-operator variability when shown identical sets of Doppler traces. Automatic CRT optimization algorithms based on intracardiac electrograms (IEGMs) have been developed to calculate the optimal AV and VV delays in substitution or in addition to echocardiographic parameters (e.g. Smart AV Delay by Boston Scientific Corporation, Minneapolis, MN, USA; QuickOpt™ by St. Jude Medical, St. Paul, MN, USA; AdaptiveCRT™ by Medtronic, Minneapolis, MN, USA; and SonR® by Sorin CRM SAS, Clamart, France). However, even though all these algorithms are operator-independent, no clear difference between automatic echocardiographic algorithms and echocardiographic CRT optimization has been found in most big randomized trials. Only in the CLEAR study the algorithm-based optimization seemed to be superior to echocardiography-based optimization in terms of NYHA class after 1 year of follow-up. The ongoing RESPOND CRT Trial will evaluate the effectiveness and safety of the SonR® optimization system in patients with HF NYHA class III or ambulatory IV and it may provide new perspectives in the field of CRT optimization. Finally, last year, Choudhuri et al. proposed a new approach for the optimization of CRT. They evaluated the feasibility of determining the optimal AV interval during low-intensity, steady-state cardiopulmonary exercise testing and they found that it was feasible and more physiologic than resting techniques.

Further investigation is required to evaluate whether the cardiopulmonary exercise testing-based AV interval optimization can improve outcomes and quality of life in CRT patients.

**Multisite pacing**

Multisite pacing (MSP) has been developed in an effort to improve CRT response. MSP can be achieved using multiple leads or multipolar single lead.

Two different pacing modalities have been proposed using multiple leads: two RV leads plus one LV lead, and one RV lead plus two LV leads inserted in two different tributaries of the CS. Bifocal RV pacing (one lead positioned at the apex and one lead in the right ventricle outflow tract) has been evaluated by Yoshida et al., showing that LV dP/dtmax and cardiac output were significantly improved compared with standard biventricular pacing. Triple-site pacing was associated with an acute reduction in LVESV and increase in LVEF, but this configuration has to be evaluated chronically in a prospective randomized trial. Pappone et al. demonstrated a significant improvement in LV dP/dtmax, pulse pressure, and LV end-diastolic pressure with dual-site LV pacing and some other authors confirmed, at least partially, his findings. However, other authors did not find the same benefits from LV dual-pacing. Although attractive, dual-vein MSP is hindered by several technical issues, above all longer duration of the procedure and more fluoroscopic exposure.

The alternative approach to deliver MSP avoiding pitfalls of multiple leads is using quadrilobar leads that offer more pacing configurations, alleviating the problem of high threshold and avoiding or at least minimizing phrenic nerve stimulation. Whether multipolar pacing can improve CRT response is not yet established. Some data on acute response of quadrilobar pacing are available and first midterm follow-up data have been published. Nevertheless, it seems a cost-effective technology from preliminary analysis.

The use of multipolar electrodes to allow MSP may be associated with less complications and down sides in comparison with multiple leads pacing, but further investigation is needed.

**PATIENTS IN ATRIAL FIBRILLATION**

Atrial fibrillation is present in about 20% of patients receiving CRT but most of the studies excluded these patients, no big randomized trials have been published since now, and the benefit of CRT in this subset of patients remains therefore controversial. The only prospective and randomized trial truly dedicated to patients with permanent AF and severe HF is the MUSTIC AF trial. It resulted neutral in the intention-to-treat analysis, while the
per-protocol analysis including only patients with a biventricular pacing rate >85% showed a slight but significant improvement in functional status at 6-month and 1-year follow-up. The small PAVE, OPSITE, AVAL CLS/CRT116 and APAF trials showed that CRT exerted a modest but significant effect on quality of life, NYHA class and LVEF, as compared with RV pacing, in patients with AF and AV node ablation and various degrees of LV function. Despite the weak evidence due to lack of large randomized trials, the 2013 ESC Guidelines recommend CRT should be considered in chronic HF patients with wide QRS and reduced LVEF or with uncontrolled heart rate who are candidates for AV junction ablation (class of recommendation IIa, level of evidence B).

In 2013 Gasparini et al. published the results of the big CERTIFY study, showing that long-term survival after CRT among patients with AF and AV junction ablation is similar to that observed among patients in sinus rhythm, while mortality is higher for AF patients treated with rate-slowing drugs. The CERTIFY study was a prospective, multi center, international, longitudinal, observational study and large randomized trials are therefore still needed. In absence of randomized trials, in 2014 two meta-analysis have been published, concluding that patients with AF benefit from CRT, although less than patients in sinus rhythm, and that AV nodal ablation is associated with a reduction in all-cause and cardiovascular mortality and non-response rate.

### BIVENTRICULAR PACING IN PACEMAKER-INDUCED CARDIOMYOPATHY

Right ventricular pacing produces long-term deleterious effects on LV because of geometry alteration, increase of left atrium and LV dimensions, and worsening of mitral regurgitation. As a consequence, it has been evaluated the potential role of biventricular pacing in preventing and treating the so-called “pacemaker-induced cardiomyopathy”. Despite the lack of large randomized trials, according to 2013 ESC Guidelines, upgrade from conventional pacemaker or implantable defibrillator is indicated in HF patients with LVEF <35% and high percentage of ventricular pacing who remain in NYHA class III and ambulatory IV despite adequate medical treatment (class of recommendation I, level of evidence B). Concerning de novo CRT implantation, CRT should be considered in HF patients with reduced EF and expected high percentage of ventricular pacing in order to decrease the risk of worsening HF (class of recommendation IIa, level of evidence B), always weighing the added complication rate and cost of CRT devices and their shorter service life. The strongest evidence in favor of biventricular pacing in this subset of patients comes from the BLOCK-HF study121. It enrolled 691 patients with AV block, NYHA class I and II HF, and LVEF of 50% or less. All patients underwent a CRT implant and were afterwards randomized to RV pacing or biventricular pacing. The study showed that biventricular pacing was superior to conventional RV pacing in patients with AV block and LV systolic dysfunction. Due to the fact that all patients were implanted with a biventricular device, no information about potential differences in complication rate between conventional and biventricular pacing are available. Results from the ongoing BIOPACE trial27 are strongly expected.

Table 3: Simplified – Selvester Scoring System (Simplified – SSc)

<table>
<thead>
<tr>
<th>Scarlocation</th>
<th>Lead</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antero - superior wall</td>
<td>I</td>
<td>R/S ≤ 1.5</td>
</tr>
<tr>
<td></td>
<td>aVL</td>
<td>Q ≥ 50 ms</td>
</tr>
<tr>
<td>Inferior wall</td>
<td>II</td>
<td>R/S ≤ 1.0</td>
</tr>
<tr>
<td></td>
<td>aVF</td>
<td>Q ≥ 30 ms</td>
</tr>
<tr>
<td>Antero - septal wall</td>
<td>V1</td>
<td>R ≥ 20 ms</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>Notch in the initial 40 ms of the QRS complex</td>
</tr>
<tr>
<td>Postero - lateral wall</td>
<td>V2</td>
<td>S/S ≥ 1.5</td>
</tr>
<tr>
<td>Apical segments</td>
<td>I</td>
<td>R/S ≤ 1.0</td>
</tr>
<tr>
<td></td>
<td>V5</td>
<td>Any Q</td>
</tr>
<tr>
<td></td>
<td>V6</td>
<td>R/S ≤ 2.0</td>
</tr>
</tbody>
</table>
CONCLUSION

Cardiac resynchronization therapy is an effective treatment for HF patients and is therefore strongly recommended in patients not sufficiently responding to medical therapy. However, implantation rates are still sub optimal and there is a non-negligible percentage of non-responders. Further efforts are therefore warranted to better identify predictors of response and to optimize implantation. Big randomized trials are warranted to clarify the role of CRT in patients with atrial fibrillation and for the prevention and treatment of pacemaker-induced cardiomyopathy.

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Review articles