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European experience with a first totally leadless cardiac resynchronization therapy pacemaker system

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Aims Totally leadless cardiac resynchronization therapy (CRT) can be delivered with a combination of Micra and WiSE-CRT systems. We describe the technical feasibility and first insights into the safety and efficacy of this combination in European experience.

Methods and results Patients enrolled had indication for both Micra and WiSE-CRT systems because of heart failure related to high burden of pacing by a Micra necessitating system upgrade or inability to implant a conventional CRT system because of infectious or anatomical conditions. The endpoints of the study were technical success of WiSE-CRT implantation with right ventricle-synchonized CRT delivery, acute QRS duration reduction, and freedom from procedure-related major adverse events. All eight WiSE-CRT devices were able to detect the Micra pacing output and to be trained to deliver synchronous LV endocardial pacing. Acute QRS reduction following WiSE-CRT implantation was observed in all eight patients (mean QRS 204.38 ± 30.26 vs. 137.5 ± 24.75 mS, $P = 0.012$). Seven patients reached 6 months of follow-up. At 6 months after WiSE-CRT implantation, there was a significant increase in LV ejection fraction (28.43 ± 8.01% vs. 39.71 ± 11.89%; $P = 0.018$) but no evidence of LV reverse remodelling or improvement in New York Heart Association class.

Conclusion The Micra and the WiSE-CRT systems can successfully operate together to deliver total leadless CRT to a patient. Moreover, the WiSE-CRT system provides the only means to upgrade the large population of Micra patients to CRT capability without replacing the Micra. The range of application of this combination could broaden in the future with the upcoming developments of leadless cardiac pacing.

Keywords Leadless • Cardiac pacing • Cardiac resynchronization therapy • Endocardial left ventricular pacing • WiSE-CRT

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What's new?

- Totally leadless cardiac resynchronization therapy (CRT) can be delivered with a combination of Micra and WiSE-CRT systems.
- This study demonstrates the technical feasibility of the WiSE-CRT system to deliver effective and stable left ventricular endocardial pacing to achieve CRT when associated with a previously implanted Micra leadless pacemaker.
- The combination of WiSE-CRT and Micra systems resulted in significant QRS reduction and LVEF improvement at 6 months in this pilot study.
- A combination of both WiSE-CRT and the upcoming Micra-AV systems could be proposed to patients in sinus rhythm and need for total leadless CRT.

Introduction

Cardiac resynchronization therapy (CRT) can improve mortality and quality of life in symptomatic heart failure patients with persistent reduced left ventricular ejection fraction (LVEF) ≤ 35% and conduction disturbances [left bundle-branch block (LBBB)- or non-LBBB-related], despite optimal medical treatment.[1] Conventional CRT with a coronary sinus lead is the first-line approach. However, 8–10% of eligible patients do not receive CRT due to anatomical constraints, such as absence of appropriate coronary sinus targets, occlusion of the upper extremity venous system phrenic nerve stimulation, or high pacing thresholds.[2] Surgical epicardial lead placement could be indicated in patients who have not responded or failed coronary sinus implantation. However, it is inherently more invasive than the percutaneous approach and can be especially challenging in patients with prior cardiac surgery.[3]

In this context, the WiSE-CRT system, a new device capable of delivering wireless LV endocardial pacing, could be an alternative to conventional epicardial LV pacing. The system comprises a passive electrode implanted in the LV endocardial wall, which converts ultrasound energy delivered by a subcutaneous system into electrical impulse.[3,4]

Meanwhile, there is a growing interest in miniaturized, self-contained leadless cardiac pacemakers (LCP), which are transvenously implanted in the right ventricle (RV) using a delivery sheath. These leadless systems were engineered to reduce the mechanical and infectious complications associated with lead use.[5] Hence, upper limbs veinous occlusion or anatomical constraints, high infectious risk are excellent indications for leadless cardiac stimulation. The LEADLESS and MICRA Trans-catheter Pacing Study (TPS) trials, published in 2014 and 2016, respectively, showed a high feasibility and a low level of short-term complications.[6,7] The use of leadless pacemakers is currently spreading, but restricted to their ability to deliver single-chamber (VVI) pacing only. There is presently no option to deliver leadless biventricular pacing to patients in whom leadless cardiac pacing is required (e.g. depressed LVEF and high expected burden of RV pacing). In addition, up to 15% of patients with high RV pacing burden could develop pacemaker-induced heart failure with depressed LVEF.[8] Such patients may benefit from a system upgrade from a single chamber ventricular system to a biventricular pacemaker.[9] The WiSE-CRT system associated with a Micra pacemaker could provide biventricular pacing in such patients while maintaining the advantages of leadless pacing (totally leadless CRT). Montemerlo *et al.*[10] first published a successful coexistence of a Medtronic Micra and the WISE-CRT system in 2019. Another case was reported by Funasako *et al.*[11] the same year. More patients have been implanted with these two systems since then. Accordingly, the purpose of this study is to show the technical feasibility and preliminary data about the safety of the combination of two leadless cardiac stimulation pacing systems, MICRA and WiSE, to achieve CRT.

Methods

Study design

This retrospective, observational, non-randomized, single-group, and multicentric ($n = 6$ centres) European study is intended to describe the technical feasibility and to depict first insights into the safety and efficacy of Medtronic Micra and EBR WiSE-CRT co-implantation.

Devices

The WiSE-CRT system comprises a tiny passive electrode (≈0.05 cm^3 displacement), a subcutaneous ultrasound emitter, and a battery. The battery is placed subcutaneously in the mid-axillary line and is wire-connected with the transmitter placed anteriorly in an intercostal space. The electrode is affixed to the LV endocardial lateral wall and delivered through transseptal or aortic retrograde approach.[12] The transmitter synchronizes with the RV pacing pulse of a pre-existing cardiac device and delivers an ultrasound beam in the area of the LV endocardial electrode. Ultrasound beam is converted to an electrical pulse by the electrode and an LV endocardial pacing impulse is delivered within 2 ms.

Study population

Patients included in this study had indications for both WiSE-CRT and Micra systems. Patients were enrolled if one of the following criteria applied: (i) upgrades: LVEF impairment related to prior Micra leadless pacemaker implantation and high VVI pacing burden; (ii) infections: after infection and the need to remove a previous CRT system, persistent high perceived risk of further system infection; and (iii) untreated: conventional CRT system implantation was attempted but failed (e.g. due to venous obstruction or difficult coronary sinus anatomy).

European patients with co-existing WiSE-CRT and Micra systems were included in this study.

Procedures

Three sequential procedures were performed in this study: (i) Micra pacemaker implantation (if not previously implanted), (ii) WiSE-CRT battery and transmitter implantation, and (iii) the WiSE-CRT electrode implantation. Timing between each of these procedures was left to the investigators discretion.

Micra leadless pacemakers were delivered to the RV through a femoral venous access using a steerable catheter and were tested for adequate fixation and appropriate electrical parameters before the delivery system was withdrawn, according to manufacturer's recommendations. This implantation procedure has been described in previous global studies.[13] Micra pacemaker programmation was left at the investigators' discretion.

The WiSE system was implanted in a two-step process. First, the battery was subcutaneously implanted at the midaxillary line and connected to the transmitter. The transmitter was placed in the 4th to 6th intercostal spaces lateral to the left parasternal border. The exact location was identified preoperatively by spotting an acoustic window, a lung- and bone-free acoustic line of sight from the implant location to the LV during transthoracic echographic screening. Next, after cutting down to the level of the intercostal muscle, an echocardiogram probe in a sterile sleeve was used to further confirm the acoustic window prior to securing the transmitter in the location using helical sutures.

For placement of the LV pacing electrode prior to delivery sheath insertion, heparin was administered to maintain an activated clotting time of 200–250 s. The use of retrograde aortic or transseptal approach to position the delivery sheath in the LV was at the investigators' discretion. Potential pacing sites were then evaluated under fluoroscopic guidance using a combination of echocardiographic considerations, electrical timing using local electrogram signals, and pacing thresholds. Once an appropriate endocardial LV pacing site was identified, the electrode was deployed and anchored into the LV endocardium by advancing the catheter to push the anchor of the electrode into the endocardial surface.

Follow-up and endpoints

After device implantation and before hospital discharge, proper device positioning and function were assessed by 12-lead electrocardiogram, chest X-ray, and device interrogation. A subsequent unblinded follow-up assessment was scheduled at 6 months post-implant with a clinical [patients subjective clinical status evaluation, New York Heart Association (NYHA) class], ECG (QRS duration, % LV-pacing), and echocardiographic assessment (LVEF, LV volumes). The endpoints of the study were technical success of WiSE-CRT implantation with RV-synchonized effective and stable LV endocardial pacing delivery to achieve CRT, acute QRS duration reduction, freedom from procedure-related major adverse events. Response to leadless-CRT (L-CRT) at 6 months defined as a 10% increase in LVEF measured using echocardiography and device performance at 6 months.

Procedure-related major adverse events were defined as events related to the study procedure or device that led to death, serious deterioration in subject health resulting in life-threatening illness, permanent impairment of body structure or function, inpatient or prolonged hospitalization, medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function.

Statistical analysis

All analyses were conducted using the SPSS Statistics software from IBM version 20 (Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation. The Wilcoxon signed rank test was used to compare performance values between implant (baseline) and follow-up intervals. A *P*-value <0.05 was considered significant.

Results

A total of eight patients from six European centres (Erlangen-Germany, Prague—Czech Republic, Guy's and St Thomas' Hospitals, London—UK, Monza-Italy, Rennes, and Grenoble—France) underwent Micra pacemaker and WiSE-CRT system implantation. A patient chest X-ray showing the two systems is presented in *Figure 1*.

Patients were predominantly male (seven male and one female). Patients were aged 76 ± 7.48 years. Four patients had ischaemic cardiomyopathy. The mean NYHA functional class was 2.63 ± 0.51. All patients were in permanent AF. Baseline characteristics of the patients are summarized in *Table 1*.

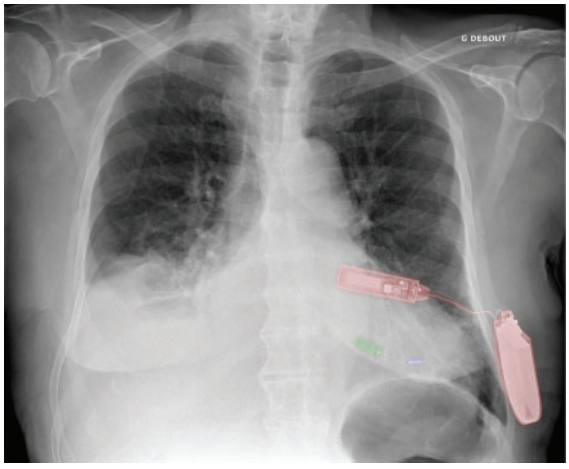

Figure 1 A patient chest X-ray showing both Micra and WiSE-CRT systems. Green: Micra leadless pacemaker; blue: WiSE-CRT system LV endocardial electrode; and red: WiSE-CRT system subcutaneous battery and ultrasound generator. CRT, cardiac resynchronization therapy.

The indication for WiSE-CRT system implantation was infection of a previous conventional CRT system in three patients and upgrade of a single chamber Micra pacemaker to a biventricular pacing system due to heart failure in five patients. The median time from transmitter implantation to electrode implantation was 5.63 days (range: 0–16 days). Three patients had transmitter and electrode implantation in the same day.

Implantation of the leadless CRT system was successful in all eight patients. There were no failed attempts unreported in this manuscript. Detection of the RV stimulus artefact delivered by the Micra was effective in all patients and biventricular endocardial pacing was confirmed following the procedure in eight patients. There was a significant acute reduction of the QRS duration after WiSE-CRT implantation (204.38 ± 30.26 vs. 137.5 ± 24.75 mS, $P = 0.012$, *Table 2* and *Figure 2*). A patient electrocardiogram before and after WiSE-CRT implantation is presented in *Figure 3*. No early complication was registered.

Seven patients reached the 6-month follow-up for clinical and echocardiographic review. One death occurred 4 months after the implantation owing to acute heart failure. This patient was excluded from volumes and LVEF analysis. No adverse event related to the procedure or device occurred in the first 6 months period for any patients.

There was no significant difference in QRS duration after WiSE-CRT system implantation and at 6-month follow-up (137.5 ± 24.75 vs. 124 ± 9.59 mS, $P = 0.14$).

There was a significant improvement in LVEF following WiSE-CRT implantation (+11.29 ± 8.46%; $P = 0.018$) but no evidence of LV reverse remodelling with unsignificant variations of LV end-diastolic volume (−30.60 ± 29.30 mL; $P = 0.22$) and LV end-systolic volume (−23 ± 27.77 mL; $P = 0.24$) (*Table 2* and *Figure 4*).

Table 1 **Baseline patient characteristics**

Patient no.	Site	Sex	Age	Comorbidities	Cardiomyopathy	NYHA	LVEF%	Cardiovascular meds	Pre-procedure rhythm	Indication for WiSE	Pre-procedure %RV paced	Pre-procedure paced QRS duration (mS)
1	Erlangen Germany	M	81	Aortic, mitral and tricuspid valve disease; hypertension	Ischaemic	3	20.0	Bisoprolol, ramipril, spironolactone, torasemid, atorvastatin, phenprocoumon	AF	Upgrade	100	183
2	Erlangen Germany	M	77	Mitral valve disease (mitraclip); hypertension; PVD; diabetes; renal failure grade III	Non-ischaemic	3	30.0	Rivaroxaban, carvedilol, torasemid, ramipril, simvastatin, eplerenon	AF	Upgrade	50.4	195
3	Na Homolce Czech Republic	M	70	Hypertension; diabetes	Non-ischaemic	2	33.0	Metoprolol, candesartan, digoxin, eplerenon, furosemid, amlodipin, rivaroxaban	AF	Upgrade	99.7	198
4	Na Homolce Czech Republic	F	77	Hypertension; renal failure Grade I	Non-ischaemic	2	43.0	Bisoprolol, digoxin, furosemide, dabigatran, rilmenidin, spironolacton	AF	Upgrade	55	160
5	Rennes France	M	81	Hypertension, diabetes, previous MI, PVD, COPD	Ischaemic	2	26.0	Furosemide, atorvastatin, ezetimib, spironolactone, rivaroxaban	AF	Infection	100	216
6	Grenoble France	M	77	Hypertension, renal failure Grade III; diabetes	Non-ischaemic	3	20	Bisoprolol, apixaban, spironolactone, furosemid	AF	Upgrade	100	208
7	San Gerardo Italy	M	82	Mechanical aortic valve; mitral valvuoplasty; diabetes	Ischaemic	N/A	26	Furosemide, canrenone, bisoprolol, coumadin, digoxin, losartan, trinitrine	AF	Infection	100	265
8	St. Thomas UK	M	63	Previous MI; renal failure Grade III; diabetes	Ischaemic	3	27	Apixaban, atorvastatin, bumetanide, bisoprolol, eplerenone	AF	Infection	77	210

AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PVD, peripheral vascular disease.

Table 2 Left ventricle function and volumes following WiSE-CRT implantation

Variables	Before WiSE-CRT implantation	After WiSE-CRT implantation	Change	*P*-value
QRS duration (ms)	204.37 ± 30.26	137.50 ± 24.75	−66.88 ±31.58	**0.012**
LVESV (mL)	117.33 ± 35.61	91.86 ± 48.43	−23 ± 27.77	0.24
LVEDV (mL)	160 ± 22.69	129.4 ± 40.70	−30.60 ± 29.30	0.22
LVEF (%)	28.43 ± 8.01	39.71 ± 11.89	+11.29 ± 8.46	**0.018**
NYHA	2.63 ± 0.51	2.29 ± 0.95		0.18

Values are reported as mean ± SD. Bold face values indicate significant differences ($P<0.05$)
CRT, cardiac resynchronization therapy; LVEF, Left ventricular ejection fraction; LVESV, Left ventricular end systolic volume; LVESDV, Left ventricular end diastolic volume; NYHA, New York Heart Association.

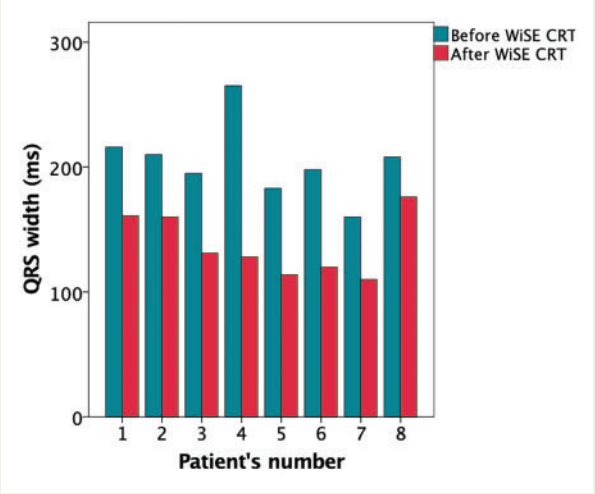

Figure 2 Individual changes in QRS width from baseline to WiSE-CRT implantation. CRT, cardiac resynchronization therapy.

Four patients had an absolute improvement in LVEF ≥10% (*Figure 5*).

Right ventricle and LV pacing percentages at 6-month follow-up were 89.42 ± 15.40% and 97.00 ± 4.93%, respectively. There was no significant change in NYHA functional status after WiSE-CRT implantation (2.63 ± 0.51 vs. 2.29 ± 0.95; $P = 0.18$); however, four patients had improvement in their clinical symptoms.

Patients with worsening LVEF consecutive to a high RV pacing burden were not considered for primary prevention with an ICD at first. Of the three patients implanted after extraction of a previous transvenous CRT system, two were deemed too severe to benefit from a defibrillator for primary prevention (age > 80, comorbidities) and one was implanted with a subcutaneous ICD.

Discussion

In this study, we describe a first European experience with a full leadless CRT system.

Technical feasibility of WiSE-CRT to operate with Micra

The WiSE-CRT system has four sensing electrodes on the transmitter, which are used to detect the RV pacing output of the co-implanted Micra pacing device. Detection of RV pacing output triggers the WiSE-CRT system to deliver its focused ultrasound beam towards the receiving electrode. Detecting the Micra stimulus artefact is critical but since the pulse width is generally set to 0.24 mS to ensure optimal battery life, which is markedly shorter than conventional pacing systems that deliver longer 0.4–0.5 mS pulse widths, sensing may be compromised. However, in each of the eight implants, the WiSE-CRT system could be successfully trained to detect the amplitude and width of the pacing pulse from the co-implanted Micra device. Biventricular pacing was successfully delivered to the patients by two independent leadless systems, the RV Micra pacemaker and the LV endocardial WiSE-CRT electrode.

Efficacy of left ventricular endocardial pacing

A significant acute QRS reduction was observed in all eight patients comparing before and after the WiSE-CRT system was turned on. These data demonstrate the ability of the system to deliver CRT with LV endocardial pacing pulses synchronized with the Micra pacemaker impulse. An absolute −67 mS mean QRS reduction was measured during this study. These data confirm the interest of endocardial LV pacing to shorten paced QRS by reducing LV activation time when compared with LV epicardial pacing.[14] Furthermore, acute QRS reduction has previously been associated with response to CRT with values as low as −10 mS in LBBB heart failure patients.[15]

The interest of endocardial pacing with an endocardial LV pacing lead was demonstrated in the ALSYNC study.[16] Analysis of these data revealed the potential of endocardial LV pacing in a non-responder population implanted with conventional epicardial LV pacing leads.[17] Forty-seven percent of prior non-responders showed response to CRT after an LV endocardial lead was implanted. However, despite these promising results transseptal LV lead placement was abandoned due to a need for anticoagulation and a higher stroke risk in the study population.[16] This approach also implied the use of a lead, which may demonstrate mechanical and infectious complications over time.

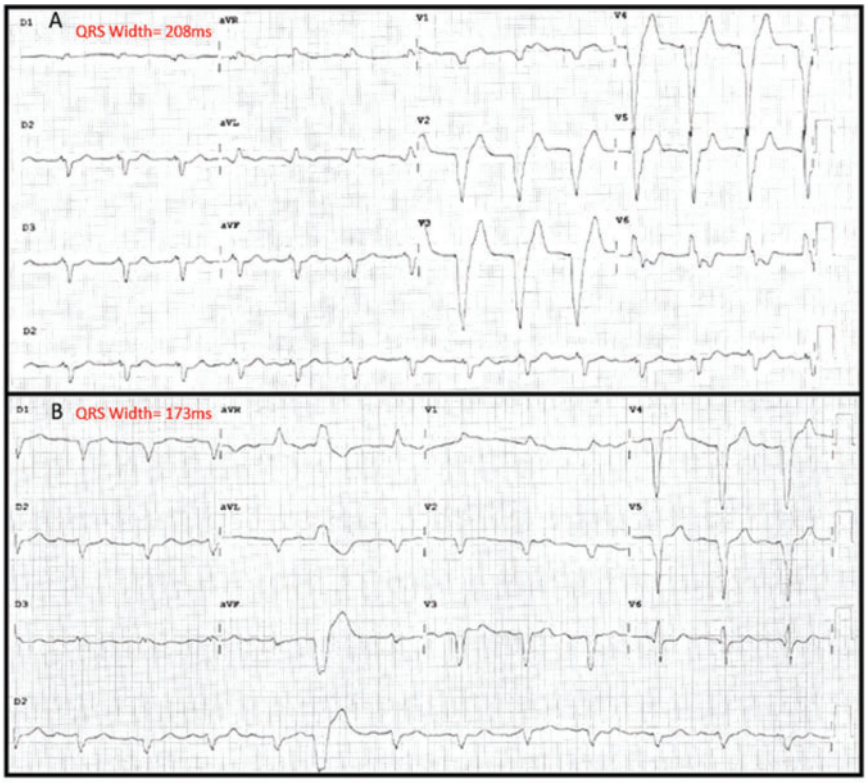

Figure 3 A patient electrocardiogram: (*A*) before WiSE-CRT implantation and (*B*) after Wise-CRT implantation. CRT, cardiac resynchronization therapy.

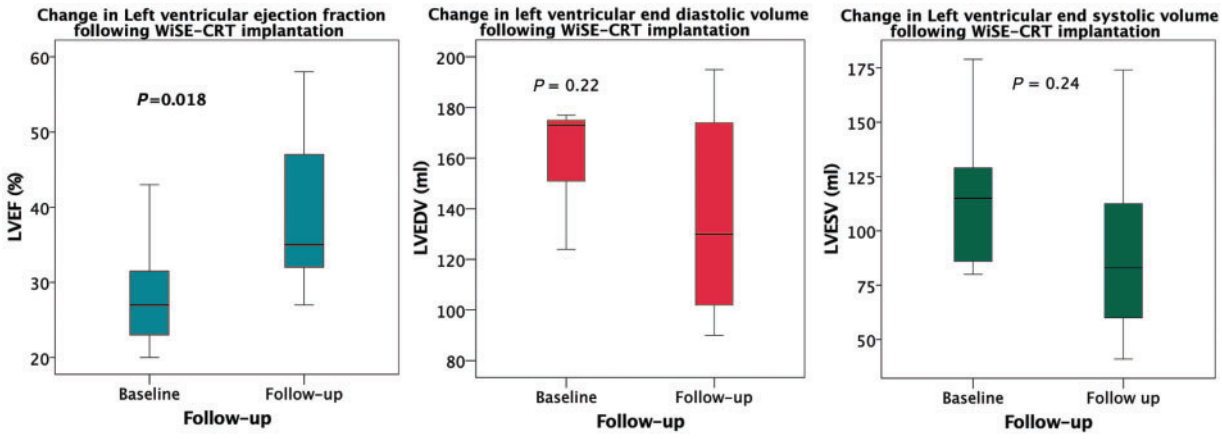

Figure 4 Box and whisker plots showing changes in left ventricular function following WiSE-CRT implantation. LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVEDV, left ventricular end diastolic volume.

In a canine model, CRT using LV endocardial pacing resulted in shorter activation delays, more homogenous LV depolarization, and better LV function when compared with conventional epicardial CRT.[18]

In 2017, Reddy *et al.*[3] published the SELECT-LV study, depicting a series of 35 patients implanted with the WiSE-CRT system. Patients were included because conventional epicardial LV lead placement had failed, was deemed too risky ($n = 25$) or because of failure to

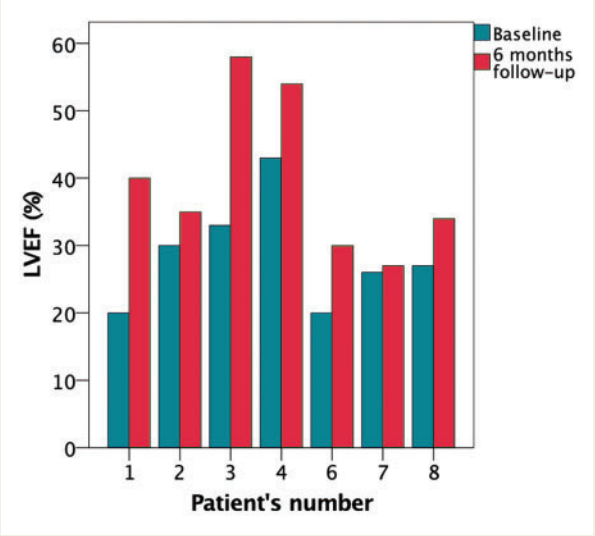

Figure 5 Individual changes in LVEF from baseline to 6 months. LVEF, left ventricular ejection fraction.

respond to CRT ($n = 10$). The authors reported 34 successful implantations, 85% of responders using a clinical composite score at 6 months, and 66% of responders when considering a ≥5% absolute increase in LV ejection fraction. Interestingly, those results compare favourably with conventional CRT studies using epicardial leads. Improvement in the clinical composite score was 52–69% in MIRACLE-ICD, REVERSE, and PROSPECT studies. The use of LV endocardial CRT pacing in the initial SELECT-LV study may account for these superior results and should be investigated further. These results have recently been confirmed in the European registry of WISE CRT in 90 patients with a symptomatic improvement in 70% of patients.[19] The SOLVE-CRT is a randomized trial currently underway and plans to implant 350 patients referred for CRT with the WiSE-CRT system after conventional epicardial lead failure (failure to implant or to deliver LV pacing) or non-response to CRT.[4]

Limitations

This study is retrospective and was therefore conducted unblinded, which may bias results. With eight patients included, the study was certainly underpowered to address any changes in clinical status or LV reverse modelling. The study was also most likely too small to affirm an absence of unpredicted device–device interactions. Patients' symptoms were evaluated subjectively, and placebo effect cannot be excluded. Objective patients' symptoms evaluation would be necessary in future studies. Further larger randomized controlled trials will be needed to confirm our results.

Potential future applications

The Micra has been on the market in Europe since 2015 and is indicated for patients requiring single chamber right ventricular pacing. It is known that patients who receive a single chamber pacemaker and have a high proportion of RV pacing or subsequently develop heart failure are often considered for upgrading to a CRT device. The WiSE-CRT system provides the only means to upgrade the large population of Micra patients to CRT capability without replacing the Micra.

A combination of Micra and WiSE CRT could be considered for atrial fibrillation patients requiring de novo CRT to take advantage of the benefits of completely leadless pacing system and physiological activation pattern of endocardial CRT pacing. Sidhu *et al.*[20] recently reported the coexistence of three systems (Micra, WiSE-CRT, and subcutaneous ICD) in one patient. This association may be considered to propose a completely leadless cardiac resynchronization defibrillator system to a patient. Furthermore, a combination of the WiSE-CRT system with the soon-to-be released Micra AV [a Micra pacemaker providing atrioventricular (VDD) synchronous pacing] could be an option for selected sinus rhythm patients with atrioventricular block requiring CRT.[21]

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Sound wave balloon-assisted device implantation: a novel approach that merits consideration

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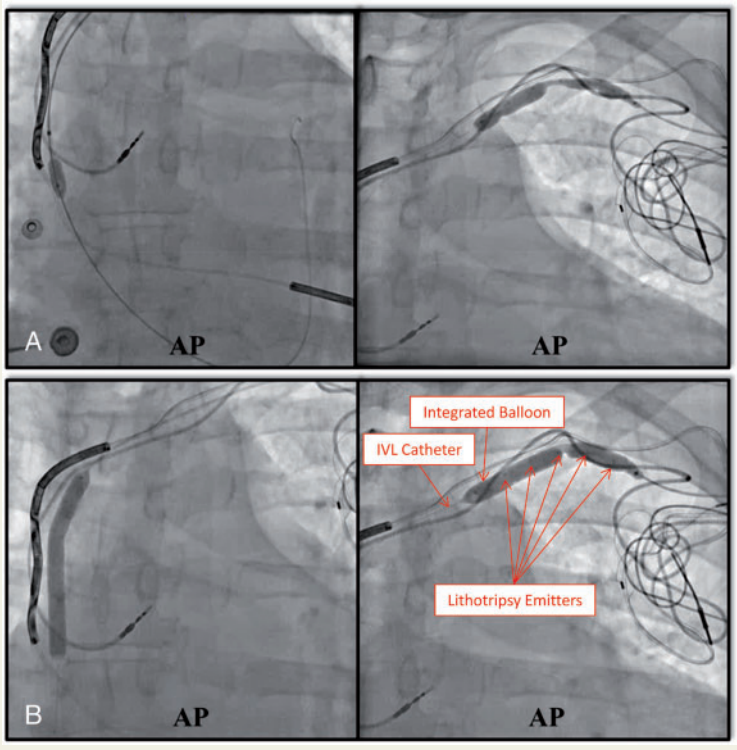
A 68-year-old male with dilated cardiomyopathy and prior cardiac resynchronization device implantation presents with progressive heart failure due to left ventricular (LV) lead dislodgement. Lead revision was undertaken due to progressive LV ejection fraction decline with loss of resynchronization.

The left axillary venogram showed occlusion of the subclavian vein and attempted venous access was unsuccessful. Access was obtained using an angioplasty wire through the existing LV lead. Attempts to serially dilate the vein were met with resistance. Venoplasty of the stenotic segments was attempted using a non-compliant balloon followed by cutting balloon without success to advance the lead delivery sheath. The decision was made to attempt venoplasty with ultrasound-based therapy using the Shockwave® balloon. After balloon expansion, cycles of shockwaves were delivered at the stenotic lesions. Desirable angioplasty results were achieved to advance the delivery sheath and implant a His-bundle pacing lead. The patient did very well with no heart failure or complications.



Calcification leading to vein stenosis can pose significant challenges to lead revision and extraction. We describe a novel approach using ultrasound-based therapy to assist in lead management. This unique technology in lead management warrants future studies.

The full-length version of this report can be viewed at: https://www.escardio.org/Education/E-Learning/Clinical-cases/Electrophysiology.