A multicenter prospective randomized controlled trial of cardiac resynchronization therapy guided by invasive dP/dt

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BACKGROUND No periprocedural metric has demonstrated improved cardiac resynchronization therapy (CRT) outcomes in a multicenter setting.

OBJECTIVE We sought to determine if left ventricular (LV) lead placement targeted to the coronary sinus (CS) branch generating the best acute hemodynamic response (AHR) results in improved outcomes at 6 months.

METHODS In this multicenter randomized controlled trial, patients were randomized to guided CRT or conventional CRT. Patients in the guided arm had LV dP/dtmax measured during biventricular (BIV) pacing. Target CS branches were identified and the final LV lead position was the branch with the best AHR and acceptable threshold values. The primary endpoint was the proportion of patients with a reduction in LV end-systolic volume (LVESV) of ≥15% at 6 months.

RESULTS A total of 281 patients were recruited across 12 centers. Mean age was 70.8 ± 10.9 years and 54% had ischemic etiology. Seventy-three percent of patients in the guided arm demonstrated a reduction in LVESV of ≥15% at 6 months vs 60% in the conventional arm (P = .02). Patients with AHR ≥ 10% were more likely to demonstrate a reduction of ESV ≥ 15% (84% of patients with an AHR ≥ 10% vs 28% with an AHR < 10%; P < .001). Procedure duration and fluoroscopy times were longer in the pressure wire-guided arm (104 ± 39 minutes vs 142 ± 39 minutes; P < .001 and 20 ± 16 minutes vs 28 ± 15 minutes; P = .002).

CONCLUSIONS AHR determined by invasively measuring LV dP/dtmax during BIV pacing predicts reverse remodeling 6 months after CRT. Patients in whom LV dP/dtmax was used to guide LV lead placement demonstrated better rates of reverse remodeling.

KEYWORDS Acute hemodynamic response; Cardiac resynchronization therapy; Heart failure; LV reverse remodeling; Targeted lead placement

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Introduction

The problem of nonresponse to cardiac resynchronization therapy (CRT) has been well documented. It is clear that heart failure substrate is not homogenous across the patient spectrum. Left ventricular (LV) pacing leads are conventionally placed in lateral or posterolateral branches of the coronary sinus (CS) but universal application of this methodology may not be prudent, particularly in patients with scar in those regions. Targeting LV lead placement has been the subject of much study and most methods have focused on noninvasive preimplant assessment. Targeting the site of latest mechanical activation (identified by echocardiography or cardiac magnetic resonance) has shown some promise in single-center studies but is not a widely utilized method.1,3

Alternatively, targeting the site of latest electrical activation has also been proposed as a means of tailoring LV lead placement.4
**KEY FINDINGS**

- In patients eligible for cardiac resynchronization therapy, acute hemodynamic response (AHR) to biventricular pacing as measured by left ventricular (LV) \( \frac{dP}{dt_{\text{max}}} \) predicts a greater likelihood of favorable LV reverse remodeling at 6 months.
- Patients randomized to LV lead placement guided by knowledge of the AHR were more likely to favorably reverse remodel.
- This effect appears to be stronger in patients with an ischemic etiology.

LV \( \frac{dP}{dt_{\text{max}}} \) reflects the rate of LV pressure increase and is a marker of cardiac contractility. It can be measured by echocardiography, but this relies on the presence of a measurable jet of mitral regurgitation. Several small studies have used echocardiography-derived LV \( \frac{dP}{dt_{\text{max}}} \) to measure the acute hemodynamic response (AHR) to CRT and there are data to support the notion that a favorable AHR translates to better clinical outcomes.\(^5,6\) LV \( \frac{dP}{dt_{\text{max}}} \) can also be measured invasively using a high-fidelity pressure wire temporarily positioned in the LV cavity at the time of implant. This method has demonstrated improved AHR with CRT and has been used in several hypothesis-generating studies investigating the utility of various pacing interventions.\(^7–9\) Whether favorable changes in invasively measured AHR result in more favorable reverse remodeling and better clinical outcomes is not clear. Small studies suggest that this might be the case.\(^10\)

In the current study, we hypothesized that targeting LV lead placement to the vein producing the best AHR (along with acceptable pacing parameters) would result in better rates of reverse remodeling and better clinical response when compared to conventional lead placement.

**Study participants**

Patients fulfilling standard criteria for CRT at the time of study inception (NYHA class II–IV drug-refractory heart failure, LV ejection fraction \( \leq 35\% \), and prolonged QRS > 120 ms) were considered eligible for the study. The trial was designed to reflect a “real-world” patient group and so patients with atrial fibrillation (AF) and those patients with pre-existing devices (upgrades) were included. The main exclusion criteria related to contraindications to pressure wire assessment, including severe aortic valve disease, mechanical aortic valve replacement, severe peripheral vascular disease, and the presence of LV thrombus.

**Interventions**

Patients were randomized (using a dedicated online platform) in 1:1 fashion to either conventional CRT implant or CRT with LV lead placement guided by the pressure wire (and knowledge of the AHR). Patients were stratified according to whether the etiology of their heart failure was ischemic or nonischemic. Patients were asked to answer the Minnesota Living with Heart Failure Questionnaire and perform a 6-minute walk test. Serum NT-proBNP was measured. All patients underwent a 2-dimensional echocardiogram to assess LV dimensions and volumes using the modified Simpson biplane method. The nature and severity of any valvular lesions were also recorded. All echocardiographic data were stored at each participating institution. A proportion of studies from each institution was selected and reviewed by the reporting sonographer and an independent expert to test for inter- and intraobserver variability.

All device implants were performed under strict aseptic conditions with patients receiving sedation and analgesia, as per local unit protocol. Venous access for the implant was left to operator discretion.

**Conventional CRT arm**

Patients randomized to the conventional arm were implanted with a right atrial (RA) lead (unless in permanent AF) and either a right ventricular (RV) pace/sense lead or RV defibrillator lead. RV lead position was left to operator discretion (septal or apical). The CS was then intubated and a balloon occlusive venogram performed to identify target vessels of LV lead placement. Lateral or posterolateral leads were preferentially targeted. If this was not possible, lead placement was left to operator discretion. The atrioventricular (AV) delay was set to 100 ms (if the patient was in sinus rhythm) with simultaneous stimulation of the right and left ventricle.

**Pressure wire–guided arm**

Venous access and positioning of the RA and RV leads was performed in the same way as for the conventional implant group. In addition, either femoral or radial arterial access was obtained and a 6F sheath used to position the PressureWire™ Certus™ wire (Abbott, St Paul, MN) into the LV cavity after a single intravenous bolus of 2500 IU unfractionated heparin. The heparin was typically given prior to the...
first incision. The PressureWire Certus (Figure 1) is a 0.014-inch high-fidelity pressure wire capable of measuring LV $dP/dt_{\text{max}}$ when coupled to a RadiAnalyzer™ Xpress loaded with PhysioMon™ software (all Abbott Medical, St Paul, MN). Details of the wire and analysis software/hardware can be found in the supplemental materials (Supplemental Figures 1, 2, and 3). Once a balloon-occlusion venogram of the CS had been obtained, potential target branches were identified and the LV pacing lead was sequentially passed into each. Operators were asked to identify targets that were likely to result in stable LV lead position once the CS venogram was acquired. There was no prespecified minimum number of targets.

The following protocol was applied in each position: The conventional bipolar pacing threshold for the LV lead was tested in that position. If this resulted in unacceptably high thresholds or phrenic nerve stimulation at very low thresholds, alternative vectors were assessed where possible. The baseline LV $dP/dt_{\text{max}}$ was assessed during AAI pacing (or VVI if the patient was in AF) 10 beats per minute above intrinsic heart rate. This was to ensure correction and control of heart rate (which is a known confounder when assessing LV $dP/dt_{\text{max}}$). After 20 seconds of AAI (or VVI) pacing, LV $dP/dt_{\text{max}}$ was measured over 10 seconds. This provided an assessment of baseline hemodynamic state. The patient was then paced in an AV synchronous biventricular fashion (DDDBiV) or biventricular fashion (VVBiV) if in AF. Baseline $dP/dt_{\text{max}}$ was reassessed at each pacing site and used as the reference in each position. LV $dP/dt_{\text{max}}$ was recorded over 10 seconds after 20 seconds of pacing. The AHR was expressed as the percentage difference between AAI (or VVI) pacing and biventricular pacing at each site. The final lead position was the one resulting in the best AHR with the acceptable indices in terms of pacing threshold and lack of phrenic nerve stimulation. Once the procedure was concluded, the AV delay (if in sinus) was set to 100 ms and the RV and LV timings were simultaneous (in both arms of the study). There was no use of proprietary optimization algorithms or multisite pacing during the study.

**Study follow-up**

All patients were scheduled to return for an assessment at 6 months post implant and completed the Minnesota Living with Heart Failure Questionnaire and also repeated the 6-minute walk. NT-proBNP levels were also measured. Two-dimensional echocardiography was performed to measure LV volumes. A clinical assessment was also performed. The Clinical Composite Score (CCS) was calculated for each patient. This score incorporates changes in NYHA class and the patient’s perception of treatment effect and combines them with harder endpoints of heart failure hospitalization and mortality to determine if the patient is either worse, the same, or better following CRT. If either of the latter outcomes occurred, the patient was scored as being
worse following CRT. The echocardiographic and clinical data were collected and recorded by study personnel blinded to treatment assignment. LV pacing vectors were only changed during chronic follow-up if there was a problem with rising threshold or phrenic nerve stimulation. AV and interventricular timings were not adjusted during follow up.

Endpoints
The primary hypothesis was that pressure wire–guided CRT would be superior to conventional CRT in terms of reverse remodeling. The primary endpoint was the change in proportion of patients demonstrating favorable reverse remodeling of the left ventricle after 6 months of CRT. A responder was defined as a patient with a reduction of LV end-systolic volume (LVESV) of ≥15%. This primary endpoint was used on the basis that it has been shown to predict favorable clinical outcomes following CRT. The secondary endpoints were as follows:

- Change in CCS
- Change in Minnesota Living with Heart Failure Questionnaire score
- Change in 6-minute walk distance
- Procedure duration
- Fluoroscopy time
- Procedural complications

The primary endpoint was analyzed on an intention-to-treat basis comparing patient data based on the randomized groups and all protocol deviations were included.

Statistical analysis
The anticipated rate of reverse remodeling with conventional CRT was 55% based on best-case estimates from several studies where this outcome was reported following conventional CRT. Our calculations suggested that we needed to recruit 282 patients (141 in each arm) in order to detect an absolute increase of 15% in the rate of reverse remodeling responders with 80% power. Baseline variables were assessed for normality, and the t test was used to compare normally distributed continuous variables and the Mann-Whitney test was used when data were not normally distributed; χ² testing was used to compare categorical variables. A P value < .05 was taken as statistically significant. The data were analyzed using SPSS v22 (IBM Corp, Armonk, NY).

Results
Patient characteristics
A total of 281 patients with a mean age of 70.8 ± 10.9 years were recruited across the 12 sites between September 2012 and May 2018 (Figure 2). Seventy-four percent were male and 54% had an ischemic etiology. The vast majority (76%) were in sinus rhythm and 61% had left bundle branch block (LBBB) (vs
22% with either nonspecific interventricular conduction delay (IVCD) or right bundle branch block and 17% with RV pacing. Over 90% of patients were on both beta-blockers and either angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and 61% were on mineralocorticoid receptor antagonists. Two-thirds of patients were in NYHA class III. In total, 140 patients were randomized to the pressure wire–guided arm and 141 to the conventional arm. The 2 groups were well matched in terms of patient characteristics (Table 1).

### Procedural characteristics

CRT devices were successfully implanted in all but 3 patients. Table 2 outlines the procedural characteristics according to treatment arm. Procedure duration was significantly longer in the pressure wire–guided arm (104 ± 39 minutes vs 142 ± 39 minutes; \(P < .001\)), as were fluoroscopy times (20 ± 16 minutes vs 28 ± 15 minutes; \(P = .002\)). The vast majority of LV leads were implanted in either a lateral or posterolateral position, and this did not differ between the treatment groups. Patients in the pressure wire–guided arm were more likely to have the RV lead in a nonapical position (38% vs 24%; \(P = .01\)). There was a fairly even distribution between the use of bipolar and quadrupolar LV pacing leads and there was no significant difference between the 2 treatment arms (52% bipolar use in the conventional arm vs 47% in the pressure wire–guided arm; \(P = .66\)).

### Procedural characteristics for the pressure wire–guided arm

Supplemental Table 1 outlines the details of the pressure wire–derived measurements in the pressure wire arm. The pressure wire could not be recorded in 6 cases. Five of these related to vascular access issues, and a technical error resulted in an inability to record hemodynamic data in 1 case. A mean of 3 CS LV lead positions were tried and the mean improvement in AHR was 22% ± 16%. Posterolateral and lateral positions produced the optimal AHR in the majority of cases, although there was a marked variation between the position producing the worst AHR and that producing

### Table 1  Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Conventional arm N = 141</th>
<th>Pressure wire–guided arm N = 140</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>72.3 ± 10.5</td>
<td>71.1 ± 9.9</td>
<td>.43</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td>.45</td>
</tr>
<tr>
<td>Male</td>
<td>110 (78)</td>
<td>98 (70)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>31 (22)</td>
<td>42 (30)</td>
<td></td>
</tr>
<tr>
<td>Etiology, n (%)</td>
<td></td>
<td></td>
<td>.21</td>
</tr>
<tr>
<td>Ischemic</td>
<td>81 (57)</td>
<td>70 (50)</td>
<td></td>
</tr>
<tr>
<td>Nonischemic</td>
<td>60 (43)</td>
<td>70 (50)</td>
<td></td>
</tr>
<tr>
<td>Mean QRS duration (ms)</td>
<td>157 ± 23</td>
<td>161 ± 23</td>
<td>.33</td>
</tr>
<tr>
<td>QRS morphology, n (%)</td>
<td></td>
<td></td>
<td>.38</td>
</tr>
<tr>
<td>LBBB</td>
<td>90 (64)</td>
<td>81 (58)</td>
<td></td>
</tr>
<tr>
<td>Non-LBBB</td>
<td>29 (20)</td>
<td>33 (24)</td>
<td></td>
</tr>
<tr>
<td>RV paced</td>
<td>22 (16)</td>
<td>26 (18)</td>
<td></td>
</tr>
<tr>
<td>Rhythm, n (%)</td>
<td></td>
<td></td>
<td>.70</td>
</tr>
<tr>
<td>Sinus</td>
<td>106 (75)</td>
<td>108 (77)</td>
<td></td>
</tr>
<tr>
<td>AT/AF</td>
<td>35 (25)</td>
<td>32 (23)</td>
<td></td>
</tr>
<tr>
<td>Mean PR interval if in SR (ms)</td>
<td></td>
<td></td>
<td>.62</td>
</tr>
<tr>
<td>LBBB</td>
<td>189 ± 31</td>
<td>187 ± 37</td>
<td></td>
</tr>
<tr>
<td>Non-LBBB</td>
<td>182 ± 27</td>
<td>186 ± 41</td>
<td>.34</td>
</tr>
<tr>
<td>Median NT-proBNP (pg/mL)</td>
<td>1479 (IQR 426–3936)</td>
<td>1046 IQR (295–2167)</td>
<td>.54</td>
</tr>
<tr>
<td>Drugs, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blockers</td>
<td>127 (90)</td>
<td>131 (93)</td>
<td>.37</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>126 (89)</td>
<td>132 (94)</td>
<td>.13</td>
</tr>
<tr>
<td>MRA</td>
<td>84 (60)</td>
<td>87 (62)</td>
<td>.66</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>98 (70)</td>
<td>104 (74)</td>
<td>.37</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td></td>
<td></td>
<td>.12</td>
</tr>
<tr>
<td>2</td>
<td>43 (30)</td>
<td>49 (35)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>94 (67)</td>
<td>91 (65)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4 (3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>QOL score</td>
<td>43 ± 23</td>
<td>39 ± 24</td>
<td>.24</td>
</tr>
<tr>
<td>6-minute walk distance (m)</td>
<td>265 ± 131</td>
<td>283 ± 147</td>
<td>.40</td>
</tr>
<tr>
<td>LV ESV (mL)</td>
<td>119 ± 44</td>
<td>129 ± 48</td>
<td>.12</td>
</tr>
<tr>
<td>LV EDV (mL)</td>
<td>165 ± 24</td>
<td>179 ± 61</td>
<td>.17</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>29 ± 6</td>
<td>28 ± 5</td>
<td>.43</td>
</tr>
</tbody>
</table>

ACEI/ARB = angiotensin converting enzyme inhibitor/angiotensin receptor blocker; AT/AF = atrial tachycardia/atrial fibrillation; IQR = interquartile range; LBBB = left bundle branch block; LV EDV = left ventricular end-diastolic volume; LV EF = left ventricular ejection fraction; LV ESV = left ventricular end-systolic volume; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; QOL = quality of life; RV = right ventricle; SR = sinus rhythm.
the best (mean absolute difference in AHR expressed as a percentage of baseline = 21% ± 18%).

Outcomes—Efficacy endpoints

Efficacy outcomes are summarized in Table 3. In total, 3 patients were lost to follow-up (2 from the conventional arm and 1 from the pressure wire–guided arm). The primary efficacy endpoint (proportion of patients demonstrating a reduction in LVEF of ≥15% at 6 months) occurred in 73% in the pressure wire–guided arm vs 60% in the conventional arm (P = .02). Importantly, in the pressure wire–guided group, patients with an AHR ≥ 10% (used as an accepted measure of acute response) were significantly more likely to demonstrate favorable reverse remodeling resulting in classification as an echocardiographic responder (84% of patients with an AHR ≥ 10% had a reduction of ESV ≥ 15% vs 28% with an AHR < 10%; P < .001). The Clinical Composite Score was used to adjudicate clinical responders (patients were deemed to have responded if the CCS was adjudicated as “better”). There was a trend towards better rates of clinical response in the pressure wire–guided arm (76% vs 67%; P = .06). There was a significantly greater increase in 6-minute walk distance in the pressure wire–guided arm (increase of 68 ± 77 m in the pressure wire–guided arm vs 43 ± 98 m in the conventional arm; P = .02). Rates of reverse remodeling were slightly lower in patients with AF, but there was a statistically significant difference between those in the guided arm and those in the conventional arm (67% vs 57%; P = .02).

Of the 139 patients implanted with devices in the guided arm, the LV lead had to be moved away from the vein with best AHR (because of phrenic nerve stimulation or high pacing threshold) in 13 cases. The absolute mean loss in AHR was 4% ± 3%.

Assessment of echocardiographic data

One-quarter of echocardiographic studies from each participating center were selected to check for inter- and intraobserver variability. The intraclass correlation coefficient for interobserver variability in LVEF measurement was 0.87 (95% confidence interval 0.77–0.93; P < .001) and the intraclass correlation coefficient for intraobserver variability was 0.84 (95% confidence interval 0.75–0.90; P < .001), thus indicating good reliability.

Ischemic vs nonischemic etiology

A post hoc comparison of the ischemic and nonischemic patients was made to explore if there was a trend towards hemodynamic guidance being more valuable in one group over the other. Patients were deemed to have an ischemic etiology if any of the following criteria were met: significant epicardial coronary disease on angiography, prior history of coronary revascularization, history of myocardial infarction. Favorable reverse remodeling was seen in 81% of nonischemic patients in the pressure wire group vs 71% in the conventional group (P = .19). For ischemic patients, the rates were 69% in the pressure wire group vs 49% in the conventional group (P = .02). In the pressure wire group, 24 out of 70 ischemic patients (34%) had a nonlateral or posterolateral position. The percentage difference in AHR between the optimal location and worst position in this group was 26% ± 16%. In the conventional arm, 11 out of 81 (14%) ischemic patients had such a position.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Procedural characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conventional arm</td>
</tr>
<tr>
<td>Procedural success, n (%)</td>
<td>139 (99)</td>
</tr>
<tr>
<td>Procedure time (min)</td>
<td>104 ± 39</td>
</tr>
<tr>
<td>Time from CS intubation to final LV lead position (min)</td>
<td>30 ± 23</td>
</tr>
<tr>
<td>Fluoroscopy time (min)</td>
<td>20 ± 16</td>
</tr>
<tr>
<td>Contrast dose (mL)</td>
<td>39 ± 39</td>
</tr>
<tr>
<td>RV lead position, n (%)</td>
<td></td>
</tr>
<tr>
<td>Apical</td>
<td>105 (76)</td>
</tr>
<tr>
<td>Nonapical</td>
<td>34 (24)</td>
</tr>
<tr>
<td>Final LV lead position, n (%)</td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anterolateral</td>
<td>18 (13)</td>
</tr>
<tr>
<td>Lateral</td>
<td>68 (50)</td>
</tr>
<tr>
<td>Posterolateral</td>
<td>49 (34)</td>
</tr>
<tr>
<td>Posterior</td>
<td>4 (3)</td>
</tr>
<tr>
<td>LV lead type</td>
<td></td>
</tr>
<tr>
<td>Bipolar</td>
<td>62 (52)</td>
</tr>
<tr>
<td>Quadripolar</td>
<td>77 (48)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Outcomes – efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conventional arm</td>
</tr>
<tr>
<td>Outcome</td>
<td>N = 139</td>
</tr>
<tr>
<td>Echo-responder, n (%)</td>
<td>83 (60)</td>
</tr>
<tr>
<td>Clinical responder (based on CCS)</td>
<td>93 (67)</td>
</tr>
<tr>
<td>ΔLVESV (%)</td>
<td>-21 ± 29</td>
</tr>
<tr>
<td>ΔLV EF</td>
<td>4 ± 9</td>
</tr>
<tr>
<td>ΔQOL score</td>
<td>-18 ± 23</td>
</tr>
<tr>
<td>Δ6-min walk (m)</td>
<td>43 ± 98</td>
</tr>
<tr>
<td>ΔNT-proBNP (pg/mL)</td>
<td>-909 ± 1102</td>
</tr>
</tbody>
</table>

CCS = clinical composite score; other abbreviations as for Table 1.
result in an excess of thromboembolic or hemorrhagic complications; however, procedure and fluoroscopy times were significantly longer when adopting a pressure wire–guided approach. A prespecified subgroup analysis suggested that patients with ischemic etiology may benefit more from assessment of AHR.

This study was designed to reflect a “real-world” CRT population. Accordingly, we included patients with non-LBBB morphology, those with existing devices and AF. The cohort studied is reflective of the cohort of patients who are currently offered CRT as described in the European Society of Cardiology CRT II Survey. This demonstrated that of 11,088 surveyed CRT implants in Europe, 28% were upgrades from dual-chamber devices, 26% had AF, and 73% had LBBB. In our study, ischemic cardiomyopathy was present in 54% of subjects (a group acknowledged to have lower rates of CRT response). Even with such a diverse population, on optimal medical therapy, rates of reverse remodeling were similar to those quoted in trials of similar size and were, in fact, significantly improved in the pressure wire–guided arm. While there was a trend in improved clinical response (based on the Clinical Composite Score), there was a strong signal that patients did better in the pressure wire–guided arm in terms of objective measures of performance status (the increase in 6-minute walk distance was significantly greater in that group). There is an acknowledged placebo effect with CRT and the clinical response rate is often seen to be higher than those for reverse remodeling. The CCS has a significant subjective element (in the form of patient global assessment).

Complications

Table 4 outlines the procedural complications identified before the patient left the cardiac catheter laboratory. The rate of procedural complications was low and there was no signal against either treatment arm. Complications detected between the patient leaving the cardiac catheter laboratory and the 6-month follow-up visit are also shown in Table 4. Again, the rate of complications was low and there was no excess in complications related to the need for arterial access or low-level heparinization during the procedure. Similarly, the rate of thromboembolic complications was extremely low.

**Table 4 Outcomes – safety**

<table>
<thead>
<tr>
<th>Complication – periprocedural</th>
<th>Conventional arm</th>
<th>Pressure wire-guided arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary edema requiring intubation</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CS dissection</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Unable to place LV lead</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Arterial complications</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complication – late</th>
<th>Conventional arm</th>
<th>Pressure wire-guided arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe TR</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lead malfunction</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lead displacement</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Phrenic nerve stimulation requiring explant</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Infection requiring system removal</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pocket hematoma requiring intervention</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Arterial complication</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Died</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

CS = coronary sinus; LV = left ventricular; TR = tricuspid regurgitation.

**LV and RV pacing site**

Ultimately, there was no overall difference in the distribution of LV lead placements between both groups. The vast majority of leads in both arms were implanted in lateral or posterolateral branches of the CS, as would be considered convention. It might be argued that simply targeting either of these sites could be a suitable approach for many patients. It should, however, be noted that there was a wide variation in AHR between the best and worst target veins (21% ± 18%), and factors such as scar distribution may play an important role in determining which vein (either lateral or posterolateral) is best. It is possible that this might be related to the presence of scar and it may be that patients with scar are more likely to benefit from assessment with the pressure wire. The current study was not powered to explore that effect, but there was a signal that the magnitude of increase in response rate was greater in those with an ischemic etiology vs those with a nonischemic etiology. The use of the pressure wire resulted in an absolute increase in rates of reverse remodeling of 20% in the ischemic group vs 10% in the nonischemic group. The optimal site for LV lead placement remains the subject of debate, and other studies using LV dP/dtmax have found a significant variation in optimal site in both nonischemic and ischemic etiologies.

RV lead placement was left to operator discretion, but patients in the conventional arm were more likely to have an...
apical RV lead position (76% vs 62% in the pressure wire–
guided arm; \( P = .01 \)). This was not anticipated and arose
by chance. It is unlikely that this affected the outcomes re-
ported. Analysis of the MADIT CRT study has shown that
echocardiographic response to CRT was comparable across
RV lead location groups (RV septal/outflow tract vs apical)
in that study cohort.18

The potential role of AHR in contemporary CRT
The data presented in this study demonstrate the utility of
acute hemodynamic guidance and we have demonstrated
that this can be measured reliably and safely. Procedure
(and fluoroscopy) times were predictably longer (104 ± 39
minutes vs 142 ± 39 minutes), and this, as well as cost, needs
to be considered when contemplating the potential role for
LV \( \frac{dp}{dt_{\text{max}}} \) measurement in the clinical arena. Those pa-
patients in sinus rhythm with LBBB, QRS duration > 150
ms, and no scar are likely to benefit from conventionally
delivered CRT, and in this group pressure-wire assessment
of AHR may not be necessary, whereas patients with lesser
QRS durations, non-LBBB morphology, and scar may stand
to benefit most. As discussed in the introduction, LV \( \frac{dp}{dt_{\text{max}}} \)
can be measured noninvasively using 2-dimensional echo-
cardiography, provided there is a sufficient jet of mitral regur-
gitation. While mitral regurgitation is not uncommon in heart
failure patients, it is not universal and is unlikely to be prac-
tical during a CRT implant. It is also prone to wide inter-
and intraobserver variability. It does not seem feasible that pres-
sure wires will be needed for all CRT implants, but the RADI
CRT study does demonstrate the potential value of having
this information. Ideally, one would like this information
before contemplating a definitive implant ,and it may be
that patients with non–class I indications for CRT may
benefit from a temporary pacing study using electrophysi-
ology catheters positioned in the right atrium, right ventricle,
and CS branches. Incorporating this with acute hemody-
amic assessment may help identify those most likely to
respond to CRT and help inform decision making in this pa-
tient group. Whether a simpler, noninvasive measurement
such as change in blood pressure will provide similar utility
remains to be seen. Change in blood pressure with biventric-
ular pacing was not systematically measured during this
study, but there is good data demonstrating that change in
blood pressure is a noninferior (and arguably much more
reproducible) means of optimizing CRT compared to
echocardiography-guided optimization.19

Limitations
Patients were not blinded to treatment allocation (although
endpoint adjudicators were), and this may have influenced
subjective outcomes but is unlikely to have had any effect
on the reverse remodeling outcomes. AV delays were not
optimized in this study, and work by Auricchio and col-
leagues22 has suggested that further increments in AHR
may be achieved by optimizing the AV delay. This effect
could be seen in patients even with intermediate QRS dura-
tions (<150 ms) and, as such, this might prove to be another
potential application for its use in CRT nonresponders. With
regards to the primary endpoint, we did not use a core lab for
echocardiographic analysis; however, a standardized imag-
ing protocol was used across each participating center and
a selection of studies from each were assessed for quality
control. Tests for inter- and intraobserver variation suggested
good reproducibility of the measurements used to calculate
the primary outcome measure (derived from change in
LVESV). An intriguing signal was the apparent benefit of
knowing the AHR in ischemic patients; however, scar data
from magnetic resonance imaging was not universally avail-
able and so it is not possible to do more than speculate as to
whether the presence of scar is responsible for the variation in
AHR seen in any given individual. It is recognized that pa-
tients with an ischemic etiology demonstrate less reverse re-
modeling but have a demonstrable benefit in mortality. This
trial was not powered to detect a difference in mortality and it
is plausible that the positive impact on reverse remodeling
may not translate to mortality benefit. Finally, the time taken
to recruit the required number of patients into the study was
long, likely related to the invasive nature of the study.

Conclusion
In summary, the RADI-CRT study has shown that the AHR
determined by invasively measuring LV \( \frac{dp}{dt_{\text{max}}} \) during bi-
ventricular pacing predicts reverse remodeling 6 months after
CRT and that using this information to help guide LV lead
placement results in better response rates. This information
may be of more use in patients with an ischemic etiology.
There is a tradeoff in procedure times, but there is no increase
in the rate of thromboembolic or hemorrhagic complications.

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study.

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Certus PressureWires used in the study.

Disclosures
Dr Rinaldi, Dr Betts, and Dr Della Bella have received
research funding and speaker fees from Abbott.

Other implications
The evidence base is replete with hypothesis-generating
studies that have used LV \( \frac{dp}{dt_{\text{max}}} \) to assess the efficacy of
various pacing interventions.9,20,21 The current study is there-
fore important, as it demonstrates that AHR predicts reverse
remodeling and also objective measures of clinical response,
therefore validating the ongoing use of LV \( \frac{dp}{dt_{\text{max}}} \) for this
indication.
Authorship
All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent
All participants gave written informed consent.

Ethics Statement
The research reported in this paper adhered to the CONSORT guidelines for the reporting of clinical trials and the guidelines set forth by the Helsinki Declaration as revised in 2013. The study was reviewed and approved by the UK Research Ethics Committee who provided approval for the participating UK centers. The Institutional Review Boards for each remaining participating center provided local approval where necessary. The study protocol was approved in March 2012 and published on ClinicalTrials.gov (NCT01464502).

Appendix

Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2021.01.005.

References