Reducing Ventricular Pacing in Sinus Node Dysfunction

DDIR versus DDDR

Toshiyuki ISHIKAWA,1 MD, Shinichi SUMITA,1 MD, Masami KOSUGE,1 MD, Chad GIESE,2 BS, Toby MARKOWITZ,2 BS, Soichi TSUNODA,3 BS, Kazuaki UCHINO,1 MD, Tsukasa KOBAYASHI,1 MD, Kohei MATSUSHITA,1 MD, Noriko INOUE,1 MD, Katsumi MATSUSHITA,1 MD, Minoru TAIMA,1 MD, Kazuo KIMURA,1 MD, and Satoshi UMEMURA,1 MD

SUMMARY

Background: The use of DDIR mode has been limited since the advent of mode switch in the DDDR mode. In patients with AV block, DDDR is necessary to maintain AV synchrony. However, DDIR mode may still be beneficial for patients with intact AV conduction. The aim of this study was to compare the incidence of ventricular pacing and atrial tachyarrhythmia in DDIR and DDDR with mode switch in a randomized, single-blind, crossover study, and discuss the utility of both modes.

Methods and results: Twenty-four patients (8 males) with bradycardia-tachycardia syndrome and no signs of AV block (mean age 70.1 ± 9.1 years) were enrolled and randomized to DDIR or DDDR modes with the leads placed at the right atrial appendage and right ventricular apex. After 12 weeks, patients were switched to the opposite mode. During the study period, atrial high rate episodes and other pacemaker diagnostic data were collected. Significantly less ventricular pacing was observed in DDIR mode (DDIR versus DDDR; 48.9%, 76.5%, P = 0.0002) and atrial high rate episodes were significantly lower in DDIR mode (DDIR versus DDDR; 1.32, 1.85 per day, P < 0.05).

Conclusion: In patients with sinus node dysfunction and intact AV conduction, DDIR mode may have important implications for simplifying device programming, device longevity, and to avoid atrial tachyarrhythmia. (Int Heart J 2007; 48: 323-336)

Key words: Pacemaker, Sinus node dysfunction, Atrial tachyarrhythmia

THE advent of mode switch was heralded as a significant advance in the pacing treatment of patients with sinus node dysfunction. Mode switch enables pacemakers to automatically change from a tracking to a nontracking mode to prevent inappropriately rapid and erratic ventricular pacing during atrial arrhythmias.1-5) When programmed to DDDR with mode switch is a functional mode in pace-
maker devices and is used as a proper noun in this manuscript, the pacing mode will alternate between DDDR and DDIR depending on the atrial rhythm. This mode is most useful for patients with AV block and paroxysmal atrial fibrillation (PAF).6)

Recognition of sinus node dysfunction (SND) and intact AV conduction complicated the practice of pacing treatment.7) Prior to the introduction of mode switch, clinicians struggled with the application of dual chamber pacers in these patients. DDDR pacemakers worked fine during periods of sinus rhythm by synchronizing the ventricle to spontaneous atrial beats. However, during PAF, ventricular pacing rate was only limited by the programmed Upper Rate. Physicians were forced to compromise the programming of Upper Rate to satisfy the patients' physiologic sinus rate during exercise and to limit the paced ventricular rate during PAF. One innovation used until mode switch arrived was the use of separate Upper Rates for atrial pacing (DDDR, sensor driven rate) and atrial sensing. The strategy was to limit the atrial tracking rate knowing that PAF would cause rapid pacing. This method relied upon the sensor to provide rapid atrial pacing during exercise or other times of high metabolic need.8,9) The drive to develop a successful tool to handle patients with SND and PAF, namely Mode Switch, led to the popularity of DDDR mode and left DDIR mode rarely used.

DDIR mode was designed to provide rate responsive atrial pacing for patients with intact AV conduction. Since DDIR does not provide ventricular pacing synchronized to spontaneous atrial beats, it is inappropriate in patients with AV block. While it may provide AV synchrony in AV block patients at rest, a sinus node rate increase above the sensor driven rate will cause AV dissociation. Lack of synchronization in DDIR to spontaneous sensed atrial beats eliminates the concern of a pacemaker-mediated tachycardia present with DDDR, but may increase the risk for atrial competitive pacing with intrinsic rate increases.10) In order to mitigate the possible deleterious effects of the two modes, in the Thera DR™ (Medtronic Inc., Minneapolis, USA), DDIR mode is available with an enhancement, an automatically varying postventricular atrial refractory period (PVARP) designed to reduce the potential for atrial competitive pacing by ending the refractory period 300 ms before the scheduled time of delivery of atrial pacing, thus maintaining an atrial sensing window greater than the refractory period of the atrial tissue. This refractory period interval is rate adaptive and shortens at higher rates. In contrast to DDIR, DDDR with mode switch has the additional following parameters: sensed AV interval, upper tracking rate, rate adaptive AV interval, and a sophisticated algorithm to detect atrial arrhythmias, switch modes, and smooth the ventricular rate during transitions. Thus DDDR has grown considerably in complexity, requiring the programming of many parameters while DDIR mode is relatively simple to program. The DDIR mode is less popular,
harder to interpret and, perhaps, less understood, but is also applicable to patients with sinus node dysfunction, intact AV conduction with or without bradycardia during atrial fibrillation.\textsuperscript{11-16}

The aim of this study was to compare the incidence of ventricular pacing and atrial tachyarrhythmia in DDIR and DDDR modes in a randomized, single-blinded, crossover study, and discuss the utility of both modes.

\begin{table}
\centering
\caption{Programming Parameters}
\begin{tabular}{|c|c|c|}
\hline
Pacing Mode & DDIR & DDDR \\
\hline
\textbf{Lower Rate} & 70 & Patient Specific (same for both arms) \\
\textbf{Upper Rate} & N/A & 160 \\
\hline
\textbf{AV Intervals:} & & \\
PAV & PQ & 230 \\
SAV & N/A & 160 \\
\hline
\textbf{Rate Adaptive AV:} & & \\
Start Rate & 100 ppm & 70 ppm \\
Stop Rate & Upper Sensor & 150 ppm \\
Min. Paced AV & 50 ms & 100 ms \\
Min. Sensed AV & N/A & 30 ms \\
\hline
\textbf{PVC Response} & OFF & \\
V. Safety Pacing & OFF & \\
Atrial Sensitivity & 0.5mV & \\
\textbf{V. PVARP} & ON & N/A \\
Mode Switch & N/A & ON \\
\textbf{NCAP} & N/A & ON - 13 \\
& & OFF - 11 \\
\hline
\textbf{AHRE Diagnostic:} & & \\
Detection Parameters: & & \\
Detect Rate & 180 ppm & \\
Detect Number & 5 beats & \\
Termination Number & 10 beats & \\
Collection Parameters: & & \\
Type & Atrial & \\
Data Collection & Rolling & \\
EGM & OFF & \\
Lead Monitor & OFF & \\
\hline
\end{tabular}
\end{table}

Programming parameters for each pacing mode in the study. Post ventricular atrial refractory period (PVARP) was programmed ON in DDIR mode and mode switch was programmed ON in DDDR mode. Noncompetitive atrial pacing (NCAP) was programmed ON in 13 and OFF in 11 patients with DDDR mode. The atrial high rate episode (AHRE) diagnostic was programmed the same in both modes.

V.PVARP adjusts PVARP based on the intrinsic or sensor driven rate. This eliminates or reduces the incidence of atrial competitive pacing by maintaining, or attempting to maintain, a 300 ms atrial sensing window prior to the scheduled delivery of atrial pacing.

The AHRE diagnostic reports frequency, duration, and date/time of rapid atrial rhythms. PAV indicates paced atrio-ventricular interval; SAV, sensed atrio-ventricular interval; and EGM, Electrogram.
**METHODS**

**Patients:** Patients with SND with intact, prolonged AV conduction, and PAF were enrolled. Previous incidences of PAF were confirmed by in-clinic ECG recordings or 24 hour Holter monitoring. Patients were excluded if at time of follow-up, pacemaker ventricular sensing and inhibition was not achieved at an AV interval setting of 230 ms. Twenty-four patients (8 males/16 females) ranging in age from 45 to 81 years (mean 70.1 ± 9.1) were enrolled. Five patients had ischemic heart disease and 4 had hypertension in the past, and no other previous cardiovascular disease was observed. Ejection fraction was 71.4 ± 13.6%. Signed written informed consent was obtained from all patients. All had their pacemaker implanted at least 3 months prior to enrollment.

**Device parameters:** The programming parameters used in this study are shown in Table I. Mode switch was programmed ON in DDDR mode. Rate Adaptive settings optimized for individual patients in the Thera DR™ include Rate Adaptive AV delay to provide ample opportunity for detection of atrial tachyarrhythmia by:

![Diagram](image)

**Figure 1.** Follow-up (Data acquisition). This diagram shows the study protocol followed. The patients were randomized and placed into one of the study arms, DDIR then DDDR or DDDR then DDIR. Each arm was 12 weeks long with interrogations taking place at 6 weeks and 12 weeks in each pacing mode, ie. at 0, 6, 12, 18, and 24 weeks on the timeline. V.PVARP indicates varied post ventricular atrial refractory period and MS, mode switch.
1) shortening the sensed AV interval during fast atrial rates and 2) shortening the paced AV interval during high sensor-driven rates. Due to forced programming in the Thera device, the sensed AV delay was rate adaptive and had a minimum of 30 ms. Varied PVARP was programmed ON in DDIR mode and mode switch was programmed on in DDDR mode. For all patients enrolled, the atrial and ventricular leads were placed at the right atrial appendage (RAA) and the right ventricular (RV) apex, respectively.

The atrial high rate episode (AHRE) diagnostic is used to record episodes of high atrial rate by detecting a specified number of beats above a specified rate threshold. The episode was considered to be terminated once a specified number of beats were detected below the rate threshold. In both modes the AHRE diagnostic feature was programmed with the following: Detection rate of 180 bpm, detection count of 5 beats, and termination count of 10 beats. These parameters did not change during the study period and were applied to all patients.

**Study design:** Patients were first randomized to programming of DDIR with Varied PVARP or DDDR with mode switch, then followed for 12 weeks in each mode with diagnostic interrogations at 6 weeks and at 12 weeks. The pacing mode was then programmed to the opposite mode from study entry and the device interrogated at 6 weeks and at the conclusion of the second 12 week period (Figure 1). The diagnostic data were retrieved from the implanted pacemaker, using a Medtronic 9790 programmer, obtaining the percentage of atrial and ven-

<table>
<thead>
<tr>
<th>Table II. Results Table</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>N = 24</td>
</tr>
<tr>
<td>Mode</td>
</tr>
<tr>
<td>AHRE Total (per day)</td>
</tr>
<tr>
<td>Ventricular pace (%)</td>
</tr>
<tr>
<td>Atrial pace (%)</td>
</tr>
<tr>
<td>AT Burden (% in 12 weeks)</td>
</tr>
</tbody>
</table>

Study results are shown with mean and standard deviation for the following study metrics: number of atrial high rate episode (AHRE) counts per day, ventricular pace percentage, atrial pace percentage, and burden of atrial tachycardia (AT). The Wilcoxon signed rank or Student t test was performed to determine if the difference between treatment modes was significant. The $P$ values are shown. AHRE counts and %ventricular pace were significantly lower in DDIR mode than in DDDR mode. Atrial pace percentage and burden of AT were similar in both modes. A test for order effect shows that the order of programming did not influence the treatment results.
tricular pacing, atrial tachycardia (AT) duration, mode switch information, and AHRE data. The recordings of markers which indicate pacing and sensing events during atrial tachycardia were stored in pacemaker memory for up to 15 episodes, allowing the review of only a limited number of episodes per patient to determine if far field R wave over-sensing occurred. Medications did not change during the study period.

**Ethics declaration:** This study complies with the Declaration of Helsinki and the research protocol was approved by the Institutional Review Board of Yokohama City University Hospital. Signed informed consent was obtained for all study subjects.

![Figure 2. Atrial pace percentage: DDDR versus DDIR (n = 24). Paired data for each patient in both pacing modes. Mean percentage of atrial pacing in DDIR mode of 71.0% ± 30 and that of DDDR mode of 68.7% ± 26.6 were not different (P = 0.61).](image-url)
Statistics: Measured variables are expressed as the median and mean ± standard deviation. Statistical analysis was performed using the Wilcoxon signed rank test and paired Student t test, and a $P$ value of less than 0.05 was considered statistically significant. Order effect was tested for crossover study to determine whether or not the programming sequence, ie, the first programmed pacing mode, played a significant part in the results of the study.

RESULTS

The results are summarized in Table II. There was no difference in the incidence of atrial pacing between DDIR and DDDR (DDIR = 71 ± 30, DDDR = 68.7
± 26.6 (P = 0.61)) (Figure 2). AT burden, defined as the total time spent in AT in days divided by the total number of days in the study (12 weeks), was similar in both arms (DDIR = 2.44 ± 6.02, DDDR = 2.24 ± 5.77 (P = 0.80)) (Figure 3). On the other hand, ventricular pacing occurred substantially more frequently in DDDR than in DDIR (DDIR = 48.9% ± 32.3, DDDR = 76.5% ± 25.3 (P < 0.001)) (Figure 4) and AHRE were significantly less in DDIR mode than in DDDR mode (DDIR = 1.32 ± 2.12, DDDR = 1.85 ± 2.28 (P < 0.05)) (Figure 5). Order of programming had no effect on the study results with all metrics having order effect P values > 0.25 (Table II).
The review of each episode of AT saved by the device became important in terms of verifying that each AHRE was reliable. In DDDR mode, atrial pacing immediately after spontaneous intrinsic atrial beats with extremely short coupling intervals was observed (Figure 6). The investigators determined that these were not to be attributable to far field R wave oversensing, but occurred due to an intrinsic beat occurring during PVARP.

Figure 5. Atrial high rate episodes per day ($n = 24$, 12 weeks). Paired data showing total atrial high rate episodes per day were significantly lower in the DDIR mode with a mean of $1.52 \pm 2.12$ compared to $1.85 \pm 2.28$ in DDDR mode ($P < 0.05$).
There are two main concerns in the disease progression of SND: atrial fibrillation (AF) and AV block. Numerous studies have shown the onset of AV block in patients with SND to be rare.\textsuperscript{17-20} Andersen, et al reported only 0.6% per year developed AV block.\textsuperscript{21} Their study, however, excluded patients with first degree or higher AV block and AV conduction times longer than 220 ms, suggesting that for patients with SND and near normal AV conduction, the development of AV conduction defects is rare. Schwaab, et al found, however, that patients with bradycardia-tachycardia syndrome, first degree AV block, and an AV interval less than or equal to 240 ms, had a 39% chance of developing second degree AV block, specifically post exercise.\textsuperscript{22} This study suggests that in a patient population with bradycardia-tachycardia syndrome and pre-existing AV conduction defects, the potential for AV block to develop is greater and AAI pacing may no

**DISCUSSION**

There are two main concerns in the disease progression of SND: atrial fibrillation (AF) and AV block. Numerous studies have shown the onset of AV block in patients with SND to be rare.\textsuperscript{17-20} Andersen, et al reported only 0.6% per year developed AV block.\textsuperscript{21} Their study, however, excluded patients with first degree or higher AV block and AV conduction times longer than 220 ms, suggesting that for patients with SND and near normal AV conduction, the development of AV conduction defects is rare. Schwaab, et al found, however, that patients with bradycardia-tachycardia syndrome, first degree AV block, and an AV interval less than or equal to 240 ms, had a 39% chance of developing second degree AV block, specifically post exercise.\textsuperscript{22} This study suggests that in a patient population with bradycardia-tachycardia syndrome and pre-existing AV conduction defects, the potential for AV block to develop is greater and AAI pacing may no
longer be sufficient. It is in this population that DDI or DDD pacing must be considered. In our study population, with long intrinsic AV intervals and SND, it was the risk of AV block that convinced us that a ventricular lead was essential. It is important to know which dual chamber mode would be more effective at maintaining normal cardiac function.

We believe two aspects of this study have particular importance: 1) the role of ventricular pacing, and 2) DDDR versus DDIR mode.

**Ventricular pacing effects:** There is preliminary evidence that ventricular pacing may cause a deterioration in atrial function, however, physiological or atrial-based pacing modes, such as AAIR, DDIR, or DDDR, may restore cardiac function, especially in patients with atrial fibrillation.\(^23\text{-}27\) It has widely been reported that AT is more likely to occur with ventricular pacing than with physiological pacing.\(^11\text{-}28\text{-}30\) Trials such as the Canadian Trial of Physiologic Pacing (CTOPP) have shown that patients with ventricular pacing had higher risk in the annual rate of development of chronic AF compared with physiologic pacing.\(^31\text{-}32\) The Dual Chamber and VVI Implantable Defibrillator (DAVID) trial results may suggest that unnecessary ventricular pacing may promote heart failure and worsen the clinical outcome of the patient.\(^33\) Nielsen, *et al* found AF significantly more frequently in the DDDR arms during a randomized comparison of AAIR and DDDR in patients with SND and intact AV conduction in a pilot study for the DANPACE trial.\(^34\) In a more direct relationship between AF and ventricular pacing, Sweeney, *et al* found that the risk of atrial fibrillation increased with increased cumulative percent ventricular pacing.\(^23\) Although it should be noted that the patient populations in the studies mentioned above were different from ours, we were able to draw conclusions from these studies that helped in the analysis of the results of this study. Our result, significantly higher ventricular pace incidence along with higher AHRE in DDDR mode, may be evidence of the deteriorating effect of ventricular pacing. In addition, device longevity is affected by device programming\(^35\text{-}36\) and a higher ventricular pace incidence may lead to shortening the device longevity.

**DDIR versus DDDR:** Both DDIR and DDDR can be recommended for patients with bradycardia-tachycardia syndrome and maintained intrinsic AV conduction. In situations of AV block, DDIR maintains AV synchrony only when the lower or sensor rate is greater than the spontaneous atrial rate. So, with little surprise, it has been reported that in patients with complete AV block, AV synchrony is better maintained in DDDR than DDIR mode and the occurrence of AT has not been shown to be affected by mode selection.\(^37\text{-}41\) However, no comparison has been made for patients with intact AV conduction. We performed a crossover study to compare these 2 modes in this patient population specifically looking at ventricular pacing percentage, atrial pacing percentage, number of mode switch epi-
sodes, and the number of AHRE. In our patients, with SND, bradycardia-tachycardia syndrome, and intact AV conduction, DDDR mode may track rapid atrial rhythms leading to rapid ventricular pacing during the detection phase of the DDDR mode switch algorithm during AT. DDDR mode attempts AV synchrony by ventricular pacing in response to sensed P-waves. Thus, for brief periods preceding a mode switch, patients may experience rapid ventricular pacing at rates up to the upper tracking rate limit. After a brief period of several seconds, AT is detected and the mode is switched to DDIR with the resulting ventricular pacing at the sensor-determined rate. The period between onset of AT and mode switch is estimated to be 15 to 20 seconds in the Medtronic Thera DR™. This period, however very brief, could potentially be stressful enough on the cardiac tissue to be arrhythmogenic.

We hypothesized that P-wave tracking resulting in ventricular pacing and unnatural ventricular activation during the DDDR mode contributed to the prevalence of AT. Due to rate adaptive AV delay, the AV interval is shortened to guarantee an adequate atrial sensing window for the detection of AT. This resulted in a greater percentage of ventricular pacing, which may lead to an increase in AT, however, this hypothesis was not tested in this study.

Limitations: There are several limitations to this study. The small number of patients, the relatively short follow-up, and lack of stored electrograms for each AT episode all contribute to the results obtained. AT burden was not different between DDIR and DDDR. This might also be attributed to an interaction between mode switch and AHRE detection. If, during an AT episode, the pacemaker no longer senses AT, the mode returns to DDDR and tracking of P-waves resumes. It is possible that the resulting ventricular pacing causes blanking and a brief pause in the AHRE detection of AT. By this mechanism, the number of AT episodes might be inflated in DDDR, and this may be detrimental if findings from DAVID and the pilot study for the DANPACE trial are in any way relevant to this patient population.

Conclusion: In conclusion, compared to DDDR with mode switch, DDIR has fewer programmable parameters, less ventricular pacing, and resulted in fewer recorded episodes of AT. In DDDR mode, an increase in ventricular pacing likely causes inflation of the number of AT episodes, and loss of ventricular synchrony. The higher ventricular pace percentage may be detrimental if findings from DAVID and the pilot study for the DANPACE trial are in any way relevant to this patient population. In patients with sinus node dysfunction and intact AV conduction, DDIR mode may have important implications for simplifying device programming and device longevity while benefiting the patient physiologically.
REFERENCES


