Efficacy of DDD+ Mode in the Prevention of Paroxysmal Atrial Tachyarrhythmias: Interim Results of a Multicenter European Study

K.H. KONZ, I. SZENDEY
Medical Clinic II - Franziskushaus, Maria Hilf Clinics, Mönchengladbach, Germany

D. EL ALLAF
Hutois Hospital Center, Huy, Belgium

J. BRACHMANN, V. SCHIBGILLA
Medical Clinic II, Coburg Clinics GmbH, Coburg, Germany

P. ATTUEL
Val d'Or Surgical Center, Saint Cloud, France

On Behalf of the "Suppression of Atrial Fibrillation
by Overdrive Pacing with Inos² CLS" Study Investigators

Summary

The DDD+ mode is an atrial overdrive pacing algorithm that can be installed in implanted Inos² CLS pacemakers for research purposes. Sensing of an atrial event in the DDD+ mode results in the pacing rate being increased by the programmed overdrive step size (typically 10 beats/min). In the absence of sensed atrial events, the pacing rate is decreased by 1 beat/min after each overdrive plateau length (typically 20 cycles). This prospective and randomized crossover study involved 111 patients with a history of paroxysmal atrial fibrillation (AF) and conventional indications for pacing. Results for the DDD+ versus the DDD mode were compared in view of the mean number of sustained (lasting for > 60 s) AF episodes per day, the mean sustained AF time per day, and the mean delay until the first recurrence of AF, as recorded in the pacemaker memory. To date, crossover data have been gathered in 41 patients followed for 164 ± 60 days in the DDD+ mode and 168 ± 61 days in the DDD mode. The incidence of sustained AF was reduced from 2.6 ± 8.0 episodes/day (DDD) to 0.8 ± 1.6 episodes/day (DDD+). The mean duration of AF decreased from 1.6 ± 3.3 hours/days (DDD) to 1.3 ± 3.0 hours/days (DDD+), while the mean delay until the first recurrence of AF was increased from 90 ± 188 hours (DDD) to 237 ± 468 hours (DDD+). So far, none of the observed improvements has reached statistical significance. The percent of atrial pacing was 98 % ± 5 % in the DDD+ and 62 % ± 32 % in the DDD mode (P < 0.05). Patients returned to their hospitals 111 times for pacemaker follow-ups while in DDD+ mode; in 108 cases, atrial overdrive pacing was well tolerated. In three patients, specific reprogramming of the overdrive parameters had to be undertaken to improve their tolerance to atrial overdrive pacing. Overall, the DDD+ mode appeared to be beneficial in 39 % of the patients, DDD mode in 32 %, while the outcome was neutral in 29 % (no AF after mode randomization). Further studies are needed to identify clinical predictors of success or failure of atrial overdrive pacing therapy.

Key Words

Atrial overdrive pacing, DDD+ mode, atrial fibrillation

Introduction

A high percentage of atrial paced events is associated with a reduced incidence of atrial tachyarrhythmia in patients with sick sinus syndrome, vagally-induced atrial arrhythmia, or sinus bradycardia caused by pharmacological treatment of atrial tachyarrhythmia [1-4]. These observations paved the way for the development

of a range of pacemaker algorithms dedicated to the prevention of the onset of atrial fibrillation (AF) by pacing the atrium at a rate slightly above the sinus rate. The goal of these algorithms is to achieve a percentage of atrial pacing above 90 % without significantly increasing the mean atrial rate, as a too-fast heart rate may impair a patient's tolerance and quality of life [1,5].

Atrial overdrive pacing could decrease atrial ectopic activity involved in the onset of AF [6,7]. It may also prevent prolonged post-extrasystolic pauses following premature atrial beats and, thus, the heterogeneous spatial dispersion of atrial refractoriness that would otherwise facilitate triggering of a sustained AF [8,9]. Overdrive pacing can also be effective in the prevention of AF associated with absolute (< 50 beats/min) or relative bradycardia (fast rate decay), and change the substrate for vagally-induced AF by modifying the tone of the autonomous nervous system [9]. With the increased time in sinus rhythm, "reverse remodeling" is initiated, making recurrence of AF even less likely [9,10]. Anticipated, long-term benefits of effective AF suppression algorithms are not only improved quality-of-life and long-term medical prognosis for patients, but also reduced medical costs for management of patients with frequently recurring, symptomatic, drug-refractory AF [11].

The clinical performance, therapeutic efficacy, and patient tolerance of different atrial overdrive algorithms are currently under investigation [9,12-18]. Our study aimed at evaluating the "DDD$^+$ mode" overdrive algorithm implemented in Inos^2 CLS pacemakers (Biotronik, Germany).

Materials and Methods

DDD$^+$ Mode

The Inos^2 CLS is a software-based, dual-chamber pacemaker that allows for additional algorithms to be downloaded to the pacemaker memory via telemetry connections. When DDD$^+$ software is installed, DDD or DDD$^+$ mode (atrial overdrive pacing) can be programmed in conjunction with increased memory capacity for the storage of data that is related to mode-switching. The operating principle of the DDD$^+$ mode is delineated in Figure 1. DDD$^+$ software stores the number and duration of sustained (lasting for > 60 s) as well as non-sustained AF episodes since the last memory deletion, the time spent in "sinus rhythm", and the exact date and time of the first 32 AF episodes. It cannot be used concomitantly with the rate-adaptive function of the pacemaker.

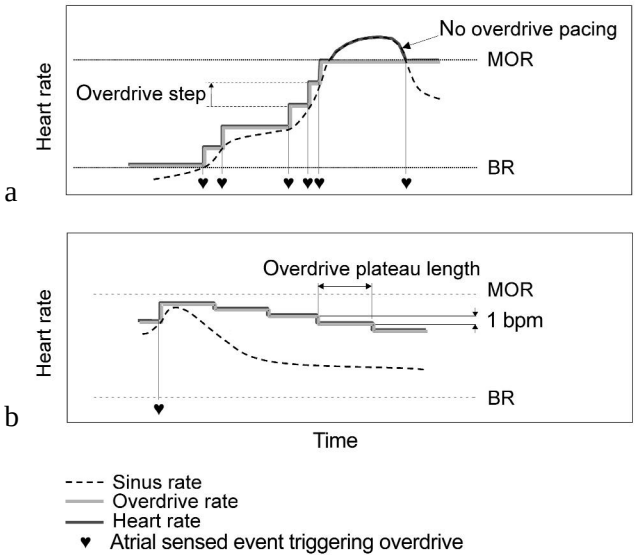


Figure 1. In the DDD$^+$ mode, sensing of an atrial event outside the post-ventricular atrial refractory period triggers pacing rate increase by the programmed overdrive step size (nominal value = 10 beats/min (bpm), range 1 – 32 bpm) (panel a). In the absence of sensed atrial events (panel b), pacing rate is decreased by 1 bpm each time when overdrive plateau length expires (nominal value = 20 cycles, programmable range 1 – 32 cycles). Atrial pacing rate cannot exceed the programmed maximum overdrive rate (MOR) or be lower than the basic rate (BR).

Mode Switching

Mode switching in the Inos^2 CLS is activated when 5 out of 8 consecutive atrial beats (P-P intervals) are faster than the mode-switching intervention rate, which is programmable from 100 – 180 beats/min. Following the mode switch, the pacemaker operates in the VDI mode until 8 out of 8 consecutive atrial beats are paced or sensed below the programmed intervention rate [19,20]. The maximum atrial sensitivity is 0.5 mV, and the next programmable value is 1 mV, etc., continuing in 0.5 mV steps. Post-atrial and post-ventricular atrial blanking periods are 125 ms and 100 ms (or 35 ms after mode switch), respectively, and are non-programmable. There is no atrial blanking after an atrial or ventricular sensed event. All sensed atrial events occurring outside these blanking periods, including the events during the atrioventricular interval, are evaluated by the mode-switching algorithm. The specified blanking periods are shorter than in the majority of other pacemakers, thanks to the advanced

amplifier circuitry technology in Inos² CLS pacemakers, and should facilitate sensing of AF.

Study Methods

"Suppression of Atrial Fibrillation by Overdrive Pacing with Inos² CLS" is a prospective and randomized crossover study carried out at 19 centers in Germany, Belgium, France, and Brazil. Eligible for the enrollment were patients who received a bipolar atrial lead and an Inos² CLS or Inos² DR pacemaker for conventional pacing indications. Additionally, the patients should have exhibited a history of paroxysmal AF – at least one sustained AF episode per month or two episodes in the last 3 months. Exclusion criteria were chronic AF (> 18 hours/day), unresolved atrial sensing problems, unstable antiarrhythmic drug therapy, as well as the presence of uncontrolled angina pectoris, malignant ventricular arrhythmia, or symptomatic chronotropic incompetence.

		No. of patients
Total eligible		111
Drop-out at mode randomization	Total	10 (9 %)
	Permanent AF	4 (3.6 %)
	Absence of AF	5 (4.5 %)
	Poor medical condition	1 (0.9 %)
Total enrolled		101
Drop-out after enrolment	Total	11 (10.9 %)
	Permanent AF	5 (5 %)
	Change in medical condition	4 (4 %)
	Protocol violation	2 (2 %)
Available crossover data		41
Expected additional crossover data by the year 2002		49

Table 1. Review of patient drop-out and follow-up status. AF (atrial fibrillation).

The patients were actively enrolled in the study at 1 – 9 months after pacemaker implantation, at which time the pacemaker mode was randomized to DDD or DDD⁺ on the basis of the pacemaker serial number. The mode crossover should take place 6 months later, and the patients should be followed for another 6 months. To monitor the medical condition of the patients and the success of the overdrive therapy, follow-up controls were scheduled for every 3 months. AF data stored in the pacemaker memory were retrieved at each hospital visit.

Results for DDD⁺ versus DDD mode were compared in view of the mean number of sustained AF episodes per day, the mean duration of sustained AF in hours per day, and the mean delay until the first recurrence of AF (in hours), as recorded in the pacemaker diagnostic memory. Differences between the mean values were evaluated on an intrapatient basis using the paired, two-tailed t-test. P-values < 0.05 were considered significant. The data are presented as mean values ± standard deviation.

Results

A total of 111 patients presented at their hospitals for enrollment in the study. Their mean age was 70.2 ± 10.4 years, 56 were male and 55 female. The average NYHA class at the time of pacemaker implantation was 1.7 ± 0.7 (range I – III). Pacing indications were some form of sinus node disease in 60 %, atrioventricular block in 22 %, and other or unknown indications in 18 %. Relevant medications were Class I antiarrhythmics taken by 9 % of the patients, Class II (47 %), Class III (18 %), Class IV (8 %), ACE inhibitors (21 %), Nitrates (24 %), and other cardiac medications in 21 % of the studied population.

Atrial leads were positioned primarily in the right atrial appendage (51 %), against the right atrial lateral wall (33 %), in the high right atrium (4 %), and at the right atrial anterior wall (3 %). No recommendation of a specific site was given in the study protocol. The measured P-wave amplitude in the bipolar configuration at the time of implantation was 3.2 ± 1.4 mV.

The basic rate was programmed to 62 ± 4 beats/min (DDD⁺ mode) and 62 ± 6 beats/min (DDD mode), the overdrive step size was programmed to 9 ± 2 beats/min (range 5 – 15), and the overdrive plateau length to 20 ± 3 cycles (range 10 – 32). The maximum overdrive rate was 129 ± 14 beats/min. These settings resulted in

	DDD$^+$ mode	DDD mode	Δ (DDD − DDD$^+$)	P-value
AF duration (hours/day)	1.3 ± 3.0	1.6 ± 3.3	0.3 ± 2.4	0.43
Number of AF episodes/day	0.8 ± 1.6	2.6 ± 8.0	1.7 ± 7.7	0.16
Time until 1st AF recurrence (hours)	237 ± 468	90 ± 188	-147 ± 296	0.09
Follow-up period (days)	164 ± 60	168 ± 61	4 ± 105	0.81

Table 2. Recurrence of atrial fibrillation (AF) following mode randomization in 41 patients in whom crossover data have been gathered.

an atrial pacing percentage of 98 % ± 5 % (range 80 – 100 %) in the DDD$^+$ mode and 62 % ± 32 % (range 1 – 100 %) in the DDD mode ($P < 0.05$). To date, patients have returned to their hospitals 111 times for pacemaker follow-ups while in DDD$^+$ mode. In 108 cases, the programmed overdrive parameters were well tolerated, and in the remaining three cases reprogramming of the overdrive step size or plateau length ameliorated discomfort that was initially caused by atrial overdrive.

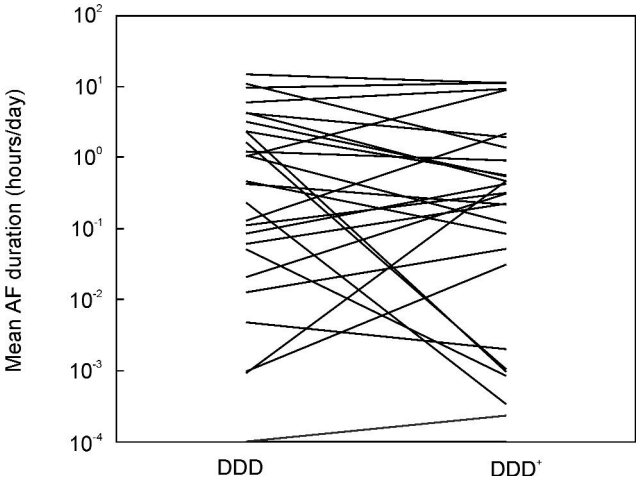


Figure 2. Duration of atrial fibrillation (AF) in the individual patients (crossover data). Persons without AF are omitted.

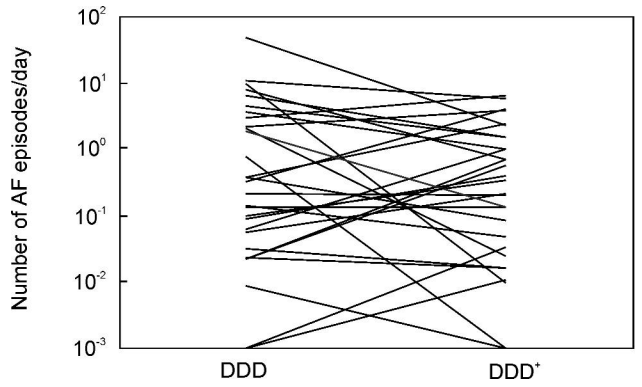


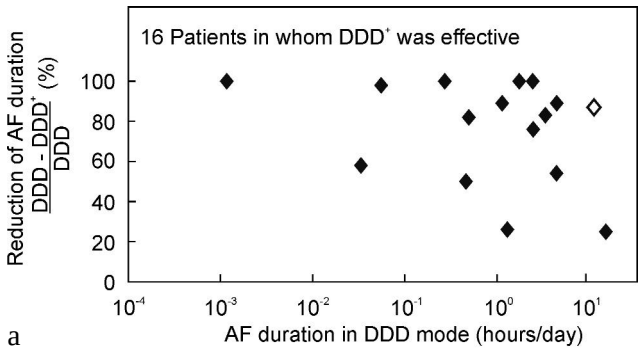
Figure 3. Incidence of atrial fibrillation (AF) in the individual patients (crossover data). Persons without AF are omitted.

Current follow-up status is illustrated in Table 1. Of 111 eligible patients, ten were excluded at the time of mode randomization (before final patient enrollment). The reasons were development of permanent AF in four patients, absence of AF between implantation and mode randomization in five, and poor medical condition in one person. Additionally, five patients were excluded during the study due to the development of permanent AF (three in DDD mode and two in DDD$^+$ mode), four due to death or significant change in medical condition or in medication regime, and two due to a violation of the study protocol resulting in loss of crossover data.

Study results for 41 patients, for whom crossover data are already available, are shown in Table 2. The reduction in the mean AF duration per day in the DDD$^+$ mode was 18.5 %, i.e., there was 17 minutes less AF per day than in the DDD mode. Atrial overdrive pacing also reduced the number of AF episodes by 67.8 %, from 2.6 per day in the DDD mode to 0.8 per day in the DDD$^+$ mode. The time until the first recurrence of AF was extended by 147 hours. However, none of the observed improvements have attained statistical significance so far.

The study results for the individual patients are illustrated in Figures 2 – 5. Slight differences in the number of patients in whom DDD$^+$ mode was effective (16 in Figure 4 versus 17 in Figure 5) are attributable to the fact that total AF burden in three patients was increased despite simultaneous reduction in the number of AF episodes, while in two patients the time under AF decreased despite a higher AF incidence.

Open squares in Figures 4 and 5 indicate patients in whom there was an increase in AF prevalence over time, potentially masking the comparative efficacy of DDD$^+$ pacing. A good example is a patient who had 1 hour/day (0.4 episodes/day) of AF in DDD mode and



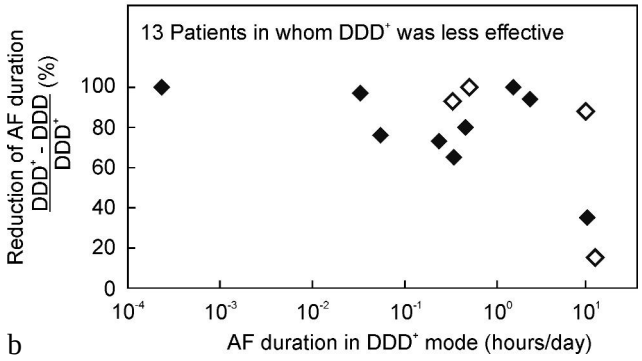
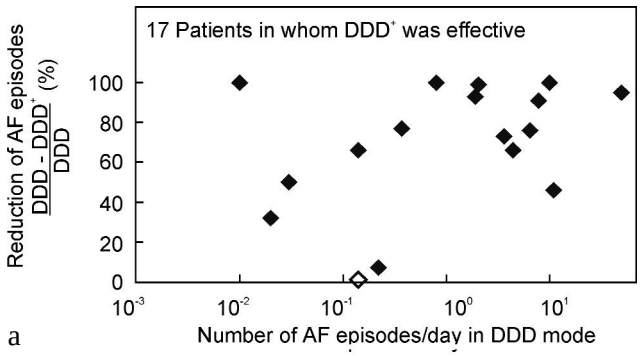


Figure 4. Reduction of atrial fibrillation (AF) duration in the more successful mode for each individual. Panel a) shows data for 16 patients in whom DDD+ mode was associated with (76 %) less AF burden than DDD mode. Panel b) shows data in 13 patients in whom DDD mode was associated with (78 %) less AF burden than DDD+ mode. 12 persons had no AF after mode randomization. Open squares indicate patients in whom there was a progression of AF prevalence with time, i.e., steady increase in AF time between successive follow-up visits.



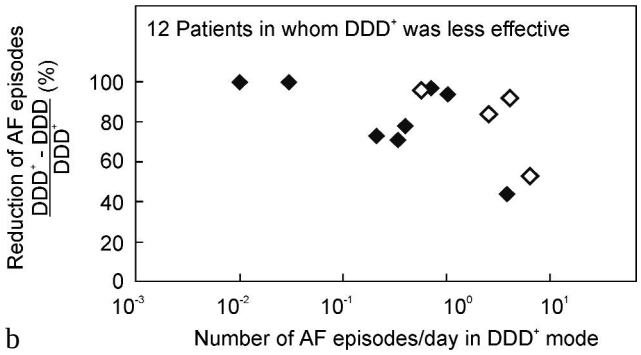


Figure 5. Reduction of the incidence of atrial fibrillation (AF) in the more successful mode for each individual. DDD+ mode was associated with (69 %) less incidence of AF in 17 patients (panel a) and DDD mode was associated with (82 %) less incidence of AF in 12 patients (panel b). 12 persons had no AF after mode randomization. Open squares indicate patients in whom there was a progression of AF prevalence with time, i.e., steady increase in AF time between successive follow-up visits.

9 hours/day (2.4 episodes/day) of AF in DDD+ mode. This result, which is represented by the most upper right square in the lower panel in Figure 4, appears to be merely a consequence of the natural progression in AF disease, since within the first 3 months and between 3 and 6 months (DDD mode) there was a total of 15 and 57 AF episodes, respectively, whereas in the period from 6 – 8 months and from 8 – 11.5 months (DDD+ mode) there were 99 and 294 episodes, respectively. In this particular patient, the number and duration of AF episodes increased with time approximately according to geometric progression and do not seem to be influenced by the programmed pacing mode. A similar steady increase of AF prevalence over time – irrespective of the programmed mode – was seen in three other patients with better results in DDD mode and in one patient with better results in DDD+ mode (Figure 4).

Discussion

The interim data analysis based on the available crossover data in 41 patients indicated that DDD+ pacing was more effective than conventional dual-chamber pacing in 16 patients (39 %) in terms of reduced AF time by 25 % – 100 %. If the highly beneficial effect of DDD+ pacing is defined as a comparative reduction of AF time by > 75 %, then DDD+ pacing was highly beneficial in 11 patients (27 %), in whom sustained AF time decreased from 2.4 ± 3.2 hours/day

(DDD) to 0.3 ± 0.4 hours/day (DDD$^+$-mode), with the simultaneous reduction in AF incidence from 7.3 ± 14.4 episodes/day (DDD) to 0.6 ± 0.8 episodes/day (DDD$^+$). The results were neutral in 12 patients (29 %) in whom there was no AF episode in either mode, and 13 patients (32 %) had more AF in DDD$^+$ than in DDD mode.

If the factor of progression of AF disease over time (steady increase in AF time between successive follow-up visits) had been used as an additional exclusion criterion, then DDD$^+$ pacing would be associated with less AF in 15 patients and conventional dual-chamber pacing in nine. Apparently, a range of factors may influence the findings and should be adequately considered in the final analysis of data from this study. Taking the factor of progression in AF disease over time into account is probably more relevant in this study than it was in earlier studies on atrial overdrive pacing [15-17], due to our long observational period (6 months) in each mode.

The presented interim study results are in line with published conclusions from other studies investigating the efficacy of different atrial overdrive pacing algorithms. All these reports demonstrated a tendency for less AF to occur during overdrive pacing, but without statistically significant reduction in AF prevalence [3,15-17]. Overdrive pacing seems to be highly effective in a sizeable portion of study patients while being ineffective in the remaining segment of the patient population [15]. Therefore, further studies are needed to identify those who will respond to atrial overdrive pacing and to tailor the algorithms (their programmable parameters) to the individual patients. The final results of this study are expected by the end of the year 2001, which should also include a retrospective examination of possible clinical predictors of success or failure of atrial overdrive pacing therapy. In addition, an analysis of AF prevalence during the first 3 months versus the second 3 months in the same mode (DDD or DDD$^+$) should help clarify the possible influence of electrical remodeling and reverse remodeling on the AF incidence observed during this study.

Conclusions

The interim crossover data analysis carried out in 41 out of 101 enrolled patients showed the beneficial effects of DDD$^+$ pacing in 39 % of the patients, a neutral outcome (no AF in either DDD or DDD$^+$ mode) in 29 %, and less AF in the DDD mode in 32 % of the patients. Although the AF burden and the incidence of sustained AF were reduced in the DDD$^+$ mode by 18.5 % and 67.8 %, respectively, the improvement was not statistically significant. Atrial overdrive pacing was well tolerated by these patients. Further studies are needed to identify patients likely to respond to atrial overdrive pacing.

Clinical Investigators

D. El Allaf (Huy, Belgium); K.H. Konz and I. Szendey (Mönchengladbach, Germany); J. Brachmann and V. Shibgilla (Coburg, Germany); P. Attuel (St. Cloude Cedex, France); C. Gomes (Taguatinga, Brazil); S. Löscher (Leipzig, Germany); C. John (Dresden, Germany); U. le Blanc and S. Rupp and M. Klutmann (Düren, Germany); T. Scheibner (Löbau, Germany); K. Malinowski (Aue, Germany); L. Griesbach (Kirchberg, Germany); H. Müller-Dieckert (Rochlitz, Germany); K. Göhl and C. Huber (Nuremberg, Germany); G. Lascault (St. Denis Cedex, France); R.U. York (Hartmannsdorf, Germany); T. Walter (Greiz, Germany); B. Hailer and H. Schäfer (Essen, Germany); D. Stockmann (Antwerpen, Belgium); S. Schüssler (Kaufbeuren, Germany).

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Contact
Dr. K.H. Konz
Kliniken Maria Hilf
Med. Klinik II – Kardiologie
D-41063 Moenchengladbach
Germany
Telephone: +49 2161 892 2240
Fax: +49 2161 892 2241
E-mail: KonzK@mariahilf.de