[Original article]

Clinical benefit of atrio-ventricular delay optimization in patients with a dual-chamber pacemaker: a pilot study. The CBRAVO trial (NCT01998256)

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Objective Outcome data on exercise capacity following atrio-ventricular (AV) optimization of dual-chamber pacing are sparse. Pacemaker settings are often left at manufacturers' nominal values upon implantation. We studied the short-term effect of AV optimization on exercise capacity in patients with a dual-chamber pacemaker.

Methods and results Twenty-eight patients (mean age 73 ± 14 y) with a dual-chamber pacemaker, were randomized towards either nominal AV settings (group 1) or echo-guided AV optimization using the iterative mitral inflow VTI (velocity time integral) method (group 2) at baseline. At 4 weeks, patients were crossed-over to AV optimization in group 1 and returned to nominal AV settings in group 2 for another period of 4 weeks.

Oxygen uptake efficiency slope improved significantly after AV optimization (by 126.7 mL/logL ± 190.7 mL/logL; $P = 0.003$).

Conclusions AV optimization in dual-chamber pacing significantly improved functional capacity after 4 weeks. These data provide the background for further validation studies.

Keywords *AV optimization – interatrial conduction delay – interatrial mechanical delay – dual-chamber pacemaker.*

INTRODUCTION

An interatrial conduction delay (IACD) is present in up to 32% of patients with a bradycardia-tachycardia syndrome and 10% of all dual-chamber (DDD) pacing candidates[1]. A conduction delay between right and left atrium may cause left AV asynchrony[2]. The delay in contraction of the left atrium can compromise left ventricular filling, leading to an early increase in atrial filling pressures and a limitation in functional exercise capacity[2].

Oxygen uptake efficiency slope (OUES) is a validated marker of exercise capacity in healthy subjects and in patients with heart failure[3].

Resolution of left AV asynchrony in DDD pacing can be obtained by AV delay optimization and has been shown to improve acute haemodynamics in patients with an important IACD[4,5]. Several validated methods for AV optimization exist[6]. However, data on the effects of this intervention on short- and long-term clinical end points as exercise capacity, morbidity and mortality, are sparse.

The aim of this pilot study was to investigate the short-term effect of AV optimization on functional

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Received 11 October 2015; revision accepted for publication 18 November 2015.

capacity as measured by OUES in patients with a dual-chamber pacemaker.

METHODS

Study overview

This investigator-initiated study was conducted in the department of cardiology of Jessa Hospital (Hasselt, Belgium) between December 2013 and February 2014. The study was conducted in accordance with the Helsinki guidelines and was approved by the local ethics committee.

All patients provided written informed consent before enrolment in the screening protocol and the prospective interventional study protocol. Since all end points were unequivocal, no specific end point adjudication committee was used. Data acquisition and interpretation (i.e. ergospirometry, questionnaire), except for echocardiography, were performed in a double-blinded fashion.

Patients

Forty-four patients with a pacemaker programmed in DDD mode were recruited from routine clinical practice. All patients had a pacemaker implanted for at least 3 months (between 2009 and 2013).

Before randomization a screening transthoracic echocardiography (TTE) was performed to evaluate echogenicity. Patients were eligible for the trial (i) if a right ventricular (RV) pacing percentage of > 50% was documented, (ii) echogenicity was acceptable, (iii) if patients were able to perform a 6MWT (six-minute walk test) and an ergospirometry and (iv) if they were motivated to participate in the intensive study scheme. Exclusion criteria were minimal and consisted of permanent atrial fibrillation (AF), end-stage chronic obstructive lung disease, severe psychiatric, orthopaedic or neurological co-morbidity, acute illness (defined as any clinical condition with a recent onset that would theoretically interfere with study data), or participation in another trial at the moment of inclusion.

Study design

A randomized, patient-blinded cross-over design was used (figure 1). The protocol mandated for a stable background therapy from at least one month before inclusion until the end of the study period.

To ensure uniform patient groups before randomization, all patients were programmed in a predefined nominal AV delay setting (sensed AV delay 120 ms, paced AV delay 150 ms) at day 0. Routine investigations as described below were started < 15 minutes afterwards.

Intervention: AV optimization

Echo-guided AV optimization was performed using the iterative mitral inflow VTI (velocity time integral) method[6]. In brief, this method consists in programming a long AV delay and reducing it in 20 ms steps until the A-wave truncates. The interval is then increased in 10 ms and the shortest AV delay without A-wave truncation and with maximization of mitral inflow VTI of EA is considered the optimal AV delay (figure 2). Every optimization was performed for the sensed (temporary decreasing the atrial pacing lower rate to a level 5-10 bpm lower than the baseline atrial pacing frequency in case of atrial pacing at baseline) and the paced (temporary increasing the atrial pacing lower rate at a level 5-10 bpm higher than the spontaneous sinus rhythm in case of sinus rhythm at baseline) AV delay.

End points

The pre-specified end point of this trial was the change in functional capacity, measured by OUES. Other parameters collected were VO2 peak, 6MWD (six-minute walking distance), NYHA (New York Heart Association) class, score on HeartQoL, BNP (serum brain natriuretic peptide (ADVIA Centaur XP Immunoassay System)), left mitral annular late diastolic peak velocity and PAPs (systolic pulmonary artery pressure). Finally, the prevalence of IACD and correlation of IACD with clinical variables were studied.

Investigations

Echocardiographic analysis

TTE was performed with a GE Vivid E9 ultrasound scanner (GE Medical Systems, Horten, Norway) equipped with a 3.4 MHz transducer. Three cardiac cycles were collected for every echo image and stored in a cine-loop format for off-line analysis (Echopac PC version 3.1.0, GE Vingmed Ultrasound AS).

The left ventricular ejection fraction (LVEF) was assessed using the biplane Simpson's method. The PW Doppler of the mitral inflow (MI) was performed from the apical four-chamber view to obtain: mitral peak early (E) and peak late (A) velocities, A-wave duration, VTI of EA and A, and diastolic filling time (DFT). Tissue Doppler imaging (TDI) was used to measure the early diastolic myocardial velocity (E') at the lateral mitral annulus and to measure the late diastolic myocardial velocity at the lateral annulus (A') level. PAPs was estimated from the sum of the peak velocity of the tricuspid regurgitation and the estimated right atrial pressure (based on the size and collapsibility of the inferior caval vein).

Myocardial velocity imaging (MVI) of the atria was performed in the apical 4-chamber view[7]. Sector depth

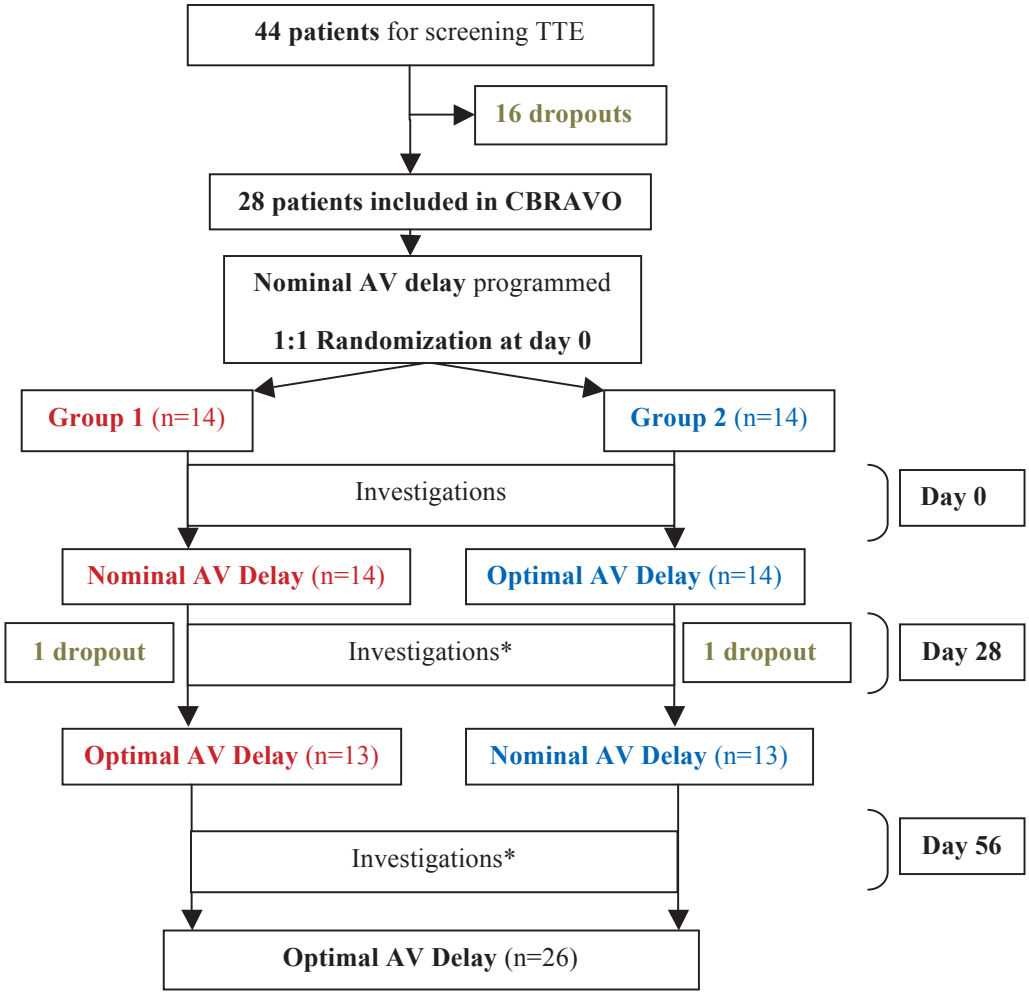

Fig. 1 Study flow chart.
Nominal AV delay settings: sensed AV delay 120 ms, paced AV delay 150 ms. Investigations included: six-minute walk test, New York Heart Association classification, HeartQoL, ergospirometry, pacemaker analysis and TTE (transthoracic echocardiography). Serum brain natriuretic peptide was analysed on day 28 and day 56. *Analysis of ergospirometry and 6MWT was excluded for two patients because of orthopaedic pathology after inclusion.
There were 16 dropouts immediately after the screening TTE because of transport problems (n = 12), orthopaedical problems (n = 2), acute bronchitis (n = 1) and sudden death (n = 1). There were 2 dropouts after inclusion after the first study contact (one in group 1 because of pulmonary sepsis and one in group 2 because of orthopaedical problems).

and size were optimized for the best resolution and higher frame rates. The MVI scale was adapted to avoid aliasing within the walls. The left and right atria were recorded simultaneously. Late diastolic peak colour Doppler velocities (A'(c)) at lateral mitral (A'm(c)) and tricuspid annular level were measured to calculate the interatrial mechanical delay (IAMD), used as a surrogate marker for IACD (IAMD = time interval between A'(c) at these two levels). An IAMD > 60 ms was considered significant[2].

Ergospirometry

Symptom-limited cardiopulmonary exercise tests were performed on an electronically braked cycle ergometer (eBike 1.8, GE Healthcare) in non-fasting conditions. Subjects were advised not to engage in vigorous or prolonged physical activity ahead of testing. Test room temperature was held constant (20°C) and the ergospirometer was calibrated automatically before every test according to manufacturer guidelines. In addition, all exercise tests were executed between 8-12 AM and 1-5 PM. The initial load was set at 10W for 1 min, and was increased by 10 or 20W every 2 min until exhaustion using a ramp protocol. Cycle load increments were based on previous exercise testing if available, resulting in a median test duration of > 10 min. All tests were continued until volitional fatigue. Maximal exercise effort was defined as: a respiratory gas exchange ratio (RER) > 1 in combination with subjective features of physical exhaustion. No patients were limited by angina.

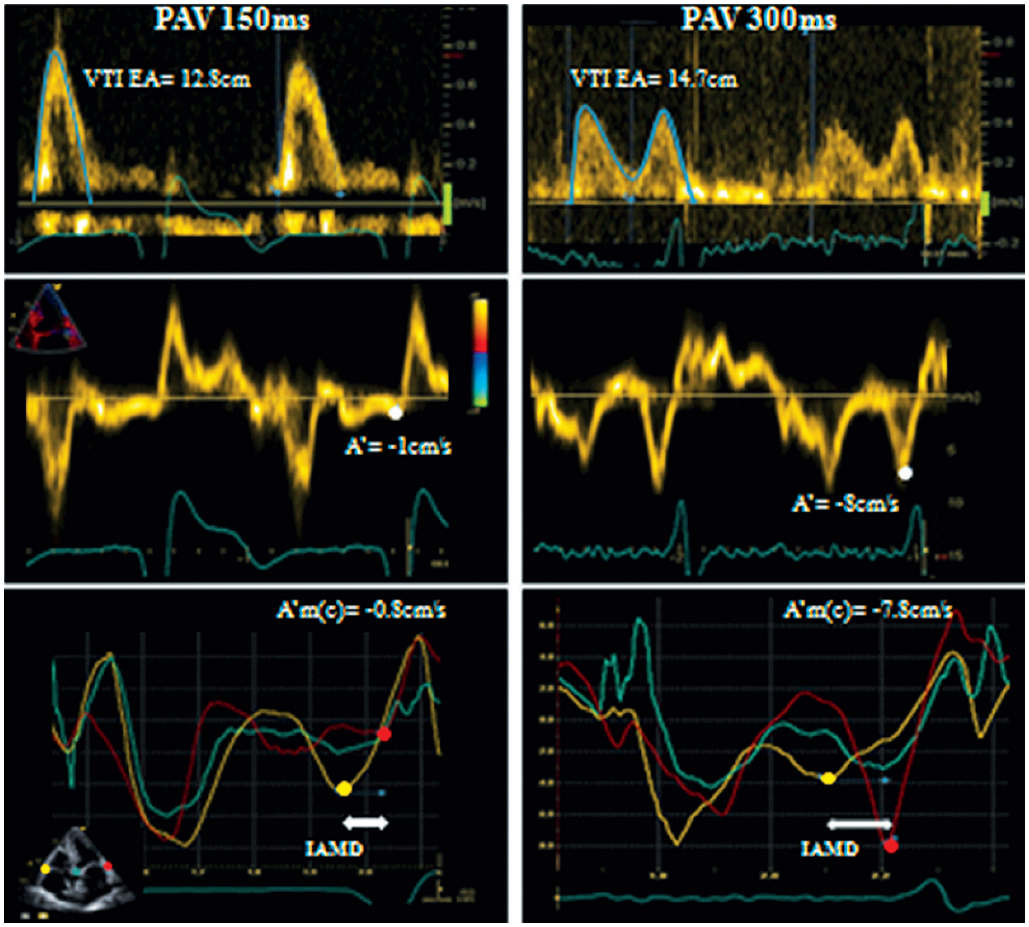

Fig. 2 Echo-guided AV optimization of a clinical, biochemical, and echocardiographic responder. Three complementary echo methods are shown: mitral inflow (upper panel), tissue Doppler imaging of the lateral mitral annulus (mid panel) and myocardial velocity imaging of the atria (lower panel). Due to a significant interatrial mechanical delay (IAMD), left atrial function is impaired in the nominal AV setting (paced AV delay 150 ms (PAV 150 ms)), resulting in left AV asynchrony (left panels). AV optimization to a paced AV delay of 300 ms (PAV 300 ms), improves left atrial function (A' and A'm(c), respectively), with a clear improvement of the mitral inflow VTI (right panels).

A 12-lead electrocardiogram was monitored continuously (Cardiosoft 6.6) and maximum heart rate and cycling power output was registered.

Minute ventilation (VE), oxygen uptake (VO2 peak), carbon dioxide output (VCO2), minimal breathing equivalents of CO2 (eqCO2) and O2 (eqO2) were acquired breath-by-breath, and averaged every 10s (Jaeger Oxycon, Jaeger gmbh, Germany). VO2 peak and peak RER were expressed using the highest 10s average obtained during the last minute of the test. The oxygen uptake efficiency slope (OUES) was calculated using [VO2 = m(log10VE)+b, where m = OUES][3].

Six-minute walk test (6 MWT) and HeartQoL questionnaire

A 6MWT was performed at least 1.5 hour before every ergospirometry, in a non-fasting condition and without cessation of medication[8]. Afterwards, a trained study nurse scored physical and emotional status with a validated HeartQoL questionnaire[9].

Statistics

SPSS v22 (SPSS Inc, Chicago, IL) was used for statistical analysis. Data were presented as percentages or means ± standard deviation (SD) when appropriate. Shapiro-Wilk tests were used to check if data were distributed normally, and boxplots for determination of outliers. Uniformity between our study groups was analysed by a Fisher's exact test for categorical data and a Mann-Whitney test for non-normally distributed data. Normally distributed data were analysed by paired t-tests, non-normally distributed variables by Wilcoxon signed-ranks tests. Correlations between variables were examined by Pearson (normally distributed) or Spearman (non-normally

distributed data) methods. All statistical tests were two-tailed and a *P*-value of < 0.05 was considered statistically significant. The significant data were indicated by * = $P<0.05$, ** = $P<0.01$ and *** = $P<0.001$.

RESULTS

Patient characteristics

Out of the 44 patients screened with TTE, 28 patients were included in this cross-over study (figure 1). Baseline patient characteristics are listed in table 1. Except for history of CABG and postoperative status, predominantly present in group 1, the groups were balanced. The mean optimal AV delay in our study population was sensed 196 ± 48 ms, paced 228 ± 48 ms. The length of the optimal AV delay correlated positively with the length of the IAMD (r = 0.65, $P=0.0004$) (Supplementary data, figure S1).

The mean right ventricular pacing percentage was 96% (± 11; median 99%) and did not change significantly during the study compared to pre-study percentages (data not shown). The mean right atrial pacing percentage was 58% (± 39; median 63%) and did not change significantly during the study compared to pre-study percentages. IAMD correlated with age (r = 0.39, $P=0.04$) and atrial pacing percentage (r = 0.70, $P<0.0001$, Supplementary data, figure S2).

A significant IAMD was present more frequently in patients with a sick sinus or bradycardia-tachycardia pacemaker indication (50% of the patients with these indications had a IAMD > 60 ms, in contrast to 19% the patients with AV block indication, $P=0.18$, data not shown), and in postoperative subjects (83% of the postoperative patients had a IAMD > 60 ms, $P=0.004$). 75% of patients reached a RER > 1; none of the patients had a RER < 0.9.

Oxygen uptake efficiency slope

OUES improved significantly after AV optimization (mean paired difference -126.67 mL/logL ± 190.68; 95% CI -207.19 – –46.15; $P=0.003$) (figure 3, table 2). In group 1 the negative effect of the nominal AV delay on OUES after 4 weeks (day 28), was compensated 4 weeks after AV optimization (day 56). In group 2 the positive effect 4 weeks after AV optimization (day 28), was neutralized 4 weeks after programming the nominal AV delay (day 56).

Other outcome measures

VO2 peak tended to improve after AV optimization. Qol, serum BNP, 6MWD and PAPs were not influenced (table 2). NYHA class did not improve after AV optimization (data not shown).

Left atrial function, measured by the amplitude of the left mitral annular late diastolic peak velocity, tended to improve after AV optimization. In the subgroup of patients with an important IACD (defined as an IAMD > 60 ms, prevalence of 30.8%) a more pronounced improvement of left atrial function was observed (mean paired difference 2.25 ± 3.16; CI -0.40 – 4.89; $P=0.08$, respectively 0.55 ± 2.53; CI -0.71 – 1.81; $P=0.37$).

DISCUSSION

Our pilot study presents for the first time data on OUES to assess functional capacity following echo-guided AV optimization in dual-chamber pacemaker patients. Four weeks after AV optimization we demonstrated a significant improvement in OUES as compared to nominal values. Likewise, VO2 peak tended to improve, in contrast to data of Khairy et al.[10].

We chose OUES as our prespecified end point, since OUES is a validated parameter of exercise capacity and a monitoring tool for assessing the effect of physical training in healthy subjects and in heart failure patients[3]. Moreover, OUES is considered superior to VO2 peak to measure exercise capacity when maximal exercise is difficult to achieve, occurring frequently in a real-life pacemaker population. Finally, OUES is more feasible and reproducible than the ventilatory anaerobic threshold[3]. All study patients reached a RER ≥ 0.9, providing values better reflecting the full OUES test value. A predefined slowly progressive ergospirometry protocol was used to limit the number of dropouts due to orthopaedic limitations. The effect on OUES was measured after 4 weeks. Though this timing was arbitrary, the aim was to examine a sustained short-term effect of AV optimization on exercise capacity, in contrast to the established acute haemodynamic effects[4,5].

AV optimization in our study was performed at rest, using the validated iterative mitral inflow VTI method[6]. We used this specific method because of our experience with this technique and because of its clinical feasibility, though aortic VTI and Ritter's method for DDD pacemaker optimization are likewise validated. Since exercise can induce differences in conduction and atrial electromechanical coupling, we used a slowly progressive ergospirometry protocol. This resulted in a 100% of RV pacing during peak exercise in 23 out of 24 patients, ensuring a continuous effect of AV optimization. The arbitrary cut-off of > 50% of RV pacing for study inclusion was based on other optimization studies and resulted in a median RV pacing percentage of 99% [11,12]. In contrast to ventricular pacing incidence, atrial pacing spikes are not easily and reproducibly recognized on ergospirometry strips. Therefore analysis

Table 1 Baseline patient characteristics.

		Group 1 (n = 13)	Group 2 (n = 13)	*P*-value
Age	Mean (years) ± SD	75 ± 13	71 ± 16	0.41
	Median	78	77	
	Min	44	26	
	Max	90	88	
Sex, n (%)	Male	10 (77)	9 (69)	1.00
	Female	3 (23)	4 (31)	
Type pacemaker, n (%)	Sorin	2 (15)	3 (23)	0.09
	Boston Scientific	1 (8)	0 (0)	
	Medtronic	3 (23)	6 (46)	
	St. Jude	5 (39)	0 (0)	
	Biotronik	2 (15)	4 (31)	
Indication, n (%)	Sick Sinus	2 (15)	3 (23)	0.64
	2° AV block	4 (31)	5 (39)	
	3° AV block	3 (23)	4 (31)	
	AF with pauses	4 (31)	1 (8)	
Time since implantation	Mean (months) ± SD	52 ± 51	60 ± 41	0.29
	Median	27	46	
	Min	6	17	
	Max	177	139	
Atrial lead, n (%)	Active	7 (54)	10 (77)	0.41
	Passive	6 (46)	3 (23)	
Ventricular lead, n (%)	Active	6 (46)	7 (54)	1.00
	Passive	7 (54)	6 (46)	
Ventricular position, n (%)	Apical	13 (100)	12 (92)	1.00
	Septal	0 (0)	1 (8)	
IAMD, n (%)	> 60 ms	6 (46)	2 (15)	0.20
Cardiovascular morbidity, n (%)	Arterial hypertension	8 (61)	11 (85)	0.38
	LVEF < 45%	2 (15)	1 (8)	1.00
	LVEF > 45%	11 (85)	12 (92)	
	Hospitalised for acute heart failure	3 (23)	1 (8)	0.59
	Pulmonary hypertension	1 (8)	0 (0)	1.00
	Ischaemic heart disease	7 (54)	3 (23)	0.23
	Coronary artery bypass grafting	5 (39)	0 (0)	0.04 *
	AF	7 (54)	3 (23)	0.23
	Ablation	3 (23)	1 (8)	0.59
	Postoperative status	6 (46)	0 (0)	0.02 *
Non-cardiac morbidity, n (%)	Prediabetes	8 (62)	7 (54)	1.00
	Type II diabetes mellitus	2 (15)	2 (15)	
	COLD	2 (15)	0 (0)	0.48
	Chronic kidney insufficiency: G1 or 2	7 (54)	5 (39)	0.70
	Chronic kidney insufficiency: G3a, 3b or 4	6 (46)	8 (62)	
	Chronic inflammatory diseases	0 (0)	0 (0)	/
Anti-arrhythmic drugs, n (%)	Beta blocker	11 (85)	7 (54)	0.20
	Sotalol	1 (8)	0 (0)	1.00
	Flecainide	1 (8)	2 (15)	1.00
	Amiodarone	2 (15)	1 (8)	1.00
	Digitalis	0 (0)	0 (0)	/
	Diuretics	4 (31)	5 (39)	1.00
	Nitrates	2 (15)	2 (15)	1.00
	ACE inhibitor	7 (54)	3 (23)	0.23
	ARB	1 (8)	5 (39)	0.16
	Calcium blocker	2 (15)	3 (23)	1.00
	Ivabradin	0 (0)	0 (0)	/
	Statin	4 (31)	8 (62)	0.24

All atrial leads were implanted at the level of the right atrial appendage. AF: atrial fibrillation. IAMD: interatrial mechanical delay. LVEF: left ventricular ejection fraction. COLD: chronic obstructive lung disease. Prediabetes is defined as a Hba1c ≥ 5.7 – 6.4%, type II diabetes mellitus as a HbA1c ≥ 6.5%. ACE inhibitor: angiotensin-converting enzyme inhibitor. ARB: angiotensin receptor blocker.

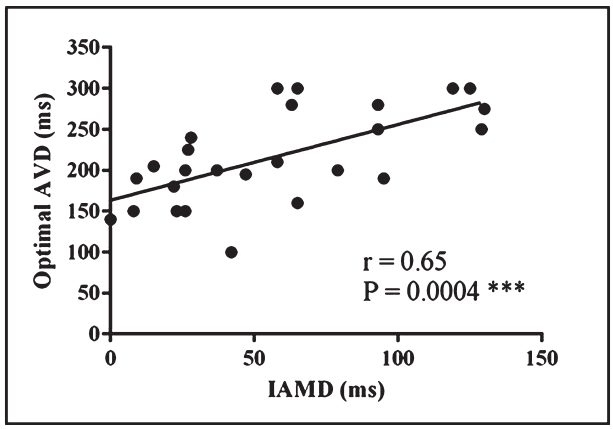

Fig. S1 Correlation between the IAMD and the optimal AVD. The longer the IAMD, the longer the AVD had to be programmed during AV optimization.
AVD: atrio-ventricular delay, IAMD: interatrial mechanical delay.

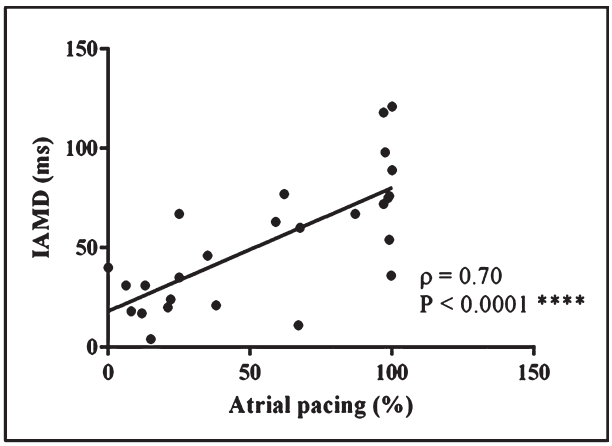

Fig. S2 Correlation between the percentage of atrial pacing and the IAMD. The higher the percentage of atrial pacing, the longer the IAMD (interatrial mechanical delay).

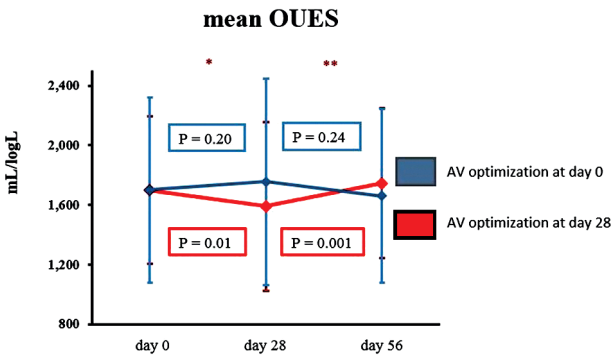

Fig. 3 Exercise capacity in group 1 (red markers) and 2 (blue markers). Mean OUES values on day 0 (nominal AV delay in all patients) depict a uniform baseline population. On day 28, patients in group 1 were at a stable nominal AV delay for a period of 4 weeks, patients in group 2 were at a stable optimal AV delay for a period of 4 weeks. After measurement of OUES on day 28, AV delay was optimized in group 1 and reset to nominal values in group 2. On day 56, patients in group 1 were at a stable optimal AV delay for a period of 4 weeks, patients in group 2 were at a stable nominal AV delay for a period of 4 weeks.

of atrial pacing incidence was not performed at peak exercise.

VO2 peak tended to improve but failed to reach significance, probably because 25% of the patients did not reach RER > 1. In contrast to the published data on AV optimization using impedance cardiography, we did not find an improvement in BNP and Qol[12]. Since 73% of the patients had a BNP within normal range in the nominal AV setting, the effect of AV optimization on BNP might be underestimated. NYHA class, walking capacity and PAPs were not influenced in our series. A reasonable explanation may be that 75% of the study patients reported a NYHA class I at the moment of inclusion. The latter also raises the question if this 75% of patients were really asymptomatic or rather presumed asymptomatic and might emphasize the superiority of OUES over NYHA class in evaluating patient functionality. Likewise the 95% CI showed PAPs within the normal range.

AV optimization tended to improve left atrial function, measured by colour Doppler mitral annular late diastolic peak velocity. These results are concordant with the findings of Yasuoka et al.[13]. Improvement of left atrial function was more pronounced in patients with a significant IACD (defined as an IAMD >60 ms), which might be considered as a predictor of echocardiographic responsiveness to AV optimization.

The mean optimal AV delay in our study was longer than the nominal settings from most of the manufacturers (Supplementary data, table S1) and longer than the mean optimal paced AV delay (150 ± 39 ms) in a recently published invasive AV optimization study in DDD patients[11]. One should notice that in the latter study the patient population consisted predominantly of AV block indications, in contrast to the higher percentage of bradycardia-tachycardia and sick sinus syndrome indications in our study, which is correlated with higher percentages of IACD[1]. Generally, AV delays in CRT are programmed shorter (< 120 ms in MADIT-CRT) compared to our data, because the focus in this patient population is to prevent QRS fusion[14]. On the other hand, recent data on CRT optimization guided by invasive left atrial pressure measurements, suggest a longer mean optimal AV delay (177 ms) [15].

In line with earlier findings in DDD and CRT pacing, we showed a positive correlation between the length of the IACD and length of optimal AV delay[16,17]. Lengthening of the AV delay lengthens atrial refractory periods and lowers the 2:1 point, which could theoretically interfere with exercise tolerance. Given the rather high mean

Table 2 End points

	Mean	Median	SD	95% CI		*P*-value
				Lower	Upper	
OUES (mL/logL)						
nominal – optimal	–126.67	–151.3	190.68	–207.19	–46.15	0.003 **
VO_2 peak (mL/min)						
nominal – optimal	–70.79	–102.5	176.40	–145.28	3.70	0.18
6MWD (m)						
nominal – optimal	–3.18	–4	36.64	–18.64	12.31	0.68
HeartQoL (score)						
nominal – optimal	–1.04	–1.00	3.99	–2.65	0.57	0.39
BNP (*pg*/mL)						
nominal – optimal	99.08	4.50	326.97	–32.99	231.15	0.53
A'm(c) (cm/s)						
nominal – optimal	1.07	0.60	2.79	–0.06	2.20	0.10
PAPs (mmHg)						
nominal – optimal	0.39	0	7.92	–2.81	3.58	0.66

Difference between nominal and optimal AV delay settings as paired differences. Oxygen uptake efficiency slope (OUES), VO2 peak, six-minute walking distance (6MWD) and HeartQoL: a negative difference implicates a higher OUES, VO2 peak, 6MWD and HeartQoL after AV optimization. Serum brain natriuretic peptide (BNP), late diastolic peak colour Doppler velocity at the lateral mitral annular level (A'm(c)) and systolic pulmonary artery pressure (PAPs): a positive difference implicates a lower BNP, a better left atrial function and a lower PAPs after AV optimization.

Table S1. Comparison of the optimal AV delay settings in our study population with manufacturers' nominal values

		CBRAVO	Sorin	Boston Scientific	Medtronic	St. Jude	Biotronik
Sensed	Mean ± SD	196 ± 48	155	150	120	150	120
	Median	195					
	Min	100					
	Max	270					
Paced	Mean ± SD	228 ± 48	220	180	150	200	150
	Median	228					
	Min	130					
	Max	300					

age of patients with a DDD pacemaker in daily clinical practice, this should not be an issue for most of the patients[2]. A rate adaptive AV delay algorithm may also prevent this theoretical obstacle.

Analogous to earlier findings, we found a correlation between the percentage of atrial pacing and length of IACD[18]. Beside the lengthening due to the *P* sense offset, one could hypothesize that larger atrial pacing percentages are found in sicker atria, showing delayed conduction. Similarly, evidence exists about a linear relationship between the degree of IACD and extent of left atrial mechanical dysfunction[2]. In this context we showed a higher prevalence of an important IACD in patients with sick sinus and bradycardia-tachycardia syndrome, in the elderly and in postoperative patients. Likewise, Kedia et al showed that atrial pacing percentage, age and left atrial diameter correlated with longer optimal AV delays (> 140 ms) in the setting of CRT[19]. The higher prevalence of postoperative status in group 1 might be an explanation for the more pronounced effect of AV optimization on OUES in this group, in contrast to group 2. Almost 1 out of 3 patients in our study showed a significant IACD, reflecting a real-life situation as previously reported[2].

LIMITATIONS

Twenty-eight patients were examined in this study. Despite the relatively small sample size, a statistical power α of 0.88 was reached for changes in OUES. Because of practical considerations and based on recent data in the context of cardiac resynchronization therapy suggesting that AV optimization at rest is superior to optimization during exercise, every AV optimization in our study was performed at rest[20]. Moreover, the physiological

background for rate-adaptive AV optimization in DDD and biventricular pacing remains ambiguous. In our study 50% of the patients had the rate response (RR) modus programmed on before inclusion. This was left unchanged at the time of inclusion, avoiding confounders as differential effect of rate response. One could hypothesize that routine AV optimization might have a greater impact in a younger population. However, given the mean age of our study patients we can only draw conclusions concerning older patients. Finally it remains worthwhile to perform a cost-efficacy analysis evaluating if the clinical impact of AV optimization on a routine basis in every DDD pacemaker patient outweighs the extra cost of, for instance, transthoracic echocardiography.

CONCLUSION

Individualized AV optimization by TTE significantly improved exercise capacity, measured by OUES, in patients with a dual-chamber pacemaker. Nominal AV settings, as proposed by different pacemaker manufacturers, can induce left AV asynchrony, due to the presence of an IACD. Higher age, higher percentage of atrial pacing, sick sinus and bradycardia-tachycardia pacemaker indication and a postoperative status can be a clue for the presence of an IACD. This mechanistic study provides a background for further validation studies.

ACKNOWLEDGEMENTS

Special thanks to Joris Schurmans and Johan Vijgen (department of electrophysiology) for assistance in the recruitment of patients and to Kim Bonne and An Stevens for assistance in the development of the ergospirometry protocol.

CONFLICTS OF INTEREST: none declared.

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