First Clinical Experience with a Novel Three-Chamber Pacemaker for Biatrial, Atrioventricular Synchronous Pacing

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Summary

A novel three-chamber pacemaker for biatrial, atrioventricular synchronous pacing was implanted in 20 patients suffering from frequent atrial fibrillation episodes and interatrial conduction block (P-wave > 120 ms). Biatrial pacing significantly decreased the P-wave duration. When left atrial sensing was activated (biatrial triggered mode), a high number of left atrial extrasystoles was detected. By analyzing automatically stored IEGMs, it could be shown that in most cases left atrial extrasystoles preceded atrial fibrillation episodes. Patients with a large number of extrasystoles showed a higher number of mode switch episodes than patients with a low numbers of atrial extrasystoles. The novel pacemaker has been shown to be safe and reliable in routine clinical use.

Key Words

Atrial fibrillation, biatrial pacing, interatrial conduction, atrial resynchronization, atrial extrasystoles

Introduction

Atrial fibrillation (AF) is a widespread progressive cardiac arrhythmia found mainly in the elderly population that is responsible for a vast worsening of patients' quality of life and for an enormous socioeconomic burden. It has been shown that patients with persistent or permanent AF are responsible for much higher healthcare costs than patients with paroxysmal AF [1]. It is therefore desirable to stop or decelerate the progressive worsening of this disease in order to enhance patients' quality of life and reduce the socioeconomic burden. Although AF is primarily not life threatening, clinical studies have clearly shown that it increases mortality compared to patients who are free from AF [2]. Because AF is an extremely heterogeneous disease with multiple types of initiating triggers and substrates, special therapies have to be used to specifically treat individual patients [3]. Interatrial conduction disturbances that may arise from an electrophysiologic block of special fibers between the right and left atrium (Bachmann's bundle) [4] are known to promote the initiation and perpetuation of AF [5]. This kind of conduction disturbances leads to delayed left atrial (LA) activation that again affects cardiac function [6]. Evidence for interatrial conduction disorders can be shown by identifying a prolonged P-wave (> 120 ms) on the surface ECG. It has been shown that patients with prolonged P-waves have an increased risk of developing AF [7].

It is important that interatrial conduction disturbances as well as dispersion of atrial refractoriness and anisotropic conduction [8,9] constitute the substrate for arrhythmia perpetuation. The fact that right atrial (RA) pacing increases atrial conduction disturbances [10-12] and can aggravate arrhythmia in some patients inspired the development of bifocal (resynchronizing) atrial pacing modes, which additionally offered preexcitation of the low posterior part of right atrium [10-16]. Despite the fact that the concept of atrial resynchronization by means of biatrial (BiA) pacing came into being in 1991 [17], the number of BiA pacing system implantations have only started increasing significantly since 1997 [18-26]. Many authors presented similar results of its clinical effectiveness: very good antiarrhythmic effect in about 30% of patients; satisfying effects in another approximately 30% of patients; weak results in the remaining 40% of patients (lack of antiarrhythmic effect or/and technical problems with correct atrial resynchronization) [10,19-25]. Daubert, the father of the concept of atrial resynchronization (French pilot Study), and later Lublin's team, showed that patients' age, severity of atrial arrhythmia, and degree of atrial enlargement does not influence the effectiveness of BiA pacing [18,20,26]. We considered the role of predominance of the triggers located in the left LA [27] as the reason for poorer antiarrhythmic effectiveness of BiA pacing in some patients [10].

At the beginning of the BiA pacing concept development, the standard (J-shaped) leads, Y connectors, and standard pacers were used [17]. The risk of coronary sinus (CS) lead dislodgement and CS exit block were relatively high. Such pacing systems made atrial resynchronization possible only during pacing [17]. Later, the introduction of DDD pacemakers with a possibility of programming a triggered pacing mode in the atrial channel (Chorus, Ela Medical, USA) theoretically allowed atrial resynchronization during sinus rhythm and premature LA and RA premature beats in most patients [19]. R-wave far-field sensing, especially in the LA channel, and a relatively high (anodal) LA pacing threshold considerably limited that pacing system's effectiveness. However, in spite of numerous technical problems, the overall results were very promising [23]. In patients without atrioventricular (AV) conduction disturbances standard DDD or units adapted for BiA pacing (Logos DS, Biotronik) were used [10,21-26]. A LA lead was connected to the ventricular channel and the AV delay was programmed as short as possible (0 ms, 15 ms, or even 50 ms) and a DDD program was mandatory. This system guaranteed significantly better sensing and pacing conditions (RA and LA potentials were sensed in separate channels, in bipolar configuration) [10,21-26], and allowed resynchronization during sinus rhythm and premature RA but not premature LA beats. Despite some disadvantages, its antiarrhythmic effectiveness was described by Mirza et al as satisfying and promising [10,21-26]. In that pioneering era, no antiarrhythmic algorithms were available in standard pacemakers. Those primary experiences strongly indicated the necessity of developing new devices designed especially for BiA pacing, with a separately programmable LA channel, a possibility of right to left and left to right resynchronization (triggering), elimination of ventricular far-field sensing, and equipped with three AF preventive atrial pacing algorithms.

This paper describes the first clinical experience with a novel three-chamber pacemaker (Stratos LA, Biotronik, Germany) that was implanted in 20 patients with interatrial conduction block and a history of frequent episodes of paroxysmal or persistent AF.

Figure 1. Stratos LA pacemaker (Biotronik, Germany) for biatrial, atrioventricular synchronous pacing.

Materials and Methods

Pacemaker

The three-chamber Stratos LA pacemaker (generic code DDDRA, Figure 1) for BiA AV synchronous pacing was used to perform atrial resynchronization. In addition to synchronous BiA sensing and pacing, this novel pacemaker allows you to activate three AF preventive algorithms:

- *Overdrive Pacing* (DDD+) to maximize the percentage of atrial pacing;
- *Post-AES Pacing* to avoid short-long sequences after atrial extrasystoles (AES); and
- *Rate Fading* to avoid sudden rate drops in the atrium that might occur in some patients e.g., after exercise.

Besides these AF preventive algorithms, LA sensing allows the early detection of AES originating in the left atrium and the instant triggering of LA extrasystoles (LAES) to the opposite atrium. This leads to a more

Figure 2. Corox LA-H lead (Biotronik, Germany) for implantation in the coronary sinus to achieve reliable pacing and sensing properties in the left atrium. Two models with different tip-to-ring distances are available to treat different coronary sinus anatomies. A distal helix guarantees safe and flexible lead fixation in the coronary venous system.

homogeneous atrial depolarization and refractoriness and therefore should offer an AF preventive effect as well. More detailed information on the pacemaker properties has been described elsewhere [28].

Leads

In principle two different kinds of leads were used for LA sensing/pacing: either screw-in leads for fixation in the proximal part of the CS or a CS lead that was specially developed for the purpose of LA pacing (Corox LA, Biotronik). The Corox LA is available in two models: either a straight version (Corox LA) with two ring electrodes and a silicone thread for reliable atraumatic fixation, or a modified version with a distal helix (Corox LA-H, Figure 2) that allows a different kind of fixation within the CS.

Patients and Therapy Concept

In order to examine the safety and reliability of the new Stratos LA pacemaker, 20 patients were

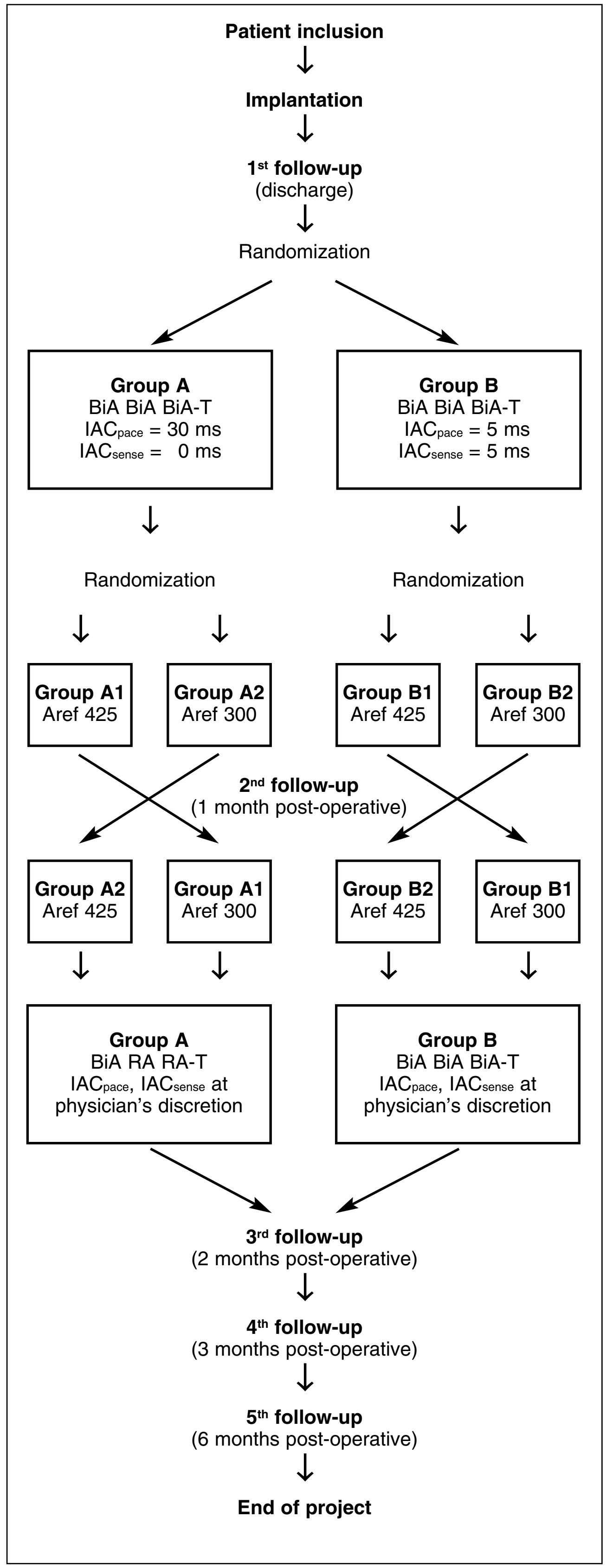

Figure 3. Flow chart of the study concept. IAC = interatrial conduction delay; Aref = atrial refractory period; BiA BiA BiA-T = biatrial pacing, sensing and triggering; BiA RA RA-T = biatrial pacing, right atrial sensing, triggering of right atrial senses to the left atrium.

implanted and observed for a period of 6 months post implantation (Figure 3). Within this period of time follow-ups were performed at patient discharge and 1, 2, 3, and 6 months postoperatively. Special examinations (24-h Holter monitoring, exercise test) were performed to verify correct pacemaker functioning in different situations. Changes of pacemaker programming allowed the inter- and intraindividual analysis of pacemaker behavior in various situations: different modes of atrial synchronization (only RA sensing and triggering into the left atrium or BiA sensing allowing BiA cross triggering), activation and deactivation of AF preventive algorithms, programming of different interatrial delays and refractory periods.
After all the patients completed the entire protocol, data were analyzed and subgroups of patients were compared to observe any potential distinctive features. A total of 20 patients (age 69.5 ± 9 years, 11 males) were implanted between August 2002 and March 2003. In 19 patients, the RA lead was implanted into the RA appendage, and one patient was implanted in the high right atrium. The position of the LA lead (distal electrode ring) was as follows: proximal CS in ten patients (50%), mid CS in seven patients (35%), and distal CS in three patients (15%). Seven patients received the Stratos LA as an exchange device due to end-of-life of their old pacemaker. These patients already had a BiA device implanted (mainly Logos DS) as well as a lead for LA pacing. Only the 13 patients who received their first pacemaker also received a CS lead at the time of Stratos implantation. Therefore, the lead data that are presented in this paper originate from the 13 patients who underwent their first pacemaker implantation.

Statistics
Descriptive analysis was performed by presenting minimum, median, and maximum or, for more than 10 metric data points, mean ± standard deviation. Statistical analysis of discrete data of two independent groups was performed using Wilcoxon's U test. For inter- and intraindividual comparison of more than 10 metric data points the two-sided t-test for paired samples or independent groups, respectively, was assumed to be reasonable. The p-values < 0.05, 0.01, 0.001 were considered statistically significant, very significant, and extremely significant, respectively.

Results

No serious adverse events occurred during the 6-month follow-up period.

Lead Data
At all follow-up examinations, the bipolar pacing threshold, bipolar sensing amplitude, and bipolar lead impedance were measured. The temporal progression of these lead parameters was compared for different positions within the CS (only for those 13 patients with a LA lead implanted during this study, Figure 4). Five leads were placed in the proximal CS, six in the mid CS, and only two in the distal CS (thus, median values will be discussed).

Proximal CS: The sensing amplitude decreased after implantation until 2 months. A peak of the pacing threshold occured at 1 month, accompanied by the largest variation of the lead impedance. However, the lead impedance increased until 3 months.

Mid CS: The lowest sensing amplitude occured at 2 months, whereas the pacing threshold was rather stable for the entire study period except a broad variation at 2 months. The lead impedance was stable as well.

Distal CS: Starting at the lowest value at implantation, the sensing amplitude and the lead impedance increased after 1 month and then decreased again. The pacing threshold increased continuously from implantation to the 6-month follow-up.

When all measured parameters for all patients during all follow-ups were averaged and compared for different locations (Figure 5), it became obvious that the best sensing amplitudes were achieved in the distal part of the CS (2.21 mV ± 1.84 mV), followed by the mid CS (1.97 ± 1.18 mV), and lastly the proximal CS (1.28 mV ± 0.88 mV). The best pacing thresholds were measured within the proximal part of the CS (1.52 ± 0.89 V) followed by the mid CS (2.51 ± 1.14 mV), while the distal part exhibited the highest threshold (3.41 ± 1.51 V). The impedance was maximal in the proximal CS (634 ± 84 Ω), followed by the mid part (541 ± 71 Ω) and the distal part (455 ± 80 Ω). Overall, this means that the mid part of the CS seems to be the part of the CS that offers the best compromise with respect to pacing and sensing behavior.

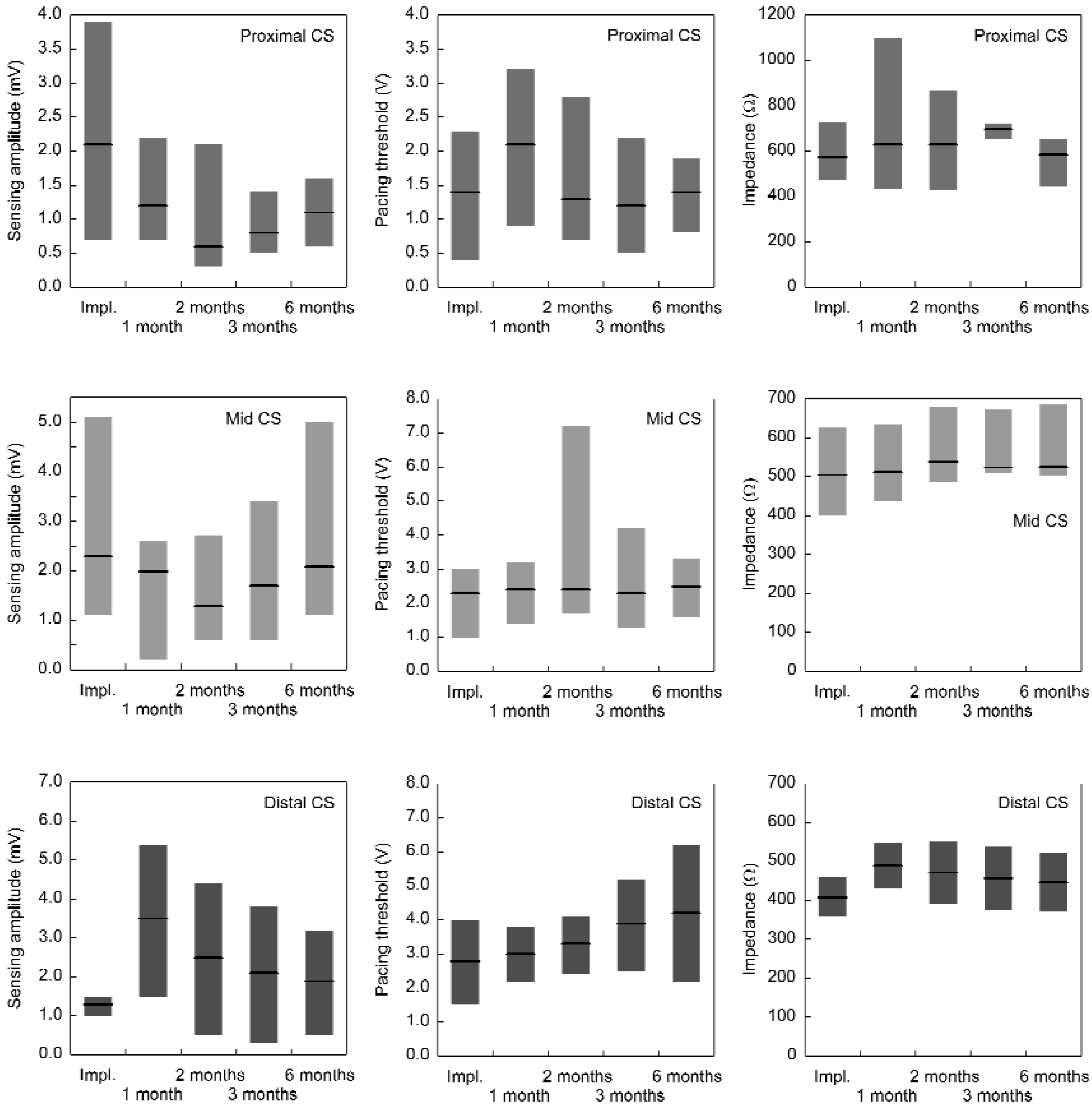

Figure 4. Pacing and sensing properties (minimum, median, and maximum) of the coronary sinus (CS) leads for the different locations (N = 5 proximal, N = 6 mid, N = 2 distal) within the CS and different follow-ups. Impl. = implantation. See text for further explanation.

Duration of the P-wave

BiA pacing is thought to be most beneficial with respect to AF prevention in patients with prolonged P-waves as an indicator of the presence of interatrial conduction disturbances. Therefore, only patients with a P-wave of at least 120 ms were included in the study. Preoperatively, a mean intrinsic P-wave duration of 153 ± 25 ms was measured, which was almost unchanged at 6 months (151 ± 31 ms). Due to this relative constancy of the intrinsic P-wave duration, no

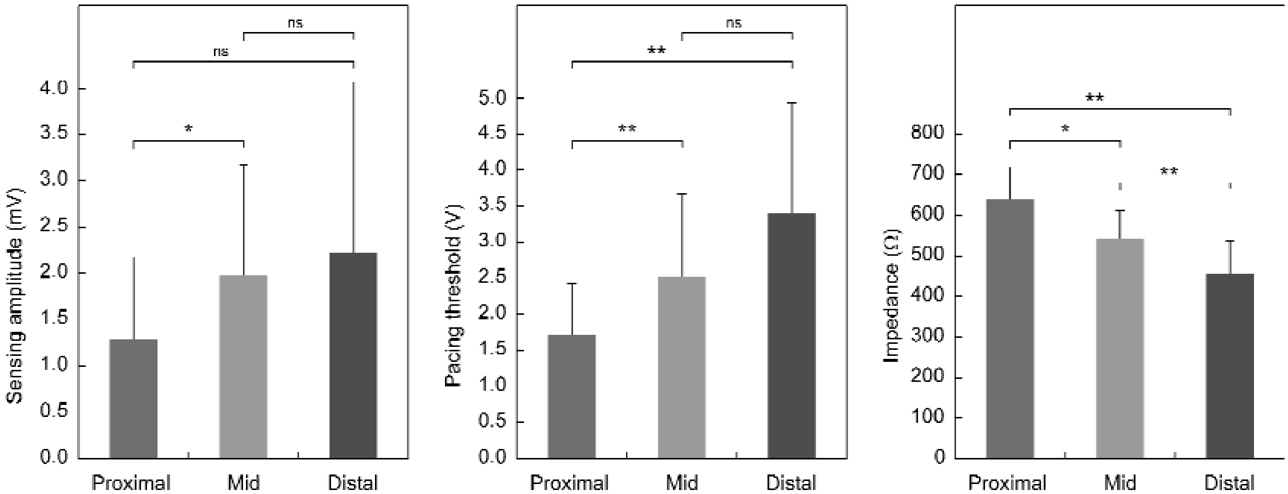

*Figure 5. Comparison of sensing/pacing parameters (mean ± standard deviation, averaged data of all patients from all follow-ups for each group) obtained in different positions within the coronary sinus. * = p < 0.05, ** = p < 0.01, ns = not significant.*

evidence of a structural remodeling process was seen that should have led to a shortening of the intrinsic P-wave. At all follow-ups, P-wave durations during intrinsic sinus rhythm and during RA, LA, and BiA pacing were measured. RA pacing even prolonged the P-wave from 193 ± 27 ms at implantation which decreased slowly to 181 ± 41 ms at 6 months. LA pacing did not change the P-wave duration significantly (152 ± 38 ms at implantation to 181 ± 41 ms at 6 months). In contrast to these effects, BiA pacing with a programmed interatrial delay of 0 ms shortened the P-wave down to 125 ± 32 ms at implantation and 130 ± 31 ms at 6 months. Intraindividual comparison showed very significant lower P-wave durations BiA pacing versus RA pacing in all follow-ups (Figure 6).

Atrial Extrasystoles (AES)

AES thought to be the most important trigger for the initiation of AF. It is known that mainly LAES are responsible for AF triggering [29]. Therefore, the occurrence of AES from the right and left atrium (as detected by the pacemaker) directly before onset of AF was determined. However, LA sensing is only possible when a BiA triggering mode (BiA BiA BiA-T) was programmed. Therefore, only data from 25 follow-ups originating from 10 patients were analyzed. The pacemakers detected a median of 75 RA extrasystoles (RAES) per patient per day and a median of 97 LAES per patient per day. In Figure 7 it is shown that patients with less than one mode switch (MS) event per day showed significantly less RAES and LAES than patients with more than one MS /day (median 15 MS/day):

- Median No. of RAES: 9 versus 1839 ($p < 0.001$) and
- Median No. of LAES: 56 versus 2850 ($p < 0.01$).

These data show that a high number of AES is associated with a high number of MS episodes. Therefore, active suppression of AES occurrences might also reduce number of AF episodes.

Extrasystoles Preceding AF Onset

Stratos LA is able to automatically record IEGM snapshots at the time of arrhythmia onset (or/and MS onset), including the last few seconds directly before the arrhythmia. Analysis of those snapshots allowed the quantification of RAES or LAES occurrences directly before AF began. Data from the last 3 months were included for this analysis, assuming optimization of pacemaker programming to be completed within the first 3 months. The number of 84 stored episodes from five patients were analyzed. In 77.4% of these cases, one or more LAES were detected, whereas in only 22.6% one or more RAES were detected that might have been responsible for triggering the AF episodes

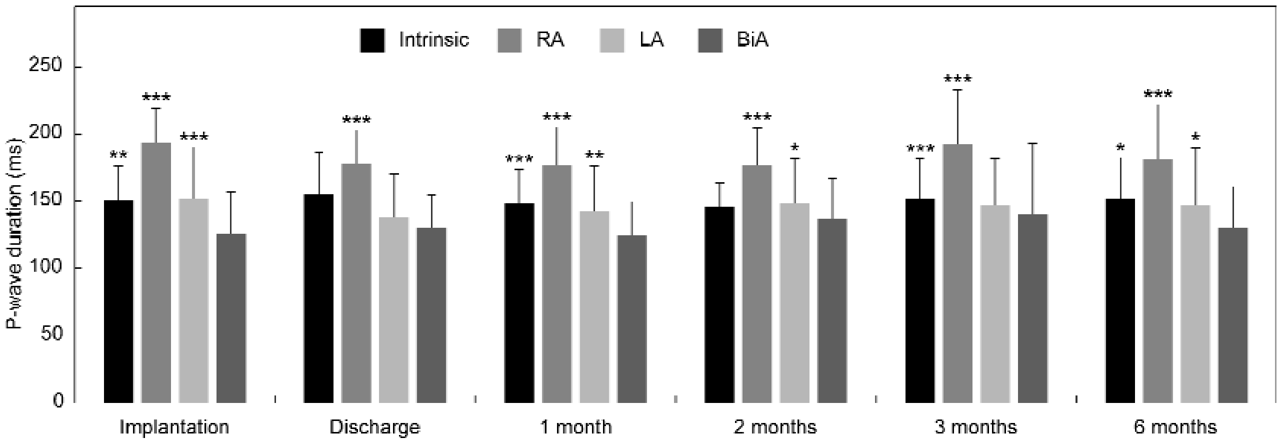

*Figure 6. P-wave duration (mean ± standard deviation) for different pacing modes and follow-ups. Note that only biatrial (BiA) pacing leads to a reduction of the broadened P-wave. Intraindividual statistical analysis of right atrial (RA), left atrial (LA), and intrinsic rhythm each versus BiA is presented. * = p < 0.05, ** = p < 0.01, *** = p < 0.001.*

(Figure 8). In summary, it can be stated that extrasystoles originating in the left atrium may strongly affect the initiation of atrial tachyarrhythmias. Therefore, fast triggering of LAES into the right atrium might provide a strong AF preventive effect. The simultaneous activation of AF preventive algorithms may even increase this beneficial effect.

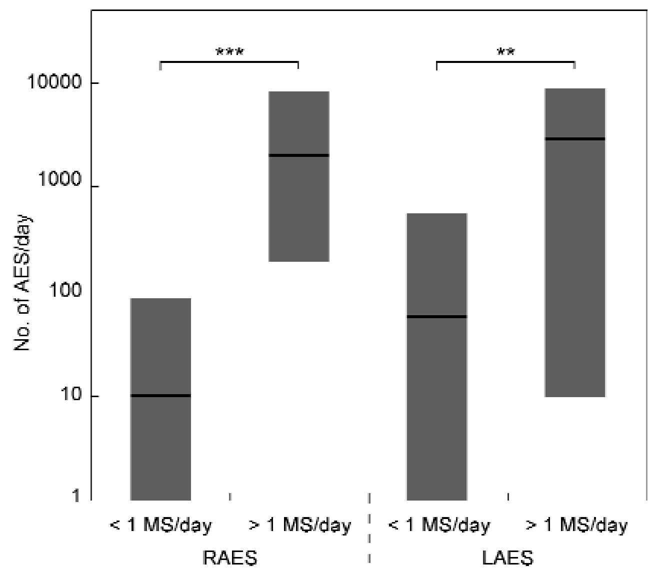

*Figure 7. Number of atrial extrasystoles (minimum, median, and maximum) on a logarithmic scale originating from the right (RAES) and left (LAES) atrium separated for patients with an average number of mode switches (MS) fewer than one per day and more than one per day. It is obvious that patients with low numbers of MS events also show a significantly lower number of RAES and LAES. ** = p < 0.01, *** = p < 0.001.*

Discussion

The therapy of AF must be adapted to patients' individual arrhythmia characteristics. Due to the heterogeneous nature of this atrial arrhythmia, several special therapies tried to eliminate the basis for AF initiation or perpetuation as suppression of premature atrial beats by three AF preventive algorithms, modification of the substrate by permanent Koch's triangle preexcitation and reconstruction of atrial synchrony during sinus rhythm, atrial pacing and premature right and left originating atrial contractions as well. BiA pacing is a special technique that aims to compensate conduction delay between right and left atrium [30, 31]. It is known that such conduction disorders build the electrophysiological basis for the perpetuation of AF that is triggered, for example, by AES. Therefore, the simultaneous pacing of both atria leads to more homogeneous depolarization and refractoriness and hampers the perpetuation of AF, which should consequently lead to a reduction of AF episodes. However, atrial resynchronization for the prevention of frequent AF by means of BiA pacing is not widely accepted. In the past, some clinical trials failed to show significant effects mainly due to technical limitations (i.e., no possibility of separate RA and LA pacing/sensing, no suit-

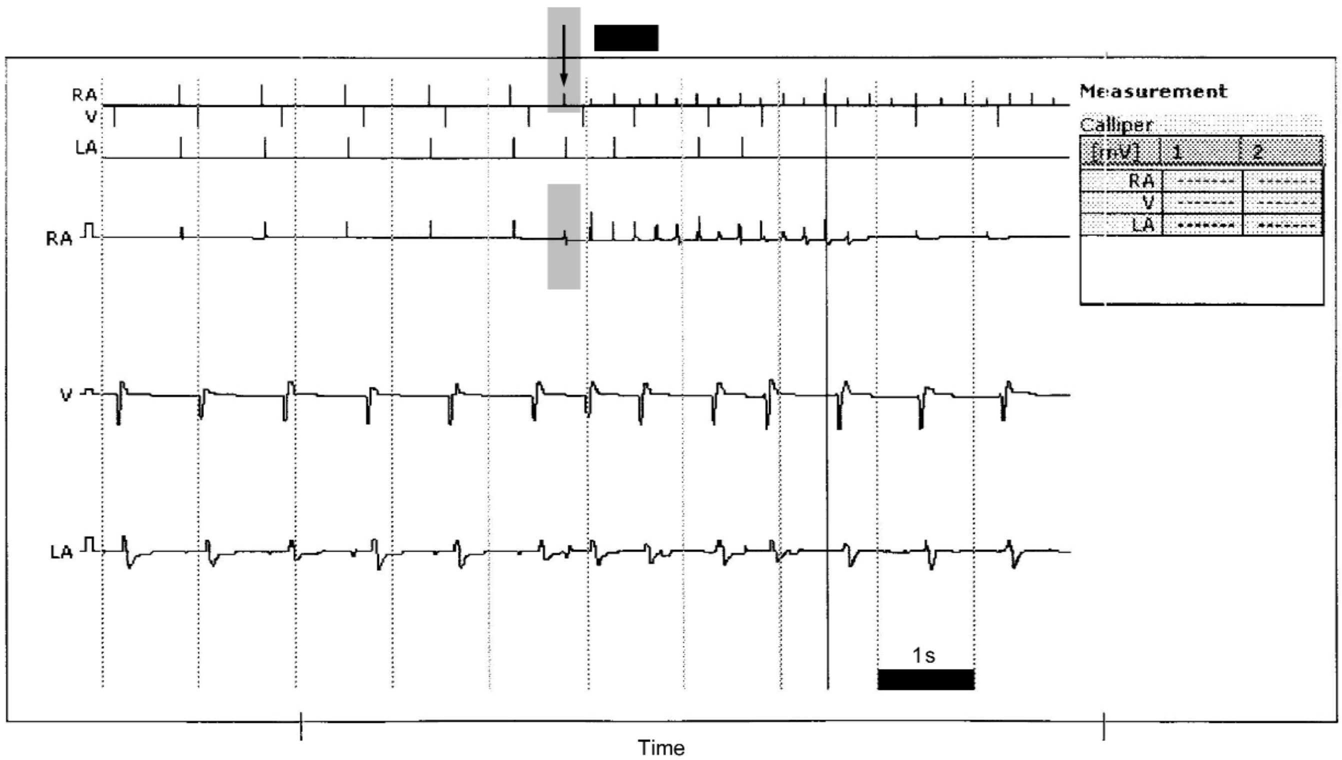

Figure 8. Example of an automatically stored IEGM during mode switch. The shadowed areas mark the onset of the atrial arrhythmia, starting with a right atrial extrasystole.

able CS leads). However, some trials clearly showed a therapeutic benefit, i.e., a reduction of AF episodes due to BiA pacing [25,32]. In light of contemporary knowledge about the (profitable) effects of coronary sinus and its ostium pacing [9,13,14] and about the key role of local conduction disturbances in the Koch's triangle region in the initiation and perpetuation of atrial arrhythmias [8,9,13-15], regarding BiA pacing system as only valuable for atrial resynchronization is an oversimplification. In 1996/97 Papageorgiou proved that CS pacing renders difficult AF induction by premature beats delivered from high right atrium (HRA) [9,11]. The presence of preference conduction permits earlier Koch's triangle activation during CS pacing than during HRA pacing [33]. It eliminates unfavorable effects of anisotropic conduction in the Koch's triangle region. Saksena's team confirmed that a similar effect reveals pacing in the CS ostium region. They showed that simultaneous HRA and CS ostium pacing prevents AF induction by prematurely paced HRA beats in 56% of patients, whereas AF was induced in 100% of patients during continuous HRA pacing [16]. The protective role of continuous CS pacing against HRA-induced AF was confirmed by Yu [14,15]. In 2001, Ogawa's team [12] confirmed easier induction of AF by a single premature beat delivered by the RA appendage (12/20) during RA appendage pacing than during BiA (7/20) and CS pacing (7/20). Differences of atrial recovery time (ACT + ERP) were smallest during CS pacing, similar during BiA pacing, and greater (less favorable) during RA appendage pacing. A reduction of the coupling interval during coronary sinus and BiA pacing results from different directions of paced rhythm and delivered premature beats [12].

It is known that AES originating from the left atrium play an important role in triggering AF [27,29]. Therefore, the separate LA sensing and instant triggering of detected LAES to the right atrium seems to be promising with respect to counteracting AF initiation. The novel Stratos LA is the first real three-chamber pacemaker for BiA AV synchronous pacing that allows separate programming of sensing and pacing parameters in both atria. Together with the specially adapted lead for LA pacing and sensing (Corox LA-H), a powerful system is available that still has to show its clinical benefit.

The data from this first, small clinical study using Stratos LA clearly showed its safety and reliability. However, the therapeutic effect of BiA pacing in combination with AF preventive algorithms has to be proven in larger, controlled clinical trials. The MISSION study (Multisite Stimulation and Overdrive Pacing for Prevention of Atrial Arrhythmias) that started in 2003 will hopefully obtain reliable data that allows an objective decision about the therapeutic power of this therapy.

Conclusion

Atrial resynchronization with the Stratos LA pacemaker is reliable and safe. No serious adverse events were observed within the 6-month follow-up period. In contrast to other pacing modes, only BiA pacing significantly reduced P-wave duration. Extrasystoles originating from the left atrium were frequent and in most cases preceded episodes of AF. Therefore, the necessity of LA sensing and pacing in patients with interatrial conduction disturbances appears to be helpful. The AF preventive effect of this therapy has to be proven in larger, controlled clinical trials.

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