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DEVICES

Leadless left ventricular endocardial pacing in nonresponders to conventional cardiac resynchronization therapy

Baldeep S. Sidhu BM[1,2] | Bradley Porter MBChB[1,2] | Justin Gould MBBS[1,2] | Benjamin Sieniewicz MBChB[1,2] | Mark Elliott MBBS[1,2] | Vishal Mehta MBBS[1,2] | Peter P. H. M. Delnoy MD[3] | Jean-Claude Deharo MD[4] | Christian Butter MD[5] | Martin Seifert MD[5] | Lucas V. A. Boersma MD[6,7] | Sam Riahi MD, PhD[8] | Simon James MBChB[9] | Andrew J. Turley MBChB[9] | Angelo Auricchio MD, PhD[10] | Timothy R. Betts MBChB, MD[11] | Steven Niederer DPhil[1] | Prashanthan Sanders MBBS, PhD[12] | Christopher A. Rinaldi MD, FHRS[1,2]

[1]School of Biomedical Engineering and Imaging Sciences, King's College LondonLondon, UK

[2]Guy's and St Thomas' Hospital, London, UK

[3]Isala Heart Center, Zwolle, the Netherlands

[4]Hopital La Timone, Marseille, France

[5]Immanuel Klinikum Bernau Herzzentrum Brandenburg, Bernau, Germany

[6]St Antonius Ziekenhuis, Nieuwegein, Utrecht, the Netherlands

[7]Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands

[8]Aalborg University Hospital, Aalborg, Denmark

[9]The James Cook University Hospital, South Tees Hospitals NHS Foundation Trust, Middlesbrough, UK

[10]Fondazione Cardiocentro Ticino, Lugano, Switzerland

[11]Oxford University Hospitals NHS Foundation Trust, Oxford, UK

[12]Centre for Heart Rhythm Disorders, University of Adelaide and Royal Adelaide Hospital, Adelaide, South Australia, Australia

Correspondence
Dr Baldeep Singh Sidhu, School of Biomedical Engineering and Imaging Sciences, St Thomas' Hospital, London SE1 7EH, UK.
Email: Baldeep.sidhu@kcl.ac.uk

Abstract

Background: Endocardial pacing may be beneficial in patients who fail to improve following conventional epicardial cardiac resynchronization therapy (CRT). The potential to pace anywhere inside the left ventricle thus avoiding myocardial scar and targeting the latest activating segments may be particularly important. The WiSE-CRT system (EBR systems, Sunnyvale, CA) reliably produces wireless, endocardial left ventricular (LV) pacing. The purpose of this analysis was to determine whether this system improved symptoms or led to LV remodeling in patients who were nonresponders to conventional CRT.

Method: An international, multicenter registry of patients who were nonresponders to conventional CRT and underwent implantation with the WiSE-CRT system was collected.

Results: Twenty-two patients were included; 20 patients underwent successful implantation with confirmation of endocardial biventricular pacing and in 2 patients, there was a failure of electrode capture. Eighteen patients proceeded to 6-month follow-up; endocardial pacing resulted in a

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significant reduction in QRS duration compared with intrinsic QRS duration (26.6 ± 24.4 ms; $P = .002$) and improvement in left ventricular ejection fraction (LVEF) (4.7 ± 7.9%; $P = .021$). The mean reduction in left ventricular end-diastolic volume was 8.3 ± 42.3 cm^3 ($P = .458$) and left ventricular end-systolic volume (LVESV) was 13.1 ± 44.3 cm^3 ($P = .271$), which were statistically nonsignificant. Overall, 55.6% of patients had improvement in their clinical composite score and 66.7% had a reduction in LVESV ≥15% and/or absolute improvement in LVEF ≥5%.

Conclusion: Nonresponders to conventional CRT have few remaining treatment options. We have shown in this high-risk patient group that the WiSE-CRT system results in improvement in their clinical composite scores and leads to LV remodeling.

KEYWORDS

cardiac resynchronization therapy, endocardial pacing, WiSE-CRT system

1 | INTRODUCTION

The management of cardiac resynchronization therapy (CRT) nonresponders who remain symptomatic following intervention remains difficult.[1,2] It is estimated that CRT nonresponders account for approximately 30% of all implants.[1] Many of these patients have organ dysfunction and comorbidities that preclude advanced heart failure therapies, such as left ventricular (LV) assist devices or heart transplantation. Indeed, only a small proportion of patients with severe LV systolic dysfunction receive advanced therapies.[3] Occasionally, reversible causes for nonresponse can be found and addressed such as suboptimal atrioventricular interval timings, inadequate biventricular pacing from ventricular ectopy or atrial arrhythmias, insufficient medical therapy or anemia.[4] Patients with LV leads may have restrictions that result in suboptimal anatomical positioning or placement in close proximity to myocardial scar and patients with persisting mechanical dyssynchrony cannot be further optimized following conventional CRT.[4-6]

Endocardial LV pacing has a number of advantages over epicardial pacing and may offer a treatment alternative in these nonresponder patients. Endocardial pacing results in a more physiological activation, access to fast endocardial activation, and a pacing location unconstrained by the coronary anatomy, thus enabling areas of latest activation to be targeted while avoiding myocardial scar. LV endocardial pacing, delivered using lead-based technology, has shown promise in the treatment of nonresponders.[7] Biffi et al demonstrated in an analysis of the ALSYNC study that in 28 prior nonresponders, LV endocardial pacing resulted in reverse remodeling in 47% of patients.[8] However, lead-based LV endocardial pacing is limited by thromboembolic complications.[9] Additionally, there is no specifically designed equipment or leads to deliver endocardial pacing and it remains technically challenging with limited options available for placement of the lead. The WiSE-CRT system (EBR systems, Sunnyvale, CA) provides wireless, endocardial LV pacing and has been shown to reliably produce biventricular pacing.[10] The purpose of this analysis was to determine the efficacy of the WiSE-CRT system in patients who were nonresponders to conventional epicardial CRT.

2 | METHODS

2.1 | Study cohort

Patients who were nonresponders to conventional CRT and underwent implantation with the WiSE-CRT system were further investigated by performing a subanalysis of the WiSE-CRT study, SELECT-LV study, and WiCS-LV Post Market Surveillance Registry (Clinical trial study number NCT02610673).[10,11] Patients with heart failure who met the standard criteria for CRT based on the European Society of Cardiology/European Heart Rhythm Association guidelines and were CRT nonresponders were included. Patients were identified as CRT nonresponders if they had no change or worsening of symptoms or New York Heart Failure (NYHA) functional class after at least 6 months of CRT. In addition, any reversible causes, such as anemia or low biventricular pacing, were addressed prior to inclusion. There was no mandate for CRT optimization prior to inclusion because this is not routinely recommended in guidelines. The exclusion criteria have been described previously.[10,11] Patients who did not meet the eligibility criteria, for example, left ventricular ejection fraction (LVEF) > 35%, but who the physician felt would benefit from endocardial pacing were discussed on a case-by-case basis to decide whether they should be included.

2.2 | Implant procedure

Eligible patients underwent ultrasonic acoustic window screening to identify potential intercostal spaces for placement of the transmitter. Spaces with a shallow angle to the basal posterior left ventricle and with no lung encroachment during breathing exercises were selected as suitable locations. The procedure started with placement of the transmitter within the preidentified intercostal space by dissecting down to the intercostal muscle and confirming using ultrasound, that there is indeed an adequate window to the left ventricle. The transmitter is then sutured into place with the battery placed in the mid-axillary line. During the second stage of the procedure, the

endocardial electrode is inserted either via a retrograde aortic or trans-septal approach. Different myocardial segments are tested to identify the optimal location for placement of the electrode and this is then deployed within the chosen LV segment. Based on the center's practice, patients on long-term anticoagulation for atrial fibrillation were allowed to hold anticoagulation for 2-3 days before implant and then restart afterward. During the electrode implant, intravenous heparin was administered to ensure an activated clotting time over 200s.

2.3 | Study endpoints

Any procedural and postprocedure complications from implant to 6 months were recorded. Patients were assessed at 6 months post WiSE-CRT implantation to determine their clinical progress. Patients were considered to have improved with endocardial pacing if they showed improvement in their clinical composite score consisting of no hospitalizations with decompensated heart failure, survival to follow-up, improvement of ≥1 NYHA functional class, or improvement in their global assessment.[1] Additionally, we considered patients to have shown reverse LV remodeling if they had an absolute improvement in LVEF of ≥5% and/or reduction of left ventricular end-systolic volume (LVESV) of ≥15%.

2.4 | Statistical analysis

The results are presented as mean ± standard deviation for normally distributed variables and as median (interquartile range) for nonnormally distributed variables. When investigating the change from baseline variables, a paired sample *t*-test was used for normally distributed data and Wilcoxon signed-rank test for not-normally distributed data. A X^2 was used for among-group comparisons or a Fisher's exact test if the expected cell count was less than five. A two sided *P*-value of $< .05$ was considered statistically significant. Statistical analyses were performed using Prism (GraphPad Software Inc., Version 8, San Diego, CA) and SPSS (IBM Switzerland, Version 25, Switzerland).

3 | RESULTS

Twenty-two patients were implanted with the WiSE-CRT system after being identified as nonresponders to conventional CRT. The baseline patient demographics are provided in Table 1. Patients were 67.6 ± 7.3 years, 90.0% male, 45.5% had an ischemic cardiomyopathy, and 54.5% suffered from atrial fibrillation. The mean NYHA functional class was 2.9 ± 0.4, mean epicardial biventricular paced QRS duration was 167.2 ± 29.2 ms, and LVEF was 26.4 ± 8.0%. Ischemic versus nonischemic patients were more likely to have undergone previous cardiac surgery (60 vs 0%; $P = .003$), have hypertension (80 vs16.7%; $P = .008$), and have suffered a previous cerebrovascular accident (40 vs 0%; $P = .035$). However, there was no significant difference in LVEF ($P = .207$), left ventricular end-diastolic volume ($P = .335$), nor LVESV ($P = .539$).

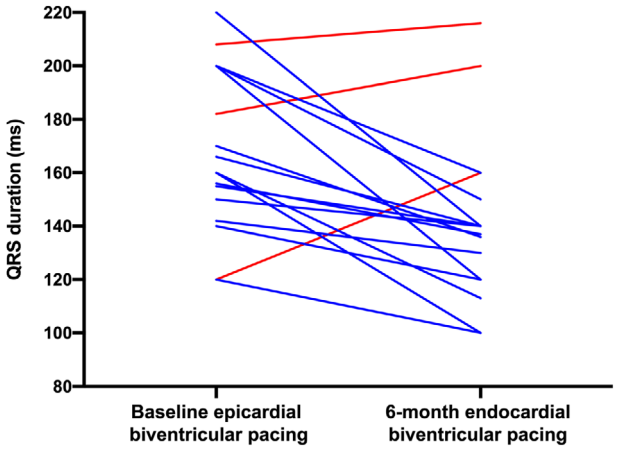


FIGURE 1 Individual changes in QRS duration following WiSE-CRT implantation.
Note: Blue line denotes the reduction in QRS duration following WiSE-CRT implantation and red line denotes the broadening of QRS duration following WiSE-CRT implantation
[Color figure can be viewed at wileyonlinelibrary.com]

3.1 | WiSE-CRT system procedure

Implantation was successful in all patients with biventricular endocardial pacing confirmed following the procedure in 20 patients. In two patients, we were unable to achieve biventricular pacing due to the failure of electrode capture from poor transducer coverage with no other intercostal spaces available for implantation. Early complications within 1 week included: one patient developed a right femoral artery fistula requiring surgical repair, one patient developed a femoral pseudoaneurysm requiring embolization, and one patient required antibiotics for cellulitis at the generator site. Late complications from 1 week to 6 months included: one patient developed a pocket hematoma treated conservatively, one patient required antibiotics for cellulitis at the generator site, two patients required a system revision due to a defective transmitter, and one patient developed a generator pocket infection at 3 months requiring removal of the subcutaneous system. There were no thromboembolic complications.

3.2 | Clinical response and LV remodeling

After 6 months follow-up, 1 patient had the device removed as described above, 1 patient was lost to follow-up, and 18 patients proceeded for clinical and echocardiographic review. Biventricular pacing was assessed at 6 months and tracking > 95% was observed in 86.7% of patients. There was a significant reduction in the QRS duration following WiSE-CRT implantation compared with intrinsic QRS duration (26.6 ± 24.4 ms; $P = .002$) (Figure 1) and baseline epicardial biventricular pacing (26.2 ± 32.0 ms; $P = .004$) (Table 2). Additionally following WiSE-CRT implantation, there was a significant improvement in LVEF (25.4 ± 7.9 vs 30.2 ± 10.7%; $P = .021$) but a nonsignificant reduction in LV end-diastolic volume (235.0 ± 90.7 vs 226.7 ± 106.2 cm^3; $P = .458$) and LVESV (184.1 ± 82.7 vs 171.0 ± 87.3 cm^3; $P = .271$) (Figures 2 and 3). Overall, 40% (6/15) of patients had a reduction in LVESV of

TABLE 1 Baseline patient demographics

Variables	Overall (n = 22)	Ischemic cardiomyopathy (n = 10)	Nonischemic cardiomyopathy(n = 12)	*P*-value
Age (years)	67.6 ± 7.3	69.0 ± 7.6	66.2 ± 7.2	.365
Male (%)	20 (90.9)	10 (1.0)	10 (0.8)	.481
Comorbidities (%)				
Cardiac surgery	6 (27.3)	6 (60.0)	0 (0.0)	.003
Atrial fibrillation	12 (54.5)	5 (50.0)	7 (58.3)	1.000
Hypertension	10 (45.5)	8 (80.0)	2 (16.7)	.008
Diabetes mellitus[a]	6 (28.6)	2 (20.0)	4 (36.4)	.635
Cerebrovascular accident[a]	4 (19.0)	4 (40.0)	0 (0.0)	.035
New York Heart Association functional class	2.9 ± 0.4	3.1 ± 0.3	2.7 ± 0.5	.055
Left bundle branch block[b] (%)	14 (82.4)	5 (62.50)	9 (100.0)	.082
Biventricular epicardial paced QRS duration (ms)	167.2 ± 29.2	153.9 ± 18.1	177.8 ± 32.7	.083
Echocardiography				
Left ventricular ejection fraction (%)	26.4 ± 8.0	24.0 ± 6.6	28.4 ± 8.8	.207
Left ventricular end-diastolic volume (cm^3)	230.4 ± 91.7	253.9 ± 83.3	206.4 ± 98.5	.335
Left ventricular end-systolic volume (cm^3)	177.3 ± 83.2	191.0 ± 68.4	165.1 ± 96.9	.539

[a]Data available for 21 patients.
[b]Data available for 17 patients.

TABLE 2 Volumetric remodeling following WiSE-CRT implantation

Variables	Before WiSE-CRT implantation	After WiSE-CRT implantation	*P*-value
New York Heart Association functional class	2.9 ± 0.5	2.7 ± 0.8	.317
Biventricular QRS duration (ms)[a]	167.6 ± 30.0	141.3 ± 30.7	.004
Left ventricular ejection fraction (%)	25.4 ± 7.9	30.2 ± 10.7	.021
Left ventricular end-diastolic volume (cm^3)	235.0 ± 90.7	226.7 ± 106.2	.458
Left ventricular end-systolic volume (cm^3)	184.1 ± 82.7	171.0 ± 87.3	.271

[a]Data available for 17 patients.

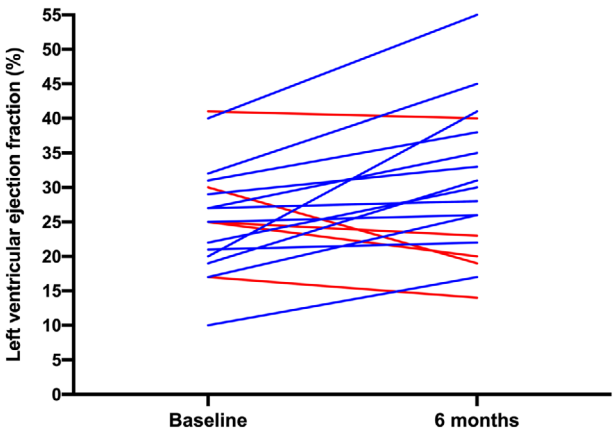


FIGURE 2 Individual changes in LVEF following WiSE-CRT implantation.
Note: Blue line denotes the improvement in LVEF following WiSE-CRT implantation and red line denotes the worsening of LVEF following WiSE-CRT implantation
[Color figure can be viewed at wileyonlinelibrary.com]

≥15%, 50% (9/18) of patients had an absolute reduction in LVEF of ≥5%, and 66.7% of patients had a reduction in LVESV ≥15% and/or absolute improvement in LVEF ≥5%. There was no significant change in NYHA functional status after WiSE-CRT implantation (2.9 ± 0.5 vs 2.7 ± 0.8; $P = .317$); however, 10 (55.6%) patients had improvement in their clinical composite scores. There was no significant difference between ischemic and nonischemic cardiomyopathy in terms of change in NYHA functional class, QRS duration, and LV function following WiSE-CRT implantation. Similarly, no difference was found between patients with a history of atrial fibrillation, hypertension, or cerebrovascular events.

3.3 | Identifying a nonresponder cohort likely to improve with the WiSE-CRT system

We performed a subanalysis to determine which nonresponders to conventional CRT were unlikely to improve with a WiSE-CRT system. We only considered patients to have improved with the WiSE-CRT system if they had an absolute improvement in LVEF ≥5% and/or improvement in LVESV of ≥15%. Patients who failed to improve compared with those who remodeled had similar baseline demographics; age

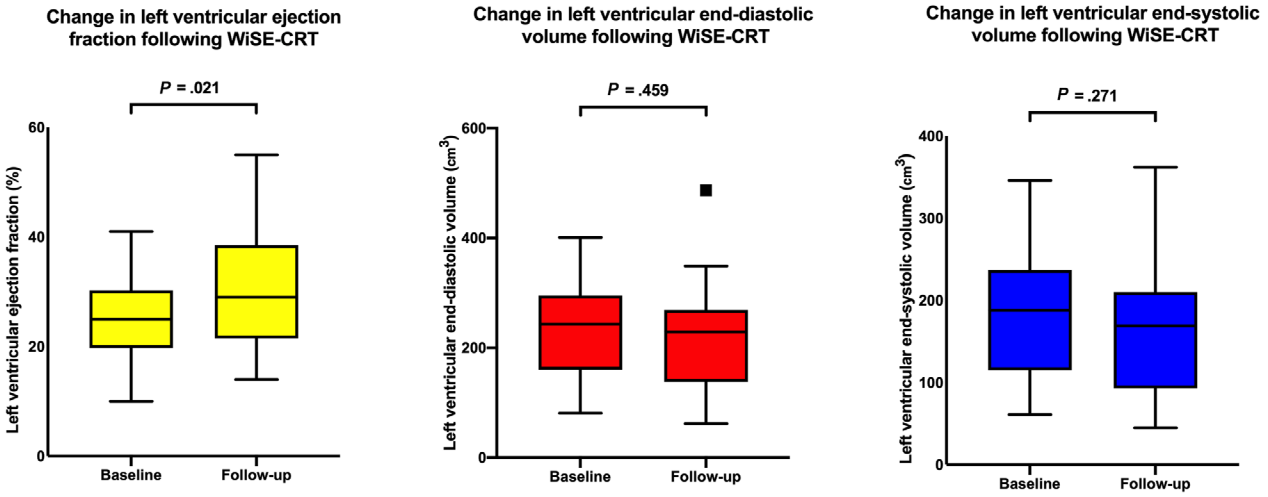


FIGURE 3 Box and whisker plots showing changes in left ventricular function following WiSE-CRT implantation [Color figure can be viewed at wileyonlinelibrary.com]

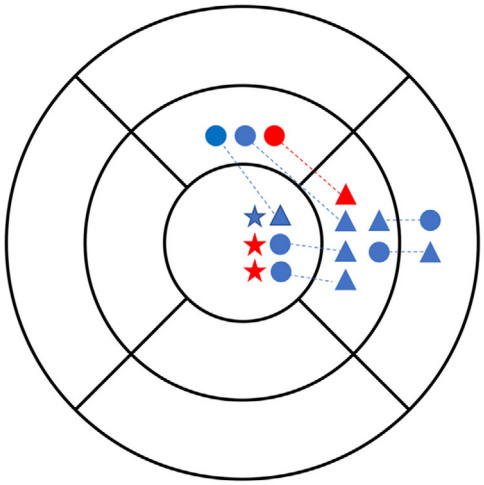


FIGURE 4 Bull's-eye plot showing the final location of the WiSE-CRT electrode relative to the epicardial lead.
Note: The myocardial segment with the epicardial lead is represented by a circle, the WiSE-CRT electrode is represented by a triangle, and a star demonstrates the position for both the lead and electrode was similar. Patients who were cardiac resynchronization therapy nonresponders are shown as red and responders as blue
[Color figure can be viewed at wileyonlinelibrary.com]

(70.4 ± 3.8 vs 66.2 ± 8.4 years; $P = .323$), ischemic cardiomyopathy (66.7 vs 33.3%; $P = .321$), male (100 vs 91.2%; $P = 1.000$), atrial fibrillation (66.7 vs 50.0%; $P = .638$), and hypertension (66.7 vs 33.3%; $P = .321$). Patients who failed to respond with the WiSE-CRT system had a nonsignificant trend toward a narrower epicardial biventricular paced QRS duration (156.3 ± 26.8 vs 172.6 ± 29.9 ms; $P = .278$), worse NYHA functional class (3.1 ± 0.4 vs 2.8 ± 0.5; $P = .076$), severely impaired LVEF (24.2 ± 4.6 vs 26.1 ± 9.2%; $P = .640$), more dilated LV end-diastolic volume (267.0 ± 83.3 vs 213.7 ± 93.7 cm^3; $P = .280$), and more dilated LVESV (210.8 ± 65.1 vs 172.3 ± 94.5 cm^3; $P = .519$). In addition, we investigated the location of the WiSE-CRT endocardial electrode relative to the original LV lead to determine how this influenced volumetric remodeling. We compared the procedural fluoroscopy and postoperative antero-posterior and lateral chest X-rays together. The lateral chest X-ray was not available in eight patients so were excluded from the analysis; seven patients had volumetric remodeling and three did not. In patients who did not display volumetric remodeling, the endocardial electrode was placed in a similar location to the epicardial lead and was placed in a mid to apical location. In patients who improved, six (85.7%) patients had the electrode placed in a different myocardial segment to the epicardial lead and all were implanted in the lateral wall in a predominantly mid LV position (Figure 4).

4 | DISCUSSION

CRT nonresponse is defined heterogeneously in terms of volumetric remodeling, clinical improvement, or both.[1] The management of these patients remains challenging and few alternative/proven treatment options currently exist. In this current analysis, we have demonstrated that 55.6% of nonresponders to conventional CRT improved their clinical composite scores and 66.7% had a reduction in LVESV ≥15% and/or absolute improvement in LVEF ≥5% with endocardial CRT. We feel this degree of clinical and volumetric improvement with the WiSE-CRT system in a difficult patient group is promising and may offer a viable treatment option for them, although this must be weighed against the invasive nature of the intervention and potential for harm.

4.1 | Comparison with prior studies

Nonresponders to CRT are regarded as a heterogeneous and challenging group to treat, who often suffer from multiple comorbidities.[8,9] Accordingly, we found a substantial number of patients who had several comorbidities, including atrial fibrillation, hypertension, and prior cerebrovascular accidents. Following implantation, there was

no significant improvement in NYHA functional class but 55.6% of patients showed improvement in their clinical composite scores. Furthermore, there was a significant reduction in QRS duration with endocardial pacing compared with epicardial biventricular pacing of 26.2 ± 32.0 ms ($P = .004$) and improvement in LVEF of 4.7 ± 7.9% ($P = .021$). There was no significant reduction in LV end-diastolic or end-systolic volume, which is likely a reflection of the small patient cohort and follow-up period of only 6 months. Overall, few studies have compared the effects of endocardial pacing in just CRT nonresponders. One notable exception was the ALSYNC study, whereby 118 patients were implanted with an endocardial lead; 90 (76.2%) with a failed epicardial lead or suboptimal coronary sinus anatomy and 28 (23.8%) were nonresponders to previous CRT, using a similar definition of "nonresponse" as our study.[8,12] In the nonresponder cohort at 6 months, 47% of patients had an improvement in LVESV of ≥15%, and 5% had an improvement ≥30%. Our results of wireless, leadless LV endocardial pacing are similar; 40% of patients had an improvement in LVESV of ≥15%, and 13.3% had an improvement ≥30%. In the ALSYNC study, 19% of endocardial leads could not be fixated at the desired location. Given that CRT nonresponders are an already difficult group who are perhaps less likely to respond, the ability to choose from any pacing location is extremely vital in improving outcomes and is an important benefit with the WiSE-CRT system.[13]

Endocardial pacing places patients at additional risks related to the procedure and thromboembolic events, with the later an ongoing risk with trans-septal leads requiring lifelong anticoagulation.[9] The WiSE-CRT system uses leadless pacing, which may reduce this long-term thromboembolic risk. However, the overall risk of endocardial pacing in solely nonresponders to conventional CRT, who are regarded as a more complex patient group, has not been fully explored and needs further assessment in larger studies.

4.2 | Identifying the nonresponder group likely to improve with endocardial pacing

Nonresponders to epicardial CRT are a sicker patient group with multiple comorbidities. This places them at a higher risk of procedural complications, especially from general anesthesia, which is often required for WiSE-CRT implantations. Therefore, it will be important to identify which nonresponders are more likely to improve and thus should be considered for endocardial pacing rather than those whose heart failure has progressed such that endocardial pacing is unlikely to be beneficial. Although our study was not powered to detect a statistically significant difference in baseline demographics in patients who underwent endocardial pacing who failed to show volumetric remodeling, we found that these patients tended to be older, with ischemic cardiomyopathy and atrial fibrillation. These characteristics are known to give an unfavorable response to conventional CRT.[1] Interestingly, patients who failed to respond with WiSE-CRT pacing had a nonsignificant trend toward a narrower baseline epicardial biventricular paced QRS duration (156.3 ± 26.8 vs 172.6 ± 29.9 ms; $P = .278$), suggesting that patients who were already relatively well resynchronized with conventional CRT are less likely to have incremental benefit with endocardial pacing. Additionally, patients who did not respond to WiSE-CRT had a trend toward a more severely impaired and dilated left ventricle at baseline, again suggesting that in these patients, their heart failure has progressed to a point where any further interventions, including endocardial pacing, are unlikely to have a positive effect. The position of the electrode relative to the LV lead may also be important since patients who did not improve following endocardial pacing were more likely to have the electrode implanted within the same myocardial segment. Furthermore, guiding endocardial pacing to the optimal desired location has been shown to improve outcomes and will be particularly important in these CRT nonresponders.[13,14] Although this subanalysis is limited by a small cohort, it does suggest that implanting patients with less comorbidities, broad epicardial biventricular paced QRS duration, a left ventricle that is not so severely dilated and implanting the electrode in a different location to the LV lead is perhaps more likely to result in a favorable response following WiSE-CRT implantation. The ongoing SOLVE-CRT clinical trial is a randomized-controlled, international, multicenter trial of the WiSE-CRT system and will provide further information on key demographics that may result in a favorable response to endocardial pacing and in those who respond, whether the improvement is due to endocardial pacing itself or due to pacing in a different myocardial segment, which is more optimal to pace.[15]

5 | LIMITATIONS

This study has the same limitations inherent with any prospectively collected data. However, we tried to reduce this bias by standardizing data collection. The small patient numbers limit the generalizability of the paper; however, as already discussed, the outcomes of nonresponders to conventional CRT who undergo endocardial pacing are sparse. Indeed, the ALSYNC study was the largest published study in the literature and included only 28 nonresponders.[12] It would have been important to determine how long patients had been nonresponders to conventional CRT; however, this was outside the scope of this paper. Biventricular pacing was only estimated at 6 months and cannot be fully relied upon without attaching a 24 h-Holter monitor to look for ectopy or arrhythmia. This monitoring was not undertaken in these studies. We did not record the number of patients who were too sick to undergo acoustic window screening and implantation of the WiSE-CRT system. This estimate would have helped to understand how many CRT nonresponders were felt ineligible to undergo this invasive procedure. This may have also resulted in underrepresentation of ischemic patients who are generally regarded as more unwell than nonischemic patients as evidenced by only 45.5% of ischemic patients in this study, similar to the ALSYNC study that included 42.9%.[8] Ischemic patients have a greater potential to benefit from targeted endocardial pacing.[14,16] An accurate Simpson's biplane was not possible for all patients and a change in LVEF ≥5% was, therefore, used but it is appreciated that this is a less reliable estimate of outcome than reduction in LV systolic volume ≥15%.

6 | CONCLUSION

Patients who fail to respond to conventional CRT are a complex patient group with multiple comorbidities. The WiSE-CRT system reliably produces endocardial biventricular pacing and has a number of advantages in these patients, including the option to pace in any location, thus avoiding myocardial scar and targeting latest activating segments. We have shown that this system results in both a clinical and volumetric improvement, which is particularly important in these patients who have few alternative treatment options. Further studies are required to determine the overall benefit in such patients, and the results of the ongoing SOLVE-CRT trial will be important.

AUTHOR CONTRIBUTIONS

Sidhu and Rinaldi designed the concept of the study. Sidhu drafted the manuscript. Sidhu, Porter, Gould, Sieniewicz, Elliott, Mehta, Delnoy, Deharo, Butter, Seifert, Boersma, Riahi, James, Turley, Aurrichio, Betts, Niederer, Sanders, and Rinaldi were responsible for acquisition, analysis, and interpretation of the data and approved of the submitted final version. Sidhu, Porter, Gould, Sieniewicz, Elliott, Mehta, Delnoy, Deharo, Butter, Seifert, Boersma, Riahi, James, Turley, Aurrichio, Betts, Niederer, Sanders, and Rinaldi performed the critical revision of the manuscript. Sidhu, Porter, Gould, and Rinaldi did the statistical analysis work.

DISCLOSURES

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ORCID

Baldeep S. Sidhu BM https://orcid.org/0000-0002-1999-7360
Benjamin Sieniewicz MBChB
https://orcid.org/0000-0002-9655-7465
Sam Riahi MD, PhD https://orcid.org/0000-0003-1849-9463
Prashanthan Sanders MBBS, PhD
https://orcid.org/0000-0003-3803-8429

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