Does treatment with ACE inhibitors or angiotensin II receptor antagonists prevent atrial fibrillation after dual chamber pacemaker implantation?☆

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Abstract Aims A retrospective observational study was performed to test the hypothesis that a lower incidence of atrial fibrillation (AF) would be observed in patients treated with either angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists (AIIRAs) than those without these drugs, 1-year following implantation of a dual chamber pacemaker for all indications.

Methods One hundred and sixty consecutive patients who underwent implantation of a dual chamber pacemaker between January and August 2002 were identified and their case notes were retrospectively analysed. The primary endpoint was the presence of persistent AF (confirmed by 12-lead ECG recorded from the visit to the pacemaker clinic) at 12-month follow-up.

Results Overall, 8% patients developed new onset persistent AF at 1-year follow-up. The incidence of AF at 1-year was 4% in patients treated with ACE inhibitors, 8% in patients taking AIIRAs or 5% on either drug. Although a trend towards a higher incidence of AF was observed at 1-year (10%) in patients not receiving either of these drugs, this was not statistically significant (P = 0.21, drug vs. no drug). The incidence of AF in patients with a previous history of paroxysmal AF or cardioversion was significantly higher (23%) than those patients without (5%), P < 0.0001. An odds ratio (95% CI) of 7.9 (2.3–27.8) was obtained.

Conclusion To confirm these interesting initial results and to investigate this important relationship further, larger prospective randomised controlled studies are required.

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Introduction

Atrial fibrillation (AF) is the most commonly encountered chronic cardiac arrhythmia affecting 5% of the United Kingdom’s population above 65 years and rising to 10% above 75 years [1]. It is associated with an increased risk of systemic embolization [2], haemodynamic dysfunction and tachycardia mediated cardiomyopathy [3–5]. Recent randomised studies [6,7] have shown dual chamber pacing (with or without rate response, DDD ± R) to be associated with a significant incidence of AF in the initial 2–3 years following pacemaker implantation. The exact mechanism for this is unknown, but as both DDD(R) and VVI(R) modes of pacing increase the incidence of AF compared with AAI(R), the likely mechanism, is thought to be right ventricular (RV) pacing causing an increase in left atrial (LA) size. Cumulative percent ventricular paced (Cum%VP) has an almost linear relationship with development of AF [6]. The incidence of new onset AF in DDD pacing can be as high as 24% at 3-year follow-up [7].

Collagen formation in atrial tissue may contribute to structural remodelling and fibrosis leading to the development of AF [8,9]. Angiotensin II is one of the substances responsible for collagen formation. Previous work has shown increased atrial expression of angiotensin converting enzyme (ACE) and angiotensin II in fibrillating human tissue [10]. In experimental models of AF both ACE inhibitors and angiotensin receptor blockade appear to have a useful role in reducing AF [11,12]. This mechanism is complex and thought to be involved in the prevention of atrial electrical and structural remodelling that promotes AF [11–14].

In a clinical setting, both ACE inhibition and specific antagonism at the angiotensin II receptor level decrease the recurrence of AF following cardioversion [15,16]. ACE inhibition also reduces the incidence of AF following myocardial infarction (MI) [17] and in patients with left ventricular (LV) systolic dysfunction [18]. Similar data in hypertensive patients have shown a reduction in new onset AF in patients treated with ACE inhibitors [19] or angiotensin II receptor antagonists [20].

This retrospective observational study tested the hypothesis that a lower incidence of AF would be observed in patients treated with either ACE inhibitors or AIIRAs than those without these drugs, 1-year following DDD ± R pacing for all indications.

Methods

One hundred and sixty consecutive patients undergoing dual chamber pacing for all indications at a regional cardiothoracic centre in United Kingdom between January and August 2002 were identified. Case notes were analysed retrospectively. Information including patient details, past medical history (including hypertension and history of previous arrhythmia), indication for pacemaker and baseline electrocardiogram (ECG) were recorded before pacemaker implantation. Patients in AF condition at the time of implant were excluded from the analysis. The primary endpoint was the presence of persistent AF (confirmed by 12-lead ECG recorded from the visit to the pacemaker clinic) at 12-month follow-up.

Data are expressed as mean ± SD for continuous variables, and frequencies were measured for categorical variables. The effect of the treatment groups (drug [ACE inhibitor, AIIRA or either drug] vs. no drug) on the development of AF was compared using the Chi-squared test. Logistic regression was used to identify significant independent predictors of AF and odds ratios were constructed for these predictors. \( P < 0.05 \) was considered statistically significant.

Results

Baseline clinical characteristics of study population

Baseline characteristics of the study group are shown in Table 1. All patients underwent successful implantation of a dual chamber pacemaker without lead displacement complications at or around the time of implant. Indications for pacing were as follows: 110 (69%) for evidence of A-V block, 15 (9%) for sinoatrial disease, 19 (12%) for implantable cardiac defibrillator (ICD) implantation and 16 (10%) for other indications, e.g. carotid sinus syndrome. Mean (±SD) age was 74 ± 13 (range 20–95) years and 93 patients (58%) were male. Forty-seven (29%) patients were taking ACE inhibitors and 13 (8%) patients were on AIIRAs, 60 (38%) patients were therefore on either drug. Fourteen (9%) patients were taking amiodarone and 25 (16%) were prescribed beta-blockers. Forty-eight (30%) patients had a history of hypertension and 30 (19%) had a past history of AF, either previously cardioverted or paroxysmal.

Incidence of AF and effect of drug treatment

Overall, 13 (8%) patients developed new onset persistent AF at 1-year follow-up. Fig. 1a illustrates...
the incidence of AF according to treatment with either ACE inhibitors or AIIRAs. The incidence of AF at 1-year was 4% in patients treated with ACE inhibitors, 8% in patients taking AIIRAs or 5% on either drug. Although a trend towards a higher incidence of AF was observed at 1-year in 10% of patients not receiving either of these drugs, this was not statistically significant \((P = 0.21, \text{drug vs. no drug})\). There was no significant difference in the incidence of AF in patients taking beta-blockers (12%) or not (7%), \(P = 0.56\), or amiodarone (7%) or not (8%), \(P = 0.82\). These data are demonstrated in Fig. 1b.

Influence of hypertension and previous AF

In hypertensive patients, the incidence of AF was 10% vs. 7% in patients who were normotensive \((P = 0.42)\). However, the incidence of AF in patients with a previous history of paroxysmal AF or cardioversion was significantly higher (23%) than those patients without (5%), \(P < 0.0001\). These data are illustrated in Fig. 1c. Logistic regression identified previous history of AF to be an independent predictor of AF at 1-year with an odds ratio (95% CI) of 7.9 (2.3–27.8). Of the 130 (81%) patients who did not have a previous history of AF, the incidence of AF at 1-year was 3%. Fifty (38%) patients in this subgroup were taking either ACE inhibitors or AIIRAs. There was a lower incidence of AF at 1-year in patients taking drug treatment (2%) vs. no drug treatment (5%), although this was not statistically significant \((P = 0.24)\).
Discussion

The results from this retrospective study show that there is a trend, although not statistically significant, towards a lower incidence of AF 1-year following dual chamber pacemaker implantation in patients receiving treatment with either an ACE inhibitor or an ARIIA (5%) than in those patients who were not on either of these medications (10%). Not surprisingly, the only clinical factor shown to be significantly associated with the development of AF was a previous history of AF.

The overall incidence of new onset AF in our study, 1-year following pacemaker implantation was 8%, which is similar to previous reports [6,7]. A previous study of elderly (>65 years) patients receiving pacemakers for a range of indications showed an AF incidence of 17% with dual chamber pacing at 30 months of follow-up [21]. Studies of patients with sinus node dysfunction having dual chamber pacing found the incidence of AF during follow-up ranging from 15.2% [22] to 23% [7] over 33 months. Although the exact mechanism whereby pacing increases the risk of AF is unknown, AF is more common with increasing amounts of ventricular pacing [6,7,22]. In addition, hospital admissions for heart failure occurred in 10.3% of patients in one study [6], and were related to the amount of ventricular pacing. The likely role of ventricular pacing in promoting heart failure (CHF) and AF in these patients is supported by echocardiographic data demonstrating that right ventricular pacing results in LA dilatation and reduced left ventricular fractional shortening [7].

Further evidence for the adverse effect of ventricular pacing on left ventricular function is seen in studies of ICD patients. In the MADIT II study [23] there was an increase in heart failure hospitalisations in those patients receiving ICDs, which has been linked to a reduction in ventricular function secondary to pacing. Right ventricular apical pacing resulting in deterioration in heart failure symptoms has also been noted by other investigators [24]. Minimising right ventricular pacing by programming dual chamber ICDs to VVI, 40/min, has previously been shown to be associated with less heart failure than with conventional dual chamber pacing [25].

This is the first study to examine whether treatment with drugs that block the effects of angiotensin II might reduce the higher incidence of AF seen in patients receiving dual chamber pacemakers. Although the result shows no significant differences in the incidence of AF at 1-year between the two groups, the trend to a slightly lower incidence is noteworthy. In this non-randomised, retrospective study one could argue that patients treated with ACE inhibitors and AIIRAs might be expected to have a higher incidence of AF than those patients not taking these. This is on the basis that the principal indications for treatment with these drugs (hypertension and cardiac failure) are also potent risk factors for the development of AF.

Previously, larger studies have shown that ACE inhibitors lower the incidence of AF in patients with congestive heart failure (CHF) [18], post-MI LV dysfunction [17] and hypertension [19]. Although the initial studies of ACE inhibitors in patients with LV dysfunction were not specifically designed to investigate their effects on the incidence of AF, subsequent analysis of the data from these studies support the use of ACE inhibitors in the prevention of AF. Follow-up data from the TRACE study [17] showed a reduction in new onset AF from 5.3% on placebo to 2.8% on trandolapril over 3 years of follow-up. The reduction in new onset AF in a group of patients at a single centre treated with enalapril in the SOLVD study was even more impressive, with a new onset AF rate on placebo of 24% vs. 5.4% on enalapril over 3 years of follow-up [18]. Data on the use of ACE inhibitors and AIIRAs to prevent recurrent AF following DC cardioversion are also emerging. The addition of lisinopril [15] or irbesartan [16] to amiodarone in the pericardioversion period has been shown to reduce the risk of recurrent AF post-cardioversion. Further evidence for the use of these drugs was provided by Madrid and colleagues [26], who performed a meta-analysis of seven trials consisting of 24,849 patients with a wide variety of cardiovascular diseases (hypertension, CHF, ischaemic heart disease and diabetes mellitus). Treatment with ACE inhibitors or AIIRAs significantly reduced the development or recurrence of AF (odds ratio 0.57; 95% CI, 0.39–0.82, P = 0.003) compared with either placebo or conventional treatment.

A lower, although not statistically significant, incidence of AF (5%) was observed in patients treated with either ACE inhibitors or AIIRAs than those without these drugs (10%) in our study is therefore consistent with previous clinical data. There are good theoretical reasons to believe that drugs that inhibit angiotensin II may be of use in preventing AF in patients undergoing dual chamber pacing, especially in the setting of LV dysfunction. The experimental induction of heart failure in dogs by rapid ventricular pacing promotes the induction and maintenance of AF [9]. The underlying mechanism of increased susceptibility to AF is
considered to be changes in atrial conduction, secondary to atrial fibrosis. Treatment of dogs with enalapril during induction of heart failure by rapid ventricular pacing reduces atrial fibrosis and the duration of induced episodes of AF [2]. Coupled with these effects, enalapril was shown to reduce atrial tissue concentrations of angiotensin II and mitogen-activated protein kinases (MAPK), important mediators of angiotensin II induced tissue changes [27]. Echocardiographic data from the same group have demonstrated that part of the beneficial effects of enalapril may be mediated by attenuation of left atrial enlargement in this animal model [28]. Furthermore, AIIRAs have been shown to have direct electrophysiological effects on potassium currents (e.g. Kv 1.5, Kv 4.3) involved in cardiac repolarisation [13,14].

Study limitations

The small number of patients in this analysis may have limited the statistical power needed to determine a significant difference in the incidence of new onset AF between those patients taking ACE inhibitors or AIIRAs and those patients not taking these drugs. To confirm these interesting initial results, larger prospective randomised controlled studies are required.

Left ventricular function data were not available for all patients and this may have affected and influenced the incidence of AF. However, assessment of left ventricular function by echocardiography or other means is often difficult and not always accurate in patients with bradyarrhythmias prior to pacemaker implantation. Cumulative percent ventricular paced data were also not available in all patients and this would need to be corrected for a future study.

Conclusions

Previous studies have shown that the drugs that inhibit angiotensin II (ACE inhibitors and AIIRAs) reduce the incidence of AF in patients with LV systolic dysfunction, following MI and electrical cardioversion. This is the first study to examine whether treatment with these drugs reduces the incidence of AF seen in patients receiving dual chamber pacemakers. We observed a trend, although not statistically significant, towards a lower incidence of AF 1-year following dual pacemaker implantation in those patients receiving treatment with either an ACE inhibitor or an ARIIA (5%) than in patients who were not on either of these medications (10%). To confirm these interesting initial results and to investigate this relationship further, larger prospective randomised controlled studies are required. Following the disappointing results of therapies designed to modify atrial electrical remodelling, the blockade of angiotensin II and prevention of atrial structural remodelling represent a new area of hope in the battle against AF.

References


