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

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10

11 **Short title:** Leadless VDD pacing – influencing factors

12

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## 28 **Abstract**

29

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

34

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

37

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

43

44 **Results:** 816 hours of Holter ECG from 20 outpatients were analyzed. During predominantly paced  
45 episodes ( $\geq 80\%$  ventricular pacing), median AV synchrony was 91% (IQR 34-100%) when patients  
46 had sinus rates 50-80/min. Median AV synchrony was lower when patients had sinus rates  $>80$ /min  
47 (33%, IQR 29-46%,  $p < 0.001$ ). During a stepwise optimization protocol, AV synchrony could be  
48 improved ( $p < 0.038$ ). Multivariate analysis showed that a shorter maximum A3 window end ( $p < 0.001$ ),  
49 a lower A3 threshold ( $p = 0.046$ ), and minimum A4 threshold ( $p < 0.001$ ) improved AV synchrony.

50

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

54

55

56

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

59 **List of abbreviations**

60	AV	–	atrio-ventricular
61	CI	–	confidence interval
62	ECG	–	electrocardiogram
63	IQR	–	interquartile range
64	LVEDD	–	left ventricular end-diastolic diameter
65	LVEF	–	left ventricular ejection fraction
66	PM	–	pacemaker
67	PVAB	–	postventricular atrial blanking
68	PVARP	–	postventricular atrial refractory period
69	SD	–	standard deviation
70	TAPSE	–	tricuspid annular plane systolic excursion
71	VP	–	ventricular pacing

## 72 **Introduction**

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

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

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

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

## 97 **Methods**

### 98 **Study design and patient population**

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

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

109

### 110 **Implantation procedure and follow-up**

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

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

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

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

128

### 129 **Long-term AV synchrony analysis**

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

138

### 139 **Statistical analysis**

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

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

## 149 **Results**

### 150 **Baseline characteristics**

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

### 159 **AV synchrony in Holter ECGs and impact of physiological factors**

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

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

173 Episodes with loss of AV synchrony were induced by different events such as premature beats (Fig.  
174 4A), intermittent p-wave (i.e. A4-wave) undersensing (Fig. 4B), the reverse AV conduction mode switch  
175 (Fig. 4C), the tracking check function (Fig. 4D) or sinus rates lower than the PMs programmed lower  
176 rate (Fig. 4E).

### 178 **Influence of programmed parameters on AV synchrony**



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

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

191

### 192 **Reliability of AV synchrony self-diagnostics**

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

## 198 **Discussion**

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

202

### 203 **Long-term AV synchrony during pacing in the outpatient setting**

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

216

### 217 **Critical parameters for AV synchrony**

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

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

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

235 A comprehensive summary of atrial sensing parameters and practical programming considerations is  
236 provided in  
237 Table 3.

238

### 239 **Clinical implications**

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

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

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

256

### 257 **Technical implications**

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

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

269

### 270 **Limitations**

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

**282 Conclusion**

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

287

288

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292

293

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- 352

353 **Tables**

<b>Patient and procedural characteristics</b>	<b>n=20</b>
<b>Clinical patient characteristics and comorbidities</b>	
- Age [years]	80 (76-86)
- Female gender	11 (55%)
- Body height [m]	1.68 (1.64-1.78)
- Body mass index [kg/m <sup>2</sup> ]	25.7 (24.5-30.3)
- Coronary artery disease	6 (30%)
- Arterial hypertension	15 (75%)
- Diabetes	6 (30%)
- Dyslipidemia	9 (45%)
<b>Echocardiography data</b>	
- LVEF [%]	60 (55-64)
- TAPSE [mm]	19 (18-25)
- LVEDD [mm]	44 (40-46)
- E/A ratio	0.86 (0.79-0.89)
<b>Pacemaker indication</b>	
- Permanent 3 <sup>rd</sup> degree AVB	3 (15%)
- Intermittent 3 <sup>rd</sup> degree AVB	11 (55%)
- Symptomatic second-degree AVB	2 (10%)
- Left bundle branch block + 1 <sup>st</sup> degree AVB	2 (10%)
- Intermittent high-degree AVB	1 (5%)
- Carotid sinus syndrome	1 (5%)
<b>Procedure duration and fluoroscopy time/dosage</b>	
- Procedure duration [min]	41 (36-54)
- Fluoroscopy duration [min]	5.5 (4.4-8.2)
- Radiation dose [cGy <sup>cm</sup> <sup>2</sup> ]	771 (502-1'698)
<b>Implantation characteristics</b>	
- 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 [ $\Omega$ ]	785 (648-938)

354 **Table 1:** Patient and procedural baseline characteristics. Median values with interquartile ranges in

355 brackets and numbers with percentages are shown. Abbreviations: AV – atrio-ventricular; AVB – AV



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

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<u>Variables</u>	<u>Univariate analysis</u>		<u>Multivariate analysis</u>	
	Coefficient $\beta$ (95%-CI)	p-value	Coefficient $\beta$ (95%-CI)	p-value
<b>Programming-related impact on AV synchrony</b>				
- A3 threshold	-0.049 (-0.089 – -0.009)	<b>0.015</b>	-0.044 (-0.088 – -0.001)	<b>0.046</b>
- 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)	<b>&lt;0.001</b>	-0.002 (-0.004 – -0.001)	<b>&lt;0.001</b>
- A4 threshold	-0.001 (-0.133 – 0.130)	0.99	-	-
- Minimum A4 threshold	-6.030 (-7.804 – -4.255)	<b>&lt;0.001</b>	-5.235 (-7.285 – -3.185)	<b>&lt;0.001</b>
- sAVD	0.003 (0.001 – 0.005)	<b>&lt;0.001</b>	0.000 (-0.002 – 0.002)	0.792
- Activated AVCMS	0.415 (0.242 – 0.588)	<b>&lt;0.001</b>	0.197 (-0.007 – 0.401)	0.058

358

359 **Table 2:** Programming-related predictors for a high AV synchrony. Uni- and multivariate beta

360 regression models were fitted. Abbreviations: AVCMS – atrio-ventricular conduction mode switch; CI –

361 confidence interval; sAVD – sensed atrio-ventricular delay.

<b>Parameter</b>	<b>Range</b>	<b>Function</b>	<b>Comment</b>
<b>A3 window end</b>	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)		
<b>A3 threshold</b>	1.0-10.0m/s <sup>2</sup> (4.0m/s <sup>2</sup> )	Blanks A3.	In case of A3 and A4 fusion at higher heart rates (=A7), an adequate A3 threshold allows tracking of A7. <u>Auto</u> A3 threshold may be deactivated and A3 threshold programmed 1-2m/s <sup>2</sup> higher than the A3 signal
<b>A4 threshold</b>	0.7-8.0m/s <sup>2</sup> (1.2 m/s <sup>2</sup> )	Prevents noise oversensing. The min. A4 threshold is the max. atrial sensitivity.	If very sensitive (<0.8ms <sup>2</sup> ), noise oversensing may occur. If insensitive, A4 undersensing occurs. Both impairs AVS.
Min. A4 threshold	0.7-1.6m/s <sup>2</sup> (0.8m/s <sup>2</sup> )		
<b>Atrial sensing vector</b>	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.
<b>SAVD (sensed AV delay)</b>	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.
<b>PVAB (postventricular atrial blanking)</b>	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.
<b>PVARP (postventricular atrial refractory period)</b>	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.
<b>Rate smoothing</b>	On, off (On)	During intermittent A4 undersensing (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)		
<b>Tracking check</b>	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)		
<b>Activity mode switch (VDIR mode)</b>	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.	
<b>AV conduction mode switch (VVI+ mode)</b>	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.

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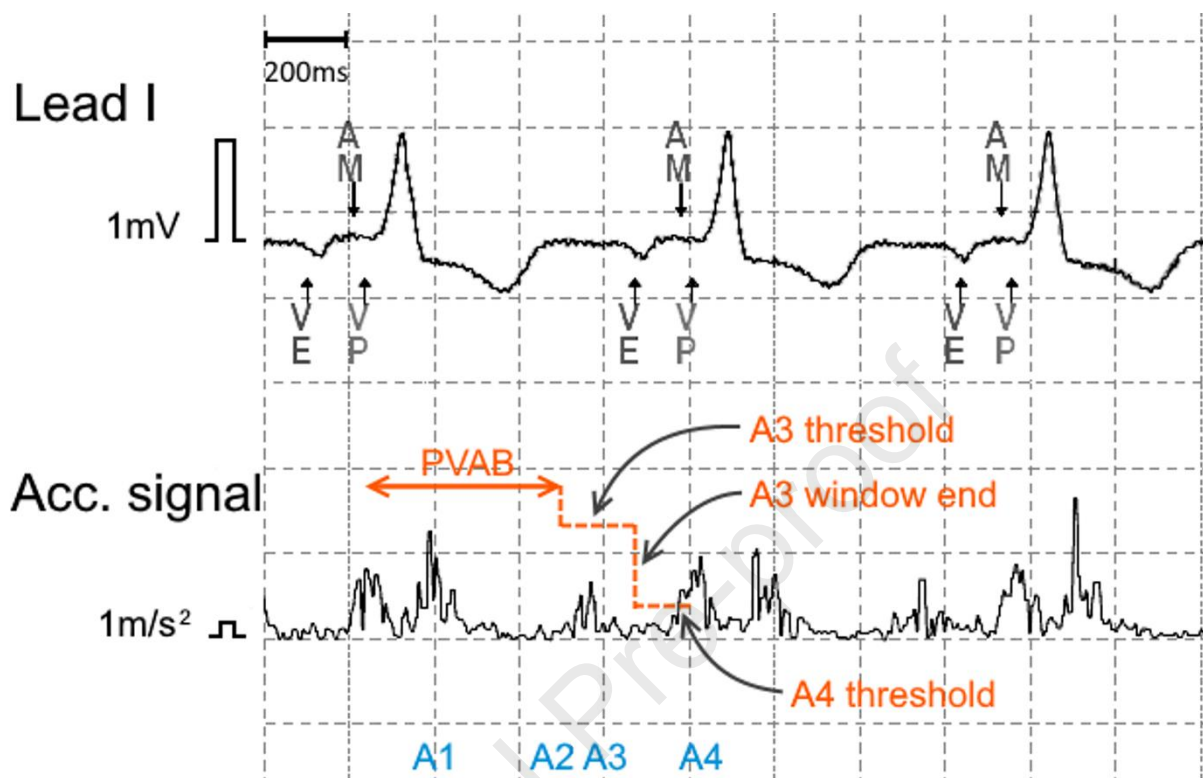
**Table 3:** Programmable parameters influencing atrial tracking in leadless VDD pacemakers.

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

367

368 **Figures and figure legends**

369



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 <u>passive</u> ventricular filling phase (i.e. the E-wave in the TTE)
A4 signal	During atrial systole (after the p-wave).	Corresponds to the <u>active</u> 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.	<u>Presumed</u> 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 <u>not</u> a physiologic event
VP	If ventricular pacing is delivered	Ventricular pacing
VS	If a ventricular sensed event occurs	Ventricular sensing

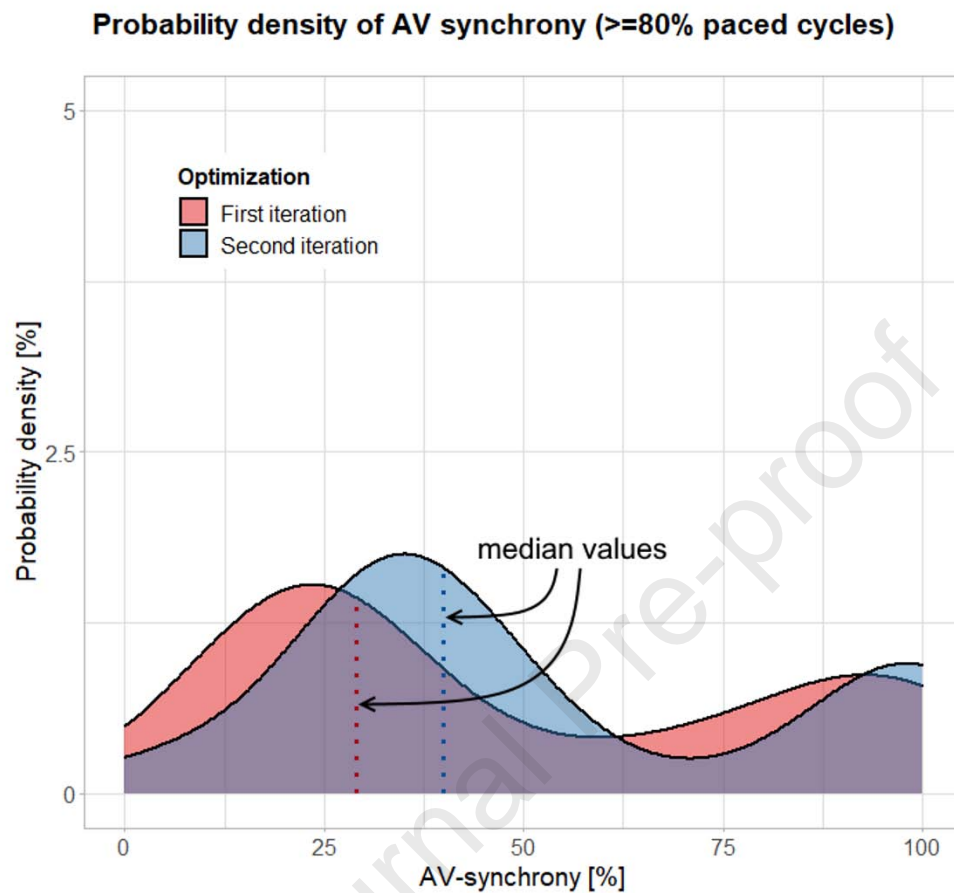
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371 **Fig. 1:** Schematic illustration and explanation of the key atrial sensing parameters. The top signal  
 372 shows the ECG, the bottom signal the rectified accelerometer signal that is used to detect the atrial  
 373 mechanical activity (A4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

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

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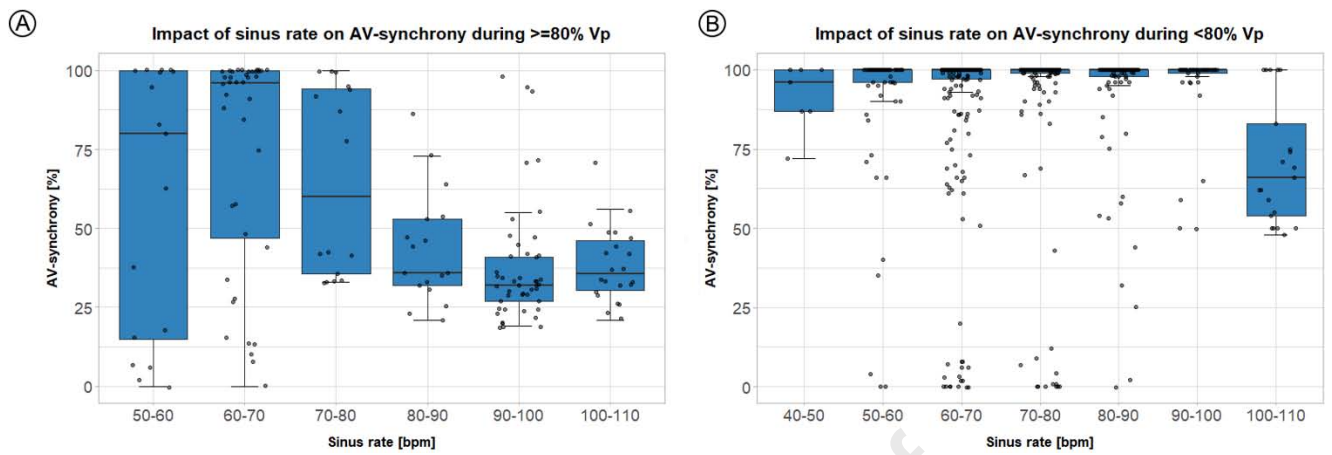


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382 **Fig. 2:** Density plot of AV synchrony during PM optimization. The density function shows the  
383 observed AV synchrony of all cardiac cycles after optimization on the first postoperative day (red) and  
384 1-3 months later during follow-up (blue). Median values are shown in red and blue for both groups. AV  
385 synchrony of predominantly paced episodes ( $\geq 80\%$  ventricular pacing) improves after the second  
386 optimization ( $p=0.038$ ). Abbreviations: AV – atrioventricular; PM – pacemaker.

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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 ( $\geq 80$  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.

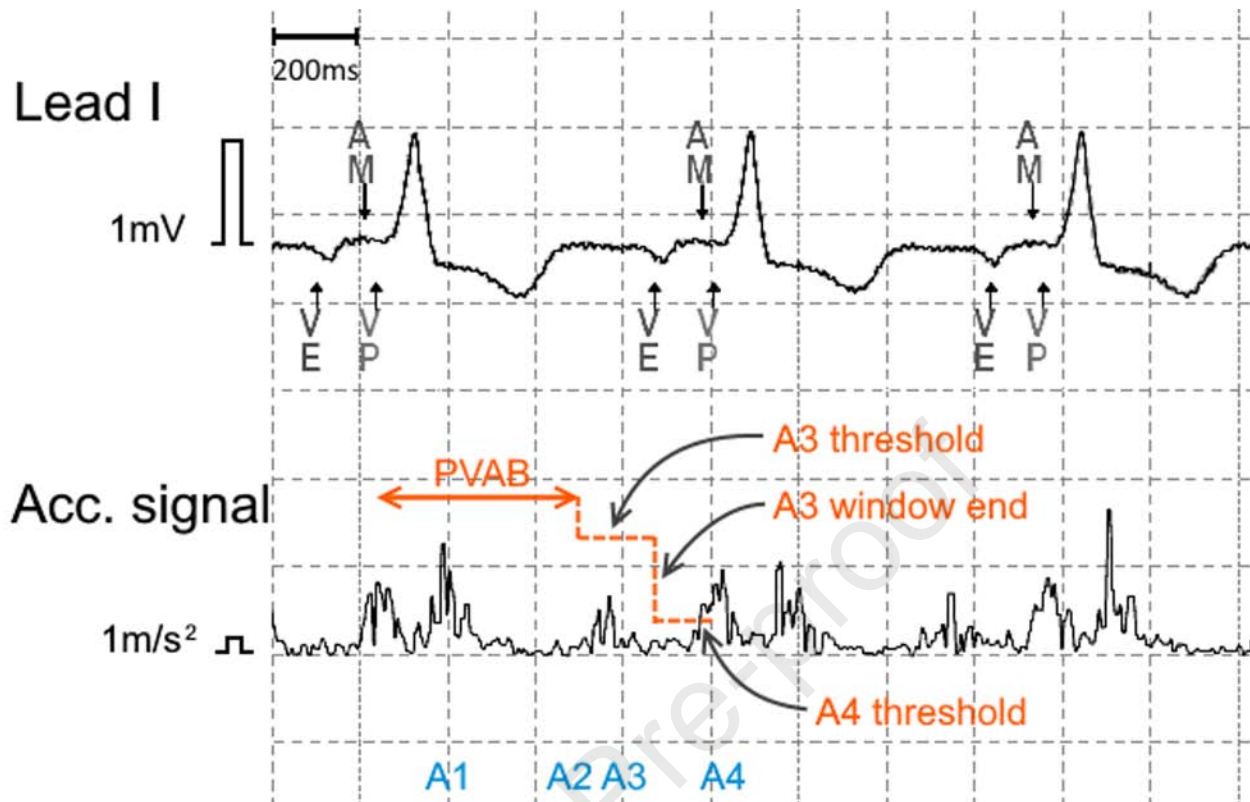




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395 **Fig. 4:** Holter ECG recordings of AV desynchronizations. Panel A shows a ventricular premature beat  
 396 (asterisk) perturbing AV synchrony (antegrade p-wave falls into the PVAB). The sinus rate is slightly  
 397 higher than the pacing rate, 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).

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



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<b>A3 signal</b>	During ventricular diastole (after the T-wave).	Corresponds to the <u>passive</u> ventricular filling phase (i.e. the E-wave in the TTE)
<b>A4 signal</b>	During atrial systole (after the p-wave).	Corresponds to the <u>active</u> ventricular filling phase (i.e. the A-wave in the TTE)
<b>A7 signal</b>	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)
<b>AM</b>	If a mechanical event is sensed during the A3/A4 window above the A3/A4 threshold. Does not occur in VVI+ mode.	<u>Presumed</u> atrial mechanical contraction (A4 signal/A-wave)
<b>AR</b>	If an atrial signal is detected during the PVARP	Atrial refractory event
<b>VE</b>	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
<b>VP</b>	If ventricular pacing is delivered	Ventricular pacing
<b>VS</b>	If a ventricular sensed event occurs	Ventricular sensing

