JACC: CLINICAL ELECTROPHYSIOLOGY
VOL. 3, NO. 5, 2017

ISSN 2405-500X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacep.2016.11.011

# Atrioventricular Interval Extension Is Highly Efficient in Preventing Unnecessary Right Ventricular Pacing in Sinus Node Disease

## A Randomized Cross-Over Study Versus Dual- to Atrial Single-Chamber Mode Switch

Valeria Calvi, MD,[a] Ennio C. Pisanò, MD,[b] Marco Brieda, MD,[c] Donato Melissano, MD,[d] Bruno Castaldi, MD,[e] Ciro Guastaferro, MD,[f] Gerardo Nigro, MD, PhD,[g] Michela Madalosso, MD,[h] Daniela Orsida, MD,[i] Nicola Rovai, MS,[j] Alessio Gargaro, MS,[j] Alessandro Capucci, MD[k]

## ABSTRACT

**OBJECTIVES** This study sought to compare the Intrinsic Rhythm Support (IRSplus) and Ventricular Pace Suppress (VpS) in terms of right ventricular pacing percentage (VP%), mean atrioventricular interval (MAVI), atrial fibrillation, and cardiac volumes.

**BACKGROUND** Modern pacemakers are provided with algorithms for reducing unnecessary ventricular pacing. These may be classified as: periodic search for intrinsic atrioventricular (AV) conduction prolonging the AV delay accordingly; or DDD-ADI mode switch. The IRSplus and VpS algorithms belong to the former and latter classes, respectively.

**METHODS** Patients with sick sinus dysfunction without evidence of II/III degree AV block were 1:1 randomized to 6-month periods of either IRSplus or VpS, and then crossed over. Subsequent follow-ups were at the 12th month after randomization for device data retrieving, and at the 18th month with the same device programming for echocardiographic assessment.

**RESULTS** A total of 230 patients (62% males, median age 75 years [interquartile range: 69 to 79 years]) were enrolled. At a linear mixed-model analysis with order of treatment and investigational sites as nested random effects, differences in VP% and MAVI reached statistical significance: VP% was 1% (0% to 11%) during IRSplus and 3% (0% to 26%) during VpS ($p = 0.029$); MAVI was 225 ms (198 to 253 ms) during IRSplus and 214 ms (188 to 240 ms) during VpS ($p = 0.014$). No differences were observed in atrial fibrillation burden and incidence, ejection fraction, and cardiac volumes.

**CONCLUSIONS** Both IRSplus and VpS algorithms ensured VP% ≤3% in most patients with sinus node dysfunction and preserved AV conduction. The IRSplus was slightly more efficient in reducing VP% at the expense of a small MAVI increase, with statistical but clinically insignificant differences. (Ventricular Pace Suppression Versus Intrinsic Rhythm Support Study; NCT01528657) (J Am Coll Cardiol EP 2017;3:482–90) © 2017 by the American College of Cardiology Foundation.

The detrimental effects of long-term unnecessary right ventricular (RV) pacing have been extensively described (1-4). During the last decade, these observations have led to the development of pacing algorithms designed to deliver RV pacing only when strictly necessary. Dual-chamber to atrial single-chamber automatic mode switches have been proposed to completely

From the [a]A.O.U. Policlinico Vittorio Emanuele, PO Ferrarotto, Catania, Italy; [b]Vito Fazzi Hospital, Lecce, Italy; [c]Santa Maria Degli Angeli Hospital, Pordenone, Italy; [d]F. Ferrari Hospital, Casarano (LE), Italy; [e]F. Veneziale Hospital, Isernia, Italy; [f]San Leonardo Hospital, Castellammare (NA), Italy; [g]AORN dei Colli - PO V. Monaldi, Napoli, Italy; [h]Dell'Angelo Hospital, Mestre (VE), Italy; [i]San Antonio Abate Hospital, Gallarate, Italy; [j]BIOTRONIK Italia S.p.A., Vimodrone (MI), Italy; and the [k]A.O.U. Ospedali Riuniti, Ancona, Italy. The VIPERS study was sponsored by BIOTRONIK SE & Co. KG. Drs. Rovai and Gargaro are employed by Biotronik Italy S.P.A. Dr. Capucci has received speaker fees from Bayer, Boehringer Ingelheim, Abbott, Pfizer, MEDA, Boston Scientific, Medtronic, and Sorin. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received July 28, 2016; revised manuscript received October 20, 2016, accepted November 17, 2016.

suppress RV pacing to the point of atrioventricular (AV) conduction block, even at the cost of persistently prolonged or very prolonged AV delays. Several studies have so far been conducted to evaluate the efficacy of such mode switch algorithms as compared to less aggressive algorithms essentially based on the periodic search for intrinsic conduction and on hysteresis of the programmed AV delay (5–9). Meanwhile in modern pacemaker generations, the increasingly extended programmability range of AV delay may have made the latter class of algorithms more efficient. This raises the question of whether the 2 approaches may perform equivalently at least in patients with sinus node disease (SND) as the primary indication for cardiac pacing. The VIPERS (Ventricular Pace Suppression Versus Intrinsic Rhythm Support Study) (NCT01528657) was a randomized study with the objective of intra-individually comparing the 2 AV delay management approaches in SND patients implanted with new generation devices capable of AV delay extensions of up to 400 ms. AV delay management algorithms were compared in pre-specified patient subgroups in terms of RV pacing percentage (VP%), mean AV interval, and atrial fibrillation (AF) incidence, while monitoring their effect on cardiac volumes during a 1-year term.

SEE PAGE 491

## METHODS

The VIPERS trial was a multicenter, randomized, cross-over, controlled clinical trial with follow-up visits scheduled at 6, 12, and 18 months after a 1-month post-enrollment run-in period. It was designed to compare the effect on VP%, AV interval, and atrial arrhythmic burden of 2 algorithms, the intrinsic rhythm support (IRSplus) and the ventricular pace suppression (VpS), both intended to minimize ventricular pacing. The study protocol was approved by the competent ethics committee of each participating investigational site and was conducted in accordance with the Declaration of Helsinki and local regulations.

**SELECTION OF PATIENTS.** Study subjects were selected among patients who were indicated for or had already received a dual-chamber pacing system no earlier than 6 months previously and according to the following inclusion criteria: 1) Class I indication for dual chamber pacemaker due to SND according to current recommendation; 2) dual chamber devices equipped with the IRSplus and VpS algorithms (BIOTRONIK SE & Co. KG, Berlin, Germany); and 3) RV lead in the apical position. Patients were excluded in case of: 1) permanent or intermittent AV block ≥ II; 2) permanent AF; 3) device replacement; 4) life expectancy <12 months; and 5) pregnant women or minor age. All patients provided written informed consent.

**ALGORITHM CHARACTERISTICS.** The IRSplus function operates to maintain spontaneous AV conduction as long as possible, essentially acting as a combination of AV hysteresis and a search for intrinsic conduction (Figure 1A). Nominal sensed and paced AV intervals can be selected in the range from 15 ms to 350 ms in 5-ms steps in 6 rate ranges, separately. When AV hysteresis is activated, the AV delay is automatically extended up to 400 ms after 1 single intrinsic ventricular event. When intrinsic conduction is lost, the system continues applying the extended AV delay for up to 10 cycles (5 during the study), before switching back to the nominal AV delay, in order to promote restoration of conduction. In addition, in case of persistent ventricular pacing, up to 10 extended AV delays (5 during the study) are applied every 180 consecutive pacing cycles to search for spontaneous ventricular activity.

The VpS algorithm is a dual- to atrial single-chamber mode switch (DDD(R) to ADI(R)) algorithm automatically activating when specific conduction tests have been successfully passed (Figure 1B). Depending on the intrinsic rhythm, the algorithm is either in the ADI(R) mode, promoting intrinsic AV conduction regardless of the PQ interval, or in the DDD(R) mode, providing ventricular pacing at the programmed AV delay. During DDD(R) activity, the algorithm systematically scans the AV delay up to 450 ms to determine whether there is intrinsic ventricular sensing. This search can be triggered by 2 different situations: 1) sensing of a single ventricular spontaneous event; or 2) persistent ventricular pacing within a time interval progressively increasing after each unsuccessful search from 30 s to 20 h thereafter. To prevent continuous forward and backward mode switches, an additional test of conduction stability is performed: a switch to the ADI(R) mode is only allowed if 2 to 8 of the last 8 ventricular events (6 during the study) are sensed with a PQ interval <450 ms. Switching back to DDD(R) mode is triggered if one of the following 4 independent conditions are fulfilled: 1) no ventricular sensed events for up to 2 s; 2) 2 consecutive cycles without spontaneous events; 3) 1 to 5 of 8 cycles (3 during the study) without spontaneous events; or 4) more than 15 switches to DDD(R) per h within the last 24 h.

**ABBREVIATIONS AND ACRONYMS**

**AF** = atrial fibrillation

**AP%** = atrial pacing percentage

**AV** = atrioventricular

**LVEF** = left ventricular ejection fraction

**MAVI** = mean atrioventricular interval

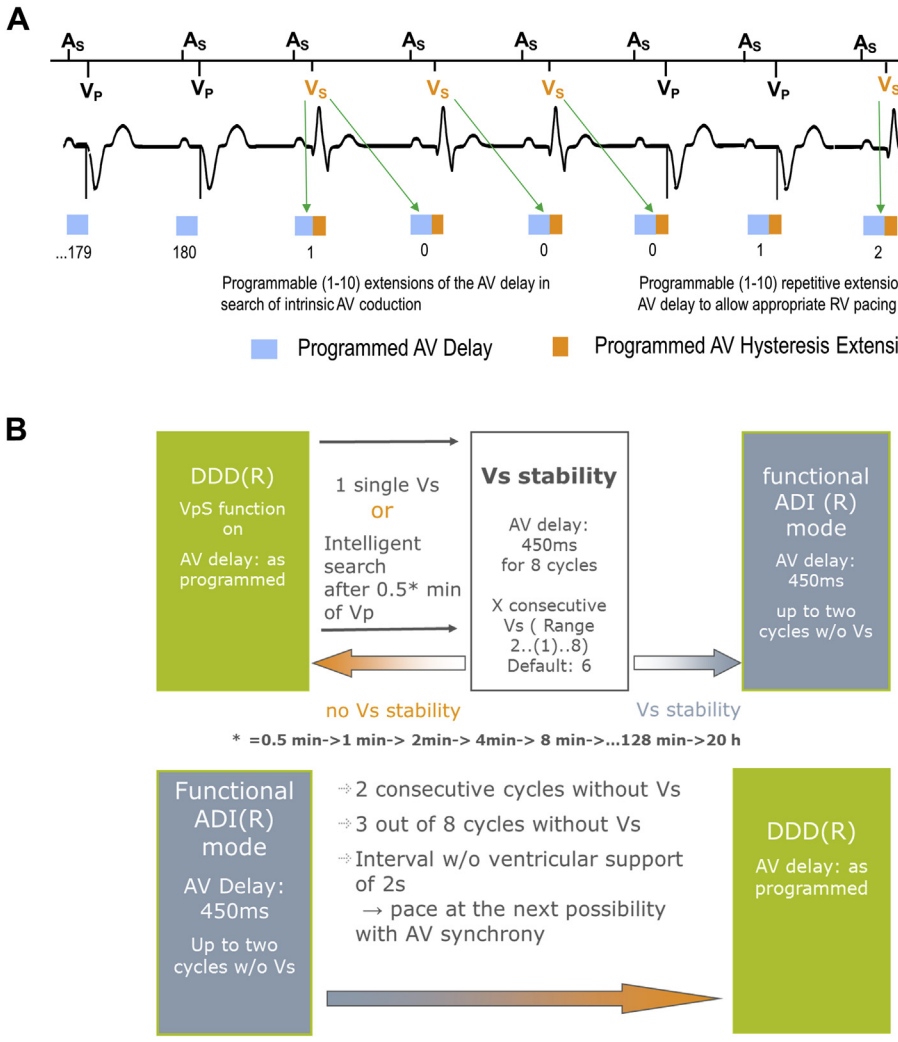
**RV** = right ventricle

**SAV** = post-atrial sensing atrioventricular interval

**SND** = sinus node disease

**VP%** = ventricular pacing percentage

**FIGURE 1 Schematic Representation of the IRSplus Algorithm and the VpS Algorithm**

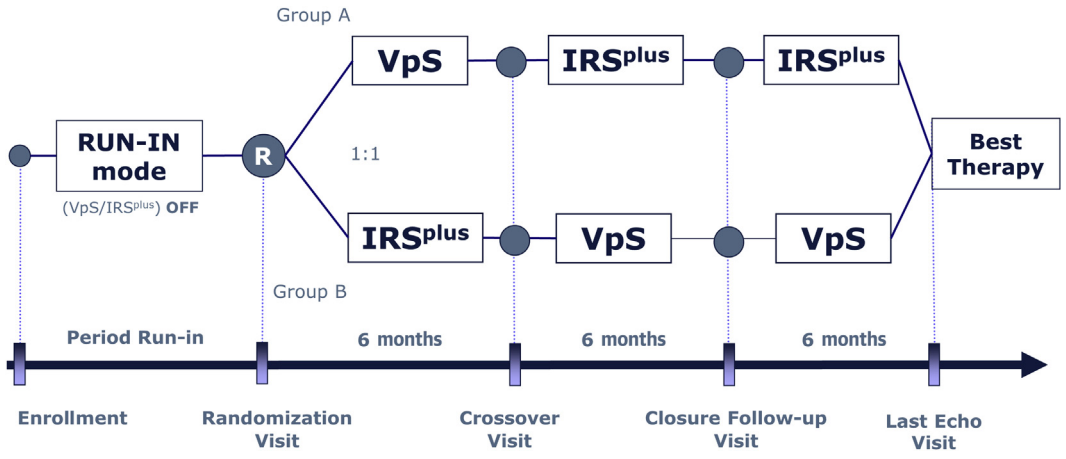



The IRSplus function **(A)** operates to maintain spontaneous atrioventricular (AV) conduction as long as possible, essentially acting as a combination of AV hysteresis (up to 400 ms) and the search for intrinsic conduction. The VpS algorithm **(B)** is a dual- to atrial single-chamber mode switch (DDD(R) to ADI(R)) algorithm automatically activating when specific conduction tests have been successfully passed.

**STUDY ENDPOINTS.** The primary endpoint of the study was the 6-month ventricular pacing percentage (VP%) with IRSplus and VpS algorithms. The mean AV interval (MAVI), AF, and changes in echocardiographic parameters after 12 months with the IRSplus and VpS algorithms were secondary study endpoints. AF was measured and reported as total arrhythmic burden percentage and incidence, defined as the percentage of patients with AF burden ≥1%. All available AF episode electrogram records were adjudicated by 1 expert physician blinded to the investigational site and not involved in the study as investigator.

**STUDY DESIGN.** After a 30-day post-enrollment run-in period, patients were 1:1 randomized to IRSplus or VpS for 6 months and then crossed over to the alternative algorithm for the following 6 months. After the 12-month follow-up, subjects continued with the last active algorithm for an additional 6 months to obtain data on cardiac volumes after a consecutive 12-month treatment period with the same algorithm. Full device interrogation was completed at each follow-up visit. Echocardiographic examinations were required at enrollment, at crossover, and at the last visit. The study design is shown in Figure 2.

**FIGURE 2** The Study Design




After a 30-day post-enrollment run-in period, patients were 1:1 randomized to IRSplus or VpS for 6 months and then crossed over to the alternative algorithm for the following 6 months. After the 12-month follow-up, subjects continued with the last active algorithm for an additional 6 months for the last echo visit.

To better investigate the efficacy of the algorithms in relation to patients' intrinsic conduction, subjects were classified into 3 subgroups according to their post-atrial sensing AV interval (SAV) evaluated at enrollment: SAV <170 ms (subgroup 1), 170 ms ≤ SAV <270 ms (subgroup 2), and SAV ≥270 ms (subgroup 3). The 170-ms and 270-ms cut-offs were expected to discriminate sufficiently large subgroups with good, medium, and poor conduction performances.

**STATISTICS.** The study was designed with a 90% statistical power to detect at least a 3% difference in VP% between the IRSplus and VpS algorithms. On the basis of data from previous studies (10,11), it was estimated that 230 subjects were necessary, including an expected 20% dropout/missing data rate at 12 months for intra-individual comparisons of the primary endpoint.

Sample distributions of continuous variables were first tested for normality with the Shapiro-Wilks test and reported as median (1st to 3rd interquartile) as non-normally distributed. Binary variables were reported as percentages. Missing data were not replaced; all available data were used for sample distribution evaluation, but cases with missing data could not contribute to intra-individual comparisons.

Primary and secondary study endpoint data were analyzed hierarchically, using subjects within study sites. Continuous and binary variables were evaluated with generalized linear mixed-models having variables of interest as response, treatment as fixed effects, and sites as random effects. Analyses on 12-month endpoints were performed with 2-level mixed models including sites as a random effect nested within a treatment order term, to control potential biases related to the order in which the pacing algorithms were activated.

The Wilcoxon signed rank test and Mann-Whitney test were also used for intra- and inter-individual comparisons, respectively; the Kruskal-Wallis test was used to test differences among the subgroups, and the Pearson chi-square test for differences among groups for categorical variables. Analyses were performed with the intention-to-treat approach. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using the 11E version of STATA software (StatCorp LP, College Station, Texas).

## RESULTS

**POPULATION CHARACTERISTICS.** Two hundred thirty patients (140 males, 90 females) were enrolled at 20 sites. At the end of the study, primary endpoint data were available for 186 patients (81%). The median age was 75 years (range 69 to 79 years). The demographics and the electrocardiogram (ECG) details are reported in Table 1. The indications for pacemaker implantation were brady-tachy SND (n = 153; 66%), SND with syncope (n = 38; 17%), and bradycardia SND (n = 31; 13%). The median SAV interval was 186 ms (interquartile range: 162 to 214 ms). Sixty-six subjects (29%) had an SAV <170 ms

**TABLE 1 Baseline Demographics and Electrocardiogram Details**

| | All (N = 230) | Subgroup 1 (n = 66) | Subgroup 2 (n = 131) | Subgroup 3 (n = 33) | p Value |
|---|---|---|---|---|---|
| Age (yrs) | 75 (69–79) | 74 (65–79) | 74 (69–79) | 77.5 (72–82) | 0.12 |
| Male | 140 (61) | 36 (54) | 81 (62) | 23 (70) | 0.25 |
| LVEF (%) | 58 (55–61) | 57 (55–60) | 60 (55–63) | 56 (54–60) | 0.30 |
| CHA2DS2-VASc score | 3 (2–4) | 3 (2–3) | 2 (2–4) | 3 (2–4) | 0.75 |
| NYHA functional class | | | | | |
| I | 124 (54) | 39 (59) | 66 (50) | 19 (57) | – |
| II | 101 (44) | 28 (42) | 59 (45) | 14 (42) | – |
| III | 5 (2) | 1 (1) | 3 (2) | 1 (3) | – |
| Disease history | | | | | |
| Coronary artery disease | 32 (14) | 7 (11) | 19 (14) | 6 (18) | 0.57 |
| Valvular disease | 17 (7) | 6 (9) | 9 (7) | 2 (6) | 0.77 |
| Hypertrophic cardiomyopathy | 4 (2) | 0 (0) | 3 (2) | 1 (3) | 0.46 |
| Congestive heart failure | 3 (1) | 0 (0) | 1 (1) | 2 (6) | 0.11 |
| Hypertension | 105 (46) | 32 (48) | 54 (41) | 19 (57) | 0.18 |
| Diabetes | 34 (15) | 8 (12) | 19 (15) | 7 (21) | 0.49 |
| Previous AF/flutter | 57 (25) | 18 (27) | 32 (24) | 7 (21) | 0.75 |
| Medications | | | | | |
| Antiplatelet/ anticoagulants | 103 (45) | 24 (36) | 64 (49) | 15 (45) | 0.34 |
| Diuretics | 62 (27) | 15 (23) | 33 (25) | 14 (43) | 0.11 |
| ARB-sartans | 51 (22) | 16 (24) | 29 (22) | 5 (15) | 0.57 |
| ACE inhibitors | 50 (22) | 16 (24) | 24 (18) | 10 (30) | 0.25 |
| Calcium antagonists | 39 (17) | 10 (15) | 20 (15) | 9 (27) | 0.26 |
| Beta-blockers | 40 (17) | 10 (15) | 22 (17) | 8 (24) | 0.54 |
| Antiarrhythmic agents | 43 (19) | 16 (24) | 22 (17) | 5 (15) | 0.34 |
| Pacemaker indication | | | | | |
| SND including brady-tachy syndrome | 184 (79) | 51 (77) | 104 (80) | 29 (88) | 0.56 |
| SND with syncope | 38 (17) | 13 (20) | 23 (17) | 2 (6) | 0.17 |
| Other | 8 (4) | 2 (3) | 4 (3) | 2 (6) | 0.25 |
| ECG details | | | | | |
| QRS duration – intrinsic (ms) | 98 (80–113) | 90 (80–102) | 102 (85–120) | 83 (70–108) | 0.02 |
| QRS duration – paced (ms) | 150 (123–162) | 140 (123–160) | 156 (120–182) | 154 (130–160) | 0.31 |
| SAV (ms) | 185 (162–214) | 151 (136–160) | 198 (180–219) | 285 (277–308) | 0.0001 |
| PAV (ms) | 255 (230–293) | 229 (202–254) | 262 (244–296) | 320 (310–348) | 0.0001 |

Values are median (25th to 75th percentile) or n (%). Subgroups were defined according to the baseline SAV: SAV <170 ms (subgroup 1), 170 ms ≤ SAV <270 ms (subgroup 2), and SAV ≥270 ms (subgroup 3).

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; ECG = surface electrocardiogram; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association functional class; PAV = post-atrial pacing atrioventricular interval; SAV = post-atrial sensing atrioventricular interval; SND = sinus node disease.

(subgroup 1), 131 (57%) between 170 ms and 270 ms (subgroup 2), and 33 (14%) longer than 270 ms (subgroup 3). There were no significant differences in patient demographics between the 3 subgroups.

**TWELVE-MONTH ANALYSIS: PACING PERCENTAGES, AV INTERVAL, AND AF.** The median VP% was 1% (interquartile range: 0% to 11%) and 3% (interquartile range: 0% to 26%) during the IRSplus and VpS periods, respectively (Figure 3). The difference reached statistical significance (p = 0.029). The percentage of patients with VP% higher than 40% was 10% during IRSplus as compared to 19% during VpS (p = 0.0007).

The subgroup analysis did not reveal significant differences in VP% between IRSplus and VpS in any subgroups. Although VP% tended to be higher during VpS in the subgroup 3, difference did not reach statistical significance.

The MAVI was also similar during both study periods, although slightly but significantly longer during IRSplus than during VpS (p = 0.014). The effect was mainly driven by the subgroup 3 where the difference in medians was approximately 30 ms, reaching statistical significance (p = 0.046) despite the small sample size.

These results were obtained with relatively high atrial pacing percentages (AP%), as expected in the selected population, which was not significantly different between the IRSplus and VpS periods (Table 2).

AF burden and incidence were not significantly different between the IRSplus and VpS periods.

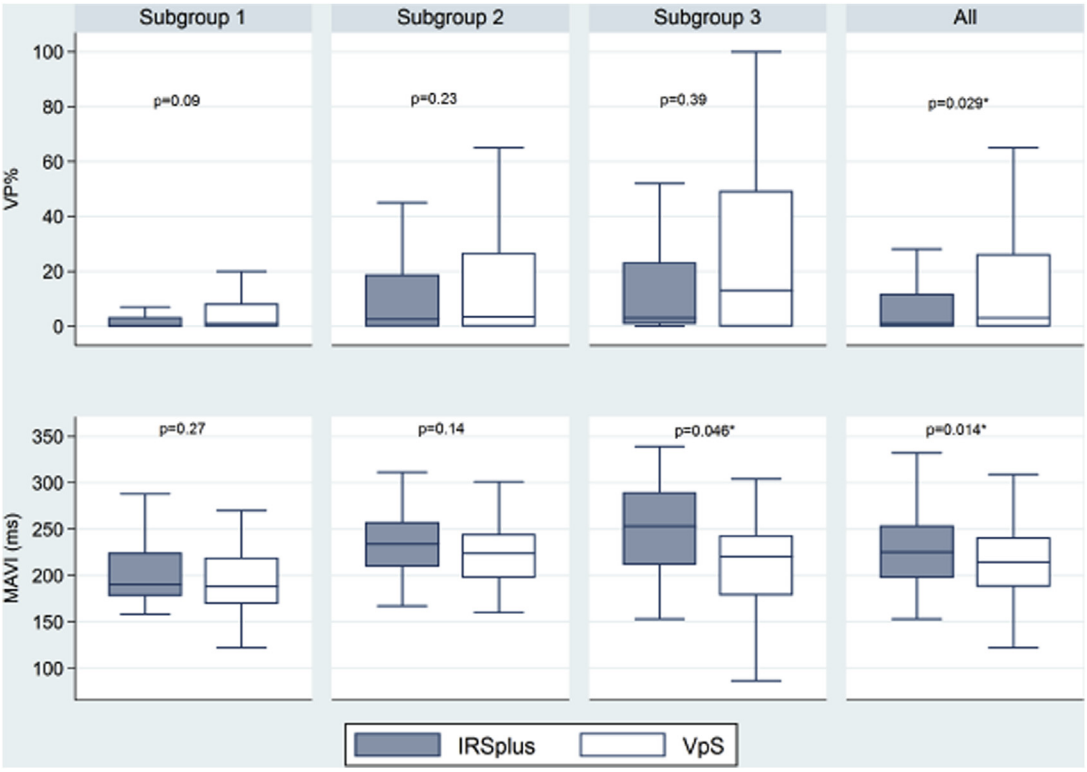
**ECHOCARDIOGRAPHIC MEASUREMENT AT 6 TO 18 MONTHS.** As expected from the very low VP% values obtained with both algorithms, none of the echocardiographic parameters showed significant variations after 12 months (Table 3).

## DISCUSSION

**MAIN RESULTS.** Our results indicated that both IRSplus and VpS algorithms were highly efficient in reducing unnecessary ventricular pacing to median values of 3% or less in the selected SND population. The IRSplus appeared particularly efficient in preventing ventricular pacing in the subgroup of patients with partially impaired AV conduction (SAV ≥270 ms). Despite the difference being statistically significant in the whole population, the cumulative number of paced ventricular beats was minimal with both algorithms, with no relevant implications in terms of AF incidence, left ventricular ejection fraction (LVEF), and cardiac chamber volumes.

**IMPLICATIONS IN HEART FAILURE AND AF.** Avoiding unnecessary RV pacing is a generally accepted requirement in current pacemaker therapy. This is based on several observations. In particular it relies on a post-hoc analysis of the MOST (Mode Selection Trial and Sinus Node Dysfunction) trial (4) and the - results of the DAVID (Dual Chamber and VVI Implantable Defibrillator) study (2). Progression to

**FIGURE 3** **Box-Whiskers Plots of VP% (Upper Panel) and MAVI (Lower Panel) in the Whole Study Population and in Each Predefined Subgroup: 1) SAV <170 ms; 2) 170 ms ≤ SAV <270 ms; and 3) SAV ≥270 ms**




The results of 2-level linear mixed models, having the treatments as fixed effect and investigational sites nested within order in which treatments were given as random effects, are shown. Boxplot graphs denote upper and lower adjacent values **(whiskers)**, 75th and 25th percentiles **(boxes)**, median **(horizontal lines within boxes)**. MAVI = mean atrioventricular interval; SAV = post-atrial sensing atrioventricular interval; VP% = ventricular pacing percentage.

heart failure and development of AF are 2 expected effects of long-term RV pacing. As single-chamber atrial pacing has shown to be associated with an increased risk of re-operation to provide ventricular support (12), algorithms to minimize ventricular pacing in dual-chamber systems have become the preferred option. However, the relationship between impairment of cardiac pump function, AF development, and cumulative RV apex pacing is still a matter of debate.

The risk of heart failure from RV pacing is low in patients without cardiac dysfunction. Both the SAVE PACe (Search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction) (11) and the DANPACE (Danish Multicenter Randomized Trial on Single Lead Atrial Pacing vs. Dual Chamber Pacing in Sick Sinus Syndrome) (12) trials failed to show any protective effect of atrial or minimal ventricular pacing modes against stroke/embolism, progression to heart failure, and death. On the other hand, negative hemodynamic effects of long or extreme AV intervals may overshadow the benefit of intrinsic ventricular contractions. A shift in atrial contractions towards the preceding systole promotes reduced ventricular filling, varying degrees of diastolic mitral regurgitation (13), atrial distension, and retrograde flow into the pulmonary or systemic veins (14). Such effects may be exacerbated by atrial pacing, which is expected to be frequent in SND. In our study, AV intervals were in the 210- to 230-ms range on average with an AP% of approximately 56%. However, post-sense and post-pace AV intervals longer than 360 ms were found in 10% and 25% of patients, respectively, both with the IRSplus and the VpS algorithm. The advantage of pacing prevention over AV decoupling is questionable when the AV interval exceeds such values. Median AV intervals were slightly higher during IRSplus than during VpS.

**TABLE 2 Total Population and Subgroups Analysis of Atrial Pacing Percentage and AF in IRSplus and VpS Operation Periods**

| | Group | IRSplus | VpS | p Value* |
|---|---|---|---|---|
| Median AP% | All | 56 (26–82) | 54 (32–78) | 0.88 |
| | Subgroup 1 | 46 (30–83) | 52 (33–78) | 0.80 |
| | Subgroup 2 | 58 (24–80) | 50 (30–77) | 0.77 |
| | Subgroup 3 | 62 (49–85) | 66 (45–76) | 0.21 |
| AF burden | All | 3 | 6 | 0.55 |
| | Subgroup 1 | 2 | 7 | 0.32 |
| | Subgroup 2 | 5 | 3 | 0.60 |
| | Subgroup 3 | 5 | 2 | 0.96 |
| AF incidence | All | 29 (16) | 27 (15) | 0.87 |
| | Subgroup 1 | 8 (15) | 9 (17) | 0.40 |
| | Subgroup 2 | 16 (15) | 14 (13) | 0.65 |
| | Subgroup 3 | 5 (20) | 4 (16) | 0.97 |

Values are median (25th to 75th percentile) or n (%). *Results of generalized linear mixed-model analysis with treatment as fixed effect, and order of treatment and investigational sites as random effects. AP% is expressed as median (25th to 75th percentile); AF burden as the 90th percentile; AF incidence is defined as n (%) with AF burden ≥1%. Subgroup definition is reported in the text or in the notes to Table 1.

AF = atrial fibrillation; AP% = atrial pacing percentage; IRSplus = intrinsic rhythm support plus; VpS = ventricular pace suppression; other abbreviation as in Table 1.

**TABLE 3 Echocardiographic Changes 6- to 18-Month Inter-Individual Comparison**

| Parameter, % | IRSplus group | VpS group | p Value* |
|---|---|---|---|
| LVEF | 0 (-3.2 to 7.9) | 0 (-5.0 to 1.7) | 0.17 |
| EDV | 0 (-15.3 to 9.3) | 0 (-12.9 to 10.9) | 0.30 |
| ESV | 0 (-27.5 to 14.2) | 0 (-20.6 to 10) | 0.62 |
| LAEDV | 0 (-10.4 to 28.8) | 0 (0 to 42.2) | 0.59 |
| LAESV | +1.7 (-15.9 to 30.7) | 0 (-1.0 to 31.5) | 0.73 |

Values are median (25th/75th percentile). *Results of generalized linear mixed-model analysis with treatment as fixed effect and investigational sites as random effects.

AF = atrial fibrillation; EDV = end-diastolic volume; ESV = end-systolic volume; LAEDV = left atrium end-diastolic volume; LAESV = left atrium end-systolic volume.

This small difference may be explained by a relatively longer time spent on average with the extended pacemaker AV delay during IRSplus as reflected by the significantly lower VP% observed. The difference in median MAVI was more evident in the subgroup 3 including patients with severe I degree AV block or even with previously unreported intermittent II degree AV blocks. In this subgroup, conduction tests for DDD(R) to ADI(R) switch may have frequently failed, likely explaining the trend to higher VP% during VpS, which could not, however, reach significance probably due to insufficient statistical power. It has been observed that dual- to atrial single-chamber pacing mode switch algorithms remain prone to AV decoupling and VA coupling (VA interval <300 ms) (15) which may be stable in patients with extreme AV intervals and induce pacemaker syndrome in patients with II degree AV block (16). Therefore, DDD-ADI mode switch algorithms should not be prescribed in patients with significant conduction disease (second- or third-degree AV block) (17). Although agreeing with this observation in general, our data showed that the conduction tests automatically performed before switching to atrial modes during VpS actually reduced such risks at the expense of a slightly higher median VP%.

The effect of cumulative RV pacing on AF development seems better established. Several studies have shown that AF incidence is higher in patients who are frequently paced in the ventricle (1,11). However, available data do not provide conclusive evidence. The MINERVA (Minimize Right Ventricular Pacing to Prevent Atrial Fibrillation and Heart Failure Trial) study could only show a reduction in AF incidence when minimal ventricular pacing was associated with automatic atrial antitachycardia pacing therapies, but failed to observe any benefit from the reduction of ventricular pacing alone (18). Interestingly, it has been reported that DDD-ADI algorithms are associated with a 3-fold higher risk of developing persistent AF in patients with a baseline PQ interval longer than 230 ms (19). This finding stresses the role of the AV interval duration, which is probably underestimated. In the DANPACE trial (12), the incidence of AF was significantly higher with single-lead atrial (AAIR) pacing than with dual-chamber (DDDR) pacing, despite a VP% of approximately 65%. Subsequent sub-analyses (20) revealed no association between atrial tachyarrhythmia episodes and VP%, nor was there any correlation with the duration of the programmed pacemaker AV delay. Conversely, it could be observed that patients with a baseline PQ interval longer than 180 ms had a higher risk of developing AF. An interval of 180 ms seems rather short if compared with currently tolerated AV intervals and common programming of device AV delays. Actually, the cut-off where the benefit of intrinsic conduction preservation is counterbalanced by the negative effect of an extended AV interval is unknown, as it largely depends on the patient's profile. However, it is unquestionable that the current paradigm "the lower the VP%, the better" should be weighted by AV coupling. This is especially worth considering, as current pacemaker design allows more flexible AV delay functioning with very large programmability ranges in addition to hysteresis, automatic AV search, and switch to atrial single-chamber modes.

We obtained similar VP% levels with similar AV intervals on average during both IRSplus and VpS algorithm periods. Moreover, we did not observe any difference in terms of AF incidence, ejection fraction, and cardiac volumes. We can therefore conclude that, at least in the selected population, which generally benefits the most from VP% restraint, we did not collect any evidence to prefer 1 algorithm to the other.

**PERFORMANCE OF THE SPECIFIC ALGORITHMS USED IN THE STUDY.** DDD-ADI mode switch algorithms have been reported to account for VP% values in the 0.2% to 9.1% range, prevalently in SND populations, in several previous studies (5-9,11,21). The VpS algorithm, which is 1 of this class of ventricular pace prevention algorithms, performed comparably with a 3% median VP%. Quite surprisingly, we observed an excellent performance from the IRSplus algorithm, which ensured a 1% cumulative VP% in the whole population and 3% in the subgroup with partially impaired AV conduction, despite it being based on a more traditional AV hysteresis approach plus automatic search.

This result may be reasonably explained by the combination of the intrinsic simplicity of the algorithm concept and the modern pacemaker timing design. Modern pacemakers tolerate very long AV delay settings. In our case, an extension to 400 ms effectively promoted spontaneous AV conduction in a vast majority of patients. In addition, detection of a single ventricular sense, either during normal operation or during automatic searches, was sufficient to trigger the IRSplus reaction. As the algorithm reaction simply consists of an AV delay extension, no further tests to confirm AV conduction stability are needed. VpS and similar algorithms need confirmation of AV conduction stability before switching to a single atrial-based pacing mode, to avoid frequent, potentially symptomatic forward and backward switches. These additional confirmation tests might have frequently prevented switches to single-chamber atrial pacing, especially in the subgroup with SAV ≥270 ms.

**STUDY LIMITATIONS.** Our results were obtained with specific proprietary algorithms and cannot be straightforwardly extended to other manufacturers' systems. However, our findings basically showed that an automatic extension of the AV delay up to 400 ms nowadays available in most last-generation pacemakers is at least as affective as automatic switch to single-chamber modes in suppressing unnecessary ventricular pacing. In addition, clinical outcomes were not different at least over the short-term. Therefore, we did not find enough evidence to prefer 1 approach to the other. From this perspective, our results might have implications for other systems.

## CONCLUSIONS

In our study, algorithms based on an automatic AV conduction search (IRSplus) and a DDD-ADI mode switch (VpS) performed equivalently in terms of VP% reduction, mean AV interval, development of AF, preservation of LVEF, and cardiac volumes in a SND population with normal or minimally impaired AV conduction. The IRSplus algorithm was efficient in reducing VP% even in patients with very prolonged SAV (≥270 ms) at the expense of slightly longer MAVI. However, differences between the algorithms were statistical but clinically insignificant.

**ACKNOWLEDGMENTS** The authors thank Michael Krauss for his friendly assistance in the early study set-up phase, Francesco Chiusso and Daniele Giacopelli for their contributions to data analysis and manuscript revision, and all the field engineers of BIOTRONIK Italia for their continuous technical assistance throughout the study.

**ADDRESS FOR CORRESPONDENCE:** Dr. Valeria Calvi, Electrophysiology Unit, Cardiology Department, A.O.U. Policlinico Vittorio Emanuele, PO Ferrarotto, Via Salvatore Citelli 6, Catania 95124, Italy. E-mail: valcalvi@unict.it.

## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** This study showed that an automatic AV hysteresis algorithm should be considered as essentially equivalent to a DDD-ADI mode switch algorithm in the modern pacemaker in terms of RV pacing percentage, mean AV interval, AF, and cardiac volumes. Our findings support the view that algorithms based on automatic extensions of AV delay up to 400 ms may be as effective as dual- to single-chamber mode switch in reducing ventricular pacing to negligible levels in SND patients with no evidence of high degree AV block.

**TRANSLATIONAL OUTLOOK:** Larger studies are needed to understand if 1 of the 2 classes of algorithms designed for reducing unnecessary ventricular pacing could provide benefits related to long-term clinical outcomes in patients with sick sinus dysfunction without evidence of advanced AV block.

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 3, NO. 5, 2017
MAY 2017:482–90

## REFERENCES

**1.** Sweeney MO, Hellkamp AS, Ellenbogen KA, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 2003;107:2932–7.

**2.** Wikoff BL, Cook JR, Epstein AE, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the dual chamber and VVI implantable defibrillator (DAVID) trial. JAMA 2002;288:3115–23.

**3.** Steinberg JS, Fischer A, Wang P, et al. The clinical implications of cumulative right ventricular pacing in the multicenter automatic defibrillator trial II. J Cardiovasc Electrophysiol 2005;16:359–65.

**4.** Sweeney MO, Hellkamp AS. Heart failure during cardiac pacing. Circulation 2006;113:2082–8.

**5.** Gillis AM, Purerfellner H, Israel CW, et al. Reducing unnecessary right ventricular pacing with the managed ventricular pacing mode in patients with sinus node disease and AV block. Pacing Clin Electrophysiol 2006;29:697–705.

**6.** Purefellner H, Brandt J, Israel C, et al. Comparison of two strategies to reduce ventricular pacing in pacemaker patients. Pacing Clin Electrophysiol 2008;31:167–76.

**7.** Murakami Y, Tsuboi N, Inden Y, et al. Difference in percentage of ventricular pacing between two algorithms for minimizing ventricular pacing: results of the IDEAL RVP (Identify the Best Algorithm for reducing Unnecessary Right Ventricular Pacing) study. Europace 2010;12:96–102.

**8.** Poghosyan HR, Jamalyan SV. Comparison of pacing algorithms to avoid unnecessary ventricular pacing in patients with sick sinus syndrome: a single-centre, observational, parallel study. Europace 2012;14:1483–9.

**9.** Chen S, Chen K, Tao Q, et al. Reduction of unnecessary right ventricular pacing by managed ventricular pacing and search AV+ algorithms in pacemaker patients: 12-month follow-up results of a randomized study. Europace 2014;16:1595–602.

**10.** Puglisi A, Favale S, Scipione P, et al. Overdrive versus conventional or closed-loop rate modulation pacing in the prevention of atrial tachyarrhythmias in brady-tachy syndrome: on behalf of the burden II study group. Pacing Clin Electrophysiol 2008;31:1443–55.

**11.** Swenney MO, Bank AJ, Nsah E, et al. Minimizing ventricular pacing to reduce atrial fibrillation in sinus-node disease. N Engl J Med 2007;357:1000–8.

**12.** Nielsen JC, Thomsen PE, Hojberg S, et al. A comparison of single-lead atrial pacing with dual-chamber pacing in sick sinus syndrome. Eur Heart J 2011;32:686–96.

**13.** Ishikawa T, Kimura K, Miyazaki N, et al. Diastolic mitral regurgitation in patients with first degree atrioventricular block. Pacing Clin Electrophysiol 1992;15:1927–31.

**14.** Naito M, Dreifus LS, Mardelli TJ, et al. Echocardiographic features of atrioventricular and ventriculo-atrial conduction. Am J Cardiol 1980;46:625–33.

**15.** Sweeney MO, Ellenbogen KA, Tang ASL, Johnson J, Belk P, Sheldon T. Severe atrioventricular decoupling, uncoupling and ventriculoatrial coupling during enhanced atrial pacing: incidence, mechanisms and implications for minimizing right ventricular pacing in ICD patients. J Cardiovasc Electrophysiol 2008;19:1175–80.

**16.** Pascale P, Pruvot E, Graf D. Pacemaker syndrome during managed ventricular pacing mode. J Cardiovasc Electrophysiol 2009;20:574–6.

**17.** Lim HS. The prescription of minimal ventricular pacing. Pacing Clin Electrophysiol 2012;35:1528–36.

**18.** Boriani G, Tukkie R, Manolis AS, et al. Atrial antitachycardia pacing and managed ventricular pacing in bradycardia patients with paroxysmal or persistent atrial tachyarrhythmias: the MINERVA randomized multicentre international trial. Eur Heart J 2014;35:2352–62.

**19.** Ricci RP, Botto GL, Bénézet JM, et al. Association between ventricular pacing and persistent atrial fibrillation in patients indicated to elective pacemaker replacement: results of the Prefer for Elective Replacement MVP (PreFER MVP) randomized study. Heart Rhythm 2015;12:2239–46.

**20.** Nielsen JC, Thomsen PE, Højberg S, et al. Atrial fibrillation in patients with sick sinus syndrome: the association with PQ-interval and percentage of ventricular pacing. Europace 2012;14:682–9.

**21.** Veasey RA, Arya A, Silberbauer J, et al. The relationship between right ventricular pacing and atrial fibrillation burden and disease progression in patients with paroxysmal atrial fibrillation: the long-MinVPACE study. Europace 2011;13:815–20.

**KEY WORDS** atrioventricular hysteresis, dual-chamber pacemaker, mode-switch algorithm, right ventricular pacing, sinus node dysfunction

**APPENDIX** For a list of the investigators and institutions that participated in the VIPERS trial, please see the online version of this article.