Avoiding unnecessary ventricular pacing is associated with reduced incidence of heart failure hospitalizations and persistent atrial fibrillation in pacemaker patients

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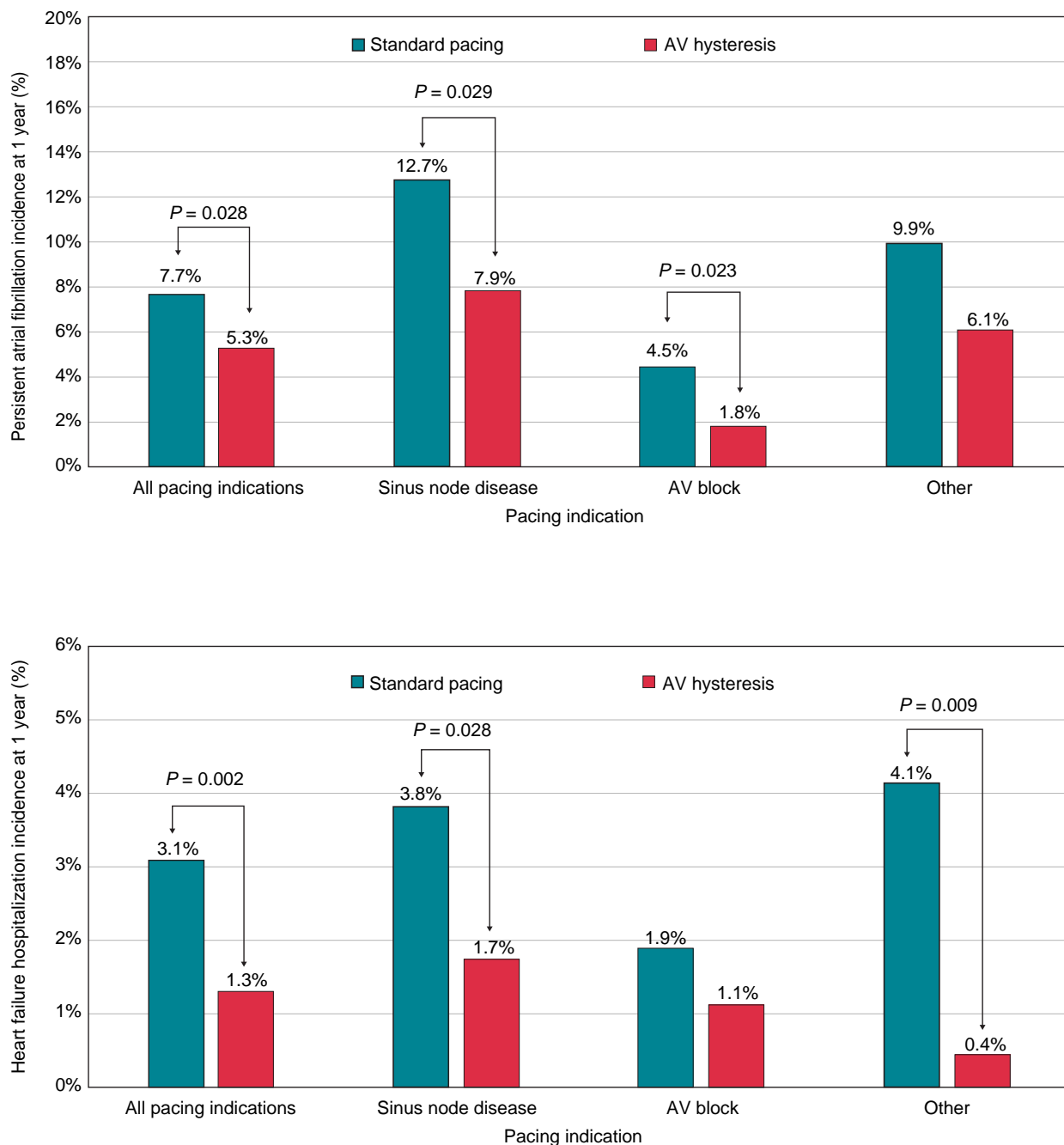|	
Aims	In bradycardia patients treated with dual-chamber pacing, we aimed to evaluate whether pacing with atrioventricular (AV) delay management [AV hysteresis (AVH)], compared with standard pacing with fixed AV delays, reduces unnecessary ventricular pacing percentage (VPP) and is associated with better clinical outcomes. Main study endpoints were the incidence of heart failure hospitalizations (HFH), persistent atrial fibrillation (AF), and cardiac death.
Methods and results	Data from two identical prospective observational studies, BRADYCARE I in the USA and BRADYCARE II in Europe, Africa, and Asia, were pooled. Overall, 2592 patients (75 ± 10 years, 45.1% female, 50% with AVH) had complete clinical and device data at 1-year follow-up and were analysed. Primary pacing indication was sinus node disease (SND) in 1177 (45.4%), AV block (AVB) in 974 (37.6%), and other indications in 441 (17.0%) patients. Pacing with AVH, compared with standard pacing, was associated with a lower 1-year incidence of HFH [1.3% vs. 3.1%, relative risk reduction (RRR) 57.5%, $P = 0.002$] and of persistent AF (5.3% vs. 7.7%, RRR = 31.1%, $P = 0.028$). Cardiac mortality was not different between groups (1.0% vs. 1.4%, RRR = 27.8%, $P = 0.366$). Pacing with AVH, compared with standard pacing, was associated with a lower ($P < 0.001$) median VPP in all patients (7% vs. 75%), in SND (3% vs. 44%), in AVB (25% vs. 98%), and in patients with other pacing indications (3% vs. 47%).
Conclusion	Cardiac pacing with AV delay management via AVH is associated with reduced 1-year incidence of HFH and persistent AF, most likely due to a reduction in VPP compared to standard pacing.

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Graphical Abstract

Persistent atrial fibrillation incidence at 1 year (%) by pacing indication, comparing Standard pacing and AV hysteresis.

- All pacing indications: Standard pacing 7.7%, AV hysteresis 5.3% ($P = 0.028$)
- Sinus node disease: Standard pacing 12.7%, AV hysteresis 7.9% ($P = 0.029$)
- AV block: Standard pacing 4.5%, AV hysteresis 1.8% ($P = 0.023$)
- Other: Standard pacing 9.9%, AV hysteresis 6.1%

Heart failure hospitalization incidence at 1 year (%) by pacing indication, comparing Standard pacing and AV hysteresis.

- All pacing indications: Standard pacing 3.1%, AV hysteresis 1.3% ($P = 0.002$)
- Sinus node disease: Standard pacing 3.8%, AV hysteresis 1.7% ($P = 0.028$)
- AV block: Standard pacing 1.9%, AV hysteresis 1.1%
- Other: Standard pacing 4.1%, AV hysteresis 0.4% ($P = 0.009$)

Introduction

High rates of right ventricular pacing (RVP) are increasingly recognized as harmful to pacemaker patients, being associated with increased rates of atrial fibrillation (AF), ischaemic stroke, heart failure (HF), and death.[1,2] Consistent with these observations, international guidelines[3,4] suggest the use of algorithms to promote intrinsic conduction, at least in patients without atrioventricular (AV) conduction block, but also caution that stretching AV pacing intervals in patients with prolonged AV conduction can cause AV dyssynchrony, diastolic mitral regurgitation, AF, and HF. To avoid the potentially deleterious effects of long-term RVP, alternative approaches have been promoted, such as a wider use of cardiac resynchronization therapy (CRT) or conduction system pacing; however, the supportive evidence is still limited.[4]

What's new?

- In patients with indications for persistent dual-chamber cardiac pacing, incidence of heart failure hospitalizations (HFH) and persistent atrial fibrillation were significantly lower in patients programmed with atrioventricular (AV) delay management via AV hysteresis (AVH) compared with patients with standard pacing with fixed AV delay.
- A previous study showed reduction of persistent atrial fibrillation, comparing pacing with AVH and pacing with fixed AV delay, in patients with sinus node disease. Our results expand those findings to the general population of bradycardia patients and show that AVH is also associated with reduced incidence of HFH.
- While it was expected that the use of AVH would lower ventricular pacing in patients with sinus node disease, our analyses also show ventricular pacing reduction in patients with high-degree AV block; this suggests that AV conduction disease may often be intermittent and paroxysmal in these patients.

Several algorithms have been proposed to reduce unnecessary ventricular pacing, and their operations are based on two different mechanisms: (i) progressive prolongation of the AV pacing delay [AV hysteresis (AVH)] and (ii) AAI-DDD pacing mode. Both mechanisms have DDD back-up when needed. Both AVH and AAI-DDD modes have been shown to reduce ventricular pacing in clinical trials.[5] While the use of these algorithms was initially proposed in sinus node disease (SND) patients, recent data from two controlled studies[6,7] indicated a benefit even in patients with AV block (AVB) as their pacemaker indication.[5] While the use of AVH has been shown to significantly reduce persistent AF,[8] a recent meta-analysis questions the clinical impact of AV management through the AAI-DDD mode in pacemaker patients.[9]

To shed more light on this important controversy, we pooled the data of two prospective observational studies, BRADYCARE I in the USA and BRADYCARE II in Europe and Asia, which evaluated the clinical benefit of AVH algorithms to reduce incidence of persistent AF, HF hospitalizations (HFH), and cardiac death.

Methods

Study design

Individual patient data from two multicentre, observational studies with 1-year follow-up post-implant, BRADYCARE I (Clinicaltrial.gov NCT01062126) and BRADYCARE II (Clinicaltrial.gov NCT02577887), were pooled to perform this analysis. The two studies were identical in design and mainly differed because BRADYCARE I included a population from the USA and BRADYCARE II included a population from Europe, Africa, and Asia. The studies were conducted in compliance with Good Clinical Practice and the Declaration of Helsinki. Investigational review board or ethics committee approval was obtained before study initiation. All patients signed an informed consent prior to participating in any study-related activities.

Eligibility criteria

Patients were eligible to participate in the studies if they had a standard indication for a pacemaker, were implanted with a dual-chamber pacemaker capable of AV sequential pacing, were within 30 days of implant, ≥18 years of age, and were able to provide written informed consent. Exclusion criteria included life expectancy of less than 1 year and current or planned pregnancy.

Intervention

Since the studies were observational in nature, clinicians programmed the pacemakers per their standard practice. Patients were categorized into two groups, named the AVH group or standard pacing group, based on the status of the AVH feature, ON or OFF, respectively. Subjects with a change in the status of this feature during the study period were excluded from the analysis.

Atrioventricular hysteresis algorithm

The AVH algorithm used in the BRADYCARE I and II studies was the Ventricular Intrinsic Preference (VIP™) algorithm (Abbott, Sylmar, CA, USA). This is an AV search hysteresis algorithm which searches for and promotes intrinsic AV conduction. When the VIP™ algorithm is activated, the device periodically (every 30 s) extends the sensed AV (SAV) and paced AV (PAV) delays by a programmable value (e.g. by 150 ms) for a number of programmed search cycles (e.g. three cycles) to search for intrinsic conduction.[10] Additionally, when three consecutive R-waves occur at the programmed SAV or PAV delays, VIP™ will extend the SAV/PAV delays by the programmed value. If an R-wave is sensed during the extended AV delay, the ventricular pulse is inhibited, and the SAV/PAV delays will remain extended until VP occurs. If intrinsic conduction does not occur during this extended AV delay, the device reverts to the programmed static AV delay. With the VIP™ algorithm, SAV/PAV delays are limited to programmable maximum value (in any case lower than 350 ms). The long AV delay is maintained until a programmable number of cycles with absent ventricular-sensed events (i.e. continuous need for ventricular pacing). The VIP™ feature is disabled during atrial high-rate events and mode switches.

Study objectives and endpoints

The primary objective of this analysis was to evaluate whether dual-chamber pacing with AV delay management (AVH algorithm), compared with standard pacing with fixed AV delays, reduces unnecessary RVP percentage and improves clinical outcomes. Main study endpoints were the incidences of cardiac death, HFH, and persistent AF. Incidences of cardiac death and HFH were evaluated in the whole cohort of 2592 patients on the basis of clinical outcomes data collected during follow-up visits. Data about AF incidence and burden, as percentage of time spent in AF by the patient, were extracted from device diagnostics. Incidence of persistent AF was evaluated in the subgroup of 2039 patients who had no previous history of persistent/permanent AF at implant. This choice was derived from the objective of evaluating the deleterious effect of unnecessary RVP on the progression of atrial disease. Patients were diagnosed with persistent AF if they spent a given percentage of the 12-month observation period in AF; this per cent threshold was set according to the results of the MINERVA trial[11] that showed that in patients who developed persistent AF, the median AF burden was ≥50% in SND patients and ≥30% in patients with other pacing indications. Appropriateness of persistent AF diagnosis, which was based on device data, was confirmed by verifying that when the device detected AF occurrence, the investigators reported AF events in the follow-up case report forms.

The secondary endpoint of our study was ventricular pacing percentage (VPP) which was evaluated in the two study groups (pacing with AVH vs. pacing with fixed AV delays) and according to pacing indication.

Data collection

Demographics, primary indication for pacemaker implant, medical history, and medication information were recorded at the time of enrolment. Patients who had both SND and AVB were classified as AVB patients. Clinical outcomes and device data, such as AF burden and VPP, were collected at the scheduled and unscheduled follow-up visits throughout the 1-year observation period. Reported clinical outcomes were verified through monitoring of data source documentation. Device data included information about all variables relevant to the pacemaker function: advanced feature usage (e.g. AVH programming), stored electrocardiograms, device-detected cardiac events (e.g. AF), and device-related measures (e.g. VPP).

Statistical analysis

Individual participant data from both studies, BRADYCARE I and BRADYCARE II, were pooled and analysed. Following best practices to perform pooled analysis,[12] we verified that the two studies were identical in terms of inclusion/exclusion criteria, follow-up schedules, and the data recorded at each visit. We compared the patient's baseline characteristics

of the two pooled studies to verify that the two studies included similar patient populations, and we compared the incidences of the studied endpoints in the two pooled studies. Sensitivity analyses did not show significant statistical differences between the two studies; therefore, no further adjustments were made to account for combining the study data.

Patient characteristics were summarized via descriptive statistics, including mean and standard deviation, or median with the interquartile range, for continuous variables, and counts and percentages for categorical/nominal variables, as appropriate. The 1-year incidence of clinical endpoints was expressed in percentage with 95% confidence intervals. The difference of clinical endpoint incidences when comparing patients with AVH and patients with standard pacing was expressed as relative risk reduction (RRR). Since the BRADYCARE studies did not randomize the use of AVH, when comparing clinical endpoint incidences between patients with AVH and patients with standard pacing, we verified that baseline characteristics were similar in the compared patient groups.

Statistical comparisons were performed through Student's *t*-test for normally distributed variables and by nonparametric tests for variables with skewed distributions. A chi-square proportion test was performed to compare incidences of the clinical endpoints. All tests were two-sided, and a *P*-value < 0.05 was considered statistically significant.

Analyses were performed using SAS or the statistics toolbox in MATLAB R2018a.

Results

Subject disposition

A total of 5490 patients were enrolled in the two BRADYCARE studies with a standard indication for pacemaker implant, respectively, 3389 (61.7%) in BRADYCARE I and 2101 (38.3%) in BRADYCARE II. In the BRADYCARE I study, consecutive patient recruitment started in February 2010 and lasted till September 2011 and the completion date was in September 2012. In the BRADYCARE II study, consecutive patient recruitment started in July 2015 and lasted till November 2016, and the completion date was in November 2017.

The main characteristics of patients included in the two studies have been already described in the clinicaltrial.gov repository and are reported in table A of the Supplementary material online, *Materials*.

For the purpose of our analyses, from this patient cohort, we included 2592 patients who had complete clinical outcomes data and complete device data regarding VPP and AF burden throughout the 1-year observation period. This patient subgroup was composed by 1544 (60%) BRADYCARE I patients and 1048 (40%) BRADYCARE II patients. Baseline characteristics of these 2592 patients are shown in *Table 1*. In particular, the primary indication for pacing was SND in 1177 (45.4%), AVB in 974 (37.6%), and other indications in 441 (17.0%), where other indications comprised syncope (defined as recurrent syncope caused by carotid sinus stimulation or symptomatic recurrent syncope associated with documented bradycardia or syncope that is not determined to be due to AVB when other likely causes were excluded), familial condition (conditions with a high risk for bradycardia such as long QT syndrome), prevention and termination of tachyarrhythmias by pacing (symptomatic recurrent SVT or sustained pause-dependent VT where the efficacy of pacing was thoroughly documented), and pacemaker replacement.

Atrioventricular block was present in 974/2592 (37.6%) patients, 72/2592 (2.8%) had first-degree AVB, 120/2592 (4.6%) had second-degree type 1 AVB, 252/2592 (9.7%) had second-degree type 2 AVB, and 530/2592 (20.4%) had third-degree AVB.

Paroxysmal AF was present in 799/2592 (30.8%), persistent AF in 223/2592 (8.6%), and permanent AF in 330/2592 (12.7%).

The AVH feature was enabled and maintained in 1296 (50%) of patients, while the other 1296 (50%) patients were continuously programmed with standard DDD pacing with fixed AV delays. Comparison of patients' baseline characteristics in the two study groups (standard DDD pacing vs. AVH pacing) is shown in *Table 1*.

Ventricular pacing lead was positioned in the right ventricular apex in 1735 (66.9%) of patients, in the right ventricular septum in 670 (25.8%) of patients, and in other right ventricular sites in 187 (7.2%) of patients.

The AF Suppression™ algorithm, designed to pace the atrium at rates faster than the intrinsic atrial rate to overdrive and suppress paroxysmal or persistent AF, was enabled in a minority (15) (0.6%) of patients, eight in the standard DDD pacing group and seven in the AVH pacing group.

Ventricular pacing percentage

Patients with the AVH algorithm programmed ON were associated with significantly lower VPP, compared with patients with standard pacing. This was observed in both the total population and in all the patient subgroups, as shown in *Table 2*. In particular, the median VPP with AVH enabled was 3% in patients with a SND pacing indication, and it was 25% in patients with AVB.

Importantly, the median VPP in first-degree AVB was 75% with standard pacing and 33% with AVH; in the second-degree AVB type, it was 98% with standard pacing and 20% with AVH; in second-degree AVB type 2, it was 97% with standard pacing and 26% with AVH; and in third-degree AVB, it was 98% with standard pacing and 22% with AVH.

Clinical outcomes as a function of atrioventricular delay management programming

The 1-year incidences of cardiac death, HFH, and persistent AF, as estimated in the pooled analyses, are shown in *Table 3*. These incidences were also separately estimated in the two BRADYCARE studies and are reported in table B of the Supplementary material online, *Materials*.

The incidence of cardiac death was not different between groups (1.0% in the AVH group vs. 1.4% in the standard pacing group, RRR = 27.8%, *P* = 0.366).

The incidence of HFH was significantly lower in the AVH group compared with the standard pacing group (1.3% vs. 3.1%, RRR = 57.5%, *P* = 0.002). This reduction, observed in the whole population, was also confirmed in SND patients and in patients with other pacing indications; however, only a trend towards reduction was observed in AVB patients (*Figure 1*). The history of persistent or permanent AF in the whole population of 2492 patients was associated with a higher risk of HFH, which occurred in 3.8% patients with AF and in 1.8% patients without AF (chi-square proportion test, *P* = 0.0032). Heart failure hospitalizations among patients with standard DDD pacing occurred in 4.7% patients with persistent or permanent AF and in 2.3% patients without AF (chi-square proportion test, *P* = 0.019) while in patients with AVH, pacing occurred in 0.8% patients with persistent or permanent AF and in 1.4% patients without AF (*P* = ns). Incidence of persistent AF was significantly lower in the AVH group compared with the standard pacing group (5.3% vs. 7.7%, RRR = 31.1%, *P* = 0.028). Specifically, persistent AF occurred in 7.9% of SND patients with AVH and in 12.7% of SND patients with standard pacing (RRR = 38.4%, *P* = 0.029). In AVB patients, persistent AF occurred in 1.8% of those with AVH and in 4.5% of patients with standard pacing (RRR = 60.0, *P* = 0.023), as shown in *Figure 2*. Of the whole study population, 2039 patients without a history of persistent/permanent AF were evaluated to compare new persistent AF between the AVH and standard pacing groups. The baseline characteristics were homogeneous between the two study groups (*Tables C, D, and E* of the Supplementary material online, *Materials*).

Safety endpoints

Incidence of adverse events in the BRADYCARE I and BRADYCARE II studies has been already described in the respective clinicaltrial.gov repositories. In our patient population, safety endpoints and adverse events were not different between patients with AVH or standard

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Table 1 Baseline characteristics in the analysed patient cohort

Patient characteristics	Whole cohort 2592 patients	Standard pacing 1296 patients	AV hysteresis 1296 patients	P-value standard vs. AV hysteresis
Age	75 ± 10	76 ± 12	74 ± 12	ns
Gender (female)	1168/2592 (45.1%)	555/1296 (42.8%)	613/1296 (47.3%)	0.022
Primary indication				ns
SND	1177/2592 (45.4%)	629 (48.5%)	548 (42.3%)	
AV block	974/2592 (37.6%)	444 (34.2%)	530 (40.9%)	
Other	441/2592 (17.0%)	223 (17.2%)	218 (16.8)	
Atrial fibrillation	1352/2592 (52.2%)	741/1296 (57.2%)	705/1296 (59.4%)	ns
Hypertension	1917/2592 (74.0%)	946/1296 (73.0%)	971/1296 (74.9%)	ns
Diabetes	644/2592 (24.8%)	328/1296 (25.3%)	316/1296 (24.4%)	ns
Cardiomyopathy	469/2592 (18.1%)	241/1296 (18.6%)	228/1296 (17.6%)	ns
Myocardial infarction	255/2590 (9.8%)	125/1294 (9.6%)	130/1296 (10.0%)	ns
NYHA class III or IV	724/2289 (31.6%)	371/1144 (32.4%)	353/1145 (30.8%)	ns
LVEF (mean ± st dev)	58 ± 10	57 ± 10	58 ± 10	ns
LVEF < 50%	250/1856 (13.5%)	133/938 (14.2%)	117/918 (12.7%)	ns

AV, atrioventricular; LVEF, left ventricle ejection fraction; ns, not significantly different (in particular P-value was >0.15 for all comparisons when P = ns); NYHA, New York Heart Association; SND, sinus node disease.

Table 2 Percentage of ventricular pacing according to pacing indication and AVH programming

Patient cohort	Median ventricular pacing percentage (interquartile range)		
	Standard pacing	AV hysteresis	P-value
All pacing indications	75% (20–99)	7% (1–48)	P < 0.0001
Sinus node disease	44% (6–76)	3% (1–21)	P < 0.0001
AV block	98% (56–99)	25% (2–74)	P < 0.0001
Other	47% (8–92)	3% (1–19)	P < 0.0001

AV, atrioventricular.

pacing; in particular, syncopal events were very rare and not different in the two groups [2/1296 (0.15%), standard vs. 1/1296 (0.08%) AVH].

Discussion

BRADYCARE studies represent two of the largest international studies on pacemaker patients performed in the last decade and provide information about a contemporary population managed in real-world practice. This analysis provides strong evidence about the clinical value of the automatic AV management algorithm (AVH) in pacemaker patients. The mechanism behind this observed reduction in persistent AF and HFH is not entirely clear but may be due to improved AV synchrony when reduction in RVP is successfully achieved.

Heart failure hospitalizations and atrioventricular hysteresis

Several studies[1,2,13] have associated HFH with high and unnecessary RVP, suggesting that non-physiological RVP pacing may induce inter- and intra-ventricular dyssynchrony and AV dyssynchrony and may cause pacing-induced cardiomyopathy.

Our results clearly show that the minimization of RVP is strongly associated with a reduction in HFH at 1 year [1.3% (AVH) vs. 3.1% (standard pacing); RRR = 57.5%, P = 0.002] in the overall population. Furthermore, this clinical benefit was observed in SND patients (1.7% vs. 3.8%, RRR = 54.4%, P = 0.028) and in patients with 'other' as their pacing indication (0.4% vs. 4.1%, RRR = 89.1%, P = 0.009). Interestingly, HFH incidence in AVB patients was low [1.1% (AVH) vs. 1.9% (standard pacing), RRR = 40.3%, P = 0.337]. This result may be evaluated in the context of the short observation period of our study. The observed low incidences of HFH in AVB patients are similar to those observed in large pacemaker trials[1,9] and may be explained by the fact that many patients enrolled in our study had normal left ventricular function and may tolerate ventricular pacing in a 1-year horizon.

Persistent atrial fibrillation and atrioventricular hysteresis

The incidence of persistent AF was significantly lower in the AVH group compared with the standard pacing group in the overall population (5.3% vs. 7.7%, RRR = 31.1%, P = 0.028). In particular, persistent AF occurred in 1.8% of AVB patients with AVH and in 4.5% of AVB patients with standard pacing (RRR = 60.0, P = 0.023). This finding has high importance because specific data on the clinical benefit of reducing ventricular pacing in AVB patients are scarce and because it also reinforces the proposal to shift to a pacing paradigm implementing AV delay management in patients with intermittent and paroxysmal AVB.[5]

As for SND patients in our study, persistent AF occurred in 12.7% patients with standard pacing and in 7.9% patients with AVH (RRR = 38.4%, P = 0.029). In the SavePACE trial,[8] which followed SND patients for a mean follow-up period of 1.7 years, the incidence of persistent AF was equal to that observed in our studies [12.7% in the dual-chamber rate-modulated (DDDR) arm and 7.9% in the arm treated with algorithms to reduce RVP]. Interestingly, the algorithm used for reducing unnecessary ventricular pacing in 90% of patients in the SavePACE trial

Table 3 Incidence rate [95% confidence interval (CI)] of study endpoints according to pacing indication and AVH programming

Patients	Endpoint	Standard pacing	AV hysteresis	RRR	*P*-value
Whole cohort	Cardiac death	18/1296	13/1296	27.8%	0.366
		1.4% (0.8–2.2) %	1.0% (0.5–1.7) %		
Whole cohort	**HF hospitalizations**	**40/1296**	**17/1296**	**57.5%**	**0.002**
		3.1% (2.2–4.2) %	**1.3% (0.8–2.1) %**		
Whole cohort[a]	**Persistent AF**	**67/870**	**62/1169**	**31.1%**	**0.028**
		7.7% (6.0–9.7) %	**5.3% (4.1–6.7) %**		
SND	Cardiac death	8/548	5/629	45.5%	0.276
		1.5% (0.6–2.9) %	0.8% (0.3–1.8) %		
SND	**HF hospitalizations**	**21/548**	**11/629**	**54.4%**	**0.028**
		3.8% (2.4–5.8) %	**1.7% (0.9–3.1) %**		
SND[a]	**Persistent AF**	**32/251**	**41/522**	**38.4%**	**0.029**
		12.7% (8.9–17.5) %	**7.9% (5.7–10.5) %**		
AV block	Cardiac death	8/530	6/444	10.5%	0.836
		1.5% (0.7–3.0) %	1.4% (0.5–2.9) %		
AV block	HF hospitalizations	10/530	5/444	40.3%	0.337
		1.9% (0.9–3.4) %	1.1% (0.4–2.6) %		
AV block[a]	**Persistent AF**	**22/488**	**8/434**	**60.0%**	**0.023**
		4.5% (2.8–6.7) %	**1.8% (0.8–3.6) %**		
Other	Cardiac death	2/218	2/223	2.2%	0.982
		0.9% (0.1–3.3) %	0.9% (0.1–3.2) %		
Other	**HF hospitalizations**	**9/218**	**1/223**	**89.1%**	**0.009**
		4.1% (1.9–7.7) %	**0.4% (0.0–2.5) %**		
Other[a]	Persistent AF	13/131	13/213	32.3%	0.193
		9.9% (5.4–16.4) %	6.1% (3.3–10.2) %		

AF, atrial fibrillation; AV, atrioventricular; HF, heart failure; RRR, risk rate ratio; SND, sinus node disease.
[a]Patients without history of persistent/permanent AF at inclusion. Bold values indicate all the endpoints with $P < 0.05$.
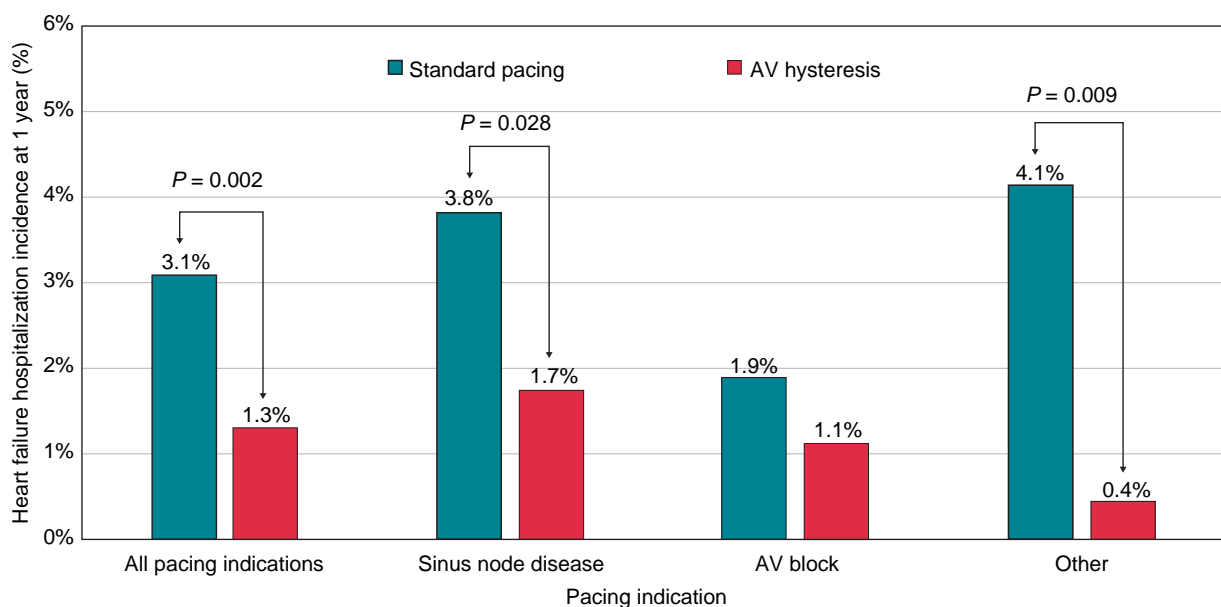
Figure 1 Incidence of the heart failure hospitalizations at 1 year according to pacing indication and AV hysteresis programming. AV, atrioventricular.
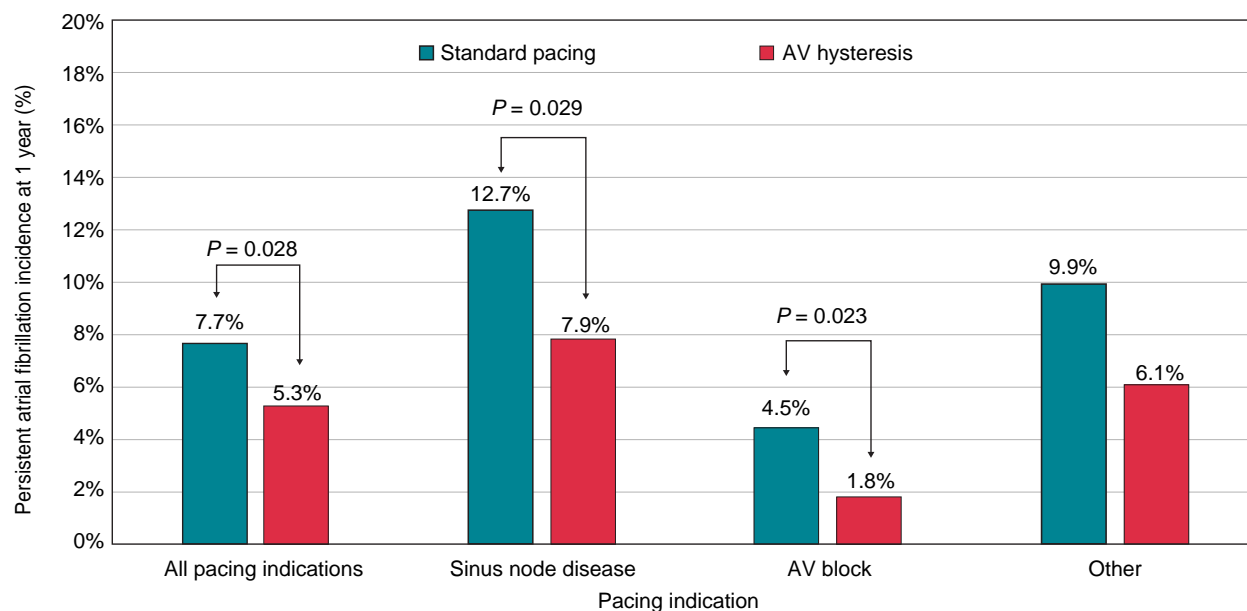
Figure 2 Incidence of persistent atrial fibrillation at 1 year according to pacing indication and AV hysteresis programming. AV, atrioventricular.

was an AVH algorithm (Medtronic Search AV), an algorithm similar to the one used here.

Several algorithms have been proposed to reduce unnecessary ventricular pacing, and their operation is based on two different mechanisms: (i) progressive prolongation of the AV pacing delay (AVH) and (ii) AAI–DDD pacing mode, with both mechanisms having DDD back-up when needed. Both AVH and AAI–DDD modes have been proven in terms of technical efficacy to reduce RVP in several studies.[5]

Several randomized studies have tested the benefit of AAI–DDD switch algorithms in pacemaker patients.[6,7,11,14,15] Even if none of these studies found a significant reduction of the study primary endpoints when comparing AAI–DDD switch algorithms with standard DDD pacing, nevertheless, the ANSWER trial[6] showed a 51% risk reduction in experiencing cardiac death or HFH and a 30% risk reduction in experiencing cardiovascular hospitalizations when using the SafeR algorithm instead of standard DDD pacing.

Furthermore in the SavePACE trial,[8] which showed persistent AF reduction using AVH (Medtronic Search AV), the AAI–DDD switch algorithm (Medtronic MVP) used in 10% of study patients was not associated with persistent AF reduction when compared with standard DDDR pacing. A recent meta-analysis of these studies confirmed that despite a reduction in ventricular pacing, AAI–DDD algorithms failed to affect all-cause death, all-cause hospitalizations, and persistent AF in patients with preserved left ventricular function[9], which constitutes an unexpected result after the clear evidence of deleterious effect of long-term ventricular pacing.

The results here should be interpreted in the context of several similar recent clinical trials.[11,16,17] In the MINERVA trial, the MVP algorithm failed to show a benefit compared with DDDR pacing,[11] but secondary analyses of that trial[16] showed that MVP was associated with a lower risk of persistent AF compared with the DDDR mode in patients with PR < 180 ms and that MVP was associated with a higher risk of persistent AF compared with the DDDR mode in patients with PR ≥ 180 ms. In the DANPACE trial,[17] a higher occurrence of AF was observed in patients with a PR interval longer than 180 ms when treated with AAI pacing compared with standard DDDR. The MVP trial[18] also observed worse clinical outcomes (HFH

and death) in patients with long PR interval treated with MVP compared with DDDR pacing. All these trials strongly suggest that AAI pacing or AAI–DDD switch algorithms, without limitations in the longest allowed AV delays, are less effective in patients with prolonged PR intervals and AV conduction. Programming that allows for markedly prolonged AV delays and does not correct first-degree AVB can worsen mitral regurgitation, shorten diastolic filling, and cause pacemaker syndrome.[19] According to these findings, in patients with prolonged AV conduction, AVH algorithms or AAI–DDD algorithms limited to AV delays shorter than 250 ms may be more physiological and improve clinical outcomes.

Unnecessary ventricular pacing and atrioventricular hysteresis

The AVH algorithm tested in our analyses was associated with a significantly lower VPP in all pacing indications (*Table 2*). The significant reduction in median VPP also observed in patients with AVBs—from 98% [interquartile range (IQR) = 56–99%] with standard pacing to 25% (IQR = 2–74%) with AVH—suggests that in a relevant proportion of patients with AV conduction disturbance, the AV conduction may be more dynamic than previously thought, possibly with significant circadian and/or monthly variations. Interestingly, VPP was reduced with AVH pacing, compared with standard DDD pacing, for all sub-types of AVB. Recently Auricchio and Ellenbogen[5] have suggested that implementation of an algorithm enabling RVP reduction is warranted not only in SND patients but also in patients with intermittent and paroxysmal AVB instead of programming fixed AV pacing intervals.

The AVH algorithm used in our studies was tested in two previous randomized studies[10,20] that showed a significant reduction of unnecessary ventricular pacing compared with standard DDDR pacing. Pakarinen and Toivonen[10] showed that VIP™ reduces VPP in SND patients with both intact and compromised AV conduction. Among 389 SND patients, 30.1% had intact AV conduction (PR interval was ≤210 ms on ECG and 1:1 AV conduction during atrial pacing up to 120 bpm with PR interval ≤ 350 ms), and 69.9% had intermittent AVB. The mean VPP at 12 months was 9.6% by VIP™ compared to

51.8% with standard AV settings in patients with intact AV conduction ($P < 0.0001$) and 28.0% vs. 78.9% ($P < 0.0001$) in patients with compromised AV conduction. In a smaller study, Yadav *et al.*[20] showed similar results; 80 patients were classified to either an intact AV conduction or compromised AV conduction and were then randomized (1 : 1) to the VIP™ algorithm or to standard DDDR with SAV and PAV delays programmed at 150 and 180 ms, respectively. The mean VPP evaluated at 12-month post-implantation follow-ups in the VIP™ ON vs. DDDR groups were 15% vs. 68% ($P < 0.01$) in the intact AV conduction groups and 39% vs. 97% ($P < 0.001$) in the compromised AV conduction groups.

Clinical implications

The observation that the AVH algorithm significantly reduced the median VPP in all the evaluated pacemaker cohorts, regardless of pacing indication (*Table 2*), without safety issues, forms the theoretical basis for proposing AVH not only to SND patients but possibly to all pacemaker patients. With this perspective, it is time to change the current pacing paradigm and attempt to also reduce ventricular pacing frequency in patients with paroxysmal AVBs.[5]

Despite the fact that at pacemaker implant, AV conduction disturbance type—persistent or intermittent—may not be fully known, AVH algorithms seem to be a safe choice because they allow both to reduce the risk of pacing-induced cardiac dyssynchrony and to address the bradycardia indication by providing AV synchrony with good transmitral left ventricle (LV) filling when needed.

The use of algorithms to reduce unnecessary ventricular pacing is indicated by AHA/ACC/HRS[3] and ESC[4] Guidelines in SND patients and suggested for use in patients with intermittent AVB (while taking into account the possibility that prolonged AV conduction in severe first-degree AVB could be disadvantageous from a haemodynamic point of view, possibly being associated with inappropriate timing of atrial and ventricular contraction and/or causing diastolic mitral regurgitation, symptoms, and AF).

Limitations

The BRADYCARE studies were not randomized trials, and therefore, they are subject to all of the limitations of observational studies; selection biases or confounding factors cannot be excluded. Importantly, the baseline characteristics of the two study cohorts—AVH pacing and standard DDD pacing—were very similar (*Table 1* and Supplementary material online, *Table C, D, E* of *Materials*). This suggests that the choice of the pacing mode was likely not driven by different patient characteristics and supports the possibility that the results of our analyses were also not biased by major differences in the patients' characteristics.

Our data did not allow us to compare the pharmacological therapy between the two study groups.

We recognize the fact that we analysed a subgroup (2592) of the whole cohort (5490) of patients included in the BRADYCARE I and BRADYCARE II studies. The selection of the 2592 patients was based on the need to have complete clinical outcomes data and complete device data throughout the 1-year observation period. The comparison of the baseline characteristics of the 2592 analysed patients and the 5490 whole cohort patients (Supplementary material online, *Table F* of *Materials*) shows that the two populations were quite homogeneous.

While the concept of reduction of unnecessary ventricular pacing may be applied also to patients wearing implantable cardioverter defibrillators, the results of our analyses apply to patients with indications for dual-chamber cardiac pacing.

The evaluated cohort of BRADYCARE I and II studies was not dimensioned to evaluate the impact of AVH in all the subgroups of patients identified according to all baseline characteristics.

While higher incidences of HFH and AF are usually associated with higher mortality risk, our data did not show higher incidence of death in the standard pacing group. The 1-year observation period of our study possibly limited the possibility to observe long-term deleterious effects of unnecessary ventricular pacing on the risk of death.

BRADYCARE studies were observational registries with source data verification monitoring activities which warranted coherent reporting from the Hospital Medical Records to the study data collection system. We cannot exclude under-reporting of clinical outcomes data, but we hypothesize that, if that occurred, that would have impacted both patients with and without AVH and therefore should not have biased study results.

Conclusions

In patients indicated to permanent dual-chamber cardiac pacing, incidence of HFH and incidence of persistent AF were significantly lower in patients programmed with an AV delay management via AVH compared with patients with standard pacing.

While it is expected that the use of AV delay managed by AVH is associated with lower VPP in patients with SND, our analyses also showed a reduction of ventricular pacing in a relevant proportion of patients with high-degree AVBs, suggesting that in these patients conduction disease may be intermittent and paroxysmal during follow-up.

Supplementary material

Supplementary material is available at *Europace* online.

Data availability

Some of the data described in this manuscript are available in Clinicaltrial.gov and can be accessed with the following trials' identifiers NCT0106212 and NCT02577887. Other data underlying this article will be shared on reasonable request to the corresponding author.

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