European Multicenter Study on the Prevention of Paroxysmal Atrial Fibrillation by Permanent Overdrive Pacing: Atrial Rate Behavior and Patient Tolerance

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Summary

The treatment of atrial fibrillation (AF) with medications is often ineffective and accompanied by adverse effects. New therapeutic options for AF involve cardiac pacemakers. As single atrial extrasystole and supraventricular tachycardia are often responsible for AF generation, new pacing algorithms aim at preventing AF by homogenization of atrial electrical activity and suppression of ectopic beats in patients with frequent AF. These new algorithms, offering refined reactions to various intrinsic conditions, can be downloaded via telemetry links into the memory of modern software-based pacemakers. The herewith presented European multicenter study, conducted in 19 centers from four countries, evaluates clinical utility of the DDD⁺ mode in the prevention of AF. Occurrence of a sinus beat in the DDD⁺ mode is followed by a pacing rate increase surpassing the intrinsic rate within 1 s. The pacing rate will thereafter decrease slowly until a new sinus beat occurs. Criteria for patient inclusion in the study are conventional indications for pacing in conjunction with at least two episodes of lasting AF in the previous 3 months or one episode of AF per month, and stable antiarrhythmic drug administration. Patients are randomized to the DDD or DDD⁺ mode at 3 – 6 months after pacemaker implantation, and the modes are crossed at 6 months after randomization. This article provides clinical characteristics and acute electrophysiological parameters in the 104 patients enrolled in the study, and evaluates patient tolerance and atrial rate behavior in the DDD⁺ versus DDD pacing mode for 47 patients who reached at least 3-month follow-up after mode randomization. The prevalence of atrial paced events was significantly higher in the DDD⁺ mode (97 % ± 7 %) than in the DDD mode (53 % ± 39 %, P < 0.001). The convenience of the DDD⁺ algorithm is a non-significant increase in the mean atrial rate: 83 ± 21 beats/min (DDD⁺ mode) versus 75 ± 12 beats/min in the DDD mode, P = 0.111. Patient tolerance of the DDD⁺ mode was very satisfactory. Final results of the present study, including randomized data on the efficacy of the DDD⁺ mode in the prevention of AF, are expected by the end of the year 2001.

Key Words

Atrial fibrillation, overdrive pacing, atrial rate behavior, DDD⁺ mode, arrhythmia prevention

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a prevalence of up to 2 % in the total adult population [1]. In the presence of risk factors such as cardiovascular disease and increasing age, the prevalence can be as high as 9 %. Due to electrical remodeling of the heart associated with prolonged AF ("AF begets AF"), paroxysmal AF should be either prevented from starting or converted to sinus rhythm as early as possible [2,3]. The treatment of AF with medications is often ineffective and accompanied

by adverse effects irrespective of whether the chosen strategy is to control the ventricular rate or to restore the sinus rhythm.

New therapeutic options for AF involve cardiac pacemakers. Numerous studies have demonstrated benefits of atrioventricular (AV) synchronous pacing (DDD, VDD, or AAI pacing modes) over non-synchronized ventricular pacing (VVI mode) in the reduction of AF incidence in patients with conventional indications for pacing. As single atrial extrasystole and supraventricular tachycardia are often responsible for AF generation, new pacing algorithms aim at preventing AF by homogenization of atrial electrical activity and suppression of ectopic beats in patients with frequent AF, with or without conventional indications for pacing. Coumel et al. [4] showed that preventive effects can be achieved simply by increasing pacing rate above the sinus rate, although this is not always well-tolerated by the patients.

In modern software-based pacemakers, various algorithms can be downloaded into the RAM (Random Access Memory) of implanted pacemakers using telemetry links. This feature facilitates clinical evaluation of new algorithms offering refined reactions to various intrinsic conditions in selected patients wearing standard pacemakers. Different pacemaker companies have developed their own algorithms for AF prevention by overdrive pacing. In the majority of the algorithms, sensing of one sinus beat or sensing of two sinus beats within a programmable interval (e.g., 15 s), results in a pacing rate increment (Pace Conditioning by Vitatron, The Netherlands; Dynamic Atrial Overdrive by St. Jude Medical, USA; DDD$^+$ Mode by Biotronik, Germany) or in a cycle length decrement (Sinus Rhythm Overdriving by ELA Medical, France; Atrial Preference Pacing by Medtronic, USA; Atrial Pacing Preference by Guidant, USA). The difference between the "rate increment" and "cycle length decrement" concepts is the most prominent at the edges of the nominal sinus rate range, i.e., at low and high sinus rates. For instance, in the "cycle length decrement" concept, a shortening of the paced PP-interval by 50 ms (the value used in the Atrial Preference Pacing, Medtronic) on the occasion of a sensed event at 60 beats/min will result in a rate increase of 3 beats/min, while the same interval shortening after a sensed event at 100 beats/min will result in a rate increase of 9 beats/min. In the "rate increment" concept, pacing rate increase is always constant (as in Pace Conditioning, Vitatron), or is programmable but independent of the rate (DDD$^+$ Mode, Biotronik). There is a lack of clinical data showing which concept better suits the needs of the patient. For instance, a rate increase of 15 – 20 beats/min might not be well-tolerated by the patients during the night.

Single premature atrial contractions (PACs) and multiple extrasystoles are often identified as triggers for AF [5,6]. Although the underlying mechanism for the occurrence of additional depolarizations remains unclear, a range of new algorithms is applied to prevent the subsequent short-long sequence by pacing during the compensatory pause (Post PAC Response by Vitatron; Post-Extrasystolic Pause Suppression by ELA Medical; Atrial Rate Stabilisation by Medtronic). In our opinion, fast reaction to PACs is desirable when permanent overpacing is not the therapy of choice. In the overdrive algorithm investigated in our study (DDD$^+$ mode, Biotronik), the post PAC response is not available as a PAC is treated as a sensed event within the total atrial refractory period and classified as "refractory sense". Such events are not used for further timing (they are only evaluated for eventual mode-switching), and the pacing rate remains unchanged.

Another novel feature under clinical investigation is the utility of pacing at an elevated rate in the DDIR mode during a programmable period of time after an AF episode has been terminated spontaneously (Post Mode-Switch Overdrive Pacing by Medtronic). The purpose of this algorithm is to avoid reinitiation of AF, which was found to recur more frequently shortly after termination. The DDD$^+$ algorithm investigated in our study has a comparable effect to that of the Post Mode-Switch Overdrive Pacing, as the first atrial sensed event after switching back from the VDI to the DDD$^+$ mode (after AF termination) activates overdrive pacing and results in the large prevalence of paced atrial beats. The foregoing considerations suggest that the DDD$^+$ mode reacts in a similar way to a variety of algorithms/features available separately in different products of various companies. The main advantages of the special algorithms for PAC and post AF period management are, however, flexible programming options and dedicated diagnostic functions aimed at evaluation of therapeutic benefits of the new features in the individual patients. The development of advanced atrial pacing algorithms coincided with the improvement of diagnostic functions related to AF detection and evaluation. All the aforementioned devices thus possess a

counter for the number of AF episodes, for the burden of AF (cumulative AF duration), and for the time to the first recurrence of AF. In some devices these parameters are extracted from the mode-switching report. This sort of diagnostic data is of great importance for the assessment of the efficacy of the applied AF therapy [7]. As the patient's safety and comfort are a matter of special concern, maximum overdrive rate is programmable in all the algorithms.

But do all these new algorithms and features provide the expected clinical benefits? A number of clinical studies currently investigate this issue. One of such studies is the European multicenter study evaluating clinical utility of the DDD+ mode in the prevention of AF. The present article provides clinical characteristics and acute electrophysiologic parameters in the 104 patients enrolled in the study, and evaluates patient tolerance and atrial rate behavior in the DDD+ versus DDD pacing mode.

Materials and Methods

The investigated DDD+ algorithm may be downloaded into the dual-chamber pacemakers Philos DR and Inos^2 CLS (Biotronik). Algorithmic procedures have been described in detail elsewhere [8,9]. In brief, occurrence of a sinus beat in the DDD+ mode is followed by a pacing rate increase surpassing the intrinsic rate within 1 s. How fast the pacing rate will increase is defined by the physician by programming the "overdrive step size" parameter (default value 10 beats/min). Pacing rate will thereafter decrease slowly in 1 beat/min steps, and each step will last for a period of time equal to the programmable "overdrive plateau length" (default value 20 beats). The DDD+ mode is supposed to minimize the incidence of atrial spontaneous activity, and thus homogenize atrial depolarization and repolarization patterns, and to suppress arrhythmogenic foci that may be active in case of sinus activity.

The design of the ongoing clinical trial has been described previously [10]. In brief, criteria for inclusion in the study are conventional indications for pacing in conjunction with at least two episodes of lasting AF in the previous 3 months or one episode of AF per month, and stable antiarrhythmic drug administration. Patients are randomized to the DDD or DDD+ mode at 3 – 6 months after pacemaker implantation, and the modes are crossed at 6 months after randomization. Data will be analyzed according to the "intention to treat" principle. The protocol has been approved by responsible ethics committees and all patients gave their written informed consents.

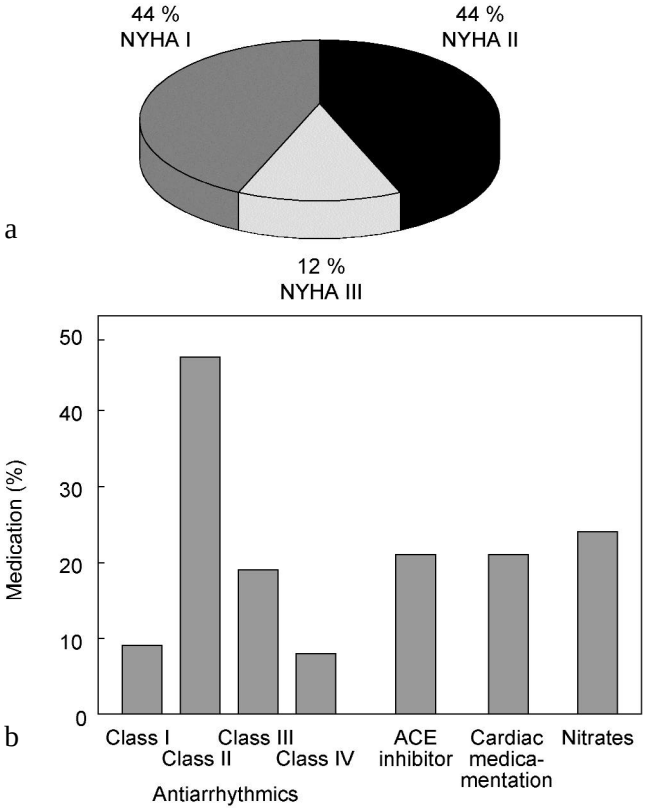


Figure 1. The New York Heart Association (NYHA) functional class of the patients (a) and the pharmacologic therapy (b) at the time of pacemaker implantation. Class I-IV means four different classes of antiarrhythmic drugs; cardiac medication means cardiac tonics, e.g., digitalis.

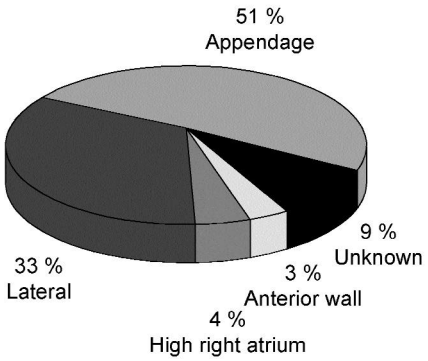


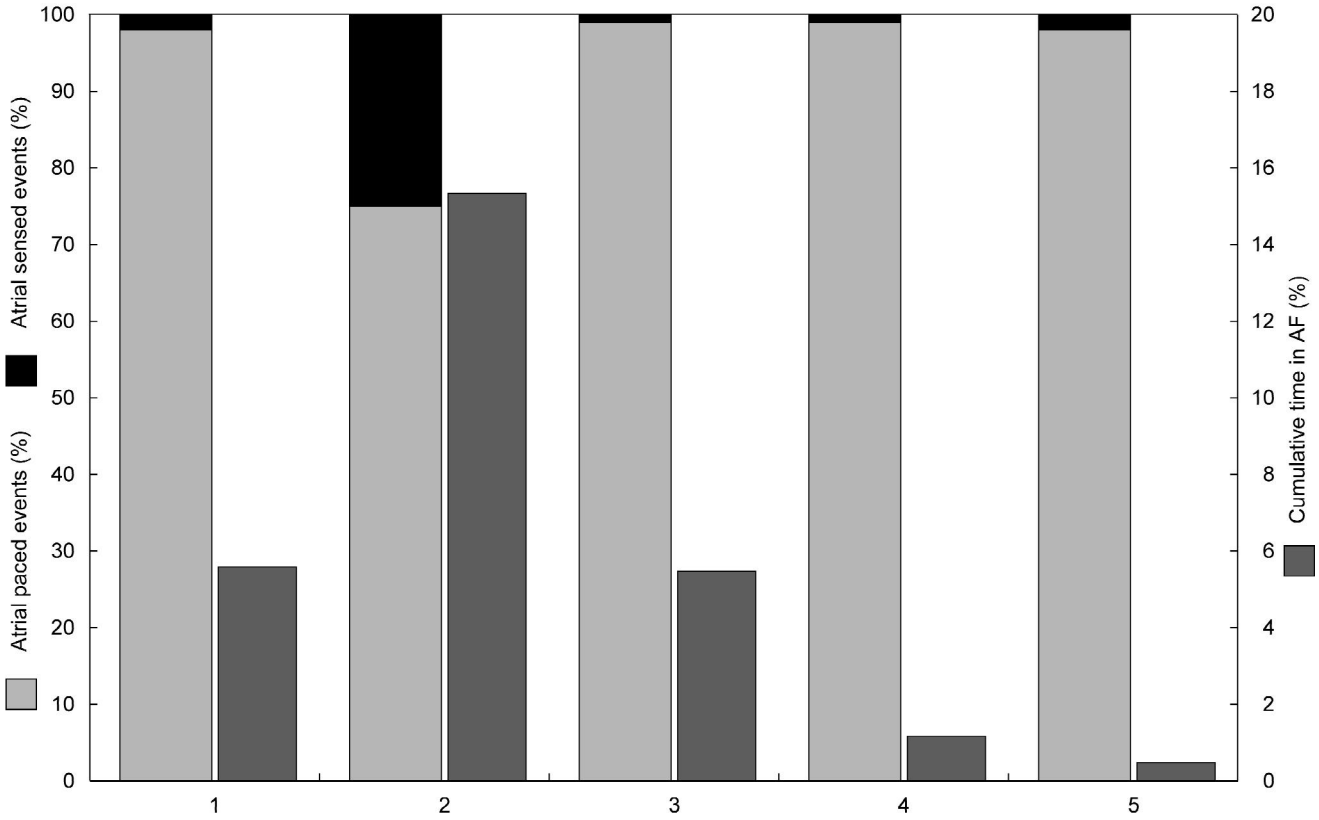
Figure 2. Position of the implanted leads in the right atrium. No recommendation of a specific site was given in the study protocol.

	Total	Group 1	Group 2
Patients/male	104/55	52/33	52/22
Age	70.3 ± 10.5	70.1 ± 11.0	70.4 ± 10.0
P-wave (mV)	3.20 ± 1.48	3.16 ± 1.49	3.24 ± 1.49
Atrial threshold (V)	0.95 ± 0.56	0.95 ± 0.48	0.94 ± 0.64
Atrial impedance (Ω)	509 ± 112	509 ± 103	509 ± 121

Table 1. Electrophysiological values during pacemaker implantation. Group 1: Patients from the DDD study leg (DDD mode to be programmed first); Group 2: patients from the DDD+ study leg (DDD+ mode to be programmed first). There were no significant differences between the two groups. Unpaired two-tailed t-tests were used in the evaluations and P value was > 0.05 in all cases.

	No. of patients	Incidence of atrial pacing (mean ± SD)	Programmed basic rate (mean ± SD)	Atrial rate (mean ± SD)
Group 1	25	53 % ± 39 %	63 ± 5 bpm	75 ± 12 bpm
Group 2	22	97 % ± 7 %	62 ± 4 bpm	83 ± 21 bpm
Statistical significance		P < 0.001	P = 0.457	P = 0.111

Table 2. Evaluation of the atrial rate in 47 patients who reached at least 3-month follow-up after mode randomization. Group 1: DDD mode; Group 2: DDD+ mode. In the comparison, unpaired two-tailed t-tests were used and a P value < 0.05 was considered significant.



	1	2	3	4	5
Pacing mode	DDD+	DDD	DDD+	DDD+	DDD+
Duration	35 days	42 days	33 days	14 days	140 days
Plateau length	20 cycles	-	20 cycles	20 cycles	10 cycles
Step size	5 bpm	-	10 bpm	10 bpm	5 bpm

Figure 3. Case report for a patient in whom DDD+ mode was used in conjunction with different programmed values for overdrive plateau length and overdrive step size. The cumulative duration of AF is given in % of the total time period.

Results

The recruitment period expired in August 2000. A total of 104 patients was enrolled in 19 clinical centers from four countries (Belgium, Brazil, France, and Germany). Ninety-two patients have already been randomized in one of the two study legs. The mean age of the 104 patients was 70.3 ± 10.5 years; 55 were males and 49 females. All patients were implanted with an Inos^2 CLS pacemaker for conventional indications for pacing. Reported symptoms were: syncope (41 %), bradycardia (10 %), brady-tachy syndrome (7 %), dyspnea (9 %), cardiac insufficiency (7 %), other or unknown (26 %). The NYHA functional class (mean 1.7 ± 0.7) and administered medications at the time of implantation are illustrated in Figure 1. Acute electrophysiologic parameters and final atrial lead positions are summarized in Figure 2 and Table 1. Since the pacing site may influence total atrial conduction time and contribute to proarrhythmic effects, the information on the implant site will be of importance in the future analysis of the clinical profiles of responders versus non-responders.

Follow-up data processed to date include 29 patients in the DDD mode (Group 1) followed for 5.2 ± 2.8 months after mode randomization, and 29 patients in the DDD$^+$ mode (Group 2) followed for 4.6 ± 2.2 months. Four patients were excluded from the DDD group and seven from the DDD$^+$ group, due to development of permanent AF (n = 4), absence of AF in the DDD mode after pacemaker implantation (n = 5) or for reasons not related to AF (n = 2, i.e., cerebral tumor, sepsis).

Programmed value for the overdrive step size was 8.0 ± 3.1 beats/min and for the overdrive plateau length 19.7 ± 5.2 cycles (mean ± SD). The basic rate was programmed at the physician's discretion to meet the individual patient needs (Table 2). Atrial rate behavior in the two different pacing modes is analyzed in Table 2. The mean atrial rate and the percentage of atrial paced events were calculated from the atrial rate histograms stored in the pacemaker memory and from the event counter data, respectively. There were also interesting individual examples showing benefits of DDD$^+$ pacing in chronotropically competent patients (Figure 3) [11,12].

Based on the available data, all patients tolerated the DDD$^+$ mode, with only two patients requiring reprogramming of the overdrive step size from 20 beats/min to 10 beats/min.

Conclusions

According to the data shown in Table 1 and additional information provided in the text, the two study groups were equivalent. Therefore, meaningful crossover results can be expected in the final analysis. A decisive factor in the performance of the study will be patients' compatibility with the DDD$^+$ algorithm. Diagnostic data collected in the pacemaker memory showed that the prevalence of atrial paced events was significantly higher in the DDD$^+$ mode (Table 2), which is an expected and favorable result. Unlike earlier studies, where basic rates were programmed to 80 – 90 beats/min to achieve as high percent of atrial pacing as possible, the convenience of the DDD$^+$ algorithm is expressed through a non-significant increase in the mean atrial rate compared to the DDD stimulation. The findings on the satisfactory tolerance of the DDD$^+$ mode by the patients confirm earlier observations of Lazarus et al. with the Sinus Rhythm Overdriving algorithm [13]. Final results of the present study, including randomized data on the efficacy of the DDD$^+$ mode in the prevention of AF, are expected by the end of the year 2001.

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