

## Reducing Ventricular Pacing Frequency in Patients With Atrioventricular Block Is It Time to Change the Current Pacing Paradigm?

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With aging of the general population, an increased incidence of conduction disease will result in an increased need for permanent pacemaker therapy. According to the 2015 European Heart Rhythm Association (EHRA) White Book, in the 56 member countries of the European Society of Cardiology (ESC), the pacemaker implantation rate has increased from a mean implantation rate of 614 per million inhabitants in 2010 to 641 in 2014, thus growing at a rate of about 0.4% to 0.6% per year.<sup>1</sup>

Much has been learned from clinical studies to identify optimal device mode selection and device programming for an individual patient to maximize the benefits of cardiac implantable electronic device therapy, as well as to minimize any potential adverse outcomes caused by ventricular pacing (VP). Several clinical studies have reported that chronic right ventricular (RV) pacing has detrimental effects on cardiovascular outcomes, including adverse cardiac remodeling, atrial fibrillation (AF), congestive heart failure (HF), and mortality. The potential mechanism(s) by which RV pacing increases the risk for HF and AF are not completely elucidated, but are likely caused by both electric and mechanical dyssynchrony, disruption of sympathetic/parasympathetic balance that alters myocardial activation pattern and contraction sequence, thereby modifying myocardial strain resulting in less efficient contraction. These changes lead to chamber enlargement, functional mitral regurgitation, reduction of parasympathetic/sympathetic balance in response to reduced ventricular output, and contribute to the development of HF and AF. Notably, not all patients paced in the RV experience adverse outcomes; these detrimental effects seem to be dependent on a high cumulative percentage of RV pacing, generally indicated by >40%. Furthermore, the increased risk of HF has been more frequently observed in those with pre-existing left ventricular (LV) systolic dysfunction. A recent review by Gillis<sup>2</sup> has covered the optimal pacing mode for RV and biventricular devices. It is clear that the abnormal ventricular activation sequence generated by spontaneous left bundle branch block (LBBB) or by RV pacing itself triggers a remodeling process. In the presence of HF and LBBB, simultaneous RV and LV pacing or LV pacing by restoring mechanical synchrony has profound effects at the genome, proteome, transcriptome,

metabolome, cellular, and phenome level.<sup>3</sup> However, full reversal of maladaptive remodeling process at all levels (from subcellular to organ level) induced by biventricular pacing is strongly related to the percentage of continuous biventricular pacing, which shall be as close as to 100% and in any case higher than 95% to maximize the effect.<sup>4-6</sup>

The American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) and ESC/EHRA guidelines recommend the use of pacing algorithms to reduce the percentage of VP.<sup>7,8</sup> This recommendation is the result of 2 decades of clinical trials that led to the deconvolution of the complex electromechanical interaction and effects of pacing on cardiac function and arrhythmias. However, the vast majority of clinical trials tested algorithms, which reduce VP primarily in patients with sick sinus syndrome. Because the most common indication for permanent pacing is intermittent or persistent complete atrioventricular block (AVB)<sup>7</sup> (Web Table 3-ESC GDL 2013); the value of reducing VP has not been tested adequately in this patient group until recently (Table 1).<sup>9-22</sup> New studies have evaluated the use of an algorithm limiting the frequency of VP in patients with advanced or complete AVB (Table 1). The purpose of the present review is to report the recent apparently contradictory data suggesting more aggressively adopting algorithms that reduce the frequency of ventricular pacing in patients with AVB—a population for whom we have typically programmed continuous and uninterrupted ventricular pacing.

### Safety Profile of Algorithmic Reduction in Ventricular Pacing in Patients With Intermittent or Permanent AVB

Clinical practice guidelines strongly recommend the reduction of RV pacing for patients with pacemakers implanted for sinus node dysfunction (SND).<sup>7,8</sup> In patients with intermittent bradycardia, pacing may be required only for short periods of time. The use of VP minimization algorithms in patients with intermittent bradycardia has been rather limited, thus guidelines tend to recommend manual programming of AV intervals ( $\leq 250$  ms) or programming AV hysteresis to prevent unnecessary RV pacing. In this situation, the benefits of preventing bradycardia must be weighed against the detrimental effects

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**Table 1. Prospective Randomized Controlled Studies Testing an Algorithm to Reduce Right Ventricular Pacing (AAI/DDD Switching Algorithm or AV Delay Hysteresis Algorithm) in Pacemaker Indicated Patients**

Study Acronym	Algorithm Tested	Pacing Indication	Study Design	Pts (n)	Follow-Up (y)	Primary End Points	Secondary and Ancillary End Points
DANPACE <sup>9</sup>	AAI/DDD modes	SND	AAIR vs DDDR	1415	5.4	Death: adjusted HR, 0.94 (0.77–1.14), <i>P</i> =0.52	Paroxysmal AF: adjusted HR, 1.24 (1.01–1.52); <i>P</i> =0.042 Chronic AF: adjusted HR, 1.01 (0.74–1.39); <i>P</i> =0.93 Stroke: adjusted HR, 1.11 (0.70–1.77); <i>P</i> =0.65 Pacemaker reoperation: adjusted HR, 2.00 (1.54–2.61); <i>P</i> <0.001
MINERVA <sup>10</sup>	AAI/DDD switching algorithm	SND: 83%	3 arms: MVP, DDDR, DDDRP+MVP	1166	2	Death, cardiovascular hospitalization, or permanent AF: MVP vs DDDR: adjusted HR, 0.89 (0.77–1.03), <i>P</i> =0.12	Death: HR, 0.97 (0.71–1.33); <i>P</i> =0.84
	MVP	AVB: 10%					CV hospitalizations: HR, 0.89 (0.74–1.08); <i>P</i> =0.23
							Permanent AF: HR, 0.90 (0.69–1.15); <i>P</i> =0.39
PreFER MVP <sup>11,12</sup>	AAI/DDD switching algorithm	SND: 62%	MVP vs DDD	605	2.2	CV hospitalization: MVP: 16.3% vs DDD: 14.5%, <i>P</i> =0.72; HR, 1.08 (0.71–1.64), <i>P</i> =0.72	Death or CV hospitalization: 23.9% vs 20.2%; <i>P</i> =0.48
	MVP	AVB: 23%					Stroke: 1.5% in MVP vs 2.1% in DDD; HR, 0.49 (0.15–1.64); <i>P</i> =0.24
							Persistent AF: 15.4% vs 11.2%; HR, 1.52 (0.95–2.42); <i>P</i> =0.08
							Permanent AF: 4.1% vs 3.1%; HR, 1.43 (0.57–3.54); <i>P</i> =0.44 Median VP: 5% vs 86%; <i>P</i> <0.0001
ANSWER <sup>13,14</sup>	AAI/DDD switching algorithm	SND: 48%	Randomized (1:1) SafeR™ vs DDD	650	3	Median VP at 1 y: 4.8% in SafeR™ arm vs 95.4% in DDD arm, <i>P</i> <0.0001 HF hospitalization, AF, or cardioversion at 3 y: HR, 0.78 (0.48–1.25), <i>P</i> =0.30	Median VP at 3 y: 11.5% in SafeR™ arm vs 93.6% in DDD arm; <i>P</i> <0.0001
	SafeR™	AVB: 52%					In AVB pts: median VP at 3 y: 55.0% in SafeR™ arm vs 97.9% in DDD arm ( <i>P</i> <0.001)
							Cardiac death or HF hospitalization HR 0.49 (0.27–0.90); <i>P</i> =0.02
							CV hospitalization: HR, 0.70 (0.49–1.00); <i>P</i> =0.05
							AF onset in patients without AA history: HR, 0.77 (0.59–1.00); <i>P</i> =0.049 40
CAN-SAVE R <sup>15,16</sup>	AAI/DDD switching algorithm	SND: 56%	Randomized (1:1) SafeR™ vs DDD	450	3	Median VP at 1 y: 0% with SafeR™ vs 4.0% with DDD, <i>P</i> <0.001	Median VP at 3 y: 0% with SafeR™ vs 10% with DDD, <i>P</i> <0.001
	SafeR™	AVB: 44%					At 3 y no difference between groups in AF burden AF related events: 3.7% with SafeR™ vs 8.8% with DDD, <i>P</i> =0.04

(Continued)

Table 1. Continued

Study Acronym	Algorithm Tested	Pacing Indication	Study Design	Pts (n)	Follow-Up (y)	Primary End Points	Secondary and Ancillary End Points
EVITA <sup>17</sup>	VIP OFF vs VIP ON (St. Jude)	SND and AVB	Randomized (1:1)	389	1	Groups VIP OFF and VIP ON in patients with compromised AV conduction (AVc: AV conduction time >325 ms) or with intact AV conduction (AVi, other patients)	AV conduction over time. At baseline 106 patients in the AVc had an AV block (12% with an episodic AV block III). After 12 mo, 113 patients were in AVB (P=0.54). In the AVi group 5 patients developed third-degree AVB (P=0.06)
						Median VP in AVi pts: 1% with VIP ON vs 60% with VIP OFF, P=0.0001	
COMPARE <sup>18</sup>	MVP and SAV+	SND: 76%	Randomized (1:1)	385	1	Median VP: in SND pts: 0.2% with MVP vs 1.4% with SAV+, P<0.0001 in AVB pts: 11.8% with MVP vs 98.1% with SAV+, P<0.001	In pts with PR intervals ≥200 ms, median VP was 1.40% with MVP group vs 98.90% with SAV+, P=0.004.
		AVB: 23%					Persistent/permanent AF: 5.8% with MVP vs 4.6% of with SAV+
MinVPace <sup>19</sup>	DDD	SND: 92% AVB: 8%	Randomized with triple crossover	110	3×2 mo	Median VP: 86% in the control phase, 2.0% in the MinVP phase, 3% in the MinVP+anti-AF algorithms	Median atrial pacing: 51.5% in the control phase, 47.6% in the MinVP phase, 81.1% in the MinVP+anti-AF algorithms
	MinVP						AF burden: 13.8% in the control phase, 14.4% in the MinVP phase, 14.7% in the MinVP+anti-AF algorithms
	MinVP+anti-AF algorithms						
Long	MinVP vs DDD	SND: 92% AVB: 8%	Randomized (1:1)	66	1.4	Median VP: 5.8% with MinVP vs 74% with DDD, P<0.001	Persistent AF: 9% with MinVP vs 42% with DDDR, P=0.004
MinVPACE <sup>20</sup>						AF (device-derived) 12.8% with MinVP vs 47.6% with DDD, P<0.001	
IDEAL RVP <sup>21</sup>	MVP and SAV+	SND: 56%	Pacemaker equipped with both algorithms	127	1 mo	% of pts with a median VP<40%: 66.1% with MVP vs 54.3% with SAV+	Median AP: 41.1% with MVP vs 35.8% with SAV+
		AVB: 46%				% of pts with a median VP<10%: 57.5% with MVP vs 38.6% with SAV+	
SAVEPACE <sup>22</sup>	MVP vs DDD	SND	Randomized (1:1)	1065	1.7	Persistent AF: 7.9% in the MVP arm vs 12.7% in the DDD arm, P=0.004, absolute reduction of AF with MVP of 3.8% at 1 y and 6.9% at 3 y, multivariate analysis showed a 40% decrease in the relative risk of persistent AF with MVP compared with DDD	Other predictors of persistent AF: age, previous AF, antiarrhythmic drug use
							Mortality rate: 4.9% with MVP vs 5.4% with DDD
							Hospitalization for HF: 2.8% with MVP vs 3.1% with DDD

AA indicates atrial arrhythmia; AAI, single-chamber atrial pacing; AF, atrial fibrillation; AP, atrial pacing; AV, atrioventricular; AVB, atrioventricular block; CV, cardiovascular; DDD, dual-chamber pacemaker; HF, heart failure; HR, hazard ratio; MVP, managed ventricular pacing; SAV, search AV; SND, sinus node disease; VIP, ventricular intrinsic preference; and VP, ventricular pacing.

of permanent pacing, particularly pacing-induced HF. In persistent AVB patients, clinical practice guidelines recommend the implantation of a dual-chamber pacemaker (DDD) with programming of an AV delay in a conventional manner. That is because of safety concerns and the lack of data on the use of VP management algorithms in permanent AVB at the time of clinical practice guidelines publication.

Over the past 2 years, 3 major studies have tested the use of an algorithm that reduces VP in a mixed pacemaker populations, which also included patients with intermittent or permanent AVB (Table 1). Of these studies, 1 study used the managed ventricular pacing (MVP) algorithm (Medtronic, Minneapolis, MN) and 2 studies tested the SafeR algorithm (LivaNova, Clamart, France). The SafeR pacing mode is currently the only algorithm that was designed to adapt to a patient's varying AV conduction depending on the severity of the AV conduction disorder and to combine the benefits of single-chamber atrial pacing (AAI) with the safety of DDD pacing (Table 2). Several randomized trials have previously confirmed effective VP prevention and safety of this algorithm. For example in the SafeR study,<sup>23</sup> SafeR reduced VP over 1 year in selected patients with preserved or minimally impaired AV conduction compared with DDD pacing. However, long-term data on the impact of SafeR on the risk of developing adverse cardiac events, including syncope, HF or AF in patients with intermittent or permanent AVB have been lacking until recently. These aspects have been investigated in CAN-SAVE R (Canadian Multi-Centre Randomised Study–Spontaneous Atrioventricular Conduction Preservation)<sup>15,16</sup> and in ANSWER (Evaluation of the SafeR™ Mode in Patients With Dual-Chamber Pacemaker Indication).<sup>13,14</sup>

The CAN-SAVE R study<sup>15,16</sup> included 373 patients with indications for DDD pacemakers in 10 Canadian centers. Patients were randomized 1:1 to SafeR™ or DDD pacing with a long AV delay (250 ms); SND was present in 73% (81% of whom had no concomitant AVB) and AVB in 41% (66% of whom had no concomitant SND). Interestingly, at 1 year of follow-up, the median proportion of VP beats was 4.0% with DDD versus 0% with SafeR ( $P<0.001$ ), respectively. In the 41% of patients with some degree of AVB at baseline, median RV pacing rates at 1 and 3 years of follow-up remained  $\leq 1\%$  with SafeR compared with 37.3% and 41.8% in the DDD group (both  $P<0.001$ ). At 3 years of follow-up, 64% of patients in the SafeR group had  $<1\%$  RV pacing and 91% had  $<40\%$  RV pacing. In comparison, corresponding RV pacing rates in the DDD group were 34% ( $P<0.001$ ) and 67% ( $P<0.001$ ). Within the subgroup of patients with intermittent AVB, the impact of SafeR remained substantial, with the proportion of RV pacing reduced from 42% to 1%. This marked reduction did not compromise patient safety; in contrast, 80.2% of patients in DDD and 80.6% of patients in SafeR mode reported an adverse event, including all-cause death and cardiovascular events. Importantly, there were no differences between the 2 groups with respect to stroke, HF, or syncope, although the number of events was small.

The ANSWER study<sup>13,14</sup> enrolled 650 consecutive patients with a pacemaker indication at 43 European centers and randomized them to programming either the SafeR algorithm or conventional DDD pacing. Approximately half

of the population had SND (52%) or AVB (48%); the vast majority of patients with AVB had an intermittent AVB. Six hundred thirty-two patients were randomized to SafeR ( $n=314$ ) or in DDD ( $n=318$ ). The ANSWER data showed that SafeR can safely reduce VP in a general AVB population. In these patients, the SafeR mode showed a significant decrease in VP compared with DDD programming (55.0% versus 97.9%,  $P<0.001$  at 3 years). The greatest benefit was noted in patients with intermittent AVB. Indeed in this latter patient group, the SafeR mode showed a significant decrease in VP compared with DDD (53.5% versus 98.2%,  $P<0.001$  at 3 years). Although patients with permanent AVB did not experience any reduction in VP with SafeR, the SafeR algorithm appeared to be safe and well tolerated in this subgroup. About 40% of patients with either intermittent or permanent AVB randomized to SafeR mode had VP  $<50\%$  over a 3 year time; indicating that, in a sizeable proportion of patients with AV conduction disturbance, the AV conduction shows significant circadian and monthly variation. In other words, AVB is more dynamic than previously thought. However, in a proportion of patients, intermittent AVB appeared to evolve to permanent AVB. Indeed, patients with intermittent AVB treated with SafeR had an increase in VP frequency from a mean value of 41.6% at 1 month to 59.6% at 3 years (Figure 1A, courtesy from M. Stockburger). Although these figures were always significantly lower than those seen in patients with DDD pacing mode, the trend was similar. All together, these data suggest the need for continuous AV conduction assessment and management even in patients with intermittent and permanent AVB and a more aggressive implementation of an algorithm enabling the reduction of VP compared with today's practice of programming a fixed AV interval in this subgroup. Importantly, no differences in the occurrence of death, syncope, or pacing mode intolerance were observed between groups and implant indications.<sup>13</sup> None of the syncope events reported in the ANSWER study was related to a recorded complete AVB episode. The event-related analysis of stored electrograms did not reveal any ventricular arrhythmias prompted by SafeR changeovers.<sup>14</sup>

#### Possible Consequences of the Use of Algorithm Reducing RV Pacing in Patients With Intermittent or Permanent AVB

Patients with cardiac implantable electronic device incur an increased risk of complications and cost related to pulse generator replacement.<sup>24</sup> Generator lifespan is an important determinant of the cost-effectiveness of pacemaker therapy. The current estimated longevity of a modern DDD pulse generator with a high burden of VP approaches 10 years. Algorithms leading to a VP reduction may further and significantly contribute to device longevity. In the ANSWER study, the significant VP reduction achieved by the SafeR pacing mode when compared with standard DDD mode translated into an additional calculated gain of about 1 year in device longevity ( $130.6\pm 23.4$  months and  $117.0\pm 20.0$  months, respectively).<sup>13</sup> This potential benefit was similar in SND and intermittent AVB patients. In contrast, in patients with permanent AVB, there was no noticeable effect on device longevity. Stockburger et al<sup>13</sup> calculated

**Table 2. Description of the 5 Algorithms Designed to Reduce Unnecessary VP**

Managed Ventricular Pacing (MVP Medtronic, Minneapolis, MN)
Atrial-based pacing in AAI(R) with switch to DDD(R) if AV block is detected, defined as 2/4 absent ventricular events. The algorithm checks for AV conduction at regular intervals and if present, it will switch back to AAI(R)
MVP remains in AAI if first AV block degree is detected; the user manual recommends programming to DDD
Search AV+ (SAV+, Medtronic, Minneapolis, MN)
The pacemaker searches for the patient's intrinsic AV conduction time and adjusts the SAV and PAV intervals either longer or shorter to promote intrinsic activation of the ventricles. The pacemaker assesses the 16 most recent AV conduction sequences and adapts the operating SAV and PAV intervals to the observed conduction time (either lengthens the operating SAV and PAV intervals by 62 ms for the next 16 pacing cycles to promote intrinsic conduction or shortens the operating SAV and PAV intervals by 8 ms for the next 16 pacing cycles). The maximum amount of time by which the SAV and PAV can be lengthened is limited by the Search AV+ Maximum Increase to AV parameter
Reverse Mode Switch (RHYTHMIQ, Boston Scientific, St. Paul, MN)
Atrial-based pacing in AAI(R) with VVI backup (LRL minus 15/min), the 2 modes operate independently from one another. If complete AVB occurs, ventricular pacing will be delivered at backup VVI rate, asynchronous to the AAI rate. If 3 slow ventricular beats are detected in a window of 11 beats, AV conduction is considered blocked and switch to DDD(R) takes place. The algorithm will switch back to AAI if intact AV conduction is recuperated
AAI to DDD switch when the VV intervals are longer than A-A+150 ms for several beats (no AV interval criterion). The pacemaker will not switch if progressive PR prolongation occurs and the VV interval stays shorter than AA+150 ms
SafeR™ mode (LivaNova, Clamart, France)
Atrial-based pacing in AAI (R). Switch to DDD(R) in response to any of the following:
<ul style="list-style-type: none"> <li>• AAI to DDD switch on 6 consecutive PR intervals longer than the programmed long PR limit (AVB I criteria). The allowed duration of PR varies with the heart rate. In addition, the maximum allowed duration of PR intervals is programmable (physicians' choice)</li> </ul>
<ul style="list-style-type: none"> <li>• 3/12 non conducted atrial events (AVB II criteria)</li> </ul>
<ul style="list-style-type: none"> <li>• 2 consecutive non conducted atrial event (AVB III criteria), ventricular pauses of 2–4 s (programmable)</li> </ul>
Ventricular Intrinsic Preference (VIP, St. Jude Medical, Sylmar, CA)
Intrinsic AV conduction is assessed by increasing AV delay at regular intervals (programmable AV extension of $\leq 200$ ms; maximum AV delay 350 ms). If present, the longer AV delay will be maintained until a programmable number of cycles of absent ventricular sensed events (ie, continuous need for ventricular pacing), thus deactivating the algorithm.
AV hysteresis (Biotronik, Berlin, Germany)
Similar to Ventricular Intrinsic Preference (St. Jude)
VP suppression (Biotronik, Berlin, Germany)
In ADI(R) mode, intrinsic conduction is monitored within a 450 ms interval after each atrial event. A cycle without intrinsic ventricular conduction triggers a further 8-cycle evaluation period. If any of the following criteria are met, the device reverts to DDD(R):
<ul style="list-style-type: none"> <li>• 2 consecutive cycles without intrinsic ventricular conduction</li> <li>• a programmable number (1–8) out of 8 cycles without intrinsic conduction</li> <li>• no VS event for 2 or more seconds</li> </ul>
If the long PR interval is shorter than 450 ms, the pacemaker will not switch to DDD

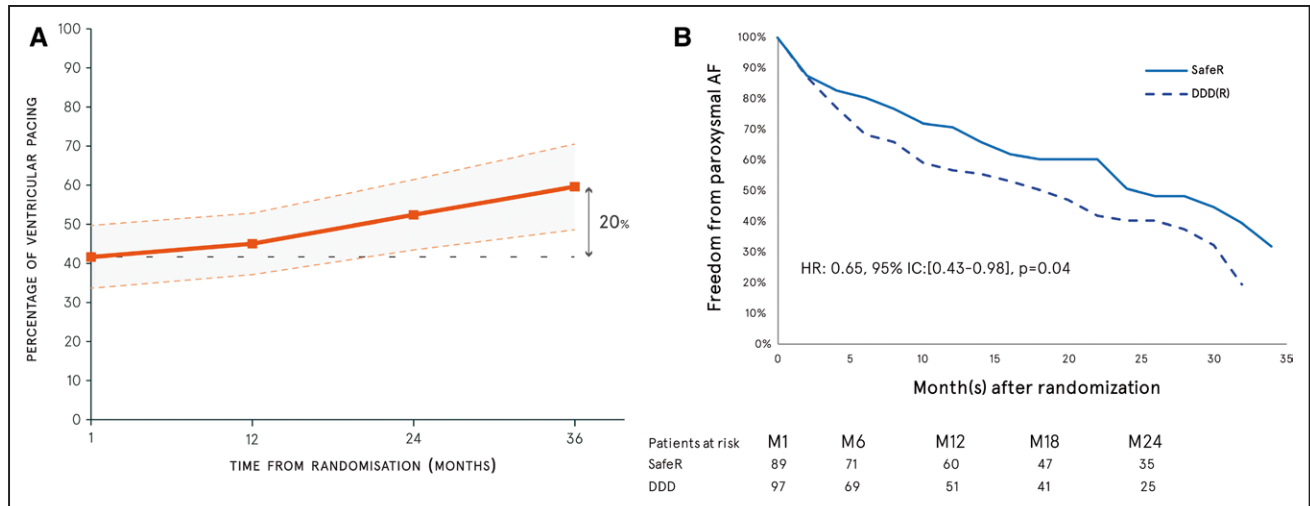
AAI indicates single-chamber atrial pacing; AV, atrioventricular, AVB, atrioventricular block; DDD, dual-chamber pacemaker; MVP, managed ventricular pacing; SAV, search AV; and VP, ventricular pacing.

the effect of the increased device longevity on SafeR versus DDD in both intermittent AVB and SND patients on device replacement. On average, 28% of women and 23% of men would avoid one pulse generator replacement with SafeR programming across their lifetime compared with DDD pacing.

Although mode switching algorithms designed to manage different types of AVB efficiently reduce RV pacing, the translation of this reduction into clinical benefit remains controversial (Table 1). This controversy stems from the report by Nielsen et al<sup>9</sup> in the Danish multicenter randomized DANPACE trial (The Danish Multicenter Randomized Study on AAI Versus DDD Pacing in Sick Sinus Syndrome) of the deleterious impact of long PR intervals in patients with SND.<sup>25</sup> The authors showed that patients with SND and prolonged PR interval should be

preferably treated with DDDR pacing with an individually programmed moderately prolonged AV delay. These results are in line with previous findings in a large community-based cohort study, where a PR interval  $>200$  ms was associated with a 2-fold increased risk of AF onset when compared with a shorter PR interval.<sup>26</sup> The issue of PR prolongation is probably even more pronounced in patients with AVB. Although previous small noncontrolled studies with short follow-up reported effective VP prevention in patients with AVB through the MVP AAI-DDD changeover algorithm,<sup>27</sup> the application of the MVP mode in patients with AVB has been questioned because of the possibility of excessively long AV delays.<sup>28–34</sup> These concerns were amplified in a trial of MVP in patients receiving a pulse generator or an ICD. The MVP algorithm





**Figure 1.** **A**, Ventricular pacing frequency (mean, 95% confidence intervals [CIs]) in patients with intermittent atrioventricular (AV) block treated with SafeR in the evaluation of the SafeR™ mode in patients with dual-chamber pacemaker indication (ANSWER) study; increase from a mean value of 41.6% at 1 mo to 59.6% at 3 y, mean difference intrapatient of 20%. **B**, Freedom from paroxysmal atrial fibrillation in complete AV block patients without history of atrial fibrillation at baseline included in the ANSWER study. DDD indicates dual-chamber pacemaker; and HR, hazard ratio.

was associated with more HF and worse outcomes in patients with longer PR intervals.<sup>12,35,36</sup> The adverse hemodynamic effects of long PR intervals, through prolonged intrinsic AV conduction, comprise shortening and impairment of LV filling and increased left atrial pressure. In some patients, symptoms resembling pacemaker syndrome are provoked by the unfavorable prolongation of the AV electromechanical sequence. Hence, VP prevention in the case of marked first-degree AVB may unintentionally impair hemodynamics, despite preserving ventricular synchrony, a situation which may be amplified in patients with decreased LV function.

### Do All Ventricular Pacing Minimization Algorithms Behave the Same in Patients With AVB?

The algorithms available for minimizing RV pacing include programming long AV delays or dynamic extension of AV delays (hysteresis), or the use of specific algorithms for RV pacing minimization switching from AAI to DDD pacing in the presence of AVB. AV delay extension algorithms have been designed for occasional AVB or first-degree AVB in patients with SND, but not for second- or third-degree AVB management; therefore, they are not further discussed in this article.

The algorithms designed to minimize VP operate by prolonging the AV interval with hysteresis or by switching between DDD and AAI modes are summarized in Table 2. The operative features differ between manufacturers, but all carry the risk of AV decoupling (defined as >40% increase of AV intervals over 300 ms) even when the baseline PR interval is normal, thus leading to worsened clinical outcomes.<sup>35</sup> This adverse effect is addressed differently (or not addressed at all) according to the specificities of each manufacturer's algorithm (Table 2).

MVP does not switch from AAI to DDD mode as long as a ventricular event is detected between 2 normal atrial events (paced or sense); consequently, it will not pace the ventricles in case of markedly prolonged PR intervals, which can adversely affect cardiovascular hemodynamics, reducing atrial contribution to ventricular filling and favoring diastolic mitral

regurgitation.<sup>26</sup> In addition, prolonged PR intervals lead to AV decoupling which may trigger increased sympathetic activation and, in some patients, autonomic reflexes leading to symptoms of pacemaker syndrome. Lim<sup>37</sup> has recently indicated that this algorithm should be confined to patients in sinus rhythm with SND, narrow QRS (<120 ms), and no significant AV conduction disease, and that patients with second- or third-degree AVB should not be prescribed MVP. The recently published prospective, randomized PREFER MVP study (Prefer MVP for Elective Replacement) has indicated that the lack of adequate PR management can be detrimental to patients<sup>11,12</sup>: 605 patients referred for generator replacement of a pacemaker or ICD were enrolled if they had a history of >40% VP. Patients were allocated to receive either standard DDD or MVP pacing.<sup>11</sup> A secondary analysis of the study<sup>12</sup> showed that history of atrial arrhythmias and VP%  $\geq 10\%$ , estimated in the first 3 months, were independent predictors for persistent atrial arrhythmias observed in 71 patients (11.7%) after 2 years of follow-up, and that MVP was associated with an increased risk of persistent atrial arrhythmias (hazard ratio [HR], 3.41; 95% confidence interval, 1.10–10.6;  $P=0.024$ ) in the subgroup of patients with baseline long PR interval (PR>230 ms). This is consistent with the results from the earlier study of Sweeney et al.<sup>36</sup>

The SafeR algorithm was designed to manage PR prolongation in patients with AVB as long as in patients with other atrioventricular conduction disorders (Figure 2). In particular, the algorithm switches from AAI to DDD when 6 long PR intervals (programmable) are detected (Table 2). As PR evolves according to patients' activity, the AVB I degree criterion can be programmed either to rest+exercise (the device will switch to DDD during rest and exercise phases) or to exercise only (the device will switch to DDD during exercise phase only). Stockburger et al<sup>38</sup> reported the validation of the SafeR algorithm for all types of AVB and its safety profile in both SND and AVB populations.<sup>13</sup>

The management of long PR seems particularly relevant as recent analyses on the ANSWER database showed that 25% of

patients with SND and 48% of patients with AVB had a long PR at baseline ( $>230$  ms), responsible for a high proportion of AVB I degree switches, and that patients with long PR ( $\geq 230$  ms) were 1.68 more likely to develop persistent AF (HR, 1.68; 95% confidence interval, 1.06–2.65;  $P=0.027$ ).<sup>39</sup> In addition, SafeR was associated with a 35% risk reduction in AF onset over 3 years in AVB patients without history of atrial arrhythmias (HR, 0.65; 95% confidence interval, 0.43–0.98;  $P=0.038$ ; Figure 1B).<sup>40</sup> This result remains in agreement with previously published data.<sup>41</sup> Other VP algorithms are briefly summarized in Table 2.

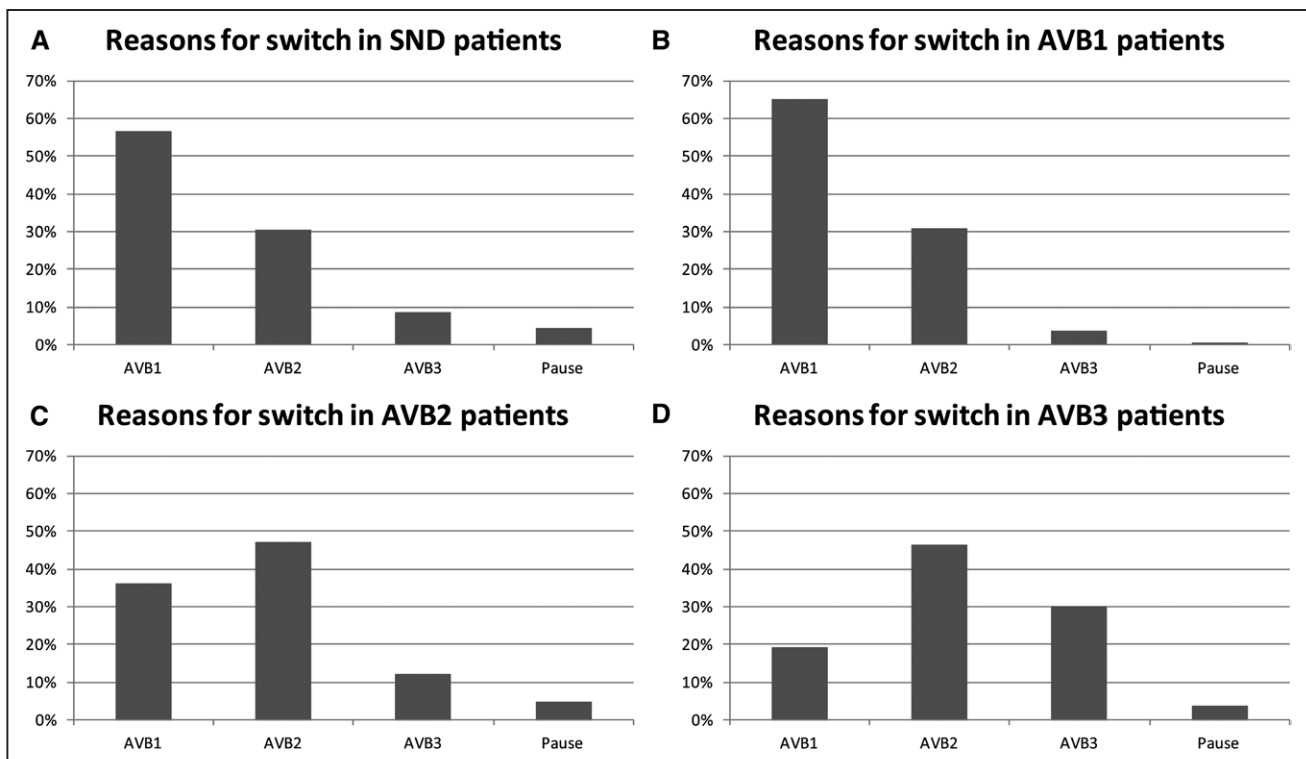
### BIOPACE, BLOCK HF, and MADIT-CRT Implication for Reduced Ventricular Pacing Mode

The recent results of both ANSWER and the CAN-SAVE R study should be further assessed within the context of recent studies on the management of patients possibly requiring a high VP burden.

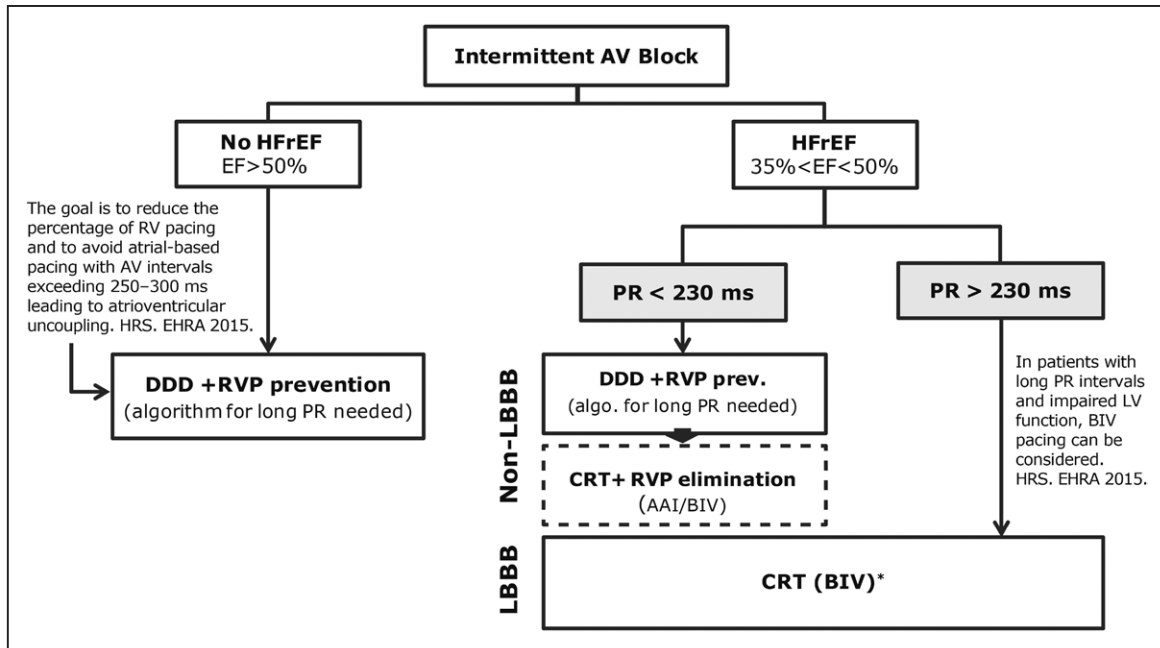
The BIOPACE study (Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization) failed to meet its primary objective (mortality and HF hospitalization) to determine whether synchronous BiV pacing confers a clinical benefit in patients with conventional indications for permanent VP, regardless of spontaneous QRS duration and morphology or LV size and function, by preventing iatrogenic ventricular desynchronization because of unilateral RV pacing.<sup>42</sup> In the BIOPACE study, the mean LV ejection fraction was  $55\pm 12\%$  and the trial included only a low proportion of patients with complete AVB or PR interval above

230 ms. The mean follow-up was 67 months. The BLOCK-HF study (Biventricular Versus Right Ventricular Pacing in Heart Failure Patients With Atrioventricular Block) met its primary end point and showed that BiV reduces the risk of all-cause mortality, HF-related urgent care visits, or an increase  $\geq 15\%$  LV end systolic volume index for patients with AVB and systolic dysfunction.<sup>43</sup> Notably, the positive result in BLOCK-HF was almost solely driven by changes in LV end systolic volume and not clinical end points. Pacemaker patients included in BLOCK-HF had a mean LV ejection fraction of  $44\pm 6.5\%$  and an LV ejection fraction lower than that reported in the BIOPACE study; moreover, the mean follow-up time was only about half of the BIOPACE study. Another important peculiarity of BLOCK-HF study was the device programming in the group randomized to conventional DDD pacemaker; in these latter patients, the AV interval was programmed to result in continuous RV pacing, which may have provoked significant LV dyssynchrony.

A recent subanalysis of MADIT-CRT study (Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy) evaluating the importance of long PR interval ( $>230$  ms) in patients with non-LBBB, showing that only those HF patients with a long PR interval and non-LBBB QRS derive a significant clinical benefit from the implantation of CRT-D versus ICD-only.<sup>44</sup> In contrast, patients with non-LBBB implanted with CRT-D with a normal PR interval have an increased risk of all-cause mortality compared with ICD only therapy, suggesting a significant bidirectional interaction between baseline PR interval and clinical benefit



**Figure 2.** Distribution of single-chamber atrial pacing to dual-chamber pacemaker switches in sinus node dysfunction (**top left**), and atrioventricular block (AVB) patients of first degree (**top right**), second degree (**bottom left**), and complete block (**bottom right**) of the evaluation of the SafeR mode in patients with dual-chamber pacemaker indication (ANSWER) study included in the SafeR arm. SND indicates sinus node dysfunction.



**Figure 3.** Proposed CRT indication as a function of left ventricular ejection fraction (EF) and ventricular pacing percentage. CRT may be indicated for patients with moderately reduced EF and high ventricular pacing demand. In patients with preserved EF and normal PR interval, ventricular pacing reduction algorithm may be preferred to standard dual-chamber pacemaker (DDD). In patients with intermediate EF and prolonged PR interval, combined CRT and ventricular pacing reduction algorithm may be a suitable option. \*Patients with left bundle branch block (LBBB) will not benefit from reduced ventricular pacing (RVP) as RVP trades VP pacing induced LBBB vs natural LBBB. AV indicates atrioventricular; BIV, biventricular pacing; and HFrEF, heart failure with reduced ejection fraction.

from CRT-D in the non-LBBB population. Furthermore, this MADIT-CRT subanalysis confirmed that the PR interval is a powerful prognostic marker of cardiac events in patients with non-LBBB, mild HF, and a wide QRS. Thus, taken together the results of BIOPACE, BLOCK-HF, ANSWER, CanSaveR, and MADIT-CRT suggest the possibility that, in patients with advanced AVB, the use of an algorithm which significantly reduces VP shall be preferred, whereas in those patients with moderately depressed LV ejection fraction and markedly prolonged PR, a biventricular device shall be preferred to a conventional DDD pacemaker (Figure 3).

## Conclusions

We should reconsider the opportunity for VP reduction for patients with AVB in the light of these recent studies. Unfortunately, not all algorithms are the same, some do not adequately manage long PR intervals and clinicians would benefit from further improvements of algorithms. Recently published studies highlight the fact that reduction of %VP can be achieved safely even in patients with AVB while managing a long PR interval. Such an option might be preferred over implanting a more complex CRT-P system.

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## Disclosures

Dr Auricchio is a consultant to Boston Scientific, Medtronic, LivaNova. He is on the speakers' bureau of Boston Scientific, Medtronic, LivaNova. Dr Ellenbogen is a consultant to Medtronic and Boston Scientific and on the speaker's bureau of Medtronic, Boston Scientific, St. Jude Medical, and Biotronik.

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KEY WORDS: atrioventricular block ■ atrial fibrillation ■ bundle branch block ■ heart failure ■ mortality

## Reducing Ventricular Pacing Frequency in Patients With Atrioventricular Block: Is It Time to Change the Current Pacing Paradigm?

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