

Prospective, randomized study of atrioventricular ablation and mode-switching, dual chamber pacemaker implantation versus medical therapy in drug-resistant paroxysmal atrial fibrillation

The PAF study

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We performed a prospective randomized 6-month evaluation of the clinical effects of atrioventricular junctional ablation together with placement of a DDDR mode-switching pacemaker vs pharmacological treatment in 43 patients with intolerable paroxysmal atrial fibrillation not controlled with antiarrhythmic drugs. Ablation and pacemaker treatment were highly effective and superior to drug therapy in controlling symptoms and improving quality of

life. However, discontinuation of drug therapy exposed patients to further recurrences of paroxysmal atrial fibrillation and the risk of developing permanent atrial fibrillation. (Europace 1999; 1: 15–19)

Key Words: Atrial fibrillation, catheter ablation pacemaker, mode-switching.

Potential candidates for ablate and pace treatment

Atrial fibrillation (AF) is by far the most frequent arrhythmia. It occurs in 1.6% to 2% of the general population and is particularly frequent in the elderly, in males and in patients with heart disease. Its prevalence is 9.1% in men and women with cardiovascular disease over 65 years of age^[1,2]. Given this high incidence, even if catheter ablation therapy were prescribed for a minority of drug-refractory patients^[3], the total number of potential candidates for this treatment would be very high. For example, we have calculated that in Europe about 396 000 patients (216 000 over 65 years) are affected by intolerable paroxysmal atrial fibrillation (Fig. 1).

The PAF study in brief

While a few, small, uncontrolled studies^[4–7] have put forward the beneficial effects of atrioventricular (AV) junctional ablation in patients with symptomatic paroxysmal AF, these did not include a control group of patients with similar arrhythmias treated without catheter ablation. The main aim of the Paroxysmal Atrial Fibrillation study (PAF study) was to compare atrioventricular junctional ablation and implantation of a DDDR mode-switching pacemaker (Diamond, Vitatron) (Abl&Pm) with pharmacological therapy (Drugs) in regard to quality of life and control of specific symptoms in patients affected by severely symptomatic paroxysmal AF not controlled by pharmacological therapy.

Methods

We performed a multicentre randomized 6-month evaluation of the clinical effects of Abl&Pm vs

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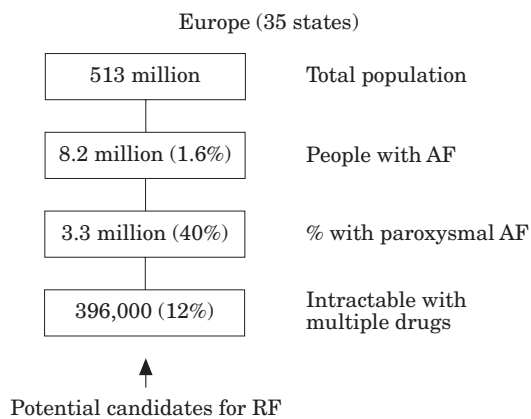


Figure 1 Ablate and pace for paroxysmal atrial fibrillation.

pharmacological treatment in 43 patients with intolerable, recurrent paroxysmal AF (≥ 3 episodes/last 6 months), not controlled with ≥ 3 antiarrhythmic drugs. Before completion of the study, three patients in the Drug group were withdrawn because of the severity of their symptoms and one patient assigned to the Abl&Pm group in whom the ablation procedure failed. The primary end-point was the evaluation of quality of life and specific symptoms during the 6th month after randomization. Secondary end-points were (1) inpatient comparison of quality of life and specific symptoms between enrolment and month 6; and, (2) major clinical events occurring during the 6-month study period, i.e. complications of the treatment, development of permanent AF, number of hospitalizations and/or electrical cardioversions. A comprehensive evaluation of the patient's quality of life was made using the Minnesota Living with Heart Failure Questionnaire^[8]

(LHFQ) and The Specific Symptoms Scale, developed as a disease-specific instrument to measure the patient's perception of the frequency and severity of arrhythmia-related symptoms^[9]. On enrolment, the patients assigned to the Drug arm were treated with the anti-arrhythmic drug regimen which had shown the best efficacy during history. The patients assigned to the Abl&Pm arm had their anti-arrhythmic drugs discontinued at the time of enrolment.

Main results of PAF study

At the end of the 6-month study period, the Abl&Pm group had significantly lower scores in LHFQ (-53%), palpitations (-71%), effort dyspnoea (-36%), exercise intolerance (-46%) and easy fatigue (-51%) in comparison with those in the Drug group (Table 1). The inpatient comparisons between enrolment and month 6 are shown in Table 1. In the Abl&Pm group, all variables decreased significantly, except for chest discomfort; in the Drug group, only palpitation scores decreased significantly. Clinical events occurring during the study period are reported in Table 2. Both the documented episodes of AF and the number of patients with permanent AF were higher in the Abl&Pm group. By contrast, the subjective perception of atrial tachyarrhythmias and the number of hospitalizations or electrical cardioversions were higher in the Drug group.

What have we learnt from the PAF study

To date, no non-pharmacological treatment for paroxysmal AF has been evaluated against a control group of

Table 1 Results of quality of life measurements

Symptoms (score)	Enrolment		P	Month 6				Difference Enrolment/month 6*			
	Abl&Pm n=22	Drugs n=21		Abl&Pm n=21	Drugs n=18	P	% reduction	Abl&Pm		Drugs	
								%	P	%	P
LHFQ questionnaire	50 ± 16	50 ± 19	1	20 ± 16	43 ± 22	·0006	-53%	-59%	·0000	-16%	·12
Specific Symptoms Scale											
Palpitations	7·5 ± 2·1	7·2 ± 2·5	·67	1·5 ± 2·4	5·1 ± 2·0	·0000	-71%	-75%	·0000	-31%	·005
Effort dyspnoea	5·8 ± 3·9	6·7 ± 2·4	·36	3·7 ± 3·0	5·8 ± 3·0	·04	-36%	-35%	·04	-15%	·21
Rest dyspnoea	3·8 ± 3·5	2·0 ± 2·5	·05	0·8 ± 1·4	1·8 ± 2·6	·13	-56%	-79%	·0003	-22%	·56
Exercise intolerance	7·0 ± 2·9	6·5 ± 2·6	·56	3·7 ± 3·0	6·8 ± 2·5	·001	-46%	-46%	·004	+8%	·33
Easy fatigue	4·6 ± 3·6	3·8 ± 3·3	·46	2·1 ± 2·5	4·3 ± 2·9	·02	-51%	-55%	·006	-2%	·84
Chest discomfort	1·8 ± 3·0	1·2 ± 1·6	·41	0·5 ± 1·5	1·0 ± 2·4	·42	-50%	-72%	·10	-17%	·78
NYHA class	2·9 ± 0·7	2·7 ± 0·7	·35	1·9 ± 0·7	2·3 ± 0·8	·08	-17%	-34%	·0002	-12%	·10

*The inpatient difference between enrolment and month 6 was calculated for the 21 patients of the Abl&Pm group and the 18 patients of the Drug group who completed the study period (paired t test). Values are mean ± SD; Abl&Pm=AV junction ablation and DDDR automatic mode-switching pacemaker.

Table 2 Clinical events during the 6-month study period (as derived from monthly visits)

Event	Abl&Pm n=21	Drugs n=18	P
Atrial fibrillation at the time of monthly visit			
Total number of visits	122*	107*	
Visit 1	3	3	
Visit 2	5	1	
Visit 3	5	1	
Visit 4	4	1	
Visit 5	7	2	
Visit 6	7	1	
Overall	31 (25)	9 (8)	·0005
Permanent atrial fibrillation at the end of the study	5 (24)	0 (0)	·04
Subjective perception of atrial tachyarrhythmia			
Visit 1	11 (52)	15 (83)	·04
Visit 2	8 (38)	14 (78)	·01
Visit 3	9 (43)	17 (94)	·0003
Visit 4	5 (24)	14 (78)	·001
Visit 5	7 (33)	15 (83)	·002
Visit 6	4 (19)	16 (89)	·0000
Hospitalization or electrical cardioversion, n	1 (5)	6 (33)	·03

Numbers indicated in parentheses are percentages. Abl&Pm=AV junction ablation and DDDR automatic mode-switching pacemaker.

*Data unavailable in 4 and 1 pts respectively.

medically-treated patients. We enrolled a small, severely symptomatic population. Apart from palpitations, patients had many symptoms which usually are encountered in patients with heart failure, as shown by the high scores recorded in both LHFQ and Specific Symptoms. The mean LHFQ score before ablation was higher than the 38–48 score registered by patients with heart failure refractory to conventional therapy who were undergoing studies on the effects of new pharmacological agents^[8].

Main results

The main result of this study is that, in a small population of patients affected by severely symptomatic paroxysmal AF not controlled by pharmacological therapy, Abl&Pm treatment is highly effective and superior to drug therapy in controlling symptoms and improving quality of life during the following 6 months. After ablation, the mean improvement varied from 36% to 71% according to the indexed parameter, and the LHFQ score approached that of asymptomatic subjects^[8]. Palpitations, the most specific symptom of paroxysmal AF, was virtually abolished in 81% of patients at the end of the 6-month study period. Although arrhythmia is paroxysmal, patients are expected to report great improvements in general, physical, emotional and social indexes of their health-related quality of life and not only in arrhythmia-specific parameters. However, the discontinuation of drug therapy exposes patients to further recurrences of paroxysmal AF and the risk of developing permanent AF, although these events do not have a negative impact on short-term outcome. Ablation and

pacings treatment is relatively simple to perform and elicits no complications.

Use of drugs

The use of anti-arrhythmic drugs has been demonstrated to significantly increase the probability of maintaining sinus rhythm. In several comparative trials, in which a no drug or placebo regimen was compared with active drug therapy after cardioversion for AF, the use of quinidine, disopyramide, flecainide, or amiodarone increased the proportion of patients remaining in sinus rhythm. Sotalol and propafenone have been found to have efficacy comparable to that of quinidine. Several studies have suggested that amiodarone may be effective where other agents have failed. Crijns *et al.*^[3] and Antman *et al.*^[10] have suggested that the sequential use of flecainide, quinidine, propafenone, sotalol and amiodarone, when one has failed to maintain sinus rhythm, increases the proportion of patients successfully treated. In the present study, patients were treated in a similar manner; the results suggest that sequential anti-arrhythmic drug therapy was superior to no drug treatment in preventing recurrence of paroxysmal AF and the development of permanent AF, even in a selected population with very severe AF which had been considered to be resistant to multiple pharmacological treatments. On 6-month inpatient comparison, the Drug group, showed a significant improvement in palpitation score and a trend towards improvement in other symptoms (Table 2). The final effect of anti-arrhythmic drugs on outcome probably depends on the sum of various

factors, including better control of arrhythmic recurrence, more thorough examination during the study than before, high motivation by the patients to have their disease treated, the negative impact (as perceived by the patient) of anti-arrhythmic drugs on quality of life and the potential toxicity and side effects of the drugs. The study was not designed to investigate whether the better outcome observed in the Abl&Pm group was due to the beneficial effect of the non-pharmacological treatment per se or also to the discontinuation of the anti-arrhythmic drugs.

Which mode of pacing?

The pacing modalities after ablation are likely to have influenced the clinical outcome. In the literature, various pacing modes (VVI, VVIR, DDD, DDDR), algorithms of recognition of atrial tachyarrhythmias, and modes of switching have been proposed. This study was not designed to compare different devices or different modalities of pacing; therefore, the results do not necessarily apply to other pacing modes and algorithms. In patients with paroxysmal AF, AV junctional ablation creates an iatrogenic effect rarely found in patients without ablation, namely the presence, at one and the same time, of total AV block and paroxysmal atrial tachyarrhythmias. We preferred DDDR to the VVIR and DDD modes, since it theoretically restores AV synchrony during sinus rhythm, prevents the development of atrial fibrillation and provides adequate ventricular rate increase during physical activity in the presence of atrial tachyarrhythmias. To overcome ventricular tracking of rapid atrial activity, various mode-switching algorithms have been developed which are able to change pacing modality automatically from an AV synchronous mode during sinus rhythm to a non-AV synchronous mode during AF. For this purpose, the pacemakers must have an algorithm able to identify pathological atrial arrhythmias and to differentiate them from physiological variations in rate. The fast mode-switching devices have been reported to be more effective than the medium and slow mode-switching devices^[11]. We preferred a fast mode-switching system, which is able to identify pathological atrial rhythms on a beat-to-beat change in atrial rate. In an acute study^[12], this system proved to be able to lower the percentage of abnormal ventricular tracked beats during AF to $\leq 4\%$ of total ventricular beats.

Future perspectives

At present, in patients in whom drugs are unable to maintain stable sinus rhythm, control of a rapid heart rate, ablation and pacemaker treatment can be proposed as the preferable mode of treatment. Since the recurrence of AF (both paroxysmal and permanent) in patients off drugs is high, one could infer that the results

of ablation and pacemaker treatment may be improved by adding pharmacological therapy or by developing more sophisticated pacing modalities able to reduce the recurrence rate of AF. Whether this approach is cost-effective remains to be demonstrated. New non-pharmacological approaches to the prevention of AF, including surgery and endocardial catheter ablation, atrial pacing or implantable atrial defibrillators, or control of rapid ventricular rate by means of AV junction modulation are encouraging, but too few data are available and their recommendation for use awaits results from clinical trials. Their efficacy should probably be compared with the definitively proven treatment, namely Abl&Pm. Several unresolved issues remain regarding the efficacy and safety of Abl&Pm treatment in the long-term.

The first concerns the long-term effect of the haemodynamic modifications caused by asynchronous ventricular activation as a result of right ventricular apex stimulation and the loss of AV synchrony in the cases in which chronic AF develops. Although some data indicate no increased risk of death or complications during long-term follow-up^[13], and cardiac performance has proved unchanged or improved during an intermediate follow-up, especially in those patients with pre-ablation left ventricle dysfunction, too few data are available on the long-term outcome of these patients to recommend a larger prescription of this treatment in cases with less severe or short-duration AF.

Conclusion

In patients with paroxysmal AF not controlled by pharmacological therapy, Abl&Pm treatment is highly effective and superior to drug therapy in controlling symptoms and improving quality of life. The discontinuation of drug therapy exposes patients to further recurrences of paroxysmal AF and the risk of developing permanent AF.

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