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

Yoshimasa Murakami1*, Naoya Tsuboi2, Yasuya Inden3, Yukihiyo Yoshida4, Toyoaki Murohara3, Zenichi Ihara5, and Mitsuaki Takami5

1Cardiovascular Center, Higashi Municipal Hospital, City of Nagoya, 1-2-23 Wakamizu, Chikusa-ku, Nagoya 464-8547, Japan; 2Social Insurance Chukyo Hospital, Nagoya, Japan; 3Nagoya University Graduate School of Medicine, Nagoya, Japan; 4Nagoya Dai-ni Red Cross Hospital, Nagoya, Japan; and 5Medtronic Japan, Tokyo, Japan

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Aims

Managed ventricular pacing (MVP) and Search AV+ are representative dual-chamber pacing algorithms for minimizing ventricular pacing (VP). This randomized, crossover study aimed to examine the difference in ability to reduce percentage of VP (%VP) between these two algorithms.

Methods and results

Symptomatic bradyarrhythmia patients implanted with a pacemaker equipped with both algorithms (Adapta DR, Medtronic) were enrolled. The %VPs of the patients during two periods were compared: 1 month operation of either one of the two algorithms for each period. All patients were categorized into subgroups according to the atrioventricular block (AVB) status at baseline: no AVB (nAVB), first-degree AVB (1AVB), second-degree AVB (2AVB), episodic third-degree AVB (e3AVB), and persistent third-degree AVB (p3AVB). Data were available from 127 patients for the analysis. For all patient subgroups, except for p3AVB category, the median %VPs were lower during the MVP operation than those during the Search AV+ (nAVB: 0.2 vs. 0.8%, P = 0.0001; 1AVB: 2.3 vs. 27.4%, P = 0.001; 2AVB: 16.4% vs. 91.9%, P = 0.0052; e3AVB: 37.7% vs. 92.7%, P = 0.0003).

Conclusion

Managed ventricular pacing algorithm, when compared with Search AV+, offers further %VP reduction in patients implanted with a dual-chamber pacemaker, except for patients diagnosed with persistent loss of atrioventricular conduction.

Keywords

Algorithm  •  Pacemaker  •  Minimizing ventricular pacing  •  Atrioventricular block

Introduction

Transvenous ventricular pacing (VP) has been traditionally performed from the right ventricular apex (RVA) because of the ease of pacing electrode positioning and the long-term pacing stability. On the other hand, recently, the adverse effects of pacing at RVA have rapidly emerged. An increase in cumulative percentage of RVA pacing in patients treated with pacemakers or implantable defibrillators results in increased risk of heart failure hospitalization, death, and atrial fibrillation (AF).1–3 It is generally considered that majority of the patients with initially normal left ventricular (LV) function well tolerate RVA pacing and the detrimental effect
of the pacing predominantly emerges in patients with pre-existing LV dysfunction, despite the presence of a small study which is insufficiently supportive of these. The detrimental effects of frequent RVA pacing are thought to be attributable mainly to the ventricular dysynchrony imposed by RVA pacing, which impairs cardiac pump function. In addition, an undesired short atrioventricular (AV) delay programming that achieves VP, especially in patients with intact AV conduction, may compromise active atrial transport and partially contribute the adverse consequences of frequent RVA pacing.

To avoid or diminish the adverse consequences of RVA pacing, currently two strategies are proposed. Substituting other VP site(s), such as right ventricular septum, left ventricle, and bi-ventricles, for RVA may be a promising approach to attenuate the adverse effects of pacing-induced ventricular dyssynchrony. This approach is somewhat technically challenging and sometimes costly compared with traditional RVA pacing at present. Moreover, which site(s) is the most appropriate for VP as an alternative to RVA is still subject to investigation. The other strategy involves preserving normal ventricular activation sequence whenever possible with manipulation of pacing mode and timing cycle. To implement this strategy effectively, contemporary dual-chamber pacemakers or implantable defibrillators are being equipped with new algorithms for minimizing unnecessary VP. Of such algorithms, managed VP (MVP) which operates in AAI/R mode with backup VP during AV block (AVB) and Search VP+ which operates in DDD/R mode with automatic extension of AV interval have been evaluated for their clinical utility in patients with sinus-node disease in a large-scale randomized clinical trial. The trial showed that dual-chamber pacing operating with either one of the two algorithms, when compared with conventional dual-chamber pacing, offered a 40% reduction in the relative risk of the development of persistent AF compared with conventional dual-chamber pacing, when compared with conventional dual-chamber pacing.

Difference in %VP between two algorithms for minimizing VP

Device characteristics

Adapta DR is a dual-chamber pacemaker equipped with MVP and Search VP+ algorithms, each of which is intended to minimize VP. The MVP operates in atrial-based pacing (AAI/R) with backup VP during AVB. When AV conduction is lost for two out of four atrial to atrial depolarization intervals, the pacemaker switches to DDD/R mode with preprogrammed sensed AV (SAV) and paced AV (PAV) intervals. Then, the checks for AV conduction are performed. The first check occurs 1 min after the switching to DDD/R mode, and if AV conduction resumes, the pacemaker switches back to AAI/R mode. If loss of AV conduction persists, subsequent checks periodically occur until AV conduction resumes. The time interval for the checks progressively double (2, 4, 8 min) up to 16 h and then the checks occur every 16 h thereafter. The Adapta DR does not provide information about the behaviour of the MVP algorithm between follow-up visits other than the simple %VP (e.g., how often did AAI/R disengage to restore DDD/R mode, what were the events that triggered restoration of DDD/R mode).

The Search AV+ operates in DDD/R mode as well as in DDI/R, DVI/R, or VDD mode with automatic extension of PAV and SAV intervals as needed to promote intrinsic ventricular activation. Search VP+ uses the 'Max increase to AV' parameter to define the maximal amount of time by which the operational SAV and PAV intervals can be automatically extended. For the Adapta DR pacemaker, SAV and PAV intervals are manually programmable from 30 to 350 ms in steps of 10 ms, with nominal values of 120 and 150 ms, respectively. 'Max increase to AV' is programmable from 10 to 250 ms in steps of 10 ms, with a nominal value of 170 ms. Therefore, the maximal operational AV intervals can differ from 40 ms (=30 + 10 ms) to 600 ms (=350 + 250 ms) according to the programmed AV intervals and the value of ‘Max increase to AV’. Search AV+ continuously attempts to adapt the operational AV intervals to a value slightly longer (15–55 ms) than AV conduction time. When Search AV+ is turned on, a conduction check is automatically started. If AV conduction is not found within the range of the extendable AV interval and the adaptation of operational AV intervals fails, the AV intervals revert to the programmed values and Search AV+ suspends operation for progressively longer periods: 15, 30 min, 1, 2, 4, 8, and 16 h. Unlike MVP, Search AV+ is automatically disabled if no AV conduction is found following 10 consecutive 16 h suspicions (~1 week). More detailed explanations of MVP and Search AV+ have been described.10,11 For the Adapta DR pacemaker, MVP and Search AV+ cannot be enabled concurrently.

Methods

Selection of patients

Symptomatic bradycardia patients implanted with a dual-chamber pacemaker equipped with two types of algorithms for minimizing VP (Adapta DR, Medtronic Inc., MN, USA) were selected for enrolment. Patients receiving their first pacemaker as well as those undergoing pacemaker generator replacement were eligible to participate. Patients were excluded if they had any of the following: age of 19 or younger, experience symptoms with the first-degree AVB, or inability to comply with study protocol. All patients gave written, informed consent to participate in the study. The study was in compliance with the Declaration of Helsinki and approved by the ethics committee or the institutional review board at each of the participant centres.

Study design

This study was conducted at 14 centres. Patients enrolled in the study were randomly assigned to dual-chamber pacing operating with MVP or Search VP+ algorithm for 1 month and then crossed over to the alternative algorithm for an additional month. Either one of the algorithms was turned on at the time of randomization, ~1 week after the pacemaker implantation. The algorithm switch-overs and final data collections were done.
at 1 and 2 month follow-up visits, respectively. Data of %VP, percentage of atrial pacing (%AP), and percentage of time spent in atrial tachycardia (%AHR) which is highly likely to represent atrial tachycardia (AT) or AF burden were obtained from stored pacemaker diagnostics on completion of 1 month operation for each algorithm. Patients were categorized into subgroups according to the AVB status at baseline: no AVB (nAVB), first-degree AVB (1AVB), second-degree AVB (2AVB), episodic third-degree AVB (e3AVB), and persistent third-degree AVB (p3AVB). For the AVB status determination, electrophysiologic testing was not mandatory and the status was determined based on each participant clinician’s recognition for the most severe form of AVB of the patient at the time of randomization. Type I and Type II 2AVB were categorized with no distinction. Patients presented with 2:1 or more advanced AVB but with intermittent AV conduction were categorized into e3AVB.

Device programming

The programmed SAV and PAV intervals during DDD/R mode for MVP or Search AV+ operation and value of ‘Max increase to AV’ for Search AV+ programming in each patient were determined at the discretion of each participant clinician. Tailorings of other device parameters that could potentially affect the %VP, such as rate-adaptive AV, automatic post-ventricular atrial refractory period, conducted AF response (i.e. ventricular rate regularization during AF), lead impedance trend which collects lead impedance data during pacing, and so forth, were also committed to each participant clinician.

In this study, Search AV+ was programmed to operate in DDD/R mode for all patients.

Statistical analysis

Data are presented as mean ± standard deviation, median, or frequencies where appropriate. Continuous variables were compared with the Wilcoxon signed-rank test, whereas comparisons for categorical variables were performed with the McNemar test. A probability value of <0.05 was considered statistically significant. Analyses were performed with SAS statistical software.

Results

Study population

One hundred and forty-one patients were enrolled in the study between April and December 2008. Of these patients, 13 dropped out from the study, seven because of being lost to follow-up, two because of symptoms related to MVP or Search AV+ operation, and remaining four because of the retractions of participation in the study. One additional patient who had presented persistent AF throughout the study was removed from the analysis, despite completion of the two phases of the study. With the exclusion of these 14 patients, we eventually analysed the data from 127 patients who successfully completed the crossover study. The demographics of these patients are summarized in Table 1. Of the analysed patients, 106 (83.5%) were enrolled in the study after undergoing their first pacemaker implantation. Three were indicated a pacemaker implantation for coexistence of sinus-node disease and AVB. Sixty-four (50.4%) were assigned to the operating MVP algorithm first.

Device programming

Pacemaker parameter settings during the MVP and Search AV+ operations are summarized in Table 2. The mean programmed SAV and PAV intervals during DDD/R mode for MVP operation were ~10 ms longer than the nominal values of 120 and 150 ms, respectively. For the Search AV+ settings, the AV intervals and ‘Max increase to AV’ were programmed to nominal values in 63 (49.6%) patients. Therefore, the maximal operational SAV and PAV intervals were 290 ms (=120 + 170 ms) and 320 ms (=150 + 170 ms), respectively, in these patients. Whereas, in 52 (40.9%) patients, Search AV+ was programmed more aggressively to permit their maximal operational SAV and PAV intervals being longer than the nominal settings. The most aggressive Search AV+ settings observed in the study permitted the SAV and PAV intervals to extend up to 450 and 500 ms, respectively. In 11 (8.7%) patients, Search AV+ was programmed modestly to permit their maximal operational SAV and PAV intervals being shorter than the nominal settings. The shortest maximal operational SAV and PAV intervals in these patients were 220 and
250 ms, respectively. In the remaining one patient, the maximal operational SAV and PAV intervals were 290 and 290 ms, respectively. Rate response was enabled in nine (7.1%) patients at the time of randomization and this setting remained unchanged throughout the study period in all of these nine patients. The information about whether these nine patients had chronotropic incompetency were not collected. Settings of other parameters seemed to have remained almost unchanged throughout the study period.

Percentage of atrial pacing and percentage of atrial high rate

The median %APs were similar between each operational period of the two algorithms except for patients categorized into 2AVB. The median %AHRs were also comparable between each operational period of the two algorithms across all patient groups (Table 3).

Difference in percentage of ventricular pacing between each operational period of the algorithms

The median %VPs during the MVP operation, when compared with those during the Search AV+ operation, were significantly lower in the entire study population and all patient subgroups except for patients categorized into p3AVB (Figure 1). Moreover, the percentages of patients who had %VP < 40 and/or patients who had %VP < 10 during the MVP operation were significantly greater compared with those during the Search AV+ operation in the entire study population and all patient subgroups except for patients categorized into p3AVB (Table 4).

Adverse events

Two patients dropped out of the study due to symptoms related to either one operation of the two algorithms, despite completion of the first 1 month phase. One patient, who was categorized into 2AVB, presented with chest discomfort resulting from frequent non-conducted atrial depolarization promptly after switching algorithms from Search AV+ to MVP and was reprogrammed to conventional DDD. The other patient, who was categorized into e3AVB, presented with a similar symptom resulting from Wenckebach periodicity promptly after switching from MVP to Search AV+ was also reprogrammed to conventional DDD. Additionally, one patient, who was categorized into p3AVB, experienced mild dizziness several times during the MVP operation phase but completed both phases of the study. No other adverse events including sustained ventricular tachyarrhythmia have been reported.

Discussion

This is the first study that assessed the two representative types of dual-chamber pacing algorithms for minimizing unnecessary VP with respect to the ability to reduce %VP in the same individuals. The results demonstrated that the algorithm based on AAI/R mode with backup VP during AVB of MVP offers further %VP reduction, when compared with that based on DDD/R mode with automatic extension of AV interval of Search AV+. This finding was observed in all dual-chamber pacing population except for patients diagnosed with p3AVB.

### Table 2 Pacing parameter settings in MVP and Search AV+ operations

| Parameter                                  | MVP                  | Search AV+             |
|--------------------------------------------|----------------------|-------------------------|
| Sensed AV interval (ms)                    | 131 ± 30             | 131 ± 28                |
| Paced AV interval (ms)                     | 159 ± 26             | 161 ± 29                |
| Max increase to AV (ms)                    | NA                   | 169 ± 33                |
| Lower rate (bpm)                           | 61 ± 5               | 60 ± 5                  |
| Upper tracking rate (bpm)                  | 125 ± 7              | 125 ± 8                 |
| Rate response on [n (%)]                   | 9 (7.1)              | 9 (7.1)                 |
| Upper sensor rate (ppm)                    | 126 ± 10             | 126 ± 10                |
| RAAV on [n (%)]                            | 0 (0.0)              | 0 (0.0)                 |
| Automatic PVARP on [n (%)]                 | 127 (100.0)          | 127 (100.0)             |
| Mode switch on [n (%)]                     | 127 (100.0)          | 127 (100.0)             |
| Atrial tachyarrhythmia detect rate (bpm)   | 175 ± 1              | 175 ± 1                 |
| Conducted AF response on [n (%)]           | 0 (0.0)              | 0 (0.0)                 |
| Lead impedance trend on [n (%)]            | 126 (99.2)           | 126 (99.2)              |

AV: atrioventricular; NA: not available; RAAV: rate adaptive AV; PVARP: post-ventricular atrial refractory period; AF: atrial fibrillation.

*Data were obtained from patients with rate response on.

### Table 3 Percentage of atrial pacing and %atrial high rate in MVP and Search AV+ operations

| %AP, percentage of atrial pacing; %AHR, percentage of time spent in atrial high rate; nAVB, no atrioventricular block; 1AVB, first-degree atrioventricular block; 2AVB, second-degree atrioventricular block; e3AVB, episodic third-degree atrioventricular block; p3AVB, persistent third-degree atrioventricular block; NS, not significant. | Median %AP | Median (mean) %AHR |
| Total | MVP: 41.1; Search AV+: 35.8 | P-value | MVP: 0.0 (2.6); Search AV+: 0.0 (3.5) | NS |
| nAVB | 65.8 | 76.6 | NS | 0.1 (2.1) | 0.0 (2.9) | NS |
| 1AVB | 72.1 | 71.8 | NS | 0.1 (8.1) | 0.4 (12.7) | NS |
| 2AVB | 18.6 | 13.7 | 0.002 | 0.0 (1.0) | 0.0 (0.9) | NS |
| e3AVB | 18.8 | 12.4 | NS | 0.0 (1.4) | 0.0 (0.0) | NS |
| p3AVB | 11.6 | 13.2 | NS | 0.0 (2.8) | 0.0 (3.8) | NS |
The magnitude of %VP could be affected not only by the algorithmic property of MVP or Search AV+ but also by programming of several pacing parameters, ever-changing patient’s conditions, and interactions of these components. In this study, the programming of pacemaker parameters that could potentially affect %VP other than the settings of MVP and Search AV+ seems not to have been drastically different between MVP and Search AV+ operation phase. Furthermore, the median %APs in both phases were similar in all patient groups except for patients categorized into 2AVB, whereas atrial pacing at the rate that exceeds intrinsic sinus rate might unmask or deteriorate an impairment in AV conduction and might increase chance to trigger VP in some patients. Similarly, the median %AHRs in both phases were comparable in all patient groups. When Mode Switch is enabled, spontaneous atrial depolarization at the rate that exceeds the predefined rate to detect atrial depolarization might trigger VP or might increase the %VP. The results of this study suggest that the programming of pacemaker parameters that could potentially affect %VP other than the settings of MVP and Search AV+ operation phase should be carefully evaluated to reduce the risk of VP.
tachyarrhythmia starts promotes VP with switching to non-atrial tracking mode from atrial tracking mode in patients with impaired AV conduction. Given the facts mentioned above, we believe that the results of this study have fewer artefacts.

Comparison with previous studies

Pürerfellner et al.\textsuperscript{16} compared the %VPs in a group of patients receiving pacing therapy with the Search AV+ operation with those in another group of patients receiving the therapy with the MVP operation. As in the present study, they reported the superiority of MVP over Search AV+ in terms of %VP reduction except in the cases with p3AVB. However, the results were derived by the post-hoc analysis of the data obtained from different two studies,\textsuperscript{10,11} while the analysis was performed with well-processed statistics. On the other hand, the present study prospectively compared the %VPs during the Search AV+ operation and those during the MVP operation in the same individuals in a crossover fashion. Furthermore, in the previous study, the AV intervals and ‘Max increase to AV’ those define the Search AV+ operation were uniformly programmed to the nominal values. In the present study, these were programmed at the discretion of the clinicians and not unified. The diversity of Search AV+- settings might be more compliant with clinical practice. Therefore, we believe that the present study reinforces the results of the previous study with robust approach.

The SAVE PACe trial\textsuperscript{14} showed that the %VP reduction through either one of the two algorithm operation linked to a risk reduction of the development of persistent AF over the mean follow-up of 1.7 years. In the present study, no patient had developed persistent AF after the enrolment. Moreover, there were no differences in the %AHR, which is likely to represent AT/AF burden, between the two phases across all patient groups, despite the observation of significant differences of the %VPs in most patient groups. We presume that these were attributed to the shorter study duration and/or the study design that did not aim to detect the difference in %AHR.

Clinical implications

The present study demonstrated not only that the median %VPs during the MVP operation were significantly lower compared with those during the Search AV+ operation but also that the percentages of patients who had %VP <40 and/or those who had %VP <10 during the MVP operation were significantly greater compared with those during the Search AV+ operation in the entire patient population and all patient subgroups except for patients categorized into p3AVB. It has been hypothesized that the risk of heart failure hospitalization could be reduced if %VP falls below 40% and the risk could be minimized if %VP falls below 10% in patients receiving dual-chamber pacing.\textsuperscript{1} In the light of this hypothesis, it is likely that MVP provides more clinical benefits compared with Search AV+. However, one question inevitably arises: MVP may be more prone to impair the ventricular filling that is regulated by AV timing, while the algorithm can permit longer intrinsic AV conduction and maintain ventricular mechanical synchrony more robustly compared with Search AV+. Most recently, Cheng et al.\textsuperscript{17} reported that prolongation of the PR interval is associated with increased risk of AF. This finding seems to suggest a potential negative effect of the permission for long intrinsic AV conduction. Such haemodynamic trade-off may compromise the advantage of MVP, especially in patients with unusually long intrinsic AV conduction.\textsuperscript{18} Conversely, Search AV+ is able to establish an upper limit on the magnitude of AV conduction time and could prevent excessive long intrinsic AV conduction. The present study has not examined the clinical impact derived from the difference in %VPs between the two algorithms. Moreover, no randomized clinical study that investigates the clinical utility of the algorithms in patients with first-degree and intermittent AVB has been performed. Therefore, it would still be unwise to conclude that MVP is superior to Search AV+ in all aspects and considerations should be given based on individual patient assessment when one applies MVP or Search AV+, especially to patients with a significant first-degree or intermittent AVB at this point.

Managed ventricular pacing allows pauses of up to twice the lower rate in the event of AVB. Although this algorithmic property of MVP is apparently more favourable for reducing %VP in patients with more intermittent AVB (e.g. persistent 2:1 AVB), that may result in more pauses and related symptoms. In the present study, three minor adverse symptoms related to either one of the algorithms were observed. The two were considered as MVP-related and the remaining one was considered as Search AV+-related. This suggests that the incidences of symptoms related to MVP and Search AV+ may be comparable. On the other hand, van Mechelen and Schoonderwoerd.\textsuperscript{19} have reported a case presented with a malignant ventricular tachyarrhythmia related to MVP. Given the previous studies\textsuperscript{11,13,20} and the present study, ventricular tachyarrhythmia events related to MVP is infrequent. Nevertheless, we hereafter recommend assessing the potential risk\textsuperscript{16} before enabling MVP to avoid such serious events.

Study limitations

There are several limitations in this study. First, in the present study, electrophysiologic testing was not mandated for the AVB status categorization. This might have led some patients who had latent impaired AV conduction into nAVB (i.e. intact AV conduction) category. In clinical practice, however, electrophysiologic testing is not routinely performed for the triage of patients with apparent symptomatic bradyarrhythmia. Therefore, we believe that our approach to categorization of the AVB status was appropriate for the consistency with clinical practice. Secondly, the AVB status in the same individuals could vary over time and this might have affected the difference in %VPs between the two phases of the study. To attenuate this potential limitation, we chose a randomized crossover study design. In addition, it has been reported that the effect of MVP on %VP reduction sustains for at least 6 months even in patients with AVB.\textsuperscript{11} This suggests that AVB status does not alter substantially over 6 months. Relatively short duration of the present study (i.e. ~2 months) also might have contributed to the attenuation of this potential limitation. Thirdly, we did not collect the information about changes in medications, which could have affected the %VP, between the two phases of the study. However, most patients enrolled in the study were clinically stable. We believe that there were few, if any, patients who underwent medication change during the study.
period. Fourthly, the results derived from relatively small patient subgroups may not apply to larger patient populations. Finally, we did not evaluate the percentage of ventricular beats that were fusion or pseudofusion of the VP and intrinsic ventricular activation. The extent of fusion of VP and intrinsic normal ventricular activation would affect ventricular contraction pattern. Although pure RVA pacing beat is likely to create abnormal ventricular contraction pattern and deteriorates ventricular function, fusion or pseudofusion ventricular beat with a near normal QRS complex would result in near normal ventricular contraction pattern and is unlikely to affect the cardiac pump function materially. In theory, Search AV+ when compared with MVP, could create more ventricular beats that are fusion of VP and intrinsic ventricular activation. Therefore, the interpretation of the difference of %VP between the two algorithms may need to be carefully applied.

Conclusions
Pacing algorithm for minimizing VP based on AAI/R mode with backup VP during AVB of MVP, when compared with that based on DDD/R mode with automatic extension of AV interval of Search AV+, offered further %VP reduction in patients implanted with a dual-chamber pacemaker except for the population diagnosed with persistent loss of AV conduction. Moreover, incidence of adverse symptoms related to both algorithms seemed to be rare and similar. Nevertheless, the present study has not formally assessed the clinical impact derived from the difference in %VPs between the algorithms. Further study will be necessary to discriminate the algorithms in all aspects.

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