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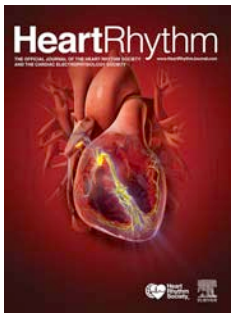

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Leadless atrio-ventricular synchronous pacing in an outpatient setting – early lessons learned on factors affecting atrio-ventricular synchrony

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Short title: Leadless VDD pacing – influencing factors

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Abstract

Background: Leadless pacemakers (PMs) capable of atrio-ventricular (AV) synchronous pacing have recently been introduced. Initial feasibility studies were promising, but limited to just a few minutes of AV synchronous pacing. Real-world long-term data on AV synchrony and programming adjustments affecting AV synchrony in outpatients are lacking.

Objective: To investigate AV synchrony and influences of PM programming adjustments in outpatients with leadless VDD PMs.

Methods: All patients who received a leadless VDD PM (Micra™ AV, Medtronic, US) between 07/2020 and 05/2021 at our center were included in this observational study. AV synchrony was assessed repeatedly postoperatively and during follow-up using Holter ECG recordings. AV synchrony was defined as a QRS complex preceded by a p-wave within 300ms. The impact of programming changes during follow-up on AV synchrony was studied.

Results: 816 hours of Holter ECG from 20 outpatients were analyzed. During predominantly paced episodes (≥80% ventricular pacing), median AV synchrony was 91% (IQR 34-100%) when patients had sinus rates 50-80/min. Median AV synchrony was lower when patients had sinus rates >80/min (33%, IQR 29-46%, $p<0.001$). During a stepwise optimization protocol, AV synchrony could be improved ($p<0.038$). Multivariate analysis showed that a shorter maximum A3 window end ($p<0.001$), a lower A3 threshold ($p=0.046$), and minimum A4 threshold ($p<0.001$) improved AV synchrony.

Conclusion: Successful VDD pacing in the outpatient setting during higher sinus rates is more difficult to achieve than can be presumed based on the initial feasibility studies. The devices often require multiple reprogramming to maximize AV sequential pacing.

Keywords: leadless pacemaker; Micra; AV synchrony; AV synchronous pacing; VDD pacemaker; outpatient; Holter ECG

List of abbreviations

AV	–	atrio-ventricular
CI	–	confidence interval
ECG	–	electrocardiogram
IQR	–	interquartile range
LVEDD	–	left ventricular end-diastolic diameter
LVEF	–	left ventricular ejection fraction
PM	–	pacemaker
PVAB	–	postventricular atrial blanking
PVARP	–	postventricular atrial refractory period
SD	–	standard deviation
TAPSE	–	tricuspid annular plane systolic excursion
VP	–	ventricular pacing

Introduction

Leadless cardiac pacemakers (PMs) have been introduced to overcome lead-associated adverse effects of conventional PMs. The implantation of a leadless PM is safe and complications may be less frequent compared to conventional PMs[1]. However, until recently, leadless PMs were only capable of delivering single-chamber ventricular pacing.

Lately, a second-generation version of the most widely used leadless PM, the Micra™ TPS (Medtronic, Minneapolis, Minnesota, US), has been introduced, which substantially widens the spectrum of patients qualifying for leadless pacing. The device provides contactless atrial sensing and allows for atrio-ventricular (AV) synchronous ventricular stimulation (VDD mode). Atrial sensing relies on the mechanical detection of the atrial contraction via the integrated accelerometer. This concept has been investigated in early short-term feasibility studies, in which the AV synchronous pacing algorithm was uploaded for a few minutes into a prior generation Micra™. Those experiments showed improved AV synchrony compared to VVI mode[2, 3]. Atrial sensing and device function appeared stable during follow-up and not disturbed by intermittent atrial arrhythmias[4]. Overall AV synchrony in these studies was in the range of 60-90%, albeit heavily dependent on patient activities and intrinsic AV conduction[2, 3].

Obtaining adequate AV synchrony in patients with this novel technology in a real-world setting may still be challenging. The intracardiac device undergoes continuous accelerations due to body and cardiac motions, making it difficult for the device to identify atrial contractions correctly. Moreover, the programming and optimization of the algorithms for mechanical sensing poses unfamiliar troubleshooting challenges to cardiac device specialists as the concept fundamentally differs from the well-known principles of conventional PMs[5, 6].

In this study, we provide the first long-term analysis of AV synchrony in outpatients in a real-life setting, who underwent implantation of a leadless VDD-PM and repetitive programming parameter optimizations. We identify critical factors for AV synchrony and provide advice for device programming in daily practice.

Methods

Study design and patient population

In this investigator-initiated observational study, we prospectively enrolled all patients that received a leadless VDD pacemaker (Micra™ AV, Medtronic, Minneapolis, Minnesota, US) at our tertiary referral center between July 2020 and May 2021. All patients had a PM indication according to current guidelines. To qualify for a leadless VDD system, they had to be in sinus rhythm without need for atrial pacing. The decision to implant a leadless system instead of a conventional PM was made based on the patient's co-morbidity and patient preference. An E/A ratio of >1.5 in a pre-interventional echocardiogram was considered a contraindication for a Micra™ AV implantation[7], no other exclusion criteria applied.

The study was approved by the local ethics committee and conducted according to the principles of the Declaration of Helsinki.

Implantation procedure and follow-up

The leadless PM implantation was performed by experienced implanters according to standard practice[8]. After implantation, the PMs were programmed in VDD mode. Implanting physicians were free to program base rates, tracking rates, ventricular sensing and output according to clinical needs. Atrial sensing parameters were adjusted automatically by the device via the "atrial sensing setup" as recommended by Medtronic. A summary of the key parameters for the detection of the mechanical atrial contraction (i.e. "A4 signal") is provided in Fig. 1.

The morning following the implantation, all devices were interrogated and atrial sensing was adjusted according to the manufacturer's instructions by an electrophysiologist trained for Micra™ AV follow-ups (F.No., H.Ta., T.Re., or A.Ha.). After this optimization, patients received a 24h Holter ECG (continuous registration of two ECG channels using a Lifecard CF ECG recorder, Spacelabs Healthcare, Washington, USA) to assess AV synchrony.

After 1-3 months, patients underwent an outpatient follow-up device interrogation. We performed a second optimization to improve atrial sensing parameters further based on the findings in the Holter ECG and from the clinical course. If physically capable, patients underwent treadmill exercise testing to assess potential rate-dependent atrial sensing issues. Patients were discharged again with a Holter

ECG to study the impact of parameter modifications if programming changes potentially affecting AV synchrony were made.

Long-term AV synchrony analysis

In the continuous Holter ECGs, we aimed to study AV synchrony over time. The required p-wave detection cannot be reliably performed by software-based ECG analysis in an outpatient setting[9]. Thus, all Holter ECGs were analyzed manually by an electrophysiology fellow (F.Ne.) using Pathfinder SL version 1.7.1.4718 (Spacelabs Healthcare, Snoqualmie, Washington, US). Every QRS complex of the first minute of every hour was assessed regarding AV-synchrony (supplementary Figure 1), current sinus rate and the percentage of paced beats. A cardiac cycle was considered AV synchronous if a p-wave proceeded a QRS-complex by 0ms up to 300ms. This definition was adopted to allow comparability with the early feasibility studies on leadless VDD pacing that used the same definition[2].

Statistical analysis

R version 4.1.1 for Windows (R Foundation, Vienna, Austria) and SPSS version 25 (IBM, Armonk, New York, US) were used for statistical analysis. Categorical variables are expressed as numbers and percentages. Continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR). Comparisons between nominal and programmed pacing parameters and AV synchrony over time were performed using a paired Wilcoxon rank-sum test. For correlation analyses, Kendall's tau-b was calculated.

To investigate the influence of PM programming parameters on AV synchrony, uni- and multivariate beta regression models were fitted. The multivariate model included all variables from the univariate models with a p-value <0.1. A two-sided p-value ≤0.05 was considered significant.

Results

Baseline characteristics

The baseline characteristics of the patient population and the corresponding procedural characteristics are shown in Table 1. No complications occurred during device implantation and the procedure was successful in 100% of cases. During the postinterventional course, four patients developed atrial fibrillation and were intermittently programmed to VVI(R) mode (excluded from the analysis and not shown in Table 1). In addition, one patient died before completing the study protocol. In six patients, only one Holter ECG was performed. This resulted in 34 24-hour Holter ECGs (816 hours) available for analysis.

AV synchrony in Holter ECGs and impact of physiological factors

No relevant ventricular arrhythmias or ventricular capture losses were observed in any patient. No patient developed a pacemaker syndrome or required a transvenous device upgrade. Ventricular pacing percentage in our cohort – as assessed by the Holter ECG – was relatively low (mean 21.6%±39%; median 0% (IQR 0%-14%)). Median AV synchrony during predominantly paced episodes (≥80% ventricular pacing) was 29% (IQR 23%-86%) after the first postoperative follow-up and increased significantly to 40% (IQR 32%-96%) after the second device optimization session (p=0.038, Fig. 2). Irrespective of the optimization, AV synchrony correlated inversely with intrinsic sinus rate during predominantly paced episodes (p<0.001, Fig. 3 A). When patients had sinus rates 50-80/min and were predominantly paced, median AV synchrony was 91% (IQR 34-100%). In contrast, median AV synchrony was lower when patients had sinus rates >80/min (33%, IQR 29-46%, p<0.001).

If episodes with <80% pacing were also included in the analysis, overall median AV synchrony of all cardiac cycles was high (median 100%, IQR 95%-100%, Fig. 3 B) – related mainly to preserved intrinsic conduction and not device function.

Episodes with loss of AV synchrony were induced by different events such as premature beats (Fig. 4A), intermittent p-wave (i.e. A4-wave) undersensing (Fig. 4B), the reverse AV conduction mode switch (Fig. 4C), the tracking check function (Fig. 4D) or sinus rates lower than the PMs programmed lower rate (Fig. 4E).

Influence of programmed parameters on AV synchrony

Predictors for a higher rate of AV synchronous pacing are shown in Table 2. In the multivariate analysis, a shorter maximum A3 window end ($p<0.001$), a lower minimum A4 threshold ($p<0.001$), and a lower A3 threshold ($p=0.046$) were independently associated with improved AV synchrony. In certain patients an activated AV conduction mode switch may also be beneficial ($p=0.058$), conversely this might also negatively affect AV synchrony in others (Fig. 4C).

Accordingly, after PM optimization during the first three months following implantation, programmed parameters deviate from the nominal device values (provided in Table ***3***). The A3 window end was shortened (median 683ms (IQR 621-713ms); $p=0.002$), as was the minimum and maximum A3 window end (median 625ms (IQR 600-650ms) and 763ms (IQR 744-801ms) respectively; both $p=0.002$). The sensed AV delay was increased (median 55ms (IQR 40-100ms); $p=0.016$). Detailed changes of the atrial sensing parameters, the optimization iterations, and resulting device performance are shown in Supplementary Table 1.

Reliability of AV synchrony self-diagnostics

The Micra™ AV pacemaker provides information on (presumed) AV synchrony by detailing delivered pacing sequences (AM-VS; AMVP; VS only; VP only; see manufacturer manual for details[10]). A high rate of “AMVS” correlates with AV synchrony ($T=0.12$, $p<0.001$), as does “VS only” ($T=0.32$, $p<0.001$); whereas “VP only” ($T=-0.38$, $p<0.001$) and “AMVP” ($T=-0.33$, $p<0.001$) inversely correlate with AV synchrony.

Discussion

In this prospective observational study, AV synchrony was assessed for the first time in outpatients with dedicated leadless VDD PMs that underwent stepwise parameter optimization. We identified critical clinical and programming parameters that heavily influence AV synchrony.

Long-term AV synchrony during pacing in the outpatient setting

AV synchrony was substantially lower during predominantly paced episodes (Fig. 2), than could be assumed from the initial short-term feasibility studies[2]. While AV synchrony in patients with complete AV block has been reported to be as low as 30%-40%, these early feasibility studies estimated overall AV synchrony to be ~80% in this patient population[2]. We, however, observed a significantly lower AV synchrony when evaluating AV synchrony for 24 hours and in an outpatient setting. The feasibility studies (MARVEL, MASS, MASS2) confined the analysis duration mostly to ~30min immediately after PM optimization, and assessed AV synchrony mainly in a supine body position[2, 3]. This quite artificial setting favors good AV synchrony. The negative effect of standing and walking on accelerometer signal quality[2, 3] as well as differences in heart rate may well explain why 24-hour AV synchrony in a real-world outpatient setting may be lower. In particular, heart rate was identified as a critical factor for AV synchrony during predominantly paced episodes, and is higher and more variable during the course of a full day.

Critical parameters for AV synchrony

Based on the multivariate regression analysis and theoretical considerations, there are key atrial sensing parameters, which need to be carefully considered in order to optimize AV synchrony:

- Timing of the A3 window: An increasing heart rate primarily leads to a shortening of the diastolic filling phase including the E- and A-wave (i.e. the A3 and A4 signal)[11, 12]. Due to the dependency of the timing of A3 and A4 on heart rate, the device's delineation of A4 signals depends on an adequate parameter setting. Otherwise, AV synchrony may be perturbed and the risk of malignant arrhythmias might increase[13]. We consistently programmed the A3 window earlier (shortening of min. and max. A3 window end) compared to nominal settings. Likely, our settings account for higher heart rates of outpatients, whereas the device's nominal values may have been optimized for resting patients.

- AV conduction mode switch: When activated, the Micra™ AV assumes intact AV conduction in case of a ventricular rate ≥40/min and switches to VVI 40/min. In patients with a faster ventricular escape rhythm or 2:1 AV block, this may lead to a decrease in AV synchrony[5, 14]. Once reverse AV conduction mode switch occurs, “lock-in” of retrograde p-waves may further compromise AV synchrony (Fig. 4C).
- Lower rate: Sinus rates lower than the programmed lower rate perturb AV synchrony in VDD mode (Fig. 4E). Consider a relatively low lower rate (50/min).

A comprehensive summary of atrial sensing parameters and practical programming considerations is provided in

Table ***3***.

Clinical implications

Leadless VDD PMs provide reliable ventricular pacing; moreover, we did not observe any ventricular arrhythmias that may have been triggered mechanically by the device.

For patient selection, however, implanters should consider AV synchrony-influencing factors. More sedentary patients with lower heart rates may be excellent candidates for leadless VDD pacing even if a high percentage of ventricular stimulation is anticipated. Ventricular backup pacing may also be a good indication even in younger patients (there is increasing evidence that leadless PM extraction is still feasible after several years[15]). On the other hand, conventional transvenous systems may be considered for physically very active persons or patients with high resting heart rates who regularly require ventricular pacing.

Moreover, patients may benefit from repetitive optimizations of the device programming. An optimization session on the postoperative day (pre-discharge) and in the outpatient setting (e.g. one month after implantation) with prior Holter ECG registration and potentially an exercise stress test may be helpful to identify difficulties with atrial sensing. Adaption of atrial sensing parameters just in a supine position at rest can improve instant AV synchrony but may not satisfy all needs of real-world outpatients. Cardiac device specialists are encouraged to undergo specific training to improve their understanding of the potentially unfamiliar programming parameters.

Technical implications

While leadless VDD pacing significantly widens the spectrum of patients potentially qualifying for leadless pacing[16], and overcomes lead-related issues[17], the technology is still in its infancy. It remains debatable if atrial mechanical sensing will prevail in leadless PMs. Since atrial leadless pacing is already on the horizon[18], other methods for ultra-low power wireless device synchronization may gain attention as they might improve AV synchronization[19, 20].

Meanwhile, programming adequate atrial sensing parameters can remain challenging. A programmable rate-dependent A3- and A4-window may be interesting as it could improve adequate atrial tracking even at higher heart rates. Moreover, a rest rate and a modifiable base rate of the AV conduction mode switch could improve AV synchrony at lower sinus rates. Finally, nominal values might be optimized in future device generations based on accumulating data from ongoing studies (i.e. Micra ACCELAV, NCT04245345) and outpatient data analyses from other centers.

Limitations

This is an observational study with limited sample size. The influence of key programming parameters on AV synchrony may be robust, whereas improvement of AV synchrony during the second PM optimization could have also been influenced by other factors such as a general improvement of the patient's health, adaption of the drug regimen and alike. In this study, we focused on AV synchrony as the parameter of interest. We did not assess clinical effects directly perceived by patients. Those may also be less pronounced in the elderly. A randomized controlled trial would be required to compare such effects in patients with leadless VDD vs. transvenous DDD PMs. Moreover, the generalizability of our results to patients with persistent complete AV block needs to be assessed externally, given the relatively low number of ventricular pacing in our study (21%) and the fact that only 15% of patients had persistent AV block. Finally, the definition of AV synchronous cardiac cycles (QRS complex with a preceding p-wave up to 300ms earlier) may be generous, but is in line with previous studies[2].

Conclusion

AV synchrony in outpatients with leadless VDD PMs, who require a relevant amount of pacing, is substantially lower than might have been expected from early feasibility studies on leadless VDD pacing. Leadless VDD PMs often require multiple reprogramming to maximize AV sequential VDD pacing and yet still may have a low percentage of AV synchrony, especially with increased heart rates.

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Tables

Patient and procedural characteristics	**n=20**
Clinical patient characteristics and comorbidities	
- Age [years]	80 (76-86)
- Female gender	11 (55%)
- Body height [m]	1.68 (1.64-1.78)
- Body mass index [kg/m^2]	25.7 (24.5-30.3)
- Coronary artery disease	6 (30%)
- Arterial hypertension	15 (75%)
- Diabetes	6 (30%)
- Dyslipidemia	9 (45%)
Echocardiography data	
- LVEF [%]	60 (55-64)
- TAPSE [mm]	19 (18-25)
- LVEDD [mm]	44 (40-46)
- E/A ratio	0.86 (0.79-0.89)
Pacemaker indication	
- Permanent 3rd degree AVB	3 (15%)
- Intermittent 3rd degree AVB	11 (55%)
- Symptomatic second-degree AVB	2 (10%)
- Left bundle branch block + 1st degree AVB	2 (10%)
- Intermittent high-degree AVB	1 (5%)
- Carotid sinus syndrome	1 (5%)
Procedure duration and fluoroscopy time/dosage	
- Procedure duration [min]	41 (36-54)
- Fluoroscopy duration [min]	5.5 (4.4-8.2)
- Radiation dose [cGycm^2]	771 (502-1’698)
Implantation characteristics	
- Number of engaged tines	2 (2-2)
- Number of pacemaker deployments	1 (1-2)
o 1 deployment	14 (70%)
o 2 deployments	4 (20%)
o >2 deployments	2 (10%)
- Used contrast medium [ml]	20 (15-31)
- Pacing threshold [V/0.24ms]	0.38 (0.38-0.5)
- Sensed R-wave amplitude [mV]	13.4 (10.3-17.3)
- Pacing impedance [Ω]	785 (648-938)

Table 1: *Patient and procedural baseline characteristics. Median values with interquartile ranges in brackets and numbers with percentages are shown. Abbreviations: AV – atrio-ventricular; AVB – AV*

block; LVEF – left ventricular ejection fraction; LVEDD – left ventricular end-diastolic diameter; TAPSE – tricuspid annular plane systolic excursion.

	Univariate analysis		Multivariate analysis	
Variables	**Coefficient β (95%-CI)**	**p-value**	**Coefficient β (95%-CI)**	**p-value**
Programming-related impact on AV synchrony				
- A3 threshold	-0.049 (-0.089 – -0.009)	**0.015**	-0.044 (-0.088 – -0.001)	**0.046**
- A3 window end	-0.000 (-0.001 – 0.001)	0.53	-	-
- Minimum A3 window end	0.000 (-0.001 – 0.001)	0.94	-	-
- Maximum A3 window end	-0.002 (-0.003 – -0.001)	**<0.001**	-0.002 (-0.004 – -0.001)	**<0.001**
- A4 threshold	-0.001 (-0.133 – 0.130)	0.99	-	-
- Minimum A4 threshold	-6.030 (-7.804 – -4.255)	**<0.001**	-5.235 (-7.285 – -3.185)	**<0.001**
- sAVD	0.003 (0.001 – 0.005)	**<0.001**	0.000 (-0.002 – 0.002)	0.792
- Activated AVCMS	0.415 (0.242 – 0.588)	**<0.001**	0.197 (-0.007 – 0.401)	0.058

Table 2: *Programming-related predictors for a high AV synchrony. Uni- and multivariate beta regression models were fitted. Abbreviations: AVCMS – atrio-ventricular conduction mode switch; CI – confidence interval; sAVD – sensed atrio-ventricular delay.*

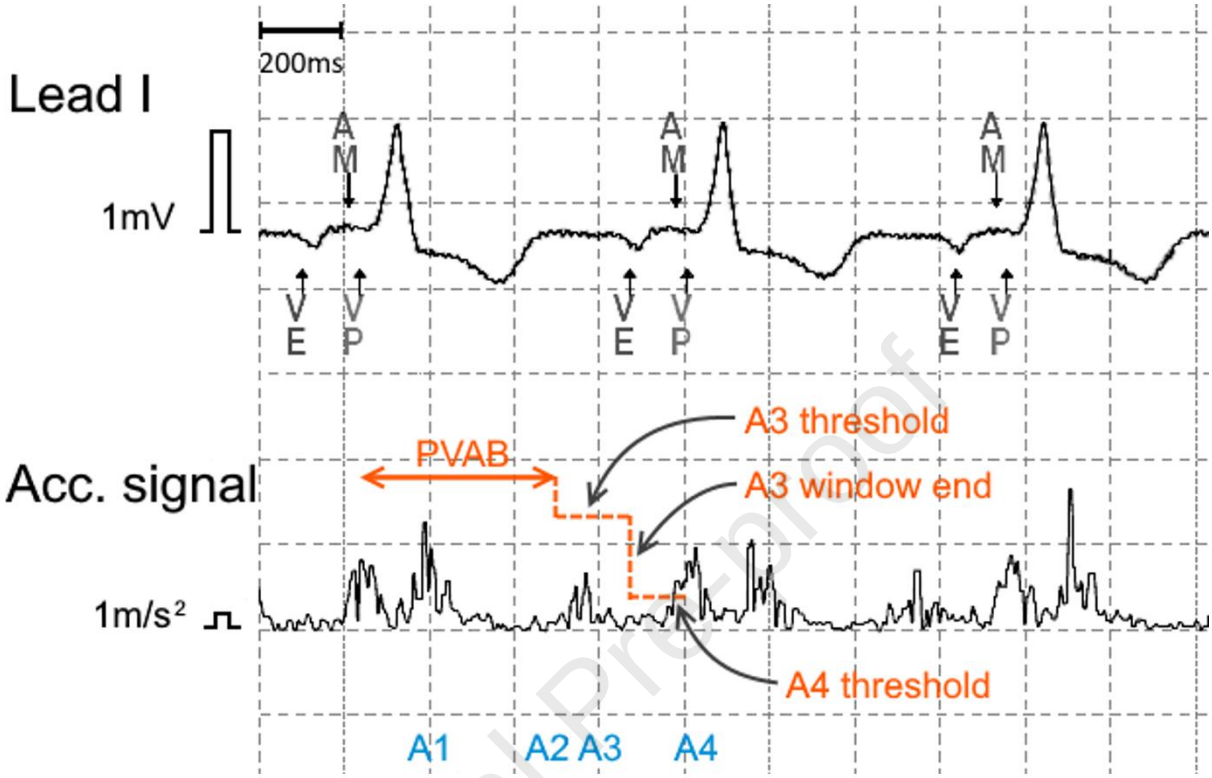
Parameter	Range	Function	Comment
A3 window end	600-1000ms (775ms)	The A3 window starts after the PVAB and ends at the A3 window end (highlighted by "VE"). The timing of the window is measured relative to Vp.	Must often be shortened compared to nominal values. If programmed too long, A4 undersensing occurs, especially at higher heart rates. If programmed too short, A3 oversensing occurs.
Min. A3 window end	600-800ms (750ms)		
Max. A3 window end	650-1000ms (900ms)		
A3 threshold	1.0-10.0m/s^2 (4.0m/s^2)	Blanks A3.	In case of A3 and A4 fusion at higher heart rates (=A7), an adequate A3 threshold allows tracking of A7. Auto A3 threshold may be deactivated and A3 threshold programmed 1-2m/s^2 higher than the A3 signal
A4 threshold	0.7-8.0m/s^2 (1.2 m/s^2)	Prevents noise oversensing. The min. A4 threshold is the max. atrial sensitivity.	If very sensitive (<0.8ms^2), noise oversensing may occur. If insensitive, A4 undersensing occurs. Both impairs AVS.
Min. A4 threshold	0.7-1.6m/s^2 (0.8m/s^2)		
Atrial sensing vector	1; 2; 3; or combinations (1+2)	The accelerometer vector(s) used for atrial sensing.	Allows choosing the input signal with the best signal/noise ratio.
SAVD (sensed AV delay)	20-200ms (20ms)	Corresponds to the SAVD in conventional PMs but is shorter (mechanical not electrical atrial activity).	Longer SAVD may reduce Vp promoting intrinsic conduction. However, a long SAVD impairs tracking of high rates.
PVAB (postventricular atrial blanking)	450-600ms (550ms)	Starts with Vp, blanks A1 and A2.	If programmed too long, A7/A4 might be blanked impairing atrial tracking. Shortening to 500ms allows increasing upper tracking rate to 115/min.
PVARP (postventricular atrial refractory period)	500-750ms (auto)	Similar to conventional devices but of minor relevance (no conventional mode switch).	If programmed too long, atrial contractions may be undersensed (particularly at higher rates or PACs), impairing AVS.
Rate smoothing	On, off (On)	During intermittent A4 under-sensing (missed "AM"), a smoothing delta is added to the ventricular escape interval. Thus, the next Vp is slightly delayed which may improve tracking of variable sinus rates.	High sinus rates require a smaller smoothing delta (consider 50ms). High sinus variability requires a larger smoothing delta.
Smoothing delta	50-200ms (100ms)		
Tracking check	On, off (On)	Periodically checks for atrial oversensing above the tracking check rate by PVARP prolongation (making one atrial contraction refractory). The occurrence of the next AM marker is predicted. If it occurs within the prediction window, atrial tracking is adequate. Otherwise, oversensing is diagnosed and the PVARP remains prolonged.	If lower or equal to the sinus rate, tracking check impairs AVS. Consider deactivation or increasing the tracking check rate. The function has been described to initiate ventricular arrhythmias.
Tracking check rate	90-110bpm (100bpm)		
Activity mode switch (VDIR mode)	On, off (On)	Compares sensor rate and ventricular rate in VDD mode. Switches to VDIR if the	May increase ventricular rate in case of low heart rates despite physical activity (e.g. sinus node dysfunction).

		intrinsic or VDD paced ventricular rate is too low.	
AV conduction mode switch (VVI+ mode)	On, off (On)	Periodically checks for intrinsic rates >40/min. If present, VVI+ is active and atrial sensing is deactivated. If 2/4 beats are paced (in VVI+, <40/min), the PM switches to VDD.	VVI+ improves PM longevity and reduces ventricular pacing. VVI+ may impair AV synchrony. Deactivate in patients with permanent total AVB, 2:1 AVB or escape rhythm >40bpm.

Table 3: *Programmable parameters influencing atrial tracking in leadless VDD pacemakers.*

Abbreviations: AV – atrioventricular; AVB – atrioventricular block; AVS – atrioventricular synchrony; bpm – beats per minute; AM – atrial mechanical signal; AV – atrio-ventricular; PAC – premature atrial contraction; PM – pacemaker; VE – ventricular end; Vp – ventricular pacing.

Figures and figure legends



Signal or marker	Occurrence	Function/meaning
A1 signal	After the beginning of the ventricular systole (after the beginning of the QRS complex)	Closure of mitral and tricuspid valve
A2 signal	At the end of the ventricular systole (at the end of the T-wave)	Closure of aortic and pulmonary valve
A3 signal	During ventricular diastole (after the T-wave).	Corresponds to the passive ventricular filling phase (i.e. the E-wave in the TTE)
A4 signal	During atrial systole (after the p-wave).	Corresponds to the active ventricular filling phase (i.e. the A-wave in the TTE)
A7 signal	During fusion of the A3 and A4 signal (i.e. E- and A-wave) due to higher heart rates or lack of AV synchrony	Corresponds to a ventricular filling phase (E/A-fusion in the TTE)
AM	If a mechanical event is sensed during the A3/A4 window above the A3/A4 threshold. Does not occur in VVI+ mode.	Presumed atrial mechanical contraction (A4 signal/A-wave)
AR	If an atrial signal is detected during the PVARP	Atrial refractory event
VE	At the end of the A3 window. Does not occur in VVI+ mode.	Marks the A3 window end according to the PM, is not a physiologic event
VP	If ventricular pacing is delivered	Ventricular pacing
VS	If a ventricular sensed event occurs	Ventricular sensing

Fig. 1: *Schematic illustration and explanation of the key atrial sensing parameters. The top signal shows the ECG, the bottom signal the rectified accelerometer signal that is used to detect the atrial mechanical activity (A4 signal). The PVAB begins once the ventricular pacing stimulus is delivered. At its end, the A3 window starts. It features an A3 threshold to blind the pacemaker for A2 and A3 signals. When the A3 window ends, the "VE" signal is triggered and the A4 window begins. The A4 threshold allows programming an appropriate sensitivity to detect A4. Once a signal is detected, either*

in the A3 window above the A3 threshold or in the A4 window above the A4 threshold, it is labelled "AM" and after the sensed AV delay, the pacing stimulus is delivered. Adjustment of the atrial sensing parameters (shown in orange) is critical for reliable detection of the atrial contraction.

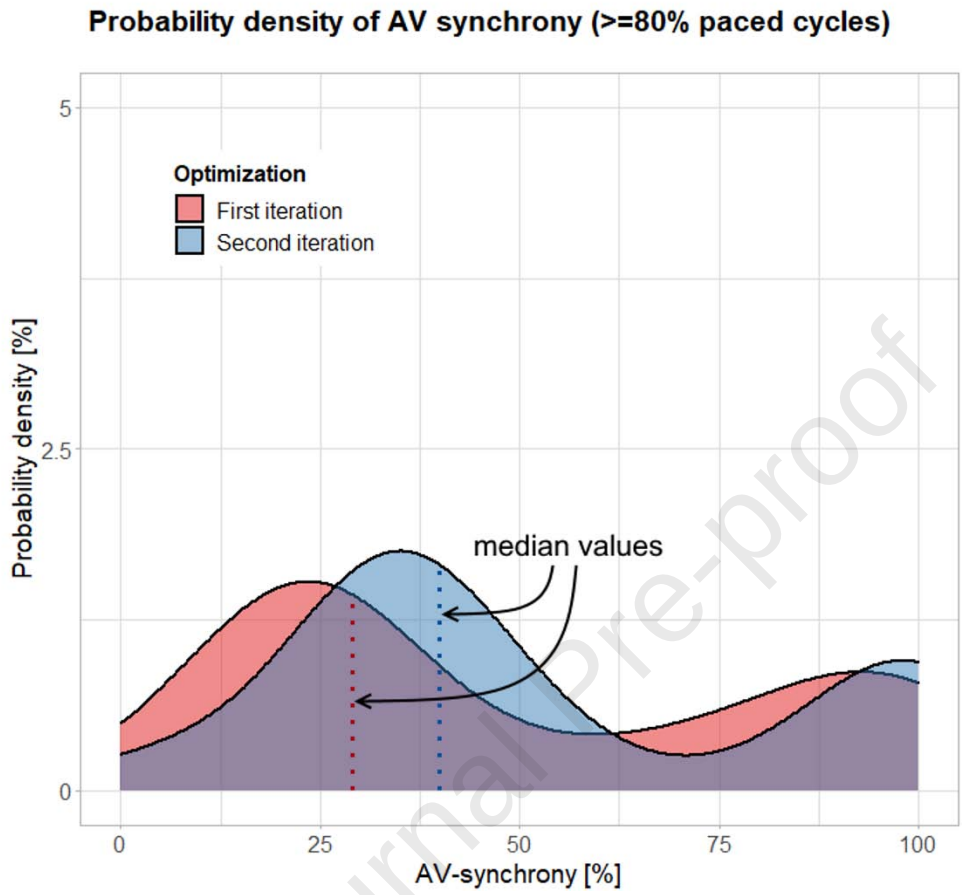


Fig. 2: *Density plot of AV synchrony during PM optimization. The density function shows the observed AV synchrony of all cardiac cycles after optimization on the first postoperative day (red) and 1-3 months later during follow-up (blue). Median values are shown in red and blue for both groups. AV synchrony of predominantly paced episodes (≥80% ventricular pacing) improves after the second optimization (p=0.038). Abbreviations: AV – atrioventricular; PM – pacemaker.*

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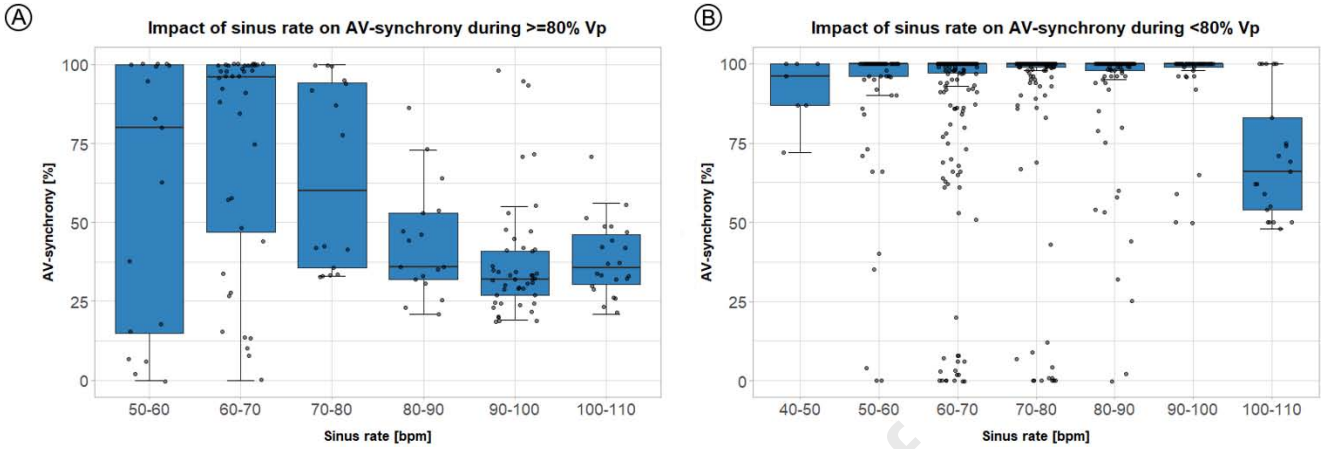

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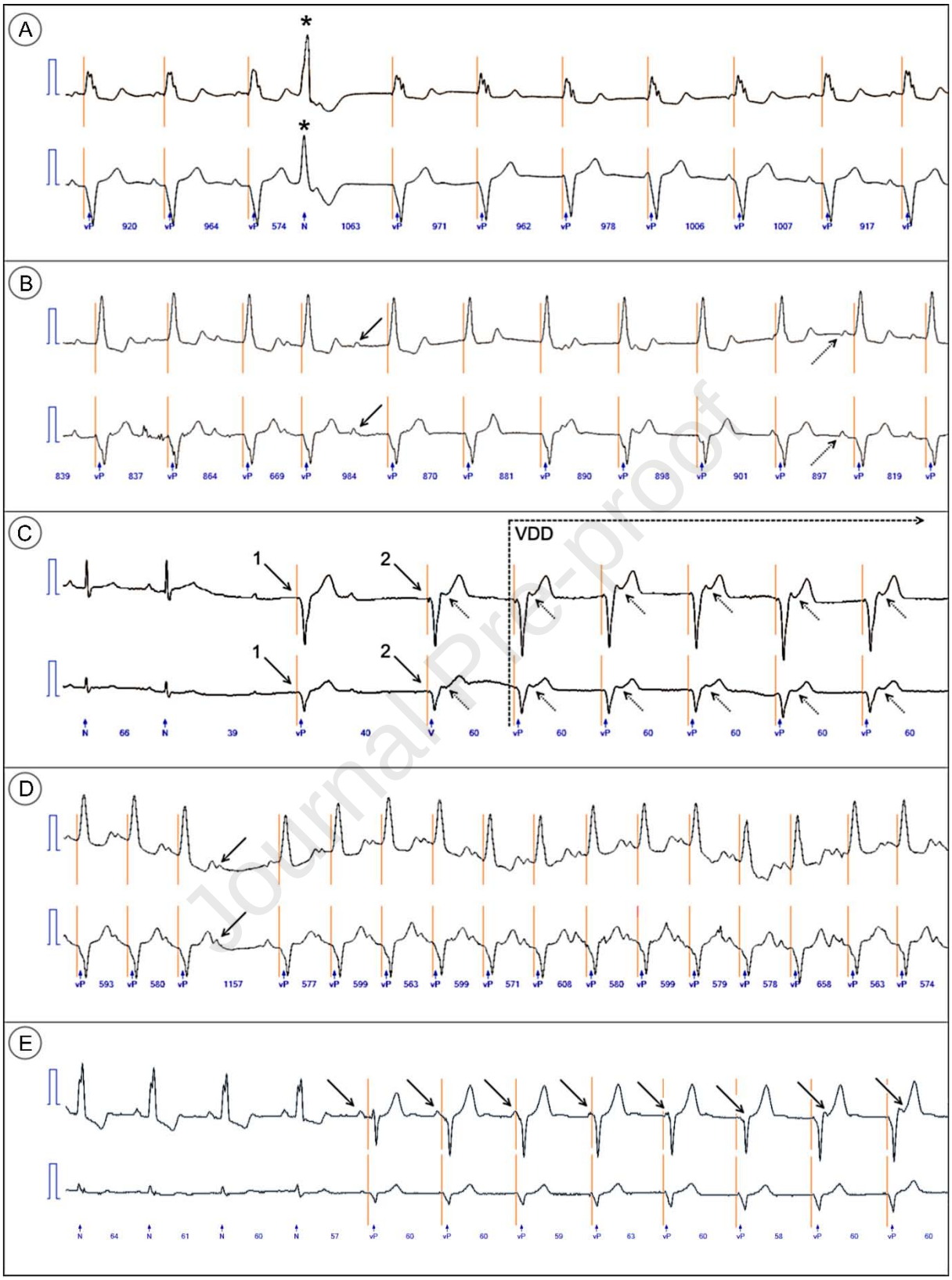
390 ***Fig. 3:*** *Impact of sinus rate on AV synchrony. Data from the first and second optimization iteration are*

391 *pooled. Panel A (≥80 ventricular pacing) and B (<80% ventricular pacing) show boxplots with*

392 *categorized data (groups represent sinus rate bandwidths). Abbreviations: AV – atrioventricular; Vp –*

393 *ventricular pacing.*



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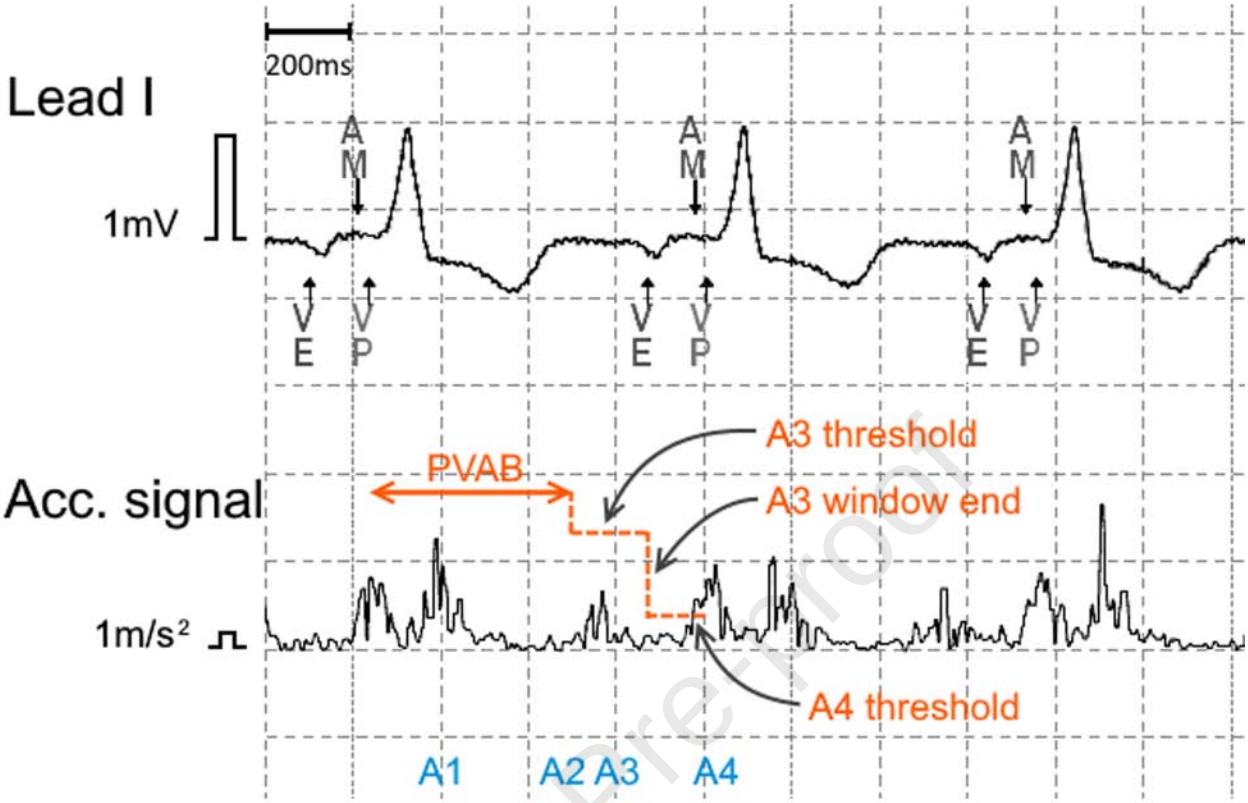
395 ***Fig. 4:*** *Holter ECG recordings of AV desynchronizations. Panel A shows a ventricular premature beat*
396 *(asterisk) perturbing AV synchrony (antegrade p-wave falls into the PVAB). The sinus rate is slightly*
397 *higher than the pacing rate, restoring AV synchrony after a few beats. Panel B shows intermittent p-*
398 *wave undersensing (arrow). The device is able to recover atrial tracking six beats later (dotted arrow).*

Panel C shows a pacemaker initially in AV conduction mode switch (i.e. VVI 40/min). After two paced beats (labelled (1) and (2)), the pacemaker switches to VDD 60/min. Due to V-A-conduction, the p-wave gets "locked" into the PVAB (dotted arrows) leading to persistent loss of AV synchrony. Panel D shows loss of AV synchrony for one beat (arrow), representing the "tracking check" function checking for inadequate A3 tracking by PVARP prolongation. Panel E shows a sinus rate (arrows) falling below the PMs programmed lower rate, leading to desynchronization. Atrial tracking is resumed subsequently. Abbreviations: AV – atrio-ventricular; PVAB – postventricular atrial blanking; PVARP – postventricular atrial refractory period.



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