



# Brady-tachy syndrome: Rapid atrial pacing efficacy in preventing atrial fibrillation recurrence assessed by reliable electrograms: the prefib pilot study

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## KEYWORDS

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**Abstract** **Aims** Recent studies have tested different atrial pacing rates, modes, and sites for preventing atrial fibrillation (AF) recurrence. Present generation pacemakers offer reliable electrograms (EGMs) storage for optimizing the arrhythmia diagnosis. Based on these EGMs, the study objective was to assess the rate of AF recurrence at two different pacing rates.

**Methods** Thirty patients suffering exclusively from symptomatic brady-tachy syndrome (BTS) resistant to  $\geq 2$  drugs, were implanted with a DDDR pacemaker. After a 5-days observation period, the DDD pacing rate was randomly programmed at 60 bpm ( $-15$  bpm hysteresis) or at 80 bpm for 12 weeks. The two sequences were crossed over at the end of this fixed period or when earlier symptomatic AF recurred. Antiarrhythmics were maintained. Stored EGMs of  $\geq 4$  s duration identified all AF recurrence.

**Results** Thirty patients (17 males,  $77.2 \pm 8.1$  years old) were included. One patient withdrew prematurely for severe heart failure associated with AF recurrence and rapid ventricular response. For the remainder of the 29 patients, fast atrial pacing neither provoked symptoms nor haemodynamic change. AF recurred in 16 patients paced at 60 ( $-15$ ) bpm (mean time: 29 days; range 1–61) and in 9 patients paced at 80 bpm (mean time: 55 days; range 5–83) ( $P < 0.05$ ). AF recurrence was asymptomatic in 50% of patients.

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**Conclusions** These results confirm that rapid atrial pacing is 1) significantly effective for preventing AF recurrence in symptomatic BTS patients, and 2) haemodynamically well tolerated.

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## Introduction

The incidence of atrial fibrillation, its haemodynamic and vascular complications associated with a decrease in the quality of life have shaped our therapeutic approach [1]. Moreover, in an ageing population the long-term use of antiarrhythmics and anticoagulation are responsible for deleterious side effects [2]. As a result, a more aggressive therapeutic approach has evolved over the last decade, comprising AF termination by an implanted atrial defibrillator [3], and AF prevention by bi-atrial resynchronisation [4], rapid atrial pacing [5–7], at multiple sites [8,9], with various pacing modes [5]. More recently, different algorithms favouring atrial overdrive have been proposed to prevent the occurrence and recurrence of premature atrial complexes [5,10–13]; in the immediate past, automatic electrophysiological pacing has been embodied in a very sophisticated device including the possibility of delivering manually a low energy internal DC shock [14]. Nevertheless, lone AF is not now a recommended indication for permanent atrial pacing [15]. Also, the optimal function of these diagnostic and therapeutic algorithms pre-suppose adequate detection of the endocardial signals. Some of the above systems relied only on mode switching counters and channel markers; even if these data have improved the function of devices, they have also misled physicians by their lack of diagnostic accuracy [16]. The latest generation of pacemakers offer the possibility to store high quality triggered EGMs allowing retrospective classification of stored arrhythmias.

The objective of this study was to re-assess the benefit of rapid atrial pacing on atrial fibrillation recurrence validated by reliable stored EGMs, in patients implanted exclusively for brady-tachy syndrome.

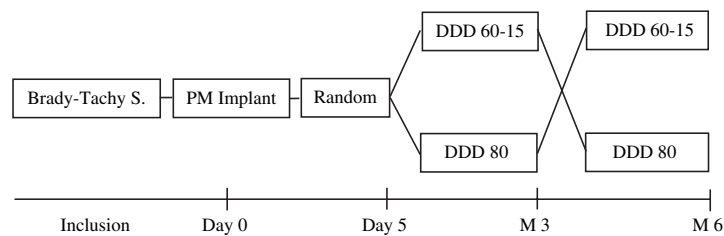
## Patients and methods

The study included 30 patients, 17 males, with a mean age of  $77.2 \pm 8.1$  years from December 1999 to December 2001. The inclusion criterion was

symptomatic brady-tachy syndrome resistant to at least two antiarrhythmics (class 1 indication for permanent pacing [15]). Brady-tachy syndrome is defined as an atrial arrhythmia formed by the alternation of various atrial tachycardias (fibrillation, focal, and flutter) with sinus bradycardia or sino-atrial block. In this very homogeneous study population, pacemaker implantation represented the final therapeutic option to prevent AF recurrence and to allow the use of classes 2 and 3 antiarrhythmics. As the main objective of this pilot study was prevention of AF recurrence by rapid atrial pacing exclusively in BTS patients, those with a symptomatic sinus pause alone, lone AF whatever the ventricular response, and AF proposed for “ablate and pace therapy” were not included. Patients were also excluded when there was unstable heart failure and ischaemic heart disease, coronary bypass surgery planned in the next 2 months, and co-existent diseases with a short or medium prognosis. The study has been approved by the local Ethical Committee and written consent was obtained in all patients. Twenty five patients had isolated brady-tachy syndrome and 5 had additional paroxysmal 2nd degree atrioventricular (AV) block. Structural heart disease was present at inclusion in 15 patients: hypertensive cardiopathy: 10 patients, and coronary artery disease: 5 patients (one with dilated cardiomyopathy and another with mitral regurgitation). Symptoms (isolated or combined) were palpitations in 19 patients, dizziness (10), heart failure (6), syncope (3), dyspnoea (2), others (2). With the exception of one who abandoned all antiarrhythmics, all patients were taking antiarrhythmics at the time of implantation, administered alone or in combination (amiodarone: 15, betablockers: 3, class 1C: 7, class 1A: 4, and digoxin: 4 patients). Despite optimal dosages, antiarrhythmics were unable to prevent AF recurrence.

Low impedance bipolar atrial leads with an inter-electrode distance of 11 mm (Vitatron, Crystalin®, Dieren, NL) were positioned in the right atrial appendage using passive fixation. All ventricular leads were low impedance, bipolar and steroid eluting leads (Medtronic 5092®, Minneapolis, MN, USA), and were positioned at the right ventricular apex. There were no lead dislodgements during follow-up.





**Figure 2** Study design.

call. At the end of the observation periods, the content of the pacemaker memory was printed out and device function was checked. Every stored event was analyzed by the physician and by an expert technician, checking the EGMs quality and accuracy, channel markers, muscle noise, over- and undersensing, mode switching counters and the documents forwarded by the remote Holter centre.

In case of recurrent AF of longer than two days duration (symptomatic or not), the patient was recommended for cardioversion, either by drugs or by external or internal DC shock. Sinus rhythm had to be restored before starting the second period of the trial. Antiarrhythmics and anticoagulants were continued as before the AF recurrence.

## Statistics

All data are reported as mean  $\pm$  standard deviation. The Student's *t*-test was used to compare mean atrial pacing percentage, mean number of ATR episodes, mean total time in AF, mean maximum time in AF, and mean minimum time in AF between the 60 bpm and the 80 bpm periods. Kaplan-Meier curves were drawn for the two comparative periods; logrank test was used to compare these two curves; statistical significance was  $P < 0.05$ .

## Results

### Main objectives

#### First endpoint

Rapid atrial pacing was shown to prevent AF recurrence longer than 4 s better than slow atrial pacing (Table 1, Fig. 3).

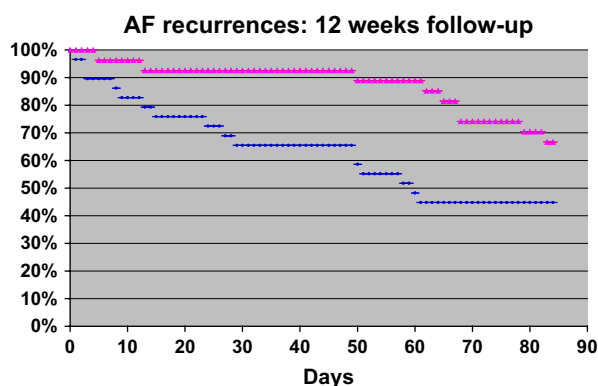
One pt withdrew prematurely because of severe heart failure precipitated by AF recurrence with rapid ventricular response (ischaemic heart disease; EF 35%) during her first observation period. In the remaining 29 patients, AF recurred in a total of 18 (62%), 16 paced at 60 (–15) bpm, after a mean time of 29 days (range 1–61), and in 9 paced at 80 bpm, after a mean time of 55 days (range 5–83) ( $P < 0.05$ ) (Fig. 3). AF recurred in both periods in 7 patients (24%).

The first episode of AF recurrence was diagnosed by the stored EGMs during regular follow-up in all 18 patients (100%). Besides the EGM storage, AF recurrence was concomitantly diagnosed by three patients themselves who called the physician immediately at the time of symptoms (17%), and by the remote Holter centre during the weekly systematic checks in five patients (28%) underlining the limited yield of this technique. AF recurrence was asymptomatic in 9 of the 18 patients (50%). Asymptomatic episodes were of variable duration but without fast ventricular

**Table 1** AF recurrence with the two pacing rates

Parameters	DDD 60 (–15)		DDD 80		Total	
	# episodes	# patients	# episodes	# patients	# episodes	# patients
AF recurrence	111	18	60	11	171	20
True positive	82	16	51	9	133	18
False positive						
(only 972 Pulsar)	16	2	2	1	18	2
Non-diagnostic (only 972 Pulsar)	13	4	7	2	20	6
Time to recurr.						
+ range (days)	29 (1–61)		55 (5–83)			

29 patients analyzed. See text for details.



**Figure 3** AF recurrence: 12 weeks follow-up. The number of patients (in %) with AF free survival is significantly lower with DDD 80 bpm pacing (exact logrank test:  $\chi^2 = 4248$ ,  $P < 0.05$ ).

rates, probably explaining the lack of symptoms. AF recurrence was converted to sinus rhythm by high dosage of oral amiodarone (30 mg/Kg) in three patients before the cross-over; direct current (DC) shock was not used.

### Second endpoint

**AF burden estimate.** The mean percentage of atrial pacing time was significantly higher in the fast pacing group (79.7 vs 27.7%,  $P < 0.001$ ) (Table 2a). These results remain statistically different ( $P = 0.003$ ) if only the seven patients who experienced AF recurrence in both pacing rates were considered (Table 2b). The parameters directly

reflecting the amount of time spent in AF (ATR parameters) were also remarkably better in the fast pacing period and are directly correlated with the mean atrial pacing time.

### EGM reliability

The main endpoint of that study was achieved by the quality of stored EGMs, by means of the pre-trigger onset recordings and the channel markers capabilities. All stored EGMs have been analyzed separately by two independent experts.

Atrial fibrillation and tachycardia episodes were correctly diagnosed in all 133 (100%) EGMs stored in the 1280 pacemaker model which provides the onset of the triggered arrhythmia. The other 38 episodes collected with the 972 pacemaker model were not appropriately classified, corresponding with *false positive* EGMs (crosstalk phenomena and myopotentials: 2 patients) and to *non-diagnostic* EGMs (sinus rhythm recovery: 6 patients) related to the absence of the arrhythmia onset capabilities (Table 1).

### Other results

In the Pulsar pacemaker models, simultaneous programming of the ATR and the atrial flutter algorithms leads to a potentially wrong classification of the diagnostic triggers.

Due to the principal objective of the study and the limited size of the memory, we did not turn on

**Table 2** a. AF Burden: total amount of time in atrial fibrillation in the two pacing periods

Pacing parameters	DDD 60 (–15) bpm		DDD 80 bpm		<i>P</i>
		No. patients		No. patients	
Mean % atrial pacing	27.7 ± 32.6	28	79.7 ± 21.3	27	$P < 0.001$
Mean % ventric. pacing	81.7 ± 26.1	28	93.7 ± 12.1	27	$P = 0.03$
No. of ATR	831.8 ± 2404	28	534.7 ± 1392	27	NS
Total time in ATR (%)	8.2 ± 14.8	9	0.4 ± 1.0	9	NS
Max time in ATR (min)	295 ± 660	9	53.7 ± 97.5	9	NS
Min time in ATR (min)	12.3 ± 22.8	9	1.4 ± 1.9	9	NS

In DDD 80 bpm, the atria are significantly more often paced. Even if not statistically significant, the number of AF episodes and the total time spent in AF are clearly lower than with DDD 60 bpm pacing. ATR: atrial tachycardia response.

b. AF Burden: same table as Table 2a but considering only the seven patients with AF recurrence in both periods

Mean % atrial pacing	8.3 ± 7.4	7	63.1 ± 28.8	7	$P = 0.003$
Mean % ventric. pacing	79.8 ± 26.3	7	91.4 ± 8.8	7	NS
No. of ATR	2719 ± 4765	7	575 ± 691	7	NS
Total time in ATR (%)	24 ± 24	2	0.0 ± 0.0	2	NS
Max time in ATR (min)	1110 ± 1281	2	10.9 ± 14.6	2	NS
Min time in ATR (min)	25.8 ± 32.1	2	1.0 ± 0.6	2	NS

the ventricular tachycardia and supraventricular tachycardia algorithms in the observation periods. Consequently, retrograde conduction and the incidence of other tachycardias were not assessed.

## Discussion

### Main findings

The main findings from this study are that rapid atrial pacing (80 bpm), delivered at the right atrial appendage, appears to be more advantageous than slow pacing from the same site in preventing recurrence of atrial fibrillation and in reducing AF burden. These findings are validated by accurate intracardiac EGMs, allowing discrimination of true atrial EGMs from myopotentials and ventricular far-field signals.

### Previous studies

#### EGMs storage and reliability

Up to the late 1990's, clinical daily practice showed the limited diagnostic appropriateness of any standard mode switching system when not controlled by EGM recordings. Recent studies have shown the usefulness of reliable EGM information especially when event onset and marker annotations are available to improve diagnosis of arrhythmias [17]. Endocardial signal filtering represents a critical point of this system where myopotentials may be superimposed on sinus rhythm but are distinguishable from atrial fibrillation.

In the present study, 100% of the signals recorded by the Pulsar 1280 model were appropriately classified. Two patients with the Pulsar 972 model provided 38 endocardial samples (representing 22% of all recorded EGMs) incorrectly classified. So, adding the trigger onset and the channel marker functions seems to be essential for improving the diagnostic capabilities of the pacemaker. The lack of EGMs allowing verification of mode switching counters weakens the diagnostic value of previously reported results.

#### Atrial overdrive

Pacing modes and atrial pacing rates have been investigated over a long period [17]. Different overdrive techniques have been proposed: the atria may be paced fast, either at a predefined rate or at a calculated fixed rate above the average sinus rate [6,7,12,18]. In 1998, the AIDA report suggested that overdrive pacing may be antiarrhythmic [19]. All available studies showed

that, up to 80 bpm, fast DDD pacing is clinically well tolerated and provides a real decrease in AF recurrence, in their total and maximum duration [6], but similar results were not found with DDD-R pacing [18]. Again, all these studies based their approach on events counters, and not on EGM recordings; moreover, patients with possible myopotential oversensing, ventricular cross-talk, atrial undersensing, and endless loop tachycardia possibly interfering with data collection were excluded [6].

By using EGMs analysis, this limited pilot study only including brady-tachy syndrome patients in an elderly population fast atrial pacing has been shown to decrease significantly true AF recurrence. Also, we found that myopotentials and crosstalk episodes were equivalent in both pacing periods. Finally, the AV delay had been systematically prolonged by 40 msec over the spontaneous P-R interval in order, as far as possible, to prevent potential left ventricular dysfunction.

#### Symptoms related to fast atrial pacing

From EGMs or simple markers, more than 50% of AF appears to be asymptomatic [6,7,18], moreover, patients complain of rate irregularity or palpitations which are not confirmed by intra-atrial recordings. More surprisingly, it has also been reported that AF was confirmed by concomitant Holter recording in only 8% of patients convinced that they were suffering from genuine AF recurrence [22]. Our study showed an absence of symptoms in 50% of AF recurrence: reliable EGMs might decrease the number of false negative (asymptomatic) patients in future studies.

### Limitations

#### Atrial pacing site

As there is no definitive consensus about the optimal pacing site(s) in the right atrium, we did not try to test different pacing sites either solely in the right atrium or by combining right and left atrial sites using the coronary sinus [23]. If the low interatrial septal and the Bachmann bundle area seem to be more effective than the right atrial appendage simultaneously to depolarize both atria, validation and routine application of these techniques remains under evaluation [20,21].

#### Study follow-up

The 6 month observation period may appear to be too short even in such a homogeneous cohort of stable brady-tachy syndrome patients with a high AF burden. A larger study designed with longer

comparative periods and quality of life (QoL) assessments would probably provide more details about the circumstances of AF recurrence, the protective effect of pacemaker implantation, the association with other arrhythmias, the impact of different antiarrhythmics and their relationship with the underlying cardiac disease.

The design of this preliminary study did not cover the evaluation of specific AF prevention algorithms. These algorithms could be tested in a larger prospective multicentre study.

With the exception of one patient in New York Heart Association class 3 who developed heart failure during an AF recurrence with fast ventricular response when programmed on DDD 80 bpm, none of the others complained of side effects due to 80 bpm atrial pacing.

The external loop recorder was underused in this study but its limited diagnostic yield would not suggest systematic use in larger studies.

## Conclusions

The results of this study concerning patients suffering from brady-tachy syndrome show that atrial pacing at 80 bpm significantly decreased the rate of AF recurrence and is haemodynamically well tolerated, over a 3-month period. Larger studies in this patient population should assess QoL associated with fast atrial pacing and the use of AF prevention algorithms.

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