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Pacing therapy for atrioventricular dromotropathy: a combined computational–experimental–clinical study

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Aims Investigate haemodynamic effects, and their mechanisms, of restoring atrioventricular (AV)-coupling using pacemaker therapy in normal and failing hearts in a combined computational–experimental–clinical study.

Methods and results Computer simulations were performed in the CircAdapt model of the normal and failing human heart and circulation. Experiments were performed in a porcine model of AV dromotropathy. In a proof-of-principle clinical study, left ventricular (LV) pressure and volume were measured in 22 heart failure (HF) patients (LV ejection fraction <35%) with prolonged PR interval (>230 ms) and narrow or non-left bundle branch block QRS complex. Computer simulations and animal studies in normal hearts showed that restoring of AV-coupling with unchanged ventricular activation sequence significantly increased LV filling, mean arterial pressure, and cardiac output by 10–15%. In computer simulations of failing hearts and in HF patients, reducing PR interval by biventricular (BiV) pacing (patients: from 300 ± 61 to 137 ± 30 ms) resulted in significant increases in LV stroke volume and stroke work (patients: 34 ± 40% and 26 ± 31%, respectively). However, worsening of ventricular dyssynchrony by using right ventricular (RV) pacing abrogated the benefit of restoring AV-coupling. In model simulations, animals and patients, the increase of LV filling and associated improvement of LV pump function coincided with both larger mitral inflow (*E*- and *A*-wave area) and reduction of diastolic mitral regurgitation.

Conclusion Restoration of AV-coupling by BiV pacing in normal and failing hearts with prolonged AV conduction leads to considerable haemodynamic improvement. These results indicate that BiV or physiological pacing, but not RV pacing, may improve cardiac function in patients with HF and prolonged PR interval.

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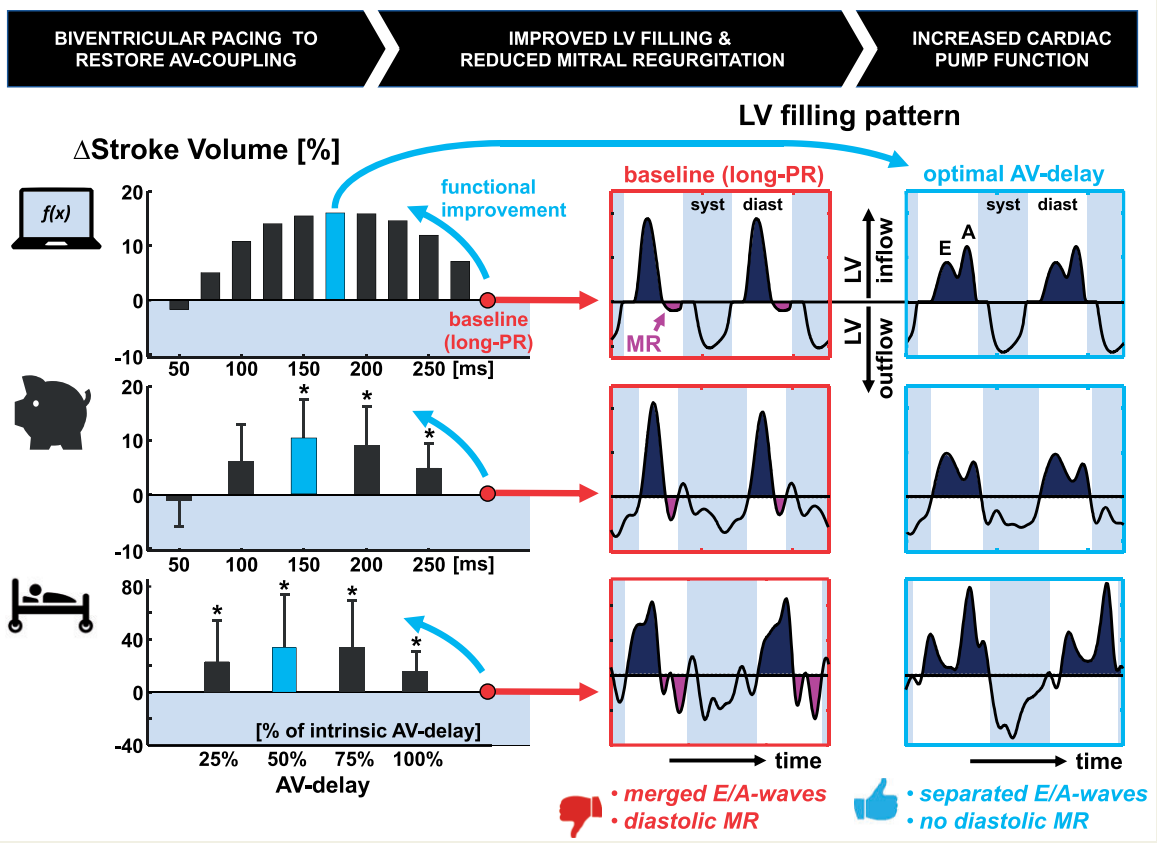
Graphical Abstract



Keywords First-degree atrioventricular block • Biventricular pacing • Heart failure • Computer modelling • Haemodynamics

What's new?

- Normalizing atrioventricular (AV) coupling using biventricular pacing in conditions of prolonged AV conduction times improves left ventricular pump function significantly, both in normal animal hearts and in failing human hearts.
- Increasing ventricular dyssynchrony by right ventricular pacing attenuates the beneficial effect of normalizing AV-coupling.
- Normalizing AV-coupling creates its haemodynamic benefit by both reducing diastolic mitral regurgitation and increasing mitral inflow.
- The similarity of the preclinical and clinical results with those from the computer simulations indicates that the mechanism of haemodynamic improvement by optimizing AV-delay can be explained by the well-established physical and physiological principles that are incorporated in the model, such as conservation of energy, inertia of blood, and length-dependent activation of myocytes.

Introduction

Atrioventricular (AV) conduction delay (or: AV dromotropathy), as evidenced by a prolonged PR interval (>200 ms) on the electrocardiogram (ECG), is present in 15–51% of patients with heart failure (HF) and increases the risk of poor clinical outcome.[1] A few small studies in the 1990s suggested that shortening the AV-delay by ventricular pacing could improve cardiac pump function.[2,3] These studies were among the first to use ventricular pacing as a treatment for HF. Notably, these studies employed right ventricular (RV) pacing, because these were performed before the era of biventricular (BiV) pacing. In subsequent years, the attention for treatment of a prolonged PR interval faded as it became overruled by cardiac resynchronization therapy (CRT). However, recent sub-analyses of clinical trials investigating the benefit of CRT revitalized the interest in this topic.[4] While patients without left bundle branch block (LBBB) generally show little clinical improvement from CRT, a significant benefit was observed in non-LBBB patients with prolonged PR interval.[5] Similarly, in a sub-study of the ReThinQ trial, which investigated the

benefit of CRT in patients with QRS duration <130 ms, only patients with a prolonged PR interval (>180 ms) showed a significant increase in maximum oxygen uptake.[6] The 2021 ESC guidelines on pacing and CRT recommend the use of pacing in patients with a PR interval >300 (Class II1, Level C) without recommending a pacing site .[7]

Therefore, we hypothesized that restoring proper AV-coupling by pacing significantly improves cardiac pump function. We investigated this hypothesis and revealed the mechanisms of action using a three-step approach. First, the haemodynamic benefits of restoring AV-coupling were studied in a porcine model and a computational model of the non-failing heart with prolonged PR interval. Second, the confounding effect of pacing-induced ventricular dyssynchrony and HF on the potential haemodynamic benefit of restoring AV-coupling was studied in the computational model. Third, a proof-of-principle clinical study was performed in patients with HF and a prolonged PR interval. In this study, a cut-off value for prolonged PR interval of 230 ms was chosen based on the subanalysis of the MADIT-CRT study.[5]

Methods

Studies were performed in the CircAdapt computer model of the human heart and circulation, in a porcine model of AV-block and in patients with HF and a prolonged PR interval (PR interval >230 ms).

Computer simulations

Previously, CircAdapt simulations of electro-mechanical and haemodynamic interventricular and atrioventricular interactions have been extensively validated and applied under physiological and pathophysiological conditions, including dyssynchronous HF and its treatment with pacing therapy (see Supplementary material online). In the CircAdapt model, a prolonged PR interval was simulated by increasing AV-delay from 150 ms to 300 ms in the reference simulation of the normal human heart with synchronous ventricular activation. Starting from this reference simulation, the following simulations were performed: (i) gradual shortening of the AV-delay from 300 to 50 ms (in steps of 25 ms) with synchronous ventricular activation (SYNC) and normal myocardial contractility, and (ii) gradual shortening of the AV-delay in a simulation of HF (LVEF < 35%) with synchronous ventricular activation and dyssynchronous ventricular activation, resembling BiV and RV pacing. Cardiac output (CO), transmitral flow patterns, mean arterial pressure (MAP), and ventricular volumes were obtained for all simulations. More methodological details about the model simulations are provided as Supplementary material online.

Animal experiments

Animal handling was performed in compliance with the Guide for the Care and Use of Laboratory Animals and in accordance with the European Community recommendations. The protocol was approved by the Dutch National Ethical Committee for Animal Handling.

Experiments were performed in seven female landrace pigs weighing 61 ± 3 kg. Animals were pre-medicated with intramuscular Zoletil (5 mg/kg). After induction with intravenous sodium thiopental (5–15 mg/kg), anaesthesia was maintained by continuous infusion of Propofol (10 mg/kg/h), Sufentanyl (5 μg/kg/h), and Rocuronium (0.1 μg/kg/h). Details of the experimental model are provided in *Figure 1*. Complete AV-block was created by radiofrequency ablation of the AV-node. Subsequently, the animals were paced at the right atrial appendage and at the RV apex and left ventricular (LV) epicardial lateral wall. A 7-Fr conductance catheter (CD Leycom, Zoetermeer, The Netherlands) was introduced into the LV cavity via the femoral artery. A 4F Millar Mikro-Tip pressure catheter (Millar, Houston, TX, USA) was used to measure left atrial (LA) pressure. A vascular flow probe (Transonic Europe B.V., Elsloo, The Netherlands) was mounted around the ascending aorta to asses aortic flow and subsequently calculate CO. Measurements were performed after instrumentation and haemodynamic stabilization using BiV pacing at 10 b.p.m. above intrinsic atrial rhythm with an AV-delay of 300 ms, mimicking prolonged PR interval, as baseline condition. Subsequently, during BiV pacing the AV-delay was programmed between 50 and 250 ms in randomized steps of 50 ms. Baseline recordings were performed before every step. Each recording lasted for at least two respiratory cycles.

Patient studies

The patient study was performed according to the principles of the Declaration of Helsinki and the study protocol was approved by the ethics committee of the Maastricht University Medical Center+ (registration number NL60764.068.17/METC 171013). All patients gave written informed consent prior to investigation, and the study was monitored by the Clinical Trial Center Maastricht. The study has been registered at clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT03973944).

Patients were included in the Maastricht University Medical Center+ ($n = 20$), the University Medical Center Utrecht ($n = 5$), and the Amsterdam University Medical Center ($n = 1$) from June 2018 to February 2020. Inclusion criteria were the presence of sinus rhythm, stable prolonged PR interval >230 ms, LV ejection fraction (LVEF) <35%, New York Heart Association (NYHA) functional class II to III, optimal HF medication, and indication for an implantable cardioverter-defibrillator (ICD). Patients were implanted with a CRT-D and LV lead for this study, considering that this additional implantation creates minimal additional risk to the patient while the option to provide CRT therapy was offered after the haemodynamic data of this study showed significant improvement. Patients were excluded when they already had a CRT device, in the presence of a class I CRT indication (LBBB or QRS duration >150 ms). Also, a resting heart rate >90 b.p.m., chronic renal failure requiring dialysis, moderate to severe aortic stenosis, frequent premature ventricular complexes (≥two complexes on a standard ECG), significant peripheral vascular disease, age below 18 years or recent (<3 months) myocardial infarction, coronary artery bypass graft, or valve surgery were exclusion criteria.

All participants underwent CRT device implantation according to routine clinical practice. The atrial lead was positioned in the right atrial appendage, the RV lead in the RV apical septum, and a quadripolar LV lead in a suitable vein on the posterolateral LV wall. A 7-Fr pressure–volume loop conductance catheter (CD Leycom, Zoetermeer, The Netherlands) was introduced into the LV cavity via the femoral artery.

The ECG and LV pressure and volume were recorded during BiV and RV pacing at four paced AV-delays. The paced AV-delay was set to ∼100%, 75%, 50%, and 25% of patient's PR interval during baseline AAI pacing −30 ms to ensure capture at the longest AV-delay.[8] The pacing protocol (in DDD mode) was performed at ±10 b.p.m. above intrinsic sinus rate. Interventricular pacing delay was set to −40 ms (LV first). Baseline measurements were performed during atrial pacing (AAI mode) at the same pacing rate before and after each mode of ventricular pacing. Pressure–volume loops were recorded for 60 s during the ventricular pacing protocol and 30 s before and after each setting in AAI mode. The latter were averaged and are referred to as baseline.

Data analysis

The acute haemodynamic effect of pacing at the different AV-delays in animals and patients was evaluated by invasive measurement of LV stroke volume and stroke work (area of the pressure–volume loop) as well as

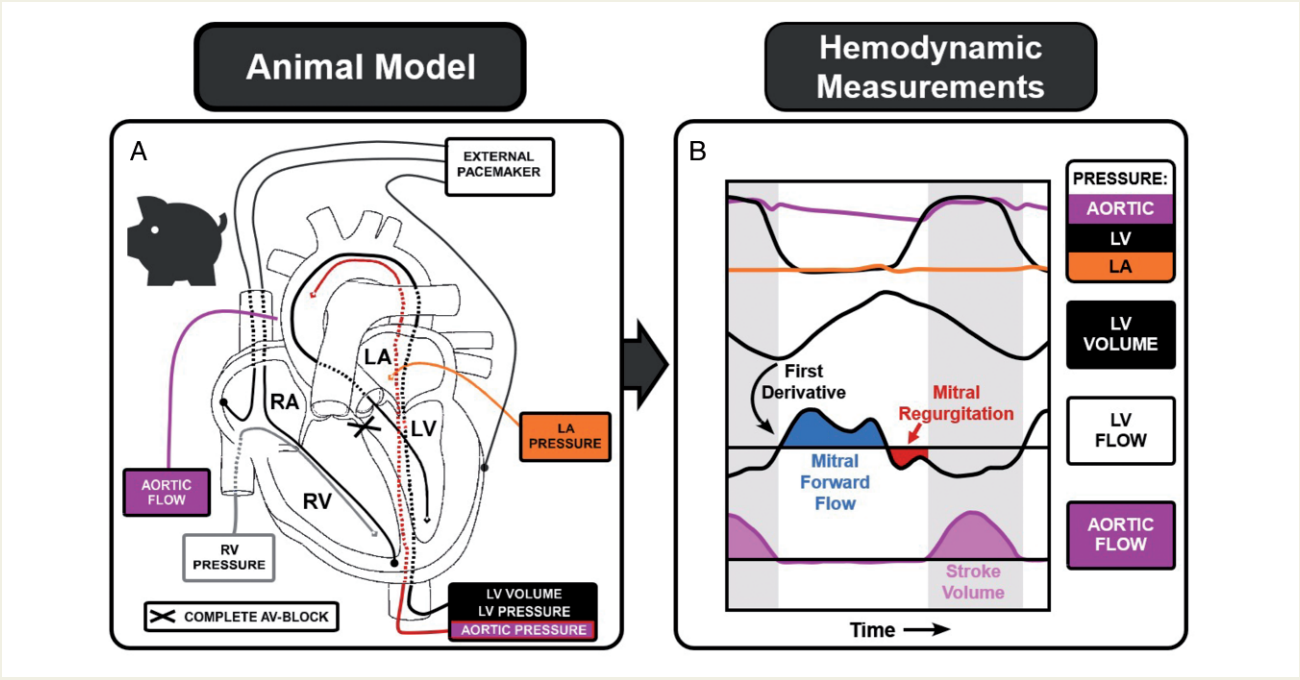


Figure 1 Schematic representation of the animal experimental set-up. (*A*) Overview of the porcine model. Pacemaker leads were transvenously inserted in the right atrial (RA) appendage and right ventricular (RV) apex and attached to the left ventricular (LV) epicardium. Complete atrioventricular (AV) block was created by radiofrequency ablation of the AV-node. The LV pressure and volume were measured using a conductance catheter and RV and left atrial (LA) pressure were measured using a cathetertip manometer. (*B*) Signal analysis. The first derivative of LV volume was used to calculate forward flow over the mitral valve (blue area under *E* and *A* wave) and diastolic mitral regurgitation (MR, red area). The integral of aortic flow, measured by a flow probe, was used to quantify forward stroke volume and cardiac output (purple area).

the diastolic flow pattern, derived from the first derivative of the LV volume signal (flow; right panel of *Figure 1*) using a combination of the Conduct NT software (CD Leycom, Zoetermeer, The Netherlands) and customized software programmed in MATLAB R2019b (MathWorks, Natick, MA, USA). Diastolic mitral regurgitation (MR) volume was quantified as the area below zero of the flow curve during diastole. Forward flow over the mitral valve was quantified as the combined area under the *E*- and *A*-waves (see also *Figures 1 and 2*). The diastolic MR fraction was defined as diastolic MR as a percentage of forward flow. In the animals, stroke volume was derived from the aortic flow probe. To account for spontaneous changes in baseline haemodynamic outcome parameters, each ventricular pacing setting was compared with the corresponding baseline. Ectopic ventricular beats and the two subsequent heart beats were excluded from the analysis. Conductance catheter measurements were volume calibrated by adjusting baseline stroke volume to stroke volume measured using Swan Ganz thermodilution catheters in animals and to pre-procedural echocardiography in patients.

Statistical analysis of clinical and experimental study

Statistical analysis was performed using Statistical Package for Social Sciences version 24.0 (SPSS Inc., Chicago, IL, USA). Continuous data are presented as mean ± standard deviation (SD). The relative change of the haemodynamic variables at various AV-delays was evaluated using a one-way repeated measures ANOVA. If significant, a Student's paired samples *T*-test and Bonferroni correction was used to test significance of the change at individual AV-delays. To evaluate differences between different pacing modes, two-way ANOVA for repeated measurements was used, followed by Student's paired samples *T*-test. A two-sided probability value of <0.05 was considered statistically significant.

Results

Restoring atrioventricular-coupling in normal hearts: animal experimental and computational analyses

Results from animal experiments and computer simulations showed good qualitative and quantitative agreement (*Figure 2*). Under baseline conditions at long AV-delay, the delay of ventricular activation resulted in (i) suboptimal LV filling with the early filling wave (*E*) being fused with or prematurely interrupted by the atrial filling wave (*A*), and (ii) diastolic MR due to atrial relaxation and related atrial pressure drop occurring before the onset of ventricular activation and, hence, papillary muscle contraction. At intermediate AV-delays (150 ms) separated *E*- and *A*-waves were observed. At short AV-delays, *A*-wave truncation occurred as well as increases in peak and mean LA pressure, presumably caused by atrial contraction against a closed mitral valve.

Figure 3 depicts that in the computer simulations and the animal studies, the largest increase in LV end-diastolic volume was observed at the AV-delay leading to the LV filling pattern with most pronounced *E–A* wave separation (175 ms in the simulations, 157 ± 7 ms in the animals) and leading to minimal diastolic MR. At this setting,

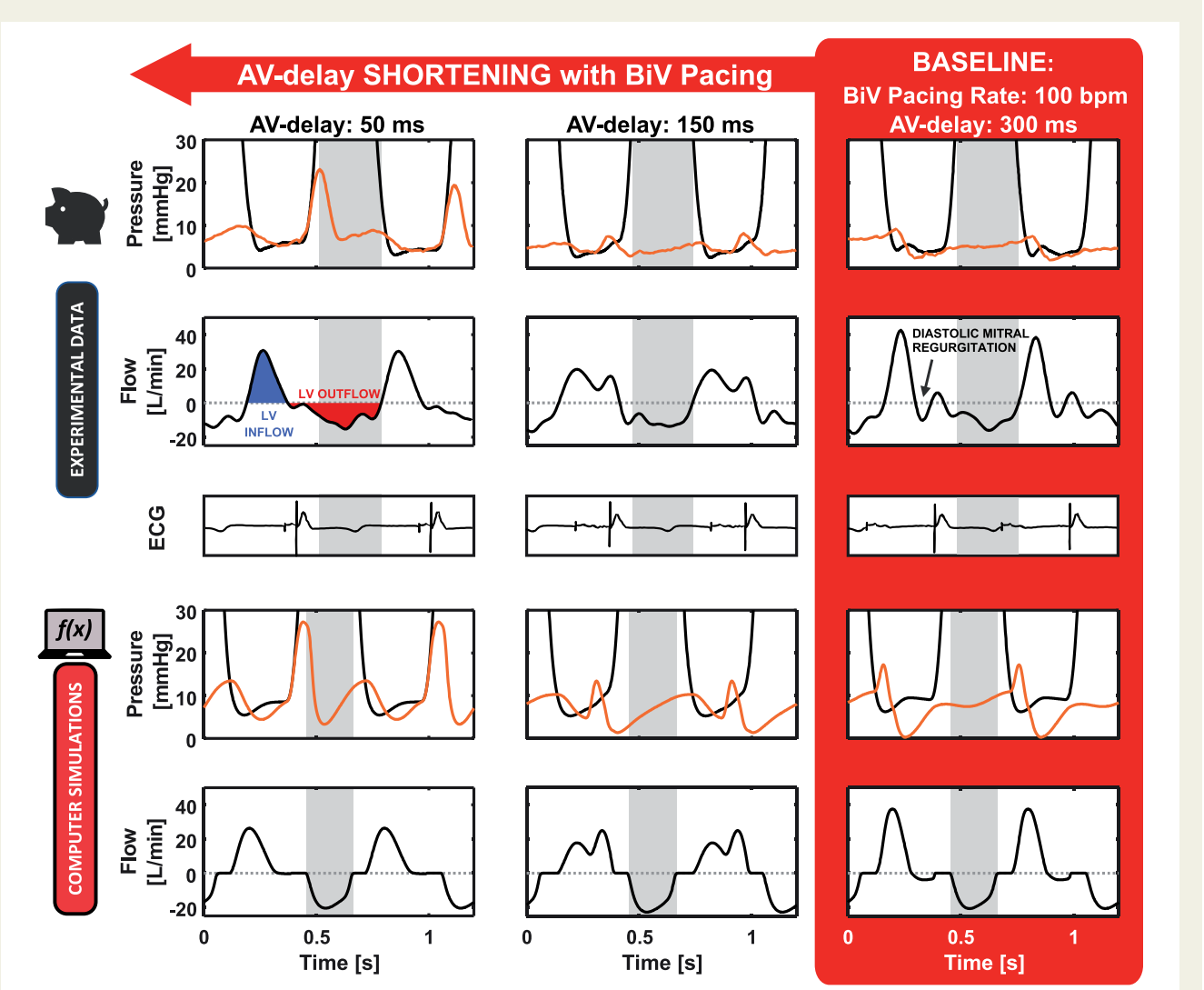


Figure 2 Haemodynamic effect of improving atrioventricular (AV)-coupling in pig experiments and computer simulations during biventricular pacing. (Top row) LV and LA pressures, (second row) flow, and (third row) ECG from a representative experiment. (Fourth and fifth row) Pressures and flow calculated from computer simulations.

MAP and CO were also increased (both ~15% in simulations and ~10% in animals). Importantly, in the animal studies, the largest increase in LVEDV (at AV-delay 150 ms) was achieved without a significant change in mean LA pressure compared with the baseline condition with long AV-delay (*Table 1*).

Both the computer simulations and animal studies showed that the increased filling at intermediate AV-delays was achieved by a dual effect: larger forward flow over the mitral valve (area under the *E*- and *A*-waves) and reduction in diastolic MR (central figure, *Table 1*).

Modulating effects of ventricular dyssynchrony: computer simulations

While the aforementioned study results concerned manipulation of AV-coupling in normal hearts at a constant degree of ventricular dyssynchrony, a next step was to investigate how different degrees of pacing-induced ventricular dyssynchrony would influence the haemodynamic response to changes of AV-coupling in the failing heart. The amount of haemodynamic improvement obtained with recovery of AV-coupling depended on the degree of pacing-induced ventricular dyssynchrony. The largest haemodynamic improvement was predicted with the simulations with synchronous ventricular activation, while RV pacing simulations showed the smallest improvement, in terms of stroke volume (*Figure 4A*), LVEDV (*Figure 4B*), and LV inflow pattern (*Figure 4C*). Most separated *E*- and *A*-waves and least diastolic MR occurred during synchronous pacing (*Figure 4C*).

Patient study

Table S1 (see Supplementary material online) shows the baseline patient characteristics. The study cohort consisted of patients with moderate to severe HF (NYHA II or III), mean LVEF of 29 ± 6%, mean PR interval of 261 ± 32 ms, QRS duration of 123 ± 19 ms, and a mix of ischaemic and dilated cardiomyopathy.

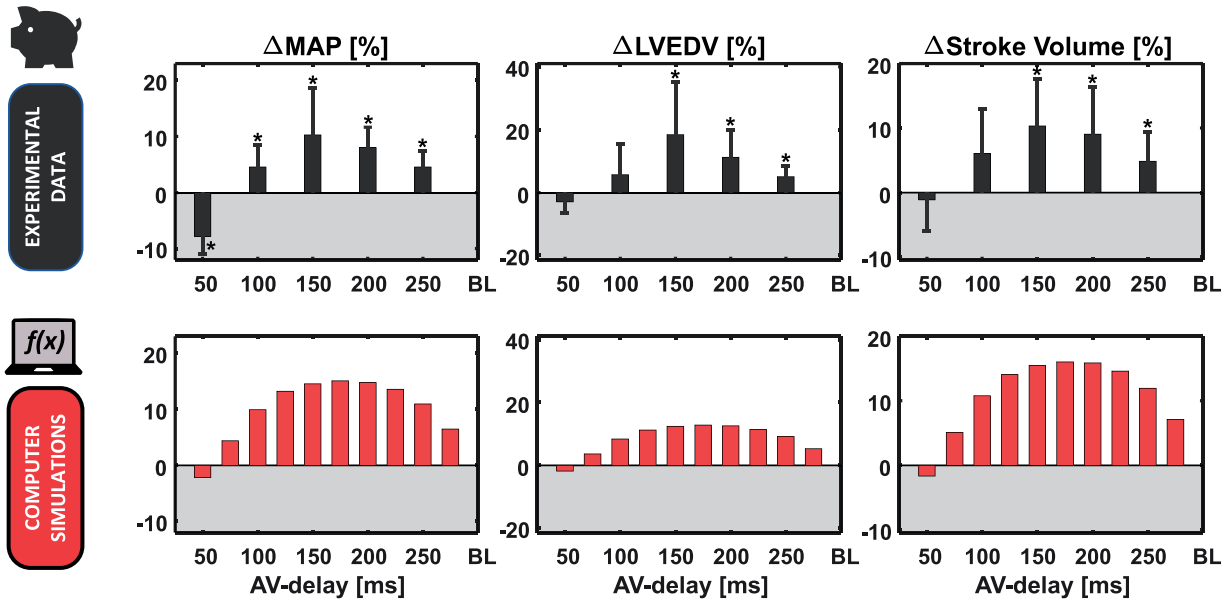


Figure 3 Haemodynamic response to improving atrioventricular (AV) coupling in pig experiments and computer simulations during biventricular pacing. Relative changes in haemodynamic function by shortening AV-delay in all pig experiments (top panel) and simulations (bottom panel) when compared with a baseline PR interval of 300 ms. For the pig experiments mean±SD are presented. * indicates $P < 0.05$ when compared with baseline. MAP, mean arterial pressure; LAP_{mean}, mean left atrial pressure; LVEDV, left ventricular end diastolic volume.

Table 1 Haemodynamic data of AV-optimization in porcine hearts during BiV pacing

	AV-delay					
	50 ms	100 ms	150 ms	200 ms	250 ms	300 ms (BL)
PQ interval (ms)	53 ± 2*	102 ± 2*	151 ± 1*	202 ± 2*	254 ± 2*	304 ± 1
MAP (mmHg)	79 ± 25*	87 ± 23	91 ± 24*	91 ± 23*	88 ± 25	84 ± 24
Cardiac output aorta (l/min)	3.0 ± 0.3	3.3 ± 0.3	3.4 ± 0.4	3.4 ± 0.4	3.2 ± 0.3	3.1 ± 0.3
Stroke work (mmHg·mL)	3732 ± 1146	4316 ± 1012	4437 ± 1042	4379 ± 1123	4169 ± 1239	3828 ± 1266
LV dP/dt_{max} (mmHg/s)	1225 ± 311*	1297 ± 282	1274 ± 259	1308 ± 282	1275 ± 295	1265 ± 311
LV SP (mmHg)	95 ± 21*	102 ± 20	106 ± 22*	105 ± 21*	103 ± 22	99 ± 21
LV EDP (mmHg)	7.0 ± 2.8	8.7 ± 2.6	9.5 ± 2.1*	7.8 ± 2.4	7.4 ± 2.9*	6.9 ± 3.0
LAP_{mean} (mmHg)	8.4 ± 2.4*	7.8 ± 2.4*	6.8 ± 2.3	6.6 ± 2.2	6.6 ± 2.4	6.5 ± 2.2
LV EDV (mL)	78 ± 39	83 ± 39	90 ± 36*	87 ± 36*	83 ± 39*	80 ± 40
Diastolic MR (mL/beat)	0.3 ± 0.5	2.5 ± 1.9	4.4 ± 2.9	4.5 ± 3.3	4.3 ± 3.3	6.1 ± 4.0
Forward flow (mL/beat)	50 ± 9	53 ± 8	53 ± 6	53 ± 6	51 ± 7	51 ± 8
MR fraction (%-point)	0.9 ± 1.5	5.2 ± 4	9.5 ± 6.2	10 ± 7.2	10 ± 7.7	15 ± 10.2

Results are presented as mean ± SD ($n = 7$).
BL, baseline; EDP, end diastolic pressure; EDV, end diastolic volume; ESV, end systolic volume; LAP_{mean}, mean left atrial pressure; LV, left ventricular; LVSP, LV systolic pressure; MAP, mean arterial pressure; MR, mitral regurgitation.
*$P < 0.05$ compared with 300 ms (BL) using one-way repeated measures ANOVA followed by Student's paired samples *T*-test and Bonferroni correction.

Similar to the computer simulations and animal studies (*Figures 2 and 4*), patients showed the characteristic pattern of *E–A* wave fusion and diastolic MR at baseline (*Figure 5A*). During BiV pacing, a clear separation of the *E*- and *A*-waves was seen at AV-delays of 50% and 75% of intrinsic PR interval, while truncation of the *A*-wave occurred at shorter AV-delay (25% of intrinsic PR interval). Restoration of AV-coupling by BiV pacing at an AV-delay of 50% of intrinsic PR interval (137 ± 30 ms) resulted in a significant increase of forward mitral flow (on average +8mL/beat) and reduction of MR fraction (on average −12%-point), *Figure 5B and C*, *Table 2*.

Figure 6A presents LV pressure–volume loops of a patient during BiV (left) and RV pacing (right). When compared with baseline, BiV

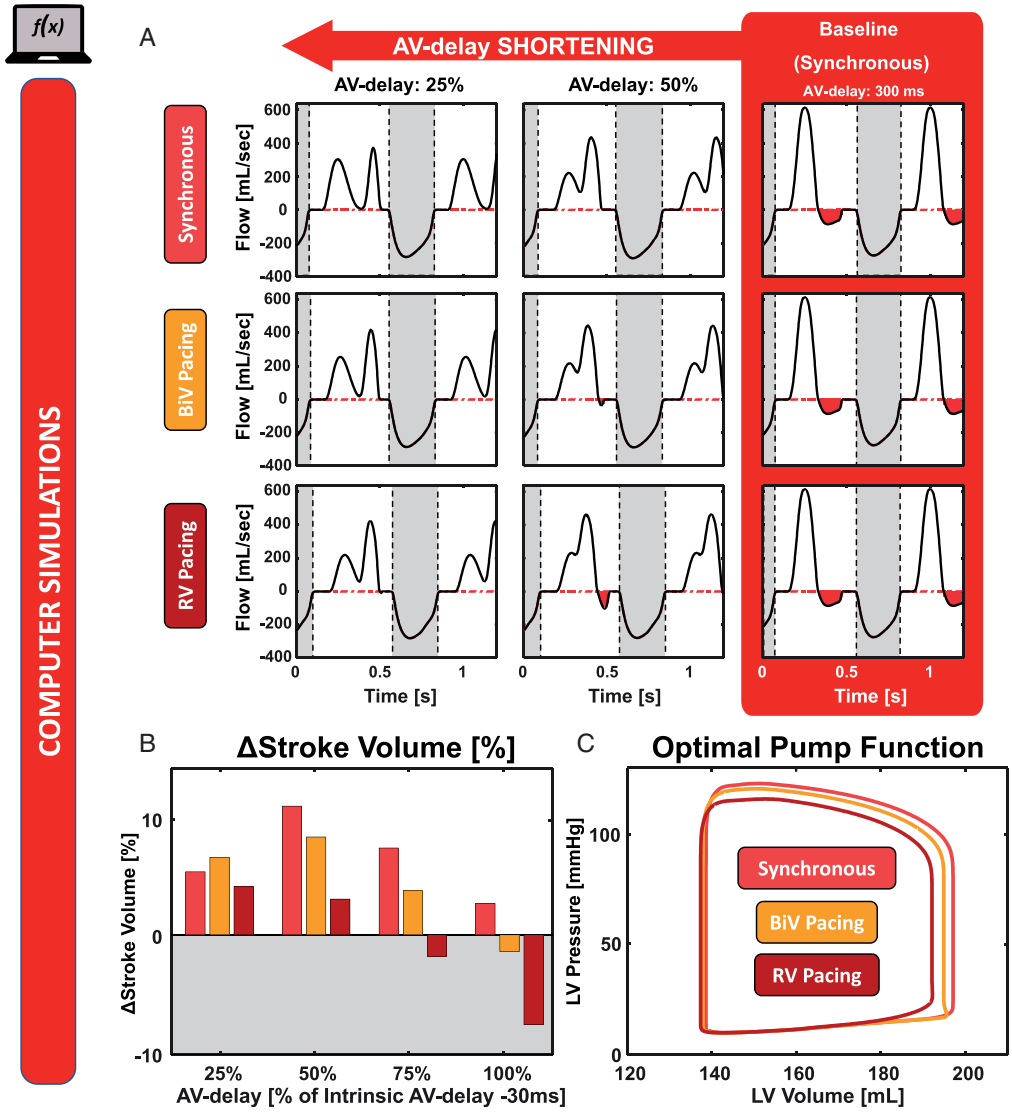


Figure 4 Effect of interventricular desynchronization on haemodynamic benefits of restoring AV-coupling. Simulation data from the protocol where restoration of AV-coupling was achieved with unchanged synchronous ventricular activation (red) or with biventricular (BiV) pacing (orange) or right ventricular (RV) pacing (purple). (*A*) Change in stroke volume. (*B*) Pressure volume loops at optimal pump function. (*C*) Mitral valve flow.

pacing increased LV stroke volume and stroke work (width and area of the loop, respectively), with the most pronounced benefit at an AV-delay of 50% of intrinsic PR interval. In contrast, RV pacing tend to reduce stroke volume and stroke work, particularly at shorter AV-delays. It can also be observed that peak LV pressure diminished during RV pacing.

In the entire cohort of patients, BiV pacing increased QRS duration moderately, whereas a more pronounced prolongation occurred by applying RV pacing (*Table 2*). BiV pacing at an AV-delay of 50% of intrinsic PR interval significantly increased LV stroke volume by 34 ± 40% (*Figure 6B*) and LV stroke work by 26 ± 31% (*Figure 6C*), when compared with baseline. The increase in LV stroke work provided by BiV pacing coincided with slight but significant increases in LV end-diastolic pressure (on average 2 mmHg) and LV dP/dt_{max} and largely unchanged systolic LV pressure (*Table 2*). In contrast, restoration of the AV-delay with RV pacing did not change or even decreased stroke volume and stroke work compared with baseline (*Table 2*). The decrease in stroke work during RV pacing at short AV-delays coincided with significant reductions in stroke volume, systolic LV pressure, and LV dP/dt_{max} (*Table 2*).

Discussion

The presented combination of computational, experimental, and clinical proof-of-principle studies provides strong evidence that restoration of AV-coupling by BiV pacing results in significant haemodynamic benefit in hearts with AV dromotropathy (evidenced by a prolonged PR interval). This benefit is caused by (i) increased ventricular filling, established by a larger forward flow across the mitral valve and less

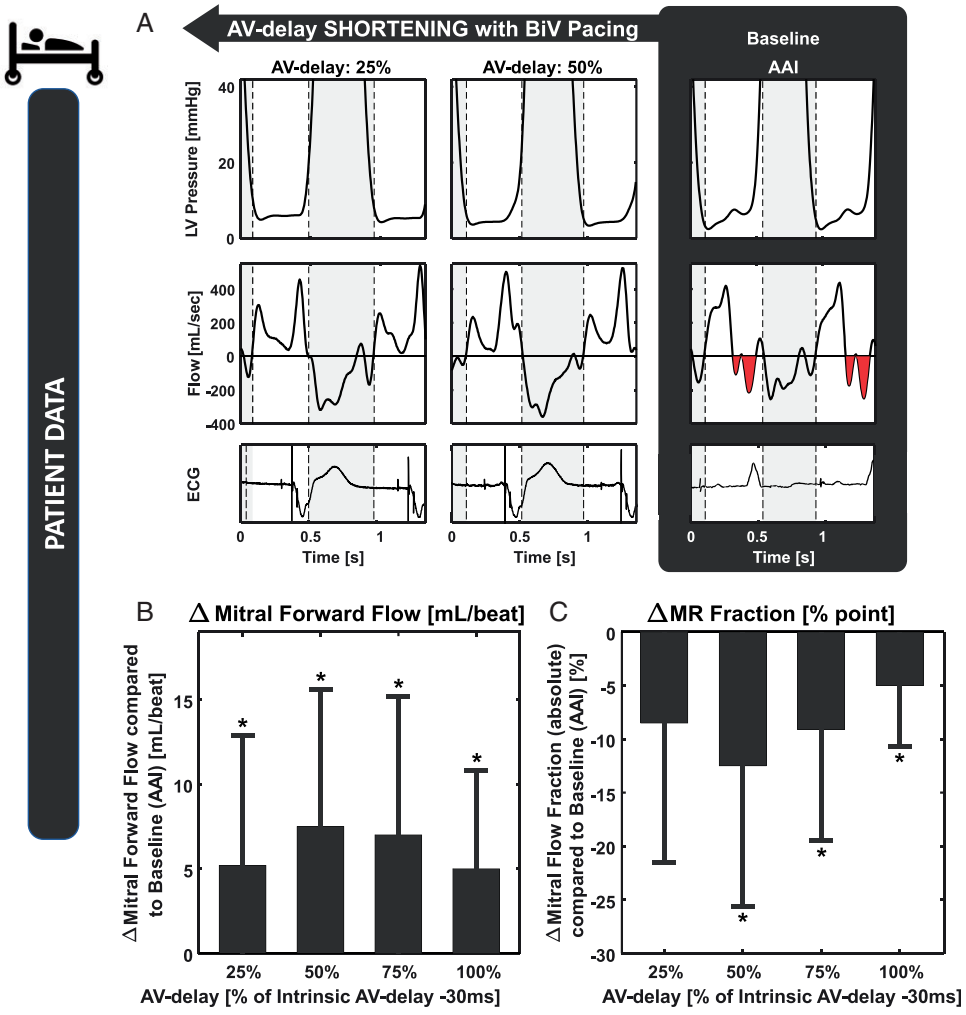


Figure 5 Haemodynamic effect of improving atrioventricular (AV)-coupling in patients. (*A*) Left ventricular (LV) pressure (Top row) and flow (Second row) and ECG (third row), as measured in a representative patient. Diastolic mitral regurgitation (MR) is presented in red. Absolute changes in (*B*) diastolic mitral forward flow, and (*C*) diastolic mitral regurgitant (MR) fraction when compared with baseline (AAI) in the entire cohort. In the ECG an atrial pacing spike is present in all conditions, in the biventricular paced beats the LV pacing spike is indicted by a large vertical bar which is followed 40 ms later by a small spike representing the RV stimulus. Mean ± SD are presented. *$P < 0.05$ when compared with baseline.

late-diastolic MR, but (ii) is attenuated by ventricular desynchronization due to RV pacing. These results indicate that the current guidelines on pacing and CRT [7] may need revision, because the lower limit of PR interval for recommending pacing therapy may be decreased (from >300 to >230 ms) and that BiV pacing is recommended. In order to avoid ventricular desynchronization, besides BiV pacing, also recently proposed modes of physiological ventricular pacing, such as His bundle, left bundle branch, and LV septum pacing[9,10] may be used to this purpose.

Restoring atrioventricular coupling provides haemodynamic improvement

A few studies in the 1990s used DDD RV pacing to restore AV-coupling.[2,3] These studies showed beneficial effects of normalization of AV-coupling in terms of reduction of diastolic MR,[2] longer filling times and larger CO[2], and higher LVEF and arterial blood pressure.[3] Notably, these studies were performed in small (12–24 patients) cohorts with variable baseline characteristics (wide and narrow QRS complex, normal, and depressed cardiac function). The results from the present study not only corroborate these findings using state-of-the-art measurements, but also extend them and provide a comprehensive understanding of mechanisms involved. The complicated interaction between (intrinsic or paced) AV-delay and ventricular dyssynchrony on haemodynamics may explain why other (unpublished) studies were not able to reproduce these results, in particular when single site pacing was used.

Improving AV-coupling is an integral part of 'conventional CRT' in patients with LBBB and/or QRS duration >150 ms (class I CRT indication) and its benefit can therefore be considered as evidence-based. Interestingly, recent analysis using the same computer model as used in the present study, and data from CRT patients indicated that

Table 2 Haemodynamic and electrocardiographic data in patients paced at various paced AV-delays (% of intrinsic PR interval—30 ms)

	AV-delay (=PR 30 ms)				
	25%	50%	75%	100%	AAI
			BiV pacing		Baseline
AV-delay (ms)	70 ± 14*	137 ± 30*	203 ± 40*	270 ± 51*	300 ± 61
QRS duration (ms)	147 ± 24*,**	149 ± 22*,**	142 ± 22**	129 ± 29	128 ± 25
LVPmax (mmHg)	110 ± 22*	115 ± 23	117 ± 24	117 ± 25	118 ± 25
Stroke volume (mL)	53 ± 19**	58 ± 20*,**	59 ± 21*	53 ± 18*	48 ± 16
Stroke work (mL·mmHg)	4993 ± 2041**	5605 ± 2263*,**	5726 ± 2369*	5273 ± 2128*	4792 ± 1992
LV dP/dt_{max} (mmHg/s)	896 ± 164**	935 ± 153**	965 ± 162**	971 ± 165*	927 ± 166
LV EDP (mmHg)	11 ± 5	13 ± 6*	13 ± 8*	11 ± 7	11 ± 6
LV EDV (mL)	208 ± 55	215 ± 56	215 ± 59	213 ± 55	215 ± 56
Diastolic forward flow (mL/beat)	65 ± 22**	69 ± 23*,**	68 ± 22*	66 ± 21*	61 ± 21
MR fraction (%)	9 ± 9*	6 ± 6*	9 ± 9*	12 ± 9*	18 ± 11
Diastolic filling time (ms)	434 ± 104*	432 ± 104	429 ± 111	415 ± 93	417 ± 87
			RV pacing		Baseline
AV-delay (ms)	70 ± 14	137 ± 30	203 ± 40	270 ± 51	300 ± 61
QRS duration (ms)	175 ± 20*	173 ± 20*	165 ± 22*	143 ± 25	128 ± 25
LVPmax (mmHg)	109 ± 19*	115 ± 22	118 ± 24	120 ± 24	118 ± 25
Stroke volume (mL)	42 ± 17	46 ± 19	48 ± 19	48 ± 18	48 ± 16
Stroke work (mL·mmHg)	3885 ± 1844*	4455 ± 2055	4811 ± 2254	4904 ± 2090	4792 ± 1992
LV dP/dt_{max} (mmHg/s)	801 ± 145*	845 ± 144*	896 ± 163	951 ± 148	927 ± 166
LV EDP (mmHg)	11 ± 7	12 ± 7	13 ± 7*	11 ± 6	11 ± 6
LV EDV (mL)	213 ± 51	220 ± 55	222 ± 56	219 ± 51	215 ± 56
Diastolic forward flow (mL/beat)	55 ± 22	59 ± 23	61 ± 24	62 ± 24	61 ± 21
MR fraction (%-point)	13 ± 12	11 ± 9	14 ± 10	17 ± 10	18 ± 11
Diastolic filling time (ms)	416 ± 99	409 ± 91	411 ± 95	414 ± 101	417 ± 87

Results are presented as mean±SD ($n = 22$).
BiV, biventricular; AV, atrioventricular; LV, left ventricular; EDP, end diastolic pressure; EDV, end diastolic volume; MR, mitral regurgitation; RV, right ventricular.
*$P < 0.05$ compared with baseline.
**$P < 0.05$ compared with RV pacing with corresponding AV-delay, using one- and two-way repeated measures ANOVA, respectively, followed by Student's paired samples *T*-test and Bonferroni correction.

improving AV-coupling in 'conventional' CRT may be responsible for more than two-thirds of the benefit of this therapy while only one-third was accounted for by ventricular resynchronization.[11] However, the feasibility, safety, and long-term efficacy of pacing-based AV-coupling in patients without LBBB and with narrow QRS complex requires further investigation in prospective clinical trials. Such studies should also provide a more precise definition of the category patients that qualify for this therapy, such as the optimal cut-off of PR interval, degree of separation of *E* and *A* wave on the mitral valve Doppler velocity recording, NYHA class, ischaemic or non-ischaemic cardiomyopathy, and LVEF. In addition, duration of the (intrinsic and paced) *P*-wave may be important to take into account, because large inter-atrial delay may safeguard LV filling in the presence of a long PR interval.

Haemodynamic improvement relates to better ventricular filling

The crucial finding of the present study is that improving AV-coupling leads to increased LV filling, thereby increasing CO at unchanged (patients) or increased (simulations, animals) blood pressure. These improvements are likely explained by the length-dependent activation of the myocardium, the cellular basis of the well-known Frank–Starling mechanism. Notably, LV dP/dt_{max} was hardly affected, whereas this is a very sensitive marker of CRT benefit in LBBB patients.[8,12] Yet, the overall haemodynamic benefit of AV-coupling in terms of CO seems at least as large as that of 'CRT'. Increases in stroke work, measured in this study using the conductance catheter technique, were on average slightly smaller than those measured during conventional CRT (28 vs. 43%).[13] However, this difference may be due to very small pressure–volume loop areas in LBBB hearts that may be associated with an artefact of the conductance catheter technique. Another important finding is that the increased LV filling during optimal AV-coupling is achieved by both improved diastolic filling pattern (i.e. larger and better separated *E*- and *A*-waves) and less diastolic MR. Finally, an important finding from the animal and simulation studies was that the improved filling was achieved while mean LA pressure was equal to or lower than baseline, indicating that the better forward pump function may even coincide with reduced backward failure.

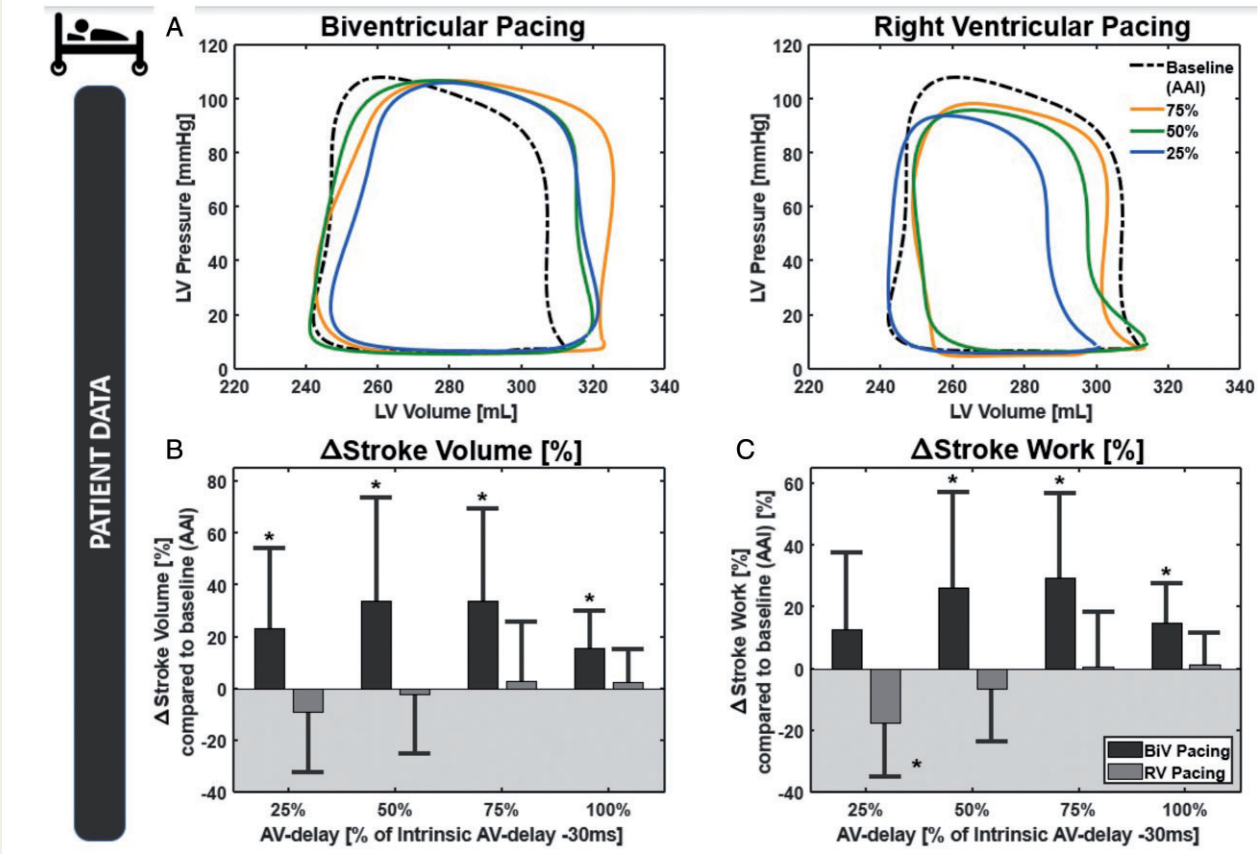


Figure 6 Haemodynamic effect of improving atrioventricular (AV)-coupling in patients during biventricular (BiV) and right ventricular (RV) pacing. (*A*) Left ventricular (LV) pressure–volume loops in a representative patient at baseline (dashed line) and at tested AV-delay settings (solid lines) during BiV pacing (left) and right ventricular pacing (right). Relative changes in stroke volume (*B*) and stroke work (*C*) when compared with baseline (AAI) for BiV (black) and RV pacing (grey) in the entire cohort. Mean ± SD are presented. *$P < 0.05$ when compared with baseline.

In the past, several studies have shown similar results concerning parts of the parameters investigated in the present study. The importance of proper AV-coupling has already been addressed by animal studies in the 1960s,[14] reporting that a properly timed effective atrial contraction is necessary for optimal LV systolic function. Similar findings were obtained in a small clinical study where echo-Doppler as well as invasive pressure and flow measurements were used. In eight patients with PR intervals >200 ms, AV-optimization using DDD RV pacing increased filling times, LV end-diastolic pressure, and CO.[15] Other clinical studies showed echo-Doppler recordings of mitral *E*- and *A*-waves with *A*-wave truncation at too short AV-delays and *E*–*A*-wave fusion combined with diastolic MR at too long AV-delays.[16,17]

The results from the present study provide the full picture with comprehensive invasive haemodynamic measurements in animals and patients, supplemented by computer simulations that enable control of experimental conditions that cannot be achieved in vivo (like disabled MR). Furthermore, the use of the first derivative of the LV volume signal of the conductance catheter provides diastolic ventricular inflow patterns, rather than velocities as is the case in echo-Doppler studies. Therefore, the forward and backward flows, determined in the present study, represent the actual blood volume displaced.

The fact that the computer model could replicate all the changes seen in the animals, indicates that the mechanism of haemodynamic improvement by optimizing AV-delay can be explained by the well-established physical and physiological principles that are incorporated in the model, such as conservation of energy, inertia of blood, and length-dependent activation of myocytes (Frank–Starling effect).

Effects of ventricular pacing-induced dyssynchrony

The RV pacing is known to increase ventricular dyssynchrony and thereby to have a negative impact on cardiac pump function.[18] Our patient and simulation data show that the benefit of normalizing AV-coupling should be weighed against the detrimental effect of pacing-induced ventricular dyssynchrony. In the present study, BiV pacing was able to acutely increase cardiac pump function in 19 out of 22 patients, indicating that the functional gain achieved by improving AV-coupling is relatively large compared with the loss of function due to BiV pacing-induced ventricular dyssynchrony. On the other hand, severe ventricular dyssynchrony occurs during RV pacing abrogates the haemodynamic benefits of restoring AV-coupling. Interestingly, shortening the AV-delay using RV pacing did not improve filling either, due to a lack of reduction in diastolic MR and no increase in

diastolic filling time or diastolic forward flow. These observations may be explained by a combination of factors, such as prolonged isovolumic contraction due to desynchronization and dyssynchronous contraction of the papillary muscles which increases the risk of diastolic MR. Our study also suggests that the presence of LV filling abnormalities, such as *E–A* wave fusion and diastolic MR, may be important selection criteria for the use of BiV pacing in patients with prolonged PR interval.

The results from the present study may also explain the lack of benefit of algorithms aiming at minimization of ventricular pacing. After all, these algorithms do so by prolonging the AV-delay, thus inducing AV dromotropathy.[19] Our study supports the idea that too aggressive prolongation of PR interval may have adverse effects on pump function and possibly clinical outcome.

Limitations

The present patient study has all the characteristics of a proof-of-principle study, showing acute haemodynamic effects in a small cohort. For ethical reasons, patients in this study all had the indication for ICD implant, so that the implant of the LV lead was only a minor extension of the medically indicated procedure. Clearly, studies in a wider population (also non-ICD indicated patients) and using long-term outcome as endpoint are required to provide further evidence for the benefit of improving AV-coupling in patients with a prolonged PR interval. Promising is that subanalyses in non-LBBB patients of the randomized MADIT-CRT[20] and RethinQ[6] trials also indicate that patients with long PR interval can benefit from BiV pacing when compared with their unpaced 'control group' counterparts.

The preclinical studies were performed in porcine hearts. While this species is frequently used for cardiovascular research, a limitation is that the amount of dyssynchrony induced by (single site) ventricular pacing is small. Therefore, for this study only BiV pacing was used to demonstrate the effect of AV-coupling at unchanged ventricular activation (BiV pacing being used for all AV-delays). Moreover, the lack of intra-thoracic negative pressure in these open-thorax experiments may have interfered with the effect of AV-interval on filling.

Conclusions

The combination of computational, experimental, and clinical studies provides strong confirmation of previous evidence that normalizing AV-coupling by BiV pacing in hearts with prolonged PR interval improves cardiac pump function. This improvement is predominantly achieved by better ventricular filling, caused by a combined effect of reduction in diastolic MR and increase in diastolic forward flow. Pacing-induced ventricular dyssynchrony, caused by RV pacing, attenuates the benefit of restored AV-coupling. Therefore, this study may pave the way for a novel pacing-based therapeutic approach in patients with HF and prolonged PR interval that is not part of current guidelines.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

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

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Fist in man implantation of a leadless pacemaker in the left atrial appendage following Mustard repair

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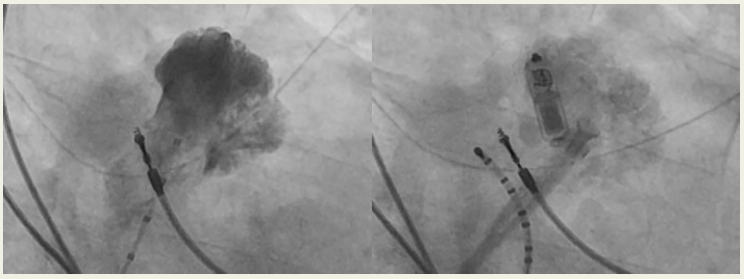
Sinus node disease is common in atrial switch patients. Transvenous and ventricular pacing can be problematic due to baffle stenosis and systemic right ventricular dysfunction, respectively.



We describe the implantation of Micra™ (Med tronic, USA) leadless pacemakers in the left atrial appendage of two patients previously treated with atrial switch operations. The left atrium was accessed via the left femoral vein using a 24-Fr Drysheath™ (Gore, USA). A Micra™ (Medtronic, USA) device was then implanted using the integrated delivery catheter (see *Figure* showing appendage injection and final position). Acceptable parameters were achieved in both cases (threshold 0.38 V at 0.24 ms, p 4.5 mV in one case, threshold 0.5 V @0.24 ms, p 1.9 mV in the other). Stability was tested using standard manoeuvres. Clinical follow-up at 6 weeks has again shown excellent pacing parameters in both patients.

These are to our knowledge the first described cases of leadless pacemaker implant in the atrium. The morphology of the left atrial appendage alongside the fact that it is readily accessed from the femoral vein makes leadless left atrial appendage pacing a feasible solution for atrial switch patients who have sinus node disease in whom both transvenous and ventricular pacing are problematic.

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