Value of mechanical dyssynchrony as assessed by radionuclide ventriculography to predict the cardiac resynchronization therapy response

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Aims
To assess the value of mechanical dyssynchrony measured by equilibrium radionuclide angiography (ERNA) in predicting long-term outcome in cardiac resynchronization therapy (CRT) patients.

Methods and results
We reviewed 146 ERNA studies performed in heart failure patients between 2001 and 2011 at our institution. Long-term follow-up focused on death from any cause or heart transplantation. Phase images were computed using the first harmonic Fourier transform. Intra-ventricular dyssynchrony was calculated as the delay between the earliest and most delayed 20% of the left ventricular (LV) (IntraV-20/80) and inter-ventricular dyssynchrony as the difference between LV- and right ventricular (RV)-mode phase angles (InterV). Eighty-three patients (57%) were implanted with a CRT device after ERNA. Median follow-up was 35 [21–50] months. Twenty-four events were observed during the first 41 months. Median baseline ERNA dyssynchrony values were 28 [3 to 46] degrees for intraV-20/80 and 9 [2 to 24] degrees for interV. Comparing survival between CRT and non-CRT patients according to dyssynchrony status, log-rank tests showed no difference in survival in patients with no ERNA dyssynchrony (P = 0.34) while a significant difference was observed in ERNA patients with high level of mechanical dyssynchrony (P = 0.004).

Conclusion
ERNA mechanical dyssynchrony could be of value in CRT patient selection.

Keywords
CRT • mechanical dyssynchrony • equilibrium radionuclide angiography • heart failure

Background
Approximately 30% of patients are non-responders to cardiac resynchronization therapy (CRT), and it is well established that QRS duration is far from a perfect marker of mechanical dyssynchrony. Several imaging techniques have been proposed as alternatives for the identification of future responders. However, these attempts have had limited success so far, and more than a decade since the first description of CRT by Cazeau et al. in 2001, patient selection in current international guidelines is still based on QRS duration and pattern. The difficulty of identifying a technique at a reasonable cost that is able to combine simple algorithms with highly reproducible results explains why cardiac imaging has never been shown to be superior to ECG for patient selection.

Equilibrium radionuclide angiography (ERNA) (known also as radionuclide ventriculography) has been used for years and is considered as a gold standard for left ventricle ejection fraction (LVEF) measurement. It has a mid-range cost and is widely available. Fourier first harmonic analysis of phase images affords additional information about mechanical synchrony in heart failure (HF) patients. However, the potential incremental value of such data in predicting response to CRT is still unclear.

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We retrospectively studied a large cohort of patients who underwent ERNA (i) to describe the relationship between electrical and ERNA mechanical dyssynchrony and (ii) to assess whether ERNA could be of any additional value to predict the benefit of CRT.

Methods

Study design

We reviewed all ERNA studies performed in patients referred to our department between 2001 and 2011 for HF prognosis evaluation using LVEF assessment and phase analysis as previously reported. Patients included in this analysis had to be in sinus rhythm, to have significant systolic dysfunction (LVEF ≤ 40%) and no CRT device at the time of the test. Only exams with available clinical data were selected. For each patient, the following parameters were collected: age, sex, cardiovascular risk factors, aetiology of the cardiomyopathy (ischaemic vs. non-ischaemic), New York Heart Association (NYHA) class, QRS duration, the presence of a left bundle branch block (LBBB), haemoglobin, creatinine, medications and implantation of a defibrillator (ICD), or a CRT device after the exam. Long-term follow-up was used to define the benefit of CRT and focused on the following events: death from any cause or heart transplantation. Events were ascertained using hospital medical records, direct phone contact with the patient or family, and municipal registries. This study was approved by the ethical committee CEERB Paris Nord (IRB00006477).

ERNAs technique

Peripheral intravenous administration of technetium-99m was preceded by an injection of stannous pyrophosphate to allow in vivo labelling of the patient’s red blood cells. A gamma camera, equipped with a high-resolution collimation with parallel holes, was used for image acquisition. Sixteen ECG-gated images were acquired in a $64 \times 64$ matrix format, with a pre-count of 600 000 per frame. To suppress premature beats during ECG synchronization, a window threshold of 10 around the mean RR was used. A General Electric post-processing station was used for image quantification and phase analysis. Planar images were acquired in a left anterior oblique view [best left ventricular (LV)—right ventricular (RV) separation]. The radionuclide ventriculography analysis software (ECCAP, General Electric) allowed the functional variables of the right and left ventricles to be measured. Count-based LVEF was then computed using two semi-automatic regions of interest at end-diastole and end-systole. Phase images were computed using the first harmonic Fourier transform to display the mechanical contraction time for all the ventricular pixels of the image during one composite cardiac cycle. Quantitative analysis was performed for each ventricle in the form of phase histograms computed separately for the LV and RV end-diastolic regions of interest. Fourier phase analysis of ERNA, by increasing the temporal resolution above the acquisition frame duration, has been shown to be able to provide accurate measurements of right and left ventricular contraction delays in settings such as bundle branch block, ventricular pre-excitation, arrhythmogenic right ventricular cardiomyopathy, and Brugada syndrome.

Mechanical dyssynchrony assessment

From these histograms representing the distribution of the pixels for each ventricle according to their phases, two parameters for LV intra-ventricular dyssynchrony were calculated: IntraV-SD (standard deviation of the LV phases) and IntraV-20/80 (the delay between the earliest and most delayed 20% of the LV phases). RV dyssynchrony was assessed as the standard deviation of the RV phases (RVdys). For inter-ventricular dyssynchrony, the difference between LV- and RV-mode phase angles (interV) was assessed. Phases were expressed in degrees on a 0$^\circ$ to 360$^\circ$ scale covering the R–R interval duration of the composite cardiac cycle. On this scale, the beginning of the cardiac cycle is 0$^\circ$ and the end of the cycle is 360$^\circ$. Compared with phase values expressed in millisecond (time from R to end-systole), phases expressed in degrees are much less dependent on heart rate. These parameters were compared with electrical dyssynchrony (QRS duration) with subgroup analysis according to the origin of the cardiomyopathy.

Statistical analysis

A D’Agostino–Pearson test was used to assess normality. Continuous variables are reported as the mean and standard deviation for normally distributed variables while non-normally distributed ones are reported as the median and inter-quartile range. Categorical variables are reported as percentages. Baseline characteristics between patients with and without later CRT device implantation were compared using a t-test or a Mann–Whitney test for continuous variables and Pearson χ² test for categorical variables.

Univariate Cox proportional hazards models were used to assess the association between risk of increased probability of death or heart transplantation and the following variables: age, aetiology of the cardiomyopathy, the presence or not of an ICD, the presence or not of a CRT device, RVdys, creatinine, haemoglobin, significant ERNA mechanical dyssynchrony, and QRS duration. Assumption for proportional hazard was verified by testing for a non-zero slope in a generalized linear regression of the scaled Schoenfeld residuals. To test whether the presence of CRT device affects mortality or heart transplantation differently in patients with and without ERNA mechanical dyssynchrony, we performed a multivariate Cox proportional hazards model on complete data, including terms for CRT device (absence or presence) and ERNA dyssynchrony (absence or presence) and their interaction, and adjusting for clinically relevant variables. Hazard ratio (HR) (with 95% confidence interval) was presented to characterize the CRT effect within dyssynchrony levels (absence or presence). Additionally, Kaplan–Meier analyses with log-rank tests were performed to compare survival outcome between patients with and without CRT. Same methods were similarly performed for subgroup analyses, comparing survival between CRT and non-CRT patient according to the dyssynchrony status. A P-value of <0.05 was considered as significant. Statistical analyses were performed using MedCalc for Windows, version 12.1.3.0 (MedCalc Software, Mariakerke, Belgium) and SAS v9.2 (SAS Institute Inc.). The authors had full access to and took full responsibility for the integrity of the data. The authors have read and agreed to the manuscript.

Results

Study population

One hundred forty-six patients were identified in our database. Eighty-two patients (56%) were implanted with a CRT device after ERNA. The decision for CRT and/or ICD device implantation was based on the European guidelines during this period and/or the patient’s specific condition. Baseline characteristics are shown in Table 1. Patients in the CRT group were significantly older, had a poorer functional status, longer QRS with LBBB pattern, poorer renal function, and higher doses of diuretics. Median follow-up was 35 [21–50] months; no follow-up data were available for 11 patients. Thirty-one events including nine heart transplantations were observed. There was a significant difference between the patients...
with and without CRT device in terms of follow-up (40 [27–54] vs. 30 [27–41] months, \( P = 0.0007 \)). Hence, subsequent survival analyses have been performed after an administrative censure at 41 months (75th percentile of the no CRT group follow-up) to allow a similar comparison between both groups (24 events occurred during this period).

### Cardiac dyssynchrony measurement by ERNA: data reproducibility

Intra- and inter-observer variabilities were tested on 20 randomly chosen patients. Intra-observer correlation coefficients for IntraV-SD, IntraV-20/80, RVdys, and InterV were 0.99, 0.98, 0.99, and 0.97, respectively (\( P < 0.0001 \)). Inter-observer correlation coefficients for IntraV-SD, IntraV-20/80, RVdys, and InterV were all 0.99 (\( P < 0.0001 \)). The scatter diagram and the Bland–Altman plot for IntraV-20/80 inter-observer variability are shown in Figure 1.

### ERNA mechanical and electrical dyssynchrony relationship

Values for LV and interV dyssynchrony are shown in Table 2. There was a significant difference between ischaemic and non-ischaemic patients in terms of electrical dysynchrony, whereas there was no significant difference detected between both groups for all ERNA mechanical parameters. The scatter diagram plotting intraV-20/80 vs. intraV-SD (see Figure 2) demonstrated two groups of patients: Group 1 (67% of the cohort) with a strong correlation between the two parameters (\( r = 0.8, P < 0.0001 \)) and Group 2 (33% of the cohort) with \(< 0.10^2\) of intraV-20/80 dyssynchrony but a large range of intraV-SD dyssynchrony. Group 2 was notable for (i) a narrower QRS than that in Group 1 (110 [91–160] vs. 140 [115–165] ms, \( P = 0.02 \)) and (ii) a greater level of intraV-SD dyssynchrony in ischaemic patients than in the non-ischaemic ones (38 [29–45] vs. 24 [22–33] degrees, \( P = 0.02 \)). Such a difference between ischaemic and non-ischaemic patients was not observed in Group 1 (\( P = 0.52 \)). Right ventricular pacing did not impact any of the dyssynchrony parameters. Finally, for RVdys, the median value was 20 [15–29] degrees, significantly higher in non-ischaemic patients (26 [16–36] vs. 17 [13–26], \( P = 0.0005 \)) and in patients with a low LVEF (\( r = −0.3, P = 0.0001 \)).

### Prognostic value of a high level of ERNA mechanical dyssynchrony

As expected, CRT patients had a better long-term prognosis than patients without such device (87 vs. 71% event-free survival at 3 years, \( P = 0.004 \)). We defined patients with high level of mechanical dyssynchrony as those who demonstrated a either intraV-20/80 or interV value above the 75th percentile (20/80 > 46, interV > 24 degrees). Two examples of patients without and with ERA

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**Table 1** Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>All (n = 146)</th>
<th>CRT − (n = 64)</th>
<th>CRT + (n = 82)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65 [56–74]</td>
<td>60 [49–70]</td>
<td>69 [59–78]</td>
<td>0.002</td>
</tr>
<tr>
<td>Male (%)</td>
<td>81</td>
<td>84</td>
<td>78</td>
<td>0.45</td>
</tr>
<tr>
<td>Ischaemic CMP&lt;sup&gt;a&lt;/sup&gt; (%)</td>
<td>55</td>
<td>62</td>
<td>49</td>
<td>0.16</td>
</tr>
<tr>
<td>NYHA Class III or IV</td>
<td>55</td>
<td>36</td>
<td>70</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVEF&lt;sup&gt;b&lt;/sup&gt; (%)</td>
<td>24 [17–31]</td>
<td>23 [18–31]</td>
<td>24 [17–32]</td>
<td>0.93</td>
</tr>
<tr>
<td>HTN&lt;sup&gt;c&lt;/sup&gt; (%)</td>
<td>50</td>
<td>44</td>
<td>56</td>
<td>0.26</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>29</td>
<td>28</td>
<td>30</td>
<td>0.94</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>105 [85–137]</td>
<td>100 [83–125]</td>
<td>113 [90–143]</td>
<td>0.07</td>
</tr>
<tr>
<td>Hb&lt;sup&gt;d&lt;/sup&gt; (g/dL)</td>
<td>13 ± 2</td>
<td>13 ± 2</td>
<td>13 ± 2</td>
<td>0.99</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>140 [100–160]</td>
<td>100 [80–140]</td>
<td>160 [130–180]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LBBB&lt;sup&gt;e&lt;/sup&gt; pattern (%)</td>
<td>69</td>
<td>52</td>
<td>83</td>
<td>0.0003</td>
</tr>
<tr>
<td>Right ventricle pacing (%)</td>
<td>12</td>
<td>7</td>
<td>16</td>
<td>0.14</td>
</tr>
<tr>
<td>β-Blockers (%)</td>
<td>88</td>
<td>84</td>
<td>91</td>
<td>0.27</td>
</tr>
<tr>
<td>ACE&lt;sup&gt;f&lt;/sup&gt; or ARB&lt;sup&gt;g&lt;/sup&gt; (%)</td>
<td>98</td>
<td>97</td>
<td>99</td>
<td>0.82</td>
</tr>
<tr>
<td>MRA&lt;sup&gt;h&lt;/sup&gt; (%)</td>
<td>41</td>
<td>41</td>
<td>42</td>
<td>0.94</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>86</td>
<td>77</td>
<td>93</td>
<td>0.01</td>
</tr>
<tr>
<td>ICD&lt;sup&gt;i&lt;/sup&gt; (%)</td>
<td>29</td>
<td>19</td>
<td>37</td>
<td>0.03</td>
</tr>
<tr>
<td>Lost to follow-up (%)</td>
<td>8 (n = 11)</td>
<td>10 (n = 6)</td>
<td>6 (n = 5)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

**Bold values indicate significant** \( P < 0.05 \).

<sup>a</sup>Cardiomyopathy.

<sup>b</sup>Left ventricle ejection fraction.

<sup>c</sup>Hypertension.

<sup>d</sup>Haemoglobin.

<sup>e</sup>Left bundle branch block.

<sup>f</sup>Angiotensin-converting enzyme.

<sup>g</sup>Angiotensin II receptor blocker.

<sup>h</sup>Mineralocorticoid receptor antagonist.

<sup>i</sup>Intra-cardiac defibrillator.
dyssynchrony are displayed in Figure 3. Thirty-six per cent of the patients were considered as having either intra-ventricular or inter-ventricular dyssynchrony. Among the 74% of our patients with a LBBB QRS morphology or duration >150 ms, 43% had also a high level of mechanical dyssynchrony measured by ERNA vs. only 13% among those with a QRS duration ≤ 150 ms and no LBBB pattern (P = 0.003). Interestingly, among patients with no CRT device and a QRS duration ≤ 150 ms or no LBBB pattern, those with ERNA dyssynchrony had the worst long-term prognosis (Figure 4, P = 0.004).

Assessing the association of potential predictors with risk of death or heart transplantation (excluding LVEF because of its status as a perfect predictor), the absence of CRT device appeared to be the only significant predictor of events in Cox univariate analysis (see Table 3). Similarly on univariate Kaplan–Meier analysis, the absence of CRT was associated with increased probability of mortality of heart transplantation (P = 0.01). We tested formally whether the presence of CRT device differentially affects mortality or heart transplantation in patients with and without ERNA mechanical dyssynchrony using a multivariate analysis including terms for CRT, ERNA dyssynchrony, and their interaction while adjusting for age and the absence of a defibrillator. Based on this model, when ERNA dyssynchrony was absent, HR for absence of CRT was 1.469 (CI 0.523–4.127), while when ERNA dyssynchrony was present, HR for the absence of CRT was 8.324 (CI 1.647–42.063). These last results have to be interpreted with caution since the

**Table 2** Cardiac dyssynchrony according to the aetiology of the cardiomyopathy

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Non-ischaemic</th>
<th>Ischaemic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS duration (ms)</td>
<td>140 [100 to 160]</td>
<td>140 [120 to 180]</td>
<td>120 [96 to 160]</td>
<td>0.03</td>
</tr>
<tr>
<td>IntraV-SD (deg)</td>
<td>37 [26 to 50]</td>
<td>32 [23 to 49]</td>
<td>38 [28 to 51]</td>
<td>0.09</td>
</tr>
<tr>
<td>IntraV-20/80 (deg)</td>
<td>28 [3 to 46]</td>
<td>30 [3 to 46]</td>
<td>27 [3 to 46]</td>
<td>0.93</td>
</tr>
<tr>
<td>InterV (deg)</td>
<td>9 [-6 to 24]</td>
<td>12 [-3 to 25]</td>
<td>6 [-6 to 18]</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Bold value indicates significant P < 0.05.

aIntra-ventricular dyssynchrony.

bInter-ventricular dyssynchrony.

**Figure 1** Scatter diagram (left panel) and Bland–Altman plot (right panel) showing an excellent agreement between two observers for InterV-20/80.

**Figure 2** Plot of intraV-20/80 vs. intraV-SD. Two groups of patients are demonstrated: Group 1 where there is a strong correlation between the two parameters and Group 2 with <10° of intraV-20/80 dyssynchrony but a large range of intraV-SD dyssynchrony.
interaction term was not statistically significant ($P = 0.07$), probably because of a lack of power: among patients without dyssynchrony, 9/40 events were observed for patients without CRT and 7/46 for patients with CRT. Among patients with high level of mechanical dyssynchrony, 6/18 events were observed for patients without CRT and only 2/30 events for patients with CRT. HR for 10 years age difference was 1.025 (CI 0.734–1.433, $P = 0.88$), and HR for the absence of a defibrillator was 1.981 (CI 0.656–5.983, $P = 0.23$).
We decided to perform additional exploratory subgroup analysis, comparing survival between CRT and non-CRT patient according to the dyssynchrony status. Log-rank tests showed no difference in survival in patients with no ERNA dyssynchrony (Figure 5A; \( P = 0.31 \)) while a significant difference was observed within ERNA patients with high level of mechanical dyssynchrony (Figure 5B; \( P = 0.004 \)).

### Discussion

This study investigated mechanical dyssynchrony by radionuclide ventriculography in a cohort of ischaemic and non-ischaemic patients comparable in size to other single-centre studies. We showed that ERNA mechanical dyssynchrony pattern is linked to the underlying cardiomyopathy and can be discordant with electrical dyssynchrony. Furthermore, we believe the trend observed in this study can be of great interest for clinical decision, as the model suggests a difference of CRT effect depending on the presence of ERNA dyssynchrony. Based on our clinical experience, those results could be of importance to better understand the impact of CRT on survival.

### Table 3  Cox proportional hazard model with death from any cause or heart transplantation as an end point

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR (95% CI)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.001 (0.971–1.033)</td>
<td>0.94&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Non-ischaemic cardiomyopathy</td>
<td>0.901 (0.405–2.003)</td>
<td>0.80</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>0.888 (0.671–1.175)</td>
<td>0.41</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.002 (0.997–1.007)</td>
<td>0.48</td>
</tr>
<tr>
<td>No ICD&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.472 (0.850–7.193)</td>
<td>0.07&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>QRS ( \geq 150 ) ms</td>
<td>0.615 (0.242–1.565)</td>
<td>0.29</td>
</tr>
<tr>
<td>ERNA dyss&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.034 (0.444–2.408)</td>
<td>0.94&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>No CRT&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2.717 (1.193–6.190)</td>
<td>0.02&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Bold values indicate significant \( P < 0.05 \).

<sup>a</sup>Variables used in the multivariable analysis.

<sup>b</sup>Intra-cardiac defibrillator.

<sup>c</sup>Significant intra-ventricular dyssynchrony or inter-ventricular dyssynchrony by ERNA.

<sup>d</sup>Cardiac resynchronization therapy.

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**Figure 5** Benefit of CRT according to baseline ERNA mechanical dyssynchrony (ERNAdys).
Electrocardiogram-gated single-photon emission computed tomography myocardial perfusion imaging ERNA, and other imaging techniques for mechanical dyssynchrony assessment

In any conventional gated single-photon emission computed tomography myocardial perfusion imaging (GSPECT MPI) study, mechanical dyssynchrony can be assessed with no need for any additional acquisition. In addition to mechanical dyssynchrony, GSPECT MPI offers important information about the degree of myocardial scar, which has been shown to be a major determinant of response to CRT. However, compared with ERNA, it suffers from a lower temporal resolution, an absence of right ventricle assessment, a lower accuracy for LVEF determination, and an absence of inter-ventricular dyssynchrony assessment. On another hand, the major limitations of planar gated blood-pool ventriculography besides the absence of myocardial scar determination are an overlap between adjacent structures and a poor anatomic localization. These two issues could be solved by the use of gated blood-pool SPECT where similar principles of phase analysis are used for detecting intra-ventricular and inter-ventricular dyssynchrony. Since the gated blood-pool SPECT data are analysed in three dimensions, a better separation of adjacent structures and superior localization is obtained, compared with gated blood-pool ventriculography. Compared with other imaging techniques, the main advantages of both nuclear methods are that they are widely available, usable in imaging fusion strategies (with CT for coronary vein anatomy for example) and based on automated software. As in previous studies, ERNA has a good signal-to-noise ratio, and our method has shown excellent intra- and inter-observer reproducibility. However, nuclear methods expose the patient to ionizing radiation and are usually more expensive than echocardiography.

ERNa parameters for mechanical dyssynchrony quantification: which parameter to choose?

The use of ERNA to assess LV mechanics has been previously reported. After drawing the regions of interest (ROI) on the planar images for left and right ventricles, time-activity curves, representing the variation of the ventricular volumes over the cardiac cycle, are computed. These time-activity curves are characterized by amplitude and phase angle with the standard deviation of the phase angles of the pixels in the LV representing intra-ventricular dyssynchrony and the difference between the means of the phase angles of both ventricular ROI representing inter-ventricular dyssynchrony. In our study, we tested one new parameter called intraV-20/80. The concept of this parameter was based on our clinical observations: intraV-SD could be significantly increased in the presence of delayed myocardium, even if the amount of such delayed myocardium compared with the entire ventricle did not seem significant. This can be explained by the fact that intraV-SD describes a normal/Gaussian distribution of the pixels which sometimes does not exist, especially in ischaemic cardiomyopathy. We hypothesized that there might be a threshold of delayed myocardium that becomes haemodynamically significant. By comparing the time to the most delayed 20% of the LV (slightly more than three segments, or one wall) with the time to the earliest 20%, intraV-20/80 could be more specific to identify patients with a significant amount of delayed myocardium: a patient with only a small amount of delayed myocardium (as expected in an ischaemic patient) may have a high intraV-SD value and a low intraV-20/80 one in comparison to a patient with more diffuse disease (like non-ischaemic cardiomyopathy) where a large part of the LV is delayed. In the absence of a gold standard for mechanical dyssynchrony assessment, this hypothesis is challenging to prove, but our results seem to support it. Figure 1 shows that some patients may have a high intraV-SD dyssynchrony without increased intraV-20/80. In this group of patients with intraV-20/80 < 10%, ischaemic patients had higher values of intraV-SD compared with the non-ischaemic ones. This supports the potential high sensitivity of intraV-SD for dyssynchrony diagnosis but its low specificity for identifying patients with significant amount of delayed myocardium. To be a CRT responder, a patient needs not only to have delayed myocardium, but also to have a significant amount of this delayed myocardium compared with the total LV mass.

Cut-offs for ERNA dyssynchrony

Faucher and colleagues studied a large population of dilated cardiomyopathies (25% with LBBB pattern) and showed that only intra-ventricular dyssynchrony with a SD cut-off of 50 ms was a marker of long-term events. Similarly, a small study with a mixed population of ischaemic and non-ischaemic patients showed that clinical improvement was observed in patients with an initial LV phase standard deviation > 50° that decreased with pacing. In contrast, Dauphin and colleagues studying a more heterogenous population (ratio non-ischaemic/ischaemic of roughly 2/1) could not find any predictive value of intra-ventricular dyssynchrony but found that an inter-ventricular dyssynchrony cut-off value of 25.5° for intra-ventricular synchrony was a good predictor of CRT response. In the absence of two distinct populations to identify cut-offs for ERNA dyssynchrony, we used the 75th percentile for intraV and interV parameters, which appeared to be close to the above cited values. These thresholds demonstrated similar predictive values as previous studies. A validation cohort is however needed to corroborate these results and test the value of these thresholds in an external population.

Potential clinical value of mechanical dyssynchrony assessment by ERNA

The trend observed in the multivariate Cox model (and comforted by the exploratory subgroup analyses) for the interaction effect between CRT and ERNA dyssynchrony on long-term events suggests that this imaging technique could be helpful to refine CRT patient selection. Since there is no gold standard measurement for dyssynchrony, sensitivity and specificity of criteria are based on response to therapy, which is not only affected by baseline dyssynchrony but also lead placement, the presence of scar, and other confounding factors. Thus, there is a growing appreciation that the use of only one or two parameters is likely to be inadequate for optimal identification of CRT responders. Our results suggest the benefit of CRT in patients without a high level of mechanical dyssynchrony might be poor. A prospective study is required to test the negative
predictive value of ERNA. If high, such information may be helpful to clinicians, especially in patients with borderline indications for CRT.

Our study has some limitations

First, despite our low rate of patients lost to follow-up (<8%), we present a retrospective study with a large and heterogeneous cohort. The patient’s treating physician was informed of the ERNA results, including dyssynchrony measurements since it was reported as a prognostic factor. This information may have influenced the decision to perform CRT implantation in borderline situations, which could have induced a selection bias. Although we are not able to accurately measure this effect, baseline characteristics of patients with a CRT device suggest that most of them met usual criteria from the guidelines at that time. Given the retrospective nature of the analysis, there were significant differences between the CRT and no-CRT groups including, for example, a lower rate of lost to follow-up, more severe HF, or a higher prevalence of ICDs in the CRT group. These differences may have influenced the outcome of the patients and consequently our findings. Our study suffers also from the absence of an intermediate parameter like reverse cardiac remodelling and of a distinct population to determine accurate cut-offs for ERNA dyssynchrony. We did not find any additional value of the measure of RV dyssynchrony, although it was significantly higher in the non-ischaemic population, suggesting a more diffuse disease involving the two ventricles. RV tomography allowing for RV volume and functional assessment would have been of great interest since it has been demonstrated that they are independent predictors of prognosis in CRT patients.22 As previously discussed, ERNA suffers from the absence of myocardium scar assessment and a poor anatomical resolution. The use of gated blood-pool SPECT could have substantial additional value. Additionally, this retrospective study was not powered to detect interaction between CRT and ERNA dyssynchrony. In particular, small number of events (8/48) was observed among patients with ERNA dyssynchrony. Subgroup analyses are promising but are known to be less formal then model with interaction. The reader should interpret them as exploratory analysis. Additional events (with or without CRT) may have led to different conclusion regarding the interaction. Results should be validated with another cohort.

Conclusion

This retrospective study suggests that phase analysis of ERNA may be helpful in pre-implantation patient assessment to predict the response to CRT. The optimal cut-offs of each parameter are yet to be determined, and the additional clinical value has to be confirmed in a large prospective cohort. If so, ERNA dyssynchrony could identify patients in whom the procedure may not be beneficial and those, in borderline situations, who may benefit from the therapy. This would improve the overall rate of therapy success.

Conflict of interest: none declared.

References

A 60-year-old man presented with chest pain after an accidental fall. Chest x-ray showed massive opacification of the left lung, implying haemothorax (Panel A). Echocardiography revealed not only a tiny pericardial effusion but also a subtle flow signal with a 0.38 m/s peak systolic velocity from the right ventricle (RV) into the pericardial space (Panels B and C; see Supplementary data online, Video S1). Contrast-enhanced computed tomography demonstrated a small pericardial effusion localized anteriorly and on the left side. The anterior lesion was partially enhanced and contiguous with the RV cavity, suggesting the spurting of contrast medium from the RV into the pericardial cavity (Panel D, arrow). The left lesion communicated with the pleural cavity, implying pericardial rupture (Panel E, arrow). These findings suggest simultaneous traumatic cardiac and pericardial rupture and that the cause of the bleeding that produced the massive haemothorax was blunt RV injury. Rapidly worsening hypoxia (saturation of 88%) drove us to perform chest drainage in preparation for urgent surgery; however, we had to halt the process due to drainage-associated excessive hypotension. Intraoperatively, we found a 15-mm-long tear in the RV free wall and a partially ruptured pericardium (Panel F, arrow). Postoperative course was uneventful.

When we encounter it, an early diagnosis followed by timely repair is crucial. Visualizing spurting from the cardiac chamber is a critical sign of coexisting cardiac and pericardial rupture, and secondary haemothorax. In this case, the pericardial rupture seemed to protect against cardiac tamponade and enabled us to detect the spurting flow signal. The pericardial rupture was blunt, and the cause was presumably cardiac tissue injury due to the impact of the external force. Performing chest drainage was not an easy decision because drainage-associated hypotension could further reduce cardiac output. The fact that we were able to diagnose and treat the patient successfully serves as an important reminder to consider pericardial rupture in patients with chest trauma.