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Guidance for Optimal Site Selection of a Leadless LV Endocardial Electrode Improves Acute Hemodynamic Response and Chronic Remodeling

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ABSTRACT

OBJECTIVES This study hypothesized that guided implants, in which the optimal left ventricular endocardial (LV_{ENDO}) pacing location was identified and targeted, would improve acute markers of contractility and chronic markers of cardiac resynchronization (CRT) response.

BACKGROUND Biventricular endocardial (BiV_{ENDO}) pacing may offer a potential benefit over standard CRT; however, the optimal LV_{ENDO} pacing site is highly variable. Indiscriminately delivered BiV_{ENDO} pacing is associated with a reverse remodeling response rate of between 40% and 60%.

METHODS Registry of centers implanting a wireless, LV_{ENDO} pacing system (WiSE-CRT System, EBR Systems, Sunnyvale, California); John Radcliffe Hospital (Oxford, United Kingdom), Guy's and St. Thomas' Hospital (London, United Kingdom), and The James Cook University Hospital (Middlesbrough, United Kingdom). Centers used a combination of preprocedural imaging and electroanatomical mapping the identify the optimal LV_{ENDO} site.

RESULTS A total of 26 patients across the 3 centers underwent a guided implant. Patients were predominantly male with a mean age of 68.8 ± 8.4 years, the mean LV ejection fraction was 34.2% ± 7.8%. The mean QRS duration was 163.8 ± 26.7 ms, and 30.8% of patients had an ischemic etiology. It proved technically feasible to selectively target and deploy the pacing electrode in a chosen endocardial segment in almost all cases, with a similar complication rate to that observed during indiscriminate BiV_{ENDO}. Ninety percent of patients met the definition of echocardiographic responder. Reverse remodeling was observed in 71%.

CONCLUSIONS Guided endocardial implants were associated with a higher degree of chronic LV remodeling compared with historical nonguided approaches. (J Am Coll Cardiol EP 2018;■:■–■) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

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ABBREVIATIONS AND ACRONYMS

AHR = Acute hemodynamic response

BiV_{ENDO} = biventricular endocardial

CMR = cardiac magnetic resonance imaging

CRT = cardiac resynchronization therapy

EAM = electroanatomical mapping

LV = left ventricular

LVEF = left ventricular ejection fraction

LV_{ENDO} = left ventricular endocardial

Q-LV = interval between the onset of the QRS complex on the surface electrocardiogram to the first large positive or negative peak of the LV electrogram during a cardiac cycle

QRSd = QRS duration

US = ultrasound

Significant numbers of patients fail to respond to cardiac resynchronization (CRT) when it is delivered through an epicardial left ventricular (LV) lead placed via the coronary sinus (1-3). Furthermore, technical and anatomical limitations mean it is not always possible to implant an LV lead (4) and patients upgrading from a preexisting pacing system may have central venous stenoses preventing transvenous LV lead implantation (5). To overcome these challenges, novel methods of CRT delivery have been developed, including LV endocardial (LV_{ENDO}) stimulation (6,7). Chronic LV_{ENDO} pacing was initially delivered via transseptal pacing leads, mandating lifelong anticoagulation, but the introduction of new wireless technology may increase the use of LV_{ENDO} pacing and avoid anticoagulation (8,9).

The optimal LV_{ENDO} pacing location exhibits marked variability in ischemic (10) and nonischemic patients (11-13), with indiscriminate LV_{ENDO} CRT being inferior to traditional transvenous epicardial CRT (6). Avoiding scarred tissue while targeting viable, late-activating sites may improve conventional CRT response (14-16). Targeting the site of latest mechanical activation using speckle-tracking in the Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy study improved the reverse remodeling rate to >70% (17). Alternative strategies include targeting the site of latest electrical activation, using the interval between the onset of the QRS complex on the surface electrocardiogram to the first large positive or negative peak of the LV electrogram during a cardiac cycle (Q-LV) (16) or using cardiac magnetic resonance (CMR) to identify late-activating, viable tissue (18).

We hypothesized that identification of the optimal LV_{ENDO} location for a wireless LV pacing electrode would result in improved acute hemodynamic response and chronic remodeling. We performed L_{ENDO} pacing using the WiSE-CRT wireless pacing system (WiSE-CRT System, EBR Systems, Sunnyvale, California) in conjunction with guidance to identify late-activating, viable LV_{ENDO} segments and measured acute markers of contractility and chronic markers of CRT response (reverse remodeling).

METHODS

Data were collected from 3 centers implanting the WiSE-CRT system. This co-implant system uses ultrasound (US) energy to activate a small leadless pacing electrode that is deployed transarterially via a retrograde transaortic approach in the LV_{ENDO} cavity. The US array, implanted subcutaneously, is triggered by the implanted pacemaker or transvenous defibrillator. Patients studied were part of the WiCS Post Market Surveillance Registry (Clinical trial study number NCT02610673), and all patients gave full written consent to participate in the study. The centers were the John Radcliffe Hospital, Oxford University Hospitals National Health Service (NHS) Foundation Trust (Oxford, United Kingdom), Guy's and St Thomas' NHS Foundation Trust (London, United Kingdom), and The James Cook University Hospital, South Tees Hospitals NHS Foundation Trust (Middlesbrough, United Kingdom).

LV_{ENDO} GUIDANCE. At each center, a combination of either preprocedural imaging and/or electroanatomical mapping (EAM) was used to identify the optimal LV_{ENDO} pacing site.

Echocardiographic-guided approach. This approach was undertaken at the James Cook University Hospital. Echocardiography using Speckle-tracking 2-dimensional radial strain analysis was used to identify and target the latest mechanically activated LV segment using multisegment models, as described previously (19). Regions of scar were defined as segments <0.5-mm thick and displaying abnormal increase in acoustic reflection. In addition, any myocardium that exhibited low-amplitude strain curves and a peak radial strain <16.5% was defined as scar (20,21). During LV_{ENDO} implantation, the LV free wall was visualized using fluoroscopy and was subdivided into 4 segments according to coronary venous anatomy; anterolateral, lateral, posterolateral, and posterior, as previously described (19). The electrode could then be implanted into the target segment.

Electrical latency (Q-LV). This work was undertaken at the John Radcliffe Hospital. Electrical latency was assessed using the WiSE-CRT delivery catheter. A minimum of 3 sites were tested. Two indices of electrical latency were used to identify the optimal pacing site; the Q-LV activation time (16) and the Q-LV/QRS ratio (7,15). Sites with a Q-LV <100 ms were excluded. The optimal target was the site that displayed the latest Q-LV during right ventricular pacing and a Q-LV/QRS ratio >0.66. Viability was assessed by excluding any sites with a pacing capture threshold >2 V.

EAM and CMR. This work was undertaken at Guy's and St. Thomas' NHS Foundation Trust. Patients were implanted using a hybrid approach of EAM and, where possible, CMR imaging, which had been performed before implantation of the co-implant device.

This technique allowed the identification of areas exhibiting late electrical activation (bipolar activation map) and areas of low voltage (bipolar scar map) using CARTO 3 (Biosense Webster, Diamond Bar, California), as previously described (22). When available, prior CMR data were also analyzed, allowing the identification of both late mechanically activated tissue and via analysis of late gadolinium enhancement imaging, areas of scared or fibrotic myocardium (Siemens Magnetom Aera 1.5-T magnetic resonance imaging scanner, Siemens Healthcare, Erlangen, Germany).

INCLUSION CRITERIA. The WiSE-CRT pacing system is CE marked for 3 indications (9). Patients classified as nonresponders to conventional CRT, those in whom LV lead deployment is not possible (because of anatomical constraints, high capture thresholds, or phrenic nerve stimulation), and those undergoing CRT upgrade where implanting an LV lead was impractical because of venous access or previous pocket infection. Patients meeting any of these criteria were included in this study. Patients were classified as having either ischemic cardiomyopathy or nonischemic cardiomyopathy using a combination of cardiac magnetic resonance imaging, coronary angiography, and clinical history. Patients were implanted via a retrograde transaortic approach, as previously described (10).

Acute hemodynamic response. Acute hemodynamic response (AHR) was used to assess the immediate response to LV_{ENDO} stimulation (23). This reproducible marker of acute contractility is best expressed as the change in the maximum rate of LV pressure, from a baseline control state measured using a pressure wire positioned within in the LV cavity (24). Temporary Biventricular endocardial (BiV_{ENDO}) pacing was performed using the patient's own co-implant device and either the WiSE-CRT delivery catheter or a mapping catheter placed within the LV cavity. During temporary BiV_{ENDO} pacing, the A-V interval was deliberately not optimized. The A-V interval of the co-implant device was used with simultaneous V-V stimulation. We assessed how AHR varied according to measures of electrical latency including Q-LV (16), Q-LV/QRS ratio, and paced QRS duration (QRSd). AHR values were obtained in multiple areas where BiV_{ENDO} capture was performed. Acute responders were defined as those that achieved a >10% increase in their AHR during LV_{ENDO} stimulation at the location chosen to deploy the WiSE-CRT LV electrode.

Chronic response to CRT (remodeling). Patients were considered echocardiographic responders to CRT if they exhibited a ≥15% reduction in end-systolic volume, measured using transthoracic echocardiography and/or a ≥5% improvement in LV ejection fraction (LVEF) 6 months postimplant (25).

TABLE 1 Patient Demographics (n = 26)

	Mean ± SD or Numbers (%)
Patients	26
Age (y)	68.8 ± 8.4
Male (%)	22 (84.6)
LVEF (%)	34.2% ± 7.8
NYHA	2.6 ± 0.5
QRS duration (ms)	163.8 ± 26.7
QRS morphology	
RV paced	24 (92)
LBBB	2 (8)
Etiology	
ICM (%)	8 (30.8)
Indication	
Difficult CS anatomy/access	14 (53.8)
Upgrades	
High-risk upgrade	7 (26.9)
Prior infection/extraction	3 (11.5)
Failure to respond to BiV EPI	2 (8.0)
Guidance technique	
Echocardiographic	9 (34.6)
Electrical latency	10 (38.%)
CMR and EAM	7 (26.9)

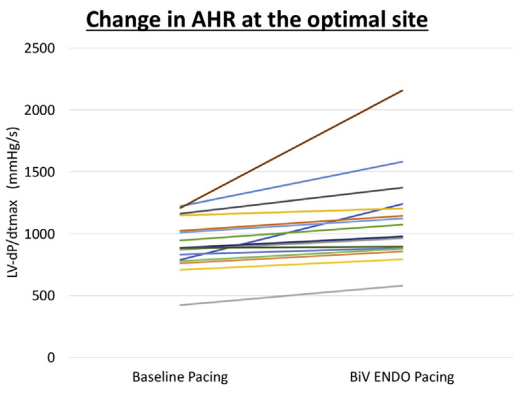
BiV = biventricular; CMR = cardiac magnetic resonance; CS = coronary sinus; EAM = electro-anatomical mapping; EPI = epicardial; ICM = ischemic cardiomyopathy; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RV = right ventricular.

STATISTICS. Continuous variables with a Gaussian distribution were described using mean values ± standard deviation. AHR and electrophysiology data were tested for normality with the Shapiro-Wilk test. Significance testing on normally distributed paired data was performed using 2 tailed paired *t*-tests. Significance testing on non-normally distributed paired data was performed using the Wilcoxon signed-rank test. Significance testing on non-normally distributed unpaired data was performed using the Mann-Whitney *U* test. To account for the clustering of data and multiple measurements within each patient, a generalized linear mixed-effect model was applied for all data points that achieved capture. Multiple data points recorded from an individual patient are displayed on the scatterplot using a specific color marker for each patient. Lines of best fit with 95% confidence intervals were shown to aid understanding. Results were considered significant at $p < 0.05$. Analysis was performed on PASW Statistics 24 (SPSS Inc., Chicago, Illinois).

TABLE 2 Complications Resulting From Electrode Deployment (n = 26)

<24 h	1 (3.8%)
Cardiac tamponade	1
>24 h-1 mo	7 (26.9%)
Pseudo-aneurysm	3
Unable to pace left ventricular electrode (1 m)	2
Pocket infection (generator)	1
Pocket hematoma (generator)	1

FIGURE 1 Change in AHR From Baseline During Biventricular Endocardial Pacing



AHR = acute hemodynamic response; BiV_{ENDO} = biventricular endocardial; LV-dp = maximum rate of left ventricular pressure.

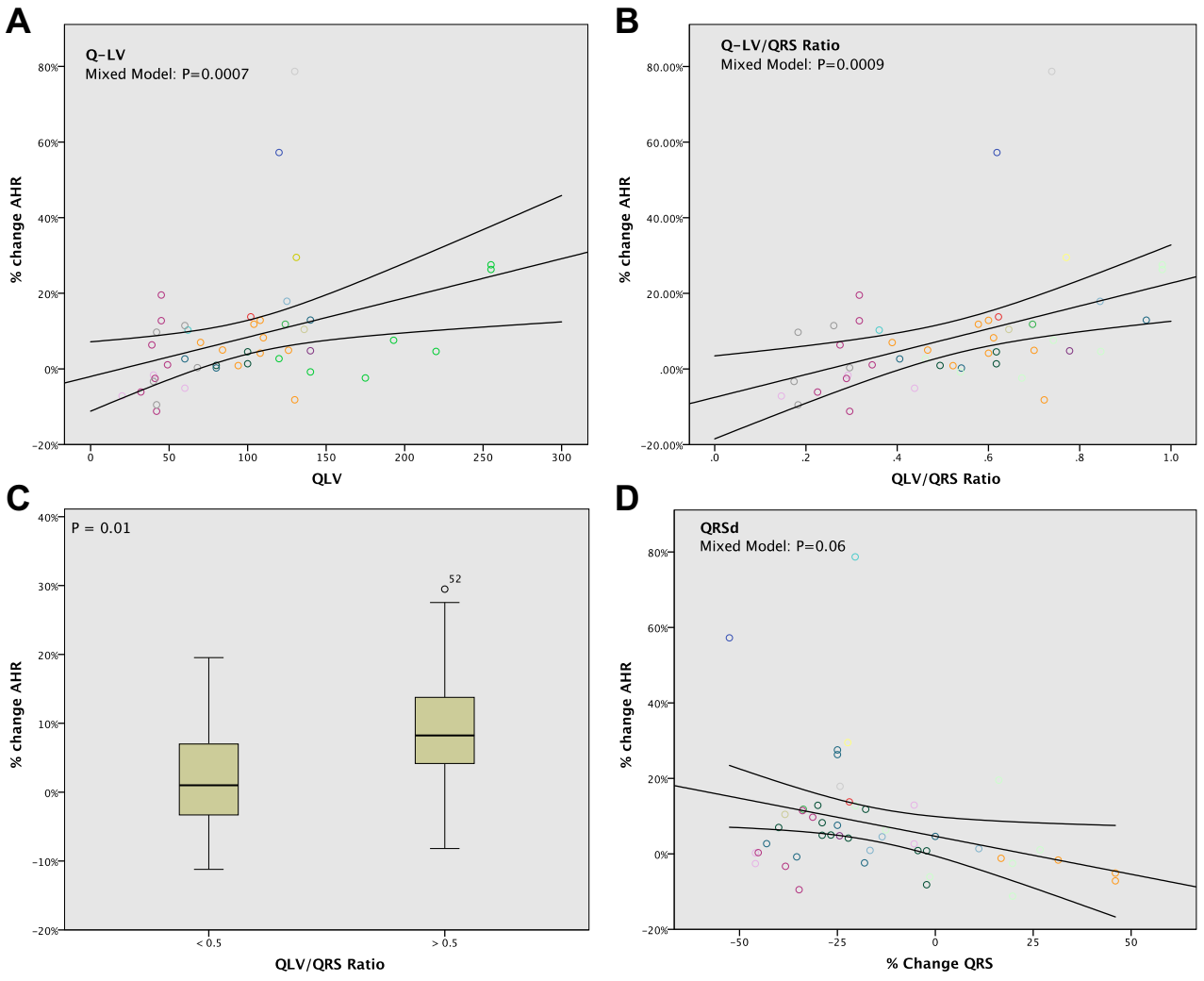
RESULTS

PATIENT CHARACTERISTICS. A total of 26 patients across the 3 centers were implanted with the WiSE-CRT system using a guided approach (Table 1). Patients were predominantly male with a mean age of 68.8 ± 8.4 years, mean LVEF 34.2% ± 7.8% (minimum: 19%; maximum: 51%). The mean QRS duration was 163.8 ± 26.7 ms. In 92% of patients, the baseline QRS morphology was a right ventricular paced rhythm because of the co-implant nature of the WiSE CRT pacing system. A total of 31% of patients had experienced AV block requiring pacemaker insertion before implantation with the WiSE CRT device, 30.8% of patients had an ischemic etiology, 53% of the patients had experienced a failed conventional transvenous CRT implant, 8% of patients were prior nonresponders, and 38% of patients had a baseline LVEF >35%. Patients with a baseline LVEF >35% were recruited if they required an upgrade to a CRT system, but it proved impossible to site a transvenous, epicardial lead. Some patients had also previously received transvenous, epicardial CRT and had experienced a degree of LV remodeling, but had gone on to develop issues with their LV lead and required an alternative means of LV stimulation.

PROCEDURAL DETAILS AND SAFETY ISSUES. Procedure times were 126 ± 65 min with a mean of 3.0 ± 2.6 LV_{ENDO} sites tested per patient. A similar complication rate was observed to that recognized in the literature (9) (Table 2). Acute complications relating to electrode implantation (<24 hours) occurred in 1 patient with cardiac tamponade requiring emergency thoracotomy. The most commonly encountered adverse events >24 hours to 1 month were complications arising from femoral arterial access. These included pseudoaneurysm formation requiring surgical intervention. In 2 cases, it was not possible to achieve consistent capture of the LV_{ENDO} pacing electrode. In both cases, failure of the screening procedure to exclude an unsuitable patient was later confirmed. One patient had comorbid chronic obstructive pulmonary disease with significant lung encroachment affecting the US signal between the subcutaneous array and endocardial pacing electrode. In the other case, the eventual distance between the LV pacing electrode and the US array was too great to achieve consistent capture.

ACUTE HEMODYNAMIC RESPONSE. In 16 of the patients undergoing guided electrode placement, AHR was measured intraprocedurally. A significant change in the mean maximum rate of left ventricular pressure was observed during BiV_{ENDO} pacing at the target site (baseline 915.3 ± 211.4 mm Hg/s vs. BiV_{ENDO} CRT 1107.4 ± 369.5 mm Hg/s; p = 0.0047) yielding a mean improvement in AHR of 21.0% (Graph 1). Six-month follow-up data were available for comparison in 14 of the patients who had undergone electrode deployment validated by AHR. Twelve patients experienced a >10% improvement in AHR at the target site; of these, 92% (n = 11) met the definition of an echocardiographic responder, whereas this was true for only 50% (n = 1) of the patients who failed to achieve a 10% improvement in AHR at the target site. Q-LV was measured at the site of endocardial stimulation, as described previously (10), and correlated against the observed AHR. Delivering BiV_{ENDO} pacing in areas of delayed electrical activation was associated with greater improvements in AHR (R = 0.356, p = 0.013; Figure 2A). This correlation remained significant, even when accounting for repeated measures in individual patients using generalized linear mixed model analysis (mixed model: p = 0.0007). An even stronger correlation was found between AHR

FIGURE 2 Change in AHR at Various LV_{ENDO} Locations vs. Electrophysiological Measures of Electrical Delay

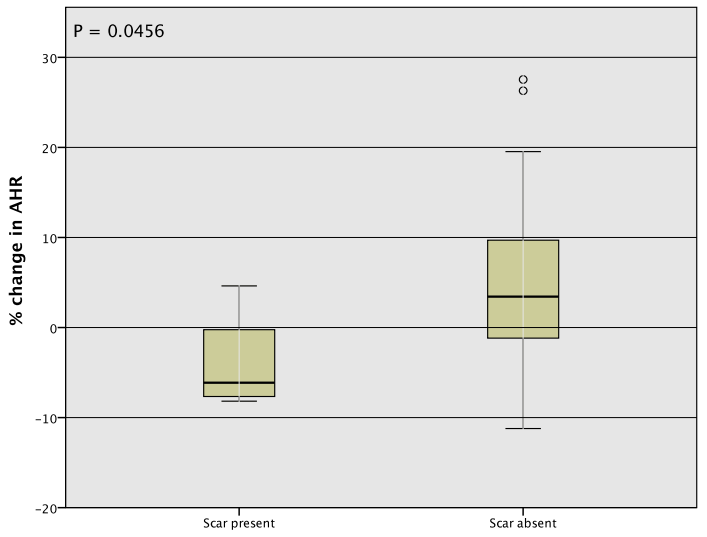


(A) Change in AHR vs. Q-LV. **(B)** Change in AHR vs. Q-LV/QRS Ratio. **(C)** Change in AHR vs. Q-LV/QRS ratio >0.5. **(D)** Change in AHR vs. change in QRSd. Q-LV = the interval between the onset of the QRS complex on the surface electrocardiogram to the first large positive or negative peak of the left ventricular electrogram during a cardiac cycle; other abbreviations as in Figure 1.

and the Q-LV/QRS ratio (R = 0.432, p = 0.003; Figure 2B). This correlation remained significant, even when repeated measures in individual patients were accounting for (mixed model: p = 0.0009). When our cohort was dichotomized into endocardial locations with an Q-LV/QRS ratio >0.5 and an Q-LV/QRS ratio <0.5, greater improvements in AHR were observed when endocardial pacing was delivered at areas displaying greater electrical latency (14.4 ± 19.7% vs. 2.3 ± 7.6%, p = 0.01; Figure 2C). Delivering endocardial pacing in a position that achieved a narrower paced QRSd showed a trend toward greater improvements in AHR (R = −0.308, p = 0.03; Graph 2D). This relationship failed to achieve statistical significance when evaluated for repeated measures (mixed model: p = 0.06).

TISSUE VIABILITY. Scar was identified using preimplant CMR and/or EAM. Seven patients had data comparing information on tissue viability and AHR, allowing the analysis of 38 positions. The mean change in AHR varied depending on whether stimulation was performed in an area of viable or scarred tissue (−3.9% ± 5.9% vs. +4.6% ± 8.8%, p = 0.0456; Figure 3).

FIGURE 3 Tissue Viability Assessment Comparing Scarred Tissue With Nonscarred Tissue



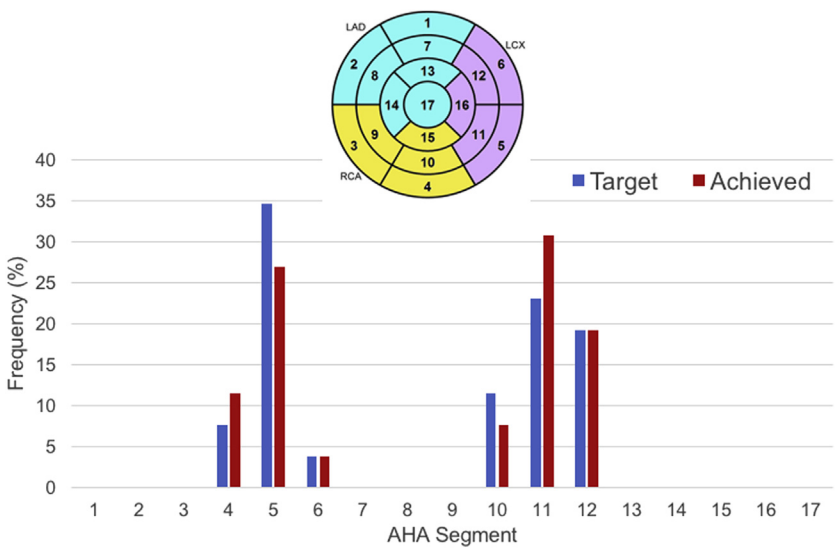
Abbreviations as in Figure 1.

OPTIMAL ENDOCARDIAL SITE SELECTION. AHR varied significantly depending on the location where LV_{ENDO} stimulation was performed. Inferior and lateral segments were frequently identified as the optimal targets using preprocedural imaging (Figure 4). The basal inferolateral segment (American Heart Association segment 5) was most frequently identified as the optimal target (n = 8). Once a segment had been selected, it proved technically feasible to deploy the LV_{ENDO} electrode in this area in 92% of patients. In the remaining cases, the electrode was successfully deployed in an adjacent American Heart Association segment.

CHRONIC RESPONSE. Six-month follow-up data were available in 21 of the 26 patients implanted with a guided approach. Chronic BiV_{ENDO} pacing could not be delivered effectively after implant in 2 patients. One patient exited the study before follow-up because of worsening dementia. One patient had poor echocardiographic windows, rendering assessment of LV performance postimplant impossible, and follow-up data were not available in 1 patient.

Follow-up data for our cohort are presented in Table 3. There was a significant reduction in QRS duration with BiV_{ENDO} pacing (baseline: 163.8 ± 26.7 ms vs. 6 months: 134.8 ± 25.6 ms; p = 0.002). LV end-systolic volume was significantly reduced at 6 months (112.7 ± 64.4 at baseline vs. 85 ± 9 ± 52.3 at 6 months; p < 0.0001). LVEF increased from a baseline of 34.2 ± 7.8% to 39% ± 9.8%, p = 0.008). Reverse remodeling (<15% reduction end-systolic volume) was observed in 71% patients (n = 15). Ninety percent (n = 19) of patients met the definition of echocardiographic responder (LV end-systolic volume: >15% reduction and/or >5% EF increase).

FIGURE 4 Target Site Selection vs. Actual Site Achieved



AHA = American Heart Association; LAD = left anterior descending artery; LCX = circumflex artery; RCA = right coronary artery.

TABLE 3 Chronic Response to Guide Implants (n = 21)

Parameter	Baseline ± SD	6 Mo ± SD	p Value
QRSd	163.8 ± 26.7	134.8 ± 25.6	0.002
LVESV	112.7 ± 64.4	85.9 ± 52.3	<0.0001
LVEF	34.2 ± 7.8	39 ± 9.8	0.008

LVESV = left ventricular end-systolic volume; SD = standard deviation; other abbreviation as in Table 1.

DISCUSSION

We hypothesized that guided placement of the WiSE-CRT LV endocardial pacing electrode would achieve greater improvements in acute markers of contractility and chronic markers of CRT response. The principal findings were as follows.

1. It proved technically feasible to selectively target and deploy the pacing electrode in a chosen endocardial segment in almost all cases with a similar complication rate to that observed in the published literature (9).
2. The use of a guided approach to facilitate optimal deployment of the WiSE-CRT LV endocardial pacing electrode was associated with a reverse remodeling rate of 71%, whereas 90% of patients met the definition of an echocardiographic responder.

PERIPROCEDURAL METRICS FOR OPTIMAL ENDOCARDIAL SITE SELECTION. The optimal LV_{ENDO} pacing site displays large inter- and intrapatient variability. Previous work identified that a "lateral area strategy" of delivering BiV_{ENDO} pacing at the lateral wall in a cohort of nonischemic cardiomyopathy patients, yielded similar hemodynamic improvements to both conventional epicardial CRT and echocardiographically guided LV_{ENDO} lead placement (10). In our analysis, infero- and inferolateral segments were most commonly identified as representing the optimal target for WiSE-CRT LV electrode delivery.

Our analysis provides several insights into how best to determine the optimal LV pacing site. Tissue characterization is fundamental to achieving optimal CRT. Leyva et al. (26) have previously shown the value of late gadolinium enhancement CMR to optimizing epicardial LV lead deployment. Our study confirms that delivering endocardial pacing in areas of scarred of fibrotic tissue, prospectively defined using either CMR or EAM, resulted in a reduction in acute hemodynamics. The mean AHR associated with delivering BiV_{ENDO} CRT in viable tissue showed statistical supremacy over stimulating fibrotic tissue and in no patient was the optimal segment noted to be scarred/fibrotic. Narrowing of the paced QRSd during acute BiV_{ENDO} pacing showed a trend favoring greater improvements in AHR, although this failed to achieve statistical significance when repeated measures in some patients were accounted for. A strong linear relationship, however, was identified between AHR and both Q-LV and Q-LV/QRSd ratio. As such, targeting locations that exhibit electrical latency would appear useful when looking to identify the optimal pacing site. Endocardial locations with a Q-LV/QRS ratio >0.5 were associated with a 14.3% ± 19.7% improvement in AHR. Achieving >10% improvement in AHR during acute biventricular epicardial CRT has been shown to be predictive of chronic reverse remodeling (24), suggesting patients will be more likely to remodel if a site with an LV/QRS ratio of 0.5 is selected.

CLINICAL IMPORTANCE. In the current study, the use of a guided approach to identify and target the optimal endocardial pacing location resulted in an impressive reverse remodeling rate of 71% and a composite echocardiographic response rate of 90%. These results compare favorably with the recently published Safety and Performance of Electrodes Implanted in the Left Ventricle (SELECT-LV) study, in which indiscriminate deployment of the LV pacing electrode achieved a remodeling rate of only 52% (9). This figure is consistent with the response rate of 40% to 50% reported in a large meta-analysis of endocardial CRT (27). Our results would suggest that a guided approach may be able to improve remodeling response rates in patients receiving BiV_{ENDO} CRT. This is in keeping with previous studies of epicardial CRT in which guidance increased LV reverse remodeling from 55% to 70% (16,17).

STUDY LIMITATIONS. The majority of our cohort were patients receiving an upgrade from a preexisting single- or dual-chamber pacing system or in which an attempt at implanting an LV lead had previously failed. Echocardiographic response rates amongst those receiving an upgrade to epicardial CRT have been found to be comparable to those receiving a de novo implant; however, the rate of reverse remodeling identified in our cohort (71%) exceeded the degree of remodeling expected (28,29). This rate of remodeling compares very favorably to that observed in the SELECT-LV study (9) although, the number of patients in our analysis whose indication for the WiSE-CRT LV pacing system was prior nonresponse to CRT was lower than in SELECT-LV (8% vs. 29%). Although each center used a combination of preprocedural imaging and electroanatomical mapping to identify the optimal pacing site, the precise guidance protocol varied between centers; however, all techniques targeted viable tissue that displayed late

electrical and or mechanical activation. Finally, the use of LV reverse remodeling as a surrogate for longer term CRT response is open to criticism, but it is an objective and reproducible metric of CRT response.

CONCLUSION

Guided endocardial implants were associated with a higher degree of chronic LV remodeling compared with historical nonguided approaches. WiSE-CRT offers a feasible alternative for patients who fail to derive benefit or who cannot be implanted with a conventional CRT system. The ability to target the LV endocardium irrespective of coronary venous anatomy, without any incidence of phrenic nerve stimulation is a unique advantage. Targeting late activating, nonscarred areas of the endocardium may further improve CRT outcomes in this patient group.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Guided electrode deployment, in which the optimal LV_{ENDO} site is identified and targeted proved technically feasible and achieved a higher rate of volumetric remodeling and echocardiographic response than has previously been described using endocardial pacing.

TRANSLATIONAL OUTLOOK: To realize the full benefits of LV_{ENDO}, it is imperative that the optimal site be identified and accurately targeted.

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