Imaging to improve the results of cardiac resynchronization therapy

Novel imaging tools have the potential to increase the proportion of responders to cardiac resynchronization therapy (CRT). Echocardiographic techniques, especially those based on tissue Doppler, may help to assess and quantify mechanical dyssynchrony and thus enable better selection of candidates for CRT. However, available echocardiographic techniques do not appear to be ready for routine practice, because of high intraobserver and interobserver variability (as demonstrated in the PROSPECT trial). Other methods to evaluate mechanical dyssynchrony include MRI and/or nuclear imaging, and both strategies are being intensively studied. Assessment of venous anatomy using computed tomography angiography, rotational angiography and/or MRI may help to improve implant rates and increase skills of the implanters, especially when integrated with online fluoroscopy. Some of the aforementioned techniques may also help to optimize left ventricular lead positioning. Evaluation of myocardial scars using MRI and/or single-photon emission computed tomography can further improve selection of responders to CRT. At this stage, multicenter trials are needed to confirm these expectations and change clinical practice.

KEYWORDS: cardiac imaging ▪ cardiac resynchronization therapy ▪ CT angiography ▪ echocardiography ▪ MRI ▪ single-photon emission computed tomography

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Cardiac resynchronization therapy (CRT) has evolved in the last decade into a routine treatment for advanced heart failure in patients with wide QRS complex who do not respond to drug therapy [1,2]. Despite the proven beneficial effects, several problems still exist. The most important is the proportion of nonresponders to this therapy, which varies between 25 and 35% [1]. As there is great variability of definitions of a response to CRT in the published studies [3], this figure may even be an underestimate. The nonresponder rate is generally lower in studies using functional clinical end points (e.g., New York Heart Association class, and 6-min walk test, among others) compared with studies that used objective parameters of left ventricular (LV) remodeling. Thus, in the latter studies, nonresponse rate reached 40–50% [4]. Therefore, research interest is mainly focused on the improvement of response rates.

The situation is quite complex, since the response rate is predominantly influenced by the following factors: first, the presence and quantification of mechanical dyssynchrony; second, difficulty to implant LV leads in the lateral wall region due to anatomical constraints; third, uncertainty about the best positioning of the LV lead; and fourth, the amount of nonviable myocardium. Other factors include severity of heart failure, degree of remodeling, and setup of atrioventricular delay, among others. All may act individually or can interact in various combinations. The resulting response to CRT influences the prognosis of the patient. The aim of this review is to discuss whether novel imaging tools may overcome at least some of these problems.

Today, a variety of imaging modalities are available in cardiovascular medicine. These include all modes of echocardiography, computed Tomography angiography, rotational angiography, MRI, including delayed enhancement and single-photon emission computed tomography (SPECT). In addition, image integration could be considered that combines different images with real-time fluoroscopy.

Mechanical dyssynchrony

So far, the indication for CRT is based on ECG criteria with QRS width ≥120 ms. Reliable measure of mechanical dyssynchrony is expected to improve selection of appropriate candidates [2]. In this respect, a myriad of echocardiographic techniques have been suggested to accomplish this task [5]. Their detailed analysis is beyond the scope of this review.

They include conventional blood-derived Doppler parameters, such as the difference of pre-ejection periods of aortic and pulmonary outflow, delay between septal and posterior wall motion assessed by M-mode echocardiography, and various techniques of Tissue Doppler Imaging [5]. Despite the fact that many single-center studies have demonstrated reasonable sensitivity and specificity, clinical utility of these parameters remains questionable. Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) was the first randomized multicenter trial that tested the hypothesis on more appropriate selection of CRT candidates based on 14 echocardiographic parameters of dyssynchrony [6]. However, the study did not confirm this and demonstrated that none of these parameters had sufficient predictive value to replace routine selection criteria for CRT. The most important finding was with regards to the limited reproducibility of these parameters. Accordingly, it was concluded that [6]:

> *"Despite promising preliminary data from prior single-centre studies, echocardiographic measures of dyssynchrony aimed at improving patient selection criteria for CRT do not appear to have a clinically relevant impact on improving response rates when studied in a multicenter setting such as PROSPECT. Thus, at present, the echocardiographic parameters assessing dyssynchrony do not have enough predictive value to be recommended as selection criteria for CRT beyond current indications."*

The hope is that novel technologies, such as 2D strain and 3D echocardiography [7,8], will have superior reproducibility, with higher accuracy to predict response to CRT. Speckle-tracking echocardiography is a more recent approach that allows for strain imaging to assess dyssynchrony (Figure 1) [9–11]. Four different types of speckle-tracking approaches have been described, including radial strain (myocardial thickening) and circumferential strain (myocardial shortening), assessed from short-axis views; and transverse and longitudinal strains, assessed from apical views.

Moreover, alternative imaging techniques (e.g., MRI and gated SPECT imaging) may also prove useful in the assessment of LV dyssynchrony and prediction of response to CRT [12,13]. For instance, MRI tissue tagging by evaluating the grid-distortion throughout the cardiac cycle allows accurate analysis of diastolic strain and 3D cardiac motion (rotation, radial contraction

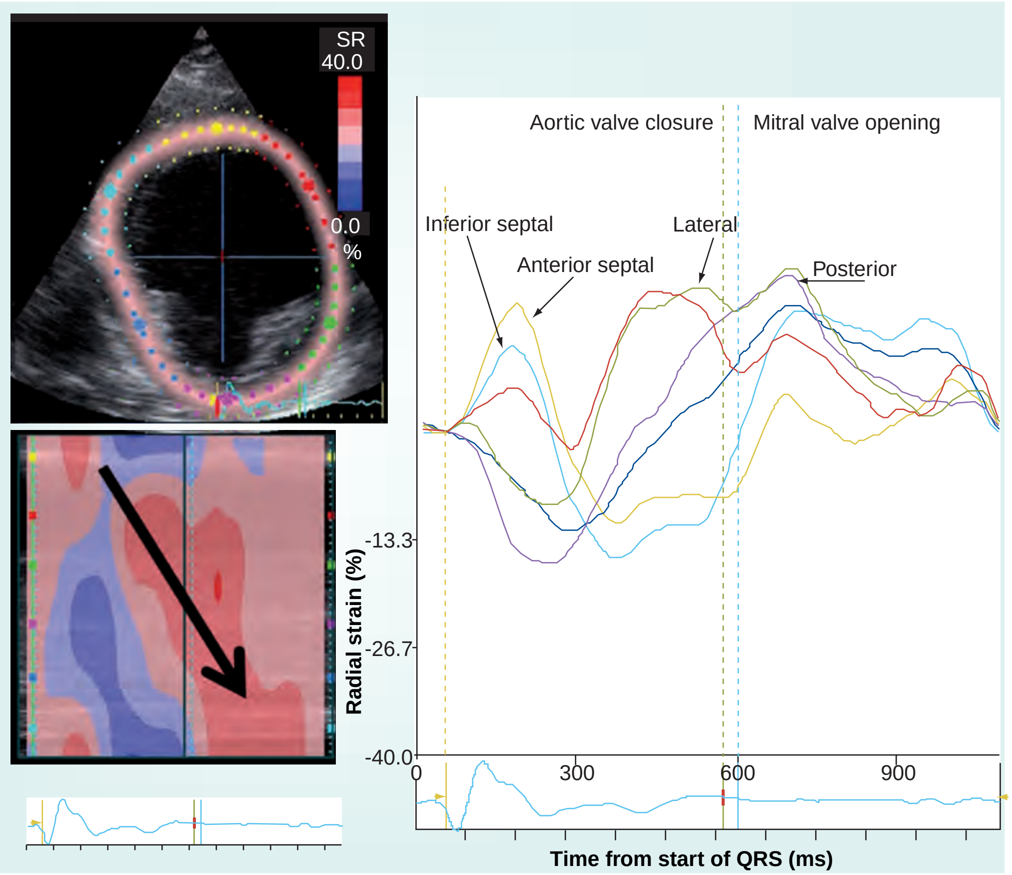

Figure 1. An example of speckle-tracking radial strain from a patient with heart failure and left bundle branch block. Dyssynchrony is shown as a time difference (arrows) between time to peak strain in the anterior septum (yellow and cyan) and posterior wall (green and purple) peak strain curves.

and translation) with high temporal resolution of approximately 40 ms [14]. Another example is phase analysis of electrocardiogram-gated SPECT myocardial perfusion imaging to assess LV mechanical dyssynchrony [15]. The superior reproducibility of phase analysis to echocardiography is a promising advantage that may improve prediction of CRT response [16,17]. The first clinical studies demonstrated that clinical response to CRT is related to the presence of LV dyssynchrony. Its quantification (histogram bandwidth and phase standard deviation) appears to be useful to predict response to CRT [18].

LV lead implant

Despite a significant improvement in technical tools for LV lead delivery, some failures to implant the lead do occur. As a reference, we may review success rates of LV lead implant in several multicenter trials on CRT [19–21]. In the CARE-HF trial, which was was terminated in 2003, the implant success rate reached 86% on the first attempt and 95% in total (390 out of 404 attempts) [19]. The Companion trial, conducted between 2000 and 2002, reported successful implants in 539 out of 617 attempts (87%) in the pacemaker group and 541 of 595 implantable cardioverter-defibrillator implants (91%) [20]. The most recent Multicenter Automatic Defibrillator Implantation Trial (MADIT) CRT Trial (2004–2008) published a rate of successful implants of 92.5% (1007 out of 1089 cases) [21]. In our institution, the failure to implant LV lead to a reasonable position varies in recent years by approximately 8–11%. Data from Cleveland Clinic (OH, USA) [22] revealed that the most frequent cause of failure to implant the LV lead was inability to cannulate the ostium of the coronary sinus (49%), followed by anatomical anomalies (24%) or phrenic nerve stimulation (17%). The question is whether imaging can help to improve the implant success rate. Obviously, one can employ intracardiac echocardiography to display the ostium of the coronary sinus and navigate introduction of the delivery sheath. Although feasible, it would substantially increase the cost of the procedure. Thus, the more acceptable option is the use of preacquired 3D CT (or MR) images overlayed with real-time fluoroscopy during the implant (Figure 2). All major manufactures offer software to support this overlay, which may help to navigate to the ostium of the coronary sinus. Auricchio *et al.* demonstrated that this approach has favorable accuracy in depicting the course of coronary veins [23]. Similarly, rotational angiography could be used to provide a roadmap for the LV lead placement [24,25].

However, there are some other techniques of the coronary sinus cannulation that do not require sophisticated imaging. Our experience suggests that one can cannulate the ostium of the coronary sinus in a very reproducible way using a simple diagnostic catheter inside the delivery sheath [26]. The pattern of intracardiac electrograms from the distal bipole of the catheter allows for easy and rapid orientation about the position of the catheter relative to the ostium. Further introduction of the catheter deeper into the coronary sinus provides a support for the delivery sheath. This can be introduced inside the coronary sinus by sliding over the catheter shaft. This strategy enables standardization of the procedure and shortens fluoroscopic times.

Cannulation of the coronary sinus ostium does not necessarily lead to successful deep delivery of the sheath into the coronary sinus and implantation of the LV lead. Analysis of failures to successfully implant the LV lead demonstrated that, besides operator's experience, the main contributing factor is the size of the left ventricle [27] or the left atrium [28]. Our explanation for this that enlargement of the left-sided cardiac chambers changes the position of the heart and distorts the plane of the coronary sinus relative to the superior vena cava and the right atrium. This results in enormous angulation between the ostium and the course of the coronary sinus, which prevents deeper introduction of the delivery sheath (Figure 3). Then, it remains mainly the operator 's experience that helps to overcome this problem using various strategies such as 'over-the-wire' techniques and additional catheters or introducers. Therefore, image integration may help less experienced implants to perform successful implantation of the LV lead. On the other hand, it may prove to be an excellent training tool to speed up implanting skills.

Optimum LV pacing site

There is ongoing discussion about the most appropriate LV pacing site. Experimental studies suggested that optimum pacing site could be the major part of the lateral wall region of the left ventricle [29]. Analysis from the recently published MADIT CRT trial demonstrated that the clinical effect of CRT in less advanced heart failure is similar, whether the LV lead is implanted anteriorly, in the lateral wall or

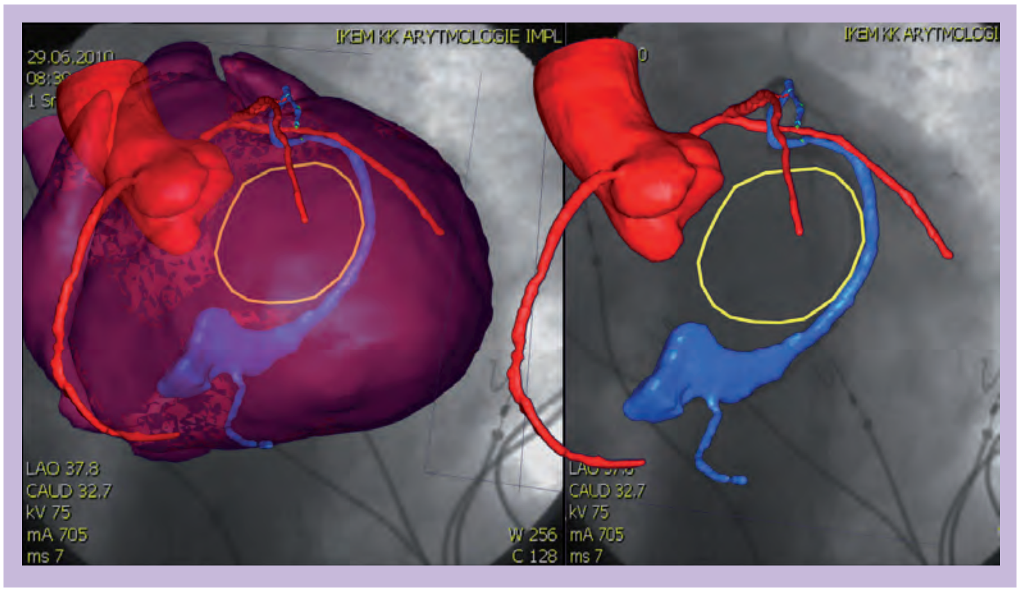

Figure 2. Computed tomography angiography of the coronary sinus and its branches overlaid with real-time fluoroscopy in modified LAO view.

posteriorly. The only position that resulted in no improvement was the apical area of the left ventricle [101]. Nevertheless, other clinical studies provided variable results. Although the left lateral wall is considered the best region by many, some studies demonstrated individual variation in each region and emphasized the need for individualized assessment using various tools [30,31]. There are even studies showing that the optimum pacing site may vary significantly within a radius of few centimeters [30]. Some hemodynamic data suggest that the pacing site is a primary determinant of the hemodynamic response to LV pacing, at least in patients with nonischemic dilated cardiomyopathy. Pacing at the best LV site was associated acutely with fewer nonresponders [30,31]. Preliminary data suggest that positioning of the LV pacing lead outside of the site of latest mechanical activation may result in poor response to CRT [31].

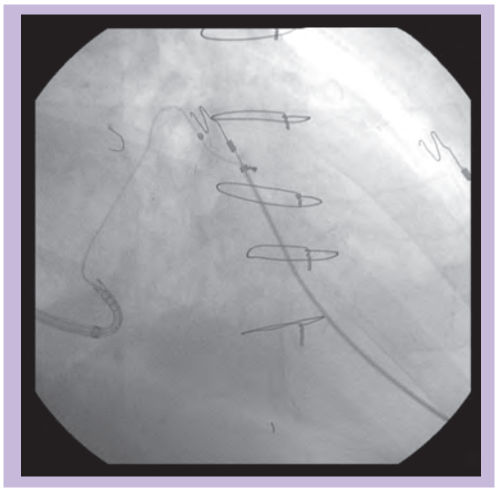

Figure 3. Fluoroscopic image depicting two delivery sheaths (telescopic system) and left ventricular lead introduced into the lateral branch (right anterior oblique projection view). Note significant mismatch between the axis of the delivery sheath and the course of the proximal coronary sinus.

Among imaging techniques, novel tissue Doppler techniques, such as speckle-tracking or triplane tissue synchronization imaging, appear to be the most promising [32,33] to assess the region of maximum mechanical dyssynchrony and help to guide the lead positioning. For example, in a preliminary study [33], 21 consecutive heart failure patients scheduled for CRT implantation were prospectively enrolled to undergo 64-slice CT to visualize the venous system, contrast venography during device implantation, and tissue synchronization imaging before and after implantation. In 12 of the 21 patients, a reasonable match was observed between the area of latest mechanical activation and LV lead position. These patients demonstrated a significant decrease in LV dyssynchrony with an acute reduction in LV end-systolic volume and an improvement in LV ejection fraction. Patients with a mismatch between the area of latest activation and LV lead position remained dyssynchronous without improvement in LV function. Therefore, such strategies may help in planning the implant procedure. Whether such an approach will result in long-term improvement of outcome remains to be confirmed in future studies.

Parallel to echocardiographic techniques, MRI is another tool to evaluate and locate mechanical dyssynchrony, either by tagging or by velocity-encoded imaging [34]. It allows quantitative strain analysis based on 3D circumferential and longitudinal myocardial activation data and has very high spatial and temporal resolution, and high reproducibility. This appears to be the advantage against echocardiography. Advances in the rapid analysis of tagged magnetic resonance images such as harmonic phase and strain-encoded imaging, and the design of novel global indexes of cardiac dyssynchrony may provide a more comprehensive method for selecting maximum dyssynchrony region and optimize location of the pacing site. The harmonic phase method measures the motion from tagged MR images by filtering certain regions in the frequency domain of the images called harmonic peaks [35,36]. The technique called strain-encoded imaging is derived from a standard myocardial tagging sequence that tags the tissue at end-diastole with a sinusoidal tag pattern designed to modulate the longitudinal magnetization orthogonal to the imaging plane. Deformations of tissue during systole will change the local frequency of the pattern in proportion to the through-plane strain component. The distribution of regional contraction (circumferential shortening in long-axis views or longitudinal compression in short-axis views) is then displayed as contrast in the images. Velocity-encoded MRI, when applied for myocardial wall motion measurement [37,38], potentially allows direct myocardial wall motion measurement similar to tissue Doppler imaging (i.e., comparing velocity graphs obtained in different parts of the myocardial wall during systole).

The third method potentially suitable for localization of the latest activation site within LV is phase analysis of ECG-gated SPECT myocardial perfusion imaging [39,40]. Ypenburg *et al.* evaluated echocardiographic and clinical outcome 6 months after CRT in a relatively large cohort of patients with ischemic or dilated cardiomyopathy [39]. A total of 153 (60%) patients had an LV lead positioned at or adjacent to the site of latest activation and these subjects presented with signs of reverse remodeling whereas the rest of the study group did not. They had also lower mortality. In the study by Boogers *et al.* [40], the patients in whom the LV lead was positioned in the latest activated region had a significant response to CRT compared with patients with a discordant LV lead position (79 vs 26%; p < 0.01). In addition to LV dyssynchrony, nuclear imaging also provides information on viability and scar.

Some authors express their scepticism at using mechanical dyssynchrony imaging to guide the lead implant, especially in patients with narrow QRS complexes. The argument is that identification of dyssynchrony regions may not mean that pacing in these sites will better correct mechanical dyssynchrony. Some studies demonstrated that such regions do not necessarily correspond with the late activated regions and, thus, may not be correctable by pacing [41,42].

However, before the aforementioned techniques will prove effective in selecting the optimum pacing site, the majority of routine implants are performed with the goal to place the lead in the lateral and/or posterolateral or anterolateral vein, depending on the individual anatomy. In this situation, preprocedural assessment of the anatomy of the coronary venous tree may prove to be very helpful in planning the implant. In particular, CT angiography is able to evaluate all branches of the coronary sinus and great cardiac veins in detail (Figure 4) [43,44]. MRI is another option that allows evaluation of cardiac venous anatomy without radiation exposure [45,46]. All these imaging techniques permit identification of potential anatomic factors that may pose difficulties in cannulating and advancing the LV pacing lead, such as valves at the ostium of the ventricular veins or absence of the lateral vein. In patients without suitable posterolateral veins, in order to allow successful implantation of the LV pacing lead, a surgical implantation (via minithoracotomy or videoassisted) at the latest activated region

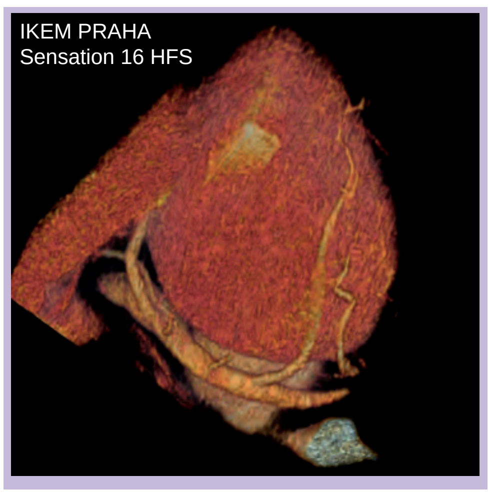

Figure 4. Volume-rendered CT angiogram of the coronary sinus (modified inferior view) depicting small cardiac vein and large lateral vein, accompanied by a marginal branch of the coronary artery.

may be preferred. Importantly, in some studies, the venous anatomy was strongly related to the presence of prior myocardial infarction; patients with previous myocardial infarction had left marginal veins significantly less frequently [44].

Assessment of myocardial viability

One imaging modality that permits noninvasive assessment of viability is nuclear perfusion imaging [13]. Some studies using SPECT in patients with an ischemic cardiomyopathy and poor systolic function found that nonviable tissue in the inferior or lateral wall was more frequently present in patients with a QRS ≥120 ms than in patients with a QRS <120 ms (29 vs 7%; $p < 0.01$) [47]. Another study evaluated the presence of scar tissue with gated SPECT using 99mTc-tetrofosmin before CRT implantation. Patients without scar tissue in the region of the LV lead placement significantly improved in functional class, quality of life, 6-min walk test, LV volumes and ejection fraction, whereas no improvement was observed in patients with scar tissue [48].

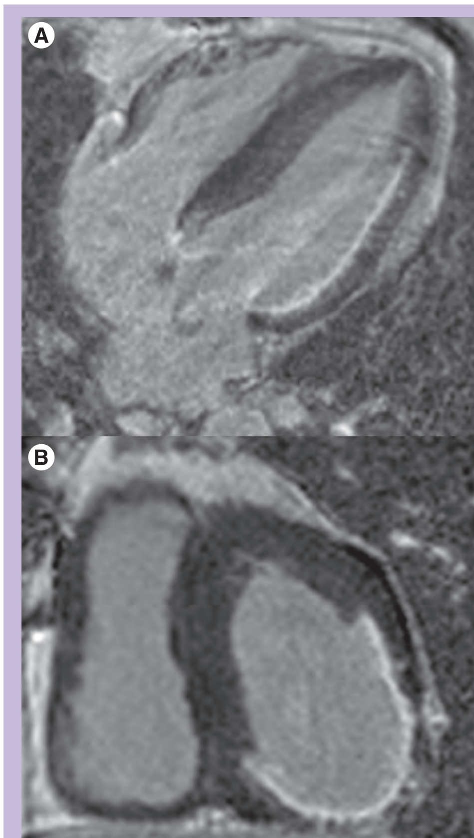

Figure 5. Long axis (A) and short axis (B) view of posterolateral scar, mainly subendocardial, depicted as a white zone in magnetic resonance angiogram with delayed enhancement.

The more promising noninvasive imaging modality to evaluate myocardial scar is cardiac MRI. In addition to the detection of wall motion abnormalities, contrast-enhanced MRI enables the depiction of transmural and nontransmural infarctions (Figure 5) with better spatial and contrast resolution and better accuracy than scintigraphic techniques [49]. This is especially pertinent in patients with ischemic cardiomyopathy who comprise a subgroup of subjects with a significantly worse response rate to CRT. One of the first studies by Bleeker *et al.* studied a total of 40 coronary artery disease patients with MRI before undergoing CRT [50]. The authors documented a transmural posterolateral scar in a third of the patients. In contrast to patients without posterolateral scar tissue, these patients demonstrated a low response rate and did not demonstrate an improvement in clinical or echocardiographic parameters. In addition, parameters of LV dyssynchrony remained unchanged after CRT implantation in the presence of scar tissue. A study by White *et al.* evaluated the ability of delayed enhancement MRI to predict clinical response to CRT and found that the amount of total scar was significantly higher in the nonresponse compared with the response group [51]. Similarly, Ypenburg *et al.* studied 34 patients with an ischemic cardiomyopathy scheduled to undergo CRT [52]. Contrast-enhanced MRI was used to determine total scar burden, using a 17-segment model with a five-point hyperenhancement scale. Again, the amount of scar tissue correlated inversely with response to CRT.

Some authors believe that patients identified by the aforementioned techniques cannot be simply considered as candidates with a very high probability of treatment failure who cannot respond to CRT. Therefore, they challenge the view that patients with ischemic cardiomyopathy and extensive scar tissue should be witheld CRT and suggest that such patients might benefit the most from invasive mapping-targeted selection of LV pacing sites and endocardial pacing [53]. Others demonstrated that the response to CRT could be independent of the presence of extensive myocardial scarring [54]. It was demonstrated that LV pacing at sites with ischemia, hibernation or nontransmural scar did not appear to modify the effect of CRT compared with viable tissue. It follows that incorporation in the standard selection criteria of algorithms to predict the response to CRT is not yet ready for clinical use.

Conclusion

Novel imaging tools have the potential to increase the proportion of responders to CRT.

Sophisticated echocardiographic techniques, MRI or phase analysis of ECG-gated SPECT myocardial perfusion imaging may help to assess and quantify mechanical dyssynchrony and, thus, better selection of candidates to CRT. However, to date, there is no agreement on which technique is best suited to this task. In addition, practical feasibility for everyday use remains an issue. 3D venous anatomy assessed by CT angiography, rotational angiography and/or MRI could be integrated with online fluoroscopy and may help to improve implant rates and increase skills of the implanters. Techniques detecting mechanical dyssynchrony are studied in order to assist LV lead positioning. Evaluation of the extent and location of myocardial scars using SPECT or MRI with delayed enhancement can further improve selection of responders to CRT. At this stage, multicenter trials are needed to confirm these expectations and change clinical practice.

Future perspective

Improvement in quantification of mechanical dyssynchrony and a better understanding of its relationship to electrical dyssynchrony is expected in the next 5–10 years to improve selection of the most appropriate candidates for CRT. Optimization of the pacing site and/or combination with other interventions such as percutaneous mitral annuloplasty may have additional value. Such a tailored approach should maximize the benefit of this therapy, possibly expanding its indications.

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Executive summary

- Novel imaging tools include all modes of echocardiography, CT angiography, rotational angiography, MRI, SPECT and image integration that combines different images with real-time fluoroscopy.

Mechanical dyssynchrony

- Reliable assessment of mechanical dyssynchrony is a prerequisite of more tailored selection of candidates for CRT. Techniques such as 2D strain, 3D echocardiography, MRI and phase analysis of electrocardiogram-gated SPECT myocardial perfusion imaging are the most promising imaging modalities.

Left ventricular lead implant

- Preacquired 3D CT (or MR) images overlaid with real-time fluoroscopy during the implant, may help to guide successful implantation of the left ventricular lead and minimize complications. A similar role may be applicable to rotational angiography.

Optimum left ventricular pacing site

- Special imaging techniques such as tissue Doppler, MRI or SPECT appear to be the most promising at assessing the region of maximum mechanical dyssynchrony and optimizing left ventricular lead positioning. Preprocedural CT or MR angiography helps to evaluate the coronary venous anatomy and select the appropriate implant strategy.

Assessment of myocardial viability

- SPECT or contrast-enhanced MRI are useful to evaluate the extent of myocardial scars, especially in patients with ischemic cardiomyopathy. Preliminary data suggest that the magnitude of scar burden is inversely proportional to degree of reverse remodeling of the left ventricle.

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▪ **Interesting review of the problem of nonresponse to CRT, with some specific suggestions for how to proceed further.**

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