Nonechocardiographic Imaging in Evaluation for Cardiac Resynchronization Therapy

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In patients with heart failure and prolonged QRS duration, randomized clinical trials have shown that cardiac resynchronization therapy (CRT) is associated with improvement in quality of life, left ventricular (LV) remodeling, and survival.\(^1\)\(^-\)\(^3\) The improvements are believed to be mediated by more effective synchronized contraction in the presence of a wide QRS, but mechanical and electrical dyssynchrony are not equivalent.\(^4\)\(^,\)\(^5\) Although the concept of CRT response remains problematic,\(^6\) 20% to 40% of patients who receive CRT based on electrical dyssynchrony criteria (ie, QRS duration) do not derive symptom improvement or demonstrate reverse remodeling.\(^7\)\(^-\)\(^10\) Scar burden\(^11\)\(^-\)\(^13\) and failure to place the LV pacing lead at the site of latest onset of contraction\(^14\)\(^-\)\(^17\) have been linked to a poor response. Thus, optimal clinical decision-making for CRT must include a comprehensive evaluation of all these factors to identify patients with heart failure who will benefit.

The standard echocardiographic parameters of LV mechanical dyssynchrony have been extensively reviewed,\(^18\) with >600 published articles. Most of this work has been done using tissue Doppler imaging, with more recent work using speckle tracking,\(^19\)\(^,\)\(^20\) 3D echocardiography,\(^21\) echocardiographic contrast imaging,\(^22\) and intracardiac echocardiography.\(^23\) Despite the important benefits of high temporal resolution, success in individual centers, and ability to assess the impact of scar burden and concordance of LV lead with latest activation site,\(^14\) fundamental limitations of tissue Doppler imaging include the inability to measure over a sufficient number of cardiac cycles to overcome beat-to-beat variation, poor image quality, and measurement error.\(^24\) In the only randomized trial of CRT in patients with wide QRS,\(^25\) the failure of 12 different echocardiographic dyssynchrony parameters to improve outcome was most likely related to the large interobserver and intraobserver variability (4% to 24% and 7% to 72%, respectively). These limitations of echocardiography have led to a search for nonechocardiographic imaging techniques to optimize decision-making before CRT (Table 1).

Cardiac CT

The role of cardiac CT (CCT) in heart failure has been reviewed recently.\(^26\) The technique assesses scar location and burden,\(^27\) anatomic location of the phrenic nerve, cardiac venous anatomy,\(^28\) LV function, and dyssynchrony indices\(^8\) (Table 1, Figure 1).

Scar Location and Burden

The role of CCT in assessing scar burden is increasing but still faces many challenges. Dual-phase evaluation has been shown to detect scar after acute and chronic myocardial infarction\(^29\)\(^,\)\(^30\) (Figure 1A) and correlates well with gadolinium delayed enhancement with cardiac MRI (CMR), although the contrast-to-noise ratio is far superior with CMR.\(^31\) However, there are no published studies that evaluated the impact of scar burden by CCT on CRT response.

Coronary Venous Anatomy

CCT has an advantage over other techniques in the assessment of the coronary venous system (Figure 1K) that correlates well with conventional catheter-based venography \((r=0.82\) to 0.95\)\(^28\)\(^,\)\(^32\) and can register venous anatomy to the site of latest activation.\(^33\) This is particularly important because LV lead placement for CRT is technically challenging in dilated ventricles with prominent tortuosity, stenosis, and acute angulation of the coronary veins\(^28\)\(^,\)\(^34\) and especially so in the 5% of subjects in whom the posterior vein of the LV is absent and the 39% among whom the left-side marginal vein is absent.\(^35\) In addition, CCT identifies the relationship of the left-side phrenic neurovascular bundle to the target vein, which allows the operator to avoid diaphragmatic stimulation.\(^36\)

Mechanical Dyssynchrony and CRT Response

Little work has been done on mechanical dyssynchrony indices with CCT, with no published data on prediction of CRT response. Recently, 3 global indices have been described in a small study \((N=38)\) using the following 3...
parameters (Figure 1G): (1) SD of the time from the R wave to maximal wall thickness (computed as the radial distance between the endocardial and epicardial borders) (≈540 data points per patient), (2) SD of time to maximal wall motion (using the endocardial borders and centerline algorithm) (≈480 data points), and (3) SD of time to minimal systolic area (≈90 data points). For segmental dyssynchrony, the average of the maximal difference in time to maximal wall thickness or wall motion among the 3 pairs of opposing walls were derived (average, 180 and 160 data points per patient, respectively). Overall, the reproducibility of global dyssynchrony was much better than regional parameters (intraclass correlation coefficient range, 0.71 to 0.95 versus 0.06 to 0.91, respectively). Among the global indices, the SD based on time to maximal wall thickening was the most reproducible (intraobserver and interobserver reproducibility, 0.95 and 0.94, respectively; \( P < 0.0001 \)), with no systematic bias by Bland-Altman analysis.\(^5\) The indices correlated moderately with 2D and 3D echocardiography in 14 patients (\( r = 0.65, P = 0.012, \) and \( r = 0.68, P = 0.008 \)). However, there was no bias evaluation performed.\(^5\) Furthermore, the CCT-derived dyssynchrony indices were significantly higher in patients with low ejection fraction (EF) and wide QRS (n=16) than in the control group. The correlation between electrical and mechanical dyssynchrony was fair (\( r = 0.51, P = 0.007 \)), which is expected because the 2 concepts are not equivalent.\(^4\) However, the dyssynchrony index could not differentiate patients with low EF and wide versus narrow QRS and did not correlate with LVEF (\( r = -0.27, P = 0.17 \)). Although the small number of patients in each group is probably the limiting factor, these findings need to be validated in larger studies.

**Challenges**

Temporal resolution remains a major challenge and is limited to 165 ms with a typical 64-slice CCT scanner. However, with the emergence of new dual-source scanners, the effective temporal resolution can be further reduced to 83 and 42 ms with single and multisegment reconstruction algorithms, respectively, which is comparable to other imaging modalities (Table 1).

The high radiation dose with CT, especially when performing prospective gating to assess wall thickening and dyssyn-
chrony (≈15 to 25 mSv), or serial scanning to optimize LV lead placement and follow-up post-CRT remain major limitations. However, with the fast scanners and radiation lowering techniques, it will be feasible in the near future to limit the radiation burden to ≈1 to 5 mSv, allowing multiple scans at a fraction of the typical radiation burden used today.37

CMR

CMR is a well-studied imaging technique with high reproducibility and high spatial resolution, which provides 3D data on LV function and dyssynchrony, allows visualization of the coronary venous anatomy, and provides viability information38,39 (Table 1, Figure 1). These features make it useful in CRT planning.

Scar Burden and CRT Response

CMR is now recognized as the gold standard for assessing myocardial viability, with excellent spatial resolution and contrast-to-noise ratio40 (Figure 1B). Not only can it detect small infarcts that may be missed by nuclear single-photon emission CT (SPECT) myocardial perfusion imaging (MPI),41 but also it avoids overestimating LV inferior and posterior scar that can occur with SPECT MPI because of attenuation artifacts.42 The scar burden also can be quantified.43,44 A total scar burden of ≥33% of LV myocardial volume, scar transmurality of ≥51%, or pacing over a posterolateral scar were associated with poor response to CRT.12,44 Similarly, another small study showed that a cutoff of 15% scar had an 85% sensitivity and a 90% specificity to predict CRT response.45 Furthermore, a linear relationship between total scar burden by MRI and LV remodeling or response to CRT has been described.45–47 T1 mapping has emerged as a potential tool to detect and quantify myocardial interstitial fibrosis,48 but there have been no studies to see whether it predicts response to CRT.

Coronary Venous Anatomy

Coronary venous anatomy also can be visualized with CMR.49,50 The contrast between the coronary veins and surrounding myocardial tissue is adequate to assess the

Figure 1. Nonchocardiographic imaging of CRT. A-J, Scar burden, LV function, and mechanical dyssynchrony are visualized with different imaging modalities. A and B, A large area of delayed enhancement (scar) (arrow) by cardiac CT (CCT) and cardiac MRI (CMR), respectively. C, A polar map of an at-rest myocardial perfusion image showing large, fixed perfusion defect size. D-F, Quantification of LV volumes and EF with CCT, CMR, and gated single-photon emission CT, respectively. G, The method of assessing mechanical dyssynchrony with CCT using time to maximal LV wall thickening curves. Reprinted with permission from Truong et al. H, Tagged CMR, which is used to derive strain and dyssynchrony indices. I and J, Phase histogram and polar map showing segmental onset of mechanical activation with LV site of latest activation (star, inferior wall), respectively. K, A 3D volume-rendered image of the coronary venous anatomy by CCT while planning LV lead placement. *Side branches of the posterior vein of the left ventricle. Reprinted with permission from Van de Veire et al. L, A reconstructed 3D CMR image showing the coronary sinus. CS indicates coronary sinus; CX, left circumflex coronary artery; EF, ejection fraction; GCV, great cardiac vein; LMV, left marginal vein; LV, left ventricle; PIV, posterior interventricular vein; PVLV, posterior vein of the left ventricle; RCA, right coronary artery; SCV, superior cardiac vein.
location, dimension, tortuosity, and branching angles of the coronary veins. The study is performed within 10 to 15 minutes with free breathing and without any contrast or radiation burden. However, the spatial resolution (typically 0.5 to 1 mm) is not quite as good as with CCT, and the study cannot be routinely performed in patients with implanted cardiac devices.51

Mechanical Dyssynchrony and CRT Response
CMR can be used to quantify dyssynchrony using several basic scan acquisition techniques (Figures 1H and 2). The relevant indices from these methods are summarized in Table 2.38,52–67 Although some of these indices were shown to predict CRT response, the studied cohorts were small.

Challenges
The broad use of CMR to plan CRT still faces many challenges. There are problems with imaging patients with implanted devices, although this has been recently attempted in well-selected and monitored patients on a case-by-case basis68,69; however, the resultant artifact remains a major challenge when analyzing dyssynchrony and response after CRT58 (Figure 3). Furthermore, despite recent advances,70 the analysis process, including use of specialized software, is still complicated, time consuming, and not fully automated. Like other imaging modalities used in CRT studies, data have been validated in very small cohorts with different indices. Lastly, access to CMR may be limited because in many areas, it often is performed only in large centers. Even when available, not all centers have expertise in the interpretation of synchrony.

Nuclear Imaging
The role of nuclear imaging with gated SPECT MPI in CRT has been recently reviewed and described as a “one-stop shop” to predict CRT response. It provides data on scar burden and location, LV function, LV site of latest contraction, and mechanical dyssynchrony from a single scan71–74 (Figure 1).

Scar Burden, Location, and Response to CRT
The presence, location, and burden of myocardial scar have been shown to affect response to CRT.71,75 In a study by Adelstein et al,11 an inverse relationship was described between the extent of fixed perfusion defect on MPI and absolute or relative increase in LVEF 6 months after CRT (r=-0.63 and -.53, respectively, P<0.01) (n=50). Furthermore, patients who responded to CRT had lower global scar burden and scar density near the LV lead versus nonresponders.11,15 Additionally, the extent of scar around the LV lead correlates negatively with improvement in LVEF,11 and is associated with no response in 29% of patients with extensive scar at the LV lead site despite having a concordant lead with latest site of activation.15 Similar findings showed that a transmural scar (<50% tracer activity) at the site of LV lead placement was associated with no response to CRT.13 These results are concordant with CMR studies as described in the previous section. An advantage of SPECT MPI is the ability to automatically quantify the scar burden with good reproducibility.76 However, the low spatial resolution and counts of the images remains a limitation, particularly when assessing viability in dilated ventricles with thin walls because it might overestimate the extent of scar. PET imaging is performed with higher tracer counts, lower radiation exposure, and better spatial resolution, solving the problem to a great extent.77 However, there are limited data on dyssynchrony or CRT response using PET images.

Coronary Venous Anatomy
SPECT MPI plays no role in identifying coronary venous anatomy.
Mechanical Dyssynchrony

**Technique Characteristics**

Nuclear imaging was used to evaluate mechanical dyssynchrony several decades ago in the era of gated equilibrium radionuclide angiography. In recent times, gated SPECT has quickly emerged as an attractive alternative to quantify dyssynchrony (Figure 1). The technique of phase analysis for SPECT MPI has been described extensively by Chen et al., using the Emory Tool Box (SyncTool; Emory University; Atlanta, GA), with other software in development. Briefly, a 3D count distribution is extracted from each of the LV short-axis data sets; a 1D fast Fourier transform is applied to the count variation over time for each voxel, generating a 3D phase distribution that describes the timing of LV onset of mechanical contraction over the entire R-R cycle (Figure 1). Two clinically relevant dyssynchrony indices are derived: SD and histogram bandwidth. The normal values have been published and validated. The technique is fully automated, has effective temporal resolution of \(110^{15}\) ms for a heart rate of 60 beats/min, interobserver and intraobserver reproducibility of 99%, and high repeatability independent of the type of camera used, the type of image reconstruction, or the tracer dose (Table 1).

**Dyssynchrony, LV Lead Placement, and CRT Response**

Although mechanical dyssynchrony is associated with the extent of cardiomyopathy, scar burden, and QRS duration, the correlation with each of these parameters is far from perfect (Table 2).

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**Table 2. Dyssynchrony Evaluation by CMR**

<table>
<thead>
<tr>
<th>Technique</th>
<th>Characteristics</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Dyssynchrony Indices</th>
<th>Prediction of CRT Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cine</td>
<td>Wall motion</td>
<td>Myocardial borders well seen</td>
<td>Automated or semi-automated contour detection often requires manual correction Time consuming</td>
<td>Septal-lateral delay of wall thickening (~65 ms) Radial dyssynchrony (tissue synchronization index)</td>
<td>SN, 90%; SP, 59% (n=40) (septal-lateral delay) Could not further stratify patients (radial dyssynchrony) (n=225)</td>
</tr>
<tr>
<td>Phase contrast</td>
<td>Tissue velocity mapping</td>
<td>3D velocity information per pixel Velocities used to derive strain Measures interventricular dyssynchrony</td>
<td>Similar to above Long scan time to acquire images Respiratory artifact</td>
<td>Aorta-pulmonary onset flow time difference for interventricular dyssynchrony (RV-LV) (milliseconds)</td>
<td>No studies</td>
</tr>
<tr>
<td>MR-TVM</td>
<td>Encodes position/tissue displacement</td>
<td>Better image contrast than MR-TVM Used to derive strain</td>
<td>Low temporal resolution (1 image/cardiac cycle) Not widely available</td>
<td>N/A</td>
<td>No studies</td>
</tr>
<tr>
<td>DENSE</td>
<td>Subtraction of 2 out of phase tagging grids to give improved persistence of tag lines</td>
<td>Tags last longer in diastole</td>
<td>Longer acquisition time Reduced temporal resolution</td>
<td>Temporal uniformity index (circular uniformity ratio estimate)</td>
<td>PPV, 87% NPV, 100% to improve patient selection (circular uniformity ratio estimate) (n=47)</td>
</tr>
</tbody>
</table>

CMR indicates cardiac MRI; CRT, cardiac resynchronization therapy; CSPAMM, complementary spatial modulation of magnetization; DENSE, displacement encoding with stimulated echoes; HARP, harmonic phase analysis; LV, left ventricle; MR-TVM, magnetic resonance tissue velocity mapping; N/A, not applicable; NPV, negative predictive value; PPV, positive predictive value; RV, right ventricle; SENC, strain-encoded MRI; SN, sensitivity; SP, specificity; SPAMM, spatial modulation of magnetization; SSFP, steady-state free precession.
0.50 to 0.65, 0.25 to 0.50, respectively) suggesting that mechanical dyssynchrony may provide incremental value. In 42 patients with heart failure, QRS >120 ms, and LVEF <35% undergoing CRT, a cutoff value for SD of 43° was shown to have 74% sensitivity and 81% specificity to predict clinical response to CRT and LV reverse remodeling.

Furthermore, in a recently published study of 90 patients undergoing CRT, Boogers et al showed that concordance of latest LV activation by phase analysis with lead placement during CRT implantation was associated with improvement in LV reverse remodeling (Figure 5). The site of latest activation was determined using a 6-segment model; the mean phase of every segment was calculated, and the highest value corresponded to the latest activated segment. These segments were located in the posterior (42%), lateral (23%), inferior (13%), and anterior (16%) walls (intraobserver and interobserver agreement of 93% and 87%, K = 0.96 and 0.92, respectively). Conversely, the LV lead position was determined by biplane fluoroscopy (Figure 5). The response rate to CRT was 79% (concordant lead) versus 26% (discordant). In addition, there were 7 patients with extensive scar at the latest activation site; excluding those patients, the response was 92%. Figure 6 illustrates some examples of CRT response.

The change of dyssynchrony parameters after CRT occurs immediately after implantation, and may predict long-term LV remodeling. It would therefore be possible, using gated SPECT with single-tracer injection, to change CRT parameters to optimize response, especially with the excellent repeatability of the technique to measure dyssynchrony.

Challenges
The major challenges with gated SPECT for CRT are the radiation burden with serial scans when assessing LV remodelling and improvement in dyssynchrony indices after therapy and the inability to visualize coronary venous anatomy, although the fusion of SPECT-CT imaging could potentially address the latter issue.

Future Directions
The search for the best modality for noninvasive cardiac imaging to predict CRT response is still ongoing. The different modalities bring different strengths and weaknesses to this process (Table 1). A universal first step should be to assess LV function; whereas CMR is the gold standard, other imaging modalities, including 3D echocardiography with
contrast, provide reliable LVEF. It is important to realize that the prognostic benefit of CRT is not based on the prediction of response (itself a controversial topic), but in some circumstances, prediction of symptomatic response may be the main consideration driving the decision to implant a device. The identification of significant mechanical dyssynchrony may be performed by detection of the site of latest activation by SPECT or echocardiography with speckle tracking. In patients with ischemic heart disease, CMR is the gold standard for scar quantification, but SPECT is a good alternative. Finally, CCT could be used to assess coronary venous anatomy in selected patients. Further multicenter studies that evaluate all modalities together or an integrative approach displaying anatomy and function are needed to define which single test or combination of techniques can best guide initial patient selection, procedural approach, and postimplant optimization.

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Figure 5. Concordance of left ventricular lead placement with latest site of activation. The figure represents the distribution of the left ventricular latest site of mechanical activation with phase analysis of gated single-photon emission CT (6-segment model) and the left ventricular lead placement. There was 58% (n=90) concordance.

Figure 6. Phase analysis of gated single-photon emission CT before and after CRT. Top, A responder to CRT. The patient had baseline LV dyssynchrony and a small scar at the apex and inferolateral wall. The LV pacing lead was placed at the posterolateral wall, concordant with the site of latest activation. The patient had favorably responded to CRT. The LV dyssynchrony parameters were reduced immediately after CRT. This patient had been followed up for >1 year and showed no end point outcomes (cardiac death, heart failure hospitalization, shocks, CRT deactivation). Bottom, nonresponder to CRT. The patient had baseline LV dyssynchrony but no scar. The latest activation site was at the inferolateral wall; however, the LV pacing lead was placed at the anteroseptal wall. The patient had deteriorated LV dyssynchrony immediately after CRT. This patient had CRT deactivation due to worsened symptoms 15 days after CRT. CRT indicates cardiac resynchronization therapy; LV, left ventricle; PHB, phase histogram bandwidth; PSD, phase standard deviation.
Disclosures
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References

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