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# Incidence of new onset atrial fibrillation in patients with permanent pacemakers and the relation to the pacing mode

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**Background:** Atrial fibrillation is a relatively common arrhythmia often seen in patients with permanent pacemakers. In this study we aimed to assess the incidence of atrial fibrillation in patients whose pacemakers were programmed to pace in the right ventricle (VVI) and compared it with patients whose pacemakers were programmed in non-VVI mode (i.e. AAI or DDD).

**Material/Methods:** Records of the patients with permanent pacemaker or implantable-cardioverter-defibrillator were evaluated and analyzed. These patients had regular periodic follow-up evaluation over the last 10 years. (January 1, 2002 to December 31, 2012).





Patient demographic, pacemaker data, pacing mode, review and analysis of arrhythmia log for occurrence of new atrial fibrillation and echocardiographic findings for left atrial size, mitral regurgitation, were analyzed and recorded. Left atrial size was classified as mild, moderate or severe enlargement, depending on the left atrial dimension.

**Results:** Average age was 68 years. There was no gender predominance (51% male). Mean follow-up duration was 6 years and 3 months. Hispanic population represented the majority of the patients (65.4%). Majority of the devices (80.0%) were programmed as DDD pacing mode. Fifty-five patients (52.8%) did not develop atrial fibrillation. 85.7% of the patients paced in VVI-mode had atrial fibrillation while atrial fibrillation occurred in 37.4% among patients paced in non-VVI-mode. This difference was statistically significant ( $P < 0.0001$ ).

**Conclusions:** Right ventricular pacing in a VVI mode was associated with higher incidence of atrial fibrillation, mitral regurgitation and left atrial enlargement. Non-VVI based pacing demonstrated lower incidence of new onset atrial fibrillation.

**MeSH Keywords:** **Mitral Valve Insufficiency • Pacemaker, Artificial • Atrial Fibrillation**

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## Background

Among cardiac arrhythmias atrial fibrillation (AF) is the most common one in the United States [1]. AF is a significant risk factor to predict ischemic stroke. Symptomatic AF may also reduce the quality of life, cardiac performance and the functional status [2]. The prevalence of AF in the US among patients who are older than 40 years is approximately 2.3%, increases to almost 6% after the age of 65 years and exponentially higher (about 70%) in patients between 65 and 85 years [3].

Guidelines for implantation of cardiac pacemakers have been established by the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society (ACC/AHA/HRS) [4]. Similar guidelines were also defined by the European society of cardiology [5].

The role of a pacemaker in the prevention of AF has been debated for >20 years. Early studies in patients with sick sinus syndrome and paroxysmal AF suggested that atrial-based pacing in and of itself might prevent AF by reducing the incidence of bradycardia-induced atrial fibrillation [6]. Atrial-based pacing has been shown to be superior to ventricular based pacing in the prevention of AF [7,8]. Pacing algorithms have evolved to minimize right ventricular pacing in patients with sick sinus syndrome and intact atrioventricular conduction. These strategies have included AAI pacing with the option to mode switch to the dual chamber pacing and sending mode should second-degree or greater atrioventricular block occur. Other strategies have included variations of an atrioventricular search hysteresis algorithm [9].

Despite some early promise, the findings from recent studies have led to the consensus that pacing preventive strategies have limited to no role in the prevention of AF [10]. Moreover, an increasing body of evidence has suggested that right ventricular (RV) pacing is detrimental to left ventricular function [11].

In this study, we attempted to assess the occurrence of AF in patients whose pacemakers are programmed to pace in the right ventricle and compare this to the patients whose pacemakers programmed to pace in atrium.

## Material and Methods

For our retrospective study charts of patients presenting for a follow up of new or previously implanted single or dual pacemaker or Implantable Cardioverter Defibrillator (ICD) to Texas Tech clinic of cardiology and electrophysiology in El Paso over 10 years period, between January 1<sup>st</sup> 2002 and December 31<sup>st</sup> 2012, were reviewed. Data were collected from medical records and pacemaker databases.

Baseline data over the reviewed period for the implanted pacemaker were registered including gender, age at implantation, indication for pacemaker implantation, cardiac risk factors, new-onset of AF, initial pacing mode (AAI/VVI/DDD/VDD) as well as changes in the pacemaker setting, analyzing the occurrence of arrhythmia log during the follow ups and significant echocardiographic changes of the left atrium. Origin of pacing mode was documented and categorized as atrial (AAI, DDD, VDD) vs. ventricular (VVI, DDD) and compared to each other.

The endpoint was the occurrence of new onset of AF in association with the underlying pacing mode (atrial versus ventricular). These data were obtained from the EKGs or from the stored logs in the pacemaker device.

Baseline echocardiographic features of all patients, so far available before the pacemaker implantation, were also reviewed. Data were collected for a baseline mitral valve assessment and the size of the left atrium. These results were followed up over the review period of 10 years and changes of the mitral valve and the size of the left atrium were compared with the baseline findings. Mitral valve regurgitation assessment was subclassified in 3 groups following the ACC/AHA guidelines [12]. The left atrium size was documented. Observed changes were gender specific sub-classified in mild moderate and severe dilation (Table 1) according to the current recommendations [13].

## Statistical analysis

Data were described using appropriate summary measures such as mean, standard deviation (SD), frequency and proportion as per the form of the variables. Baseline conditions were compared according to pacing mode using either unpaired t-test or Fisher's exact test. Simple logistic regression was used to

**Table 1.** Reference limits and partition values for left atrial dimensions.

| Left atrium size in cm |         |         |          |        |
|------------------------|---------|---------|----------|--------|
| Gender                 | Normal  | Mild    | Moderate | Severe |
| Female                 | 2.7–3.8 | 3.9–4.2 | 4.3–4.6  | ≥4.7   |
| Male                   | 3.0–4.0 | 4.1–4.6 | 4.7–5.2  | ≥5.2   |

**Table 2.** Comparison of baseline characteristics and pharmacological agents according to pace modes.

| Variable                       | Overall<br>(N=104)<br>n, % | VVI<br>(N=21)<br>n, % | Non-VVI<br>(N=83)<br>n, % | p-Value |
|--------------------------------|----------------------------|-----------------------|---------------------------|---------|
| Age (mean, SD)                 | 68.15 (17.63)              | 67 (23.34)            | 68.45 (16.03)             | 0.791   |
| BMI (mean, SD)                 | 29 (5.65)                  | 27.94 (6.08)          | 29.26 (5.54)              | 0.343   |
| Creatinine (mean, SD)          | 1.02 (0.4)                 | 1.001 (0.41)          | 1.03 (0.403)              | 0.763   |
| LA Size (mean, SD)             | 45.85 (8.20)               | 51.1 (10.4)           | 44.5 (6.98)               | 0.013   |
| Gender (male)                  | 54 (51.92)                 | 10 (47.62)            | 44 (53.01)                | 0.807   |
| Ethnicity (Hispanic)           | 68 (65.38)                 | 15 (71.43)            | 53 (63.86)                | 0.831   |
| Diabetes mellitus (yes)        | 28 (26.92)                 | 7 (33.33)             | 21 (25.3)                 | 0.582   |
| Hypertension (yes)             | 76 (73.08)                 | 14 (16.67)            | 62 (74.70)                | 0.582   |
| Dyslipidemia (yes)             | 55 (52.88)                 | 10 (47.62)            | 45 (54.22)                | 0.631   |
| Coronary artery disease (yes)  | 26 (25.00)                 | 7 (33.33)             | 19 (22.89)                | 0.398   |
| Congestive heart failure (yes) | 31 (29.81)                 | 6 (28.57)             | 25 (30.12)                | 1.000   |
| History of smoking (yes)       | 47 (45.19)                 | 12 (57.14)            | 35 (42.17)                | 0.231   |
| History of alcohol use (yes)   | 37 (35.58)                 | 10 (47.62)            | 27 (32.53)                | 0.212   |
| History of illegal drugs (yes) | 10 (9.62)                  | 3 (14.29)             | 7 (8.43)                  | 0.418   |
| ACE-inhibitor (yes)            | 58 (55.77)                 | 10 (47.62)            | 48 (57.84)                | 0.465   |
| ARB-inhibitor (yes)            | 8 (7.69)                   | 1 (4.76)              | 7 (8.43)                  | 1.000   |
| Statin (yes)                   | 52 (50.00)                 | 9 (42.86)             | 43 (51.81)                | 0.626   |
| Diuretics (yes)                | 39 (37.50)                 | 9 (42.86)             | 30 (36.14)                | 0.619   |
| Antiarrhythmics (yes)          | 23 (22.12)                 | 5 (23.81)             | 18 (21.69)                | 0.777   |

determine the association of considered variables with AF. The significant variables in unadjusted logistic regression at 5% level of significance were considered for multivariable logistic regression analysis. The results of logistic regression were presented using odds ratio (OR) with 95% confidence interval (CI) and p-values. P-values less than 5% were considered as significant results. All statistical analyses were carried out using STATA 12.1.

## Results

### Patient characteristics

Crosscheck of the medical record at Texas Tech Health Science Center cardiology and electrophysiology clinic, El Paso, Texas, revealed a total of 136 patients. After exclusion of 32 patients due to incomplete follow-up period, incomplete echocardiography documentation or follow up interruption, 104 patients comprised the final study population. Average age was 68 (SD:

17.6) years. There was no gender predominance (51% male). Mean follow-up duration was 6 years and 3 months. Hispanic population represented the majority of the patients (65.4%). All the patient's characteristics were found to be similar between VVI and non-VVI pacing modes except LA size and history of AF. VVI-pacing mode patients had larger mean LA as compared with non-VVI pacing mode patients (Table 2).

Fifty-five patients (52.8%) did not develop atrial fibrillation. 85.7% of the patients paced in VVI-mode had atrial fibrillation while atrial fibrillation occurred in 37.4% among patients paced in non-VVI-mode. This difference was statistically significant ( $P < 0.0001$ ). Table 3 describes univariate association of cofactors with presence of AF. The incidence of AF (85.7%) was more frequent with VVI-pacing as compared with non-VVI-pacing (37.4%). The odds of AF are 10 times more likely with VVI-pacing as compared with non-VVI-pacing ( $p = 0.001$ ). Coronary artery disease was also found to be associated with new-onset AF ( $p = 0.034$ ). A boarder line association between

**Table 3.** Unadjusted association of cofactors with presence of AF.

| Variables                | OR    | 95% CI |       | p-Value |
|--------------------------|-------|--------|-------|---------|
| Single pace mode         | 10.07 | 2.74   | 36.95 | 0.001   |
| Age                      | 1.00  | 0.98   | 1.02  | 0.915   |
| BMI                      | 0.95  | 0.89   | 1.02  | 0.180   |
| Creatinine               | 2.05  | 0.75   | 5.57  | 0.160   |
| LA size                  | 1.18  | 1.10   | 1.28  | <.0001  |
| Male gender              | 1.27  | 0.59   | 2.76  | 0.541   |
| Hispanic race            | 0.99  | 0.44   | 2.23  | 0.987   |
| Diabetes mellitus        | 0.96  | 0.40   | 2.30  | 0.932   |
| Hypertension             | 1.27  | 0.53   | 3.03  | 0.598   |
| Dyslipidemia             | 1.90  | 0.87   | 4.14  | 0.109   |
| Coronary artery disease  | 2.72  | 1.08   | 6.85  | 0.034   |
| Congestive heart failure | 2.27  | 0.96   | 5.36  | 0.062   |
| History of smoking       | 2.53  | 1.14   | 5.58  | 0.022   |
| History of alcohol use   | 2.59  | 1.13   | 5.92  | 0.024   |
| History of illegal drugs | 2.89  | 0.70   | 11.85 | 0.141   |
| ACE-inhibitor            | 1.30  | 0.60   | 2.83  | 0.509   |
| ARB-inhibitor            | 0.65  | 0.15   | 2.88  | 0.573   |
| Statin                   | 1.47  | 0.68   | 3.19  | 0.327   |
| Diuretics                | 1.31  | 0.59   | 2.90  | 0.510   |
| Antiarrhythmics          | 2.04  | 0.79   | 5.26  | 0.138   |

**Table 4.** Adjusted association of pacing mode with presence of AF.

| Variables                | OR    | 95% CI |        | p-Value |
|--------------------------|-------|--------|--------|---------|
| Single pace mode         | 15.78 | 2.36   | 105.57 | 0.004   |
| LA size                  | 1.18  | 1.07   | 1.29   | 0.001   |
| Coronary artery disease  | 2.69  | 0.69   | 10.41  | 0.152   |
| Congestive heart failure | 1.32  | 0.38   | 4.60   | 0.667   |
| History of smoking       | 0.95  | 0.30   | 3.01   | 0.933   |
| History of alcohol use   | 1.63  | 0.51   | 5.22   | 0.407   |

congestive heart failure and presence of AF was also found ( $p=0.062$ ). The history of smoking and drinking increased more than 2 fold the odds of AF as compared with their counterparts. The odds of AF were more likely with history of alcohol use ( $p=0.024$ ). No association between increased onset of newly developed AF and several pharmacological classes was noticed.

Table 4 describes the association of pacing mode after adjusting for confounders. After adjusting for all significant variables from univariate analysis, only pacing mode and LA size remained significant.

The odds of AF was 15.8 times more likely with single pacing mode as compared with dual pacing mode even after

**Table 5.** Distribution of change in pacing mode according to mitral valve regurgitation, gender and LA size.

|   | N (%)      | Change in PM<br>N (%) |
|---|------------|-----------------------|
| <b>Mitral valve regurgitation (MVR)</b> |            |                       |
| None                                    | 43 (41.35) | 1 (2.33)              |
| Mild                                    | 35 (33.65) | 7 (20.00)             |
| Moderate                                | 20 (19.23) | 4 (20.00)             |
| Severe                                  | 6 (5.77)   | 1 (16.67)             |
| <b>Gender</b>                           |            |                       |
| Male                                    | 54 (51.92) | 11 (20.37)            |
| Female                                  | 50 (48.08) | 2 (4.00)              |
| <b>LA size</b>                          |            |                       |
| Abnormal                                | 74 (76.29) | 13 (17.57)            |
| Normal                                  | 23 (23.71) | 0 (0.00)              |

adjusting for other significant variables obtained from the univariate analysis ( $p=0.004$ ). Per unit increase in the LA size increased the odds of AF by 18% after adjusting other variables ( $p=0.001$ ).

#### Association between mitral valve and atrial fibrillation

Twenty-five patients (24% of the total population) were found to have a new development of moderate or severe mitral regurgitation, as determined by echocardiography, after the pacemaker implantation. Majority of the patients who developed mitral regurgitation were paced in VVI mode (Table 4). Among the patients with moderate mitral regurgitation, which was developed over the period after the pacemaker implantation, 20% had subsequent changes in the pacing mode (from non-VVI to VVI) and one patient with documented severe mitral valve regurgitation ( $n=6$ ) were switched to VVI-pacing. Dilation of the left atrium as defined in Table 1 without gender predominance was noticed in 74 of the total patient's population (male  $n=37$  versus female  $n=37$ ). However, settings of pacemaker pacing modus were adjusted more frequently in males (20.4% in male versus 4% in female) (Table 5).

## Discussion

The purpose of this study was to assess if the primary pacing mode, whether atrial or ventricular based, contributes in the prevention of atrial fibrillation in patients with implanted permanent pacemaker. In general population an atrial-based

pacing (ABP) is beneficial in reducing the incidence of AF compared with ventricular pacing. ABP reduces the relative risk of AF by 18% over the period of 3-year follow up [14,15]. A meta-analysis from 2006 outlined the data of 5 trials and came to the conclusion that ABP reduces the AF-incidence (HR, 0.80; 95% CI, 0.72–0.89;  $P$ , 0.001) and stroke (HR, 0.81; 95% CI, 0.67–0.99,  $P$ , 0.035) compared with ventricular pacing [13].

Careful review of the literature about the role of electrical pacing associated with the onset of AF delivers controversial results. In a single center study ABP was not found to be protective against atrial arrhythmias including atrial fibrillation [16]. However the interpretation of such results should be handled with care. The reasons of these misleading interpretations may be related to increased vulnerability to develop or contribute congestive heart failure with subsequent atrial arrhythmias with advanced age. Also the presence of cardiosurgical scars with other factors like hypertension, diabetes, obesity and hypercholesterinemia increase the risk of postoperative atrial fibrillation, and falsify the role of ABP [17,18].

In contrast the Mode-Selection-Trial (MOST) showed a significant reduction in atrial fibrillation associated with pacing from dual-chamber-pacemakers compared with primary ventricular pacing [19]. However this was documented only in patients without existing history of atrial fibrillation while patients with previously known history of AF did not benefit primarily from selection the pacing mode. It is possible that the right ventricular pacing results in asynchronous contraction of the left ventricle; this then leads to the mitral regurgitation due to papillary muscle dysfunction, left atrial enlargement and propensity for the development of atrial fibrillation. AV dissociation, that generally accompanies right ventricular pacing in a VVI mode, may also contribute to left atrial enlargement, fibrosis and occurrence of atrial fibrillation. The affect of AF on the mitral valve regurgitation conversely can have a significant left ventricular hemodynamic relevance and may require long-term valvular surgical correction [20].

Insight into the future of prevention pacing mode induced-AF may guide us into the branch of electrical compensation. Atrial overdrive pacing algorithms and/ or other location of atrial pacing (i.e. septal pacing) can play complementary role together with ABP in the primary prevention of atrial fibrillation. Yet this hypothesis has not been well established. The recent ASSERT study did not show significant effect of overdrive atrial pacing in the primary prevention of AF [21]. Further studies are needed to clearly explore these modalities. Furthermore septum pacing (SP) compared with right appendage pacing (RAP) and the impact of atrial overdrive pacing may represent the next interesting field that can help to smooth the next burden. Literature review revealed one study exploring the benefit of different pacing sites in association with atrial overdrive

pacing [22]. Persistent AF-free survival was not statistically different between SP and RAP and between different atrial overdrive pacing algorithms.

The current study demonstrated a clear beneficial effect of ABP in preventing atrial fibrillation (p 0.0001). Nevertheless at this point it should be mentioned that the rate of peri-procedural complications in the general population is nearly twice as high with ABP compared with ventricular pacing (6.2 vs. 3.2%), primarily due to a significant increase in the rate of lead failure and infection [23].

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## Conclusions

Atrial fibrillation is in the literature well known to be associated with a higher incidence of hospitalization. The Pacing mode can affect the onset of AF. In this current study among our unique population on an US-Mexican border city highly statistical significance was noticed with predominantly atrial pacing (in AAI or DDD mode) resulting in a lower risk to develop a new-onset of AF. Furthermore dilation of the left atrium (LA) and new onset of clinically significant moderate to severe mitral regurgitation was documented in patients with new-onset AF, which can be related to the pacing mode.