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AV-optimized conduction system pacing for treatment of AV dromotropathy: A randomized, cross-over study

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Abstract

Background: Severe first-degree atrioventricular (AV) block may produce symptoms similar to heart failure due to AV dyssynchrony, a syndrome termed AV dromotropathy. According to guidelines, it should be considered for permanent pacemaker implantation, yet evidence supporting this treatment is scarce.

Objectives: This study aimed to determine the impact of AV-optimized conduction system pacing (CSP) in patients with symptomatic severe first-degree AV block and echocardiographic signs of AV dyssynchrony.

Methods: Patients with symptomatic first-degree AV block (PR > 250 ms), preserved left ventricular ejection fraction, narrow QRS, and AV dyssynchrony were included in the study. In a single-blind cross-over design, patients were randomized to AV sequential CSP or backup VVI pacing with a base rate of 40 bpm. We compared exercise capacity, echocardiographic parameters, and symptom occurrence at the end of 3 months of each period.

Results: Fourteen patients completed the study. During the AV-optimized CSP compared to the backup pacing period, patients achieved a higher workload on exercise test (147.2 ± 50.9 vs. 140.7 ± 55.8 W; $p = .032$), with a trend towards higher peak VO2 (23.3 ± 7.1 vs. 22.8 ± 7.1 mL/min/kg; $p = .224$), and higher left ventricular stroke volume (LVSV 74.5 ± 13.8 vs. 66.4 ± 12.5 mL; $p < .001$). Symptomatic improvement was recorded, with fewer patients reporting general tiredness and 71% of patients preferring the AV-optimized CSP ($p = .008$).

Conclusions: AV-optimized CSP could improve symptoms, exercise capacity and LVSV in patients with severe first-degree AV block.

KEYWORDS

AV coupling, AV dromotropathy, AV dyssynchrony, conduction system pacing, first-degree AV block

Abbreviations: AV, atrioventricular; CPET, cardiopulmonary exercise test; CRT, cardiac resynchronization therapy; CSP, conduction system pacing; ECG, electrocardiogram; HBP, His bundle pacing; HF, heart failure; LA, left atrial; LBBAP, left bundle branch area pacing; LV, left ventricular; LVEF, left ventricular ejection fraction; MV, mitral valve; PM, pacemaker; PW, pulsed wave; RV, right ventricular; VTI, velocity–time integral.

Clinical Trial Registration: NCT04544345.

1 | INTRODUCTION

First-degree atrioventricular (AV) block with markedly prolonged PR interval can produce symptoms similar to heart failure (HF).[1] While these symptoms are subtle in some patients, they may also be very pronounced and coupled with diminished ventricular filling and reduced cardiac output, a state termed AV dromotropathy[2] (Figure 1).

In symptomatic patients with marked first-degree AV block (PR interval > 300 ms) with preserved EF, the guidelines recommend treatment with implantation of a permanent pacemaker (PM) without any preference for optimal pacing site.[3,4] However, this recommendation is based on a case report and expert opinion.[1,5] While several small studies with conventional right ventricular (RV) pacing showed only a modest effect,[6,7] subanalyses of clinical trials investigating cardiac resynchronization therapy (CRT), albeit in HF patients, showed a positive effect of restored AV-coupling on exercise capacity, symptoms and mortality.[8,9] RV pacing induces ventricular dyssynchrony, which might hamper the hemodynamic benefit of AV resynchronization. While biventricular pacing is a better pacing option, it requires an additional left ventricular (LV) lead and still induces some degree of ventricular dyssynchrony in patients with narrow QRS.[10,11] Therefore, conduction system pacing (CSP) with either His bundle pacing (HBP) or left bundle branch area pacing (LBBAP) could represent a more physiological alternative.[12–14]

Data on the effect of restoring AV coupling with CSP in patients with symptomatic first-degree AV block and preserved left ventricular ejection fraction (LVEF) is lacking. The aim of this study was to assess the impact of AV-optimized CSP on exercise capacity, symptoms and haemodynamics in patients with symptomatic first-degree AV block and echocardiographic signs of AV dyssynchrony.

2 | METHODS

2.1 | Study design and participants

This was a single-center, investigator-initiated, randomized, single-blind cross-over study. Patients eligible for inclusion had symptomatic first-degree AV block (PR > 250 ms) or second-degree AV block Mobitz type 1, narrow QRS < 130 ms, echocardiographic signs of AV dyssynchrony (diastolic filling time/RR interval ratio < 0.4 or fusion of E and A waves on transmitral pulsed wave [PW] Doppler or diastolic mitral regurgitation) and preserved LVEF (>50%). Exclusion criteria were previous or current atrial fibrillation, chronotropic incompetence, defined as failure to reach 80% of the maximum

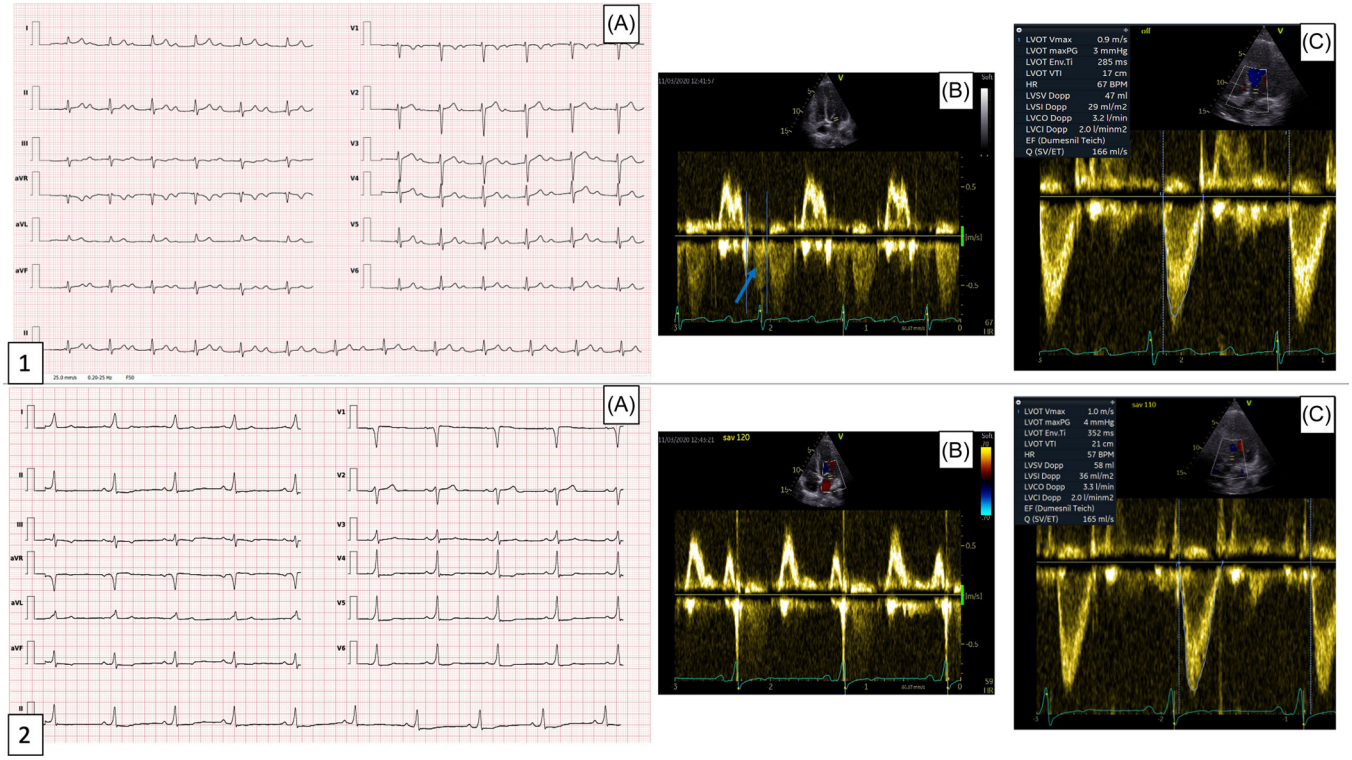


FIGURE 1 AV dyssynchrony and AV-optimized CSP. (A) ECG of a patient with extreme first-degree AV block (PR interval 380 ms) before (A) and after CSP (2A). (B) Transmitral PW Doppler with the fusion of early (E) and late (A) diastolic filling waves, the time gap between the end of A wave and the start of the QRS complex and diastolic mitral regurgitation (blue arrow). Separation of E and A waves and disappearance of diastolic mitral regurgitation after CSP (2B). (C) LVOT VTI. Note the increase of LVOT VTI with a decrease in heart rate with CSP. AV, atrioventricular; CSP, conduction system pacing; ECG, electrocardiogram; LVOT VTI, left ventricular outflow tract velocity–time integral; PW, pulsed wave.

age-predicted heart rate, shortening of PR interval during exercise to <200 ms, advanced AV conduction block, active bacterial infection, anemia, and inability to undergo exercise testing. All patients signed informed consent, and the study was approved by the national ethics committee and registered at clinicaltrials.org (NCT04544345).

Patients were randomized to an echocardiographically AV-optimized CSP or backup pacing period and crossed over to the other study period after 3 months (Figure 2).

2.2 | Baseline evaluation

At baseline, all patients underwent a detailed history and clinical examination, excluding potentially reversible causes of AV block (ongoing ischemia, electrolyte disturbances, infection with Borrelia burgdorferi, and transient excessive vagal tonus). Laboratory tests included complete blood count, potassium, creatinine, and natriuretic pro-B type natriuretic peptide (NT-proBNP). A digital resting 12-lead electrocardiogram (ECG) was recorded using a Mesi mTablet ECG (Mesi Ltd.). All the measurements were made with digital callipers at 50 mm/s sweep speed.

2.3 | PM implantation and programming

A dual-chamber PM with CSP was implanted in all patients. The preferred pacing method was HBP using the SelectSecure 3830 lead and C315HIS catheter (Medtronic Inc.), as it provides the most physiological ventricular activation. If HBP could not be achieved after three attempts, the ventricular lead was placed transseptally on the left bundle branch.[15,16] A 12-lead ECG and CSP lead electrogram were displayed using an EP-TRACER 2 Portable (Cardio Tek B.V.). Conduction system capture was approached as previously described.[17,18] The atrial lead was positioned in the right atrial appendage. Procedure and fluoroscopy times were noted.

In the AV-optimized CSP period, PMs were programmed to DDD mode with a base rate of 40 bpm to avoid unnecessary atrial pacing, while the upper tracking rate was set to 10 bpm above the maximum heart rate reached on the exercise test. The AV delay was set to the shortest delay without truncating the A wave on the transmitral PW Doppler assessed at rest, with dynamic shortening during exercise. In the backup pacing period, the PMs were programmed to VVI mode with a base rate of 40 bpm, allowing for the patient's intrinsic rhythm. Device telemetry with lead measurements and pacing percentages was performed after implantation and at the end of each study period.

Medical therapy was left unchanged during the entire study period. Patients were blinded to the device programming throughout the study.

2.4 | Exercise testing

A symptom-limited cardiopulmonary exercise stress test (CPET) on a cycle ergometer Cardiovit CS 200 Excellence ErgoSpiro (Schiller) using an adjusted ramp protocol was performed at baseline and after the end of each study period. Importantly, the technician recording the exercise test was unaware of the study protocol and the programming of the device. The exercise protocol was individually adjusted to the estimated exercise capacity calculated by the Wasserman equation assessed before the PM implant. Exercise capacity was measured as a relative peak oxygen consumption (peak VO_2) in mL/kg/min. In addition, workload, heart rate, respiratory exchange ratio (RER), oxygen-uptake to work-rate relationship (VO_2/WR), and the relationship of minute ventilation to CO_2 production (VE/VCO_2) were noted.

Due to the Covid-19 pandemic, performing CPET was limited in our institution between September 2020 and March 2021. Therefore, it was omitted at baseline and replaced by an ECG exercise test to evaluate adherence to inclusion criteria. Follow-up CPET dates were postponed appropriately.

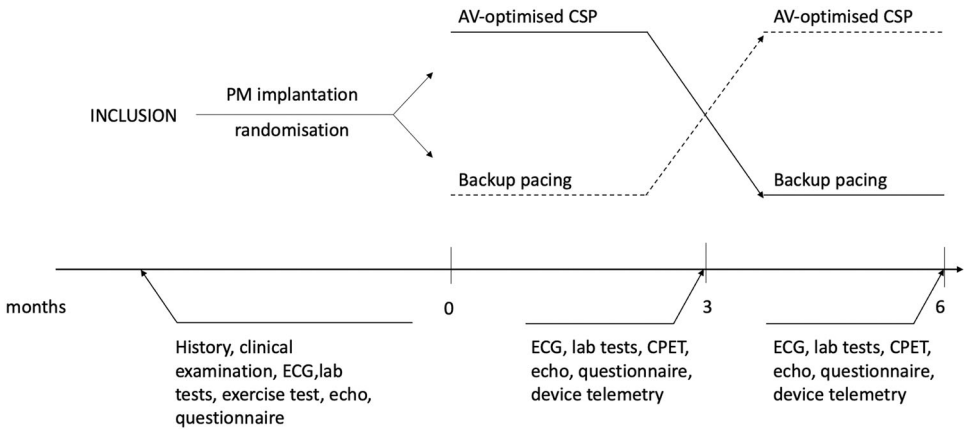


FIGURE 2 Study design. AV, atrioventricular; CPET, cardiopulmonary exercise test; CSP, conduction system pacing; ECG, electrocardiogram; PM, pacemaker.

2.5 | Echocardiographic evaluation

A standard transthoracic echocardiogram was performed on the Vivid S60 (GE) at baseline and at the end of each study period, always at rest. Left ventricular volumes were measured using a biplane Simpson's method. Left ventricular stroke volume (LVSV) was calculated from left ventricular outflow tract diameter and PW Doppler velocity–time integral (VTI), obtained from apical five- and three-chamber views and averaged over at least five cardiac cycles. Mitral valve (MV) inflow velocities were assessed with PW Doppler, with the sample volume placed at the tips of the MV leaflets. MV inflow timings and VTI were measured using PW Doppler with the sample volume positioned at the level of the MV annulus. Left atrial (LA) volume was calculated using the method of disks from apical four- and two-chamber views and indexed to body surface area. The measurements were performed independently by two echocardiographers.

2.6 | Symptom evaluation

Symptoms were assessed at baseline and after each study period using a EuroQol 5 dimension visual analog scale (EQ-5D VAS). In addition, patients were asked about the presence or absence of dyspnea, tiredness, palpitations, chest fullness, and dizziness. At the end of the follow-up, they were asked to choose the preferred study period.

2.7 | Outcomes

The primary outcome measures were exercise capacity, measured as peak VO_2, LVSV, and the presence or absence of individual symptoms, EQ-5D VAS score, and the preferred pacing period. The secondary outcomes included LA volume, MV VTI, diastolic filling time, early diastolic filling velocity, and the presence of diastolic mitral regurgitation. Left ventricular volumes, ejection fraction, paced QRS width, NT-proBNP values, and pacing characteristics were evaluated as safety outcomes.

2.8 | Sample size calculation

A subanalysis of the RethinQ trial showed that in patients with narrow QRS and first-degree AV block (PR interval > 200 ms), AV-optimized biventricular pacing improved peak oxygen consumption by 10%. As there was no improvement in patients with normal PR intervals, this could be ascribed to AV interval correction.[8] The within-subject coefficient of variation for reproducibility of peak VO_2 measurement on a cycle ergometer is approximately 7%.[19] To detect a treatment difference of 10%, assuming a 7% within-subject coefficient of variation, we would need to include 13 patients in a cross-over design to achieve a 90% power at a two-sided 0.05 significance level. To allow for a potential 10% dropout, we opted to include 16 patients in the study.

2.9 | Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences version 29.0 (IBM SPSS). The Kolmogorov–Smirnov test was used for testing the normality of distribution. Continuous data are presented as mean ± standard deviation or median and quartiles as appropriate. Categorical data are presented as frequencies and percentages. To evaluate differences between pacing modes Student paired samples and Wilcoxon signed-rank tests were used as appropriate. Categorical variables were compared using McNemar's test, and one-sample χ^2 test was used to assess the preferred pacing mode. A two-sided $p < .05$ was considered statistically significant.

3 | RESULTS

Between February 2020 and September 2022, 17 patients were enrolled in the study. The PM implantation was successful in all patients, and they all underwent randomization. Two patients developed complete AV block during the backup pacing period and were excluded from the study. One patient suffered an acute ST-elevation myocardial infarction and was excluded due to the inability to undergo a maximum stress test. Fourteen patients underwent the cross-over, completed the follow-up, and were included in the final analysis (Figure 3).

3.1 | Patient characteristics

Nine (64%) patients were male, the median age was 68.8 (interquartile range [IQR]: 26.2) years. Nine (64%) patients had arterial hypertension, five (36%) had diabetes mellitus, and three (21%) had coronary artery disease. Nine patients (64%) received renin–angiotensin–aldosterone system inhibitors, and none were on beta blockers. All patients had preserved LVEF (59 ± 6%). PR interval ranged from 310 to 520 ms with a mean of 395 ± 54 ms. Four patients had second-degree Mobitz 1 type of AV block. Diastolic mitral regurgitation was present at baseline in 11 (79%) patients.

Among symptoms, patients were most commonly reporting general tiredness (nine; 64%), dyspnea (eight; 57%), palpitations (five; 36%), chest fullness (three; 21%), and dizziness (three; 21%). The general quality of life measured by a visual analog scale was 74 ± 14 (Table 1).

3.2 | Pacing data

HBP was successful in 11 (79%) patients. In the remaining three patients, LBBAP was achieved. The mean baseline QRS was

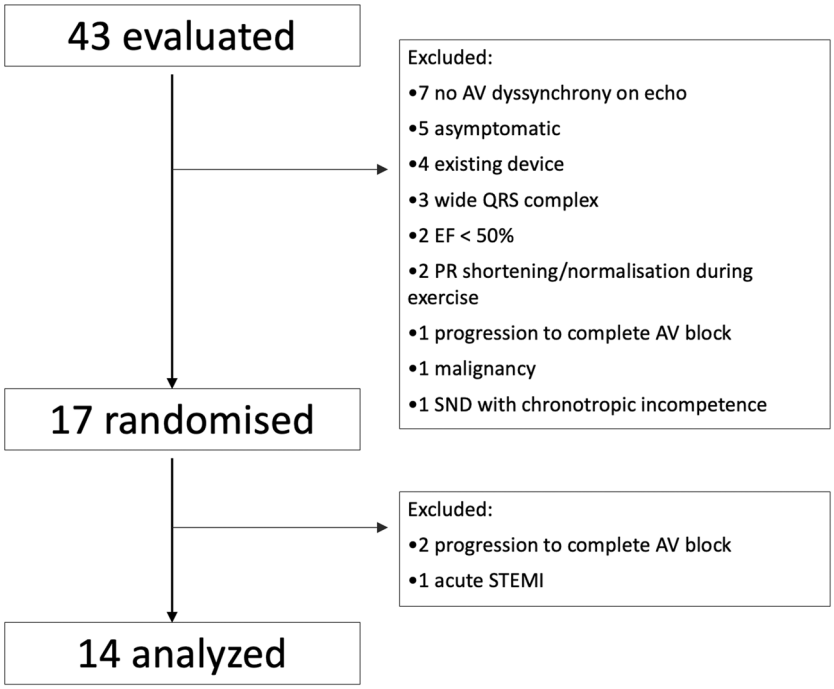


FIGURE 3 Consort flow diagram. AV, atrioventricular; EF, ejection fraction; SND, sinus node dysfunction; STEMI, ST-segment elevation myocardial infarction.

103 ± 21 ms and did not differ from the QRS during CSP (116 ± 22 ms, $p = .1$). Procedure and fluoroscopy times were 83 ± 24 and 10 ± 6 min, respectively. The pacing thresholds at 1.0 ms for HBP and 0.5 ms for LBBAP were stable between the implant and the final follow-up (median 0.80 V; IQR: 0.85 and 0.90 V; IQR: 0.65; $p = .3$). Ventricular sensing values (His or LBBAP lead) were stable during the follow-up (3.6 mV; IQR: 6.7 mV at implant and 4.6 mV; IQR: 7.5 at the end of follow-up; $p = .6$). There were no acute procedure-related complications. Atrial lead dislodgement occurred in one patient 3 months after implantation during the backup pacing period. The patient underwent lead repositioning and continued to participate in the study.

During the AV-optimized CSP period, atrial and ventricular pacing percentages were 3 ± 1% and 98 ± 2%, respectively. During the backup pacing period, the percentage of ventricular pacing was 12 ± 4% (Table 2).

3.3 | Exercise capacity

During the CPET, patients had 1:1 AV conduction with a persistently prolonged PR interval during the backup pacing period. However, no advanced AV conduction disorders were noted. During the AV-optimized CSP period, appropriate tracking of sinus rates was observed in all patients up to their maximum heart rates. The peak VO_2 during the AV-optimized CSP period was 23.3 ± 7.1 mL/kg/min, and during the backup pacing period, 22.8 ± 7.1 mL/min/kg ($p = .2$). During the AV-optimized CSP period, patients achieved a higher workload (147.2 ± 50.9 W) than during the backup pacing (140.7 ± 55.8 W; $p = .03$). RER in both periods was high and constant, demonstrating maximal patient effort. There were no differences in other CPET parameters—oxygen pulse, dVO_2/dWR, and VE/VCO_2. (Table 3).

3.4 | Echocardiography measures

LVSV during the AV-optimized CSP period was greater than during backup pacing (74.5 ± 13.8 vs. 66.4 ± 12.5 mL; mean difference 8.1 mL (6.0–10.3); $p < .001$). Left ventricular filling parameters significantly improved; we observed longer diastolic filling times, larger mitral VTI and lower early diastolic filling velocities. AV-optimized CSP eliminated diastolic mitral regurgitation in all patients. LA volumes were significantly lower during the AV-optimized CSP (LAVi 27.1 ± 5.5 vs. 34.1 ± 6.4 mL/m^2; mean difference −7.0 mL/m^2; 95% CI: −10.0 to −4.0; $p < .001$) (Table 3).

3.5 | Symptoms

Symptomatic parameters are presented in Figure 4. Significantly fewer patients experienced general tiredness and palpitations during the AV-optimized CSP than during the backup pacing period. Patients were significantly more often without any symptoms during the active pacing period. The generic quality of life score (EQ-5D VAS) showed a trend toward improvement but did not reach statistical significance (mean difference 3.2, 95% CI: −2.7 to 9.2, $p = .2$). Out of 14 patients in the study, only one (7%) preferred the backup pacing period, 10 (71%) reported they felt better during the AV-optimized CSP period, while 3 (21%) did not have any preference ($p = .008$).

TABLE 1 Baseline characteristics ($n = 14$).

Sex (male)	9 (64%)
Age	68.8 (26.2)
Weight (kg)	72.5 (22.5)
Hemoglobin (g/L)	142 ± 13
NT-proBNP (ng/L)	170 ± 145
Arterial hypertension	9 (64%)
Diabetes mellitus	5 (36%)
Coronary artery disease	3 (21%)
RAAS inhibitors	9 (64%)
Beta-blockers	0 (0%)
EQ-5D visual analog scale	74 ± 14
PR interval (ms)	395 ± 54
QRS duration (ms)	103 ± 21
LVEDVi (mL/m^2)	61 ± 11
LVEF (%)	59 ± 6
LAVi (mL/m^2)	36 ± 9
Diastolic filling time (ms)	284 (84)
Diastolic filling time/RR interval	0.32 ± 0.08
Diastolic mitral regurgitation	11 (79%)
AVB2 Mobitz 1	4 (29%)

Note: Continuous variables are presented as mean ± SD or median and interquartile range in brackets, according to the normality of distribution. Categorical variables are presented as count and percentage.

Abbreviations: EQ-5D, EuroQol 5 dimension; LAVi, left atrial volume index; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; NT-proBNP, natriuretic pro-B type natriuretic peptide; RAAS, renin–angiotensin–aldosterone system.

TABLE 2 Pacing characteristics.

Procedure time (min)	83 ± 24	His bundle pacing	11 (79%)
Fluoroscopy time (min)	10 ± 6	Left bundle branch area pacing	3 (21%)
Parameter	*At implant*	*End of FU*	*P*
Pacing threshold (V)	0.80 (0.85)	0.90 (0.65)	.3
Sensing (mV)	3.6 (6.7)	4.6 (7.5)	.6
	Baseline	*Paced*	*P*
QRS duration (ms)	103 ± 21	116 ± 22	.1
	AV-optimized CSP period	*Backup pacing period*	
Atrial pacing (%)	3 ± 1	n/a	
Ventricular pacing (%)	98 ± 2	12 ± 4	

Note: Continuous variables are presented as mean ± SD or median and interquartile range. Categorical variables are presented as count and percentage.

Abbreviations: AV, atrioventricular; CSP, conduction system pacing; FU, follow-up, n/a, not applicable.

3.6 | Safety outcomes

There was no significant change in left ventricular end-diastolic or end-systolic volumes. The ejection fraction showed a trend towards improvement in the active pacing period (mean difference 3.3, 95% CI: 0.3–6.5, $p = .05$).

Hemoglobin and creatinine levels did not change significantly during the follow-up. NT-proBNP levels were lower during the AV-optimized CSP period (mean difference −39.5 ng/L, 95% CI: −79.1 to −0.01; $p = .05$).

4 | DISCUSSION

The study evaluated the effect of CSP in patients with preserved LVEF with symptomatic first-degree AV block and echocardiographic signs of AV dyssynchrony. There were three major findings. First, patients could reach a higher workload on CPET; however, peak VO_2 did not reach statistically significant improvement. Second, AV-optimized CSP could improve diastolic filling parameters, stroke volume, and reduce LA volume. Third, significant symptom improvement and a clear preference for AV-optimized CSP to intrinsic rhythm were noted (Central Illustration 1).

4.1 | Exercise capacity

While the peak oxygen consumption was higher during the AV-optimized CSP period, the difference did not reach statistical significance. However, the maximal workload achieved during the AV-optimized CSP period was higher than during backup pacing. While the LVSV increased at rest by 10%, it is known that the contribution of stroke volume to cardiac output diminishes with increasing heart rate.[20] Additionally, as our patients did not have other exercise limitations than AV block, their baseline oxygen consumption was higher than in the RethinQ trial, which probably reflected in the smaller relative increase of oxygen consumption than expected.[8] Since during peak exercise, heart rate contributes more to the cardiac output than the stroke volume and symptoms of first-degree AV block are predominantly expressed with mild exercise, peak VO_2 might not be the optimal outcome to be evaluated in future trials of these patients.[5]

Recently, the HOPE-HF trial that included patients with prolonged PR interval, albeit with reduced LVEF, also failed to demonstrate an increase in peak VO_2 with AV-optimized HBP.[21] The PR prolongation in the HOPE-HF was significantly less pronounced than in our study (249 ± 59.2 vs. 395 ± 54 ms), and there is no data on

TABLE 3 Outcomes.

	AV-optimized CSP	Backup pacing	Δ	*p* Value
Exercise capacity				
Peak VO_2 (mL/kg/min)	23.3 ± 7.1	22.8 ± 7.1	0.5 (−0.3 to 1.4)	.2
Max workload (W)	147.2 ± 50.9	140.7 ± 55.8	6.5 (0.7 to 12.3)	.03
Max HR (beat/min)	140.1 ± 24.1	132.7 ± 23.4	7.4 (2.2 to 12.5)	.009
RER	1.10 ± 0.12	1.09 ± 0.09	0.01 (−0.05 to 0.07)	.78
VE/VCO_2	25.2 ± 4.2	27.0 ± 4.9	−1.8 (−4.5 to 0.9)	.18
VO_2/WR	10.3 ± 1.0	10.4 ± 1.5	−0.07 (−0.9 to 0.8)	.87
Echocardiographic parameters				
LVOT SV (mL)	74.5 ± 13.8	66.4 ± 12.5	8.1 (6.0 to 10.3)	<.001
LVSV (mL)	72.9 ± 15.0	67.2 ± 14.0	5.6 (3.1 to 8.1)	<.001
LV EDVi (mL/m^2)	59.4 ± 10.9	59.1 ± 10.9	0.4 (−3.0 to 3.7)	.8
LV ESVi (mL/m^2)	21.1 ± 7.5	23.1 ± 7.7	−1.9 (−4.9 to 1.1)	.2
LVEF (%)	65.2 ± 6.9	61.9 ± 7.0	3.3 (0.3 to 6.5)	.05
E (cm/s)	0.62 ± 0.14	0.81 ± 0.22	−0.19 (−0.32 to −0.05)	.009
Diastolic filling time (ms)	417 ± 46	291 ± 96	125 (78 to 172)	<.001
MV VTI (cm)	15.4 ± 1.7	13.4 ± 2.9	1.9 (0.6 to 3.3)	.009
LAVi (mL/m^2)	27.1 ± 5.5	34.1 ± 6.4	−7.0 (−10.0 to −4.0)	<.001
Symptom				
EQ-5D visual analog scale	83.2 ± 14.9	80.0 ± 14.3	3.2 (−2.7 to 9.2)	.2
Laboratory measures				
Hemoglobin (g/L)	146.5 ± 10.6	146.7 ± 11.1	−0.2 (−3.4 to 3.0)	.9
Creatinine (μmol/L)	83.0 ± 20.4	84.2 ± 19.9	−1.2 (−6.5 to 4.2)	.6
NT-proBNP (ng/L)	188.1 ± 128.7	227.6 ± 144.2	−39.5 (−79.1 to −0.01)	.05

Note: Means and standard deviations for different endpoints. The Δ column shows mean differences with 95% confidence interval in brackets.

Abbreviations: AV, atrioventricular; CSP, conduction system pacing; EQ-5D, EuroQol 5 dimension; HR, heart rate; LAVi, left atrial volume indexed by body surface area; LV EDVi, left ventricular end-diastolic volume indexed by body surface area; LVEF, left ventricular ejection fraction; LV ESVi, left ventricular end-systolic volume indexed by body surface area; LVOT SV, left ventricular stroke volume measured with PW Doppler in left ventricular outflow tract; LVSV, left ventricular stroke volume measured by the Simpson's method; MV VTI, mitral annulus velocity time integral; peak VO_2, peak oxygen uptake; RER, respiratory exchange ratio; VE/VCO_2, ventilation and CO_2 production ratio; VO_2/WR, VO_2 increase for a given work rate.

mechanical AV dyssynchrony, so the extent of haemodynamic benefit obtained by pacing is difficult to interpret.

4.2 | Haemodynamic improvement

Our results showed both the improvement of LV stroke volume and LV filling parameters. With AV resynchronization, active diastolic filling times were longer, and backward flow due to diastolic mitral regurgitation was abolished. This is in line with previous studies which showed acute haemodynamic benefits of restored AV coupling.[10,14] However, this is the first study to show a sustained haemodynamic benefit of AV-optimized CSP even after 3 months of pacing.

In the early studies, the acute and chronic negative effects of conventional RV pacing might have counteracted the hemodynamic benefit of AV coupling.[6,7,22] The optimal selection of ventricular pacing site is of utmost importance as these patients are expected to be continuously paced. Indeed, during the AV-optimized CSP period, the percentage of ventricular pacing in our study was high (98 ± 2%).

4.3 | Reduction of LA size

In addition to improving hemodynamic parameters, our study also showed a substantial reduction in LA volumes. The reduction of atrial volume overload could explain this. With first-degree AV block and

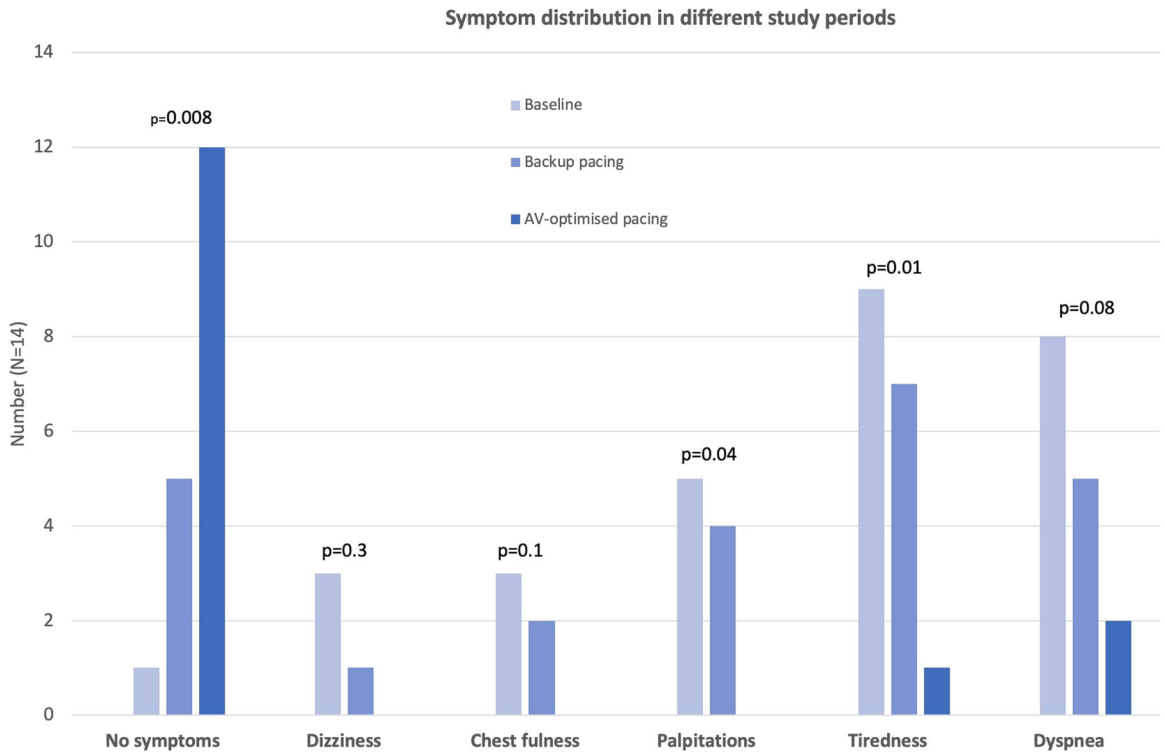


FIGURE 4 Symptom distribution in study periods *p* values were calculated with McNemar's test for the difference between the backup pacing and atrioventricular (AV)-optimized pacing period.

AV dyssynchrony, there is a fusion of conduit and booster pump phases of atrial function and prolongation of the reservoir phase.[23,24] Atrial volume overload may increase further with diastolic mitral regurgitation. AV-optimized CSP restores normal atrial filling and emptying and abolishes diastolic mitral regurgitation. A reduction of NT-proBNP accompanied the reduction of LA volume.

4.4 | Symptoms and safety

When comparing both pacing periods, for which they were blinded, patients preferred the AV-optimized CSP. This was associated with a significant reduction in the incidence of individual symptoms such as palpitations and general tiredness. The symptom improvement did not reach statistical significance when scored by the visual analog scale. However, it is important to note that the study was not powered to detect self-reported symptom improvement.

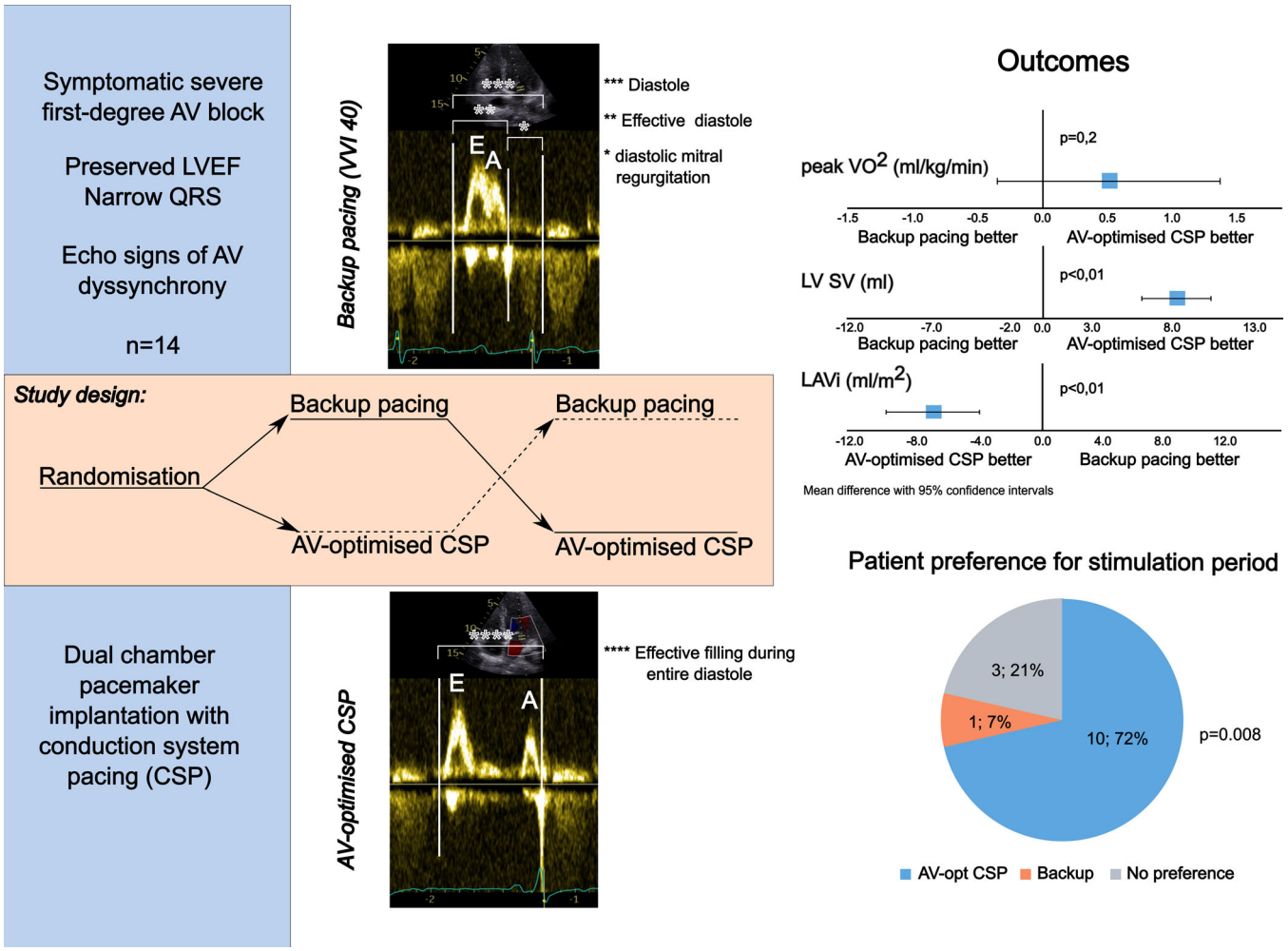
Safety needs to be ensured in invasive procedures with symptom improvement as the main therapy goal. The detrimental effects of conventional RV pacing are well recognized, and there is increasing evidence that CSP reduces the long-term risk of pacing-induced cardiomyopathy.[25,26] Indeed, in our study, paced and intrinsic QRS durations were similar, and we found no significant difference in left ventricular diastolic and systolic volumes, with a trend towards higher ejection fraction after 3 months of AV-optimized CSP. Pacing and sensing parameters were within the desired ranges and stable during the follow-up, not compromising device battery life. In addition, there were no acute procedure-related complications.

4.5 | The importance of mechanical AV dyssynchrony

In contrast to previous trials, we enrolled only patients with echocardiographic signs of mechanical AV dyssynchrony. As PR interval encompasses depolarization of right and left atria, AV node, and His bundle, its prolongation does not necessarily translate to mechanical AV dyssynchrony.[27,28] With interatrial conduction delay, LA systole might be delayed and synchronized with the left ventricle despite the long PR interval.[29] In fact, during enrollment, we often observed patients with a complete absence of mechanical dyssynchrony despite extreme prolongation of the PR interval (Figure 5). We believe that in patients without mechanical dyssynchrony, there is no functional substrate to be ameliorated by pacing therapy. Therefore, echocardiographic AV dyssynchrony should be assessed in symptomatic patients with prolonged PR intervals when treatment with cardiac pacing is considered.

4.6 | Clinical implications

To the best of our knowledge, only 17 cases of symptomatic marked first-degree AV block with extreme PR prolongation have



CENTRAL ILLUSTRATION 1 AV-optimized CSP in patients with symptomatic first-degree AV block. A randomized cross-over **study** in patients with symptomatic severe first-degree AV block and mechanical AV dyssynchrony showed improvement of symptoms, LVSV, reduction of left atrial volume, and a trend toward higher peak oxygen uptake on exercise test during the AV-optimized CSP period in comparison to backup pacing (intrinsic rhythm). AV, atrioventricular; CSP, conduction system pacing; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVSV, left ventricular stroke volume.

been described in the literature.[30] However, PR interval prolongation (>200 ms) occurs in 1%–2% of the population and reaches up to 50% in HF patients eligible for CRT.[2] It is conceivable that the prevalence of AV dromotropathy is underestimated, as first-degree AV block has traditionally been considered a benign disease. Large population-based studies have linked first-degree AV block with a significant increase in atrial fibrillation, HF, and mortality.[31,32] Beneficial effects of AV-optimized CSP on the improvement of haemodynamic parameters (diastolic filling parameters, stroke volume), structural remodeling (reduction of LA size), and reduction of natriuretic peptide levels in our study might indicate a potential causal relationship between the first-degree AV block and unfavorable outcomes. Further studies are needed to investigate whether pacing therapy can improve survival by amending AV uncoupling.

4.7 | Limitations

The study has some limitations. The main limitation of our study was the small number of included patients. Since severe first-degree AV block is relatively rare, we used a cross-over design to reduce the number of needed participants who were enrolled according to the sample size calculations. In addition, the inclusion of patients was prolonged due to the Covid-19 pandemic. Nevertheless, this is the largest study so far in a population of patients with such extreme prolongation of the PR interval (mean value 395 ± 54 ms). It was a single-center study, lacking external validity, which would be required to support the findings. Although single-blinding may have introduced potential experimenter bias, we took steps to mitigate this by ensuring the CPET technician was unaware of the study protocol. While the echocardiographer was

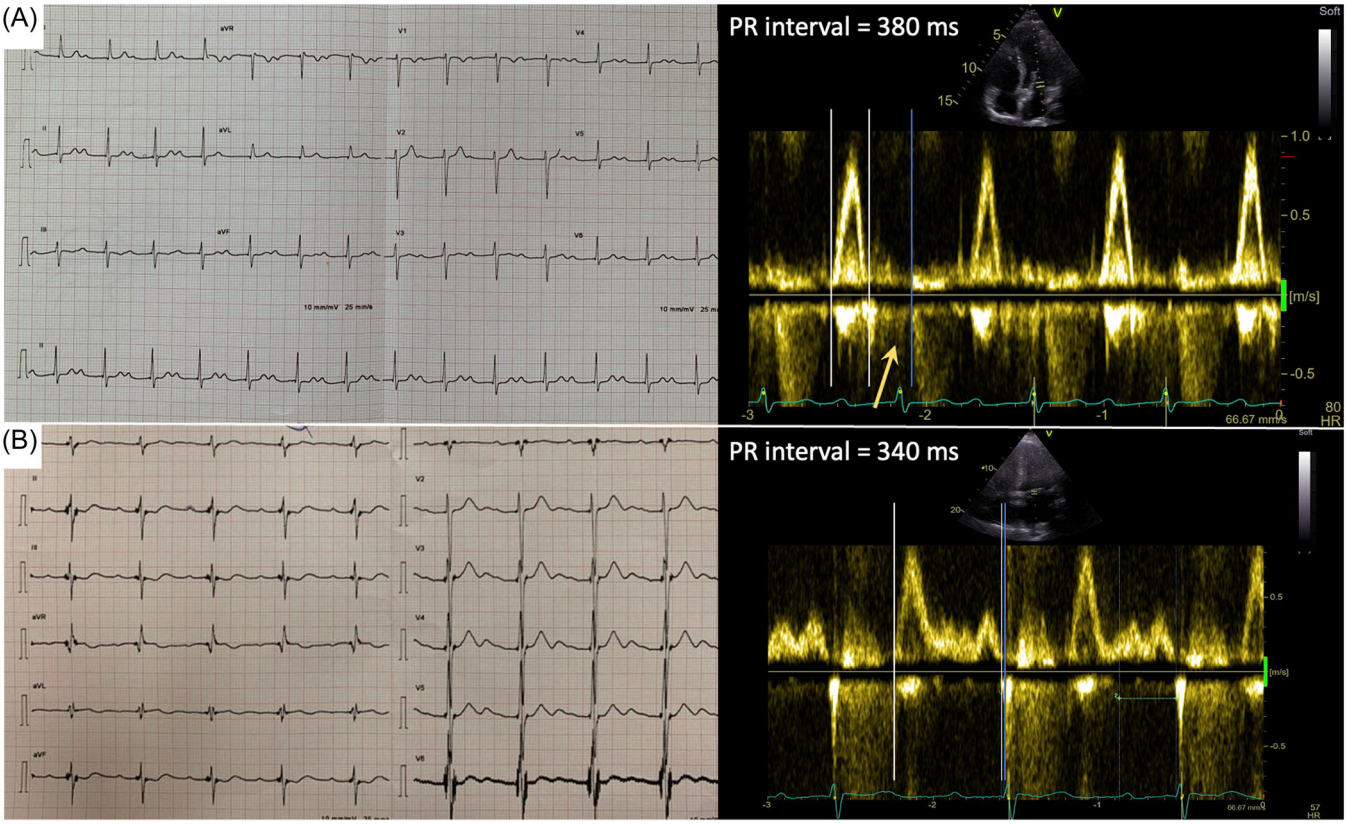


FIGURE 5 PR interval/AV dyssynchrony The difference in echocardiographically assessed AV dyssynchrony between two patients with prolonged PR interval. In patient (A), the extreme first-degree AV block causes the fusion of E and A waves on transmitral PW Doppler, which leads to a shortened diastolic filling time (two white lines). In a period between the end of atrial systole and the beginning of ventricular systole (onset marked by blue line), diastolic mitral regurgitation occurs (yellow arrow). In patient (B), despite a similarly prolonged PR interval, the E and A waves are completely separate, and ventricular systole immediately follows the end of atrial systole. AV, atrioventricular.

not blinded to the study period, all measurements were verified by a second echocardiographer to maintain accuracy. Larger studies in a broader population of patients, with longer follow-ups, are warranted to confirm our findings.

5 | CONCLUSION

AV-optimized CSP could improve symptoms in patients with severe first-degree AV block and echocardiographic presence of AV dyssynchrony. Although there was no increase in peak VO_2, improvement of haemodynamic parameters after AV-optimized CSP was associated with a higher workload on exercise test.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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