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CHAPTER 6

Prediction of cardiac resynchronization therapy response: value of calibrated integrated backscatter imaging.

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Background. Left ventricular (LV) fibrosis is important for the response to cardiac resynchronization therapy (CRT). Calibrated integrated backscatter (IB) derived by 2D-echocardiography quantifies myocardial ultrasound reflectivity which may provide a surrogate of LV fibrosis. The aim of the study was first to investigate the relation of myocardial ultrasound reflectivity assessed with calibrated IB on CRT-response; second to explore the "myocardial ultrasound reflectivity-CRT-response" relation in ischemic and non-ischemic heart failure (HF) patients.

Methods and Results. 159 HF patients referred for CRT underwent an extensive echocardiographic evaluation at baseline and at 6-month follow-up. LV dyssynchrony was derived from speckle-tracking analysis. Calibrated IB was obtained from the parasternal long-axis view. The mean value of calibrated IB of the antero-septal and posterior wall was used to estimate myocardial ultrasound reflectivity. CRT-response was defined as reduction ≥15% of LV end-systolic volume. At baseline LV dyssynchrony was significantly larger in responders as compared to non-responders (188±96ms vs. 115±68ms, p<0.001) and CRT-responders showed less myocardial ultrasound reflectivity as compared to non-responders (-20.8±3.0dB vs. -17.0±3.0dB, p<0.001). In multivariable logistic regression analysis independent predictors for CRT-response were LV dyssynchrony, renal function and myocardial ultrasound reflectivity. Importantly, myocardial ultrasound reflectivity provided an incremental value to CRT-response (Chi-square change=40, p<0.001). Considering ischemic HF patients, the only independent predictor of CRT-response was myocardial ultrasound reflectivity whereas in non-ischemic HF patients independent predictors of LV reverse remodeling were myocardial ultrasound reflectivity, LV dyssynchrony and renal function.
Conclusions. Assessment of myocardial ultrasound reflectivity is important in the prediction of CRT-response in ischemic and non-ischemic patients.

INTRODUCTION

Landmark randomized clinical trials have shown the benefits of cardiac resynchronization therapy (CRT) on heart failure (HF) symptoms, left ventricular (LV) function and survival.\(^1\)\(^2\) Thus far, despite current selection criteria,\(^1\) up to 30% of the patients does not show clinical response to CRT. Furthermore, considering LV reverse remodeling as end-point of the treatment, non-response rate is even higher (40-45%).\(^4\)

Among different reasons proposed to explain the lack of response to CRT, the etiology of HF remains still controversial. In the CARE-HF trial, ischemic HF patients showed a reduction in LV volumes or improvement in LV function to a lesser degree than non-ischemic HF patients.\(^5\)\(^6\) Previous data suggest that the extent and location of LV fibrosis, strongly influence response to CRT in patients with ischemic etiology of HF.\(^7\)\(^12\) The presence of LV fibrosis has been also demonstrated in mixed population of ischemic and non-ischemic HF patients.\(^13\) However, particularly in non-ischemic HF patients, little is known about the influence of the LV fibrosis on CRT response. At present, contrast-enhanced cardiac magnetic resonance (CMR) is considered the gold standard to detect LV fibrosis,\(^14\) but its use is limited by low availability.\(^15\) Two-dimensional (2D) echocardiography imaging is more widely available than contrast-enhanced CMR and, ultrasonic integrated backscatter (IB) derived by 2D echocardiography provides information on myocardial ultrasound reflectivity which may be a surrogate for fibrosis of the insonified tissue.\(^16\)\(^17\) Recent studies demonstrated the use of this technique in different groups of patients to characterize myocardial ultrasound reflectivity.\(^18\)\(^20\) The echocardiographic assessment of myocardial ultrasound reflectivity along with the evaluation of LV mechanical dyssynchrony may provide more comprehensive and valuable information to select candidates to CRT. In the current study calibrated IB was used to quantify myocardial ultrasound reflectivity in HF candidates for CRT. The aim of the study was twofold: first to investigate the influence of myocardial ultrasound reflectivity on CRT-response in general; second to explore the “myocardial ultrasound reflectivity -CRT response” relation specifically in ischemic and non-ischemic HF patients.
**METHODS**

**Patient population and protocol**

A total of 184 consecutive HF patients scheduled for CRT were prospectively included. According to current guidelines, the inclusion criteria were: New York Heart Association (NYHA) functional class III-IV, sinus rhythm, LV ejection fraction (LVEF) ≤35% and QRS duration ≥120 ms. Etiology of HF was considered ischemic in the presence of significant coronary artery disease (>50% stenosis in ≥1 major epicardial coronary artery) on coronary angiography and/or a history of myocardial infarction or revascularization.

All patients underwent a clinical and echocardiographic evaluation at baseline and 6 months after CRT assessing NYHA functional class, hemoglobin and renal function, LV volumes and LVEF. Finally, the extent of myocardial ultrasound reflectivity was estimated as the mean of calibrated IB of the antero-septal and posterior walls in order to: 1. determine the role of myocardial ultrasound reflectivity on CRT-response; 2. study the relation between myocardial ultrasound reflectivity and CRT-response in ischemic and non-ischemic HF patients.

**Standard echocardiography**

All patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed Vivid 7, General Electric-Vingmed, Milwaukee, Wisconsin, USA). Standard 2D images were obtained using a 3.5-MHz transducer and, digitally stored in cine-loop format; the analysis was performed offline using EchoPAC version 7.0.0 (General Electric-Vingmed).

From the standard apical views (4- and 2-chamber) LV volumes and LVEF were calculated according to the American Society of Echocardiography guidelines. At 6 months follow-up, patients were classified as echocardiographic responders based on a reduction ≥15% of LV end-systolic volume (LVESV).

**Mechanical dyssynchrony**

In the current study 2 types of mechanical dyssynchrony were assessed: the interventricular mechanical dyssynchrony and the intra-LV mechanical dyssynchrony (LV dyssynchrony). Interventricular mechanical dyssynchrony was quantified using the interventricular mechanical dyssynchrony index. LV dyssynchrony was assessed using speckle-tracking echocardiography. LV dyssynchrony was derived from the radial
Calibrated integrated backscatter

Calibrated IB is a parameter based on gray-scale 2D images which evaluates myocardial ultrasound reflectivity. In the heart, the pericardium is the anatomic structure with the highest content of fibrosis and with the highest ultrasound reflectivity; whereas blood pool has the lowest ultrasound reflectivity since no fibrous tissue exists. The myocardium shows an intermediate ultrasound reflectivity and this reflectivity may increase together with the amount of fibrosis.\textsuperscript{16, 18-20} Gray-scale 2D images were obtained at parasternal long-axis view, with frame rates between 80 and 120 frames/s, depending on the sector width, and 3 cardiac cycles were stored in cine-loop format for the offline analysis (EchoPAC version 7.0.0, General Electric-Vingmed). A fixed 9x9-mm region of interest was positioned in the mid-myocardium of the antero-septal and posterior walls of the LV and a fixed 2x3-mm region of interest was positioned in the pericardium. A measure of myocardial ultrasound reflectivity or tissue density was obtained with calibrated IB by subtracting pericardial IB intensity from myocardial IB intensity of the LV antero-septal and LV posterior walls. The measurements of calibrated IB were performed at a fixed point in the cardiac cycle (peak of the QRS complex) and expressed in decibel (dB).\textsuperscript{16, 18-20} The mean value of calibrated IB of the LV antero-septal and posterior walls was calculated to indicate the myocardial ultrasound reflectivity (Figure 1).\textsuperscript{16}

CRT implantation

All patients received a biventricular pacemaker with cardioverter-defibrillator function (Contak Renewal, Cognis, Boston Scientific St. Paul, Minnesota; or InSync Sentry, Consulta, Medtronic Inc. Minneapolis, Minnesota; Lumax 340 HF-T, Biotronik, Berlin). The right atrial and ventricular leads were positioned conventionally. All LV leads were implanted transvenously, and placed preferably in a (postero-)lateral vein. A coronary sinus venogram was obtained using a balloon catheter, followed by the insertion of the LV pacing lead. An 8-F guiding catheter was used to place the LV lead (Easytrak, Boston Scientific, or Attain-SD, Medtronic, or Corox OTW Biotronik) in the coronary sinus.
Continuous variables are presented as mean ± standard deviation. Categorical data are presented as numbers and percentages. Unpaired T test was used to compare continuous variables between HF patients with vs. without 6 months follow-up, responders vs. non-responders, and ischemic vs. non-ischemic HF patients. Paired T test was used to compare baseline and 6 months follow-up data either in responders and non-responders. Chi-square test was used to compare categorical variables. To determine the reproducibility of calibrated IB, 20 HF patients were randomly selected. For each of the selected patients, the measurements of calibrated IB were repeated by the same observer in a blinded-fashion and at a separate time (1 week later). To evaluate interobserver variability, a second independent observer re-analyzed the same dataset.

Intra- and inter-observer variability were assessed using intraclass correlation coefficients.
Linear regression analysis was performed to assess the correlation between the relative change of LVESV and calibrated IB in the overall population, in ischemic and non-ischemic HF patients.

In order to identify variables related to a positive response to CRT, uni- and multivariable logistic regression analyses were performed including baseline clinical (age, gender, etiology, NYHA functional class, QRS duration, renal function and hemoglobin) and baseline echocardiographic (LVESV, LVEF, LV dyssynchrony, calibrated IB) characteristics of the patients. Only variables with p<0.10 in univariable analysis were entered as covariates in the multivariable model. The multivariable logistic regression analysis was performed using a forward selection method with entry p value <0.05. Model discrimination was assessed using c-statistic and model calibration using Hosmer-Lemeshow statistic. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. To increase clinical utility, OR and 95%CI of continuous variables were reported as per 1 year increase in age, per 10ms increase in QRS width at baseline, per 30ml/min increase in estimated glomerular filtration rate, per 1mmol/l increase in hemoglobin, per 50ml increase in LVESV, per 5% increase in LVEF, per 50ms increase in LV dyssynchrony, and per 5dB increase in calibrated IB. The incremental value of myocardial ultrasound reflectivity over other variables was assessed by calculating the global chi-square test for each model. In order to identify variables related to a positive response to CRT in the subgroups of patients with ischemic and non-ischemic etiology of heart failure, uni- and multivariable logistic regression analyses were performed including the same baseline variables as indicated above, using the same inclusion criteria for the multivariable logistic regression analysis.

All statistical tests were 2-sided, and a p value <0.05 was considered significant. The statistical software program SPSS 16.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

In 13(7%) of 184 patients, calibrated IB analysis was not feasible due to suboptimal gray-scale 2D images with poor differentiation between myocardium and pericardium, and these patients were excluded from the analysis. Furthermore, of the 171 patients included, 12(7%) did not complete the 6 months follow-up; 4 patients died, 2 patients had LV pacing switched off due to intolerable phrenic stimulation and 6 patients were
lost to follow-up. Therefore, baseline and 6 months follow-up data were available for 159 patients.

**Patient population**

The general characteristics of the overall patient population are summarized in Table 1. The mean age was 66±10 years and 132 patients were male. Importantly, 58% of the patients had ischemic etiology of HF; the mean LV end-diastolic volume (LVEDV) was 218±81ml and the mean LVEF was 25±7%. No significant differences were observed between HF patients with and without 6 months follow-up data.

**Calibrated integrated backscatter**

The mean myocardial ultrasound reflectivity of the LV at baseline quantified with calibrated IB was -19.2±3.7dB. The intra- and inter-observer agreements for calibrated IB were 0.91 and 0.92, respectively.

In addition, myocardial ultrasound reflectivity was not related to QRS duration ($r=0.09$, $p=0.24$), whereas a weak but significant inverse relation between myocardial ultrasound reflectivity and renal function ($r=-0.17$, $p=0.039$) was observed.

**Responders vs. non-responders**

Table 2 shows the baseline clinical characteristics of CRT responders and non-responders. There were no differences in clinical characteristics, although non-responders showed a trend to higher prevalence of ischemic etiology ($p=0.10$). Conversely, QRS duration, estimated glomerular filtration rate and hemoglobin were higher in responders as compared to non-responders. There were no differences in baseline LV volumes and LVEF for responders and non-responders (Table 3). LV dyssynchrony was significantly larger in responders as compared to non-responders (188±96ms vs. 115±68ms, $p<0.001$), whereas only a trend towards a larger interventricular dyssynchrony in responders as compared to non-responders was observed (41±23 ms vs. 35±33ms, $p=0.17$). Finally, CRT responders showed lower myocardial ultrasound reflectivity as compared to non-responders (-20.8±3.0dB in responders vs. -17.0±3.0dB in non-responders, $p<0.001$; Table 3).
At 6 months follow-up, only responders showed a significant decrease in LVEDV and LVESV (by definition), with a significant increase in LVEF (Table 3). In addition,
responders revealed a more synchronous LV contraction after 6 months of CRT whereas in non-responders the LV dyssynchrony remained unchanged (Table 3). Of note, the relative change in LVESV (delta LVESV %) at 6 months follow-up was significantly related to calibrated IB ($r=0.50$, $p<0.001$; Figure 2A).

Prediction of LV reverse remodeling

At univariable logistic regression, ischemic etiology, QRS duration, estimated glomerular filtration rate, hemoglobin, LV dyssynchrony, calibrated IB were significantly related to LV reverse remodeling at 6 months follow-up (Table 4). At multivariable logistic regression analysis, the independent predictors of response to CRT were estimated glomerular filtration rate, LV dyssynchrony and calibrated IB (Table 4). Furthermore, calibrated IB had incremental value over LV dyssynchrony and estimated glomerular filtration rate for prediction of response to CRT (chi-square change=40, $p<0.001$, degree of freedom=1).

Table 2. Clinical characteristics of responders vs. non-responders at baseline.

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Non-responders</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65±9</td>
<td>67±11</td>
<td>0.43</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>71/20</td>
<td>52/16</td>
<td>0.85 (df=1)</td>
</tr>
<tr>
<td>Medication, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>83(91)</td>
<td>61(90)</td>
<td>0.95 (df=1)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>78(86)</td>
<td>59(87)</td>
<td>0.96 (df=1)</td>
</tr>
<tr>
<td>Diuretics and/or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>77(85)</td>
<td>57(84)</td>
<td>0.96 (df=1)</td>
</tr>
<tr>
<td>Etiology, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>48(53)</td>
<td>45(66)</td>
<td></td>
</tr>
<tr>
<td>Non-ischemic</td>
<td>43(47)</td>
<td>23(44)</td>
<td>0.10 (df=1)</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>159±32</td>
<td>148±32</td>
<td>0.028</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (ml/min)</td>
<td>76±31</td>
<td>64±35</td>
<td>0.023</td>
</tr>
<tr>
<td>Hemoglobin (mmol/l)</td>
<td>8.4±0.9</td>
<td>8.0±0.9</td>
<td>0.040</td>
</tr>
<tr>
<td>NYHA class (III/IV)</td>
<td>85/6</td>
<td>62/6</td>
<td>0.60 (df=1)</td>
</tr>
</tbody>
</table>

Abbreviations see Table 1.
Of the 159 patients with 6 months follow-up data, 93 patients had ischemic etiology of HF, whereas 66 had a non-ischemic HF. The baseline clinical characteristics were not different between patients with ischemic and non-ischemic cardiomyopathy. Conversely, patients with ischemic cardiomyopathy had significantly higher LVEF (26±7% vs. 23±7%, p<0.001) and less LV dyssynchrony (144±92ms vs. 175±90ms, p=0.036) as compared to patients with non-ischemic cardiomyopathy. In addition, myocardial ultrasound reflectivity estimated with calibrated IB was higher in patients with ischemic as compared to non-ischemic cardiomyopathy (-18.5±3.8dB vs. -20.2±3.0dB, \( * \leq 0.001 \)).
Finally, the relationship between the relative change of LVESV at 6 months follow-up and calibrated IB was stronger in patients with ischemic cardiomyopathy (r=0.56, p<0.001; Figure 2B) as compared to patients with non-ischemic HF (r=0.35, p=0.005; Figure 2C).

**Prediction of LV reverse remodeling in ischemic etiology**

In the subgroup of patients with ischemic HF, in univariable logistic regression, LVEF, LV dyssynchrony, calibrated IB were significantly related to LV reverse remodeling at 6 months follow-up (Table 5). In multivariable logistic regression analysis, the only independent predictor of response to CRT was calibrated IB (Table 5).
Prediction of cardiac resynchronization therapy response: value of calibrated integrated backscatter imaging

In the subgroup of patients with non-ischemic etiology of HF, in univariable logistic regression, estimated glomerular filtration rate, LV dyssynchrony and calibrated IB were significantly related to LV reverse remodeling at 6 months follow-up (Table 6). In multivariable logistic regression analysis, these variables were all independent predictors of response to CRT (Table 6).

<table>
<thead>
<tr>
<th>Dependent variable: Response to CRT at 6 months follow-up</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95%CI)</td>
<td>p value</td>
</tr>
<tr>
<td><strong>Independent variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per 1 years)</td>
<td>0.98(0.96-1.02)</td>
<td>0.42</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.09(0.52-2.31)</td>
<td>0.82</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>0.58(0.30-1.09)</td>
<td>0.09</td>
</tr>
<tr>
<td>NYHA class IV</td>
<td>0.73(0.22-2.37)</td>
<td>0.60</td>
</tr>
<tr>
<td>QRS width at baseline (per 10ms)</td>
<td>1.12(1.01-1.24)</td>
<td>0.029</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (per 30ml/min)</td>
<td>1.43(1.04-1.96)</td>
<td>0.026</td>
</tr>
<tr>
<td>Hemoglobin (per 1mmol/l)</td>
<td>1.46(1.01-2.12)</td>
<td>0.043</td>
</tr>
<tr>
<td>LVESV at baseline (per 50ml)</td>
<td>1.15(0.92-1.45)</td>
<td>0.22</td>
</tr>
<tr>
<td>LVEF at baseline (per 5%)</td>
<td>0.80(0.63-1.01)</td>
<td>0.060</td>
</tr>
<tr>
<td>LV dyssynchrony at baseline (per 50ms)</td>
<td>1.77(1.38-2.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calibrated IB (per 5dB)</td>
<td>0.11(0.05-0.24)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

c-statistic: 0.89
Hosmer and Lemeshow Test: chi-square=9.5, p=0.30 (df=8)

CI: confidence intervals; CRT: cardiac resynchronization therapy; df: degree of freedom; IB: integrated backscatter; LV: left ventricular; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; OR: odds ratio.

Prediction of LV reverse remodeling in non-ischemic etiology

In the subgroup of patients with non-ischemic etiology of HF, in univariable logistic regression, estimated glomerular filtration rate, LV dyssynchrony and calibrated IB were significantly related to LV reverse remodeling at 6 months follow-up (Table 6). In multivariable logistic regression analysis, these variables were all independent predictors of response to CRT (Table 6).
The current study investigated the role of LV fibrosis in the prediction of CRT response and demonstrated that: 1) myocardial ultrasound reflectivity assessed with calibrated IB together with LV mechanical dyssynchrony and renal function were the major determinants of LV reverse remodeling after CRT; 2) myocardial ultrasound reflectivity assessed with calibrated IB provided incremental value over LV mechanical dyssynchrony and renal function for prediction of CRT response; 3) myocardial ultrasound reflectivity was the only independent predictor of CRT response in patients with ischemic HF; 4) myocardial ultrasound reflectivity was also an independent determinant of CRT response in non-ischemic HF.

**DISCUSSION**

Currently, contrast-enhanced CMR provides accurate assessment of the extent of LV fibrosis with high spatial resolution, but CMR remains limited for daily practice.

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**Table 5.** Univariable and multivariable logistic regression analysis for prediction of response to CRT (defined as reduction in LVESV≥15%) in ischemic heart failure

<table>
<thead>
<tr>
<th>Dependent variable: Response to CRT at 6 months follow-up</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95%CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Independent variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per 1 years)</td>
<td>0.98 (0.94-1.03)</td>
<td>0.45</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.68 (0.23-2.02)</td>
<td>0.49</td>
</tr>
<tr>
<td>QRS width at baseline (per 10ms)</td>
<td>1.13 (1.00-1.27)</td>
<td>0.053</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (per 30ml/min)</td>
<td>1.30 (0.90-1.89)</td>
<td>0.16</td>
</tr>
<tr>
<td>Hemoglobin (per 1mmol/l)</td>
<td>1.51 (0.91-2.48)</td>
<td>0.11</td>
</tr>
<tr>
<td>LVESV at baseline (per 50ml)</td>
<td>1.21 (0.89-1.66)</td>
<td>0.23</td>
</tr>
<tr>
<td>LVEF at baseline (per 5%)</td>
<td>0.71 (0.51-0.99)</td>
<td>0.041</td>
</tr>
<tr>
<td>LV dyssynchrony at baseline (per 50ms)</td>
<td>1.37 (1.06-1.78)</td>
<td>0.017</td>
</tr>
<tr>
<td>Calibrated IB (per 5dB)</td>
<td>0.07 (0.02-0.23)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

c-statistic: 0.87
Hosmer and Lemeshow Test: chi-square=12.6, p=0.13 (df=8)
Abbreviations as in Table 4
dimensional echocardiography permits assessment of myocardial ultrasound reflectivity or tissue density using calibrated IB analysis. The analysis of myocardial reflectivity with IB relies on the quantification of ultrasonic energy returned to the transducer after interactions with individual scattering elements within the myocardium. Picano et al. showed a modest but significant relation (r=0.55, p<0.05) between the percent connective tissue area determined in histologic sections of myocardial biopsies obtained from the LV septum and the ultrasonic reflectivity of the same region of myocardium assessed with 2D echocardiography. Moreover, experimental and clinical studies demonstrated the usefulness of this technique for the detection of subtle alterations of myocardial function and structure. In an animal model, Perez et al. found that myocardial areas with increased IB corresponded histologically to discrete fibrocalcific lesions whereas areas with normal IB corresponded to normal myocardium.

The present study explored the value of calibrated IB to estimate myocardial ultrasound reflectivity as a surrogate of LV fibrosis in HF patients who are candidates for CRT. No significant relation was found between myocardial ultrasound reflectivity and QRS duration. Furthermore, although QRS duration was larger in non-ischemic as compared to ischemic HF patients (162±25 ms vs. 149±35 ms, p=0.006), myocardial...
dial ultrasound reflectivity was higher in ischemic as compared to non-ischemic HF patients (-18.5±3.8dB vs. -20.2±3.0dB, p=0.002). These results extend the findings of previous studies indicating the lack of relation between the QRS duration and fibrosis in dilated cardiomyopathy. Therefore, the extent of fibrosis or a surrogate such as myocardial ultrasound reflectivity can not be estimated by the QRS duration on the surface ECG. In addition, renal function was weakly but significantly related to myocardial ultrasound reflectivity underscoring that worse renal function was associated with higher IB reflectivity (possibly indicating more extensive LV fibrosis).

Myocardial ultrasound reflectivity and CRT response

Previous studies showed that beyond mechanical dyssynchrony, the quantification of myocardial fibrosis is an important pathophysiological determinant of CRT response. In particular, studies performed with nuclear imaging and contrast-enhanced CMR underscored the importance of the assessment of LV fibrosis for clinical and echocardiographic response to CRT. For example, White et al. studied 23 HF patients with previous myocardial infarction and demonstrated that the extent of scar tissue in the LV, assessed with contrast-enhanced CMR, was significantly less in CRT responders as compared to non-responders (1.0% vs. 24.7%, p=0.002). Furthermore, a recent study from Bilchick and colleagues used CMR to assess both mechanical dyssynchrony and LV fibrosis in a small group of 20 HF patients with ischemic and non-ischemic etiology referred for CRT. The authors showed that the combined approach (assessment of mechanical dyssynchrony and quantification of LV fibrosis) significantly improved predictive accuracy for clinical CRT response.

In the current study, mechanical dyssynchrony and myocardial ultrasound reflectivity (a potential surrogate of LV fibrosis) were comprehensively evaluated with 2D echocardiography techniques (speckle-tracking imaging and calibrated IB). Myocardial ultrasound reflectivity was larger in non-responders as compared to responders (-17.0±3.0dB vs. -20.8±3.0dB, respectively, p<0.001). Moreover, myocardial ultrasound reflectivity was directly related to the extent of reverse remodeling after CRT and provided incremental value over LV dyssynchrony and renal function for prediction of CRT response, in line with previous studies.

Myocardial ultrasound reflectivity in ischemic and non-ischemic HF patients

Various studies have focused on the relation between LV fibrosis and CRT response in ischemic HF patients. In particular, Ypenburg et al. demonstrated in
ischemic HF patients the close relation between the total scar burden assessed with contrast-enhanced CMR and LV reverse remodeling after CRT \( (r=0.91, \ p<0.05) \). In the present study, in ischemic HF patients, the amount of myocardial ultrasound reflectivity was not only significantly related to LV reverse remodeling, but also the strongest independent predictor of LV reverse remodeling. These findings underscore the relevance of this indirect parameter of LV fibrosis for CRT response in the setting of ischemic HF.

Few studies have reported on the presence of LV fibrosis in patients with non-ischemic dilated cardiomyopathy,\textsuperscript{14, 32} but none have explored the relation between LV fibrosis and CRT response in patients with non-ischemic HF. The current results demonstrated a significant direct relation between the extent of myocardial ultrasound reflectivity, as a potential surrogate of LV fibrosis, and LV reverse remodeling after CRT. Moreover, in non-ischemic HF patients myocardial ultrasound reflectivity was an important and independent predictor of CRT response. Accordingly, the current findings underscore the role of the assessment of myocardial ultrasound reflectivity to improve CRT response rate in non-ischemic HF patients.

**Study limitations**

As previously described,\textsuperscript{16, 18-20} calibrated IB assessed in the antero-septal and posterior wall was used to detect myocardial ultrasound reflectivity. The measurement of calibrated IB in the antero-septal and posterior wall is dependent on ultrasound machine settings (focus, depth, gain and insonation angle). These settings were adjusted in all patients in order to optimize the image quality for offline analysis. In addition, by correcting calibrated IB of the antero-septal and posterior walls for the calibrated IB of the pericardium, the effect of these technical issues on the accuracy of this analysis may be minimized. In addition, no independent technique as CMR was used to prove the association between myocardial ultrasound reflectivity and fibrosis. However, previous studies showed a potential relation between myocardial ultrasound reflectivity and fibrosis.\textsuperscript{16, 17}

**CONCLUSIONS**

In the current study, myocardial ultrasound reflectivity assessed with calibrated IB was related to CRT-response. In particular, myocardial ultrasound reflectivity provided incremental value to CRT response over mechanical LV dyssynchrony and renal function. Furthermore, myocardial ultrasound reflectivity was a strong determinant of LV reverse remodeling after CRT, both in ischemic and non-ischemic HF patients.
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