Atrial High Rate Episodes Detected by Pacemaker Diagnostics Predict Death and Stroke

Report of the Atrial Diagnostics Ancillary Study of the MOde Selection Trial (MOST)

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Background—Some current pacing systems can automatically detect and record atrial tachyarrhythmias that may be asymptomatic. We prospectively studied a 312-patient (pt) subgroup of MOST (MOde Selection Trial), a 2010-patient, 6-year randomized trial of DDDR versus VVIR pacing in sinus node dysfunction (SND). The purpose of the study was to correlate atrial high rate events (AHREs) detected by pacemaker diagnostics with clinical outcomes.

Methods and Results—Pacemakers were programmed to log an AHRE when the atrial rate was >220 bpm for 10 consecutive beats. Analysis was confined to patients with at least 1 AHRE duration exceeding 5 minutes. The 312 patients were median age 74 years, 55% female, and 60% had a history of SVT. 160 of 312 (51.3%) patients enrolled had at least 1 AHRE >5 minutes duration over median follow-up of 27 months. Cox proportional hazards analysis assessed the relationship of AHREs with clinical events, adjusting for prognostic variables and baseline covariates. The presence of any AHRE was an independent predictor of the following: total mortality (hazard ratio AHRE versus no AHRE and 95% confidence intervals 2.48 [1.25, 4.91], \(P=0.0092\)); death or nonfatal stroke (2.79 [1.51, 5.15], \(P=0.0011\)); and atrial fibrillation (5.93 [2.88, 12.2], \(P=0.0001\)). There was no significant effect of pacing mode on the presence or absence of AHREs.

Conclusions—AHRE detected by pacemakers in patients with SND identify patients that are more than twice as likely to die or have a stroke, and 6 times as likely to develop atrial fibrillation as similar patients without AHRE. (Circulation. 2003;107:1614-1619.)

Key Words: fibrillation ■ pacemakers ■ arrhythmia detection ■ mortality ■ clinical trials

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disturbance in adults and is a leading cardiac cause of morbidity and mortality. The prevalence of AF in the United States is estimated at 5.5 million patients. AF is associated with over 120,000 strokes per year and increases the relative risk for death by 1.5 in men and by 1.9 in women.1,2 Thus, the early detection of AF may have clinical importance.

Current pacemaker technology has evolved such that modern pacemakers have high-density, low-power consumption memory and are capable of automatically recording and storing episodes of spontaneous atrial tachyarrhythmias according to programmable detection criteria. Such episodes may be recorded as interval data, local electrograms, or both. These episodes that are thought to represent nonsustained AF may be harbingers of sustained AF. Small cross-sectional studies of unselected pacemaker patients reported a high prevalence of atrial high rate events (AHREs), but their clinical significance has remained a question.3,4 For example, should there be clear clinical significance to these AHREs, clinical trials of antiarrhythmic and anticoagulant therapy could be developed to define whether there are reductions in clinical events.

The specific aims of this study were as follows: (1) to define the prevalence and clinical significance of AHREs in pacemaker recipients with sinus node dysfunction (SND); (2)
to verify that AHREs detected by the pacemaker could be confirmed by 24-hour ambulatory monitor recordings; and (3) to determine the associations between pacemaker detected AHREs, symptoms of atrial arrhythmias, and clinical outcomes.

**Methods**

MOST (MOde Selection Trial) was a 6-year prospective, randomized, multicenter trial designed to compare ventricular rate-modulated (VVI\(_R\)) pacing with dual-chamber, rate-modulated pacing (DDDR) in patients whose SND required permanent pacing for bradycardia. Patients were eligible if they were at least 21 years old, were undergoing initial implantation of a dual-chamber, rate-modulated pacing system for SND, and were in sinus rhythm when randomized. After both atrial and ventricular leads were positioned, a 24-hour randomization line was called and the pacemaker programmed accordingly to the randomized mode (DDDR or VV\(_R\)). Patients were blinded to mode assignment. All guidelines for use of human subjects were followed. Baseline cardiac status including indications for pacing, medications, and history of atrial arrhythmia were recorded. Follow-up occurred 4 times during year one and twice yearly afterward.

The atrial diagnostics ancillary study was an investigator-initiated study approved by both the MOST Ancillary Studies Committee and an independent data and safety monitoring board. Within approved sites, patients with implanted, ancillary study-capable pacemakers (CPI (Guidant) Discovery DR, Medtronic Thera DR, Medtronic Prodigy DR, Medtronic Kappa, Medtronic 7271) were approached and asked to sign a separate informed consent for ancillary study participation. Enrollment into the ancillary study occurred concurrent with MOST randomization in 70% of patients. The remaining 30% were enrolled in the ancillary study a median of 2 years after initial MOST randomization.

In all ancillary study patients, the atrial bipolar sensitivity was programmed to 0.5 mV, and the AHRE diagnostic was programmed ON. In order for atrial events to be recorded in patients randomized to the VV\(_R\) pacing mode, the device was programmed to the VDI\(_R\) mode. In VDIR, the atrial sense amplifier was ON for diagnostic purposes, but pacing therapy was not affected, and pacing operation was identical to VV\(_R\) mode. The atrial detection rate was programmed to 220 bpm so as to include only episodes of atrial fibrillation and exclude slower atrial tachycardias. The onset detection number of beats was 10 and the termination number was 20 consecutive beats at a rate below the detection rate, for the purpose of excluding short episodes of atrial premature beats. Intracardiac electrograms were not recorded in order to preserve pacemaker memory to register a greater number of events. Only AHREs lasting at least 5 minutes were analyzed, based on previously published data that the 5-minute cutoff excludes most episodes of oversensing.

Data from the AHRE diagnostic bin were downloaded and sent to the Data Coordinating Center at 1, 3, and 6 months after ancillary study enrollment and every 6 months thereafter. At the 6-month follow-up, a 24-hour ambulatory monitor was performed. The AHREs were interrogated at the end of the ambulatory monitoring period to provide a comparison of the pacemaker AHRE data with the ECG tracing. Clinicians were blinded to the results of the atrial diagnostics data. A Clinical Events Committee, blinded to assigned pacing mode, classified cause of death and adjudicated all suspected strokes. An ECG Core Laboratory reviewed ECGs and confirmed diagnoses of AF.

Symptoms were determined from a one-page AF Burden Index questionnaire specifically designed for the ancillary study and collected at the follow-up visits. Patients were asked to rank each of 7 symptoms: palpitation (heart racing or pounding), chest pain or tightness, shortness of breath, dizziness or lightheadedness, nausea, sweating or perspiring, and tiredness or fatigue, on a scale of 1 (none) to 5 (incapacitating). We defined as symptomatic only patients who had a severity score of 3 (moderate) or greater for any one symptom at any time during follow-up.

Baseline categorical variables are summarized with percent (number), and group comparisons were performed using likelihood ratio chi-square tests. Baseline continuous variables are summarized with median (25th, 75th percentile), and groups were compared using Wilcoxon rank sum tests. Cox proportional hazards models were used to examine the association between AHREs and the primary endpoint (death or nonfatal stroke), death, and atrial fibrillation. Models were adjusted for other known predictors of each endpoint and for variables that showed an imbalance between the ancillary study patients and the rest of the MOST patients (gender, race, and prior AF).

AHREs were entered into the models as time-dependent covariates, with patients entering the AHRE risk class at the time of the first recorded episode. Twenty-two patients who were enrolled into the ancillary study after their initial enrollment in MOST and after reaching the AF endpoint for the main MOST trial (ECG documented AF) were not included in the AF analysis. To graphically illustrate the relationship of AHREs with the primary endpoint, ancillary study patients who had not met the primary endpoint within the first year were divided into groups who did and did not have an AHRE by 1 year. Kaplan-Meier estimates for primary endpoint events occurring after 1 year in each group were calculated and graphically displayed. The association of pacing mode with AHREs was examined using an unadjusted log rank test.

**Results**

There were 2010 patients enrolled in the main trial from 91 clinical sites. They had a median follow-up of 33.1 months. There were 312 patients enrolled in the ancillary study with a median follow-up of 27 months. There was a higher proportion of women and a lower proportion of minorities in the ancillary study compared with the main trial. Ancillary study patients also had a higher prevalence of prior supraventricular arrhythmias (SVT) (60% versus 51%; \(P=0.003\)).

The 312 patients in the ancillary study had a median age of 74 years, 55% were female, and 60% had a history of SVT. There were 160 (51.3%) patients with at least one AHRE. The median time to first AHRE was 100 days from ancillary study enrollment (25th, 75th percentile: 16, 303 days). Patients with AHREs were more likely to have a history of SVT, atrioventricular block, antiarrhythmic drug use, and heart failure than patients without AHREs (Table).

**Clinical Events**

ECG documented AF was confirmed in 56/144 (38.9%) patients with AHRE (20 before the first recorded AHRE) and in 3/146 (2.1%) without AHREs (Figure 1). The primary trial endpoint of death or nonfatal stroke occurred in 33/160 (20.6%) patients with AHREs (1 event occurred before the first recorded AHRE) and in 16/152 (10.5%) without AHREs (Figure 2). There were 28/160 (17.5%) deaths in the group with AHREs and 16/152 (10.5%) deaths in the no-AHRE group. There were 10 strokes in the ancillary study population; 8/10 (80%) of them occurred in the AHRE group (1 before the first recorded AHRE).

Multivariable analyses demonstrated that the presence of any AHRE was an independent predictor of the following: total mortality (hazard ratio AHRE versus no AHRE and 95% confidence intervals = 2.48 [1.25, 4.91]; \(P=0.0092\)), death or nonfatal stroke (2.79 [1.51, 5.15]; \(P=0.0011\)), and atrial fibrillation (5.93 [2.88, 12.2]; \(P=0.0001\)).
Baseline Characteristics for Patients With Atrial High Rate Episodes (AHREs) vs Those Without

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Patients With AHREs (n=160)</th>
<th>Patients Without AHREs (n=152)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>75 (68,81)</td>
<td>73 (68,79)</td>
<td>0.16</td>
</tr>
<tr>
<td>Female, % (n)</td>
<td>55 (88)</td>
<td>55 (83)</td>
<td>0.94</td>
</tr>
<tr>
<td>Caucasian, % (n)</td>
<td>93 (149)</td>
<td>88 (133)</td>
<td>0.091</td>
</tr>
<tr>
<td>Weight, lb</td>
<td>164 (140, 192)</td>
<td>157 (134, 185)</td>
<td>0.067</td>
</tr>
<tr>
<td>Prior stroke/TIA/embolism, % (n)</td>
<td>20 (32)</td>
<td>15 (23)</td>
<td>0.26</td>
</tr>
<tr>
<td>Charlson Comorbidity Index, % (n)</td>
<td>0 30 (48)</td>
<td>36 (55)</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>1 or 2 48 (76)</td>
<td>51 (77)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 or 4 14 (22)</td>
<td>10 (15)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 or more 9 (14)</td>
<td>3 (5)</td>
<td></td>
</tr>
<tr>
<td>Diabetes, % (n)</td>
<td>23 (37)</td>
<td>18 (27)</td>
<td>0.24</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>133 (120, 150)</td>
<td>140 (124, 150)</td>
<td>0.24</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>70 (62, 80)</td>
<td>73 (68, 82)</td>
<td>0.036</td>
</tr>
<tr>
<td>Prior supraventricular arrhythmia, % (n)</td>
<td>81 (129)</td>
<td>39 (59)</td>
<td>0.001</td>
</tr>
<tr>
<td>Prior ventricular arrhythmia, % (n)</td>
<td>3 (4)</td>
<td>5 (7)</td>
<td>0.31</td>
</tr>
<tr>
<td>Prior atrioventricular block, % (n)</td>
<td>36 (57)</td>
<td>18 (27)</td>
<td>0.001</td>
</tr>
<tr>
<td>Antiarhythmic at admission, % (n)</td>
<td>29 (46)</td>
<td>11 (16)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension, % (n)</td>
<td>61 (98)</td>
<td>58 (88)</td>
<td>0.55</td>
</tr>
<tr>
<td>Hypercholesterolemia, % (n)</td>
<td>43 (68)</td>
<td>34 (52)</td>
<td>0.13</td>
</tr>
<tr>
<td>Prior angina, % (n)</td>
<td>31 (49)</td>
<td>24 (37)</td>
<td>0.21</td>
</tr>
<tr>
<td>Prior myocardial infarction, % (n)</td>
<td>23 (37)</td>
<td>28 (42)</td>
<td>0.36</td>
</tr>
<tr>
<td>Prior CHF, % (n)</td>
<td>22 (35)</td>
<td>11 (16)</td>
<td>0.006</td>
</tr>
<tr>
<td>Prior CABG, % (n)</td>
<td>18 (29)</td>
<td>18 (28)</td>
<td>0.95</td>
</tr>
<tr>
<td>Prior PTCA, % (n)</td>
<td>13 (20)</td>
<td>9 (14)</td>
<td>0.36</td>
</tr>
<tr>
<td>NYHA CHF class, % (n)</td>
<td></td>
<td></td>
<td>0.51</td>
</tr>
<tr>
<td>I</td>
<td>43 (68)</td>
<td>48 (73)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>44 (71)</td>
<td>37 (56)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>12 (19)</td>
<td>14 (22)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>1 (2)</td>
<td>1 (1)</td>
<td></td>
</tr>
</tbody>
</table>

Continuous variables are presented as median (25th, 75th percentile). Categorical variables are presented as percent (number). AHRE indicates atrial high rate episode; TIA, transient ischemic attack; CHF, congestive heart failure; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; and NYHA, New York Heart Association.

Ambulatory Monitoring
Ambulatory monitor data recorded at precisely the same time and date as pacemaker download data were available from 47 of 312 patients. Of these, 41 patients had no AF on the Holter tracing and no AHRE detected by the pacemakers. In one patient, the pacemaker stored an AHRE but there was no atrial arrhythmia on the ambulatory monitor. In 5 patients, an AHRE was detected by the pacemaker and corresponded to AF on the ambulatory recording. The sensitivity and specificity for detection of AF using AHREs recorded by pacemakers in this study was 100% and 97.6%, respectively. The false-positive rate was 2.4%.

Symptoms
Symptom data were available from 308/312 (98.7%) patients. The majority of patients (223/308, 72.4%) were symptomatic at some time. Of 159 AHRE patients, 131 (82.4%) were symptomatic, and of 149 non-AHRE patients, 92 (61.7%) were symptomatic. When symptoms (using moderate severity) are assessed as an indicator of AHREs, their sensitivity is 82.4%, but their specificity is 38.3%, with a positive predictive value of 58.7%.

Effect of Pacing Mode Assignment
Of 190 DDDR patients in the sample, 95 (50.0%) had AHREs. Of 122 VVIR patients, 65 (53.3%) had AHREs. There was no significant effect of pacing mode on the presence or absence of AHREs (log rank P=0.79).

Discussion
Technological advances in cardiac pacing initially focused on therapeutic modalities such as the development of dual...
chamber pacing or the development of rate modulation. More recently, the use of the cardiac pacemaker as an implanted arrhythmia monitor has been refined. The application of these capabilities to bradycardia pacing can be traced to the development of both ventricular and atrial cardioverter-defibrillators.¹²,¹³ These diagnostic features can evaluate the appropriateness of atrial and ventricular sensing, can test lead integrity, can be used to modulate features such as rate-responsiveness, and can provide continuous arrhythmia surveillance.¹⁴–¹⁶ Like many other technological advances in pacing, however, the clinical impact of this advanced capability has not been thoroughly studied. To our knowledge, the present report is the largest prospective observational study to assess the clinical significance of nonsustained episodes of atrial tachyarrhythmias in pacemaker patients.

A critical issue in assessing the clinical significance of AHREs is validating the technique and achieving optimal programming of the detection parameters. Pollack et al.⁸ analyzed the stored intracardiac electrograms from pacemakers to validate the digital data. They reported that stored episodes digitally classified by the pacemaker as 220 beats per minute and 5 minutes in duration had a high correlation (88%) with the tachyarrhythmia validated by simultaneous stored intracardiac electrograms. With regards to actual electrocardiographic confirmation of arrhythmia, Seidel et al.⁷ compared Holter monitor recordings to pacemaker diagnostic reports. They concluded that optimal programming for reliable arrhythmia detection (98% sensitivity and 100% specificity) could be attained with exactly the same programming as pacemakers were programmed in our study: detection rate 220 beats per minute, onset number of beats 10, and termination number of beats 20. The ELA algorithm for identifying atrial arrhythmias detected atrial arrhythmias verified by ambulatory monitoring with 93% sensitivity and 94.2% specificity.⁶ Our ambulatory monitoring sample, although small, provided almost identical sensitivity and specificity results to these prior studies.

The incidence of device-detected atrial arrhythmias in this study and in others is far higher than that of clinically reported arrhythmias. Gillis et al.⁴ detected atrial arrhythmias in 68% of 231 patients with pacemakers for SND. The Automatic Interpretation for Diagnostic Assistance (AIDA) study found that 179/354 (50.6%) patients had supraventricular arrhythmias detected by the ELA Chorus pacemakers.³ The results of the studies outlined above reveal a consistent 50% incidence of unsuspected SVT when stored pacemaker data are analyzed. This is quite comparable to our present report showing AHREs in 51% of 312 patients.

The enhanced monitoring capabilities of cardiac pacemakers, as well as the unexpectedly high incidence of atrial arrhythmias in a population of pacemaker patients, raises the question of whether there is any clinical significance to these, generally nonsustained, dysrhythmias. We found that patients with AHREs are more likely to have adverse clinical outcomes, including a higher incidence of stroke, death, and subsequent AF than are patients without AHREs. Multivariable analyses, controlling for multiple prognostic factors, demonstrated that the presence of any AHRE meant that a patient was 2.5 times more likely to die, 2.8 times more likely to die or have a nonfatal stroke, and nearly 6 times as likely to develop AF as one without any AHRE.

The present pathophysiological understanding and clinical staging of AF is based on the paradigm of AF as a chronic, progressive condition that passes through definable clinical stages.

**Figure 1.** Documented AF in patients with AHREs vs patients without AHREs; P=0.0001. AHRE indicates atrial high rate episodes; AF, atrial fibrillation.

**Figure 2.** Kaplan-Meier plot of death or nonfatal stroke after 1 year of ancillary study follow-up in patients with AHREs vs those without AHREs; P=0.001. MOST indicates Mode Selection Trial; AHRE, atrial high rate episodes.
phases. Specifically, before the development of permanent AF, patients pass through an intermediate clinical stage during which AF recurs and may be persistent, but does not yet become permanent. The present analyses demonstrate that the spectrum of recurrent AF includes multiple nonsustained episodes of atrial tachycardia that presage persistent or permanent AF. Furthermore, these nonsustained arrhythmias have independent clinical significance.

The relationship of AHRE with stroke cannot be fully elucidated based on the small number of observed strokes. It is, however, well accepted that AF is a risk factor for stroke. Although there are few clear data correlating the length of time in AF to risk of stroke, we report that the presence of AHRE lasting at least 5 minutes is correlated with a higher stroke rate. We cannot, however, conclude that an atrial arrhythmia of 5 minutes in duration merits treatment to prevent stroke.

Our study demonstrates that AHREs are an independent predictor of all-cause mortality after adjustment for baseline variables. It is unlikely that AHREs were causal in the increased mortality. It is, however, far more likely that patients with AHREs have more severe underlying heart disease and, consequently, higher mortality. In the statistical analysis, we sought to account (adjust) for multiple other factors that characterize the underlying severity of disease. Nonetheless, regardless whether this relationship is one of causation or association, it remains clinically valuable to detect AHRE in a pacemaker recipient with SND.

Not all SND patients with implanted pacemakers have devices with the monitoring capabilities described here. With this in mind, we also investigated whether symptoms could be used to differentiate patients with or without AHRE. Our study extends prior observations that reliance on patient reported symptoms for clinical recognition of AHREs is unreliable. The AIDA study compared stored pacemaker data to Holter monitors and to patients’ clinical history of symptoms. The AIDA investigators, like us, found a poor correlation between symptoms and the presence of AHRE detected by the pacemaker. Previous studies have shown that unlike paroxysmal SVT, which is usually symptomatic, paroxysmal atrial fibrillation is often entirely asymptomatic. When symptoms were assessed as an indicator of AHREs in our study, they had a moderate degree of sensitivity and very poor specificity leading to an unacceptable positive predictive value of 58.7%. As such, symptoms are not a reliable predictor of which patients have AHREs.

Atrial-based, as compared with ventricular-based, pacing has been previously shown to reduce the incidence of AF. In MOST, dual chamber–paced patients had a lower risk of developing clinically evident AF. In contrast, in the ancillary study cohort reported in this article, we did not find an effect of pacing mode on the presence or absence of AHREs. Perhaps this is because many AHREs are short lived and only some AHREs represent a precursor to AF. Nonetheless, it is possible that in a larger sample of patients, a reduction of the burden of AHREs with dual chamber pacing might be detected.

Study Limitations
There were some differences in our ancillary study population in gender, race, and arrhythmia history, compared with the MOST population as a whole. Although we included these factors as adjustment variables in the analyses, there may be some impact of these differences on the ability to generalize our results to the overall MOST population. The AHRE group and the non-AHRE group also had some differences in prior SVT history, antiarrhythmic drug use, and history of heart failure, implying that the patients with AHREs were generally a sicker population. Although we sought to adjust for these differences in the statistical analyses, it is possible that the outcome differences observed represent an association with unmeasured or unknown descriptors of more severe heart disease, and not causation of events by AHREs. We do not believe these differences limit the applicability of our findings to the overall population of patients with SND. To date, there are few descriptions of high risk features for patients with SND.

Conclusions
In patients with SND, pacemaker-detected AHRE, lasting at least 5 minutes, identify patients that are more than twice as likely to die or have a stroke, and are nearly 6 times as likely to develop atrial fibrillation as similar patients without AHRE. These data strongly suggest that AHRE data should be collected from capable pacemakers and used to risk-stratify pacemaker patients with sick sinus syndrome. Further study will be required to determine if early treatment and intervention could impact on mortality and morbidity.

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References
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