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BASIC SCIENCE

Pulse arrival time variation as a non-invasive marker of acute response to cardiac resynchronization therapy

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Aims Successful cardiac resynchronization therapy (CRT) shortens the pre-ejection period (PEP) which is prolonged in the left bundle branch block (LBBB). In a combined animal and patient study, we investigated if changes in the pulse arrival time (PAT) could be used to measure acute changes in PEP during CRT implantation and hence be used to evaluate acute CRT response non-invasively and in real time.

Methods and results In six canines, a pulse transducer was attached to a lower limb and PAT was measured together with left ventricular (LV) pressure by micromanometer at baseline, after induction of LBBB and during biventricular pacing. Time-to-peak LV dP/dt (Td) was used as a surrogate for PEP. In twelve LBBB patients during implantation of CRT, LV and femoral pressures were measured at baseline and during five different pacing configurations. PAT increased from baseline (277 ± 9 ms) to LBBB (313 ± 16 ms, $P < 0.05$) and shortened with biventricular pacing (290 ± 16 ms, $P < 0.05$) in animals. There was a strong relationship between changes in PAT and Td in patients ($r^2 = 0.91$). Two patients were classified as non-responders at 6 months follow-up. CRT decreased PAT from 320 ± 41 to 298 ± 39 ms ($P < 0.05$) in the responders, while PAT increased by 5 and 8 ms in the two non-responders.

Conclusion This proof-of-concept study indicates that PAT can be used as a simple, non-invasive method to assess the acute effects of CRT in real time with the potential to identify long-term response in patients.

Keywords Cardiac resynchronization therapy • Left bundle branch block • Dyssynchrony • Non-invasive • Heart failure • Response prediction

What's new?

- We study pulse arrival time (PAT) as an acute marker for response to resynchronization in animals and patients undergoing cardiac resynchronization therapy (CRT) implantation.
- Shortening of PAT demonstrated acute improvement by CRT in patients with long-term response to CRT, while it was not shortened in the ones that did not respond.
- PAT could be an attractive, non-invasive method for assessing acute response to CRT during implantation and optimization of CRT.

Introduction

In the left bundle branch block (LBBB), an electrical conduction defect causes delayed activation of the left ventricular (LV) lateral wall compared with the septum. This originates a highly inefficient contraction pattern that delays and slows down the rapid LV pressure rise that opens the aortic valve to start ejection.[1] The LV pre-ejection period (PEP) from the onset of ventricular electrical activation to start ejection and time-to-peak LV dP/dt (Td) are therefore prolonged.[2]

Cardiac resynchronization therapy (CRT) aims to resynchronize the LV electrical activation in patients with LBBB by simultaneously pacing

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the septum and the LV lateral wall, and has proven to be effective.[3] However, up to 40% of patients selected for CRT do not respond to, or even deteriorate after implantation,[4] so there is a high demand to improve the methods to identify which patients should receive this treatment. Suboptimal lead positioning is one of the main causes of diminished response to CRT in addition to poor device programming, inadequate viable myocardium, lack of baseline dyssynchrony, and heart failure severity.[5] While most research may be focused on improving the selection methods before CRT implantation, there may also be considerable benefits of methods that can measure the acute effect of CRT during and after implantation to address both lead positioning and device programming. After implantation, device programming could be tailored to patient-specific needs using fusion-optimized intervals.[6] Thus, a method that can be used to guide optimal placement of the pacing electrodes and programming of the pacemaker device may potentially solve issues related to poor outcomes and could increase the response rate of CRT. Future developments in CRT may also introduce more advanced pacing and programming options, thus having acute feedback to optimize the therapy for each patient could be of great value.

Although studies have shown that measuring acute haemodynamic parameters helps predict reverse remodelling and improves the response rate to CRT,[7] other studies have presented conflicting results regarding these haemodynamic parameters.[4] CRT resynchronizes the septum and the LV lateral wall, and we found that this reduces both ESV and EDV, shifting the entire pressure-volume loop leftward, thus reducing preload.[8] This reduction may be a reason for the conflicting results as most haemodynamic parameters are preload dependent. In this way, improvements by resynchronization may be masked by a preload-induced reduction.[6] Hence, there is a need for a preload-independent haemodynamic marker of acute response to CRT.

We recently proposed Td as an acute marker of response to CRT.[2] This methodology, which requires LV catheterization, provides a robust and accurate measurement of the LV electromechanical timing with potentially great benefits to the patient. However, despite cardiac catheterization having a low incidence of complications and becoming safer over the past decades, the procedure still entails some risk for the patient.[9] Thus, non-invasive methods could be advantageous for acute and long-term assessment in patients. Echocardiography has been the most recognized method for pacemaker optimization.[10] Furthermore, measurement of PEP by echocardiography has been proposed as an acute marker of response to CRT.[11] However, echocardiography is still not used for acute assessment of response to CRT in clinical practice during the implantation, probably due to its high demand for time, personnel, and space. To overcome this problem, a method that can assess the effect of CRT in-real time with a simple interface requiring little space and personnel involvement would be ideal. In post-implantation studies, a simple non-invasive measurement of changes in PEP to improve CRT settings has been used.[12,13] The changes in PEP were assessed as the changes in the pulse arrival time (PAT) to arterial pulse curves measured at the radial artery with tonometry. The PAT is the time from ventricular activation until the upstroke of the pulse at the arterial measurement site and is hence the sum of the PEP and the time it takes for the pulse wave to travel from the aortic valve to the measurement site. Thus, assuming that there is no acute change in the arterial pulse wave velocity when CRT settings are altered, a change in PAT will reflect a change in PEP.

In this combined animal and patient study, we tested the performance of the PAT method during the implantation of CRT to evaluate its potential to serve as an acute response parameter. We hypothesized that there would be a distinct shortening of PAT with successful CRT and a larger reduction in PAT when pacing from an optimal position compared with any other. For this purpose, different lead placements and pacing configurations were tested to obtain a range of improvements from the therapy, which would indicate if the methodology had the potential of being used during pacemaker optimization. Furthermore, the preload dependence of PEP and PAT is not clear. Time-to-peak LV dP/dt was initially proposed as preload-independent marker of contractility,[14] while in contrast, Chan *et al.*[15] proposed monitoring changes in PEP and PAT as an early marker of central hypovolemia. We, therefore, also studied the sensitivity of PAT measurements to changes in preload and evaluated its accuracy compared with Td and stroke work (SW).

Methods

Experimental animal study

Animal preparation

Six mongrel canines of either sex (three males) and a weight of 32 ± 3 kg were used in the validation of the measurement of PAT. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Norwegian Food Safety Authority (FOTS ID: 8628). The animals were supplied by the Centre for Comparative Medicine (Oslo University Hospital, Rikshospitalet, Oslo, Norway). The animals were ventilated, anaesthetized by propofol and opioids, and surgically prepared as previously described,[16] including the partial splitting of the pericardium from apex to base and loose re-suturing of the pericardial edges after completed instrumentation. Sonometric crystals (Sonometrics, London, Ontario, Canada) were used to estimate LV volume. A pair was implanted subendocardially in a long-axis-diameter pair (apex to base), and two other pairs were placed subendocardially in the LV equator (posterior to anterior wall and septum to the lateral wall). From these three diameter pairs, the continuous LV volume was estimated using the formula[17]:

$$V = \pi 6 \cdot (longaxisdiameter \cdot shortaxisdiameter_1 \cdot shortaxisdiameter_2)$$

The four crystals placed in the equatorial plane were equipped with electrodes for measuring intramyocardial electromyograms to assess regional electrical activation times of the LV.

An epicardial pacemaker lead was attached to the right atrium, allowing measurements at a fixed heart rate. To facilitate CRT by biventricular pacing, a right ventricular (RV) lead was placed on the septum in the RV apex. Three epicardial pacing leads were placed on the LV free wall: in a lateral position, in an apical position, and close to the base on the anterior wall. The reason for placing three LV leads was to allow biventricular pacing from different LV locations to vary the degree of improvement. An additional pacing electrode was placed basally on the RV free wall for pacing-induced dyssynchrony. The pacing was performed with 40 and 70 ms AV delays to avoid fusion with intrinsic conduction. LV pressure was measured with a calibrated micromanometer-tipped catheter (MPC-500; Millar Instruments Inc., Houston, TX, USA) which was drift adjusted using a fluid-filled catheter in the left atrium.[16] In order to measure changes in PAT, a pulse transducer (TN1012/ST; PowerLab, ADInstruments LTD, Oxford, UK) was placed on the hind limb to mimic a distal position of the sensor in humans. The sensor used a piezo-electric element to convert force from the arterial pulse wave applied to the surface of the transducer into an electrical analogue signal. The strap of the sensor was adjusted to capture a signal of adequate strength. The transducer was then left in place during the data acquisition without having to be held and was only adjusted when the signal quality was poor.

Experimental protocol

Data were obtained at a fixed heart rate by atrial pacing at 120 beats per minute in all settings. After baseline recordings, RV free wall pacing was turned on to induce pacing-induced dyssynchrony to mimic an LBBB activation pattern. LBBB was subsequently induced by radio-frequency ablation (Celsius Catheter; Biosense Webster, Inc), with confirmation of successful induction by QRS widening, limb lead R wave notching, and LV contraction patterns. When applying biventricular CRT, the three different LV pacing locations were tested in combination with the lead on the septum in the RV apex. All pressures, sonomicrometry, and pulse wave data were recorded simultaneously at 200 S/s.

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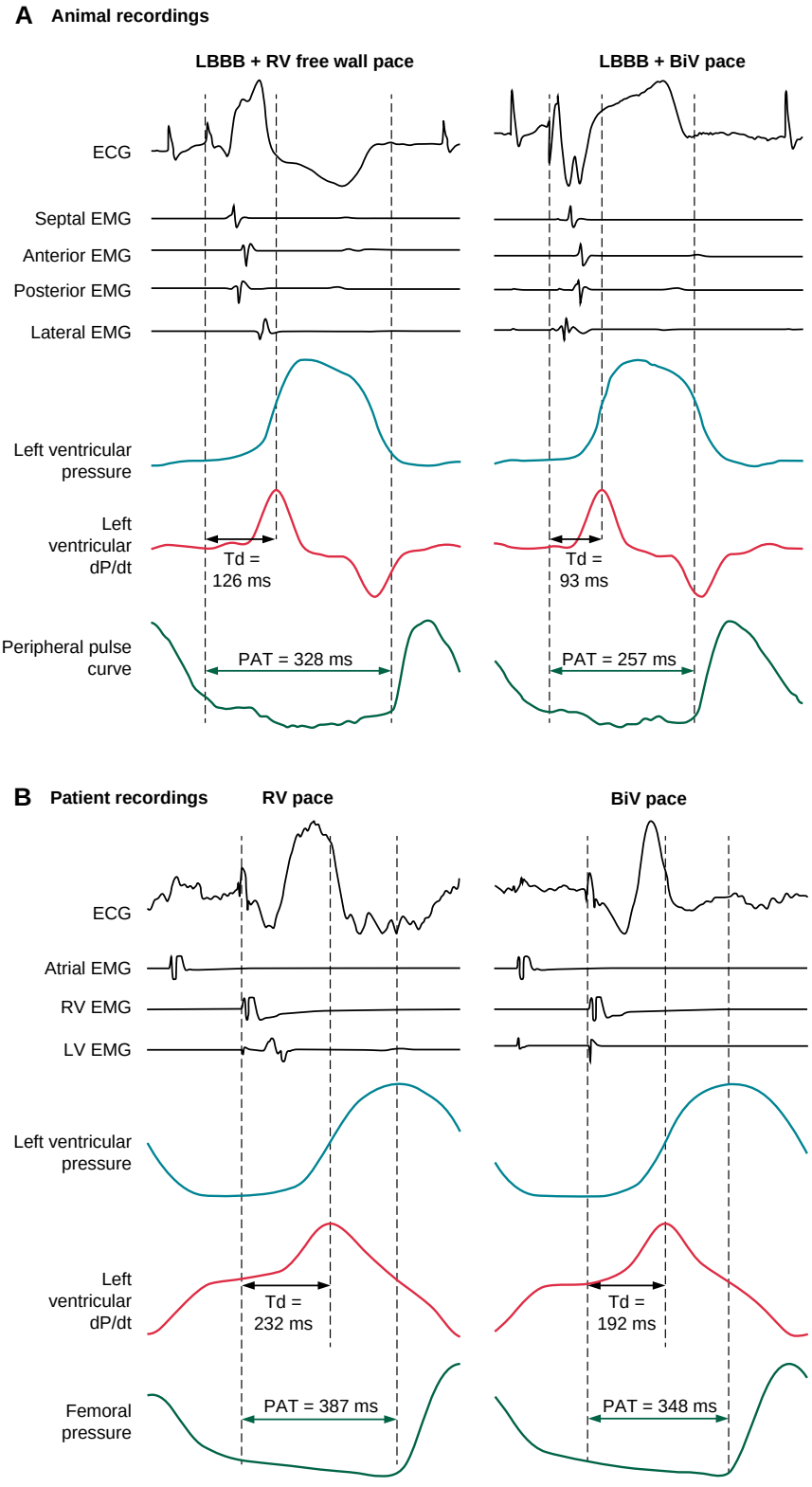

Figure 1 Measurements and assessment of the changes in PAT and Td in a representative animal in (*A*) and in a representative patient in (*B*). In the left subpanel in *A*, signals were recorded during LBBB with RV free wall pacing. There is a dyssynchronous contraction with wide QRS, where the electrical activation sequence is early in the septal electrode and last in the lateral one. In the right subpanel, CRT abolished the dyssynchronous contractions at start systole, reducing the delay of pressure rise; hence, both PAT and Td are shortened. The left subpanel in *B* shows signals recorded during a heartbeat with LBBB and RV pacing and the right subpanel with BiV pacing. In the right subpanel, BiV pacing resynchronizes the electrical activation and shortens Td and PAT. BiV, biventricular; CRT, cardiac resynchronization therapy; dP/dt, pressure derivative; EMG, electromyogram; LBBB, left bundle branch block; LV, left ventricle; PAT, pulse arrival time; RV, right ventricle; Td, time-to-peak left ventricular dP/dt.

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Table 1 Haemodynamic values at baseline, RV free wall pacing, LBBB, and biventricular pacing (BiV) for all animals ($n = 6$)

	Baseline	RV—free wall	LBBB	BiV—lateral wall	BiV—apex	BiV—base
LV end-diastolic volume (mL)	70 ± 18	70 ± 20	72 ± 19	69 ± 18*	70 ± 19*	69 ± 18*,§
Stroke work (mL·mmHg)	1275 ± 271	1045 ± 195†	924 ± 124†	877 ± 166†	1070 ± 195†,*	928 ± 147†
Stroke volume (mL)	15 ± 2	13 ± 4	13 ± 2	12 ± 3	15 ± 3‡	13 ± 2
Cardiac output (mL/min)	1752 ± 255	1613 ± 426	1689 ± 265	1518 ± 324	1951 ± 407‡	1624 ± 333
Ejection fraction (%)	22 ± 4	20 ± 2	19 ± 3†	19 ± 6	23 ± 4*,‡	20 ± 6
LV dP/dt_{max} (mmHg/s)	1503 ± 67	1303 ± 178†	1198 ± 173†	1709 ± 229$^{\dagger,\phi,*}$	1629 ± 152$^{\phi,*}$	1662 ± 193$^{\dagger,\phi,*}$
Stroke work preload-corrected (mL·mmHg)	1117 ± 306	772 ± 261†	627 ± 144†	776 ± 97†	886 ± 170†,*	814 ± 73†,*
Time-to-peak LV dP/dt (ms)	96 ± 8	150 ± 10†	122 ± 10$^{\dagger,\phi}$	107 ± 8$^{\dagger,\phi,*}$	107 ± 6$^{\dagger,\phi,*}$	109 ± 7$^{\dagger,\phi,*}$
Pulse arrival time (ms)	277 ± 9	340 ± 23†	313 ± 16$^{\dagger,\phi}$	290 ± 16$^{\phi,*}$	295 ± 16$^{\dagger,\phi,*}$	296 ± 8$^{\dagger,\phi,*}$

Values are mean ± SD.
BiV, biventricular; BiV—anterior, biventricular pacing with the LV lead placed on the anterior wall, BiV—apex, biventricular pacing with the LV lead placed near the apex; BiV—lateral wall, biventricular pacing with the LV lead placed on the lateral wall; LV, left ventricle; LV dP/dt_{max}, maximum time derivative of left ventricular of left ventricular pressure; RV, right ventricle.
$^{\dagger}P < 0.05$ compared with baseline.
$^{\phi}P < 0.05$ compared with RV free wall.
$^{*}P < 0.05$ compared with LBBB.
$^{\ddagger}P < 0.05$ compared with BiV—lateral wall.
$^{\S}P < 0.05$ compared with BiV—apex.

Pulse arrival time measurements and signal processing

All signals were transferred in real-time from the recording system to a data acquisition unit (PowerLab, ADInstruments LTD) with each event logged in the LabChart Pro 8.0 software (ADInstruments LTD). QRS onset was marked as the first fluctuation above the isoelectric line. When pacing, the edge of the first deflection of the stimulus artefact was used as a reference. We measured PAT as the average of the time interval between QRS or pacing onset and onset of the pulse wave measured with a pulse transducer on five subsequent beats after full capture of both atrium and ventricle (*Figure 1A*). Time-to-peak LV dP/dt was measured from the same starting point to peak LV dP/dt on five subsequent beats. We have previously observed an approximate 15 ms delay from pacing until capture.[2] Hence, 15 ms was added to PAT baseline recordings where QRS onset was used instead of the deflection of the pacing artefact to correct for this difference between paced and non-paced beats.

Preload dependency

In order to assess the preload dependency of Td and PAT, we made continuous recordings in each experiment where transient caval veins constrictions were performed. This resulted in a gradual reduction of end-diastolic volume (EDV), which allowed measurements of the variation of all indices with variation in preload. In addition to that, to evaluate how LV function was altered during the different settings independently of changes in preload, we used heartbeats with identical EDV found from these transient vena cava constrictions performed in all settings to calculate SW at identical EDV. This preload-corrected SW, SW_{EDV}, was obtained from the beats with the highest common EDV values from baseline, LBBB and CRT recordings and used as an index of global cardiac performance.[17]

Clinical study

Study population

We included patients undergoing CRT implantation from two different acute observational studies approved by the Regional Committees for Medical and Health Research Ethics in Norway.[2] Twelve of these patients had femoral artery pressure recordings, which allowed measurements of PAT, and these twelve were included in this proof-of-concept study. The study was conducted following the principles of the Declaration of Helsinki. Written, informed consent was obtained from all patients. Inclusion criteria were sinus rhythm, New York Heart Association functional Classes II and III heart failure on optimal medical therapy, LBBB morphology, QRS duration larger than 130 ms and an LV ejection fraction (EF) <35%. Exclusion criteria were age <18 years and above 80 years, ongoing atrial fibrillation, and complete atrioventricular block. An echocardiogram was performed in all patients before implantation and after more than six months of follow-up.

Device implantation and intervention

Device implantation (CRT devices from Medtronic Inc., Fridley, MN, USA) followed a standard left subclavian approach with a subcutaneous pocket. The RV lead was positioned in the apical endocardial portion of the right ventricle, while the LV lead (Attain Performa [4298, 4398, 4598]; Medtronic Inc.) was positioned first in the anterior portion of the LV before permanent positioning in a lateral vein in all patients to test different placements. All positions were confirmed by biplane fluoroscopic imaging. The pacing was performed in an atrioventricular synchronized fashion with a fixed AV delay (<80% of the intrinsic AV delay) for each patient to ensure proper biventricular stimulation. Confirmation of capture was carried out by visual inspection of the surface electrocardiogram (ECG). The heart rate was set at 10% above the intrinsic rate in sinus rhythm, and intrinsic AV delay was measured. Sequential biventricular pacing was performed with the EPS 320 cardiac stimulator (Micropace EP Inc., Santa Ana, CA, USA) connected to the implanted leads with alligator clips. A 3.5 Fr pressure sensor catheter (Micro-Cath™, Millar Instruments Inc.) was positioned through a 6 Fr delivery catheter from the right femoral artery to the LV cavity. Heparin was given as a bolus of 100 IE/kg IV. A fluid-filled pressure sensor was connected to the 6 Fr introducer sheet in the femoral artery for femoral artery pulse curve measurements.

Signal processing

Electrophysiology signals and ECGs were collected with the BARD Pro EP recording system and the Clearsign Amplifier (Boston Scientific Inc., Marlborough, MA, USA). LV pressure was measured with the 3.5 Fr Micro-cath pressure catheter and the PCU-2000 Pressure Control Unit (Millar Instruments Inc.). All signals were transferred in real-time from the recording system to a data acquisition unit (PowerLab, ADInstruments LTD), with each event logged in the LabChart Pro 8.0 software (ADInstruments LTD). Pressures were then filtered with a low-pass filter of 15 Hz to remove noise.

In the patients, PAT was measured using the femoral artery pressure recordings and quantified as the time interval between QRS or pacing onset and the first deflection in the femoral pressure curve (*Figure 1B*). We used five subsequent beats after full capture in all measurements, and PAT and Td were corrected at baseline by adding a 15 ms delay as described above.

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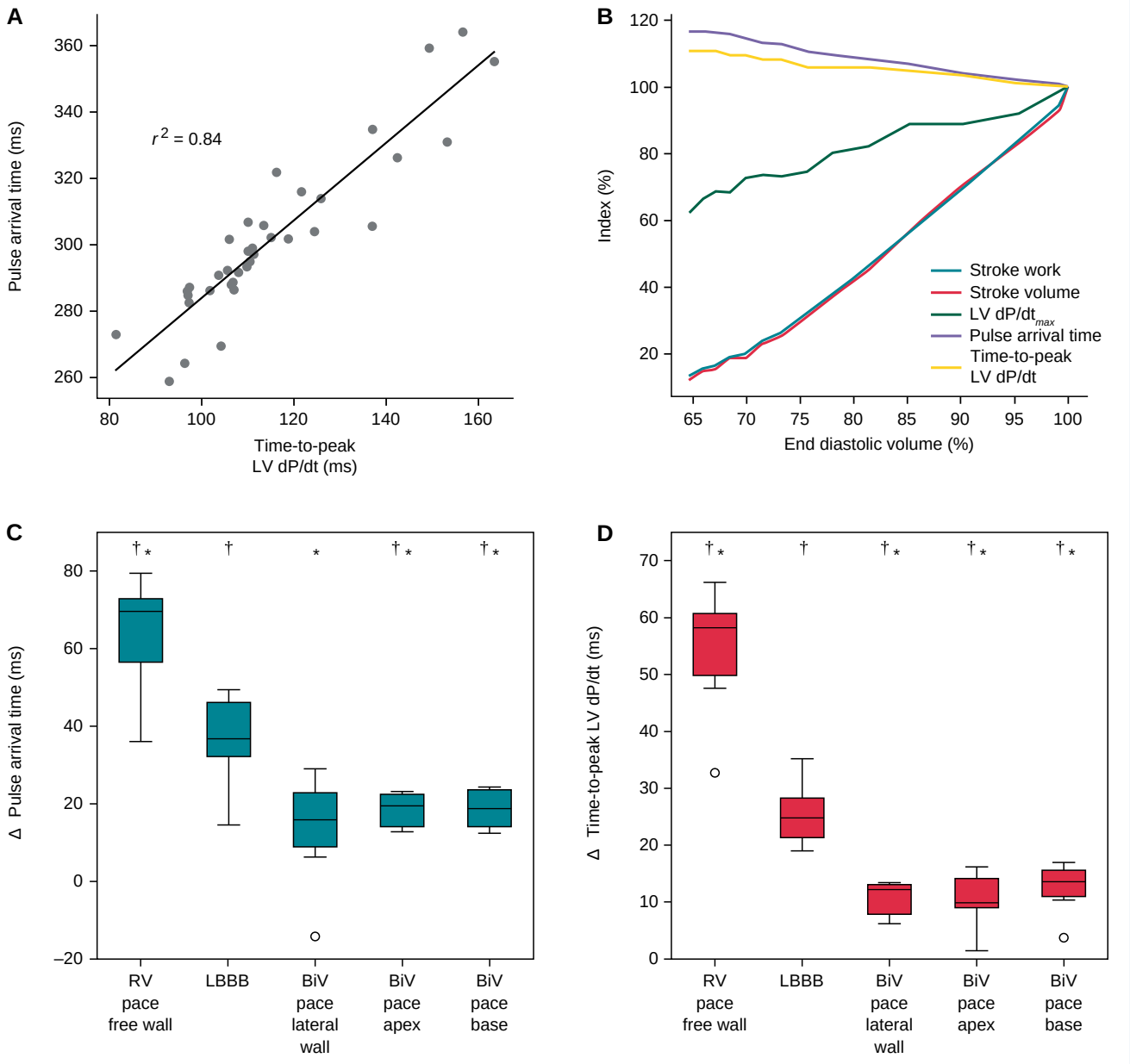

Figure 2 Results from the animal study. *(A)* Correlation between PAT and Td was calculated for all animals with all pacing modes and intrinsic conduction with narrow QRS pooled. *(B)* Preload dependence of haemodynamic indices in a representative animal. The plot shows the indices as the end-diastolic volume (EDV) was reduced (towards the left) during the constriction of the caval veins. The values are in percent of the initial values at the start of constriction when EDV is at its highest (100%). The pressure and volume indices are drastically reduced with a reduction of preload, while PAT and Td are much less preload dependent with a small increase with lower EDV. *(C and D)* Box plots of changes in PAT and Td, respectively, relative to baseline from the six animal experiments. Induction of LBBB increased both indices, while CRT returned them closer to baseline values. RV free wall pacing resulted in an additional prolongation due to the extra time for the activation to reach the LV as explained in the text. Pacing with the LV lead on the lateral wall shortened PAT the most. BiV, biventricular; CRT, cardiac resynchronization therapy; dP/dt, pressure derivative; LBBB, left bundle branch block; LV, left ventricle; PAT, pulse arrival time; RV, right ventricle; Td, time-to-peak left ventricular dP/dt. †$P < 0.05$ compared with baseline, *$P < 0.05$ compared with LBBB.

Cardiac resynchronization therapy response

Programming of the device, including selecting the LV pacing electrode, was carried out at the physicians' discretion. At a follow-up of more than 6 months, patients were classified as volumetric responders or volumetric non-responders with a cut-off at a 15% reduction in end-systolic volume (ESV). In order to reduce any possible bias caused by the labelling of response, the investigators in charge of analysing the data were blinded to the response of each patient under study.

Statistical analyses

All statistical analyses were computed with SPSS software (version 28; SPSS Inc, Chicago, IL, USA). No statistical power calculation was conducted

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Table 2 Variation in percentages of different parameters when EDV is reduced by approximately 5, 10, and 20%

ΔEDV	ΔTd	ΔPAT	ΔLV dP/dt$_{max}$	ΔSW
−4.3 ± 0.6%	2.1 ± 1.1%	2.1 ± 0.6%	−6.4 ± 5.9%	−15.6 ± 4.1%
−9.8 ± 0.8%	4.1 ± 1.4%	6.6 ± 3%	−9.6 ± 9.4%	−38.4 ± 10.9%
−19.6 ± 0.8%	7.4 ± 3.1%	14.4 ± 4.6%	−26.5 ± 6.5%	−64.3 ± 8.7%

Values are mean ± SD.
EDV, end-diastolic volume; LV, left ventricle; LV dP/dt$_{max}$, maximum time derivative of left ventricular pressure; PAT, pulse arrival time; SW, stroke work; Td, time-to-peak LV dP/dt.

before the study as it was intended as a proof of concept. The sample size in this study is therefore relatively low and the statistical tests must therefore be considered with caution. The normality of distributions was determined using Shapiro–Wilks test. To test for significant effects of the interventions, we used a two-tailed Student's paired sample *t*-test on those with normal distribution and Wilcoxon signed-ranks test for the rest. Statistical significance was determined as $P < 0.05$. All values represent the mean of five consecutive heart cycles. Values are reported as mean ± SD. For the correlation analysis, the Pearson correlation coefficient was computed. No outliers have been excluded from the statistical tests.

Results

Experimental animal study

Haemodynamic values from the interventions of the animal study are reported in *Table 1*. After inducing dyssynchrony, SW, SW$_{EDV}$, EF, maximum time derivative of left ventricular pressure (LV dP/dt$_{max}$), Td, and PAT showed significant changes. EDV was not significantly increased after induction but was subsequently reduced with biventricular pacing from the lateral wall and base positions.

We found a strong correlation between PAT and Td (*Figure 2A*). *Figure 2C* shows the changes in PAT and Td from baseline with RV free wall pacing, LBBB, and biventricular pacing. PAT increased from baseline (277 ± 9 ms) to LBBB (313 ± 16 ms, $P < 0.05$) and shortened with biventricular pacing (290 ± 16 ms, $P < 0.05$). There were no significant changes between pacing sites for neither of the two variables and there were no significant differences in preload-corrected SW as a reference for differences in function (*Figure 2C*, *Table 1*). As can be seen in *Table 1*, RV free wall pacing before induction of LBBB resulted in larger prolongations of Td and PAT than LBBB. The difference was consistent with a prolonged time to activate the septum: the time from first ventricular electrical activation to septal EMG activation was 25 ± 8 ms longer ($P < 0.05$) when pacing from the RV free wall than during LBBB, signifying that it takes longer for the activation to reach the LV in the former case.

Preload dependency

There was a relatively modest preload dependency of PAT and Td compared with the other conventional parameters as seen in the example in *Figure 2B* and the pooled data in *Table 2* from the analyses during gradual caval constriction. PAT and Td increased slightly with reduced preload, while the other parameters showed marked reductions. CRT decreased EDV on average by 4% from LBBB. The average preload-induced changes for this degree of decrease of EDV can be seen in *Table 2*: At an approximately 5% decrease of EDV, an average of 2% increase can be expected in PAT and Td, while a reduction of more than 6% and 15% would be expected in LV dP/dt$_{max}$ and SW, respectively.

Clinical study

In the patients, the changes in PAT induced by the five different pacing configurations relative to LBBB were consistent with the changes in Td: $r^2 = 0.91$ between ΔPAT and ΔTd (*Figure 3A*). The Bland–Altman analysis (*Figure 3B*) showed that the bias of ΔPAT compared with ΔTd was 4.3 ms with limits of agreement at -9.5 and 18.1 ms. *Table 3* presents the acute response parameters (LV dP/dt$_{max}$, Td, and PAT) for each pacing intervention with all patients pooled as well divided into responders and non-responders.

Cardiac resynchronization therapy response

At six months follow-up, ten patients were classified as CRT responders and two as non-responders with an ESV reduction <15% where both also had a decrease in EF (*Table 4*). The two patients classified as non-responders had infarcted regions confirmed by late gadolinium enhancement and had had coronary interventions in the past, both of which are associated with non-response. When pooling all patients, LV dP/dt$_{max}$ showed a significant increase from all pacing positions. On the other hand, while PAT and Td exhibited a shortening with both biventricular positions, they were only significantly shortened when paced biventricularly from the lateral wall, which was the presumed best placement that was tested.

As there were only two non-responders, statistical significance could not be evaluated. However, both patients exhibited an increase in PAT and Td relative to LBBB regardless of the pacing configuration. In contrast, LV dP/dt$_{max}$ increased for some pacing configurations (*Table 3*).

Figure 3C shows the changes in PAT and Td relative to LBBB values for all pacing configurations. The two non-responders are marked separately and showed a distinct increase of Td and PAT from LBBB in all pacing configurations. It can be observed how both PAT and Td only had a small change with RV pace. Both indices were shortened in all ten responders with the biventricular pace with the LV lead on the lateral wall, the presumed best placement, beyond any other configuration in contrast with the two non-responders which showed an increase of these indices.

Discussion

The present study highlights the potential value of PAT as a sensitive acute non-invasive marker of CRT response. We investigated the immediate response of this index relative to LV dyssynchrony with different setups and pacing configurations. PAT was measured as the time between the electrical onset and the foot of the peripheral pressure waveform. It is therefore equivalent to the sum of the PEP and the time taken for the pressure wave to travel from the aortic valve to the peripheral artery which depends on the speed of the pressure wave. With CRT, the ventricular contraction becomes more efficient, shortening the time it takes to open the aortic valve. Thus, unless there is a large change in blood pressure, the pulse wave velocity will presumably remain constant during CRT testing, and any changes in PAT that occur when changing pacing can be attributed to changes in the PEP.[15,18]

Our results agreed with this, as we found that the accuracy of PAT to estimate relative changes in LV function was comparable to that of Td, a

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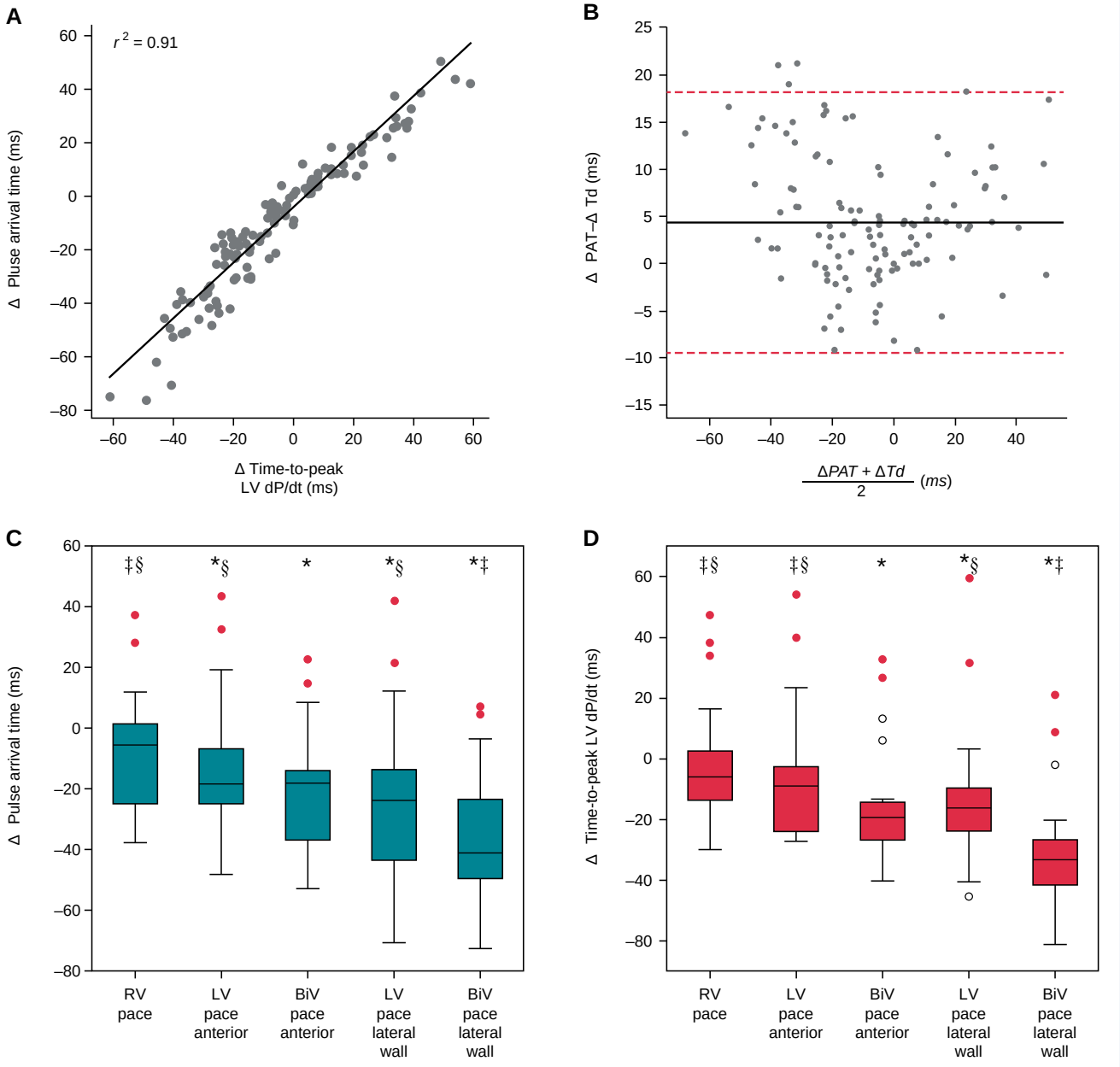

Figure 3 Results from the patient study. (*A*) Correlation between PAT and Td was calculated for all patients with all pacing modes pooled. (*B*) Bland–Altman plots showing the agreement between ΔPAT and ΔTd. The bias (1.96 SD) was 4.3 (13.8) ms. The data were pooled from all patients. Black, solid line indicate the bias, while dashed lines signify bias ± 1.96 SD. (*C and D*) Box plots from the 10 responders of changes in PAT and Td, respectively, relative from LBBB with the two non-responders added as filled in circles. Biventricular pacing with LV lead placement on the lateral wall created a greater shortening of the indices than pacing from an anterior position. The two non-responders showed no reduction of either PAT or Td in any pacing configuration. BiV, biventricular; LBBB, left bundle branch block; LV, left ventricle; PAT, pulse arrival time; RV, right ventricle; SD, standard deviation; Td, time-to-peak left ventricular dP/dt; ΔPAT: relative change in pulse arrival time from LBBB. ΔTd, relative changes in time-to-peak LV dP/dt from LBBB. **P*<0.05 compared with LBBB. ‡*P*<0.05 compared with BiV pace anterior. §*P*<0.05 compared with BiV pace lateral wall.

surrogate of PEP, that has shown potential as a biomarker to identify dyssynchronous heart failure and to help optimize CRT.[2] There is significant variation in PAT between individuals as a result of differences in blood pressure and vascular compliance. To avoid this affecting interpretation of our results, we analysed the changes in PAT for each subject. The correlation between changes in Td and PAT was high in animals and patients for different pacing sites and configurations. As this method can be applied non-invasively using a wide variety of transducer sensors, it does not require much in terms of additional procedures or equipment.

A further advantage of both PAT and Td is that they are less preload dependent than the more conventional parameters of LV dP/dt_{max}, EF, and SW. We observed an average preload reduction of 4 ± 2% when pacing in the animal experiments. Based on our preload sensitivity

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Table 3 Acute CRT response indices in the patients during baseline (LBBB), biventricular pacing (BiV), RV pacing, and LV pacing

$n = 12$	LBBB	BiV—anterior	BiV—lateral wall	RV pace	LV pace—anterior	LV pace—lateral wall
All patients ($n = 12$)						
LV dP/dt_{max} (mmHg/s)	775 ± 203	875 ± 222*	967 ± 246*	$827 \pm 198^{‡,§}$	905 ± 232*	$971 \pm 272^{*,‡}$
Time-to-peak LV dP/dt (ms)	182 ± 26	172 ± 20	$157 \pm 17^{*,‡}$	$183 \pm 19^{‡,§}$	$183 \pm 22^{‡,§}$	$174 \pm 22^{§}$
Pulse arrival time (ms)	308 ± 50	293 ± 41	$276 \pm 39^{*,‡}$	$305 \pm 41^{‡,§}$	$301 \pm 42^{‡,§}$	$290 \pm 38^{§}$
Responders ($n = 10$)						
LV dP/dt_{max} (mmHg/s)	787 ± 202	$913 \pm 200^{*}$	$1012 \pm 225^{*,‡}$	$859 \pm 175^{*,‡,§}$	$950 \pm 208^{*}$	$1015 \pm 261^{*,‡}$
Time-to-peak LV dP/dt (ms)	189 ± 22	171 ± 20*	$155 \pm 18^{*,‡}$	$183 \pm 20^{‡,§}$	$180 \pm 21^{‡,§}$	$170 \pm 22^{*,§}$
Pulse arrival time (ms)	320 ± 41	298 ± 39*	$280 \pm 37^{*,‡}$	$310 \pm 37^{‡,§}$	$304 \pm 40^{*,§}$	$291 \pm 39^{*,§}$
Non-responders ($n = 2$)						
LV dP/dt_{max} (mmHg/s)	516, 911	469, 902	530, 954	452, 879	480, 879	547, 954
Time-to-peak LV dP/dt (ms)	164, 134	197, 161	173, 155	198, 173	218, 174	195, 194
Pulse arrival time (ms)	292, 205	306, 228	296, 213	329, 233	335, 238	313, 247

Values are mean ± SD, while for the two non-responders, both individual values are shown.
BiV, biventricular; BiV—anterior, biventricular pacing with the LV lead placed on an anterior position; BiV—lateral wall, biventricular pacing with the LV lead placed on the lateral wall; LBBB, left bundle branch block; LV, left ventricle; LV dP/dt_{max}, maximum time derivative of left ventricular pressure; LV pace—anterior, LV pace from an anterior position; LV pace—lateral wall: LV pace from the lateral wall; RV, right ventricle.
*$P < 0.05$ compared with LBBB.
‡$P < 0.05$ compared with BiV pacing—anterior.
§$P < 0.05$ compared with BiV pacing—lateral wall.

Table 4 Follow-up data of non-responders to CRT

Patient	Time of recordings	QRS duration (ms)	LV dP/dt_{max} (mmHg/s)	Td (ms)	PAT (ms)	Pacing	EF (%)	ESV (mL)	EDV (mL)	SV (mL)	CO (L/min)
1	Preimplantation	163	516	164	292	LBBB	22	363	463	101	7
	Post-implantation	186	530	173	298	BiV-lat	19	413	512	99	7
2	Preimplantation	142	893	127	197	LBBB	36	128	201	73	4
	Post-implantation	161	954	156	221	BiV-lat	29	117	163	47	3

Values are reported as mean. QRS duration, LV dP/dt_{max}, Td and PAT were acute markers obtained during implantation. EF, ESV, EDV, SV, and CO were obtained before the intervention and six months after.
BiV, biventricular; BiV-lat, biventricular pacing with LV lead in the lateral wall; CO, cardiac output; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LBBB, left bundle branch block; LV dP/dt_{max}, maximum time derivative of left ventricular pressure; PAT, pulse arrival time; SV, stroke volume; Td, time-to-peak LV dP/dt.

analysis, the conventional parameters, LV dP/dt_{max} and SW, showed a reduction in the function of more than 6 and 15% each for this level of reduced EDV, while PAT and Td only increased (i.e. indicating impaired function) by 2% or about 6 and 2 ms, respectively. On average, CRT shortened PAT close to 20 ms. In theory, the reduction in preload caused by pacing would conceal part of the shortening of PAT. We were able to test this as the caval constriction allowed comparison of beats at identical EDV, i.e. when preload alterations were cancelled out. We thus compared the change in PAT from LBBB to CRT without correcting for reduction in EDV and at identical EDV and found that on average PAT shortened 9 ms more at identical EDV. Despite this variation with preload, the acute changes in PAT that occur when pacing are big enough to be statistically significant and could therefore be of clinical use.

Increased heart rate shortens the different cardiac phases. However, heart rate can be fixed for our purpose by atrial pacing. Furthermore, assessing the shortening of PAT and Td relative to RV pace may be beneficial instead of assessing pure LBBB. RV pace produces a relatively similar activation pattern as LBBB, so the advantage is that a fixed atrioventricular delay can be used when testing biventricular pacing and the deflection of the pacing artefact in the ECG can be used as starting point for the calculation of PAT and Td without the need to add the 15 ms delay for LBBB as described in the Methods section.

Time-to-peak LV dP/dt was initially introduced as a load-independent marker of contractility in hearts with intact electrical conduction.[14] Time-to-peak LV dP/dt shortens with increased contractility which would therefore contribute to shortened PAT. However, while CRT improves function by synchronizing and coordinating the timing of contractions of the different LV regions, it does not change the intrinsic contractility or calcium handling in the cells. So, the contractility of the myocardial cells is not expected to change acutely as CRT is turned on and should not affect the PAT measurements.

We believe that our study is strengthened by the translation of the method from animals to patients. The animal study allowed investigation of the PAT index in a highly controlled environment with more advanced instrumentation, facilitating a more detailed examination of preload dependence and preload-corrected indices of LV function. However, the human heart differs from the canine heart and patients

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typically present with more heterogeneous hearts than laboratory animals. Hence, a method should also be validated in humans. In our study, the reduction of PAT demonstrated successful resynchronization both in animals and in patients. It was also capable of differentiating between lead placement in patients, where the LV lead was positioned in an anterior position before its final placement on the lateral wall. We expected to see a better performance with the latter option, which was demonstrated with a significantly greater shortening of PAT and Td. In addition to this, our results showed that a reduction in PAT has the potential of predicting different outcomes for CRT within the LBBB population. In our clinical study, we observed that the shortening of PAT and Td with CRT only occurred in patients classified as responders. The two non-responders had a prolongation of both indices when paced. This is a proof-of-concept study and thus the number of observations is small. It, therefore, needs to be verified in a larger population if it is generally the case that a shortening of PAT with pacing is a distinctive characteristic of patients with reversible dyssynchrony, and if the patients without this feature do not benefit from CRT.

These findings indicate that PAT could find its place as a marker of acute response to CRT and thereby help to prevent suboptimal lead placements and optimize CRT settings. The main advantage is that PAT is a non-invasive method which is easy to perform. It should be possible to develop automatic algorithms to detect PAT and display it in real time, making it operator independent and with no need for advanced training.

Limitations

The measurements in this study were done acutely in animals under anaesthesia, and we retrospectively investigated patients from a study where invasive femoral artery pressure recordings were available as a substitute for non-invasive peripheral pulse curve measurements. Consequently, this method did not include the level of motion artefacts that would presumably be present in conscious patients undergoing implantation and post-operative follow-ups. In the animals, there were some challenges getting a good connection with the sensor and obtaining a good signal from this quite distal site with relatively weak pulsations also after shaving off the fur. In patients, there are several alternatives regarding the type of sensors and measurement sites to obtain the peripheral pulse curves. Future studies will have to determine the optimal sensor and measurement site.

In the animals, we placed three pacing leads on the LV free wall in order to obtain varying responses when pacing from the different sites. However, the results showed no significant differences in function for the different sites. This could be due to the smaller hearts in the animals and a faster activation of the whole LV. Thus, we were unable to investigate the method's ability to guide optimal lead placement in the animals. However, in the patients, there were significant differences between the five different pacing configurations tested, and the method showed significantly better performance for the presumed best pacing configuration compared with the others.

In the animal study, data were obtained from long interventions performed on heavily instrumented animals under anaesthesia; hence, heart function was depressed also at baseline. Furthermore, sonometric crystals are placed somewhere in the ventricular wall, and hence, when calculating the LV volume, some myocardial masses were included in the volume estimation effectively underestimating the EF values.

This was a small sample size proof-of-concept study. Further studies are therefore required to verify the applicability of the method in a larger population.

Conclusion

This proof-of-concept study showed that shortening of PAT demonstrated acute improvement by CRT both in animals with LBBB and in the ten patients with long-term response to CRT, while it was not shortened in the two patients who did not respond to CRT. As PAT can be measured easily with non-invasive methods and show response in real-time, it seems an attractive method for assessing acute response to CRT during implantation and optimization of CRT. Future studies should be conducted to investigate its accuracy to guide the search for optimal lead placement and CRT settings and predict long-term outcomes.

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Conflict of interest: H.H.O. holds patents within the field of CRT and is a stockholder at Pacertool. The remaining authors report no potential conflicts of interest.

Data availability

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

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