Suppression of Atrial Fibrillation Using a New Pacing Algorithm

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Summary

Atrial fibrillation (AF) is the most common type of arrhythmia. With an incidence of 0.4% in the overall population, elderly people predominantly suffer from AF. Since AF is observed in up to 40% of all pacemaker patients, there are several therapeutic measures available to treat or prevent AF using technology available within the pacemakers. Multisite pacing focuses on minimizing the interval between right and left atrial excitation (interatrial conduction block), often observed in patients suffering from AF [5]. In contrast to multisite stimulation, pacing at an elevated rate focuses on the suppression of atrial extrasystoles (AES), which trigger rotors and therefore, AF [8]. The suppression of extrasystoles by pacing at an elevated rate was reported in the early 1980s. Technological problems limited the effectiveness of this therapy. This paper reports on a new pacing algorithm (DDD$^+$ mode) designed to almost always pace at a programmable step above the sinus rate. The new algorithm is clinically tested in a multi-centric, controlled, randomized single-blind study. This paper presents the algorithm, the study design, and the preliminary results.

Key Words

Atrial fibrillation, overdrive stimulation, DDD$^+$ mode

Introduction

Atrial fibrillation (AF) is the most common type of arrhythmia. With an incidence of 0.4% in the overall population, elderly people predominantly suffer from AF (> 60 years: 2-4%, > 70 years: > 13%) [1-3]. Atrial fibrillation causes one third of all strokes; therefore, this hemodynamically yet often unnoticed non-lethal arrhythmia gives rise to high costs in the healthcare system. In addition, AF often appears in combination with other heart conditions such as congestive heart failure [4], and further reduces the already impaired exercise tolerance in this group of patients.

Since AF is observed in up to 40% of all pacemaker patients, there are several therapeutic measures available to treat or prevent AF using technology available within the pacemakers. Multisite pacing in either the right atrium at the appendage near the Koch-triangle, and in the right and left atria via the coronary sinus approach, focus on minimizing the interval between right and left atrial excitation (interatrial conduction block), often observed in patients suffering from AF [5]. Daubert et al. reported that biatrial pacing is technically superior (but not statistically significant) to simple right atrial stimulation [6]. In contrast, Witte et al. reported that more than 80% of patients with drug-refractory paroxysmal AF successfully responded to biatrial stimulation [7]. Both studies are encumbered by methodological problems: Daubert reported 30% lead dislodgment, and an unsatisfactory interatrial delay of 30 ms. In Witte's study these technological problems were solved, but there was no control group with simple right atrial pacing instead of multisite stimulation.

In contrast to multisite stimulation which re-synchronizes the atria, pacing at an elevated rate focuses on the suppression of atrial extrasystoles (AES), which trigger rotors and therefore, AF [8]. The suppression of

extrasystoles in the atrium and ventricle by pacing at an elevated rate was reported during early electrophysiological investigations. In 1983, Coumel et al. used this phenomenon to suppress the incidence of AES and therefore of AF. In this study, the basic rate was simply increased to 90 ppm, remarkably reducing the incidence of AF [9]. The main drawback was that the elevated rate was not tolerated in all patients, and the study was terminated. Later on, Murgatroyd reported a more sophisticated algorithm, which increased the heart rate if an AES occurred. Here technological problems limited the basic message that pacing at an elevated rate suppressed AF and was tolerated by the patients [10-11].

This paper reports on a new pacing algorithm (DDD$^+$ mode), based on the first algorithms to pace at an elevated rate. In contrast to the former approaches, the algorithm is designed to:

- pace almost always;
- pace at a programmable step above the sinus rate.

These main principles of the new algorithm (DDD$^+$) combine the above requirements including permanent over-stimulation, and an increased tolerance by the patients. The new algorithm is clinically tested in a multi-centric, controlled, single-blind study. This paper presents the algorithm, the study design, and the preliminary results.

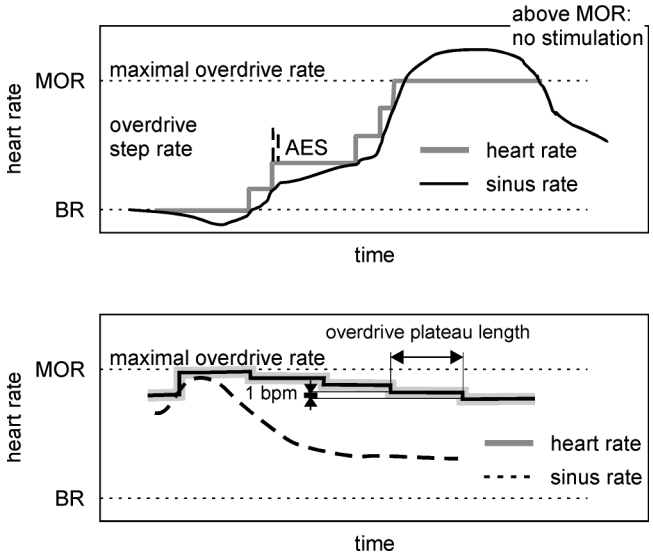

Figure 1. Schematic stimulation rate in DDD$^+$ mode. After every A-Sense event, the stimulation rate is increased by the programmable step size. If sinus rate plus step size is over the maximum overdrive rate (MOR), stimulation is inhibited.

Methods

DDD$^+$ - Algorithm

The algorithm is based on a normal P-wave-synchronized atrio-ventricular pacing (DDD) mode. Additionally, in the overstimulation mode (DDD$^+$) the basic rate (BR) is increased after every valid atrial sensed event. The increase in BR is calculated by the sum of the mean atrial rate and the programmed step size (1 to 32 ppm, nominal 10 ppm). The BR is then permanently decreased by 1 bpm every n-cycle (n: 1 to 32 cycles, nominal: 20 cycles) (Figure 1). The nominal settings are designed to ensure an overpacing interval of 4 min.

The DDD$^+$ algorithm consists of several safety functions to prevent permanent overstimulation at non-physiologically high rates. This is necessary since atrial far-field sensing will then lead to high rates. The maximum overdrive rate (MOR, nominal 140 ppm) limits the maximum pacing rate in the atrium. The safety limit ensures that the mean pacing rate is below a critical value (nominal 120 ppm).

The algorithm is implemented in the Inos^2 DR/CLS pacemaker (BIOTRONIK, Germany).

Study Design

The algorithm is tested in a controlled, multi-centric, randomized single-blind study. The primary hypotheses of the study are that the DDD$^+$ mode decreases the total number of AF, decreases the total duration of AF, and increases the interval to the first occurrence of AF in an individual when compared to the conventional DDD mode. The secondary hypothesis is that DDD$^+$ provides a long-lasting therapeutic effect that increases the interval of the first occurrence of AF in DDD mode, if DDD$^+$ was formerly programmed.

The inclusion criteria were documented for paroxysmal AF without uncontrolled angina pectoris. A rate responsive DDD$^+$ algorithm was not tested since the effect of overdrive pacing controlled by the sinus rate (and therefore by the cardiovascular system) was assumed to be different for overdrive pacing using an accelerometer sensor.

Exclusion criteria during the study were permanent

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BIOTRONIK PMS 1000

Release    : DDDplus002.W
Date/Time  : 17.03.1999    13:42

INOS2CLS/DR      S/N:
Initialization        Overpacing

          Atrial Rate History
Pacing mode                          DDD
Interrogation time    17.03.1999 13:37
Number of AES                      25847


Mode Conversion                    150 ppm
Number of AF-Episodes                402
 Non-Sustained among                 159
Total non-AF Time          19d:04h:46m
Total AF-Time               7d:13h:37m
 Non-Sustained among            0h:44m

---Event Time---       Event Type
14.03.1999 14:32          On
14.03.1999 16:41                Off
15.03.1999 01:17          On
15.03.1999 01:36                Off
15.03.1999 01:37          On
15.03.1999 03:10                Off
15.03.1999 03:12          On
15.03.1999 03:13                Off
15.03.1999 03:19          On
15.03.1999 03:20                Off
15.03.1999 03:24          On
15.03.1999 07:53                Off
15.03.1999 19:31          On
15.03.1999 19:32                Off
16.03.1999 03:33          On
16.03.1999 03:33                Off
16.03.1999 04:43          On
16.03.1999 05:07                Off
16.03.1999 05:08          On
16.03.1999 08:16                Off
16.03.1999 19:34          On
16.03.1999 21:11                Off
16.03.1999 21:12          On
16.03.1999 21:50                Off
16.03.1999 21:51          On
16.03.1999 21:52                Off
16.03.1999 21:52          On
16.03.1999 22:17                Off
16.03.1999 22:18          On
17.03.1999 00:15                Off
17.03.1999 00:17          On
17.03.1999 00:32                Off
17.03.1999 00:33          On
17.03.1999 00:48                Off
17.03.1999 00:50          On
17.03.1999 04:06                Off
End of data
```

Figure 2. Programmer print-out of the AF-statistics. The total number and total time in AF is automatically calculated and displayed after interrogation.

AF, unstable antiarrhythmic drug therapy, unresolved far-fieldsensing problems, chronotropic incompetence, and intolerance to the DDD or DDD$^+$ mode.

Every patient was randomly programmed in DDD and DDD$^+$ mode for 6 months and then switched to the other mode. Short follow-up intervals of 3 months ensured that almost every AF episode was stored in the pacemaker memory.

Pacemaker AF-Memory

The pacemaker memory was completely re-organized in comparison to the conventional Inos^2 CLS/DR statistics. This was done not only to collect data confirming or rejecting the primary endpoint of the study, but also to gather data about the major mechanism underlying AF suppressed by overdrive pacing.

Atrial fibrillation is classified in non-sustained periods of less than 60 s and sustained periods of more than 60s. From this data the total number and duration of sustained and non-sustained AF is calculated (see the programmer print-out in Figure 2).

The date and time of 32 AF and non-AF episodes were stored in a non-rolling memory to document the first occurrence of AF and the next episodes in time between two follow-up visits. Since the basic assumption of this study was that the suppression of atrial extrasystoles is a major prerequisite for prevention of AF, a detailed AES statistic was stored in the memory. The AF statistic can be controlled with the help of the IEGM-marker stored preceding 25 AF episodes (Figure 3).

Patients

Until now, 34 patients have been included in the study. Mean age was 69.6 ± 9.8 years. Indication for pacemaker implantation was SSS in 50%, higher AV-block in 30%, and brady-tachy-syndrome. Medication consisted of class III and IV antiarrhythmic drugs.

Sixteen patients were programmed to DDD, the rest were in DDD$^+$ mode. There was no difference in age, symptoms, or gender in both groups. Pacemaker parameters were programmed similarly in both groups of

	n	P - wave (mV)	atrial threshold (V)
Group 1	16	4.2	0.9
Group 2	18	3.3	3.3

Table 1. Atrial charakteristics for group 1 (starts crossover with DDD - stimulation) and group 2 (starts crossover with DDD$^+$ - stimulation), crossover of stimulation modes after six months.

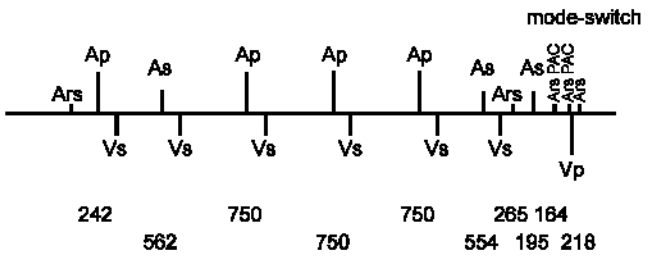

Figure 3. IEGM-marker preceding a mode-switch event. The event classification and the cycle length are shown. A series of atrial extrasystoles (AES) triggers the mode-switch of the pacemaker.

patients, to a basic rate at 60 bpm. AV-delay was set to 170 ± 24 ms at 60 bpm individually for every Patient. In addition, no significant difference was observed in electrical parameters such as stimulation or sensing thresholds (Table 1).

Statistics

Presently, only a small amount of cross-correlated data allowing an individual comparison between DDD and DDD⁺ is available. Therefore, the entire data were analyzed after separation into DDD and DDD⁺ groups.

Results

The functionality of the DDD⁺-mode was ensured using ECG recordings. The surface ECG documents that atrial stimulation was achieved in 98%. In the DDD group, a significantly lower ratio of atrial paced events was documented in the pacemaker memory (DDD: 65.8 ± 19.9%; DDD⁺: 98.0 ± 1.8%). DDD⁺ parameters were programmed in the following manner to realize such a high portion of atrial paced events. The step size (which increases the basic rate following an atrial sensed event), was programmed to 8.3 ± 4.3 ppm, and the plateau length (which determines the duration of overdrive stimulation), was set at 14 ± 11 cycles resulting in a mean overdrive duration of 2.1 ± 0.8 min. The basic rate and upper tracking rate were not different in either the DDD or the DDD⁺ mode.

In Figure 4 the histogram of atrial intervals as well as the ratio of paced and sensed events in these intervals were documented in DDD and DDD⁺ mode. The mean rate was increased from 70 bpm to 75 bpm, reflecting the step size of 5 bpm within a 10% error. The ratio of paced events rose from 67% to 98% demonstrating the efficacy of the DDD⁺ algorithm.

The former results clearly demonstrate that the algorithm reliably paces more than 95% of all intervals and

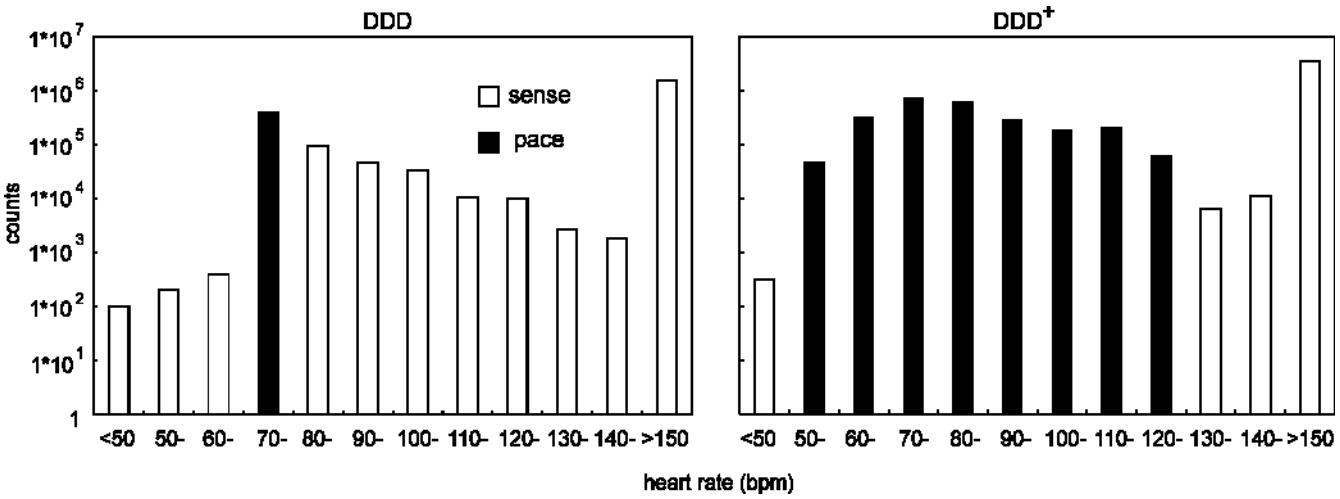

Figure 4. Histogram stored in pacemaker memory recorded during DDD (left) and DDD⁺ (right) mode. Besides the remarkable increase of the ratio between atrial paced and atrial sensed events from 67 to 98%, the mean heart rate increased from 70 to 75 bpm in respect to the step size. In DDD⁺ mode, the MOR was programmed to 120 bpm. Therefore, above 120 bpm only atrial sensed events can be observed. The high ratio of intervals above 150 bpm indicates the occurrence of atrial tachycardia. Rates lower than base rate due to hanling of extrasystoles.

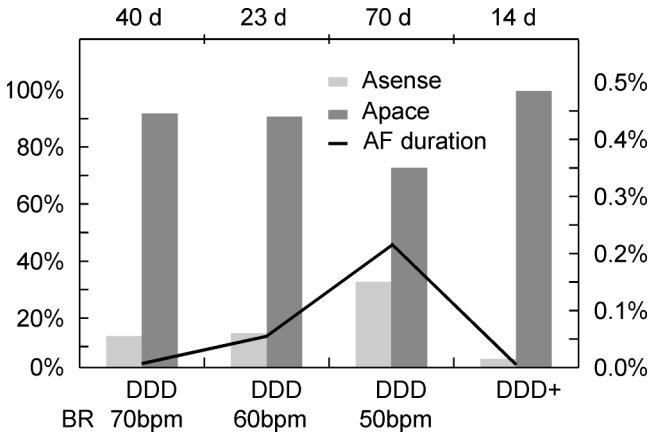

Figure 5. Ratio of Ap to As events and total time of AF in patient PIT in DDD and DDD⁺ mode. The total time of AF is reduced in DDD⁺ mode. The linear correlation between the ratio of atrial paced events and AF-time was calculated to R = -0.96 with p = 0.036.

holds the pacing rate in a programmable window above the sinus rate. Furthermore, the data now shows that the stimulation pattern provided by DDD⁺ remarkably reduces atrial extrasystoles and the number of sustained episodes of AF per day. Even in this small cohort of patients available from this preliminary evaluation, the number of AES per day decreased significantly from 1020 ± 575 to 183 ± 283. Patients who felt skipped beats in heart rhythm during the periods of DDD reported a far more stable heart rhythm in DDD⁺ mode, indicating from a subjective point of view, the reduction in short-long-short sequences. In all but one case, patients felt more comfortable in DDD⁺ than in DDD mode.

Figure 5 shows the ratio between As and Ap events as well as the total time of AF in the patient PIT during periods of DDD and DDD⁺ mode. The total time of AF is reduced in DDD⁺ mode. The graph suggests that the total time of sustained AF is correlated to the ratio of atrial paced events. The linear correlation between the ratio of atrial paced events and AF-time was calculated to R = -0.96 with p = 0.036. Therefore, the suggestion of a correlation between the ratio of an atrial paced event and the total time in AF is supported.

The data of the entire group show that the number of AF episodes per day (4.7 ± 4.8 to 2.2 ± 1.8) and the total time of AF was reduced (16.2 ± 15.7 h to 13.1 ± 17.1 h). At this time, the results are not statistically significant due to the small group of patients available. The large standard deviation indicates that even within this group a very non-homogeneous distribution of the number of AF events is present. The number of AF events per day range from 0.0 to 6.1 in the DDD⁺ group and from 0.4 to 15.2 in the DDD group. The total time of AF also shows a wide distribution (DDD⁺: 0 - 43%; DDD: 0.02 to 38%).

Discussion

The preliminary results clearly show that the algorithm fulfills to a great extent the requirement for permanent and dynamic overdrive pacing within a specific window above the sinus rate. The ratio of atrial paced events in DDD⁺ mode is higher than 97%. The algorithm works reliably. The algorithm was tolerated well in all but one patient, who needed re-programming of the DDD⁺ parameter to a less aggressive setting. The other patients felt more comfortable with the DDD⁺ mode since the skipped heart beat due to AES is suppressed and, therefore, a more stable rhythm is established. There was no impairment of exercise tolerance or sleep reported in this first group of patients.

Until now, data existed for only a few patients who already performed the switch, and changed from DDD to DDD⁺ or vice versa. In all 7 of these patients, the primary study hypotheses were fulfilled. The total time of AF and total number of AF decreased in the -individual comparison, while the time of the first occurrence of AF increased. These preliminary results are not yet statistically significant but are very promising.

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