



recurrences of atrial fibrillation and adverse side effects of drugs may decrease the potential benefits of DDDR pacing.

Randomized studies comparing these two modes of pacing in patients with persistent atrial fibrillation who underwent AV node ablation still do not exist. We conducted a prospective randomized study to compare the clinical effects of VVIR pacing with those of DDDR pacing and antiarrhythmic therapy in patients with persistent atrial fibrillation after the AV node ablation. We assumed that VVIR pacing would not be inferior to DDDR pacing and antiarrhythmic therapy.

## Patients and Methods

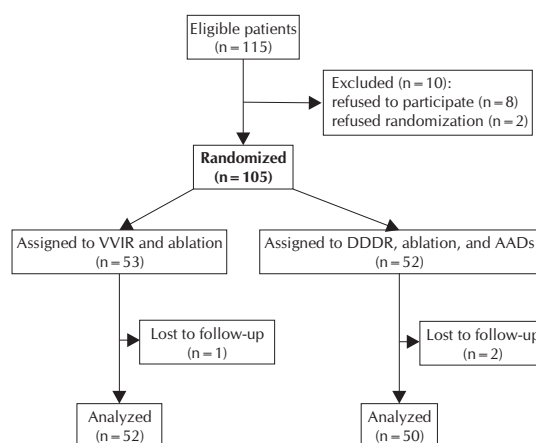
### Patients

The study population consisted of patients with persistent atrial fibrillation referred for AV node radiofrequency ablation and permanent pacemaker implantation between December 2000 and December 2003. Noninvasive cardiac examination was performed before therapeutic procedures in all patients. Persistent atrial fibrillation was defined as non-self-terminating arrhythmia requiring electrical cardioversion to obtain sinus rhythm (14).

All patients aged 18-75 years were eligible for the study if they had persistent atrial fibrillation causing severe symptoms or heart failure, and failure to maintain sinus rhythm with three pharmacological trials, including amiodarone. The exclusion criteria were the duration of atrial fibrillation longer than a year, left atrial size > 50 mm, left ventricular ejection fraction < 20%, contraindications against oral anticoagulation therapy, Wolff-Parkinson-White syndrome, known sick-sinus syndrome, or a life expectancy less than 12 months due to a non-cardiac medical condition, such as cancer or terminal lung disease (1).

### Study Design

This was an open randomized pilot study to compare two different pacing strategies in patients with persistent atrial fibrillation who had an indication for AV node ablation. After the restoration of sinus rhythm by electrical cardioversion, the eligible patients who gave their written informed consent were randomly assigned to the therapy with VVIR pacemaker or DDDR pacemaker and antiarrhythmic drugs (Fig. 1). After pacemaker implantation, radiofrequency ablation



**Figure 1.** Flow of the patients through the study. VVIR – ventricular rate responsive pacemaker; ablation – ablation of atrioventricular node; DDDR – dual chamber rate responsive pacemaker; AADs – antiarrhythmic drugs.

of the AV node was performed according to standard techniques (2). Complete AV block was achieved in all patients. After ablation, patients in both pacing groups were receiving anticoagulation therapy during the entire study period (international normalized ratio [INR], 2.0-3.0).

The choice of antiarrhythmic drugs in patients with DDDR pacing depended on the underlying heart disease and left ventricular function (15). If there was no contraindication, propafenone (450-900 mg daily) was recommended as the first, sotalol (160-320 mg daily) as the second, and amiodarone (400 mg for three weeks, and thereafter 200 mg daily) as the third choice of the treatment. If there was a recurrence of atrial fibrillation, electrical cardioversion was repeated and either propafenone was replaced by sotalol or amiodarone, or sotalol was replaced by amiodarone, when indicated. Patients with DDDR pacemakers who remained in atrial fibrillation were then programmed in VVIR pacing mode. The patients from both pacing groups were also treated with the conventional medical therapy for underlying heart pathology.

### Study End Points

The primary end point of the study was the occurrence of either stroke or death due to cardiovascular causes. Stroke was defined as focal neurological deficit of sudden onset, which did not resolve within 24 hours. Death due to cardiovascular causes was defined as death that did not

have a clear noncardiovascular cause, such as trauma, cancer, infection, or respiratory failure (16).

The secondary end points were death from any cause, development of permanent atrial fibrillation, and hospitalization for congestive heart failure, myocardial ischemia, or electrical cardioversion. Permanent atrial fibrillation was defined as arrhythmia that could not be converted in sinus rhythm by electrical cardioversion (for DDDR pacing group), or which was present at two consecutive follow-up visits and persisted until the end of the study (for VVIR pacing group). Heart failure was defined as an episode of congestive heart failure requiring hospitalization, as ascertained by evidence of either interstitial or alveolar edema on chest x-ray. Myocardial ischemia was defined as an occurrence of angina pectoris requiring coronary angiography (17). Quality of life was not an objective of this study.

#### Follow-up

Patients were seen at the pacemaker clinic every three months during the period between 12 and 36 months. At each follow-up visit, clinical, electrocardiographic, and pacemaker data were obtained, and any primary or secondary outcome event was determined. Cause of death was determined by a review of hospital records and death certificates, and by telephone interviews with local physicians or family members.

#### Statistical Analysis

Continuous numerical data were presented as mean  $\pm$  SD. Student t-test was used to verify the difference in means, and  $\chi^2$ -test for the frequency data analysis. The risk of primary or secondary end points in the two pacing groups was estimated by the Kaplan-Meier method, and the results were compared with the use of log-rank tests. A value of  $P < 0.05$  for two-sided comparison was considered significant. MedCalc program (MedCalc Software, Mariakerke, Belgium) was used for the statistical analysis.

#### Results

A total of 123 patients with persistent atrial fibrillation underwent a pacemaker implantation and successful AV node ablation during the study enrollment period (Fig. 1). Of these, 105 were eligible for the study and randomly assigned to the therapy with either VVIR pacemaker or DDDR pacemaker and antiarrhythmic drugs. The

remaining 18 patients were not enrolled because they either did not meet inclusion criteria or refused to participate. Three patients were lost to follow-up within 8 months after therapeutic procedures and they were withdrawn from the analysis. The resulting 52 patients with VVIR pacing and 50 patients with both DDDR pacing and antiarrhythmic drugs were analyzed for the purposes of the study.

The patients in the two pacing groups were typical for the population with persistent atrial fibrillation and did not significantly differ in their baseline characteristics (Table 1). About 63% of patients were male and hypertension was the most frequent associated condition. More than 64% of the patients were in the New York Heart Association (NYHA) functional class II; left ventricular dysfunction was present in 18% of patients. At the time of hospital discharge, 20 patients with DDDR pacing received the treatment with propafenone, 10 with sotalol, and 20 with amiodarone.

**Table 1.** Baseline characteristics of patients with persistent atrial fibrillation undergoing pacemaker implantation and atrioventricular node ablation according to mode of pacing\*

Characteristics	Treatment	
	VVIR (n=52)	DDDR+AADS (n=50)
Age (mean $\pm$ SD, years)	62 $\pm$ 10	60 $\pm$ 11
Male (%)	30 (57.7)	30 (60.0)
Underlying heart disease (%):		
hypertension	26 (50.0)	30 (60.0)
ischemic	12 (23.1)	8 (16.0)
valvular	1 (1.9)	3 (6.0)
cardiomyopathy	10 (19.2)	8 (16.0)
cor pulmonale	2 (3.9)	0
none	1 (1.9)	1 (2.0)
History of heart failure (%)	12 (23.1)	6 (12.0)
NYHA functional class (%):		
I	9 (17.3)	12 (24.0)
II	37 (71.2)	32 (64.0)
III	6 (11.5)	6 (12.0)
Left atrium diameter (mean $\pm$ SD, mm)	44 $\pm$ 4	44 $\pm$ 4
Left ventricular end-diastolic diameter (mean $\pm$ SD, mm)	54 $\pm$ 8	54 $\pm$ 9
Left ventricular ejection fraction <50% (%)	12 (23.1)	8 (16.0)
Mitral regurgitation $\geq$ 2 (%)	8 (15.4)	6 (12.0)

\*Abbreviations: VVIR – ventricular rate responsive; DDDR – dual chamber rate responsive; AADS – antiarrhythmic drugs; NYHA – New York Heart Association.

After  $26.6 \pm 9.5$  months, the primary end point of stroke or cardiovascular death occurred in 6 out of 52 patients with VVIR pacing (5.3% per year) and in 6 out of 50 patients with DDDR pacing and antiarrhythmic drugs (5.9% per year) (Table 2). According to the Kaplan-Meier estimates of the first occurrence of primary end point over time, there was a relative risk reduction by 4% in

**Table 2.** Clinical events in patients with persistent atrial fibrillation undergoing pacemaker implantation and atrioventricular node ablation according to mode of pacing\*

Clinical events	Treatment	
	VVIR (n=52)	DDDR+ADDs (n=50)
Follow-up (mean±SD, months)	27±10	26±9
Primary end point (%):	6 (11.5)	6 (12.0)
cardiovascular death	4 (7.7)	4 (8.0)
stroke	2 (3.9)	2 (4.0)
Secondary end points (%):		
total mortality	5 (9.6)	5 (10.0)
permanent AF development	46 (88.5)	16 (32.0)†
hospitalization for cardiovascular causes	9 (17.3)	31 (62.0)†
heart failure	6 (11.5)	8 (16.0)
myocardial ischemia	3 (5.8)	5 (10.0)
electrical cardioversion (%)	0	18 (36.0)†
Severe adverse effects of AADs (%)	0	2 (4.0)

\*Abbreviations: VVIR – ventricular rate responsive; DDDR – dual chamber rate responsive; AADs – antiarrhythmic drugs; AF – atrial fibrillation.  
† $P < 0.001$  vs VVIR group,  $\chi^2$  test.

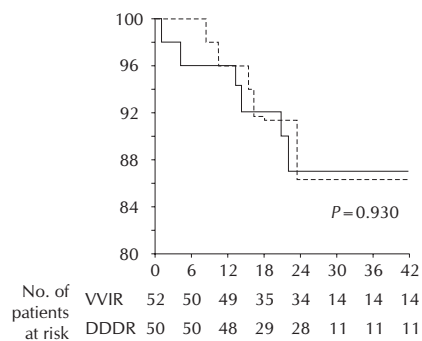
VVIR in comparison with DDDR pacing and antiarrhythmic drugs group (odds ratio [OR], 0.96; 95% confidence interval [CI], 0.28-3.19;  $P = 0.9$ ; Fig. 2).

The mode of pacing had no effect on the annual rate of death from all causes, which was 4.3% per year among the patients with VVIR pacing and 4.8% per year among those with DDDR pacing and antiarrhythmic drugs (OR, 0.98; 95% CI, 0.25-3.53;  $P = 0.74$ ). In the group with VVIR pacing, 4 patients died from cardiovascular causes (2 from heart failure and 2 from sudden death) and one from noncardiovascular cause (cancer). In the group with DDDR pacing and antiarrhythmic drugs, 4 patients died from cardiovascular causes (3 from heart failure and one from sudden death) and one patient died from noncardiovascular cause (cerebral stroke). Cerebral stroke occurred with frequency of 1.6% per year and 2.9% per year in VVIR and DDDR pacing groups, respectively.

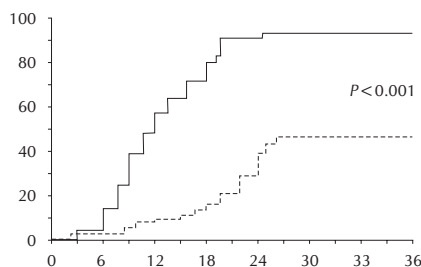
The development of permanent atrial fibrillation was significantly lower among the patients with DDDR pacing (31%) than among those with VVIR pacing (88%), with absolute risk reduction by 56% and relative risk by 64% (OR, 0.06; 95% CI, 0.02-0.17;  $P < 0.001$ ) (Table 2). For the cumulative risk of permanent atrial fibrillation development, the difference between the groups increased progressively after 9 months and reached maximum after 2 years (Fig. 3). The percentage of patients developing permanent atrial fibrillation in VVIR pacing group versus DDDR pacing group during the follow-up period was 15% versus 2% at six months, 58% versus 8% at 12 months, 75% ver-

sus 14% at 18 months, 86% versus 28% at 24 months, and 88% versus 32% at 30 and 36 months.

A total of 31 and 9 hospitalizations for cardiovascular causes occurred in DDDR and VVIR pacing groups, respectively ( $P < 0.001$ ). There was no difference in the occurrence of the congestive heart failure or myocardial ischemia between the two groups. During the follow-up period, 24 (48%) patients with DDDR pacing underwent electrical cardioversion and in 14 of them antiarrhythmic therapy was changed because of recurrence of atrial fibrillation (sotalolol to amiodarone in 3 cases and propafenone to amiodarone in 11 cases). In two patients, amiodarone was replaced with propafenone due to side effects. Four patients underwent electrical cardioversion three times, and 8 patients underwent it twice. Severe adverse effects of antiarrhythmic drugs occurred in two patients with DDDR pacemaker, one had sotalolol-in-



**Figure 2.** Kaplan-Meier estimates of the probability of cardiovascular death or stroke in the patients assigned to ventricular rate responsive pacing (VVIR – full line) and those assigned to dual chamber rate responsive pacing (DDDR – broken line) and antiarrhythmic drugs.



**Figure 3.** The cumulative risk of development of permanent atrial fibrillation according to ventricular rate responsive pacing (VVIR – full line) or dual chamber rate responsive pacing (DDDR – broken line) and antiarrhythmic drugs.

duced torsades de pointes and the other had propafenone-induced heart failure.

### Discussion

We conducted a randomized trial comparing VVIR pacing with DDDR pacing and antiarrhythmic drugs in patients with persistent atrial fibrillation after the AV node ablation. During the follow-up of 26.6 months, two pacing modes were associated with similar number of cardiovascular death or stroke, and the pacing modes had no effect on the rate of overall mortality. These results were consistent with the drug trials comparing rhythm and rate control (9,11,18,19), and strongly suggested that VVIR pacing was not inferior to DDDR pacing and antiarrhythmic drugs for the treatment of patients with persistent atrial fibrillation who had an indication for the AV node ablation.

In a non-randomized trial, Kay et al (1) prospectively assessed the effects of AV node ablation and permanent pacemaker implantation on clinical outcome in patients with chronic, persistent, or paroxysmal atrial fibrillation and found no difference in survival in the first year of follow-up between patients with single and those with dual chamber pacemakers. However, they did not examine the outcome of patients with persistent atrial fibrillation regarding to pacing mode.

Two large-scale randomized prospective trials, the Canadian Trial of Physiologic Pacing (CTOPP,  $n=2,568$ ) and the Mode Selection Trial (MOST,  $n=2,010$ ), demonstrated that dual chamber pacing did not reduce the incidence of stroke or improve survival in patients with AV block and/or sinus node dysfunction when compared with ventricular pacing (13,20). Although these studies included patients at low risk of atrial fibrillation, who were completely different from ours, their main results were similar to the results we obtained in this study.

The second important finding of our study was that DDDR pacing with prophylactic antiarrhythmic drugs was associated with a significant reduction in the rate of permanent atrial fibrillation development in patients with persistent atrial fibrillation undergoing pacemaker implantation and AV node ablation. Compared to VVIR pacing, treatment with DDDR pacing and antiarrhythmic drugs reduced the risk of development of permanent atrial fibrillation by 64%, from 36%

to 17% per year. This risk reduction became highly significant after 9 months and continued to increase during the follow-up.

Few studies have prospectively evaluated the effect of pacing on the development of permanent atrial fibrillation in patients who underwent ablation and pacing therapy. Moreover, these studies included patients with paroxysmal atrial fibrillation and DDDR pacing. The risk of development of permanent atrial fibrillation in these studies was higher and more rapid in patients who were followed in the absence of antiarrhythmic drugs therapy (10,21,22), suggesting that DDDR pacing alone could neither prevent recurrence of paroxysmal atrial fibrillation, nor delay the development of permanent atrial fibrillation in patients with frequent paroxysmal atrial fibrillation after total AV junction ablation.

Although a reduction in the development of permanent atrial fibrillation by DDDR pacing and antiarrhythmic drugs is of potential patient benefit, the recent results of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study indicate that clinical impact of this effect may be less important than previously thought (19,23). AFFIRM study has shown that maintenance of sinus rhythm by antiarrhythmic drugs does not reduce stroke and mortality rates (23). Similarly, we were unable to translate the reduction in development of permanent atrial fibrillation into reduced cardiovascular mortality or lower morbidity in patients treated with DDDR pacing and antiarrhythmic drugs. It seems that the regular ventricular rate provided by AV node ablation and pacing is the most important objective to be obtained and probably minimizes the importance of preserving atrial contraction and AV synchrony. On the other side, any beneficial effects of antiarrhythmic drugs may be offset by their adverse effects, as was shown in the recent analysis of AFFIRM and PAF 2 studies (24,25).

Other secondary end points in our study were not significantly different in the two pacing modes except for hospitalization for cardiovascular causes. Hospitalizations, mostly for repeated electrical cardioversion and initiation of new antiarrhythmic drugs therapy, were more frequent in patients with DDDR pacing and antiarrhythmic drugs. Proarrhythmia was uncommon in this study, because patients with VVIR pacing were without any antiarrhythmic drugs, and majority of pa-

tients with DDDR pacing received amiodarone. Therefore, torsade de pointes occurred only in one patient with DDDR pacing.

The main limitation of our study was the relatively small number of patients, which made the analysis of endpoints in the subgroups of patients more difficult. Another potential limitation of this study was somewhat arbitrary nature of antiarrhythmic drug selection for the patients treated by DDDR pacing. Our preference for propafenone instead amiodarone as the first antiarrhythmic drug choice may have had some influence on higher recurrence rate of AF and higher number of electrical cardioversion in patients with DDDR pacing. However, the majority of patients had previously tried and failed amiodarone, and we wished to avoid its potentially serious side effects, especially in patients with hypertension and normal systolic function.

In conclusion, regarding to cardiovascular mortality and morbidity VVIR pacing is not inferior to DDDR pacing and antiarrhythmic drugs for the treatment of patients with persistent atrial fibrillation who have had an indication for the AV node ablation. Therefore, VVIR pacing seems to be an appropriate therapy in such patients. However, not all patients with persistent atrial fibrillation after AV node ablation should start with VVIR pacing, nor should VVIR pacing be necessarily used in younger patients or patients with low proarrhythmic risk. The decision about whether to use VVIR or DDDR pacing in these patients should be made on an individual basis. Further investigations are needed to determine which subgroups of patients with persistent atrial fibrillation undergoing AV node ablation may have more benefits from VVIR or DDDR pacing mode. It should be noted that an ablation of atrial fibrillation via pulmonary vein isolation represents a new therapeutic possibility for patients with pharmacologically refractory paroxysmal or persistent atrial fibrillation. The first results of this technique in comparison with AV node ablation plus pacing therapy are encouraging, although the incidence of cardiac death or ischemic stroke is similar (26).

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**Correspondence to:**

Dubravko Petrač

Sisters of Mercy University Hospital

Vinogradska cesta 29

10000 Zagreb, Croatia

*d.petrac@inet.hr*