The cumulative effects and clinical safety of repeat magnetic resonance imaging on an MRI-conditional pacemaker system at 1.5 tesla

Thuy D. Nguyen, MD,* Sarah A. Sandberg, MD,*† Amir K. Durrani, MD,*‡ Kevin W. Mitchell, BS,§ Matthew D. Keith, MS,§ Marye J. Gleva, MD, FHRS,* Pamela K. Woodard, MD*

*From the *Divisions of Cardiovascular Medicine and Mallinckrodt Institute of Radiology, Washington University, Saint Louis, Missouri, †Brookwood Baptist Health, Birmingham, Alabama, ‡Division of Cardiovascular Medicine, Washington Permanente, Seattle, Washington, and §Clinical Studies Division at Biotronik, Inc, Lake Oswego, Oregon.*

BACKGROUND Studies have demonstrated magnetic resonance imaging (MRI) safety in the presence of MRI-conditional permanent pacemakers (PPM). However, since patients' care may require serial MRIs, it is necessary to evaluate device safety and performance after multiple scans.

OBJECTIVES We evaluated safety and performance of MRI-conditional PPMs after serial MRIs over various anatomic regions performed during a multicenter, prospective, single-arm study (ProMRI).

METHODS ProMRI was a multiphase observational study designed to evaluate PPM performance after MRI scans. Our study evaluated PPM function in a cohort of patients who underwent multiple 1.5-T MRI scans. Selected patients underwent separate head, chest, and lumbar spine MRIs. Pacing capture threshold (PCT), lead impedance (LI), sensing amplitude, and battery capacity were collected before and after scanning. Freedom from serious adverse device effects (SADE) through 1 month post MRI served as a primary endpoint. Changes in PPM function parameters, including threshold success rate and sensing attenuation, were analyzed for statistical significance and clinical relevance.

RESULTS In 81 patients no adverse events or SADE occurred. Statistically significant changes in ventricular PCT (0.034 ± 0.15 V) immediately after, ventricular LI immediately after (-18.7 ± 44.2 Ω) and 1 month post phase B (-19.8 ± 44.9 Ω), and atrial sensing attenuation immediately after (-0.27 ± 0.92 mV) and 1 month post phase B (-0.22 ± 0.92 mV) were noted. However, these changes were not clinically relevant in degree.

CONCLUSION These results demonstrate the safety and performance of the ProMRI PPM in patients undergoing 3 serial MRIs over various anatomic regions.

KEYWORDS Cumulative; Magnetic resonance imaging; MRI-conditional; Pacemaker; Specific absorption rate

Introduction

Magnetic resonance imaging (MRI) has emerged as an indispensable diagnostic tool largely owing to favorable tissue characterization, time resolution, and lack of ionizing radiation. However, a number of disadvantages and limitations of MRI use persist, including concern for electromagnetic interactions with electronic devices, metallic objects, and implants. MRI historically has been considered inadvisable in patients with cardiac implantable electronic devices (CIED). Professional guidelines initially permitted the use of MRI in such patients only when the clinical benefits strongly outweighed the risks of scanning.[1] It was not until 2011 that the US Food and Drug Administration (FDA) approved an MRI-conditional permanent pacemaker (PPM) for the first time.[2] Since then, multiple studies have demonstrated the safety of MRI-conditional PPMs under prespecified MRI conditions.[3,4] Some institutions have even developed protocols for imaging of MRI-nonconditional PPMs. Nevertheless, many medical providers remain hesitant to perform MRI in patients with PPMs not only owing to concerns of acute safety but also because of potential long-term effects on PPM function.

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KEY FINDINGS

- Patients with a conditional permanent pacemaker safely underwent serial magnetic resonance imaging (MRI) over various anatomic regions performed over time during the Pro-MRI phase A and B trials.
- Pacing parameters remained clinically stable and no device- or MRI-related serious adverse device effects occurred.
- This study provides another step forward in advancing the use of MRI scanning in patients with cardiac implantable electronic devices.

Uncertainty over MRI safety remains a significant issue in healthcare today, as CIED placement has increased over time. Between 1993 and 2008, 4.2 million CIED units were implanted in the United States.[5] Doubt over MRI safety potentially limits these patients' access to clinically recommended diagnostic evaluations throughout their lifetime. Reservations will undoubtedly improve with increasing institutional experience and inclusion within guidelines.

The majority of clinical human safety data is founded on freedom of adverse events during single imaging encounters. Limited data exist on how MRI-conditional PPMs perform following sequential examinations spread out over time. This is an important consideration, as many disease states require follow-up evaluation for progression or resolution.

In this analysis, we evaluated PPM function in a cohort of patients from the ProMRI Trial who underwent at least 3 sequential research MRIs and a possible fourth clinical MRI. The ProMRI trial is a prospective, single-arm, nonrandomized, multicenter study designed to evaluate the clinical safety of a specific PPM system (Evia/Entovis SR-T and DR-T with Setrox/Safio S 53-cm/60-cm leads; Biotronik, Berlin, Germany) under 1.5-T MRI conditions.[6,7] Each MRI had a peak radiofrequency (RF) power specific absorption rate (SAR) surpassing 1.5 W/kg.[8]

Methods

Study design

This is a retrospective analysis of a subset of prospectively collected observational data from 2 phases (A and B) of the ProMRI Trial.[6,7] Briefly, phase A MRI scans included imaging of the brain and lumbar spine. Phase B MRI scans included cardiac or thoracic spine imaging. Scan sequences were prespecified within the constraints of each participating site.

All patients provided informed consent before enrollment in both phases. Both phases were approved by the institutional review board / ethics committee at each site. This research conformed to the human subject research guidelines as put forth in the Helsinki Declaration as revised in 2013.

Three independent, nonstudy investigators, blinded to participating sites, comprised an independent data monitoring committee and adjudicated all PPM and MRI procedure adverse events, hospitalizations, and deaths to determine any relation to the MRI procedure and/or endpoints.

Inclusion criteria for the ProMRI trial included the following: (1) age $\geq$18 years, informed consent, and ability to complete the MRI studies and required follow-up, including ability to be followed remotely by Home Monitoring® (Biotronik, Berlin, Germany); (2) stable lead position and pacemaker indices for 5 weeks before the study; (3) pacing thresholds $\leq$2.0 V at 0.4 ms; (4) pacing impedances between 200 and 1500 Ω; (5) spontaneous rhythm allowing measurement of atrial and ventricular sensing indices; (6) battery capacity >30%; and (7) absence of phrenic nerve stimulation at 4.8 V @ 1.0 ms.

Exclusion criteria from the ProMRI trial included (1) persistent atrial arrhythmia (>7 days) or permanent atrial arrhythmia with an atrial lead; (2) planned cardiac surgery within 3 months of enrollment; (3) pregnancy; (4) life expectancy <3 months; and (5) other implanted medical devices or metallic items that may complicate MRI studies.

Pacemakers were interrogated at all study visits: baseline, immediately before MRI, immediately post MRI, 1 month post MRI, and 3 months post MRI for changes in discrete system parameters, including P-wave and R-wave sensing amplitude (SA), pacing capture threshold (PCT), lead impedance (LI), battery capacity (BC) used as a surrogate for battery voltage (BV), and PPM system status. All patients were also remotely monitored using a home monitoring system to collect daily SA, PCT, and LI data.

Subjects were included in this study if they had undergone the protocol MRI scans for both phases of the ProMRI Trial. Of the 226 and 216 patients that completed phase A and phase B, respectively, there were a total of 81 patients who met this criterion. Five of 81 patients also received additional clinically indicated MRI scans after completing phase B (Figure 1).

Prior to the initiation of the human ProMRI trial (NCT 01761162 and NCT 02009696), preclinical animal testing was performed in 21 canines with MRI-conditional Setrox S (Biotronik, Berlin, Germany) pacing leads implanted in the right atrium and right ventricle. Five sequential 30-minute continuous exposures to RF power, ranging from 0 mW to 490 mW at 64 MHz, demonstrated no chronic change in PCT greater than 0.5 V and maximally induced power to 67.62 mW. This confirmed lead-tip safety in exposures corresponding to a series of MRI worst-case scenarios.[9]

MRI

Study scans were performed with General Electric, Siemens, or Philips scanners. In phase A, head and lumbar spine MRI scans were selected, as they are common sites of clinical imaging. In phase B, cardiac and thoracic spine MRI scans were selected to investigate the effects of RF energy–related deposition at the PPM site. Of the 5 patients who underwent a fourth clinically indicated MRI, 4 had head and neck MRIs and 1 had a lumbar spine MRI. Research MRIs were configured at a field strength of 1.5 T. The whole-body SAR was

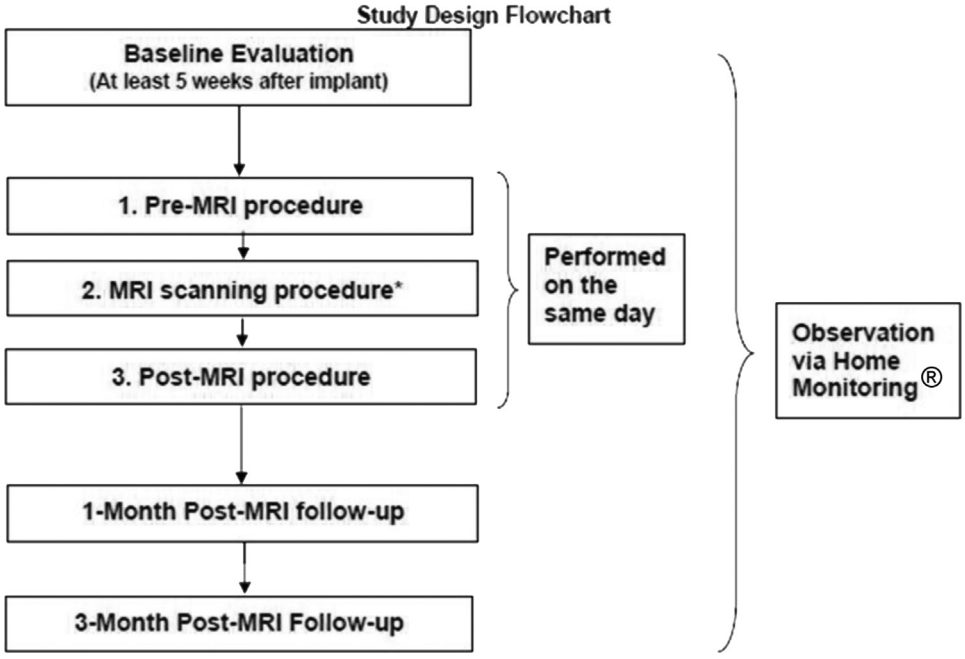

Figure 1 Study flow chart. *Not earlier than 7 days after baseline visit and not later than 2 months after baseline evaluation. MRI = magnetic resonance imaging.

limited to 2.0 W/kg for the body and 3.2 W/kg for the head. Similar constraints were also applied to the clinical MRIs.

During MRI examination, patients were assessed by electrocardiogram, pulse oximetry, and/or blood pressure monitoring. Following scanning, patients were examined for adverse events.

Pacemaker evaluation

The Entovis and Evia PPM systems were engineered with minimal ferromagnetic or paramagnetic materials, mitigating torque and force exerted by a high magnetic field. The system's electronic module design selectively rejects electromagnetic interference from MRI. It is equipped with a mode that limits functional interference and enacts clinical algorithms in the face of magnetic interference. Devices were interrogated prior to MRI scanning to assess individual lead SA, PCT, LI, and BC. Devices were then programmed to either asynchronous mode or off, based on physician preference. Following each MRI the devices were again interrogated and returned to their initial programmed state. Home Monitoring was used to assess for long-term trends. Devices were formally interrogated at 1-month and 3-month follow-up visits following the MRI for each phase.

Study objectives

The objective of this study was to determine the safety and performance of a PPM system in patients who had greater than or equal to 3 research and clinical MRI scans. Study endpoints included serious adverse device event (SADE)-free rate and changes in PPM discrete parameters. SADEs were defined as clinical or technical events occurring during or after MRIs that led to death, hospitalization, life-threatening condition, or irreversible hardware/software damage resulting in additional procedure for PPM revision/replacement. Discrete parameters were analyzed for significant changes from baseline evaluation. Phase A and ProMRI AFFIRM literature defined endpoint-relevant changes in discrete parameters.[6] Atrial and ventricular threshold was defined as a success if the increase was not >0.5 V. P-wave and R-wave sensing attenuation was defined as a P-wave or R-wave amplitude decrease of $>50\%$ or a P-wave amplitude <1.5 mV or R-wave amplitude of <5.0 mV at 1 month post MRI.

Statistical analysis

Endpoint analysis of PCT success rate and attenuation-free SA was based on the proportion of leads or patients satisfying endpoint criteria using exact binomial tests. Means were compared for equality between pre-MRI phase A and post-MRI phase B for PCT, LI, and SA using paired t tests. Endpoints were evaluated on a per-lead basis. No alpha adjustment for multiple testing was required. A value of $P \leq .05$ was considered evidence of statistical significance for any of the analyses.

Results

Study population

From the 226 and 216 patients enrolled in ProMRI phase A and phase B, respectively, we identified 81 patients from 20 sites who participated in both phases, receiving 3 or more MRI scans. All patients underwent head and lumbar MRI during phase A, followed by either a cardiac or a thoracic spine MRI in phase B of this study, the distribution of which is shown in Table 1. All scans were planned as

Table 1 Baseline characteristics and medical history

	No. of patients	Percentage	No. of MRIs
PM indications (multiple entries per patient)			
Sick sinus syndrome	45	55.6	NA
AVN disease	22	27.1	NA
Afib and bradyarrhythmia	3	3.7	NA
Fascicular block	2	2.5	NA
Atrial tachycardia	8	9.9	NA
Vasovagal syncope	3	3.7	NA
Other	23	28.4	NA
PM implant to first MRI duration			
11–90 days	51	63.0	NA
91–180 days	22	27.2	NA
>180 days	8	9.9	NA
Anatomical regions imaged			
Head	81	NA	84
Lumbar	81	NA	3
Neck	1	NA	1
Cardiac	10	NA	10
Thoracic	71	NA	71
Total	81	NA	169
PM type			
Dual-chamber	75	92.6	NA
Single-chamber	6	7.4	NA
Atrial lead only (AAI)	2	2.5	NA
Ventricular lead only (VVI)	4	4.9	NA

Afib = atrial fibrillation; AVN = atrioventricular node; MRI = magnetic resonance imaging; NA = not applicable; PM = pacemaker.

continuous and uninterrupted. No MRI was terminated owing to patient decompensation or arrhythmia.

Within our subset of 81 patients, PPM implant indications were most commonly sinus and atrioventricular nodal pathology (Table 1). The majority of patients received dual-chamber devices (Table 1). The median (interquartile range) implant duration to the first MRI was 74 (58–107) days. The median (interquartile range) time period between the phase A and B scans was 194 (146–259) days.

MRI SAR values

The mean maximum achieved SAR (W/kg) of all sequences was 1.58 ± 1.05 (phase A head), 1.50 ± 0.66 (phase A lumbar spine), 2.12 ± 0.37 (phase B cardiac), and 1.86 ± 0.28 (phase B thoracic spine). Scan locations, sequences, and results are seen in Table 2.

Device performance

A total of 156 pacing leads were followed. There were no reports of major SADE, including cardiac perforations, device infections, lead dislodgements, or deaths. Differences in pacemaker parameters immediately post and 1 month post MRI phase B were assessed relative to before MRI phase A (Table 3). There were no adverse events reported owing to any of these parameter changes.

Primary endpoint analysis

Primary endpoint 1: SADE-free rate

No adverse events or SADE relating to the PPM system or MRI studies were reported. This produced a SADE-free event rate of 100%. No deaths occurred during either trial phase.

Primary endpoint 2: Atrial pacing capture threshold

Nearly all patients (98.7%) achieved atrial PCT success immediately post MRI phase B and all 77 patients implanted with atrial leads achieved atrial PCT success 1 month subsequent to the completion of phase B. On average, the atrial PCT change was 111-fold less than the previously defined clinically significant level of 1 V.[10]

Table 2 Specific absorption rate, scan sequence, and imaging location for patients who underwent magnetic resonance imaging

Scan type	Predefined scan sequence types	Mean maximum SAR ± SD(n)
Phase A		
Head (landmark on eyes)	3 Plane Localizer, SAG SE T1, AX TSE T2, T2 TIRM, Diffusion, 3D TOF MT, CE-MRA, Perfusion	1.58 ± 1.05 (n = 81)
Lumbar (landmark on trochanter)	Localizer, SAG T1, SAG T2, AX T1, AX T2, SAG diffusion	1.50 ± 0.66 (n = 81)
Phase B		
Cardiac	3 Plane Localizer, AX HASTE, COR HASTE, AX SSFP, 2CHLA SSFP CINE, 4CHLA TRUFISP CINE, SA SSFP CINE, Ao Outflow TRUFISP CINE, PA Outflow SSFP Cine, SA DCE, SA GRE PERFUSION, Ao Flow Quant, COR GRE	2.12 ± 0.37 (n = 10)
Thoracic spine	Localizer, SAG T2 TSEr, SAG TSE T1, SAT IR, Ax TSEr T2	1.86 ± 0.28 (n = 71)

2CHLA = 2 chamber long axis; 4CHLA = 4 chamber long axis; AX = axial; CE-MRA = contrast enhanced-magnetic resonance angiography; COR = coronal; DCE = delayed contrast enhanced; GRE = gradient recalled echo; PA = pulmonary artery; SA = short axis; SAG = sagittal; SAR = specific absorption rate; SAT IR = saturation inversion recovery; SSFP = steady state free precession; TIRM = turbp inversion recovery magnitude; TOF MT = time-of-flight magnetization transfer; TSEr = turbo spin echo with restore pulse.

Table 3 ProMRI pacemaker parameters

	Mean ± SD	Range	*P* value
Pacing capture threshold change (V)			
Atrium (n = 77)			
Post-MRI phase B and pre-MRI phase A	-0.004 ± 0.17	-0.3 to 0.6	.84
1 month post-MRI phase B and pre-MRI phase A	0.01 ± 0.2	-0.3 to 0.5	.60
Ventricle (n = 79)			
Post-MRI phase B and pre-MRI phase A	0.034 ± 0.15	-0.4 to 0.4	.04
1 month post-MRI phase B and pre-MRI phase A	0.029 ± 0.2	-0.5 to 0.4	.09
Sensing amplitude change (mV)			
P-wave sensing amplitude (n = 77)			
Post-MRI phase B and pre-MRI phase A	-0.27 ± 0.92	-3.9 to 2.3	.01
1 month post-MRI phase B and pre-MRI phase A	-0.22 ± 0.92	-2.8 to 1.6	.04
R-wave sensing amplitude (n = 78)			
Post-MRI phase B and pre-MRI phase A	-0.11 ± 2	-4.7 to 5.9	.63
1 month post-MRI phase B and pre-MRI phase A	-0.14 ± 1.88	-4.7 to 5.1	.52
Chamber pacing impedance change (Ω)			
Atrial impedance change (n = 74)			
Post-MRI phase B and pre-MRI phase A	-2.8 ± 35	-98 to 78	.49
1 month post-MRI phase B and pre-MRI phase A	-3.7 ± 34.4	-78 to 59	.36
Ventricular impedance change (n = 75)			
Post-MRI phase B and pre-MRI phase A	-18.7 ± 44.2	-253 – 78	.0005
1 month post-MRI phase B and pre-MRI phase A	-19.8 ± 44.9	-253 to 98	.0003
Battery capacity (%) (n = 81)			
Pre-MRI phase A	99.9 ± 0.8	95 to 100	
Difference between pre-MRI phase A and 3 months post-MRI phase B	-7.6 ± 2.8	-10 to 0	<.0001
3 months post-MRI phase B	92.3 ± 2.7	90 to 100	

Primary endpoint 3: Ventricular pacing capture threshold

All 79 patients with ventricular leads achieved ventricular PCT success both immediately after and 1 month post MRI phase B. Initially, there was a statistically significant difference of minor magnitude in average ventricular pacing thresholds ($P \leq .05$) when comparing the means of the immediate phase B MRIs to the pre–phase A MRIs. However, the ventricular PCT was 35-fold less than the previously defined level of clinical significance. Cumulatively this parameter became statistically insignificant ($P = .09$) when remeasured, comparing the means of the 1 month post–phase B MRI to the pre–phase A MRI (Table 3).

Primary endpoint 4: Atrial sensing attenuation

The freedom from P-wave amplitude attenuation was 98.7% at the end of the phase B MRI. The largest single change experienced between pre–phase A and immediate post–phase B MRI was -3.9 mV. However, at 1 month post phase B, the largest decrement was -2.8 mV (Table 3). Only 1 patient with an atrial lead experienced a change ≥50% in sensing attenuation. Thus, atrial sensing remained clinically stable 1 month post phase B.

Primary endpoint 5: Ventricular sensing attenuation

The freedom from R-wave amplitude attenuation was 100% at the end of the phase B MRI. The largest single change experienced between pre–phase A and both immediate post– and 1 month post–phase B MRI was -4.7 mV (Table 3). No patient with a ventricular lead experienced a change ≥ 50% in sensing attenuation. Thus, ventricular sensing remained clinically stable 1 month post phase B.

Additional pacemaker parameters

Although not listed as endpoints for the trial, measurements of LI and BC were also obtained. In our study, the mean BC capacity at baseline was 99% ± 0.8% and following the serial MRIs was 92.3% ± 2.7% (Table 3).

Discussion

This study analyzes data from the first multi-institutional prospective evaluation of MRI-conditional PPM function and safety in patients who underwent multiple MRI scans. The results of this study demonstrate that the ProMRI PPM system remains safe after 3 MRI evaluations. Eighty-one PPMs were imaged under these parameters, all of which remained clinically unchanged at the conclusion of the trial. The RF energy deposition resulted in higher SAR proximate to the PPM than in prior series, since all study participants underwent 3 or more MRI scans, including 1 scan evaluation of the chest.

Prior series performed similar analyses of parameter changes, programming, and clinical event rates without restricting the type of PPM. These studies reported significant changes in PCT and BV in up to 10% of their study populations as well as in 2 patients requiring reprogramming.[8,11,12] Compared to earlier studies, our discrete PPM data were obtained with higher resolution, allowing for evaluation of degree of effect. For example, a change of 0.05 V was previously treated the same as a 10-fold higher change, as 0.05 V and 0.55 V were both displayed as 1 V.[8]

Another prospective, nonrandomized single-center study included 26 PPM patients who had more than 2 MRI studies suggested sensing attenuation, but their results did not reach

Table 4 SIELLO pacemaker parameters

	Mean ± SD	Range	*P* value
Pacing capture threshold change (V)			
Atrium (n = 1001)			
(12 mo threshold – 3 mo threshold)	0.03 ± 0.32	-2.7 to 3.7	.0122
Ventricle (n = 1142)			
(12 mo threshold – 3 mo threshold)	0.08 ± 0.36	-4.4 to 4.7	<.0001
Sensing amplitude change (mV)			
P-wave sensing amplitude (n = 1121)			
(12 mo sensing – 3 mo sensing)	-0.22 ± 1.32	-10.8 to 6.5	<.0001
R-wave sensing amplitude (n = 1025)			
(12 mo sensing – 3 mo sensing)	-0.28 ± 2.39	-9.4 to 13.8	.0002
Chamber pacing impedance change (Ω)			
Atrial impedance change (n = 1165)			
(12 mo impedance – 3 mo impedance)	-1.65 ± 54.4	-273 to 331	.3015
Ventricular impedance change (n = 1165)			
(12 mo impedance – 3 mo impedance)	-22.5 ± 55.01	-254 to 233	<.0001
Battery capacity (%) (n = 1143)			
(12 mo % - 3 mo %)	-8.69 ± 2.41	-15 to 5	<.0001

statistical significance.[13] Similarly, our analysis of 81 patients showed statistically significant changes in atrial sensing, ventricular PCT, and ventricular lead impedance but found that these changes were clinically irrelevant in degree. No permanent programming changes or invasive procedures were required.

Prior studies showed a significant decrease in BV with cumulative MRI examinations but were unable to discern how much of that decrease was owing to normal battery depletion over time vs multiple MRI effect.[8] A decrease in BV by 0.05 V does not decrease PPM longevity in a clinically relevant fashion.[14] Our study used BC as a surrogate for BV. No individual patient had a measured BC of ≤90% at 3 months post phase B MRI, suggesting that the decrease in BC following 3 MRI scans is clinically unimportant and does not pose a safety risk.

To further interpret these findings, the patients undergoing MRIs in our study were compared with 1284 subjects in the SIELLO Pacing System study (NCT01791127) who had identical dual-chamber PPM generator and pacing leads but were not exposed to MRI (data source: manufacturer's in-house data, Biotronik Inc, Lake Oswego, OR). In the SIELLO trial identical lead parameters were investigated over a similar follow-up duration. There were no clinically significant differences in atrial or ventricular pacing thresholds, sensing amplitudes, lead impedance, or battery capacity in the SIELLO subjects who were not exposed to MRI (Table 4). However, owing to the large sample size, most parameters reached statistical significance. The magnitude of changes in those subjects who had multiple MRIs in the ProMRI trials and the SIELLO subjects who were not exposed to MRI was nearly identical (Tables 3 and 4). No statistical comparison between the ProMRI and SIELLO groups was conducted owing to the large imbalance of sample size between these groups (81 vs 1284, respectively).

The FDA has emphasized the need for data on the effects of multiple MRI examinations on PPM systems. Ideally, device reliability and patient safety of FDA-approved MRI-conditional PPM is best demonstrated in large multicenter trials. This analysis of data from the prospective, nonrandomized, single-arm, multicenter ProMRI trial demonstrated the clinical safety and cumulative MRI effects on a PPM system specifically designed for the MRI environment.

Limitations

Prior work suggests SADE events are inherently low in human studies and may only be predictable by large-size computer modeling or phantom testing.[15] As our study population is an extraction of 2 larger trials, the number of participants who met the inclusion criteria is smaller than either of the initial studies (n = 81 vs n > 200). Thus, our ability to detect any rare SADE may have been hindered. Although we looked at the cumulative effects of multiple MRI scans in our population, this study was limited to 3 or 4 evaluations over various anatomic regions and does not speak to the outcome in patients who require more MRI scans or multiple serial scans over a single anatomic region. This is especially true in patients who require multiple MRI scans of the cardiothoracic region at which the device is at the scanner isocenter, as only 1 of the scans for each patient involved the chest (was a thoracic or cardiac scan). However, our study does answer the safety question of multiple-device MRI RF electromagnetic field exposures. Finally, as noted in the previous 2 trials, the patients in this study were not technically pacemaker dependent.

Conclusion

Our results contribute relevant evidence on the safety and device performance of the studied PPM system following cumulative MRI examinations over various anatomic regions. Pacing parameters remained clinically stable and no device- or MRI-related SADEs occurred, thus providing another step forward in advancing the use of MRI scanning in patients with CIEDs.

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Disclosures

KM is employed by Biotronik Inc, and MK was employed by Biotronik Inc when the statistical analysis was completed; MG and PKW were ProMRI trial investigators. AKD, SAS, and TDN disclosed no relevant relationships.

Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent

All patients provided informed consent before enrollment in both phases.

Ethics Statement

This research conformed to the human subject research guidelines as put forth in the Helsinki Declaration as revised in 2013. Both phases were approved by the institutional review board/ethics committee at each site.

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