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Impact of closed loop stimulation on prognostic cardiopulmonary variables in patients with chronic heart failure and severe chronotropic incompetence: a pilot, randomized, crossover study

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Aims Clinical effects of rate-adaptive pacing in heart failure patients with chronotropic incompetence (CI) undergoing cardiac resynchronization therapy (CRT) remain unclear. Closed loop stimulation (CLS) is a new rate-adaptive sensor in CRT devices. We evaluated the effectiveness of CLS in CRT patients with severe CI, focusing primarily on key prognostic variables assessed by cardiopulmonary exercise (CPX) testing.

Methods and results In the randomized, crossover, multicentre BIO|CREATE study, 20 CRT patients with severe CI and NYHA Class II/III (60%/40%) were randomized 1:1 to the sequence DDD-40 mode to DDD-CLS mode, or the sequence DDD-CLS mode to DDD-40 mode (1 month in each mode). Patients underwent symptom-limited treadmill-based CPX test in each mode. An improvement (decrease) of the ventilatory efficiency (VE) slope of ≥5% during CLS was regarded as positive response to CLS. Seventeen patients with full data sets had a mean intra-individual VE slope change of −1.8 ± 3.0 (−4.1%) with CLS ($P = 0.23$). Eight patients (47%) were CLS responders, with a −6.1 ± 2.7 (−16.4%) slope change ($P = 0.029$). Compared to non-responders, CLS responders had a higher left ventricular (LV) ejection fraction (46 ± 3 vs. 36 ± 9%; $P = 0.0070$), smaller end-diastolic LV volume (121 ± 34 vs. 181 ± 41 mL; $P = 0.0085$), smaller end-systolic LV volume (65 ± 23 vs. 114 ± 39 mL; $P = 0.0076$), and were predominantly in NYHA Class II ($P = 0.0498$).

Conclusion The data of the present pilot study are compatible with the notion that CLS activation may improve VE slope in CRT patients with severe CI and less advanced heart failure. Further research is needed to determine the long-term clinical outcomes of CLS.

Keywords Cardiac resynchronization therapy • Severe chronotropic incompetence • Rate-adaptive pacing • Closed loop stimulation • Cardiopulmonary exercise testing • Ventilatory efficiency slope

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What's new?

- The clinical effects of a rate-adaptive pacing are unclear in heart failure patients with a cardiac resynchronization therapy (CRT) device and chronotropic incompetence (CI).
- Closed loop stimulation (CLS) is a new rate-adaptive sensor technology in CRT devices, measuring intracardiac impedance as a surrogate for ventricular contractility.
- BIO|CREATE is the first study to evaluate CLS in CRT patients with severe CI by focusing primarily on key prognostic variables assessed during cardiopulmonary exercise testing.
- The most important prognostic variable, the ventilatory efficiency slope, improved by 4.1% for CLS vs. no rate-adaptive pacing. About one-half of patients were responders to CLS, experiencing at least 5% improvement.
- This pilot study identified a significant difference in baseline variables for CLS responders vs. non-responders, generating a hypothesis that CLS activation is more beneficial in CRT patients with less advanced heart failure.

Introduction

Although chronotropic incompetence (CI) contributes to exercise intolerance, reduces quality of life, and independently predicts mortality and adverse outcome in patients with cardiovascular disease, it receives limited attention in clinical practice.[1,2] The prevalence of CI in the heart failure population ranges between 25% and 85%, depending on the severity of heart failure and rigor of CI criteria.[1–3] Cardiac resynchronization therapy (CRT) has been shown to improve exercise capacity, quality of life, morbidity, and survival in a majority of heart failure patients with mechanical dyssynchrony.[4,5] Some authors suggested that rate-adaptive pacing can further improve exercise capacity and clinical outcomes in chronotropically incompetent CRT patients.[1,3,6,7]

However, the results of several studies evaluating the impact of rate-adaptive pacing on exercise performance of CRT patients with CI are inconsistent and controversially interpreted.[6,8–10] The rate-adaptive systems used in these studies were based on an accelerometer sensor, which is unspecific to physical activity type.[11] A novel closed loop stimulation (CLS) sensor has recently been integrated in CRT devices to measure intracardiac impedance as a surrogate for ventricular contractility and thus provide a more physiologic pacing rate according to the cardiac contractile state and the patient's true metabolic demands.[12] Clinical studies are needed to assess the potential benefit of CLS and its impact on prognosis in CRT patients with CI.

Cardiopulmonary exercise (CPX) testing is a well-established diagnostic and prognostic method in heart failure. Among CPX parameters, the ventilatory efficiency (VE) slope [minute ventilation (VE) plotted against CO_2 production (VCO_2)] has been shown to be a superior prognostic indicator.[13–16] However, accelerometer-based CRT pacing was instead primarily investigated in terms of exercise capacity indicated by maximum oxygen uptake (VO_2max), which improved only in a proportion of patients ('responders' to rate-adaptive pacing), mostly those with severe CI.[6,8–10] Furthermore, severe CI is generally associated with a higher cardiovascular mortality than a moderate CI.[2]

In the BIO|CREATE pilot study, we primarily used the VE slope (i) to assess the effectiveness of CLS vs. no rate-adaptive pacing, including clinical prognosis, in CRT patients with severe CI and (ii) to identify responders to CLS.

Methods

Study design

The Creation of physiologic Rhythm by closed loop stimulation in hEart failure pAtients with chronoTropic incompEtence (BIO|CREATE) study was a randomized crossover (sequence DDD-40 mode to DDD-CLS mode, or sequence DDD-CLS mode to DDD-40 mode, with 1 month in each mode) pilot multicentre trial. Patients and experts involved in a symptom-limited treadmill-based CPX evaluation were blinded to the programmed mode. To be a CLS responder, the patient had to exhibit ≥5% improvement in the VE/VCO_2 slope with CLS. Patients' baseline characteristics were analyzed to identify predictors of CLS responders.

The 5% cut-off value for responders has been derived from the work of Arena *et al.*,[16] who analyzed the risk of major cardiac events (cardiac death, left ventricular assist device implantation, and urgent heart transplantation) according to VE class ranges. We assumed that the mean VE/VCO_2 slopes in the two modes in our study would be within a 30–35 range, where a relative improvement in the VE/VCO_2 slope of ≥5% would according to linear interpolation applied to these previous data[16] be expected to translate into a ≥ 25% lower relative risk of major cardiac events over 3 years—a risk reduction level considered to be of clinical relevance. Super responders with a ≥10% improvement in the VE/VCO_2 slope would according to this model be expected to have a ≥50% lower risk of major cardiac events.

Appropriate national and local ethics committees approved the study which was performed in compliance with good clinical practice guidelines and the Declaration of Helsinki (ClincialTrials.gov Identifier: NCT03157076). All patients provided written informed consent.

Patients

Enrolled patients had a CRT device (pacemaker or defibrillator) including CLS option (Biotronik SE & Co. KG, Berlin, Germany), implanted for a CRT Class I indication at least 6 months before enrolment. Patients also had a stable heart failure status, were in New York Heart Association (NYHA) Class II or III and received optimal cardiovascular drug treatment according to current guidelines. Major exclusion criteria were age <18 years, cardiac ischaemia, persistent atrial fibrillation, severe chronic obstructive pulmonary disease, planned cardiovascular intervention, admission for decompensated heart failure or acute coronary syndrome in the preceding 3 months, or participation in another interventional clinical study.

Severe chronotropic incompetence

Chronotropic function was evaluated by bicycle ergometry after patient enrolment. Severe CI was defined either as a maximum heart rate <75% of the age-predicted maximum heart rate (APMHR = 220-age, for healthy populations)[7] or as inability to utilize at least 50% of heart rate reserve at end-exercise, or both. Patients without severe CI were discontinued from the study.

Study protocol

At the enrolment visit, chronotropic impairment was assessed, with the CRT device programmed to the DDD mode with a basic pacing rate of 40 pulses/min (ppm) (the 'DDD-40' mode). The initial bicycle workload of 20 W was incremented by 20 W every minute until the patient no longer sustained pedalling at 50 cycles/min. Heart rate and maximum workload were recorded. Only patients exhibiting severe CI continued the study. Their CRT devices were programmed to the rate-adaptive (DDD-CLS) mode.

At the baseline visit (1–4 weeks after enrolment), patients were randomized 1 : 1 to either DDD-40 or DDD-CLS mode for 1 month, followed by crossover for another month. No strata were implemented in the randomization procedure as it was unclear which subgroup of patients might particularly benefit from CLS. Block randomization was used with block sizes of four or six. Each block size was used four times in a random order to ensure a 1 : 1 randomization after 40 patients.

At the baseline visit (prior to randomization) and at 1- and 2-month follow-up visits, echocardiographic parameters and the plasma level of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) were determined, health-related quality of life and patient activity status were assessed, and a mental test, 6-min walk, and a treadmill-based CPX test were performed.

The study was terminated after the 2-month follow-up. Prior to study termination, each patient was asked in which period his/her well-being was better: during the first or second month of follow-up. The corresponding pacing mode was then regarded as the preferred mode by the patient.

Device programming

In both DDD-40 and DDD-CLS modes, basic rate was set to 40 ppm and the upper sensor rate to 220-age. At enrolment, patients who remained in the study after bicycle ergometry performed a 6-min walk in the DDD-CLS mode to allow for the adjustment of CLS response (low, medium, and high) based on device diagnostics evaluation and patient perception during the walk.

At the baseline visit, atrioventricular delay was optimized in all patients in the resting state according to the Koglek method.[17] A 40 ms longer atrioventricular delay was recommended during atrial pacing than during atrial sensing. It was reassured that CRT pacing was effective, without fusion or pseudofusion beats. The randomized pacing modes (DDD-40, DDD-CLS) were crossed over at the end of 1-month follow-up.

Cardiopulmonary exercise testing and derived variables

A symptom-limited CPX test was performed using a low to moderate intensity treadmill protocol after an initial resting phase of 2 min. Each of ten treadmill stages lasted for 1 min, with a stepwise increase in speed (starting 1.6 km/h and maximum 5.2 km/h) and elevation (from 0% up to 18%) of the running belt. Patients wore a well-sealed sterile mask connected to a flow transducer. Inspired and expired air was rapidly (breath by breath) sampled by a Quark CPET gas analyzer system (COSMED, Rome, Italy). The treadmill exercise was terminated upon reaching a target respiratory exchange ratio (VCO_2/VO_2) of at least 1.05, or upon flattening of the VO_2 curve. Measures were undertaken to minimize the impact of inter-observer variability and circadian or metabolic variations on the intra-individual exercise performance. Further details on CPX protocols and equipment are provided in Supplementary material online, *Appendix*.

The major variables derived from the CPX test were (i) VE/VCO_2 slope; (ii) oxygen uptake efficiency slope (OUES); (iii) VO_2max; (iv) end-tidal CO_2 at end-exercise; (v) resting heart rate before exercise (HR_{REST}); (vi) peak heart rate at the end of exercise (HR_{PEAK}); and (vii) percentage of heart rate reserve utilized at end-exercise [%HRR, computed as (HR_{PEAK}—HR_{REST})/(APMHR—HR_{REST})]. Since different software for automatic determination of VE/VCO_2 slope and OUES could produce different results in different CPX systems, all slopes were manually calculated by an expert who was blinded to the pacing mode (author D.J.M., see Supplementary material online, *Appendix*).

Other assessments

Resting echocardiographic measurements (parameters listed in *Table 1*), quality of life assessment using EuroQol-5D and Minnesota Living with Heart Failure questionnaires, the Duke Activity Status Index, the d2-R test of concentration (mental test), and 6-min walk test, performed at the baseline and 1- and 2-month follow-up visits, are described in Supplementary material online, *Appendix*.

Outcome measures

The primary outcome measures were the VE/VCO_2 slope and a CLS responder rate (≥5% improvement in the VE/VCO_2 slope vs. DDD-40 mode). A ≥10% improvement in the VE/VCO_2 slope indicated super responders. Based on a comprehensive set of patient-related parameters at baseline, including echocardiographic data, we identified predictors for CLS responders.

The secondary outcome measures were the OUES, VO_2max, end-exercise end-tidal CO_2, %HRR utilized at end-exercise, HR_{REST}, and HR_{PEAK} during CPX testing. Further secondary outcome measures were selected echo parameters, NT-proBNP, health-related quality of life, activity status, mental performance, 6-min walk distance, and pacing mode preferred by the patient.

Statistical methods

As this is a pilot study, no primary hypothesis was defined and a sample size was not formally calculated. The plan was to obtain full data sets for the VE/VCO_2 slope in at least 30 patients. Clinical and baseline patient characteristics are descriptively presented by mean and standard deviation for continuous variables and absolute and relative frequencies for nominal data.

All outcome measures were analyzed accounting for the crossover design in patients with full data sets for the VE/VCO_2 slope. Mean and standard deviation are given for each randomization group and programmed mode separately, for the intra-individual differences per group, and for the effect of CLS on the outcome measure (treatment effect). The treatment effect of CLS and the presence of a carry-over or a period effect were analyzed by an unpaired exact Wilcoxon test.

Baseline characteristics of CLS responders (≥5% better VE/VCO_2 slope with CLS) and non-responders were compared with an unpaired Wilcoxon test (for continuous variables) or a Fisher's test (nominal variables). Correlation of two outcome measures was assessed with a regression fit; Pearson correlation coefficient (r) was calculated and tested for $r \neq 0$.

In all evaluations, a P-value <0.05 indicated statistical significance in an exploratory sense, multiple testing was not accounted for. Data were analyzed with the SAS 9.4 (SAS Institute, NC, USA) statistical software.

Results

Patients

Between 18 April 2017 and 23 January 2019, 36 patients were enrolled in six German and one Hungarian centre (see Supplementary

Table 1 Clinical characteristics of randomized patients[a]

	Group 1 (DDD-40 first), *N* = 10	Group 2 (DDD-CLS first), *N* = 10
Age (years)	68 ± 6	69 ± 9
Male gender	7 (70)	7 (70)
Body mass index (kg/m^2)	30.4 ± 4.6	28.5 ± 4.5
NYHA Class II/III	6 (60)/4 (40)	6 (60)/4 (40)
Ischaemic aetiology	5 (50)	5 (50)
Type of heart failure		
Left heart failure	8 (80)	8 (80)
Right heart failure	0	0
Global heart failure	2 (20)	2 (20)
NT-proBNP (pg/mL)[a]	840 ± 984	462 ± 329
Intrinsic QRS duration (ms)	137 ± 35[b]	139 ± 35
History of paroxysmal atrial fibrillation	6 (60)	5 (50)
Comorbidities		
Hypertension	7 (70)	9 (90)
Pulmonary hypertension	2 (20)	0
Diabetes	5 (50)	5 (50)
Chronic renal insufficiency	3 (30)	4 (40)
Echocardiographic parameters[a]		
LVEF (%)	40 ± 10	44 ± 8
Cardiac output (L/min)	3.9 ± 1.5[b]	4.3 ± 1.1
Left atrial volume (mL)	77 ± 35	57 ± 18[b]
LVEDV (mL)	168 ± 52	137 ± 49
LVESV (mL)	103 ± 47	77 ± 36
Pulmonary arterial pressure (mmHg)	28 ± 7[b]	29 ± 12[c]
Type of CRT device		
Pacemaker (CRT-P)	3 (30)	2 (20)
Defibrillator (CRT-D)	7 (70)	8 (80)
Cardiovascular medication		
ACE-inhibitor	4 (40)	5 (50)
Angiotensin receptor blocker	6 (60)	4 (40)
Aldosterone antagonist	6 (60)	8 (80)
Beta-blocker (excluding Sotalol)	8 (80)	10 (100)
Diuretic	9 (90)	8 (80)
Calcium channel blocker	1 (10)	2 (20)
Digoxin	3 (30)	0
Statin	7 (70)	8 (80)
Neprilysin inhibitor	0	0
Anticoagulant	7 (70)	4 (40)
Platelet aggregation inhibitor	4 (40)	5 (50)
Antiarrhythmic drug	3 (30)	4 (40)

Data are shown as *N* (%) or mean ± standard deviation.
ACE, angiotensin converting enzyme; CLS, closed loop stimulation; CRT, cardiac resynchronization therapy; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association.
[a]Except for the NT-proBNP and echo parameters, which were obtained at the baseline visit, all other data were obtained during the enrolment visit.
[b]*N* = 9.
[c]*N* = 7.

material online, *Appendix*). Severe CI was detected in 23 patients (64%). After exclusion of three patients due to worsening condition or consent withdrawal, 20 patients were randomized (*Figure 1*). *Tables 1 and 2* depict patients' baseline characteristics and bicycle ergometry data at enrolment. During the study, the programmed atrioventricular delay was 102 ± 15 ms (atrial sensing) and 143 ± 13 ms (atrial pacing). The last patient completed the study on 6 February 2019.

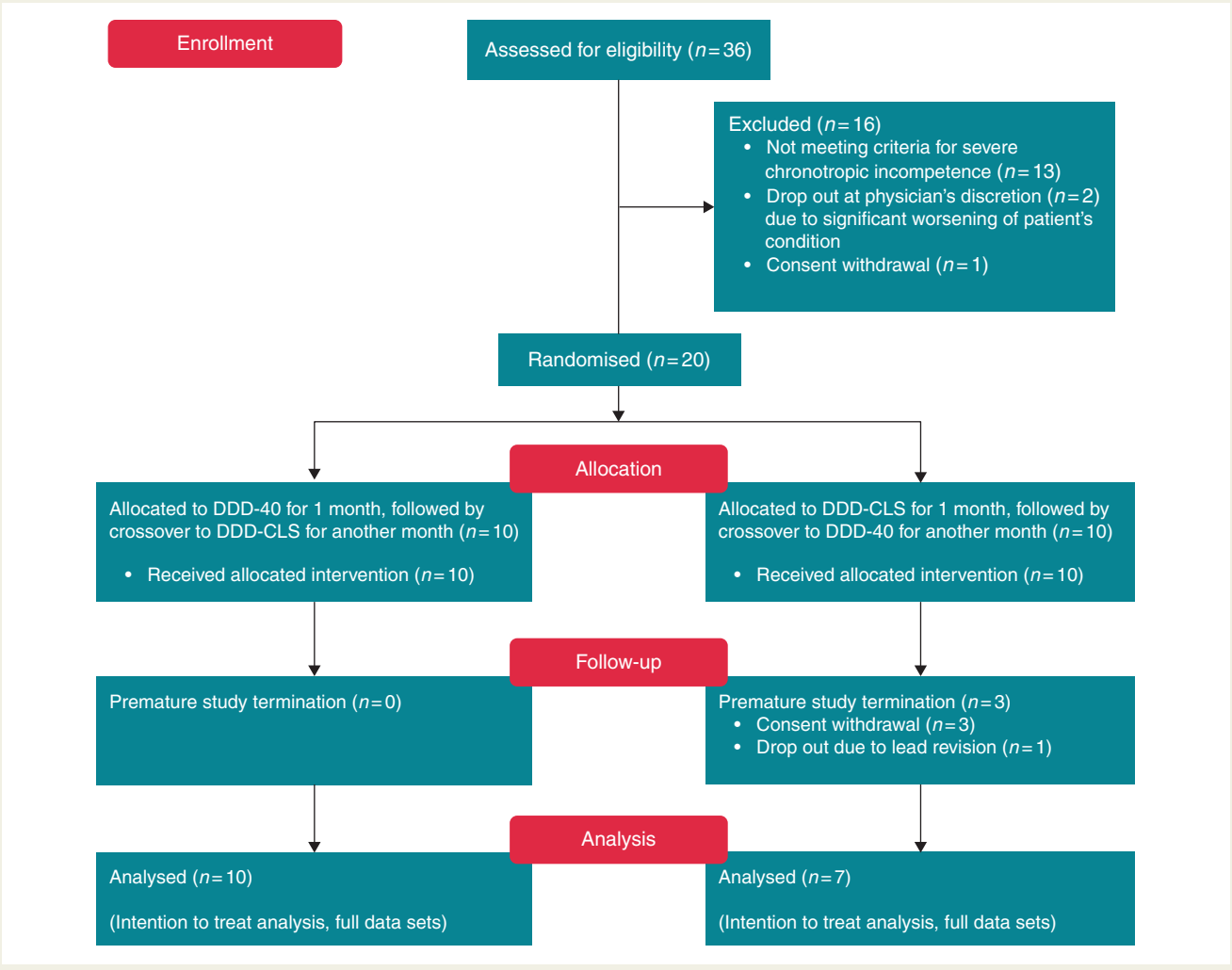

Figure 1 Trial flowchart.

Table 2 Bicycle ergometry data in randomized patients[a]

	Group 1 (DDD-40 first), N = 10	Group 2 (DDD-CLS first), N = 10
Heart rate at rest (b.p.m.)	61 ± 12	69 ± 13
Heart rate at end-exercise (b.p.m.)	96 ± 13	99 ± 14
Maximum workload reached (W)	102 ± 35	106 ± 33
%APMHR achieved	63 ± 9	66 ± 8
%HRR utilized	38 ± 12	36 ± 10

Data are shown as mean ± SD.
%APMHR, percentage of the age-predicted maximum heart rate; %HRR, percentage of heart rate reserve; CLS, closed loop stimulation.
[a]Testing was conducted at enrolment, 1–4 weeks before randomization. All patients in the table had severe chronotropic incompetence.

Ventilatory efficiency slope and other cardiopulmonary exercise outcome measures

Full datasets for the VE/VCO_2 slope are obtained from 17 patients (*Figure 1*). The difference in the VE/VCO_2 slope for CLS vs. no rate-adaptive pacing was −1.8 ± 3.0, indicating a trend toward improved (decreased) slope with CLS (*Table 3* and *Figure 2*). The intra-individual relative change with CLS was −4.1% ($P = 0.23$). No significant difference between the two modes was observed for the OUES, VO_2max, and end-tidal CO_2 (*Table 3*). The VE/VCO_2 slope strongly correlated with two other important

Table 3 Cardiopulmonary exercise-derived values and change in CLS

	DDD-40 mode	DDD-CLS mode	Change in DDD-CLS[a]	Total change in DDD-CLS,[a,b] N = 17
VE/VCO_2 slope				
Group 1 ($n = 10$; DDD-40 first)	35.0 ± 12.0	33.7 ± 12.3	−1.2 ± 3.5	−1.8 ± 3.0[c] (+)
Group 2 ($n = 7$; DDD-CLS first)	35.7 ± 5.3	33.4 ± 6.9	−2.4 ± 8.3	($P = 0.23$)
OUES (mL/min)				
Group 1 ($n = 10$)	2.0 ± 0.7	1.9 ± 0.5	−0.1 ± 0.4	0.2 ± 0.3 (+)
Group 2 ($n = 7$)	1.6 ± 0.4	2.0 ± 1.0	0.4 ± 0.9	($P = 0.87$)
VO_2max (mL/kg/min)				
Group 1 ($n = 10$)	17.9 ± 4.2	17.9 ± 5.4	0.1 ± 2.3	0.6 ± 1.4 ($n = 16$) (+)
Group 2 ($n = 7$)	16.8 ± 4.3	17.6 ± 4.4 ($n = 6$)	1.0 ± 3.4 ($n = 6$)	($P = 0.94$)
ET CO_2 (mmHg)				
Group 1 ($n = 10$)	35.2 ± 7.5	34.7 ± 7.9	−0.5 ± 2.0	0.3 ± 1.5 ($n = 16$) (+)
Group 2 ($n = 7$)	32.4 ± 4.5	33.3 ± 3.4 ($n = 6$)	1.2 ± 4.1 ($n = 6$)	($P = 0.73$)
%HRR utilized (%)				
Group 1 ($n = 10$)	51 ± 18	59 ± 23	9 ± 19	13 ± 9
Group 2 ($n = 7$)	41 ± 12	59 ± 25	17 ± 15	($P = 0.012$)
Heart rate (b.p.m.)				
At rest before exercise[b]				
Group 1 ($n = 10$)	65 ± 8	65 ± 8	1 ± 5	4 ± 3
Group 2 ($n = 7$)	60 ± 16	68 ± 17	8 ± 9	($P = 0.022$)
End-exercise				
Group 1 ($n = 10$)	109 ± 17	117 ± 19	8 ± 17	13 ± 8
Group 2 ($n = 7$)	96 ± 16	114 ± 22	18 ± 13	($P = 0.0030$)

Data are shown as mean ± standard deviation in patients with full data sets for the VE/VCO_2 slope. *P*-values are reported to 2 significant decimal places.
%HRR, percentage of heart rate reserve; CLS, closed loop stimulation; CPX, cardiopulmonary exercise testing; ET CO_2, end-tidal carbon dioxide; OUES, oxygen uptake efficiency slope; VE/VCO_2, ventilatory efficiency; and VO_2max, maximum oxygen uptake.
[a]Intra-individual difference between DDD-CLS and DDD-40.
[b]Treatment effect. Plus or minus in brackets indicates favourable (+) or unfavourable (−) change in spiroergometry parameters.
[c]The 95% confidence interval for the mean value was −4.9 to 1.3.

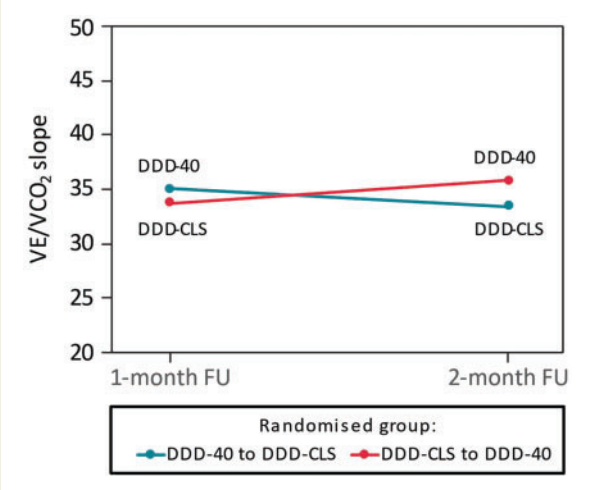

Figure 2 Results for the ventilatory efficiency (VE/VCO_2) slope in the two randomized groups. Lower values are more favourable. FU, follow-up.

prognostic variables: OUES ($r = -0.538$; $P < 0.0001$) and VO_2max ($r = -0.539$; $P < 0.0001$) (*Figure 3*).

Heart rate related parameters were significantly increased with CLS: the %HRR utilized during exercise increased by 13 ± 9% ($P = 0.012$), HR_{REST} by 4 ± 3 b.p.m. ($P = 0.022$), and HR_{PEAK} by 13 ± 8 b.p.m. ($P = 0.0030$) (*Table 3*). There was no significant carry-over or period effect for any CPX variable, except for HR_{REST} (period effect, $P = 0.031$).

Responders to Closed loop stimulation

Eight patients (47%) experienced at least a 5% improvement in the VE/VCO_2 slope during CLS and were classified as CLS responders. The VE/VCO_2 slope in these patients decreased by 6.1 ± 2.7 (mean intra-individual relative change: −16.4%) ($P = 0.029$). Six super responders had a ≥10% slope decrease. In nine patients (53%) who did not show a positive response to CLS, the VE/VCO_2 slope increased by 2.7 ± 1.1 (mean intra-individual relative change: 6.8%; in three cases ≥5%).

Table 4 compares baseline characteristics of eight CLS responders and nine non-responders. Responders had a more preserved left ventricular ejection fraction (LVEF: 46 ± 3% vs. 36 ± 9%; $P = 0.0070$),

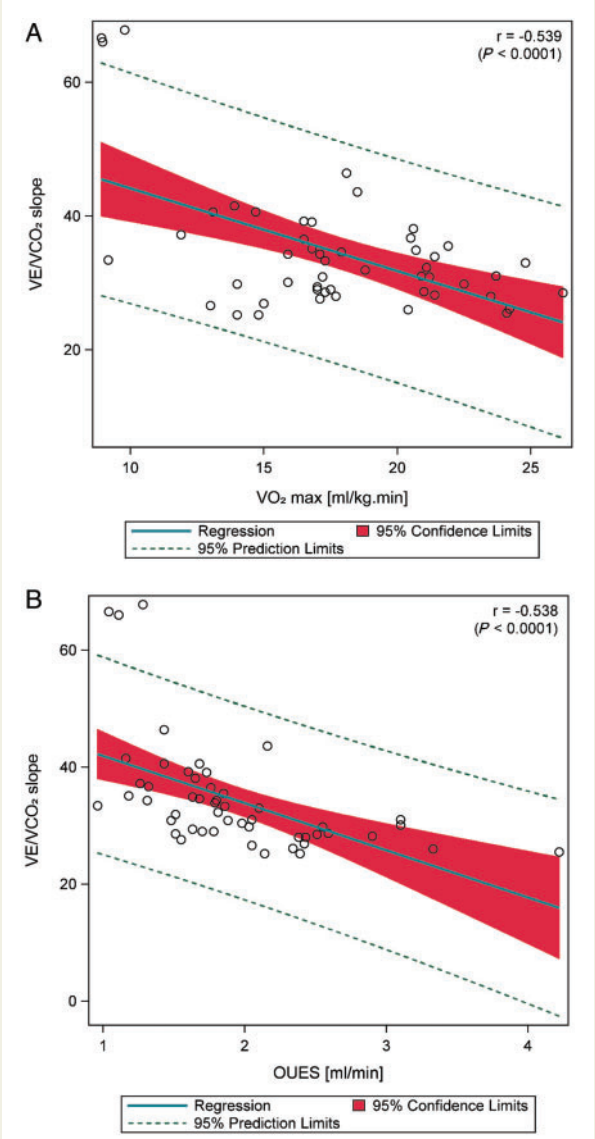

Figure 3 Correlation between ventilatory efficiency (VE/VCO_2) slope and two other important prognostic variables, oxygen uptake efficiency slope (OUES) and maximum oxygen uptake (VO_2max). The Pearson correlation coefficient (*r*) is indicated. There are 51 data points in (*A*) [17 patients with full data sets × 3 treadmill tests (baseline visit, 1-, and 2-month follow-ups)]. In (*B*), 1 of the 51 data points is missing.

smaller end-diastolic volume (121 ± 34 vs. 181 ± 41 mL; $P = 0.0085$), and end-systolic volume (64 ± 22 vs. 114 ± 39 mL; $P = 0.0076$) of the left ventricle and were predominantly in NYHA Class II (88% of responders vs. 33% of non-responders; other patients were in NYHA Class III) ($P = 0.0498$). In addition, responders to CLS tended to be hypertensive (100% vs. 56% of patients; $P = 0.082$) and to have lower NT-proBNP levels (mean 348 ± 332 vs. 1033 ± 945 pg/mL; $P = 0.074$).

Other assessments and observations

No significant difference between the two modes was observed for other secondary outcomes (see Supplementary material online, *Appendix*). No death or any other serious adverse event occurred during the study. At the end, 12 (75%) of 16 interviewed patients preferred the DDD-CLS mode.

Discussion

Main study findings

Initiated in 2017, BIO|CREATE is the first study worldwide that systematically evaluated the treatment effects of CLS in heart failure patients with severe CI and a CRT device, focusing primarily on key prognostic CPX variables. The VE slope improved by −1.8 during DDD-CLS compared to DDD-40, which according to the ventilatory classification system of Arena *et al.*[16] addressed in Study design would translate into a roughly 23% lower relative risk of major cardiac events over 3 years. Also, VO_2max and OUES improved and both correlated well with VE/VCO_2.

The intra-individual effects of CLS on the VE/VCO_2 slope revealed that about half (47%) of the patients were CLS responders, experiencing at least 5% improvement. In these patients, the mean slope decrease of 16.4% would translate into a roughly estimated 70% relative risk reduction for major cardiac events over 3 years.[16] Conversely, in non-responders, the mean VE/VCO_2 slope deterioration of 6.8% potentially increases the risk of events by ≈29%. A comparison of baseline characteristics of CLS responders and non-responders showed a more preserved left ventricular function in the responder group (greater LVEF, smaller left ventricle, and lower NYHA class). Therefore, this pilot study generates a hypothesis that CLS activation is more beneficial in CRT patients with less advanced heart failure. In other words, better responders to CRT at study baseline (after at least 6 months of CRT), characterized by higher LVEF and smaller left ventricular volumes, had also a higher chance of responding to CLS.

The mean CLS-driven HR_{PEAK} during CPX of 116 b.p.m. [achieved by programming the upper sensor rate to ≈150 ppm (=220-age)], significantly improved the mean %HRR utilized at end-exercise, from 47% (DDD-40) to 59% (DDD-CLS). Dobre *et al.*[7] previously showed that each 10%-step decrease in %HRR utilization below the 60% mark is associated with a 13% increase in the risk of a composite endpoint of cardiovascular mortality or heart failure hospitalization over a median follow-up of 32 months in patients with heart failure and LVEF <35%. However, our study patients had a higher mean LVEF and the prognostic benefit of greater %HRR utilization may therefore be lower than in the Dobre study.

Health-related quality of life was not significantly improved with CLS, yet 75% of patients preferred the DDD-CLS mode after study termination.

Scientific background and its impact on study design

Although CI is common among CRT patients with chronic heart failure and associated with reduced exercise capacity, impaired quality of life, and increased risk of mortality,[1,2] clinical research on therapies

Table 4 Baseline characteristics of CLS responders and non-responders

	CLS responders,[a] N = 8	Non-responders, N = 9	P-Value
Patient characteristics at enrolment			
Age (years)	70 ± 8	70 ± 8	0.98
Male gender	6 (75)	6 (67)	1.00
Body mass index (kg/m^2)	29.4 ± 2.3	29.3 ± 5.9	0.69
NYHA Class II/III	7 (88)/1 (13)	3 (33)/6 (67)	**0.0498**
Ischaemic aetiology	4 (50)	5 (56)	1.00
QRS duration (ms)	134 ± 25 (*n* = 7)	137 ± 30	0.90
Heart rate (b.p.m.)	59 ± 7 (*n* = 7)	66 ± 12	0.13
History of paroxysmal atrial fibrillation	5 (63)	5 (56)	1.00
Hypertension	8 (100)	5 (56)	0.082
Diabetes	3 (38)	5 (56)	0.64
Chronic renal insufficiency	3 (38)	3 (34)	1.00
Medications at enrolment (heart rate related)			
Beta-blocker (excluding Sotalol)	8 (100)	7 (78)	0.47
Digoxin	2 (25)	1 (11)	0.58
Antiarrhythmic drug	4 (50)	2 (22)	0.33
Baseline visit			
NT-proBNP (pg/mL)	348 ± 332	1033 ± 945	0.074
Echocardiographic parameters			
LVEF (%)	46 ± 3	36 ± 9	**0.0070**
Cardiac output (L/min)	3.9 ± 0.9 (*n* = 7)	4.0 ± 1.5	0.66
Left atrial volume (mL)	64 ± 39	71 ± 21 (*n* = 8)	0.49
LVEDV (mL)	121 ± 34	181 ± 41	**0.0085**
LVESV (mL)	65 ± 23	114 ± 39	**0.0076**
Pulmonary arterial pressure (mm Hg)	34 ± 10 (*n* = 7)	25 ± 8 (*n* = 7)	0.090

Data are shown as *N* (%) or mean ± standard deviation. *P*-values are reported to 2 significant decimal places. Bolded P-values are indicatingpotential predictors for CLS responding.
CLS, closed loop stimulation; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association.
[a]≥5% improvement in the ventilatory efficiency slope in CLS vs. no rate-adaptive pacing during cardiopulmonary exercise testing.

such as rate-adaptive pacing gained little attention in this population. To date, three small studies with a total of 47 chronotropically incompetent CRT patients investigated incremental benefit of rate-adaptive (DDDR) pacing over intrinsic rhythm (DDD mode) in terms of exercise capacity and haemodynamic effects.[6,8,9] Tse *et al.*[8] studied 20 patients with severe CI defined as a maximum heart rate <70% of the APMHR, and reported a significant acute improvement in VO_2max (by ≈1.5 mL/kg/min) during DDDR pacing in only a subgroup of 11 patients (55%). In contrast, Sims *et al.*[6] could not show acute improvement in VO_2max with DDDR in 13 patients with severe CI, but only an increase in peak heart rate and a 5% longer 6-min walk distance.[6] In a third study, van Thielen *et al.*[9] studied 14 patients with a milder CI defined as a failure to achieve 85% of the APMHR, to observe a significant increase in cardiac index (from 3.0 to 3.5 L/min/m^2) in the DDDR mode. There was no significant change in peak VO_2 and VE/VCO_2.

In conclusion, there are conflicting results regarding the effect of rate-adaptive pacing on VO_2max, a variable that reflects exercise capacity and prognosis. One of the reasons may be a DDDR pacing based on an accelerometer sensor measuring body movements, with a fast response to physical activity and a low specificity.[18] Closed loop stimulation, which has been recently introduced in CRT devices, senses the changes in right ventricular impedance as a surrogate for the inotropic state of the heart, thus providing a higher specificity for physical and mental exertion and good proportionality to metabolic needs.[12,18,19] We therefore assumed that this more physiological sensor can lead to more favourable clinical results in patients with chronic heart failure. Another reason for the conflicting results of the previous studies with the accelerometer sensor may be inconsistent enrolment of patients with severe CI, who seem predominantly to benefit from rate-adaptive pacing.

Against this background, we used CLS-based rate-adaptive pacing in BIO|CREATE and recruited only patients with severe CI defined as a maximum heart rate <75% of the APMHR, or as inability to attain ≥50% of %HRR at end-exercise. The rationale to focus on severe CI was that (i) accelerometer-based CRT pacing improved VO_2max only in severe CI,[8] (ii) cardiovascular mortality is higher in severe than less severe CI (HR 1.80),[2] and (iii) a decreasing %HRR below 60% is associated with a progressive increase in the risk of mortality and heart failure hospitalization.[7]

While CPX testing is a well-established diagnostic and prognostic tool in heart failure, VO_2max is the most extensively evaluated CPX parameter. However, in recent years, VE/VCO_2, OUES, and end-tidal CO_2 received substantial attention in clinical research. Today, there

is compelling evidence that the VE/VCO_2 slope (the ability to efficiently expire CO_2) is prognostically superior to VO_2max,[13–16] since it is easily obtainable and highly reproducible (independent from patient effort). Hence, BIO|CREATE primarily assessed the effect of CLS on the VE/VCO_2 slope, including clinical prognosis and identification of CLS responders.

In contrast to previous studies that used up to 1-week adaptation period in each pacing mode before CPX test,[6,8–10] we allowed a training effect in both modes to mature over 1 month.[18] The robustness of our data was further increased by a double-blind CPX test design and by minimization of confounding factors such as inter-observer variability and circadian or metabolic variations. Finally, we included patients after at least 6 months of CRT device implantation to avoid a bias on CLS effects due to reverse remodelling.

Discussion of HR_{PEAK} and Closed loop stimulation responders

Appropriate programming of the upper sensor rate is important in heart failure patients. Gierula *et al.*[20] suggested to use a personalized echocardiography-based approach to determine a critical heart rate above which ventricular function deteriorates due to impaired force-frequency relationship. In their CRT patient cohort, the mean critical rate was 109 b.p.m.[20] In our study, the mean CLS-induced HR_{PEAK} was 116 b.p.m. (similar to 109 b.p.m.) despite the simplistic programming of the upper sensor rate to 220-age. Namely, when the contractility reaches a plateau during exercise, the pacing rate driven by the contractility sensor arrives at a steady state with no further increase toward the programmed upper sensor rate. This mechanism may automatically navigate pacing rate to a value close to an individual optimum HR_{PEAK} during exercise.

Due to the complex interplay of various physiological parameters in regulating cardiac output in failing hearts, we rightly assumed that both responders and non-responders to CLS will be observed. Furthermore, our study is first to show a significant difference in the characteristics of responders and non-responders to rate-adaptive CRT pacing. Patients with advanced heart failure did not respond positively to CLS. The possible pathophysiological background is an impaired left ventricular diastolic compliance (a blunted pressure/volume relationship) with increased wall tension in advanced heart failure. In conditions when faster sensor-driven heart rates shorten the diastolic filling time, impaired diastolic compliance can lead to worse haemodynamic and exercise performance due to lower oxygen supply which is based on stroke volume decrease and myocardial oxygen consumption increase, than for the intrinsic (slower) heart rates. However, due to the specific features of CLS systems, characteristics of CLS responders may not be fully translatable to other rate-adaptive sensors. By comparison, for the accelerometer sensor, Tse *et al.*[8] did not find any significant difference in clinical characteristics of patients with and without improvement in VO_2max.

In the near future, our findings can have significant impact on clinical practice. In CRT patients with severe CI, activation of CLS could be based on specific baseline variable cut-offs rather than on CPX testing which is time consuming, costly, and not feasible in all heart failure patients. At present, patient triage by CPX testing is recommended because activation of rate-adaptive pacing may cause harm, as evidenced by worsening gas exchange and ventilatory work of breathing.

In Supplementary material online, *Appendix*, we discuss criteria for severe CI, our attitude to atrial pacing in heart failure, and sensors in CRT devices.

Study limitations

Major study limitations were small sample size and consequently low statistical power. We originally planned to collect full data sets on the VE/VCO2 slope from 30 patients, but due to a lower-than-expected recruitment rate, 17 data sets were obtained. However, this is an exploratory study aimed primarily at identifying characteristics of CRT patients who will get the most benefit from CLS therapy and at obtaining a first estimate of a potential effect size in order to calculate more precisely the sample size for a potential confirmatory study.

Conclusion

The present pilot study suggests that activation of CLS may provide an improvement of the VE slope in CRT patients with CI and less advanced heart failure. In the future, activation of CLS may be based on patient characteristics rather than on CPX evaluation. Further clinical research is needed to verify and refine predictors of positive CLS response and to assess the impact of CLS on long-term clinical outcomes.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: J.P. and K.I. are employees of Biotronik. P.N. is conducting clinical research sponsored by Biotronik, Boston Scientific, Medtronic, Abbot, and Liva Nova and is member of the speaker's bureau for Biotronik and Boston Scientific. D.J.M. received honorarium for consultancy on cardiopulmonary exercise testing. U.L. has received speaker or advisory honorary from Biotronik and Boston Scientific. Other authors declare no competing interests.

Data availability

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

References

1. Brubaker PH, Kitzman DW. Chronotropic incompetence: causes, consequences, and management. *Circulation* 2011;**123**:1010–20.
2. Magri D, Corra U, Di Lenarda A, Cattadori G, Maruotti A, Iorio A *et al.* Cardiovascular mortality and chronotropic incompetence in systolic heart failure: the importance of a reappraisal of current cut-off criteria. *Eur J Heart Fail* 2014;**16**:201–9.
3. Jorde UP, Vittorio TJ, Kasper ME, Arezzi E, Colombo PC, Goldsmith RL *et al.* Chronotropic incompetence, beta-blockers, and functional capacity in advanced congestive heart failure: time to pace? *Eur J Heart Fail* 2008;**10**:96–101.

4. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L *et al.* The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–49.
5. Maass AH, Buck S, Nieuwland W, Brugemann J, van Veldhuisen DJ, van Gelder IC. Importance of heart rate during exercise for response to cardiac resynchronization therapy. *J Cardiovasc Electrophysiol* 2009;**20**:773–80.
6. Sims DB, Mignatti A, Colombo PC, Uriel N, Garcia LI, Ehlert FA *et al.* Rate responsive pacing using cardiac resynchronization therapy in patients with chronotropic incompetence and chronic heart failure. *Europace* 2011;**13**:1459–63.
7. Dobre D, Zannad F, Keteyian SJ, Stevens SR, Rossignol P, Kitzman DW *et al.* Association between resting heart rate, chronotropic index, and long-term outcomes in patients with heart failure receiving beta-blocker therapy: data from the HF-ACTION trial. *Eur Heart J* 2013;**34**:2271–80.
8. Tse HF, Siu CW, Lee KL, Fan K, Chan HW, Tang MO *et al.* The incremental benefit of rate-adaptive pacing on exercise performance during cardiac resynchronization therapy. *J Am Coll Cardiol* 2005;**46**:2292–7.
9. Van Thielen G, Paelinck BP, Beckers P, Vrints CJ, Conraads VM. Rate response and cardiac resynchronisation therapy in chronic heart failure: higher cardiac output does not acutely improve exercise performance: a pilot trial. *Eur J Cardiovasc Prev Rehabil* 2008;**15**:197–202.
10. Jamil HA, Gierula J, Paton MF, Byrom R, Lowry JE, Cubbon RM *et al.* Chronotropic incompetence does not limit exercise capacity in chronic heart failure. *J Am Coll Cardiol* 2016;**67**:1885–96.
11. Martin DO, Day JD, Lai PY, Murphy AL, Nayak HM, Villareal RP *et al.* Atrial support pacing in heart failure: results from the multicenter PEGASUS CRT trial. *J Cardiovasc Electrophysiol* 2012;**23**:1317–25.
12. Coenen M, Malinowski K, Spitzer W, Schuchert A, Schmitz D, Anelli-Monti M *et al.* Closed loop stimulation and accelerometer-based rate adaptation: results of the PROVIDE study. *Europace* 2008;**10**:327–33.
13. Kleber FX, Vietzke G, Wernecke KD, Bauer U, Opitz C, Wensel R *et al.* Impairment of ventilatory efficiency in heart failure: prognostic impact. *Circulation* 2000;**101**:2803–9.
14. Arena R, Guazzi M, Myers J. Ventilatory abnormalities during exercise in heart failure: a mini review. *Curr Respir Med Rev* 2007;**3**:179–87.
15. Sarullo FM, Fazio G, Brusca I, Fasullo S, Paterna S, Licata P *et al.* Cardiopulmonary exercise testing in patients with chronic heart failure: prognostic comparison from peak VO2 and VE/VCO2 slope. *Open Cardiovasc Med J* 2010;**4**:127–34.
16. Arena R, Myers J, Abella J, Pinkstaff S, Brubaker P, Kitzman D *et al.* Defining the optimal prognostic window for cardiopulmonary exercise testing in patients with heart failure. *Circ Heart Fail* 2010;**3**:405–11.
17. Koglek W, Kranig W, Kowalski M, Kronski D, Brandl J, Oberbichler A *et al.* A simple method for AV-delay determination in dual chamber pacemakers [in German]. *Herzschr Elektrophys* 2000;**11**:244–53.
18. Zweerink A, van der Lingen ACJ, Handoko ML, van Rossum AC, Allaart CP. Chronotropic incompetence in chronic heart failure: a state-of-the-art review. *Circ Heart Fail* 2018;**11**:e004969.
19. Santini M, Ricci R, Pignalberi C, Biancalana G, Censi F, Calcagnini G *et al.* Effect of autonomic stressors on rate control in pacemakers using ventricular impedance signal. *Pacing Clin Electrophysiol* 2004;**27**:24–32.
20. Gierula J, Paton MF, Lowry JE, Jamil HA, Byrom R, Drozd M *et al.* Rate-response programming tailored to the force-frequency relationship improves exercise tolerance in chronic heart failure. *JACC Heart Fail* 2018;**6**:105–13.

IMAGES IN ELECTROPHYSIOLOGY

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Transcatheter pacing system replacement for AV synchrony

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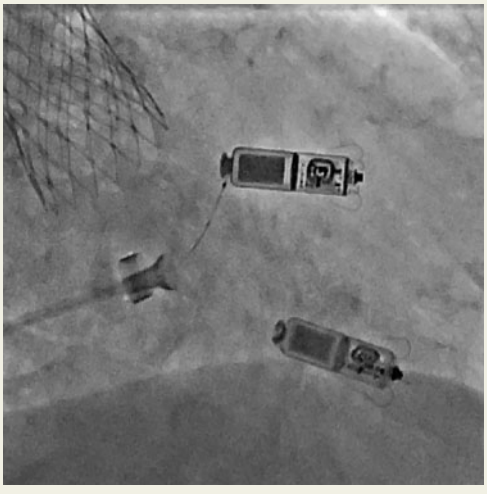
An 80-year-old patient had received a Micra™ VR leadless pacemaker (Medtronic Inc.) 30 months ago for back-up pacing due to loop recorder revealed intermittent atrioventricular (AV) block after transcatheter aortic valve implantation. Two years later, he developed sustained complete AV block with pacemaker syndrome. As he was committed to leadless pacing only and the left ventricular ejection fraction was normal, we decided to implant a Micra™ AV leadless pacemaker and extract the VR model. The Micra™ AV was placed in a remote position to guarantee proper pacing, also in case of unsuccessful retrieval of the VR capsule. Then, the VR capsule could be caught with a 7-mm loop snare and retrieved (*Figure*).



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