

Relevance of Electrical Remodeling in Human Atrial Fibrillation

Results of the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial Mechanisms of Atrial Fibrillation Study

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Background—In animal models of atrial fibrillation (AF), changes in atrial electrophysiological properties are associated with the development of AF. Their relevance to human AF is unclear.

Methods and Results—The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial enrolled 2580 patients receiving a dual-chamber pacemaker, who were older than the age of 65 and had a history of hypertension, but no history of AF. Serial noninvasive electrophysiological testing was performed over 2 years in a subgroup of 485 patients. There were no differences in the clinical characteristics between patients with and those without device-detected atrial tachyarrhythmias during the first year. Patients with atrial tachyarrhythmias had longer paced (153 ± 29 versus 145 ± 28 ms; $P=0.046$) and sensed (128 ± 46 versus 118 ± 25 ms; $P=0.06$) P-wave durations and were more likely to have AF induced during electrophysiological testing (23.5% versus 13.6%; $P=0.03$). They had similar corrected sinus node recovery times at 90 bpm (388 ± 554 versus 376 ± 466 ms; $P=0.86$), atrial effective refractory periods at 90 bpm (250 ± 32 versus 248 ± 36 ms; $P=0.70$), and rate-adaptive shortening of the atrial effective refractory periods (14 ± 13 versus 12 ± 14 ms; $P=0.11$). There were no significant differences in the change in electrophysiological properties over 2 years between patients with and those without atrial tachyarrhythmias.

Conclusions—Prolonged P-wave duration, but not differences in atrial effective refractory periods, was associated with the development of atrial tachyarrhythmias in pacemaker patients. (*Circ Arrhythm Electrophysiol.* 2012;5:626-631.)

Key Words: atrial fibrillation ■ electrophysiology ■ hypertension ■ pacemakers ■ remodeling

Many patients with permanent pacemakers are at risk of developing atrial fibrillation (AF) as a result of asynchronous single-chamber ventricular pacing^{1,2} or because of unnecessary ventricular pacing.³ However, in addition to these factors, pacemaker recipients are typically elderly and often have hypertension,² which are the two most prevalent risk factors for AF in North America.^{4,5} Thus, even with the routine use of dual-chamber pacing and with optimal atrioventricular delay programming, pacemaker patients remain at risk for AF.³

Clinical Perspective on p 631

Several experimental AF animal models have demonstrated that changes in the electrophysiological (EP) properties of the atria facilitate the development of AF and that the development of AF leads to further evolution of these EP changes.⁶⁻⁸ This process has been termed electrical remodeling.⁷ In rapid atrial pacing models of AF, the dominant change is a shortening of the atrial effective refractory period (AERP) in both atria, which occurs within 24 hours of rapid pacing.^{6,7}

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Prolongation in conduction velocity was seen in only one⁶ of these models.^{6,7} In contrast, in a rapid ventricular pacing heart failure model, changes in AERP were not noted, but a significant prolongation of conduction velocity was observed and was associated with the development of AF.⁸

Although much of our current understanding of AF is based on these animal models, it is unclear how relevant they are to the development of clinical AF in humans, as invasive assessment^{9,10} or use of a noninvasive surrogate is needed to measure these parameters.^{11–13} This has limited the direct evaluation of human atrial remodeling in all but short-term studies.^{9,10,14} Furthermore, as a large percentage of AF may be clinically silent,¹⁵ it is difficult to accurately define which patients actually have AF and to correlate this with changes in atrial EP properties. However, the limited human studies suggest that atrial EP remodeling does occur^{10,12,13,16} but are too small and have follow-up that is too short to characterize the evolution of clinical AF.

The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT)^{17,18} enrolled 2580 patients receiving a dual-chamber pacemaker or an implantable defibrillator who were ≥ 65 years of age with a history of hypertension but who did not have any history of symptomatic AF. As all episodes of AF were documented by the pacemaker, ASSERT permits accurate characterization of AF status in a large number of patients during extended follow-up. The presence of a right atrial pacing electrode in all patients facilitates serial evaluation of atrial EP properties in a noninvasive, outpatient setting. Together, these design features permit a unique opportunity to study the EP changes associated with the very early development of clinical AF.

Methods

The methods of ASSERT have been previously published in detail.¹⁷ All patients were programmed to dual-chamber pacing with atrioventricular delay programming optimized to reduce ventricular pacing frequency.¹⁷ Patients were followed up for a mean of 2.8 years for the development of clinical AF, stroke, or systemic embolism. All episodes of pacemaker-detected atrial tachyarrhythmias (ATs) were documented and sent for independent adjudication by a committee blinded to the results of electrophysiology testing. In the main ASSERT trial¹⁸ and in this substudy, pacemaker-detected AT ≥ 6 minutes and with an atrial rate of ≥ 190 /min were prospectively defined as the threshold for significance. Atrial rates were manually calculated for all ATs by counting all of the high-frequency atrial electrogram signals during a time of at least 3 s and were documented along with the automatic rates recorded by the pacemaker. ASSERT also contained an embedded, randomized, controlled trial of dynamic atrial overdrive pacing for the suppression of AF.^{17,18} Patients were randomized in a 1:1 fashion to receive this pacing algorithm, which encouraged atrial pacing just slightly faster than the intrinsic sinus rate.

Mechanisms of AF Substudy

At selected sites, with experience with invasive and noninvasive EP testing, a subgroup of patients underwent serial noninvasive EP testing using their St. Jude Medical dual-chamber pacemaker (Identity-DR models 5380/5386 and Victory-DR, St. Jude Medical, St. Paul, MN). Patients with severe angina (Canadian Cardiovascular Society classes III and IV) were not eligible for participation in this substudy. None of the patients in this substudy was receiving antiarrhythmic medications at baseline. EP testing was conducted in the

pacemaker clinic with the patient in the resting, supine, nonsedated state and was completed at the time of randomization and repeated at the 1- and 2-year visits. The sinus cycle length was recorded, and examples of a sensed and paced P wave was printed, using the maximum sweep speed (50 or 100 mm/s) that would permit clear determination of the onset and offset of the P wave (Figure). Lead II was typically used; however, in the event that the P wave was not seen well in this lead at baseline, a better lead was chosen and then used for all follow-up measurements. Next, the sinus node recovery time (SNRT) was measured at atrial pacing rates of 90 and 120 bpm and was corrected for the underlying sinus cycle length in the standard fashion (Figure). Following a 2-minute rest period between tests, patients were atrially paced at these two rates for 30 s, and the interval between the last atrial-paced beat and the first spontaneous sinus node activity was measured. Next, right AERP was measured at drive train rates of 90 and 120 bpm using 8 S1 stimuli followed by a single S2. The S2 coupling interval was started at 200 ms, then increased in steps of 10 ms until atrial capture was confirmed and then repeated at +10 ms and +20 ms to confirm consistent capture. A step-up protocol was used to minimize the number of S2 stimuli capturing the atrium, thereby minimizing the risk of AF induction. Atrial capture was confirmed by demonstration of an evoked response on the atrial bipolar (Atrip-Aring) electrogram channel (Figure). Observation of a P-wave on the surface electrocardiogram was used to corroborate this finding, and in cases in which polarization artifact precluded the observation of an evoked response, observation of surface P-waves was used as the principal means of confirming atrial capture. At each basic cycle length, AERP testing was done twice and was performed a third time if there was a difference of >20 ms between AERP measurements. The average of all AERP values at each cycle length was recorded.

The details of any AT (>3 beats) induced by EP testing were recorded as a marker of atrial vulnerability. Printouts for all P-wave durations, SNRT, and AERP measurements were labeled and sent for adjudication by an experienced committee, whose members did not know if the patient had experienced any device-detected AT. If the first adjudicator disagreed with the values obtained by the site, the case was sent to a second adjudicator for review. A third adjudicator resolved any discrepancies between the first two adjudicators, involving a difference in AERP of >20 ms or a difference in SNRT or P-wave duration of $>20\%$. Lesser discrepancies were resolved by taking the average value of the two adjudicators.

Normally distributed continuous variables are expressed using mean and SD and are compared between groups using the Student *t* test. Nonnormally distributed variables are expressed using the median and intraquartile range and are compared using the Wilcoxon test. Categorical variables were compared using the Fisher exact test.

Results

A total of 485 patients were enrolled in the ASSERT mechanisms of AF substudy at 43 of the 135 clinical centers. All had bipolar atrial leads that were placed in the right atrial appendage (86%), the interatrial septum (6%), or other locations (8%). No patient received amiodarone during follow-up, and other antiarrhythmic agents were used by 1.3% of the patients at 12 months and 1.8% of the patients at 24 months. A total of 100 patients (21%) had at least one device-detected AT ≥ 6 minutes with an atrial rate ≥ 190 bpm during the first year after enrollment. The median time between the most recent episode of AT and the 12-month EP evaluation was 157 (interquartile range, 18–232) days, and 8.5% of individuals with AT had an episode within 48 hours of testing. There were no significant differences in the clinical characteristics between patients with and without device-detected AT during the first year (Table 1). The average number of device-detected AT in this substudy was 8 ± 11 , their average atrial rate was 447 ± 124 bpm, and their median duration was 6.3 (interquartile range, 45) hours. Clinical AF was

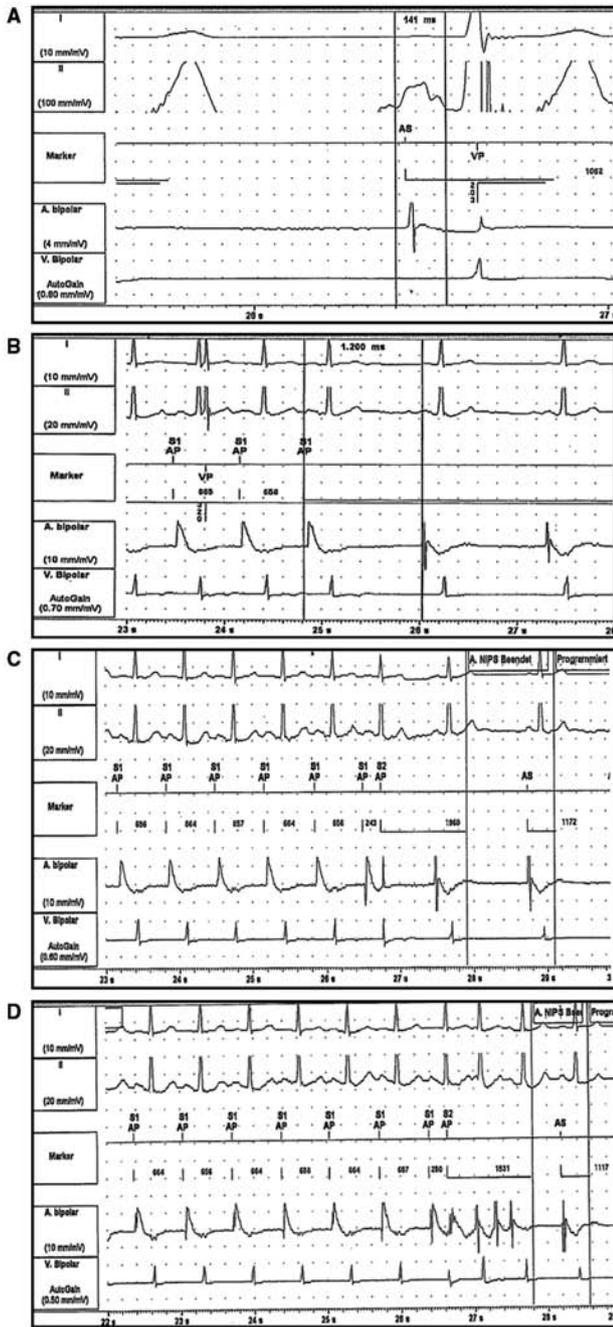


Figure. Noninvasive electrophysiological measurement of (A) sensed P-wave duration of 141 ms; (B) sinus node recovery time at 90 bpm of 1200 ms; (C) atrial effective refractory period (AERP) testing at 90 bpm showing no capture with S2 coupling of 240 ms (ie, AERP=240 ms); (D) AERP testing at 90 bpm showing atrial capture with S2 coupling of 250 ms and with induction of a brief episode of atrial tachycardia.

documented by surface electrocardiographic recording in 19 of the 485 (4%) patients during the course of this substudy, all of whom had device-detected AT.

EP testing was typically completed in <15 to 20 minutes.¹⁹ ATs were induced during 126 noninvasive EP testing procedures (13.4%) but required intervention (oral propafenone) to terminate in only 1 case. No other serious complications were seen. Baseline EP testing was performed in 410 patients and was interpretable for 368 patients. In 42 cases, EP testing was

Table 1. Clinical Characteristics of Patients With and Without Device-Detected AT During the First Year After Enrollment

Patient Characteristic	Patients With Device-Detected AT (n=100)	Patients Without Device-Detected AT (n=385)	P Value
Age, y	81±7	81±7	0.86
Female, %	45	45	0.95
Prior stroke, %	7	9	0.46
Hypertension, %	100	100	1.0
Heart failure, %	13	16	0.41
Diabetes mellitus, %	23	31	0.12
Atrioventricular block, %	54	59	0.37
LVEF, %	60±11	59±12	0.33
Atrial pacing (12-month visit), %	68.6±31.5	61.8±35.8	0.063
Ventricular pacing (12-month visit), %	56.0±38.7	49.5±39.7	0.14

AT indicates atrial tachyarrhythmia; LVEF, left ventricular ejection fraction.

done incorrectly, had insufficient documentation retained for adjudication, or was not interpretable because of the use of atrial leads with polarization artifact.

Baseline EP Properties and Development of AT

Compared with patients without AT, the 100 patients who developed device-detected AT during the first year had longer sensed and paced P-wave durations and had greater atrial vulnerability, with AT more frequently induced in these patients during EP testing (Table 2). However, they had similar AERP, rate-adaptive behavior of the AERP and had similar corrected SNRT (Table 2). Prolongation of baseline P-wave duration in patients who developed AT was more often observed in the subgroup of patients with atrioventricular block (sensed

Table 2. Baseline EP Properties of Patients With and Without Device-Detected AT ≥6 min During the First Year After Enrollment

Patient Characteristic	Patients With Device-Detected AT (n=81)	Patients Without Device-Detected AT (n=287)	Difference (95% CI)	P Value
Sinus cycle length, ms	975±174	949±233	26 (−22 to +75)	0.26
cSNRT-90, ms	320 (180 to 430)	280 (180 to 410)	40	0.58
cSNRT-120, ms	320 (190 to 520)	290 (174 to 430)	30	0.33
AERP-90, ms	250±32	248±36	2 (−8 to +11)	0.70
AERP-120, ms	235±28	236±32	−1 (−10 to +7)	0.68
Rate adaption of AERP, ms	10 (5 to 15)	10 (5 to 15)	0	0.19
Sensed P-wave duration, ms	128±46	118±25	10 (−1 to +21)	0.06
Paced P-wave duration, ms	153±29	145±28	7 (0 to +14)	0.046
Atrial vulnerability, %	23 (15 to 34)	14 (10 to 18)	10 (0 to +20)	0.03

EP indicates electrophysiological; AT, atrial tachyarrhythmia; cSNRT, corrected sinus node recovery time; AERP, atrial effective refractory period.

Table 3. Baseline EP Properties of Patients With and Without Device-Detected AT \geq 24 or Clinical AF

Patient	Patients With \geq 24 h or Clinical AT/AF (n=43)	Patients Without AT \geq 24 h or Clinical AT/AF (n=325)	Difference (95% CI)	P Value
Sinus cycle length, ms	1027 \pm 200	945 \pm 222	82 (9 to +156)	0.01
cSNRT-90, ms	286 (180 to 505)	286 (180 to 417)	0	0.67
cSNRT-120, ms	275 (179 to 480)	299 (180 to 440)	-24	0.75
AERP-90, ms	250 \pm 30	248 \pm 36	2 (-10 to +14)	0.74
AERP-120, ms	234 \pm 27	236 \pm 31	-2 (-13 to +8)	0.60
Rate adaption of AERP, ms	13 (10 to 20)	10 (5 to 20)	3	0.13
Sensed P-wave duration, ms	138 \pm 57	118 \pm 25	21 (2 to +39)	0.02
Paced P-wave duration, ms	160 \pm 28	145 \pm 28	14 (5 to +23)	0.002
Atrial vulnerability, %	28 (17 to 43)	14 (11 to 18)	14 (0 to +28)	0.02

EP indicates electrophysiological; AT, atrial tachyarrhythmia; AF, atrial fibrillation; cSNRT, corrected sinus node recovery time; AERP, atrial effective refractory period.

P-wave: 129 \pm 26 versus 116 \pm 25 ms, difference 12 ms [95% CI: 5–20 ms], $P=0.001$; paced P-wave: 156 \pm 24 versus 143 \pm 26 ms, difference 13 ms [95% CI: 6–21 ms], $P=0.0002$) and was less pronounced in patients with sinus node dysfunction (sensed P-wave: 125 \pm 53 versus 118 \pm 25 ms, difference 7 ms [95% CI: -9 to 23 ms], $P=0.36$; paced P-wave: 152 \pm 33 versus 146 \pm 29 ms, difference 6 ms [95% CI: -5 to 17 ms], $P=0.28$).

Finally, electrocardiographically diagnosed clinical AF or episodes of device-detected AT \geq 24 hours developed in 43 patients over the course of the study. Compared with those without such episodes, these patients had longer P-wave durations and greater atrial vulnerability (Table 3). The profile of EP changes with these longer episodes was qualitatively similar to the changes seen with episodes >6 minutes; however, the magnitude of the changes was approximately 2-fold greater, and the results were more highly significant (Tables 2 and 3).

Change in Atrial EP Properties Over Time

Over the course of 2 years, there was no significant difference in the change in EP parameters between those with and those without device-detected AT \geq 6 minutes (Table 4).

Atrial Tachycardia Rate: Changes Over Time and Relationship to Duration

The atrial rate was manually calculated from stored electrograms for all episodes of AT. The average atrial rate of patients' AT was faster among patients experiencing AT episodes \geq 1 hour compared with those with shorter episodes (472 \pm 120 versus 384 \pm 112 bpm; $P<0.001$), in those having episodes \geq 24 hours (484 \pm 113 versus 433 \pm 125 bpm; $P=0.02$), and in those developing sustained clinical AF (506 \pm 92 versus 439 \pm 126 bpm; $P=0.02$). Among patients who had AT, both between baseline and 1 year and between 1 and 2 years, there

Table 4. Change in EP Parameters Between Baseline and 24 Months in Patients With and Without Device-Detected AT \geq 6 min

Patient Characteristic	Patients With Device-Detected AT (n=68)	Patients Without Device-Detected AT (n=179)	P Value
Sinus cycle length, ms	+47 \pm 269	+16 \pm 208	0.37
cSNRT-90, ms	+25 (-179 to 190)	+4.5 (-146 to 100)	0.40
cSNRT-120, ms	+5 (-277 to 294)	-9 (-192 to 180)	0.39
AERP-90, ms	+10 \pm 31	+10 \pm 48	0.94
AERP-120, ms	+4 \pm 43	+8 \pm 39	0.54
Sensed P-wave duration, ms	-5 \pm 58	-3 \pm 42	0.69
Paced P-wave duration, ms	-27 \pm 141	+28 \pm 459	0.34

EP indicates electrophysiological; AT, atrial tachyarrhythmia; cSNRT, corrected sinus node recovery time; AERP, atrial effective refractory period.

was no significant change in the AT atrial rate between time periods (435 \pm 118 versus 476 \pm 107 bpm; $P=0.70$).

Effect of Dynamic Atrial Overdrive Pacing on Atrial Electrophysiology

The randomized portion of ASSERT demonstrated that dynamic atrial overdrive pacing did not reduce the incidence of clinical AF.¹⁸ However, patients randomized to receive dynamic atrial overdrive had shorter AERP measurements after 1 year (Table 5).

Discussion

In this large, well-characterized group of pacemaker patients without prior AF, prolongation of P-wave duration at baseline was associated with an increased risk of developing AT. Unlike some animal models,^{6,7} a shorter AERP was not observed in patients developing AT, as measured directly using the right atrial pacing electrode. Perhaps this is not surprising given the broad range in the phenotype of human AF and the limitations

Table 5. EP Parameters at 12 Months Based on Treatment Allocation in ASSERT Randomized Trial: Dynamic Atrial Overdrive On vs Off

Patient Characteristic	Dynamic Atrial Overdrive on (n=153)	Dynamic Atrial Overdrive off (n=155)	Difference (95% CI)	P Value
Sinus cycle length, ms	954 \pm 226	968 \pm 265	-14 (-70 to +40)	0.62
cSNRT-90, ms	270 (180 to 400)	247 (129 to 462)	23	0.35
cSNRT-120, ms	270 (170 to 410)	270 (141 to 494)	0	0.86
AERP-90, ms	243 \pm 32	254 \pm 38	-11 (-19 to -3)	0.0065
AERP-120, ms	235 \pm 45	246 \pm 35	-11 (-20 to -1)	0.026
Sensed P-wave duration, ms	118 \pm 25	117 \pm 29	1 (-5 to +7)	0.53
Paced P-wave duration, ms	137 \pm 29	139 \pm 25	-2 (-8 to +4)	0.21

EP indicates electrophysiological; ASSERT, Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial; cSNRT, corrected sinus node recovery time; AERP, atrial effective refractory period.

of extrapolating the results of any single animal model to a human condition. It is also possible that the slowing of conduction observed in the rapid ventricular pacing heart failure model,⁸ and in dog models of AF associated with aging,²⁰ may be more reflective of the elderly, hypertensive patients who participated in this study rather than rapid atrial pacing models of AF.^{6,7} It is well known that hypertension is associated with left ventricular hypertrophy,²¹ left atrial enlargement,²² and slowing of atrial conduction velocity,²³ all of which predict the development of AF^{13,24} and are seen in the heart failure model of AF.⁸ The rapid atrial pacing model^{6,7} may be more relevant for patients with lone AF, none of whom was included in this current study.

Electrical Remodeling

Although the measurement of AERP in ASSERT was sensitive enough to document important differences in AERP between patients with sinus node disease and atrioventricular block,¹⁹ it failed to detect any difference in baseline AERP or AERP shortening among patients who developed AT. Perhaps this was because AERP was only measured in the right atrium; however, the AERP shortening observed in both animal models and humans is seen in both the right and left atria.^{7,10} More likely, this was because AERP shortening in animal models is both rapid (<24 hours) and transient in nature,^{6,7,16} and in ASSERT, AERP was directly measured on only three occasions over 2 years. However, ASSERT documented that AT cycle length became shorter as AT episode duration became longer, which, given the established correlation between shortening of the atrial cycle length during AT and shortening of measured AERP,^{25,26} suggests that AT-induced AERP shortening occurs and likely leads to AT episodes becoming longer in duration.^{6,7,16} Still, in patients who go on to develop AT, AERP shortening is not measurable before AT develops, at a time when atrial vulnerability is increased, suggesting that other factors like prolonged conduction play a larger role during this early phase.¹⁰

Patients in the ASSERT mechanisms of AF study were elderly, with an average age of 81 years. An age-related slowing of transverse propagation has been documented in the experimental models of AF, which correlates with the development of collagenous septa and fibrosis and increased atrial vulnerability without significant changes in AERP.²⁷ Prolongation of P-wave duration is a function of both slowed atrial conduction velocity and increased atrial size. Unfortunately, neither direct measurements of atrial conduction velocity nor precise measurements of atrial volume were performed in this study, so it is impossible to separate the relative contribution of each. Still, there are conflicting data from other small studies that suggest that an increased P-wave duration predicts the development of AF in pacemaker patients.^{28,29} The ASSERT mechanisms of AF study further support this hypothesis; however, it did not detect a clinically useful threshold P-wave duration that could reliably identify a significant group of patients at risk for AT.

The observation of shorter AERP values among patients randomized to dynamic atrial overdrive pacing is surprising, particularly in the context of the neutral effect this algorithm had on the development of AF.¹⁸ The reasons for this are unclear, but it is possible that chronic atrial overdrive pacing,

even at relatively slow rates, may produce a measurable change in AERP when performed continuously for a period of 12 months.

The results of the ASSERT mechanisms of AF substudy give some insights into the EP changes that occur during the very early development of human AF, in most cases before AF is clinically detected. However, one should note the important characteristics of this study population. First, these are elderly, hypertensive patients with pacemakers and, therefore, not representative of the general population. However, advanced age and hypertension are the two most prevalent risk factors for AF in our society.³⁰ Second, the episodes of AT in this study had an average length of 6 hours, and clinical AF was rare. Longer episodes may have had a greater impact on atrial electrical remodeling. Finally, although this is the largest, chronic study of EP changes in human AF, in many cases, the changes observed were only nominally statistically significant. Thus, one must consider the possibility of α error.

Conclusions

Among elderly, hypertensive pacemaker recipients without prior AF, P-wave prolongation and increased atrial vulnerability are the main baseline EP predictors of AT. Once AT develops, there is indirect evidence that AERP shortening occurs with the development of longer lasting episodes of AT.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Changes in the electrophysiological (EP) properties of the atria have been shown to facilitate the development of atrial fibrillation (AF) in several experimental animal models. This process, termed electrical remodeling, includes changes, such as shortening of the atrial refractory period and slowing of conduction velocity. However, long-term human studies have not been performed; thus, the relevance of these data to human AF is uncertain. The most common risk factors for clinical AF are advancing age and hypertension. The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial enrolled 2580 patients ≥ 65 years of age with a history of hypertension, but no prior AF, who were receiving a dual-chamber pacemaker. The primary goal of the study was to determine the incidence of pacemaker-detected AF and to determine its association with stroke. However, as all patients had pacemakers capable of performing noninvasive EP testing, a substudy was performed to examine changes in atrial EP properties over 2 years, comparing patients who developed AF against those who did not. Of the 485 patients in this substudy, 100 developed AF. Patients who developed AF had longer P-wave durations and were more likely to have AF induced during EP testing; however, their atrial effective refractory periods and corrected sinus node recovery times were similar to those who did not develop AF. Patients who developed AF did not have any significant changes in their EP parameters over 2 years of follow-up; however, the atrial rate during longer episodes of AF was significantly faster compared with the shorter episodes of AF.

Relevance of Electrical Remodeling in Human Atrial Fibrillation: Results of the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial Mechanisms of Atrial Fibrillation Study

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