Cardiac resynchronization therapy: the role of equilibrium radionuclide angiography

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Investigations and research

The clinical problem and CRT

Heart failure (HF) is the largest growing field in cardiology and the most frequent reason for hospitalization in the USA. Severe HF effects 5,000,000 patients, with 1,000,000 hospitalizations and 250,000 deaths yearly. In spite of advances in its pharmacotherapy, many patients have severe, refractory HF symptoms, and a poor prognosis [1].

Cardiac resynchronization therapy (CRT) is a relatively new, invasive, expensive but effective non-pharmacologic method which helps many with severe, medically refractory HF. CRT implants pacemaker leads in the right atrium, right ventricle (RV), and coronary sinus to innervate the left ventricle (LV), in order to minimize electrical disturbances that exacerbate HF, and achieve synchronous biventricular pacing.

Abnormal conduction, left ventricular dyssynchrony and heart failure

Abnormal electrical conduction, common in advanced HF, worsens cardiac function. One-third of patients with systolic heart failure have a QRS duration > 120 ms [2]. Intraventricular conduction abnormalities such as left bundle branch block (LBBB) delay regional wall motion, leading to dyssynchrony. Dyssynchrony is inefficient contraction, where contraction of the septum and lateral walls to circulate the blood are not synchronized. LV dyssynchrony is associated with increased HF mortality [3].

Cardiac resynchronization therapy (CRT) seeks to restore synchrony, coordinating contraction. It improves HF symptoms and overall clinical status, and reduces hospitalizations and mortality [4, 5]. CRT is the standard care for selected patients with moderate to severe HF. Yet, owing to broad CRT inclusion criteria and limited knowledge regarding its mechanism, 30% - 40% of CRT patients do not improve clinically, or worsen. Those improving do so unpredictably and variably. Also, CRT candidates represent only 30% of patients with refractory HF, excluding those with narrow QRS complexes [6] where 30% - 50% have dyssynchrony and could benefit from CRT [7, 8].

The Guidelines for the Diagnosis and Management of Chronic Heart Failure [9] present the inclusion criteria for CRT:
• severe HF symptoms
• sinus rhythm
• New York Heart Association (NYHA) Class III-IV symptoms despite optimal medical therapy
• LV ejection fraction (EF) ≤ 35%, with cardiac dyssynchrony defined as an electrocardiographic QRS duration > 120 ms.

The Guidelines exclude those with QRS ≤ 120 ms. Even among such selected patients, only 60% - 70% improve with CRT.

The needs

Measuring dyssynchrony
A wide QRS complex is a surrogate for mechanical dyssynchrony used to select CRT patients. Baseline QRS duration is a good marker of *interventricular* dyssynchrony, but left *intraventricular* dyssynchrony, which is a more accurate predictor of CRT response, does not correlate with baseline QRS duration [10]. Some patients with intractable HF and wide QRS have no left intraventricular dyssynchrony and may not respond to CRT, while others with a narrow QRS have left intraventricular dyssynchrony and would benefit from CRT but are excluded from the Guidelines [11]. There is a need for a reproducible measure of ventricular synchrony to guide patient selection and optimize CRT.

Pacemaker location
Pacing the LV from the “latest contracting segment” could improve the response to CRT.
There is no currently accepted method which
directs the location of the lead, which is placed
by rote in the lateral wall.

The right ventricle
Here, there are some unanswered questions. How
does RV synchrony relate to the RV pacemaker
site and to success in CRT? Do patients with
RV failure have right ventricular dyssynchrony?
Would they benefit from CRT? We are currently
unable to evaluate RV synchrony.

Imaging solutions

The current state
There is no established method to measure
regional or global synchrony. This relates in part
to the challenging problem and, also, to the fact
that until recently only echocardiographic
applications have been explored.

Echocardiography
Echocardiography assesses LVEF in patients with
advanced HF, assesses mechanical dyssynchrony,
is applied to program optimal post-CRT
atrioventricular and interventricular pacemaker
timing, and is used to assess the long-term CRT
effects on the LVEF and ventricular volumes [12].

Echocardiography is the most widely applied
imaging modality for synchrony evaluation,
using a variety of functional indices generated on
M-mode, 2D and 3D [8] including strain rate
imaging, tissue synchronization imaging and
tissue Doppler, which is the most documented
of methods. A variety of echocardiographic
indices have demonstrated a relationship to CRT
outcome [13], an ability to select patients
benefiting from CRT, and aids to optimally
localizing the pacemaker.

Yet, echocardiography is imperfect.
Measurement of echocardiographic parameters
are operator-dependent, sometimes have limited
viewing and sampling windows, as well as
sampling errors, and others are complex with
prolonged acquisition and limited availability.
In this application, some studies reveal a reduced
reproducibility [14] of echocardiographic
measures and an inconsistency between
measurements and predicted CRT outcome
[15, 16].

Magnetic resonance imaging (MRI)
Cine MRI is an excellent imaging modality for
dyssynchrony. MRI tagging measures
myocardial deformation during contraction and
quantitates regional LV function. Comprehensive color-coded 3D strain maps can
be constructed and displayed, and LV
dyssynchrony can be calculated [17]. However,
MRI is more expensive than echocardiography,
with lower temporal resolution. Parameters
related to wall motion and thickening are not
well developed. Furthermore, MRI is
contraindicated in patients with pacemakers and
is not an option after CRT.

Scintigraphic methods
Scintigraphic methods present the optimal
environment for digitization of physiologic data,
with high reproducibility, and tomography.
Recent work presents evidence of potential
benefit when widely available scintigraphic
methods, such as equilibrium radionuclide
angiography (ERNA) and myocardial perfusion
scintigraphy (MPS), are applied in unique ways
to CRT evaluation.

Myocardial perfusion scintigraphy
(MPS)
Gated SPECT myocardial perfusion scintigraphy
(MPS) accurately measures LV wall thickening.
It has been applied to measure ventricular
synchrony with a correlation to CRT outcome
[18]. This scintigraphic method compares well
with echocardiographic synchrony indices [19]
and can also evaluate viability. However, such
scintigraphic data is generally undersampled and
burdened with (unrecognized) noise related to
underperfused segments [18, 19].

There is a need for a widely available,
inexpensive, accurate, objective, reproducible way
to measure the pattern and extent of ventricular
synchrony and apply it in order to select CRT
patients, and predict and optimize their outcome
[20]. Such a method applied to the RV could be
of great value in patients with conditions
affecting the RV.

Equilibrium radionuclide angiography
(ERNA)
Overview
Equilibrium radionuclide angiography (ERNA)
provides widely available, objective, accurate,
inexpensive, and reproducible biventricular
function analysis, not contraindicated in
pacemaker patients. The method is being
developed in collaboration with Philips
Healthcare as a tool for synchrony evaluation.
The ERNA method presents a new basis for
ventricular synchrony analysis and could help
optimize CRT treatment.

ERNA relates intensity, or counts, to
(ventricular) chamber volume, independent from
volume measurements. Digitization can express
this data as “parametric” images unavailable to other modalities. Such methods can extract information not otherwise evident, presenting them in graphic form [21].

**Phase image analysis**

Phase image analysis is an ERNA-derived parametric imaging method, generated by the first Fourier harmonic, cosine curve, and fit of the blood pool time versus radioactivity curve. It presents a graphic representation of regional ventricular contraction which parallels regional excitation. This fitted curve is characterized by its amplitude, the curve magnitude, similar to the stroke volume of the raw curve, and phase angle, Ø, the timing of the curve within the cardiac cycle (Figure 1).

Ø relates to the sequence of regional contraction which is closely related to conduction [22, 23]. Earliest Ø relates to ventricular activation, mean Ø relates to the mean time of ventricular contraction, and the standard deviation (SD) of ventricular phase relates to the synchrony of contraction onset. Phase analysis, accurately and reproducibly evaluating the sequence and magnitude of regional wall motion, seems naturally adaptable to synchrony measurement.

ERNA phase image analysis identifies and characterizes the pattern of regional and global ventricular contraction and synchrony [24]. We established a powerful phase image display and analysis method, supportive of objective quantitation, and have applied it to characterize contraction abnormalities [24-26] and a wide variety of conduction abnormalities including right and left bundle branch block (RBBB and LBBB) [27], left anterior hemiblock [28], pre-excitation with Wolff Parkinson White Syndrome [29], augmented pre-excitation with pacing [30] and adenosine [31], the contraction/conduction pattern related to Mahaim fibers [32] and artificial pacemakers [24, 25].

We have displayed and characterized the effects of various pacing modes and the advantages of A-V synchrony [33] and we have developed a 3D SPECT reconstruction and display method to evaluate ventricular phase [34]. Faucher [35] used the SD of RV and LVØ as the measure of synchrony to characterize the contraction patterns of myopathic ventricles, while Kerwin [36] applied it to assess the benefits of biventricular pacing.

**New synchrony parameters**

We developed two reproducible ERNA parameters to assess left intraventricular dyssynchrony: “synchrony”, S and “entropy”, E.

In preliminary studies S and E were compared with other methods, and showed the best correlation with clinical response in HF patients requiring CRT.

**Definitions**

“S” expresses the degree of synchrony when the region of interest, the ventricle, contains more than one Ø. A pixel’s amplitude and Ø define its vector, where a vector’s length is the amplitude written as |vᵢ|, and:

$$S = \sum_{i=1}^{N} |vᵢ| / \sum_{i=1}^{N} |vᵢ|$$

| is the vector sum of all amplitudes based on the angular distribution of Ø, divided by the scalar sum of all vector lengths. S ranges from 0 (no synchronous contraction) to 1 (complete synchrony). Because S uses both phase and amplitude, it can be applied to the estimate of contraction potential if the region of interest were synchronized. If S is not 0, the potential functional gain is 1 - S.

Entropy, “E” – S may approach 0:
- if contraction is random
- if the region of interest consists of two sub-regions which are 180° out of synchrony.

Although ventricles present with a blend of these possibilities, their response to pacing may be very different. So we developed E:

![Figure 1a. Cosine curve fit. This image shows the raw time plotted against radioactivity (dotted line) and the first harmonic curve fit, derived from a normal ventricle. The fitted curve defines the phase angle, measured from 0° to 360°, while the amplitude (vertical white lines) parallels the stroke volume and represents one-half the depth of the curve excursion. The background has not been subtracted, giving the appearance of a reduced ejection fraction. (Reproduced by permission from: Frais M, Botvinick E, Shosa D et al. Phase Image Characterization of Ventricular Contraction in Left and Right Bundle Branch Block. Am J Cardiol. 1982; 50: 95-103).](image)

![Figure 1b. Phase analysis. The diagram presents a ventricle that is gray-scale coded for increasing delay in contraction sequence, from septum to lateral wall. Resultant cosine curves fitted to the regional time versus radioactivity curves are shown below. The septum and its corresponding curve begins contraction at the R wave. The region has a phase angle of 0° and is coded dark gray. The lateral wall and its related curve fill when the ventricle should empty. This wall would demonstrate paradoxical motion and the curve would have a phase angle of 180°. (Reproduced by permission from: Frais M, Botvinick E, Shosa D et al. Phase Image Characterization of Ventricular Contraction in Left and Right Bundle Branch Block. Am J Cardiol. 1982; 50: 95-103).](image)
where $M$ = the number of phase angles ($\theta$) in a region of interest and $p_i$ is the frequency of occurrence of $\theta_i$. $E$ measures the degree of randomness within the region, ranging from 0 (complete order), to 1 (fully random, dyssynchronous contraction).

**Early work**

We performed a simulation study [37] measuring left ventricular $S$ and $E$ in normal planar ERNAs acquired clinically in the left anterior oblique projection. To analyze the response of $S$ and $E$ in ventricles with variable dyssynchrony, we applied these parameters to model regions of interest (ROI). An ROI over the LV evaluated parameters in the normal group (N). An ROI spanning the left atrioventricular boundary served as a model for an LV aneurysm (An), while a random background region served as a model for severe diffuse global dysfunction (Diff). An area of background, with approximately two-thirds over the LV, was a model of severe regional dysfunction (Reg).

ROIs are shown in Figure 2, with related phase histograms in Figure 3. Figure 4 shows planar and SPECT amplitude and phase images in a normal patient.

The results are shown in Table 1. The mean phase angle, $\theta$, in the N group was similar to that previously reported, but was different from that in the other groups. The SD LV$\theta$ in the An, Diff and Reg groups were not different from each other. However, the $S$ and $E$ parameters were significantly different in all groups.

$S$ and $E$ calculated in ten varying ROIs of the same LV showed a variation of $\leq 0.02$. The new parameters were highly reproducible, well differentiated between patterns of systolic

\[
E = \sum_{i=1}^{M} p_i \log_2(p_i) - \log_2(M),
\]

Table 1. Comparison of left ventricular $S$ and $E$ in normal planar ERNAs and in ventricles with variable dyssynchrony.

<table>
<thead>
<tr>
<th></th>
<th>Mean LV$\theta$</th>
<th>SD LV$\theta$</th>
<th>LV $S$</th>
<th>LV $E$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normals (n = 22)</td>
<td>328.2° ± 19.3°*</td>
<td>12.2° ± 5.4°**</td>
<td>0.99 ± 0.01**</td>
<td>0.37 ± 0.08***</td>
</tr>
<tr>
<td>An (n = 22)</td>
<td>228.7° ± 21.1°*</td>
<td>92.1° ± 9.1°</td>
<td>0.41 ± 0.11 #</td>
<td>0.67 ± 0.07 ***</td>
</tr>
<tr>
<td>Diff Dysfunction (n = 22)</td>
<td>157.6° ± 28.0°*</td>
<td>95.1° ± 28.5°</td>
<td>0.24 ± 0.14 #</td>
<td>0.97 ± 0.02 ##</td>
</tr>
<tr>
<td>Reg Dysfunction (n = 22)</td>
<td>74.0° ± 19.3°*</td>
<td>97.6° ± 12.3°</td>
<td>0.70 ± 0.15</td>
<td>0.91 ± 0.03</td>
</tr>
</tbody>
</table>

* = all $p < 0.01$ vs each other; ** = $p < 0.01$ vs An, D and Diff; *** = $p < 0.01$ vs D and Diff; # = $p < 0.05$ vs each other and $p < 0.01$ vs Diff; ## = $p < 0.05$ vs Diff

Table 2. Post-CRT $S$ and $E$ compared with change in NYHA class

<table>
<thead>
<tr>
<th>Clinical Improvement in NYHA Class</th>
<th>0 (n = 13)</th>
<th>1 (n = 18)</th>
<th>2 (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean LV-RV$\theta$</td>
<td>18.2</td>
<td>1.2</td>
<td>14.7</td>
</tr>
<tr>
<td>LVEF</td>
<td>2.7 ± 4.5</td>
<td>4.3 ± 6.7</td>
<td>10.9 ± 9.2</td>
</tr>
<tr>
<td>SD$\theta$</td>
<td>7.7 ± 33.2</td>
<td>12.4 ± 24.4</td>
<td>28.4 ± 23.7</td>
</tr>
<tr>
<td>$S$</td>
<td>-0.06 ± 0.11</td>
<td>0.03 ± 0.11</td>
<td>0.13 ± 0.14</td>
</tr>
<tr>
<td>$E$</td>
<td>-0.05 ± 0.16</td>
<td>0.03 ± 0.11</td>
<td>0.11 ± 0.13</td>
</tr>
</tbody>
</table>

Table 3. Pre-CRT $S$ and $E$ compared with change in NYHA class.
dysfunction. We have measured normal values for both RV and LV $S$ and $E$.

$S$ and $E$ compared with clinical outcome
We studied 46 patients selected for CRT [38]. Seventy-two percent of the patients improved, but variably, after CRT. Patients were followed for more than six months and graded 2, 1 or 0 based on improvement in NYHA Class 2, 1 or 0 levels, respectively. Clinical change was correlated with LVEF changes, with the established measure of intraventricular synchrony, SD of LV $\varnothing$, the established measure of interventricular synchrony, mean LV$\varnothing$ - mean RV$\varnothing$, $S$, and $E$ after CRT. Table 2 shows the results.

Patients graded 2 showed large improvements in $S$ and $E$, less in LVEF, and still less in SD LV$\varnothing$. SD LV$\varnothing$-SD RV$\varnothing$ correlated not at all. While change in LVEF and SD LV$\varnothing$ could separate patients who improved by two NYHA classes from those not improving, 0, these were not sensitive enough to differentiate moderate clinical improvement (1) from no improvement (0). A change in $S$ was the only statistically significant parameter ($p < 0.02$) that differentiated patients in grade 1 from grade 0, while the intergroup differences in $E$ approached significance. The study also suggested the lack of importance of measures of interventricular synchrony. Figure 5 shows serial images in a patient who improved by two NYHA classes.

$S$ and $E$ Pre-CRT
We sought to establish baseline cutoff values of $S$ and $E$ that predict a good CRT outcome [38]. LVEF, SD LV$\varnothing$, and $S$ and $E$ calculated from pre-CRT ERNA, were compared with change in NYHA class, graded 2, 1, 0, as evaluated before and 6 months after CRT in the same group of 46 patients as described above. Table 3 shows the results. Baseline values of LVEF and SD LV$\varnothing$ could not differentiate clinical responders from non-responders.

When applied for patient selection, preoperative LVEF did not predict outcome. While overall 72% improved, a combined preoperative value of $S \leq 0.87$ and $E \geq 0.69$ predicted clinical improvement after CRT in 86% of patients. Patients with $S \leq 0.87$ and $E \geq 0.69$ showed a mean improvement of 1.48 NYHA Classes after CRT.

Figure 2. Regions of Interest (ROI) superimposed on the same phase image in a patient with normal systolic ventricular function. The examples show ROI applied for the calculation of mean $\varnothing$ and SD $\varnothing$ as well as $S$ and $E$ parameters in normal (N), LV aneurysm (An), diffuse global dysfunction (Diff), and severe regional dysfunction (Reg) groups.

Figure 3. Phase histograms extracted from the regions of interests shown in Figure 2 for the N, An, Diff, and Reg groups. The normal, bell-shaped distribution of $\varnothing$ values near 0° is seen in relation to the N region of interest, with the typical biphasic distribution of $\varnothing$ values in the An region of interest, a random $\varnothing$ distribution in the Diff region of interest, and a combination of N and Diff patterns in the Reg histogram.

Figure 4. Pre- and post CRT images. Above: pre-CRT images; phase (left) and amplitude (right). Gross dyskinesis in the apical and septal regions of the phase image before CRT is evident in the yellow coloration in these ventricular regions (arrow), matching that of atrial phase. The amplitude image on the right is the first harmonic counterpart of regional stroke volume, showing large black regions of reduced emptying (arrow). Below: Phase (left) and amplitude (right) images in the same patient post-CRT. Dyskinesis in the apical and septal regions of the phase image before CRT is now replaced with synchronous inward systolic wall motion evident in the orange coloration in these ventricular regions (arrow). The amplitude image on the right now shows large regions of restored amplitude and emptying (arrow).

Figure 5. Planar (left) and SPECT (right) ERNA Phase Synchrony Display. The images on the left are planar ERNA phase images in a pre-CRT heart failure patient with severe dyssynchrony. At the top are the unthresholded phase image (left), and intensity thresholded for amplitude image (right). The image below is the phase histogram, plotting phase angle on the abscissa against the number of pixels with each phase angle on the ordinate. The earliest ventricular phase is shown in red, followed by orange, yellow green and finally blue, the atrial phase. The images on the right are SPECT images of the isolated left ventricle, acquired in the same patient with polar map (top left), SPECT phase image in the anterior view (top right) and the histogram (below).
CRT while patients with $S \geq$ and $E \leq 0.69$ did not improve, changing only 0.98 NYHA Classes.

Parameters of $S$ and $E$ can be used to determine patients with the best likelihood of significant improvement after CRT. An earlier study demonstrated the value of phase imaging for location of the latest contracting segment.

**ERNA phase imaging for guiding CRT pacemaker placement**

In HF patients requiring CRT, there is no reliable method for determining the optimal site to place the LV pacemaker, i.e. the coronary sinus lead. However, ERNA provides an assessment of LV function and the location of dyssynchrony.

To determine the value of ERNA phase imaging for identifying the latest contracting LV segment as a guide to placement of the LV pacemaker lead, we compared the clinical outcome after CRT in 28 patients with NYHA Class III and IV HF who had been referred for CRT device implantation. All patients had given informed consent. The patients were divided into two groups. In one group of 16 patients, coronary sinus lead placement was based on the ERNA determination of the latest contracting segment. In the other group of 12 patients, the pacemaker was placed in the conventional lateral wall location [39].

We found that 6/12, i.e. 50%, of patients who underwent traditional coronary sinus lead placement showed improvement in NYHA class, while 14/16, i.e. 88%, of patients who had ERNA-guided lead placement had an improvement in NYHA class. More patients in the ERNA-guided group, whether the latest contracting segment was found to be in the lateral wall or elsewhere, showed clinical improvement, compared with the traditional placement group ($p = 0.02$ by Chi square analysis). In one patient in the ERNA-guided group who showed no clinical benefit from CRT, a PET scan demonstrated scar at the pacemaker lead site. This probably explains why this patient did not benefit. In this group too, the change in $S$ also significantly predicted the clinical response to CRT.

However, although promising, this was not a randomized study and used planar data to localize the latest contracting segment.

**RV synchrony**

Normal values were established for SD RVØ, $S$ and $E$. Over one-third of patients demonstrated abnormal RV $S$ and $E$ prior to CRT [40]. However, unlike LV parameters of synchrony, the pre-CRT RV parameters of synchrony could not predict outcome post-CRT, nor did the serial change in RV synchrony correlate with clinical improvement [41].

**Short QRS**

SD LV Ø, LV $S$ and $E$ were significantly worse in 12 patients with advanced HF and LVEF < 35% than in 11 patients without HF, all with a narrow QRS [42]. Further, 25% of these HF patients with a narrow QRS had synchrony parameters in the range previously shown to provide a high likelihood of significant clinical improvement post-CRT [38]. ERNA with synchrony analysis can potentially identify those HF patients with a narrow QRS complex who might benefit from CRT.

**SPECT**

We have adapted synchrony analysis to SPECT ERNA images. The method separates ventricles from atria and from each other, purely assessing biventricular synchrony in a polar display. In 16 of 17 cases imaged by both planar and SPECT ERNA, SPECT $S$ was lower and SPECT $E$ higher than planar values, $p < 0.05$ [43]. In 11 of 17 cases the contraction sequence appeared similar in SPECT and planar synchrony analysis. Six cases had an apical aneurysm which obscured planar basal segments where $S$ was 10% greater than SPECT $S$. SPECT ERNA promises to provide a global synchrony assessment.

**Conclusion**

The ERNA method described above presents a new basis for ventricular synchrony analysis and could help optimize CRT and its cost-effectiveness. The phase synchrony parameters described already show promise for optimizing CRT patient selection, helping to determine the benefit of the CRT intervention, guiding pacemaker placement among those with standard selection criteria, and identifying new categories of patients who may benefit from CRT. Further adaptation of the method to SPECT technology and its integration with the findings of other imaging studies, as well as those for assessing regional viability, will refine these methods, expand their capabilities, and could well establish them clinically.
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