Optimizing the Philos Overdrive Step Size: The Concept of the OPOSS Multicenter Study

K.H. KONZ
Medical Clinic II – Franziskushaus, Maria Hilf Clinics, Mönchengladbach, Germany

S. HANSEN
Clinical Project Management, Biotronik, Berlin, Germany

On Behalf of the OPOSS Multicenter Study Group

Summary

Permanent atrial overdrive pacing aims at preventing or reducing the occurrence of atrial tachyarrhythmias. Dynamic overdrive algorithms, characterized by an atrial pacing rate that is slightly higher than the intrinsic sinus rate, reduce the familiar problems of a fixed overdrive stimulation with a high rate (overpace symptoms). First experiences gained in the clinical practice point to a rise in the efficacy of overdrive pacing for reducing atrial tachyarrhythmias when the rate increase (overdrive step size) is high. On the other hand, a general maximization of the overdrive step size could have negative effects on the quality of life, because fast heart rate increases might be poorly tolerated by the patients. The recently launched OPOSS multicenter study has the goal to show the preventive effect of the DDD$^+$ overdrive algorithm of the dual-chamber pacemakers Philos DR and D in reducing paroxysmal atrial tachyarrhythmias. Additionally, it aims at determining that overdrive step size out of the three step sizes that results in the most effective overdrive pacing in most patients (high percentage of atrial pacing with a low incidence and short duration of atrial tachyarrhythmias) while maintaining a high quality of life. This article describes and discusses the goals and methods of the OPOSS study.

Key Words

Atrial overdrive pacing, DDD$^+$ mode, overdrive step size, atrial tachyarrhythmia

Introduction

Atrial overdrive pacing aims at preventing or reducing the occurrence of atrial tachyarrhythmias such as atrial flutter, atrial fibrillation, sinus tachycardias, and premature atrial extrasystoles [1]. Prevention of atrial arrhythmias by overdrive stimulation of the intrinsic rhythm has been attempted for a long time: DDD pacing in combination with high basic rates of 90 beats/min led to a high percentage of atrial pacing and benefits in arrhythmia reduction [2]. However, not all patients were able to tolerate the high basic rates, and their quality of life generally suffered with these high basic rates [3]. Dynamic overdrive algorithms, characterized by an atrial pacing rate that is slightly higher than the intrinsic sinus rate, reduce the problems mentioned in connection with fixed-rate, high overdrive pacing. Furthermore, the percentage of atrial pacing achievable with dynamic overdrive pacing (> 90 %, depending on the algorithm) is higher than that in fixed-rate AAI or DDD pacing at 70 – 90 beats/min and in rate-adaptive pacing [4-10]. This is important because of the inverse relationship between the percentage of atrial pacing and the occurrence of atrial arrhythmias [11].

A prospective, randomized, multicenter study for Optimizing the Philos Overdrive Step Size (OPOSS) began in June 2001, with the aim to study the efficacy

of the atrial overdrive therapy in the Philos DR and D pacemakers (Biotronik, Germany) and to determine an optimal overdrive step size leading to the most effective overdrive stimulation (a high percentage of atrial pacing and the lowest incidence and shortest duration of paroxysmal atrial tachycardias), while maintaining a high quality of life.

Description of the Overdrive Algorithm

The timing concept of the overdrive mode is based on that of the DDD mode. However, if an intrinsic atrial rhythm is sensed, the pacemaker increases the pacing rate in programmable steps (overdrive step size), in order to overdrive the spontaneous rhythm. The overdrive step size determines the slew of the rate increase. The elevated rate lasts for a programmable number of intervals. After the plateau, the rate decreases decrementally either until a new atrial event is sensed or until it equals the programmed basic rate.
If the pacing rate reaches the programmable maximum overdrive rate, overdrive pacing is inhibited. It starts anew as soon as the spontaneous rate is below the maximum overdrive rate. In the Philos DR and D, the following parameters can be programmed in the overdrive mode:

- Overdrive modes: DDD$^+$, DDTA$^+$, DDTV$^+$, AAI$^+$, AAT$^+$;
- Overdrive step size: low, medium, high (2, 4, 6 beats/min). The step size is added to the last pacing rate. There is always a minimum of two senses before increasing the rate (recognition cycle and reprogramming cycle). Therefore the settings correspondes to a step size of 2, 4, 6 beats/min resulting in 4, 8, 12 beats/min rate increase, if two atrial events are sensed.
- Rate decrease after: 1...(1)...32 cycles by 1 beat/min;
- Maximum overdrive rate: 100...(10)...160 beats/min.

Rationale of the OPOSS Study

For patients with a pacemaker indication and a diagnosis of paroxysmal atrial tachyarrhythmias, which already have a Philos DR or D dual-chamber pacemaker implanted, the attending physician has the opportunity to activate preventive overdrive pacing for reducing tachycardic events. The default overdrive step size is medium. However, the choice of the overdrive step size presents a theoretical dilemma: on the one hand, based on the current state of scientific insight, it is assumed that the reduction of atrial tachyarrhythmias by atrial overdrive stimulation is more effective for higher percentage of atrial pacing [2,3,11]. On the other hand, the mean heart rate of the patient should not rise significantly, especially if the patient tolerates the fast rate increase poorly [2,3,8].
Figure 1 shows the result of a simulated increase of the sinus rate for the three possible overdrive step sizes in the Philos pacemaker. For this example, the heart simulator HSIM 20 (Biotronik) simulated an increase of the sinus rate from 75 – 85 beats/min with a rate increase of 1 beat/s. While, in this example, seven atrial sensed events (A_s) occurred before the next atrial pace when the overdrive step size was set to low, there were four A_s with the medium setting, and three A_s with high. According to this, a maximal percentage of atrial pacing would be best realized with the high overdrive step size.
On the other hand, the choice of the overdrive step size also influences the mean pacing rates: in this example, the new overdrive pacing rate after the last A_s increased by 14 beats/min when the setting was low (2 beats/min x 7 A_s); with the medium overdrive step size the increase was 16 beats/min (4 beats/min x 4 A_s) and in the high setting 18 beats/min (6 beats/min x 3 A_s).
This means that the lower percentage of atrial sensing events at a high overdrive step size is accompanied by a more pronounced increase in the heart rate when compared to the low and medium settings. This aspect can be of particular importance if a high number of cycles had been programmed when setting the rate decrease. This example illustrates that a desired maximization of the pacing percentage by means of the maximal overdrive step size may lead to an increase of the mean heart rate that is significantly higher than the sinus rate. This could possibly result in a decrease of the quality of life for the patient.
Therefore, the OPOSS multicenter study also has the goal of determining an optimal overdrive step size for most of the patients, aside from the general proof of efficacy of the overdrive DDD$^+$ modes.
Proof of efficacy of the overdrive function:

- Percentage of atrial pacing: DDD < DDD$^+$;
- Atrial tachyarrhythmias: DDD > DDD$^+$ (incidence and duration of the mode switching events);
- Quality of life (SF-36 score): DDD ≤ DDD$^+$.

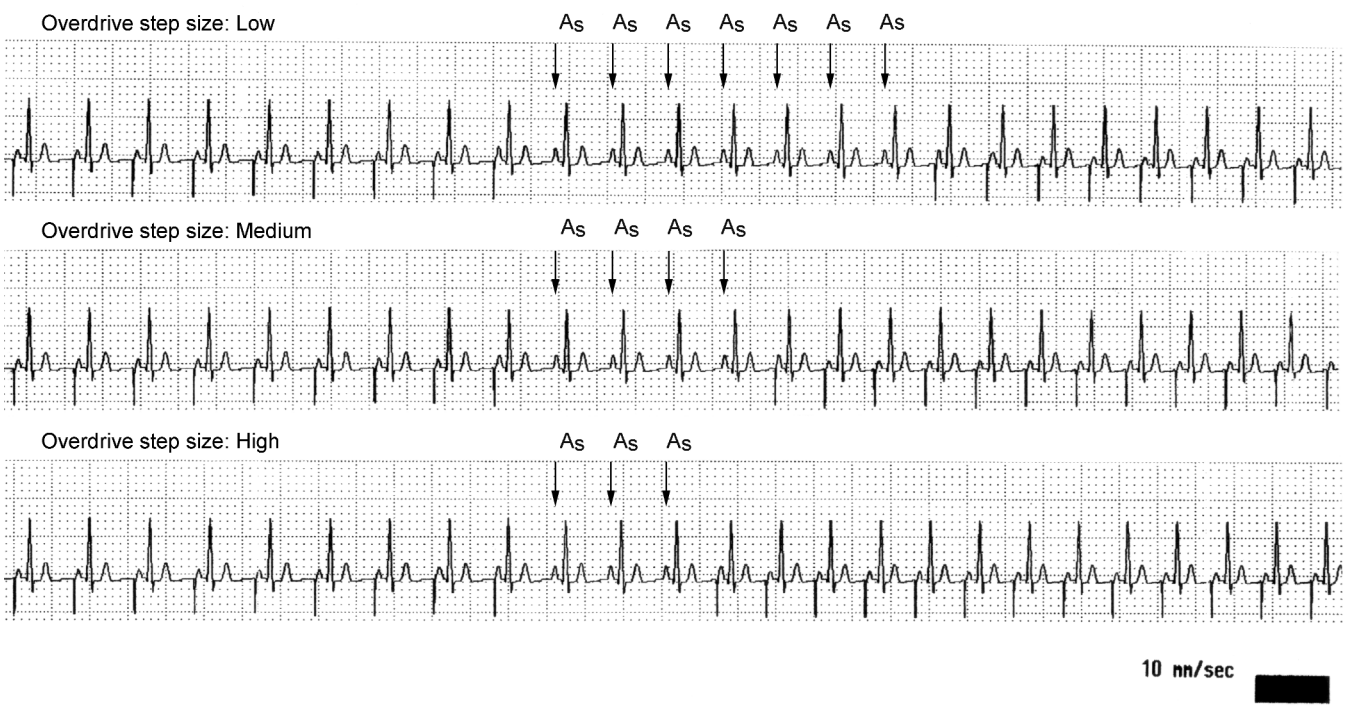

Figure 1. Simulation of an increase in the sinus rate with the three overdrive step sizes (low, medium, and high) available in the Philos pacemakers (Biotronik, Germany). The intracardiac electrograms (IEGM) are shown. The simulated sinus rate was in each case increased with a rate increase of 1 beat/s, from 75 beats/min to 85 beats/min. The atrial sense events (A_s) are marked by arrows. Pacemaker mode: DDD$^+$, maximum overdrive rate: 120 beats/min, rate decrease after 10 cycles.

Optimization of the overdrive step size: The optimal overdrive step size is the lowest of the three selectable settings (low, medium, high) that meet the following criteria significantly better compared to the others:

- High percentage of atrial pacing;
- Low incidence and duration of atrial tachy-arrhythmias;
- High quality of life (SF-36 score).

Materials and Methods

The OPOSS study is performed as a prospective, randomized, single blinded, multicenter study. A total of 80 patients are to be included into this study, and the duration of study participation will be nine months for each patient, starting from the implantation.

Aside from a pacemaker indication [12,13], patients who can be included into the OPOSS study must have a history of paroxysmal atrial tachyarrhythmias during the last three months prior to the implantation (electrographic or clinical diagnosis). They must be scheduled for implantation of a dual-chamber pacemaker of the type Philos DR or D, and they need a bipolar atrial lead with a tip-ring distance ≤ 15 mm. According to the physician's judgment, the patients should be principally able to tolerate all the settings prescribed in the study, and their medication must be stable no later than one month after the implantation and until the end of the study. Furthermore, only such patients are included who are able to grasp the character of the study, who have read and understood the patient information approved by the ethics commission, who have given their written consent to participate in the study, and who are able to keep the prescribed follow-up appointments. Minors and pregnant patients may not participate in the study. Other exclusion criteria are an uncontrolled angina pectoris, the existence of chronic atrial tachycardias, an ICD indication, symptomatic chronotropic incompetence, and unresolved atrial sensing problems (the latter applies from the implantation on).

The study design of the pilot study is schematically depicted in the flow chart shown in Figure 2. The

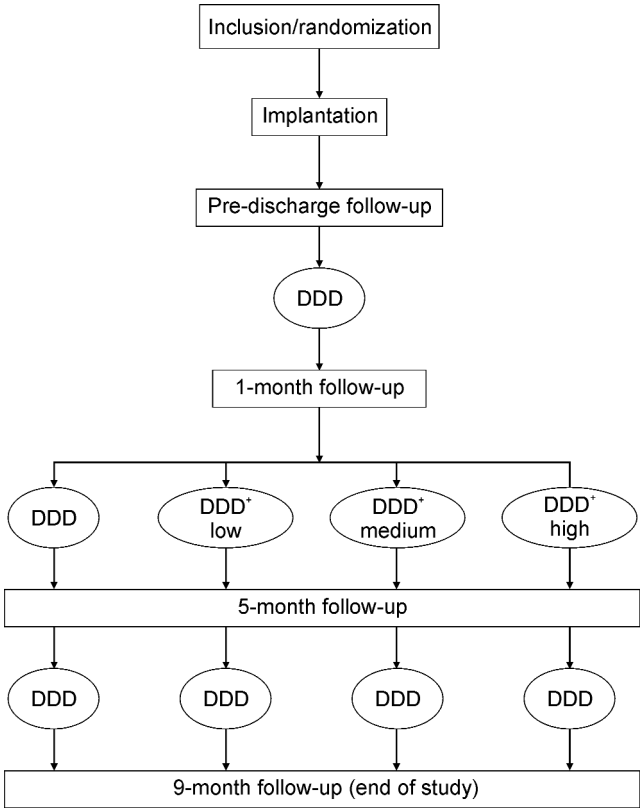

Figure 2. Flowchart of the OPOSS study.

patients are randomized into four groups (A, B, C, and D) as part of the inclusion phase and according to the principle of randomness (random list). The required pacemakers and leads are implanted according to the procedures established in the respective clinic. The period between the discharge follow-up and the 1-month follow-up serves as electrode grow-in phase (wash-in), during which the pacemakers of all patients are programmed to the DDD mode.

During the 1-month follow-up, the pacemakers of the patients are programmed to DDD mode (group A) or to DDD$^+$ mode (overdrive) with the overdrive step sizes low (group B), medium (group C), or high (group D). The four-armed inter-group comparison has mainly the purpose to minimize the influence of time-dependent factors. During the 5-month follow-up, the pacemakers of the patients in all groups are programmed to the DDD mode. The study period 5^{th} – 9^{th} month is used for the intra-group comparison between the data from the follow-up intervals 1^{st} – 5^{th} and 5^{th} – 9^{th} month to check for programming effects under consideration of individual influences. The study ends for the patients with the 9-month follow-up.

Besides the prescribed settings for programming the mode and the respective overdrive step size, the following settings are recommended: maximum overdrive rate = 120 beats/min (or adjusted to the intrinsic rate), rate decreases after ten cycles, mode switching = on (switching to DDIR), intervention rate = 160 beats/min, X-out-of-8 on-switch criterion = 5-out-of-8, Z-out-of-8 off-switch criterion = 8-out-of-8, far-field blanking chosen in such a way that far-field sensing can be excluded, basic rate = 60 beats/min, arrhythmia detection recording (ADR) to high atrial rate (serves to check for a correct desynchronization). The remaining pacemaker functions are programmed according to the individual needs of the patients.

During each follow-up, the diagnostic memory functions of the Philos DR or D are interrogated and printed out with the programmer (PMS 1000 or PMS 1000^{plus}, programming head PGH 1000 or PGH 3000, software module SWM 1000 version B-k00.V.A/2, all Biotronik). Data from the statistics memory that are relevant for this study are subsequently analyzed. The quality of life is recorded by means of the SF-36 Health Survey questionnaire (German-language version, Hogrefe Verlag, Göttingen, Germany, 1998), which is completed by the patients as part of the inclusion phase, the 5-month and the 9-month follow-ups. The items and scales of the SF-36 are calculated such that a higher value corresponds to a better state of health.

The primary objective is the percentage of atrial pacing in the period 1^{st} – 5^{th} month (parallel group comparison). The secondary objectives are the number and cumulative duration of the mode switching events (= measure for atrial tachyarrhythmias) in the period 1^{st} – 5^{th} month (parallel group comparison), the quality of life (sum scale of the SF-36) in the period 4 weeks before 5-month follow-up (parallel group comparison), and the intra-group differences in the parameters percentage of atrial pacing, number and cumulative duration of the mode switching events (1^{st} – 5^{th} month vs. 5^{th} – 9^{th} month, respectively), and quality of life (sum scale of the SF-36: inclusion phase vs. 5-month follow-up vs. 9-month follow-up). A multiple test strategy is used for the parallel group comparison. In the first test series, the three DDD$^+$ settings vs. DDD mode were tested (Wilcoxon test). The seven tests of the test series are evaluated by Closed-Testing-Principle (α = 5 %,

two-sided). If all Null-hypotheses are rejected, the trend in the three settings is tested (Jonckhere test, Wilcoxon test). The two tests are evaluated by Closed-Testing-Principle ($\alpha = 5$ %, two-sided). The secondary objectives are evaluated in a descriptive manner. The intra-group differences are statistically tested by means of the Wilcoxon matched pairs test.

Results and Discussion

So far seven patients have been included in the study. Since the pilot study was only started in June 2001, the available data are not yet sufficient to discuss first results in regard to the study goal. Therefore, a discussion at this early time must be limited to aspects of the method and the study goals.

A problem with the accurate detection and classification of atrial tachyarrhythmias that applies to all pacemaker models with overdrive function concerns the possibility of oversensing, especially by far-field R-wave (FFRW) sensing. To minimize the risk of FFRW sensing, only bipolar atrial leads with a tip-ring distance ≤ 15 mm should be implanted in the study patients. The implantation location should have the greatest distance from the septum as possible, e.g., in the auricle or in the lateral wall. The atrial sensitivity should be selected in such a manner that atrial fibrillation is reliably detected, but without sensing interference signals, such as FFRW sensing (control in the ECG/IEGM). If necessary, the far-field blanking period must be extended in a suitable manner. The atrial sensitivity is tested at implantation and during all study follow-ups.

The Short Form (SF) 36 Health Survey questionnaire was chosen for recording the quality of life in the context of the OPOSS study because it is a an internationally widely used, validated quality-of-life test [14], which has also been validated in its German-language version for several years [15] and has already been used several times for studying the quality of life in patients with atrial tachycardias [16,17]. The SF-36 and the shorter version SF-12 have also been used in various studies on atrial overdrive pacing for evaluating the quality of life [4,18].

As far as we know, the OPOSS study is so far the only study in connection with atrial overdrive pacing for the reduction of atrial tachyarrhythmias, in which the efficacy of special overdrive parameter settings is investigated. Most ongoing studies aim mainly at showing the general efficacy of overdrive algorithms to diminish the incidence and duration of atrial tachyarrhythmias. However, regarding a reduction of atrial tachyarrhythmias by atrial overdrive pacing, hardly any significant effects have been found so far, though it has to be considered that in most cases only preliminary results from a part of the experimental patient populations have been published [4,10].

The latest preliminary results of 41 patients with paroxysmal atrial fibrillation from a still ongoing overdrive study with the dual-chamber pacemaker Inos^2 CLS (Biotronik) have shown that:

- the mean pacing rate in the right atrium is for most patients significantly increased in the overdrive mode (DDD$^+$) compared to DDD mode (98 % vs. 62 %),
- the average time until the first occurrence of atrial fibrillation was increased in the DDD$^+$ mode (237 vs. 90 hours),
- the mean incidence and duration of atrial fibrillation were reduced in the DDD$^+$ mode (0.8 vs. 2.6 episodes/day and 1.3 vs. 1.6 hours/day, respectively), and that
- the DDD$^+$ mode was well tolerated by most patients (108 of a total 111 patients included in the study) [10].

The overdrive algorithm in the Philos DR or D functions is similar to the one in the Inos^2 CLS, though with one difference: in the Philos, the increase by the programmed overdrive step size takes place only after two sensed cycles of sinus rhythm (one recognition cycle and one reprogramming cycle). Therefore, the results from the Inos DDD$^+$ study cannot simply be applied to the Philos. Furthermore, the patients in the Inos study were not randomized according to overdrive step size, the optimization of which is a central goal of the OPOSS study.

For the optimal functioning of an overdrive algorithm to prevent atrial tachyarrhythmias, the pacing rate in the atrium should be slightly above the intrinsic sinus rate [10]. The percentage of atrial pacing should be higher than 90 % without causing a significant increase in the mean atrial rate, since a heart rate that is too fast could compromise the tolerance and quality of life of the patient [2,3]. A recently published prospective study on 626 patients showed a highly significant inverse relationship between the percentage of atrial pac-

ing and the occurrence of atrial arrhythmias [11]. An optimal setting of the overdrive step size in the Philos overdrive algorithm aims at achieving a percentage of atrial pacing that is as high as possible while at the same time increasing the rate as little as possible, thereby reducing the incidence and duration of paroxysmal atrial tachyarrhythmias to a therapeutically respectable magnitude and achieving a high quality of life for the patients. The OPOSS study shall determine such an optimal overdrive step size, which ideally applies to the majority of the potential patients, thus guaranteeing an optimal pacemaker operation for most patients already from the implantation on.

It is, however, still not clear whether a uniform optimal overdrive step size exists or whether different indications or atrial arrhythmia types might also call for different overdrive step sizes. Partially still continuing studies have investigated different overdrive algorithms of various pacemaker models. All results published so far have shown a tendency towards a decrease in atrial fibrillation with overdrive pacing [1,4,10, 18,19], with overdrive pacing apparently being very effective in a large part of the patient population, while its is less effective in other patients [10,19]. The clinical characteristics of the patients who respond to overdrive pacing (responders) are yet as little known as the answer to the question whether there are individualized overdrive algorithms or settings for the non-responders, which would allow effective overdrive pacing in these patients, too [10,19]. The results of the OPOSS study will have to show whether the problem responders/non-responders has any influence on the optimization of the overdrive step size in the Philos.

Conclusion

Atrial overdrive pacing can reduce the occurrence of paroxysmal atrial tachyarrhythmias. An effective overdrive algorithm should cause atrial pacing slightly above the intrinsic sinus rate, and according to the current state of scientific insight, the percentage of atrial pacing should be higher than 90 %, without significantly increasing the mean atrial rate.

The dual-chamber pacemakers Philos DR and D offer the option of an overdrive function (DDD$^+$ mode), which allows, among others, setting the slew of the pacing rate increase via the so-called overdrive step size with the three steps: low, medium, and high. In a total of 80 patients, a prospective, randomized, multicenter study to Opimize the Philos Overdrive Step Size (OPOSS), was started in June 2001. The study attempts to prove the efficacy of the Philos DDD$^+$ overdrive function in reduction of paroxysmal atrial tachycardias, as well as to determine an optimal overdrive step size leading to the most effective overdrive pacing in most of the patients (i.e., high percentage of atrial pacing, the lowest incidence and shortest duration of paroxysmal atrial tachycardias), while maintaining a high quality of life.

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Current Participants of the OPHIR Multicenter Study Group

Principal Investigator: K.-H. Konz (Mönchengladbach); Investigators: R. Cramer (Warstein); B.-D. Gonska, H. Baumann, M. Müller (Karlsruhe); G. Hoffmann (Landshut); M. Hubmann, T. Ruppert (Erlangen); Y. Kabel (Rothenburg/Fulda); W. Knobloch (Essen); M. Konermann, B. Rawert (Kassel); E. Meisel (Dresden); M. Novak (Prague); W. Rödiger, H. Nägele (Hamburg); F. Saborowski, H.W. Angenent (Cologne); K. Weindl (Landau).

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