JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 6, NO. 1, 2020
© 2020 THE AUTHORS. PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION. THIS IS AN OPEN ACCESS ARTICLE UNDER THE CC BY-NC-ND LICENSE (http://creativecommons.org/licenses/by-nc-nd/4.0/).

PACING

Atrioventricular Synchronous Pacing Using a Leadless Ventricular Pacemaker

Results From the MARVEL 2 Study

Clemens Steinwender, MD,[a,b] Surinder Kaur Khelae, MD,[c] Christophe Garweg, MD,[d] Joseph Yat Sun Chan, MD,[e] Philippe Ritter, MD,[f] Jens Brock Johansen, MD, PHD,[g] Venkata Sagi, MD,[h] Laurence M. Epstein, MD,[i] Jonathan P. Piccini, MD, MHS,[j] Mario Pascual, MD,[k] Lluis Mont, MD,[l] Todd Sheldon, MS,[m] Vincent Splett, MS,[m] Kurt Stromberg, MS,[m] Nicole Wood, BS,[m] Larry Chinitz, MD[n]

ABSTRACT

OBJECTIVES This study reports on the performance of a leadless ventricular pacemaker with automated, enhanced accelerometer-based algorithms that provide atrioventricular (AV) synchronous pacing.

BACKGROUND Despite many advantages, leadless pacemakers are currently only capable of single-chamber ventricular pacing.

METHODS The prospective MARVEL 2 (Micra Atrial tRacking using a Ventricular accELerometer 2) study assessed the performance of an automated, enhanced accelerometer-based algorithm downloaded to the Micra leadless pacemaker for up to 5 h in patients with AV block. The primary efficacy objective was to demonstrate the superiority of the algorithm to provide AV synchronous (VDD) pacing versus VVI-50 pacing in patients with sinus rhythm and complete AV block. The primary safety objective was to demonstrate that the algorithm did not result in pauses or heart rates of >100 beats/min.

RESULTS Overall, 75 patients from 12 centers were enrolled; an accelerometer-based algorithm was downloaded to their leadless pacemakers. Among the 40 patients with sinus rhythm and complete AV block included in the primary efficacy objective analysis, the proportion of patients with ≥70% AV synchrony at rest was significantly greater with VDD pacing than with VVI pacing (95% vs. 0%; $p < 0.001$). The mean percentage of AV synchrony increased from 26.8% (median: 26.9%) during VVI pacing to 89.2% (median: 94.3%) during VDD pacing. There were no pauses or episodes of oversensing-induced tachycardia reported during VDD pacing in all 75 patients.

CONCLUSIONS Accelerometer-based atrial sensing with an automated, enhanced algorithm significantly improved AV synchrony in patients with sinus rhythm and AV block who were implanted with a leadless ventricular pacemaker. (Micra Atrial Tracking Using a Ventricular Accelerometer 2 [MARVEL 2]; NCT03752151). (J Am Coll Cardiol EP 2020;6:94–106)
© 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Cardiology, Kepler University Hospital, Linz, Austria; [b]Department of Cardiology, Paracelsus Medical University Salzburg, Salzburg, Austria; [c]Department of Electrophysiology, Institut Jantung Negara, Kuala Lumpur, Malaysia; [d]Department of Cardiovascular Sciences, Department of Cardiology, University Hospitals Leuven, Leuven, Belgium; [e]Department of Medicine and Therapeutics, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, Hong Kong; [f]Department of Electrophysiology and Cardiac Stimulation, Hôpital Haut- Lévêque - CHU de Bordeaux, Pessac, France; [g]Department of Cardiology, Odense University Hospital, Odense, Denmark; [h]Baptist Heart Specialists, Baptist Medical Center Jacksonville, Florida, USA; [i]Department of Electrophysiology, North Shore University Hospital, Manhasset, New York, USA; [j]Division of Cardiology, Duke University Medical Center and Duke Clinical Research Institute, Durham, North Carolina, USA; [k]Miami Cardiac & Vascular Institute, Baptist Hospital, Miami, Florida; [l]Institut Clinic Cardiovascular (ICCV), Hospital Clínic, Universitat de Barcelona, Catalonia, Barcelona, Spain; [m]Medtronic, Inc., Mounds View, Minnesota, USA; and the [n]Leon H. Charney Division of Cardiology, NYU Langone Medical Center, New York, New York, USA. The MARVEL 2 study was funded by Medtronic, Inc. Dr. Steinwender has been a

ISSN 2405-500X https://doi.org/10.1016/j.jacep.2019.10.017

Permanent cardiac pacing has provided substantial benefits for millions of patients with bradyarrhythmias since its introduction in the 1950s. For many decades, cardiac pacing has been exclusively performed by systems consisting of subcutaneously implanted pulse generators with ≥1 transvenous leads. However, approximately 1 in 8 patients treated with these traditional pacing systems experiences a complication attributed to the pacemaker pocket or leads, such as hematoma, pneumothorax, hemothorax, lead dislodgement, lead failure, or infection (1).

SEE PAGE 107

Leadless pacemakers were developed to overcome pocket- and lead-related complications. Results from the Micra Transcatheter Pacing Study and Micra Post Approval Registry demonstrated a high implantation success rate and a low major complication rate, with a >60% reduction in complications versus transvenous pacemakers (2–4). These encouraging results have led to an increased interest in a broader use of leadless pacemakers; however, currently available leadless pacemakers only provide single-chamber ventricular rate responsive pacing.

Use of transvenous single-chamber ventricular pacemakers is limited to <15% of the pacemaker population (5). Patients with sinus rhythm and atrioventricular (AV) block have been shown to benefit from dual-chamber pacemakers that can provide AV synchrony (6–8). Previous proof-of-concept studies tested the performance of an AV synchronous algorithm downloaded into an already implanted Micra device (Model MC1VR01; Medtronic, Inc, Minneapolis, Minnesota) that detected atrial contractions using the device's built-in 3-axis accelerometer. Results from early feasibility studies demonstrated that accelerometer-based atrial sensing was feasible and significantly improved AV synchrony in patients with AV block and a Micra single-chamber leadless pacemaker implanted in the right ventricle (9,10). Based upon results from the MARVEL (Micra Atrial tRacking using a Ventricular accELerometer) study, enhancements were made to the algorithm, including automated programming features and mode switching algorithms to accommodate changes in patient rhythm and activity. We report on the performance of this enhanced algorithm to provide AV synchronous pacing in patients with persistent third-degree (complete) AV block and normal sinus rhythm implanted with a Micra leadless pacemaker in the right ventricle.

ABBREVIATIONS AND ACRONYMS

AV = atrioventricular
CI = confidence interval
ECG = electrocardiogram
EGM = electrogram
LVOT-VTI = left ventricular outflow tract velocity-time integral

METHODS

STUDY DESIGN. The MARVEL 2 study was a prospective, nonrandomized multicenter clinical trial. The primary aim of the MARVEL 2 study was to confirm the ability of an enhanced downloadable algorithm (hereafter referred to as the MARVEL 2 algorithm) to provide AV synchronous pacing by mechanically sensing atrial contractions via the accelerometer signal (VDD pacing) from a Micra leadless pacemaker implanted in the right ventricle. A detailed description of the algorithm is provided in the Online Appendix. Briefly, the algorithm uses signal components from the Micra accelerometer corresponding to passive ventricular filling (A3) and atrial contraction (A4) to provide AV synchronous pacing (Online Figure S1). In addition, 2 mode switching algorithms enable automatic switching to VVI-40 and VVIR pacing. Approval of the study protocol by local ethics committees and

member of the Advisory Board for Biotronik and Medtronic; and has been a member of the Speakers Bureau for Abbott, Biotronik, Boston Scientific, and Medtronic. Dr. Khelae has been a member of the Speakers Bureau for Bayer/Schering Pharma, Boston Scientific, Medtronic, and Pfizer. Dr. Garweg has been a consultant for Medtronic. Dr. Chan has received honoraria from Medtronic. Dr. Ritter has received fees for services from Medtronic. Dr. Johansen has been a speaker for Medtronic and Merit Medical; and has received honoraria as a member of the Scientific Board for Medtronic and Biotronik. Dr. Epstein has received honoraria for speaking and consulting for Medtronic, St. Jude Medical, and Spectranetics Corporation. Dr. Piccini has received grants for clinical research from Abbott, American Heart Association, Association for the Advancement of Medical Instrumentation, Bayer, Boston Scientific, and Philips; and has been a consultant for Abbott, Allergan, ARCA Biopharma, Biotronik, Boston Scientific, LivaNova, Medtronic, Milestone, Sanofi, and Phillips. Dr. Mont has received honoraria as a lecturer and consultant from Abbott, Boston Scientific, and Medtronic; and has received financial support for fellowship/research projects from Abbott, Biotronik, Boston Scientific, and Medtronic. Mr. Sheldon, Mr. Splett, Mr. Stromberg, and Ms. Wood are also employees of Medtronic. Mr. Sheldon holds stock in Medtronic. Mr. Splett holds stock in Medtronic. Mr. Stromberg holds stock in Medtronic. Ms. Wood holds stock in Medtronic. Dr. Chinitz has received fees services from Abbott, Biosense Webster, Pfizer, Biotronik, and Medtronic; and had received fellowship support from Biotronik, Boston Scientific, and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

Manuscript received October 24, 2019; revised manuscript received October 31, 2019, accepted October 31, 2019.

national regulatory agencies was sought at each participating institution. All patients provided written informed consent.

PATIENTS AND PROCEDURES. The MARVEL 2 study enrolled patients with a history of AV block (including patients with normal sinus function and complete AV block) who were age 18 years or older and were previously implanted or undergoing implantations (newly implanted patients) with a Micra pacemaker that had a remaining projected device longevity of ≥6 years. Following informed consent, baseline procedures were performed, and medical history obtained.

Most enrolled patients completed the study procedures during a single study visit. However, patients who enrolled in the study at the time of their Micra implantation (newly implanted patients) had the algorithm downloaded and completed the study procedures after Micra implantation, but before hospital discharge (pre-hospital discharge) and approximately 1-month post-implantation. At the study visit(s), the algorithm was downloaded into the patient's implanted device, and a specialized Holter monitor capable of storing accelerometer waveforms, electrograms (EGMs), device markers, and electrocardiogram (ECG) data was placed for the duration of the study procedures. Initial algorithm parameter settings, including accelerometer vector combination, A3 end time, A3 threshold, and A4 threshold, were set by the algorithm auto-setup feature during VVI-50 pacing. Following auto-setup, the algorithm parameters were adjusted to optimize A4 detection, if needed.

After the algorithm parameters were set, the pacing mode was programmed to VDD, and the patient rested in a supine or sitting position for approximately 20 min. Following the resting period, the patient assumed a series of postures (supine, lying on right side, lying on left side, sitting, and standing) for 2 min each. In addition, patients walked at a comfortable and vigorous pace for 2 min to promote an activity mode switch.

Echocardiograms were collected from each patient during both VVI and VDD pacing following a standardized echo protocol. An echocardiography core laboratory (United Heart and Vascular Clinic, St. Paul, Minnesota), blinded to patient and pacing mode, measured the left ventricular outflow (LVOT) velocity-time integral (VTI) during 6 cardiac cycles in each pacing mode.

In addition to the preceding procedures, newly implanted patients had the algorithm downloaded to their devices; they underwent Holter monitoring and completed the auto-setup procedure immediately following device implantation. For newly implanted patients, the MARVEL 2 software was removed following each evaluation time point. Evaluation of algorithm performance in these patients allowed the MARVEL 2 features to be tested at multiple points in the device life cycle.

ENDPOINTS. The primary efficacy endpoint was defined as a paced or sensed ventricular beat within 300 ms following a surface ECG–confirmed P-wave for at least 70% of ECG–confirmed P-waves. For each patient, the primary efficacy endpoint was evaluated during the auto-setup phase, which occurred during VVI pacing, and during the resting phase, which occurred during VDD pacing. The primary safety endpoint was defined as freedom from pauses lasting >2 cardiac cycles (defined by the programmed lower rate interval) and freedom from episodes of oversensing-induced tachycardia >100 beats/min for >3 min. The secondary endpoint was LVOT-VTI as obtained from echocardiogram while the algorithm was programmed to VVI mode and VDD mode. All enrolled patients who had the investigational algorithm was downloaded to their devices were assessed for the primary safety endpoint, whereas the subset of patients with complete AV block and normal sinus function were evaluated for the primary efficacy and secondary endpoints.

STATISTICAL METHODS. A priori determination of sample size indicated that 35 patients with normal sinus node function and complete AV block would provide >90% power to test the primary efficacy endpoint, assuming ≥50% of patients would have discordant results between pacing modes and ≥90% of discordant results would favor algorithm-mediated VDD pacing. A sample size of 70 patients (with any predominant rhythm) provided 90% power to test the primary safety endpoint against a predefined performance goal of 87%, assuming the true underlying endpoint rate exceeded 98%. Finally, a sample size of 35 patients with normal sinus node function and complete AV block provided 89% power to test for a difference in LVOT-VTI between pacing modes, assuming a mean difference that favored algorithm VDD pacing of 2.1 ± 3.8 cm. All sample size calculations assumed a 2-sided type I error rate of 5%.

Each patient's predominant heart rhythm was determined as complete AV block with normal sinus function, intact AV conduction, or other (e.g., atrial arrhythmias, sinus node dysfunction, other AV block) based on PR intervals (during auto-setup) and PP intervals during the auto-setup and resting phases.

For each cardiac cycle, AV synchrony status was determined as described in the Online Appendix. AV synchrony percentage was calculated for each patient

TABLE 1 Patient Baseline Characteristics

	Enrolled (n = 77)	Downloaded MARVEL 2 Software (n = 75)	Evaluable for Primary Efficacy Objective (n = 40)
Age, yrs			
Mean ± SD	77.6 ± 11.8	77.5 ± 11.8	76.7 ± 12.9
Median	81.0	81.0	80.0
Female	31 (40.3)	30 (40.0)	22 (55.0)
Months from Micra implantation			
Mean ± SD	13.7 ± 14.5	13.8 ± 14.6	14.6 ± 16.6
Median	9.7	9.7	9.3
Comorbidities			
Hypertension	53 (68.8)	52 (69.3)	28 (70.0)
Atrial fibrillation	14 (18.2)	14 (18.7)	3 (7.5)
Diabetes	14 (18.2)	13 (17.3)	6 (15.0)
Coronary artery disease	23 (29.9)	23 (30.7)	8 (20.0)
COPD	7 (9.1)	7 (9.3)	4 (10.0)
Dialysis	3 (3.9)	3 (4.0)	1 (2.5)
Device location			
RV apex	12 (15.6)	12 (16.0)	8 (20.0)
RV high septum	11 (14.3)	11 (14.7)	7 (17.5)
RV mid-septum	27 (35.1)	26 (34.7)	11 (27.5)
RV low septum	12 (15.6)	12 (16.0)	8 (20.0)
RVOT	12 (15.6)	12 (16.0)	4 (10.0)
Other	2 (2.6)	2 (2.7)	2 (5.0)
Not reported	1 (1.3)	0 (0.0)	0 (0.0)
Predominant rhythm*			
Complete AV block with normal sinus function	40 (51.9)	40 (53.3)	40 (100.0)
Intact AV conduction	18 (23.4)	18 (24.0)	0 (0.0)
Other rhythm	15 (19.5)	15 (20.0)	0 (0.0)
Indeterminate rhythm†	2 (2.6)	2 (2.7)	0 (0.0)
Patient exited before software download	2 (2.6)	0 (0.0)	0 (0.0)

Values are mean ± SD and n (%). *Predominant rhythm at pre-hospital discharge visit for 10 newly implanted patients. †Noise on surface electrocardiographic signal prevented assessment of predominant rhythm.

AV = atrioventricular; COPD = chronic obstructive pulmonary disease; RV = right ventricular; RVOT = right ventricular outflow tract.

during the auto-setup and resting phases by dividing the number of synchronous cycles by the total number of cardiac cycles. The primary efficacy analysis cohort included patients with complete AV block and normal sinus rhythm who had at least 500 evaluable cardiac cycles during the auto-setup and resting phases. For newly implanted patients, the pre-hospital discharge visit was used. McNemar's test was used to compare the proportion of patients with ≥70% AV synchrony during VVI and VDD pacing, respectively. In addition, AV pacing percentages and atrial detection rates were compared between pacing modes and estimated during each posture and maneuver using logistic regression models that incorporated generalized estimating equations to account for correlation in algorithm performance within each patient. Similar models were used to compare AV Synchrony percentage between the pre-hospital discharge and 1-month study visits for newly implanted patients. Due to skewness observed in AV synchrony proportions of individual patients, both the expected AV synchrony proportion based on the logistic model and the median percentage were reported.

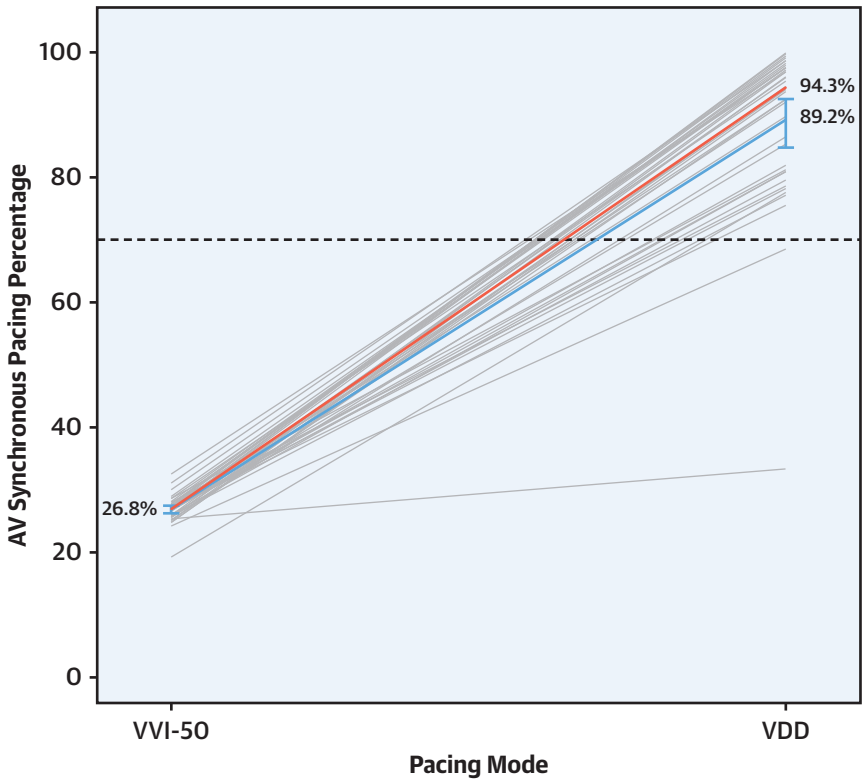
Holter recordings from all patients were assessed for the primary safety endpoint using both programmatic and manual review. The proportion of patients who met the primary safety endpoint was compared with the performance goal using an exact binomial test.

A paired Student's *t*-test was used to evaluate the change in mean LVOT-VTI between VVI and VDD modes in patients with complete AV block and normal sinus rhythm after averaging LVOT-VTI across measurements.

Type I error was controlled at the 0.05 level for analysis of the primary and secondary endpoints using a hierarchical closed testing procedure.

In a post hoc analysis, sinus rates computed between successive PP intervals were compared between the last 5 min of VVI and VDD pacing during the auto-setup and resting periods in patients who were evaluated for the primary efficacy endpoint

CENTRAL ILLUSTRATION **AV Synchronous Pacing Percentage**



Steinwender, C. et al. J Am Coll Cardiol EP. 2020;6(1):94–106.

Atrioventricular (AV) synchronous pacing percentage during auto-setup (VVI-50 mode) and resting (VDD mode) in 40 patients with complete AV block and normal sinus rhythm. **Gray lines** indicate individual patients. **Blue line** connects average AV synchrony percentage and the **red line** connects medians. Error bars are 95% confidence intervals. **Black dashed line** is the primary objective of 70%. During VVI-50 pacing, 0% of patients had ≥70% AV synchrony, during VDD pacing 95% had ≥70% AV synchrony ($p < 0.001$).

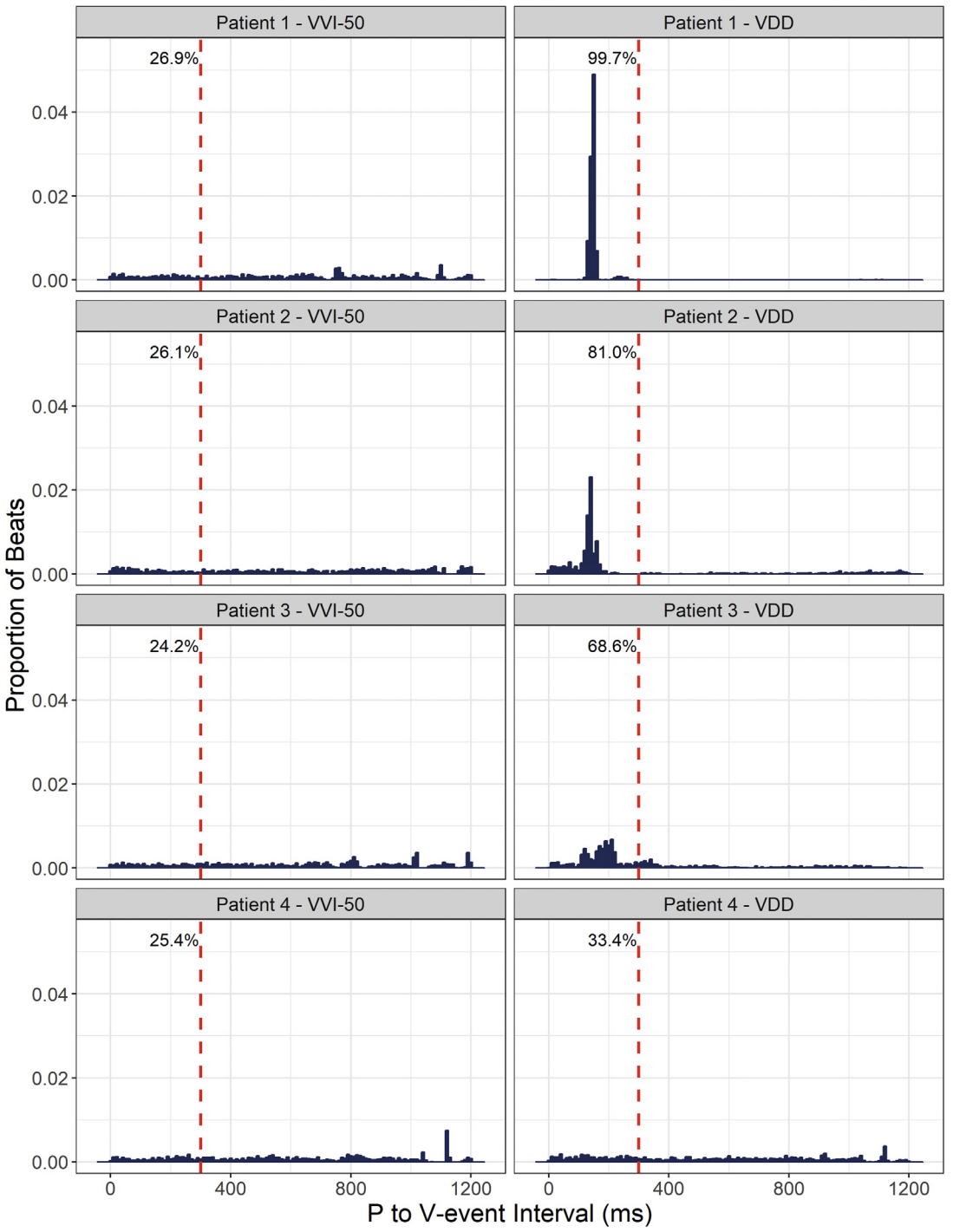
using a repeated measures analysis of variance model. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina) or R software (R Foundation, Vienna, Austria).

RESULTS

PATIENTS. A total of 77 patients from 12 centers in Europe, Malaysia, Hong Kong, and the United States were enrolled in the MARVEL 2 study. Of the 77 enrolled patients, 75 devices received the software download, and 74 (96%) patients completed the study procedures, with 1 exiting after the software download, but before completing the echocardiographic procedure to evaluate LVOT-VTI. Average age of the enrolled patients was 77.6 ± 11.8 years (range 21 to 94 years), and 31 (40%) patients were women. Patients had been implanted with a Micra device for a median of 9.7 months (range 0 to 62.1 months) (Table 1). Ten patients were enrolled on the day of implantation and were considered newly implanted patients. The most common primary pacing indication was third-degree AV block without atrial arrhythmias (n = 47; 61.0%). Of the 77 enrolled patients, 40 (51.9%) had a predominant rhythm of complete AV block with normal sinus function during Holter monitoring during the MARVEL 2 procedure (pre-hospital discharge visit for newly implanted patients) and were eligible for inclusion in the primary efficacy objective (Online Figure S2). The remaining patients had a predominant rhythm of intact AV conduction (n = 18; 23.4%), other rhythm (n = 15; 19.5%), or indeterminate rhythm due to poor ECG quality (n = 2; 2.6%) and were not included in the primary efficacy objective analysis.

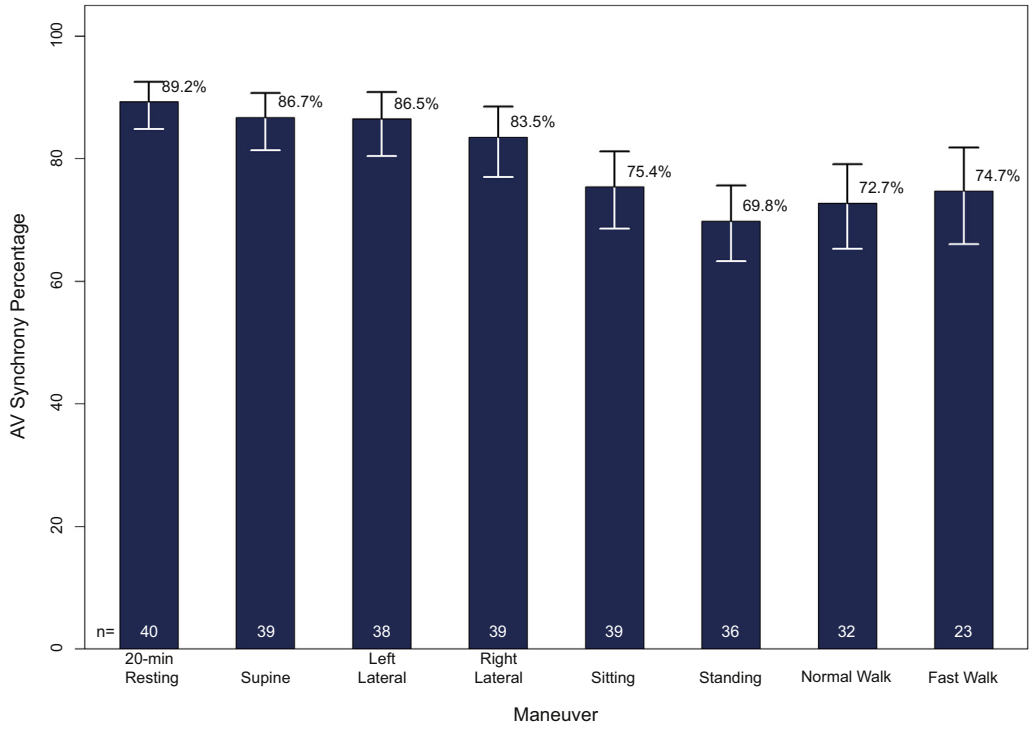
EFFICACY RESULTS. All 40 patients with a predominant rhythm of complete AV block with normal sinus rhythm were included in the primary efficacy analysis. AV synchrony percentage increased from an

FIGURE 1 **Distribution of P-V Intervals**



Distribution of P-V intervals during auto-setup (VVI-50 mode) and during resting (VDD mode) for 4 patients with percentage of atrioventricular (AV) synchrony during VDD pacing ranging from 99.7% to 33.4%. **Red dashed line** indicates 300 ms.

FIGURE 2 AV Synchrony Percentage by Maneuver



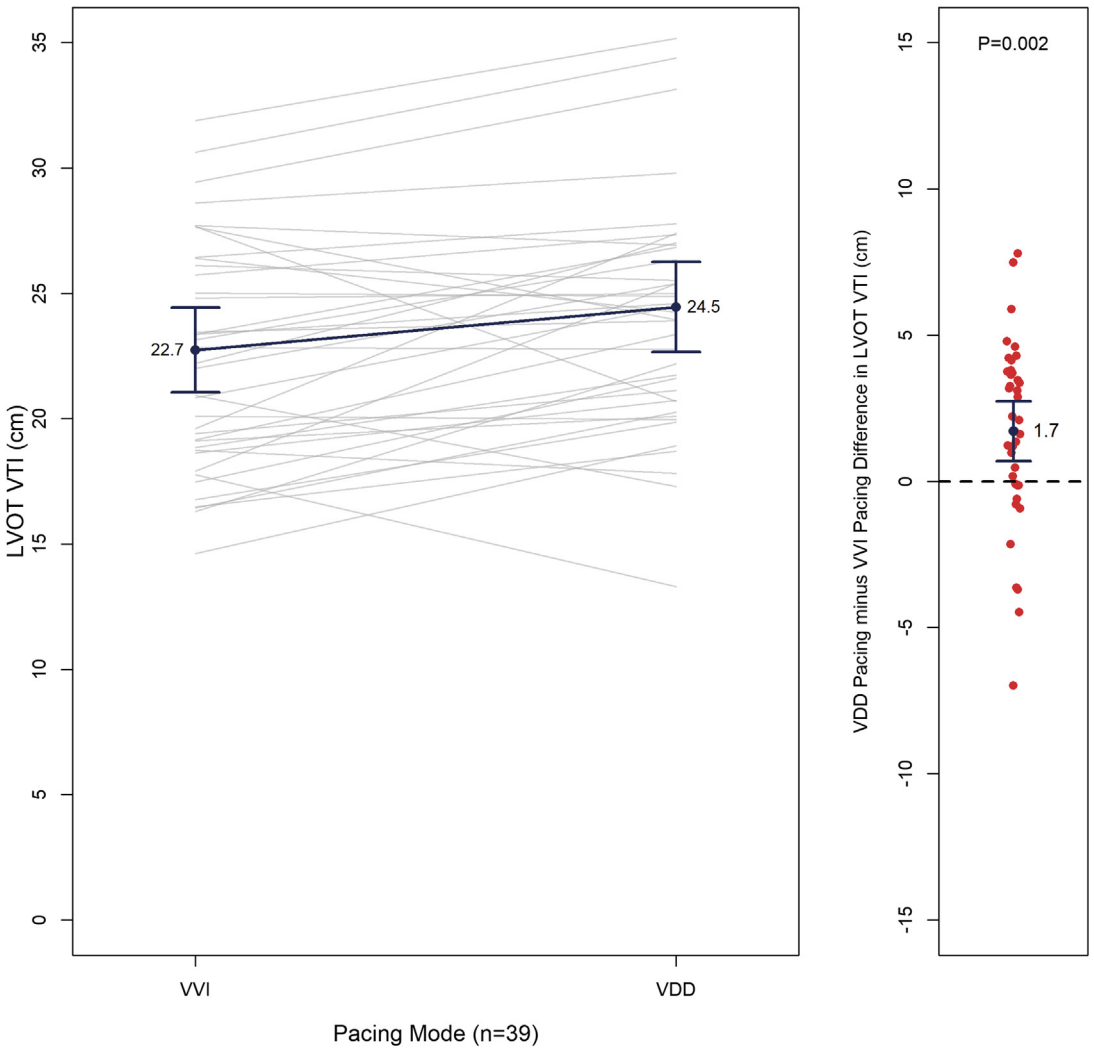
AV synchrony percentage by maneuver for patients with complete AV block and normal sinus function. Error bars represent 95% confidence intervals. Abbreviation as in **Figure 1**.

average of 26.8% (95% confidence interval [CI]: 26.2% to 27.5%; median: 26.9%) to 89.2% (95% CI: 84.8% to 92.5%; median: 94.3%) during VVI-50 and VDD pacing, respectively (**Central Illustration**). Zero patients had ≥70% AV synchrony during VVI-50 pacing, whereas 38 (95%) had ≥70% AV synchrony during algorithm-mediated VDD pacing ($p < 0.001$ for proportion of patients with ≥70% synchrony). The distribution of P-wave to V-event (PV) intervals during VVI-50 pacing were generally uniform between 0 and 1,200 ms, whereas they were peaked and centered at values <300 ms during VDD pacing (**Figure 1**). The 2 patients who failed to meet the primary efficacy endpoint during VDD pacing were from 2 different centers and had AV synchrony percentages of 68.6% and 33.4%, respectively. The first patient had low and variable amplitude A4 signals. The accelerometer signals for the second patient were exemplified by small signals related to both atrial and ventricular contraction (i.e., small A4 and A1 signals, respectively) and large signals during passive ventricular filling (A3). Notably, this patient had a history of repaired tetralogy of Fallot in childhood with pulmonary valve replacement.

During posture and maneuver testing assessed over 2 min each among all 40 patients, AV synchrony ranged from 89.2% during the resting period to 69.8% while standing (**Figure 2**). During the resting period, the ability of the rate smoothing operation to maintain synchrony during intermittent A4 undersensing allowed the AV synchrony percentage to exceed the A4 detection rate (89.2% vs. 80.3%) (Online Figure S3). There was no association between AV synchrony percentage and time since implantation (Online Figure S4). There was also no evidence to suggest that the percentage of AV synchrony differed by physician-reported Micra implantation location ($p = 0.287$).

Among patients with intact AV conduction, the mean AV synchrony percentage was 74.8% (95% CI: 53.6% to 88.4%; median 98.9%) during VVI-50 pacing and 79.6% (95% CI: 59.1% to 91.3%; median: 99.7%) during VDD pacing. There were 2 patients with long PV intervals, with >97% of PV intervals >300 ms (prespecified definition of synchrony); therefore, both patients had <3% AV synchrony in both pacing modes. Of the 15 patients with other rhythms, 7 had visible P waves confirmed and/or detected. The

FIGURE 3 **LVOT-VTI During VVI-50 and VDD Pacing**

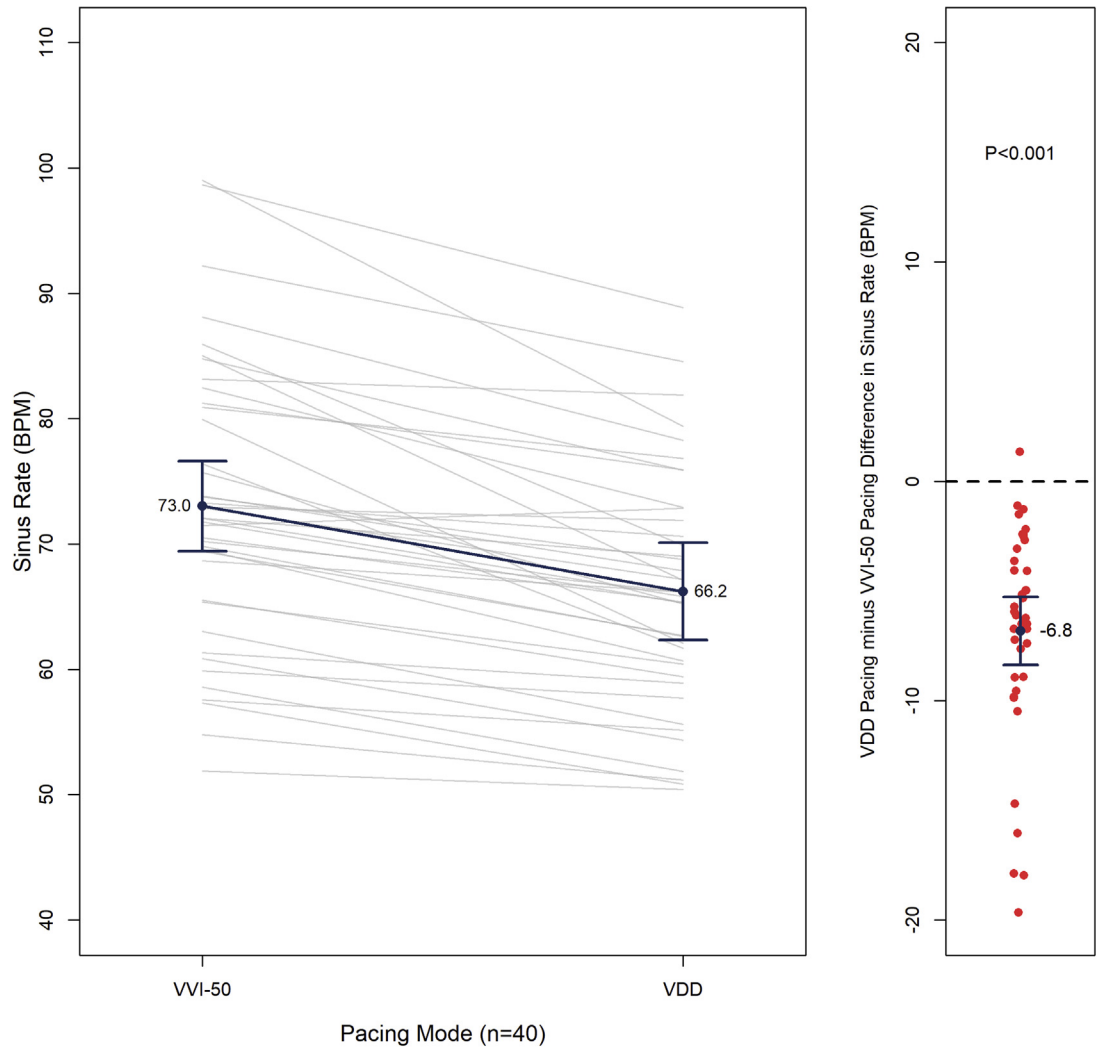


Left ventricular outflow tract velocity-time integral (LVOT-VTI) (cm) during VVI-50 and VDD pacing in 39 patients with complete AV block and normal sinus function. **(Left)** LVOT-VTI during VVI-50 and VDD pacing for individual patients **(gray lines)** and on average **(blue lines)**. **(Right)** Absolute change in LVOT-VTI during VDD relative to VVI-50 pacing for individual patients **(red circles)** and on average **(blue circle)**. Error bars represent 95% confidence intervals. BPM = beats per minute.

remaining 8 had no visible P-waves due to atrial fibrillation or atrial flutter. For the 7 patients with other rhythms and identifiable P-waves, mean AV synchrony increased from 41.3% (95% CI: 24.6% to 60.3%; median: 37.7%) during VVI-50 pacing to 70.2% (95% CI: 42.3% to 88.4%; median: 89.3%) during VDD pacing. In patients with atrial fibrillation, the A4 accelerometer signal was of low amplitude, and there was infrequent sensing, which resulted in median ventricular pacing at the lower rate (50 beats/min). In the patient with atrial flutter, the accelerometer signal was intermittently detected, which resulted in ventricular pacing at 67 beats/min (interquartile range: 66 to 67 beats/min). Among the 10 newly implanted patients, the mean AV synchrony percentage was not significantly different between the pre-hospital discharge and 1-month visit ($p = 0.329$). For additional details on algorithm performance in the newly implanted patients, refer to the Online Appendix and Online Figure S5.

Among the 40 patients with complete AV block and normal sinus rhythm, 39 had paired echocardiographic data available for analysis. LVOT-VTI as a proxy of left ventricular stroke volume increased by

FIGURE 4 Sinus Rate During VVI-50 and VDD Pacing



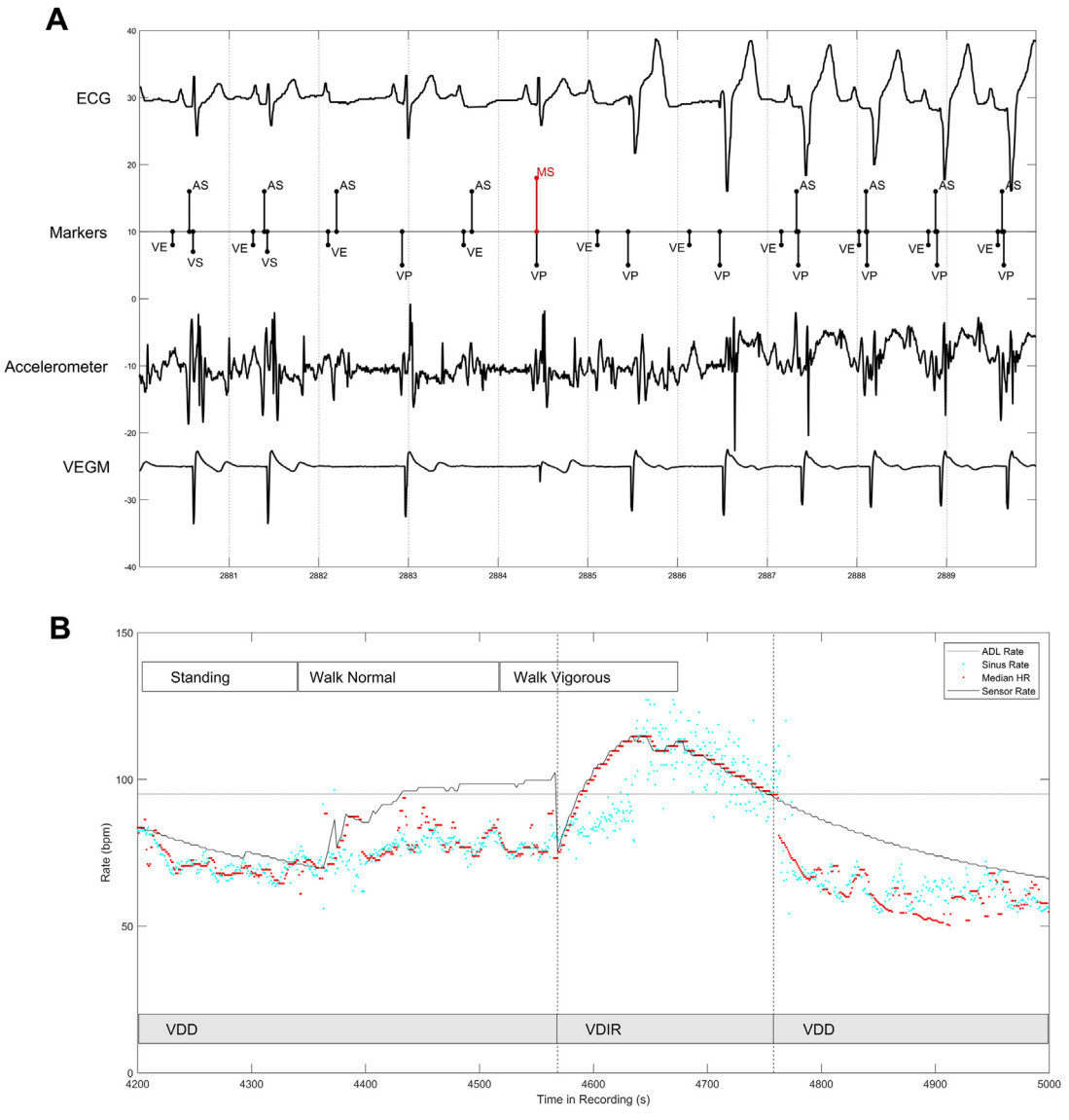
Sinus rate during VVI-50 and VDD pacing in 40 patients with complete AV block and normal sinus function. **(Left)** Sinus rate during VVI-50 and VDD pacing for individual patients **(gray lines)** and on average **(blue lines)**. **(Right)** Change in sinus rate during VDD relative to VVI-50 pacing for individual patients **(red circles)** and on average **(blue circle)**. Error bars represent 95% confidence intervals. BPM = beats per minute; other abbreviation as Figure 1.

1.7 cm (95% CI: 0.7 to 2.7 cm; p = 0.002) or 8.8 ± 15.4% during VDD pacing from a baseline average of 22.7 cm (95% CI: 21.0 to 24.4 cm) during VVI pacing (Figure 3). Similar results were observed for the 15 patients with other predominant heart rhythms (mean increase: 2.4 cm; 95% CI: 0.9 to 4.0 cm, during VVI pacing over an average 22.0 cm during VDD pacing).

For the 40 patients with complete AV block and normal sinus rhythm, the sinus rate decreased from an average of 73.0 beats/min during VVI-50 pacing to 66.2 beats/min during VDD pacing (p < 0.001) (Figure 4).

MODE SWITCHING. All Holter files from the 75 patients who had the algorithm was downloaded to their devices were reviewed to identify both AV conduction and activity mode switches. During the entire Holter recording period, there were 470 AV conduction mode switches in 73 patients. During these mode switches, the pacing mode remained in VVI-40, promoting intrinsic AV conduction and functioning as intended. Figure 5A shows an example of a patient with intermittent third-degree AV block with an AV mode switch from VVI-40 to VDD when AV block occurred. There were 41 activity mode switch

FIGURE 5 **AV Conduction Mode Switch and Activity Mode Switch**



(A) AV conduction mode switch in patient with intermittent third-degree AV block. Before the mode switch at 2,884 s, the patient exhibits AV conduction in VVI-40 mode. The patient then goes into second-degree AV block, and the device mode-switches to VDD. Two cycles after the mode switch, the device begins tracking the atrium in VDD mode. **(B)** Activity mode switch in patient with complete AV block and normal sinus rhythm. During the standing and/or walking maneuvers, good AV synchrony is indicated by the similarity of median heart rate (HR) and sinus rate. Mode switch to VVIR occurs when the sensor rate diverges from the pacing rate. The sensor rate decreases to the median HR and gradually increases to minimize large rate changes. After the activity ceases, the mode returns to VDD promoting AV synchronous pacing. ADL = activities of daily living; AS = atrial sense; ECG = electrocardiogram; MS = mode switch; VE = ventricular end; VEGM = ventricular electrogram; VP = ventricular pace; VS = ventricular sense; other abbreviations as in Figures 1 and 4.

episodes observed in 26 patients. Among the 41 activity mode switches, the median duration of VVIR pacing was 191.7 s. Figure 5B shows an example of an activity mode switch in a patient with complete AV block and normal sinus rhythm. Examination of each activity mode switch episode showed appropriate pacing support during the hall walk exercise and the activity mode switch operated as intended. The automatic algorithm was effective in choosing the appropriate accelerometer vector(s), A3 threshold, and A4 threshold, and adjusted the parameters throughout the study (see Online Appendix).

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 6, NO. 1, 2020
JANUARY 2020:94–106

SAFETY RESULTS. Among the 75 patients who had the algorithm downloaded, there were a total of 95 Holter recordings (newly implanted patients had 3 Holter recordings) that included 647,384 cardiac cycles for the primary safety endpoint analysis. There were no instances of ventricular pauses and no instances of oversensing-induced tachycardia; therefore, all 75 patients (100%) whose devices were downloaded with the algorithm met the primary safety endpoint. The lower 2-sided CI was 95.2%, which exceeded the performance goal of 87%; therefore, the primary safety objective was met ($p < 0.001$).

Among the 77 enrolled patients, 6 adverse events were reported in 5 patients. Of the 6 adverse events, none were considered by the investigator to be related to the algorithm or procedures. There was 1 event (right atrial hematoma) that was discovered during echocardiography and was considered to have a probable relationship to the Micra device. This adverse event was noted 4.8 months after Micra implantation on the day of the MARVEL 2 study procedures and was considered serious by the investigator. The patient was hospitalized for observation, but no clinical actions were reported during the course of the study.

DISCUSSION

There were several important findings from this study of AV synchronous pacing in patients with single-chamber right ventricular leadless pacemakers capable of accelerometer-based atrial sensing. First, the automated, enhanced MARVEL 2 algorithm robustly tracked mechanical atrial contraction and facilitated AV synchrony. Specifically, the study intervention improved median AV synchrony from 27% with VVI pacing to 94% in VDD pacing mode, with 95% of the cohort (38 of 40 patients with complete AV block) achieving ≥70% AV synchronous pacing. Second, the VDD pacing algorithm improved ventricular performance 9% as measured by LVOT-VTI, a proxy for left ventricular stroke volume. Finally, during the study period, the algorithm proved safe, with no instances of pauses or oversensing-induced tachycardia, regardless of predominant heart rhythm.

AV synchrony was best achieved at rest. Maintenance of high AV synchrony at high sinus rates could be complicated by superposition of accelerometer signals related to the atrial contraction with early periods of ventricular filling. Sitting and standing postures demonstrated a decrease in AV synchrony, but the mean value remained ≥70%. The reasons for the reduction in AV synchrony could be related to orthostatic tachycardia and a slight decrease in A4 signal due to decreased venous return during the postural change and the limited 2-min postural testing period. We found no evidence of a relationship between time since implantation and the ability for the algorithm to produce a high percentage of AV synchrony. Specifically, the performance of the algorithm did not appear to have diminished efficacy in newer implantations versus long-term implantations. These encouraging results reaffirmed the observations from those previously reported in the MARVEL trial, which also demonstrated an increase in AV synchrony and stroke volume with VDD pacing (9).

A preliminary proof-of-concept study that used a simpler algorithm reported an average AV synchrony of 80.0% in patients with AV block during VDD pacing, with 72.7% having ≥70% synchrony (9). Following this study, enhancements were made to the algorithm to improve detection in patients with low A4 signals, including an enhanced filter for atrial signal sensing and the ability to use a combination of 2 different accelerometer vectors. These enhancements, along with auto-adjusting detection parameters, might explain the higher proportion of patients with ≥70% AV synchrony observed in the MARVEL 2 study.

Cardiac output is reduced in patients with complete AV block and slow ventricular response compared with normal resting heart rates, despite compensatory mechanisms, including increased sinus rates and stroke volumes (11). It is a well-known phenomenon that restoration of heart rate with a pacemaker to a more physiological level results in decreased sympathetic tone and lower sinus rates. The significantly lower sinus rate observed with VDD pacing compared with VVI-50 pacing likely reflects a similar physiological phenomenon, with more physiological AV synchrony and ventricular rates reducing sympathetic tone and sinus rates. The observed reduction in sinus rates and the improvement in LVOT-VTI demonstrated the positive impact of AV synchronous pacing in patients with complete AV block.

Inhibition of ventricular pacing in patients with intrinsic AV conduction and sensor-based VVIR pacing during exercise were reliably delivered by 2 different mode-switching algorithms implemented in the MARVEL 2 algorithm. The intact AV conduction mode switch (**Figure 5A**) regularly checks for intrinsic AV conduction. This feature was developed to limit pacing to the minimum amount necessary, and in turn, to prevent conflicts between pacing triggered by the algorithm and the patient's intrinsic sinus rhythm. By reducing unnecessary pacing, it helps to prevent right ventricular pacing–induced cardiomyopathy and to extend battery life.

Although AV synchrony was excellent at rest, it decreased during physical activity. Two phenomena contributed to this effect by hampering detection of atrial contraction. First, an increase in heart rate with these maneuvers led to fusion of the atrial and ventricular components of the accelerometer signals. Second, additional accelerations caused by body motion were superimposed on the intra-cardiac signals. To overcome the decreased AV synchrony during exercise, the activity mode switch (**Figure 5B**) was implemented in the MARVEL 2 algorithm. When detecting a significant difference between the tracked sinus rate and heart rate suggested by the pacemaker's rate response function, VDD mode automatically switched to VVIR, and the pacing rate was slowly raised to the sensor rate level. Loss of AV synchrony due to activity mode switching might be seen as a downside of the MARVEL 2 algorithm; however, it was previously shown that the heart rate itself contributed much more to cardiac output at higher heart rates than AV synchrony (12,13). Importantly, none of the patients under investigation reported adverse events due to intermittent lack of AV synchrony or VVIR pacing during exercise.

The algorithm demonstrated a clear increase of AV synchrony compared with VVI mode, although it did not achieve 100% AV synchrony, similar to transvenous VDD pacemakers (14,15). To the best of our knowledge, the optimal percentage of AV synchrony required to maintain benefit and minimize pacemaker syndrome has not been characterized. It is plausible that 100% AV synchrony might not be required to allow normal exercise capacity and lifestyle. A lower percentage of AV synchrony might be sufficient, especially with the substantially lower complications associated with a leadless device. In the Micra global clinical trials, in which only VVI(R) pacing was delivered, approximately one-third of patients had normal sinus rhythm, which suggests that physicians were willing to sacrifice synchrony for the benefits of leadless pacemakers (3). Therefore, selection of this pacing mode will require a consideration of the benefits of leadless pacing versus the patient's need for even higher degrees of AV synchrony.

STUDY LIMITATIONS. The observational period and sample size were limited and might not reflect the total variability of use conditions in the long term. Thus, results must be confirmed in larger patient populations with longer follow-up. The downloadable nature of the algorithm increased current drain by approximately 100×, precluding continuous long-term AV synchrony evaluation or the use of the algorithm in existing implanted Micra devices. Incorporation of the algorithm into the electronics of an upgraded leadless device could reduce the current drain, allowing long-term implantation. For such a future device, it will be important to assess the robustness of ambulatory AV synchrony over real-world conditions and demonstrate that AV synchrony is maintained continuously over time. Symptomatic and functional assessment data were not collected; therefore, determination of the precise amount of AV synchrony required to avoid symptoms or maintain appropriate cardiac performance was not assessed.

CONCLUSIONS

Accelerometer-based atrial sensing with a novel, automated, enhanced algorithm significantly improved AV synchrony and stroke volume in patients with sinus rhythm and AV block implanted with a single-chamber leadless pacemaker in the right ventricle.

ACKNOWLEDGMENTS The authors thank Dedra Fagan of Medtronic for assistance in the preparation of this manuscript. The authors also thank Jean Hayman, Keelia Doyle, Alyssa Paul, Julie Pronovici, and Alex Mattson for technical support, and Nina Kristiansen, Sheikh Abdul Aziz, and Lindsay Werder for study management. The authors also thank Francesca Lemme for statistical support.

ADDRESS FOR CORRESPONDENCE: Dr. Clemens Steinwender, Department of Cardiology, Kepler University Hospital, Johannes Kepler University Linz, Medical Faculty, Krankenhausstrasse 9, 4021 Linz, Austria. E-mail: clemens.steinwender@kepleruniklinikum.at.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The enhanced MARVEL 2 algorithm allowed for AV synchronous ventricular pacing with a leadless pacemaker in patients with normal sinus activity and complete heart block. The algorithm worked safely and robustly, even when changing posture or during physical activity. An increase in stroke volume was observed with AV synchronous pacing using the enhanced MARVEL 2 algorithm compared with VVI pacing.

TRANSLATIONAL OUTLOOK: Until now, leadless pacemakers have only been capable of single-chamber pacing (VVI/R). If implemented in clinical practice, this new technology will help to further expand the spectrum of patients who might be eligible for leadless pacing.

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 6, NO. 1, 2020
JANUARY 2020:94–106

REFERENCES

1. Udo EO, Zuithoff NP, van Hemel NM, et al. Incidence and predictors of short- and long-term complications in pacemaker therapy: the FOLLOWPACE study. Heart Rhythm 2012;9:728–35.

2. Duray GZ, Ritter P, El-Chami M, et al. Long-term performance of a transcatheter pacing system: 12-month results from the Micra Transcatheter Pacing Study. Heart Rhythm 2017;14:702–9.

3. El-Chami MF, Al-Samadi F, Clementy N, et al. Updated performance of the Micra transcatheter pacemaker in the real-world setting: a comparison to the investigational study and a transvenous historical control. Heart Rhythm 2018;15:1800–7.

4. Reynolds D, Duray GZ, Omar R, et al. A leadless intracardiac transcatheter pacing system. N Engl J Med 2016;374:533–41.

5. Greenspon AJ, Patel JD, Lau E, et al. Trends in permanent pacemaker implantation in the United States from 1993 to 2009: increasing complexity of patients and procedures. J Am Coll Cardiol 2012;60:1540–5.

6. Lamas GA, Ellenbogen KA. Evidence base for pacemaker mode selection: from physiology to randomized trials. Circulation 2004;109:443–51.

7. Lamas GA, Orav EJ, Stambler BS, et al. Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual-chamber pacing. Pacemaker Selection in the Elderly Investigators. N Engl J Med 1998;338:1097–104.

8. Nielsen JC, Andersen HR, Thomsen PE, et al. Heart failure and echocardiographic changes during long-term follow-up of patients with sick sinus syndrome randomized to single-chamber atrial or ventricular pacing. Circulation 1998;97:987–95.

9. Chinitz L, Ritter P, Khelae SK, et al. Accelerometer-based atrioventricular synchronous pacing with a ventricular leadless pacemaker: results from the Micra atrioventricular feasibility studies. Heart Rhythm 2018;15:1363–71.

10. Garweg C, Splett V, Sheldon TJ, et al. Behavior of leadless AV synchronous pacing during atrial arrhythmias and stability of the atrial signals over time-results of the MARVEL Evolve subanalysis. Pacing Clin Electrophysiol 2019;42:381–7.

11. Stack MF, Rader B, Sobol BJ, Farber SJ, Eichna LW. Cardiovascular hemodynamic functions in complete heart block and the effect of isopropylnorepinephrine. Circulation 1958;17:526–36.

12. Ausubel K, Steingart RM, Shimshi M, Klementowicz P, Furman S. Maintenance of exercise stroke volume during ventricular versus atrial synchronous pacing: role of contractility. Circulation 1985;72:1037–43.

13. Benditt DG, Milstein S, Buetikofer J, Gornick CC, Mianulli M, Fetter J. Sensor-triggered, rate-variable cardiac pacing. Current technologies and clinical implications. Ann Intern Med 1987;107:714–24.

14. Antonioli GE, Ansani L, Barbieri D, Guardigli G, Percoco GF, Toselli T. Italian multicenter study on a single lead VDD pacing system using a narrow atrial dipole spacing. Pacing Clin Electrophysiol 1992;15:1890–3.

15. Folino AF, Buja G, Ruzza L, Nava A. Long-term follow-up of patients with single lead VDD stimulation. Pacing Clin Electrophysiol 1994;17:1854–8.

KEY WORDS atrioventricular synchrony, AV block, leadless pacemaker

APPENDIX For expanded Methods and Results sections as well as supplemental figures, please see the online version of this paper.