Atrial antitachycardia pacing and atrial remodeling: A substudy of the international, randomized MINERVA trial

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BACKGROUND Atrial tachycardia (AT) and atrial fibrillation (AF) are common in pacemaker patients and are associated with bad prognoses.

OBJECTIVE The purpose of this study was to evaluate atrial antitachycardia pacing impact on AT/AF–induced atrial remodeling, measured by early recurrence of AT/AF (ERAF) and by change in left atrial diameter (LAD), and to evaluate the impact of AT/AF duration on ERAF incidence.

METHODS Pacemaker patients were randomized to dual-chamber pacing (Control DDDR: 385 patients), managed ventricular pacing (MVP: 398 patients), or atrial antitachycardia pacing plus MVP (DDDRP+MVP: 383 patients). LAD change, estimated by echocardiography, was considered significant if the relative difference between baseline and 24-month measurements was >10%.

RESULTS At median follow-up of 34 months, ERAF incidence was significantly lower in the DDDRP+MVP arm for all AT/AF durations, in particular, ERAF followed AT/AF longer than 3 hours in 53% cases in Control DDDR, in 51% cases in MVP, and in 39% cases in DDDRP+MVP (P <.001 vs other groups). ERAF incidence showed a U-shaped pattern when evaluated as a function of previous AT/AF duration, decreasing for durations from 5 minutes to 12 hours and increasing for longer durations. Among patients with significant LAD change, the proportion of patients with a reduction in LAD was 35% in Control DDDR, 37% in MVP, and 70% in DDDRP+MVP (P <.05 vs other groups).

CONCLUSION Our data suggest that atrial electrical remodeling becomes important after about 12 hours of continuous arrhythmia. Compared to DDDR or MVP, DDDRP+MVP reduces ERAF and favors LAD reduction, suggesting that atrial antitachycardia pacing may reverse electrical and mechanical remodeling.

KEYWORDS Pacemaker; Atrial fibrillation; Atrial antitachycardia pacing; Atrial reverse remodeling; Reactive antitachycardia pacing; Atrial fibrillation early recurrence; Left atrial diameter

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Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the developed world. It is associated with significant mortality and morbidity, including heart failure and stroke, and is becoming increasingly prevalent because of an aging population.[1]

Pioneering experiments in goats and dogs[2,3] showed that maintenance of AF led to shortening of the atrial refractory period. This preclinical work led to the hypothesis that AF itself is the cause of atrial remodeling and that changes in the atrial electrophysiologic substratum are responsible for AF recurrence and/or perpetuation, as subsequently confirmed also in humans.[4] The presence of an excitable gap during atrial tachycardia (AT), atrial flutter, and AF and the feasibility of local capture by pacing during AF have been demonstrated in both animal experiments[5] and clinical studies in human atria.[6,7] Various types of atrial antitachycardia pacing (ATP) therapies have been incorporated in many modern dual-chamber pacemakers and defibrillators with the aim of terminating reentrant atrial tachyarrhythmias (AT/AF).[8]

The recent MINimizE Right Ventricular pacing to prevent Atrial fibrillation and heart failure (MINERVA) randomized trial showed that a combination of pacing algorithms, comprising ATP, was associated with a significant 61% lower risk of permanent AF after 2-year follow-up in pacemaker patients with bradycardia and paroxysmal or persistent AT/AF compared with standard dual-chamber (DDDR) pacing.[9] It has been reported that atrial electrical remodeling increases vulnerability for early recurrences of AF (ERAF) after AF termination.[10,11] In particular, Daoud et al[10] showed that AF significantly shortens the right atrial effective refractory period and that upon termination of several-minute AF episodes, which cause atrial remodeling, there is an increased propensity for induction of ERAF. The aim of this study was to evaluate the effects of ATP on atrial remodeling and to assess whether atrial electrical remodeling occurs after a specific AF episode duration.

Methods

Study design, patient population, and follow-up

The MINERVA trial, as previously described was a multicenter, randomized, single-blind controlled study involving 63 cardiology centers in 15 countries.[9] The study was approved by the ethics committee of all participating centers and was conducted in compliance with the Declaration of Helsinki. All patients provided written informed consent. Inclusion criteria were standard indications for permanent dual-chamber pacing and a history of AT/AF. The main exclusion criterion was a history of long-standing persistent AF and third-degree AV block. After implantation of a dual-chamber pacemaker (EnRhythm, Medtronic Inc, Minneapolis, MN), eligible patients were randomly assigned to standard dual-chamber pacing (Control DDDR), DDDR with managed ventricular pacing (MVP), or atrial preventive pacing, atrial ATP, and MVP (DDDRP+MVP). Patients underwent follow-up examination at 3 and 6 months after implantation and every 6 months thereafter, until the last enrolled patient reached 2 years of observation.

Reactive ATP

The EnRhythm pacemaker can respond to a sustained AT/AF by delivering a special set of atrial ATP therapies (Reactive ATP). This feature, as described in the Supplemental Appendix and in a previous publication,[9] monitors atrial rhythm and delivers ATP therapies according to AT/AF cycle length and regularity.

Analysis objectives, endpoints, and design

The primary objective of this secondary analysis of the MINERVA trial was to evaluate whether DDDRP+MVP programming reverses atrial remodeling compared with standard DDDR pacing or MVP. Because atrial remodeling has 2 components—electrical remodeling and mechanical remodeling—we assessed 2 main endpoints. The first endpoint was vulnerability for ERAF, defined as recurrence of AT/AF starting within 5 minutes from termination of the previous AT/AF episode and lasting >5 minutes. The second endpoint was change in left atrial diameter (LAD), assessed in patients who underwent echocardiographic measurements at baseline and at 24-month follow-up. Left atrial dilation, measured by echocardiography, was a prespecified secondary endpoint in the study protocol. LAD was estimated through an anteroposterior measurement in the parasternal long-axis view using M-mode echocardiography. Echocardiographic measurements were performed by expert echocardiographers, in each center, who were blinded to study objectives and patients' randomization arm. The secondary objective of this analysis was to investigate the relationship between AT/AF episode duration and ERAF incidence.

AT/AF episodes were defined to form clusters if they were <5 minutes distant of each other. The AT/AF duration cutoffs used in the analyses were chosen based on several clinical and statistical considerations, including the following:

1. Episodes shorter than 5 minutes may be related to noise or runs of premature atrial contractions without clinical relevance
2. ERAF incidence was compared between episodes longer than 5 minutes but shorter than 3 hours and episodes longer than 3 hours, because Schwartzman et al[12] found that an AF duration cutoff of 3 hours was predictive of lower ERAF incidence
3. Recurrence of AT/AF after episodes longer than 7 days was estimated in order to compare results with studies that evaluated AF relapses after atrial cardioversion of persistent AF
4. ERAF incidence was evaluated according to 11 ranges of previous AT/AF duration, and the duration width of each range was chosen according to clinical relevance of the duration cutoff and warranting an appropriate number of episodes in each range.

AT/AF episodes terminated by atrial cardioversion were excluded by the analyses.

Statistical analysis

The analysis set included all patients randomized in the MINERVA trial, according to the intention-to-treat principle. Continuous data are given as mean ± SD or, in the case of skewed distributions, as median (25th–75th percentile range). Categorical data are expressed as counts and percentages.

In order to adjust for multiple episodes per patient, ERAF incidence was adjusted using the generalized estimating equation (GEE) method and together with binomial 95% confidence interval (95% CI) was compared between groups using a Poisson regression approach. Logistic regression was used to evaluate the association between ERAF risk and patients' characteristics, and the odds ratio (OR) with 95% CI was reported. After checking for colinearity, all variables that were significant at the 0.20 level were analyzed in a multivariable backwards elimination model.

The LAD relative change was estimated as the difference between LAD measurements at 24-month follow-up and at baseline, divided by baseline LAD, and was expressed as a percentage. Patients were defined as having reduced LAD if the diameter relative reduction was ≥10%, increased LAD if the diameter relative increase was ≥10%, or unchanged if not reduced or increased. The distributions of LAD were compared between randomized groups using the Kruskal–Wallis test, whereas the χ^2 test was used to compare the percentage of patients with reduced vs increased LAD. The Cox proportional hazard analysis was used to analyze the risk of AT/AF occurrence longer than 7 days, and the hazard ratio (HR) with 95% CI was reported. The proportional hazard assumptions were tested using Schoenfeld residuals. All tests were 2-sided, and $P < .05$ was considered significant. SAS 9.3 (SAS Institute Inc, Cary, NC) was used for statistical analyses.

Results

The patient flow diagram and patient baseline characteristics have been previously described.[9] Approximately half of the patients were female (mean age 74 ± 9 years). AF was documented in 84% of patients. The remaining patients had atrial flutter or AT history. Atrial tachyarrhythmias were characterized by paroxysmal temporal patterns in 78% of patients.

Patients were randomly assigned to 1 of 3 groups: Control DDDR (385 patients), MVP (398 patients), or DDDRP+MVP (383 patients). Median (25th–75th percentile range) follow-up duration was 34 (24–45) months. The analysis dataset comprised 25,395 AT/AF episodes of 276 Control DDDR patients; 23,421 AT/AF episodes of 276 MVP patients; and 40,249 AT/AF episodes of 283 DDDRP+MVP patients. In the latter group, 25,979 AT/AF episodes were treated with ATP, and the GEE-adjusted Reactive ATP efficacy was 44.4% (95% CI 41.3%–47.6%).[13]

The median (25th–75th percentile range) number of AT/AF episodes was 79 (11–152) in the Control DDDR group, 51 (7–148) in the MVP group, and 62 (5–226) in the DDDRP+MVP group. Median AT/AF burden was 17 minutes/day in Control DDDR patients, 9 minutes/day in MVP patients, and 4 minutes/day in the DDDRP+MVP patients ($P = .002$ vs Control DDDR; $P = .032$ vs MVP).

Median (25th–75th percentile) percentage of atrial pacing was 70% (39%–90%) in the Control DDDR arm, 73% (42%–92%) in the MVP arm, and 93% (81%–97%) in the DDDRP+MVP arm ($P < .001$ vs other groups). Median (25th–75th percentile) percentage of ventricular pacing was 53% (15%–84%) in the Control DDDR arm ($P < .001$), 1% (0%–9%) in the MVP arm, and 2% (0%–11%) in the DDDRP+MVP arm ($P < .001$ vs Control DDDR).

Atrial electrical remodeling: Vulnerability for early AT/AF recurrences

ERAF was less common in DDDRP+MVP patients. In particular ERAF was observed in 230 of 276 Control DDDR patients (83%), 232 of 276 MVP patients (84%), and 210 of 283 DDDRP+MVP patients (74%) ($P < .01$ vs other groups). ERAF followed AT/AF termination in 15,497 of 25,395 Control DDDR episodes (61%); 14,721 of 23,421 MVP episodes (63%); and 22,846 of 40,249 DDDRP+MVP episodes (57%) ($P < .001$ vs other groups) (Table 1). In particular, AT/AF episodes longer than 3 hours were followed by ERAF in 53% of cases in the Control DDDR group, 51% in the MVP arm, and 39% of cases in the DDDRP+MVP group ($P < 0.001$ vs other groups). Beyond the absolute numbers of ERAF, the number of ERAF per patient was significantly reduced in the DDDRP+MVP arm (Figure 1).

In the DDDRP+MVP group, the percentage of ERAF after episodes longer than 3 hours was significantly lower (51/251 [20%]) for episodes terminated by ATP compared with episodes in which ATP failed (1488/3794 [39%]; $P = .004$).

Logistic analyses show that the risk of ERAF was significantly reduced in DDDRP+MVP patients compared with the other 2 groups (OR 0.65, $P = .004$) (Table 2).

ERAF incidence was evaluated as a function of the duration of the previous AT/AF episode and showed a U-shaped pattern (Figure 2). AT/AF burden in clusters of ERAF was 4653 hours (88% of total AT/AF burden of 5311 hours in all considered episodes) in Control DDDR patients and 2416 hours (71% of total AT/AF burden of 3397 hours in all stored episodes) in DDDRP+MVP patients ($P < .001$ vs Control DDDR).

Atrial remodeling: Change in LAD

Echocardiographic data were available in 388 of 1166 patients (33%): 124 Control DDDR patients, 136 MVP patients, and 128 DDDRP+MVP patients. Baseline characteristics of patients with vs those without echocardiographic data were not significantly different (all $P > .36$). Baseline LAD was 43 ± 7 mm in Control DDDR patients, 43 ± 7

Table 1 Percentage of ERAF as a function of previous AT/AF episode duration and of the 3 arms studied

Percentage of ERAF	All episodes	Episode duration ≤5 minutes	Episode duration >5 minutes–3 hours	Episode duration >3 hours	*P* value (>5 minutes–3 hours vs >3 hours)
Control DDDR	61% (15,497/25,395)	59% (7742/13,023)	67% (5663/8435)	53% (2092/3937)	<.001
MVP	63% (14,721/23,421)	62% (7440/12,090)	69% (5741/8312)	51% (1540/3019)	<.001
DDDRP+MVP	57% (22,846/40,249)	56% (12,960/23,048)	64% (8123/12,711)	39% (1763/4490)	<.001
P value DDDRP+MVP vs Control DDDR	<.001	<.001	<.001	<.001	
P value DDDRP+MVP vs MVP	<.001	<.001	<.001	<.001	

AF = atrial fibrillation; AT = atrial tachycardia; DDDR = standard dual-chamber pacing; DDDRP+MVP = atrial antitachycardia pacing and MVP; ERAF = early recurrence of atrial fibrillation; MVP = DDDR with managed ventricular pacing.

mm in MVP patients, and 43 ± 7 mm in DDDRP+MVP patients (all P = NS). Occurrence of long-lasting persistent AT/AF was significantly and independently associated with baseline LAD (HR 1.07, 95%CI 1.01–1.13; P = .024) and by DDDRP+MVP programming (HR 0.26, 95%CI 0.10–0.72; P = .009). LAD at 24-month follow-up was 43 ± 4 mm in Control DDDR patients, 43 ± 8 mm in MVP patients, and 40 ± 7 mm in DDDRP+MVP patients (all P = NS). LAD at 24 months was a significant predictor of occurrence of long-lasting persistent AT/AF during the follow-up period, after adjustment for randomization group (HR 1.16, 95%CI 1.01–1.33; P = .04).

The relative change in LAD (24 month value – baseline value) showed a median increase of 4.9% (quartile range between –6.7% and 12.8%) in Control DDDR patients, a null median change of 0% (quartile range between –5.0% and 9.8%) in MVP patients, and a median decrease of –2.2% (quartile range between –11.1% and 7.1%) in DDDRP+MVP patients (P = .054 vs Control DDDR). Figure 3 shows the percentage of patients with unchanged, enlarged, or reduced LAD in the 3 study arms and shows a higher proportion of patients with reduced vs increased LAD in the DDDRP+MVP arm.

AT/AF recurrences in patients with AT/AF episodes longer than 7 days

AT/AF duration longer than 7 days occurred in 91 patients (actuarial incidence 26.2%, 95% CI 21.8%–31.2%) in the Control DDDR group, 83 patients (actuarial incidence 25.0%, 95% CI 20.6%–30.1%) in the MVP arm, and 48 patients (actuarial incidence 15.1%, 95% CI 11.6%–19.6%) in the DDDRP+MVP group (HR 0.52, 95% CI 0.36–0.73, P <.001 vs Control DDDR; HR 0.57, 95% CI 0.40–0.81, P = .002 vs MVP).

Atrial cardioversion, external DC cardioversion, or pharmacologic cardioversion occurred in 15 patients (4%) and 18 episodes in the Control DDDR arm, 24 patients (6%) and 28 episodes in the MVP arm, and 8 patients (2%) in 9 episodes in the DDDRP+MVP arm (incidence rate ratio 0.55, 95% CI 0.37–0.81, P = .003 vs Control DDDR; incidence rate ratio 0.37, 95% CI 0.23–0.52, P <.001 vs MVP). After

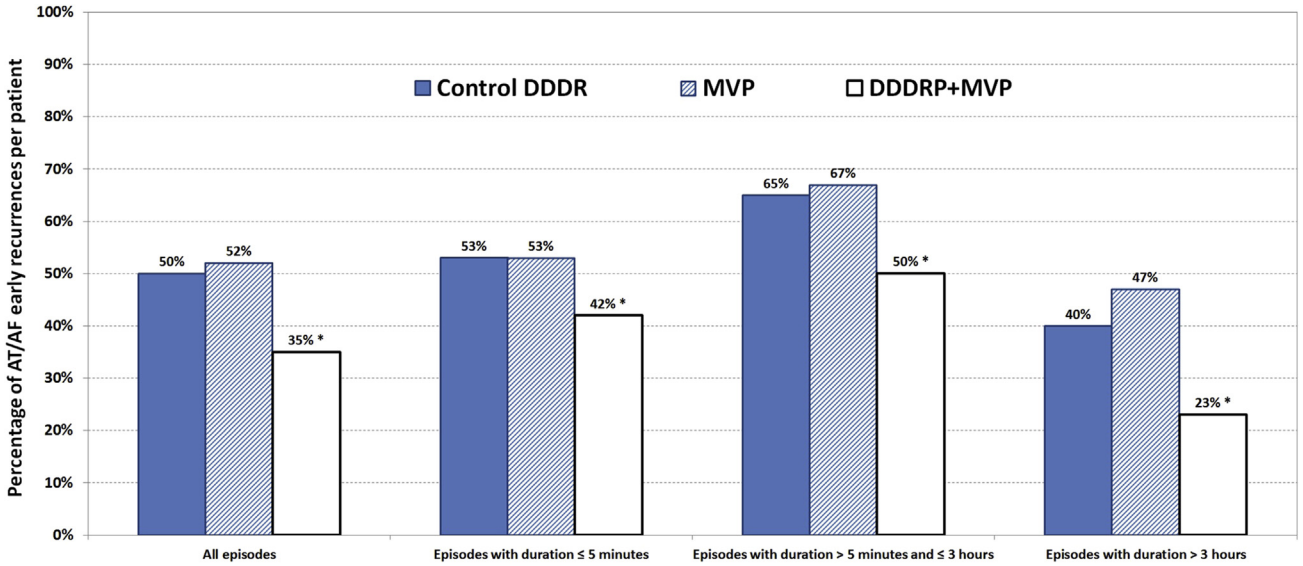

Figure 1 Median percentage of early recurrence of atrial fibrillation per patient as a function of previous atrial tachycardia/atrial fibrillation (AT/AF) duration for the 3 study arms. DDDR = standard dual-chamber pacing; MVP = DDDR with managed ventricular pacing; DDDRP+MVP = atrial antitachycardia pacing and MVP. * P < .001.

Table 2 Univariate and multivariable logistic regression models for ERAF risk

Parameter	Univariate odds ratio (95% CI)	Univariate *P* value	Multivariable odds ratio (95% CI)	Multivariable *P* value
DDDRP+MVP	0.64 (0.48–0.85)	.002	0.65 (0.48–0.87)	.004
Male gender	1.21 (0.92–1.59)	.164		
Age at implant ≥75 years	0.78 (0.59–1.02)	.067		
Cardioversions	1.52 (1.10–2.08)	.010	1.57 (1.14–2.16)	.005
Hypertension	1.24 (0.92–1.67)	.159		
Transient ischemic attack/stroke	0.75 (0.48–1.18)	.215		
Diabetes	0.99 (0.69–1.41)	.941		
History of cardiovascular hospitalization	1.32 (0.99–1.75)	.055		
History of AT/AF hospitalization	1.22 (0.90–1.65)	.195		
NYHA functional class III–IV	1.80 (0.84–3.84)	.129		
PR ≥185 ms	0.83 (0.62–1.12)	.227		
Atrial cycle median ≥240	1.04 (0.67–1.62)	.868		
Oral anticoagulant or antiplatelet	1.06 (0.74–1.53)	.743		
Antiarrhythmic class I	0.94 (0.68–1.28)	.687		
Amiodarone	1.06 (0.78–1.44)	.691		
Beta-blocker	0.89 (0.68–1.17)	.402		
Digitalis	1.03 (0.58–1.83)	.928		
Diuretic	1.05 (0.78–1.40)	.751		
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker II	1.01 (0.77–1.33)	.925		
Calcium antagonists	0.92 (0.68–1.25)	.595		
Statin	0.89 (0.67–1.18)	.411		

CI = confidence interval; NYHA = New York Heart Association. Other abbreviations as in Table 1.

exclusion of AT/AF episodes, which were treated by atrial cardioversion, recurrence of AT/AF after spontaneous termination of a previous episode longer than 7 days occurred in 78% of patients and was concentrated (70%) in the first 5 days after sinus rhythm restoration (Figure 4).

Discussion

Main findings

The main results of this secondary analysis of MINERVA trial data show that (1) in pacemaker patients with bradycardia and paroxysmal or persistent AT/AF, ERAF are very frequent (83% of patients and 61% of episodes); (2) ATP reduces the incidence of ERAF (35% risk reduction); (3) reduction in LAD is more frequent in patients with ATP; and (4) ERAF incidence as a function of the duration of the AT/AF episode preceding ERAF has a U-shaped pattern (Figure 2), showing an initial decrease in recurrence incidence when previous AT/AF episode duration increases from 5 minutes to 12 hours and a subsequent increase in the incidence of recurrences when previous AT/AF duration is longer than 12 hours. These data add important insights into the atrial remodeling process, suggesting that changes in electrophysiologic and/or structural properties in the atria become clinically important when AF is maintained over 12 hours and that ATP may attenuate, delay, and, in some patients, reverse atrial remodeling.

In their pioneering work, Wijffels et al[2] found that sustained AF was associated with significant shortening of the atrial effective refractory period. Of note, the AF duration threshold of 15 hours observed by Wijffels et al to establish a steady fibrillation state compares well with the 12 to 18 hours of AT/AF duration that are followed by ERAF incidence rise observed in our analysis (Figure 2A). On the basis of continuous AF monitoring, our data therefore confirm the hypothesis from previous animal studies that AF with a duration longer than 12 hours causes atrial electrical remodeling in humans as well.

Schwartzman et al[12] evaluated the timing of ERAF after AF cardioversion and found a lower ERAF incidence for AF durations longer than 3 hours. This result was unexpected, as earlier studies suggested that longer AF durations are associated with higher recurrence rates, linking AF susceptibility to arrhythmia-induced atrial electrophysiologic substrate remodeling.[10,11] The U-shaped curve (Figure 2) seen with the present data could reconcile this apparent conflict based on the hypothesis that AF durations before cardioversion were shorter in the study by Schwartzman et al,[12] and therefore in the descending branch of the U-shaped curve, and longer in the previous studies[10,11] and therefore in the ascending branch of the U-shaped curve.

Previous studies on AT/AF recurrences

Several studies have evaluated ERAF after transthoracic and transvenous cardioversion, reporting per-patient incidences of ERAF ranging from 9% to 57% and a per-episode ERAF incidence in the range from 25% to 27%.[4,12,14,15] These studies applied different definitions of AT/AF recurrences, from AF reinitiation within a month to AF reinitiation within1 minute after the previous episode. The data from our study, with a definition of ERAF as recurrence of AT/AF starting within 5 minutes from the

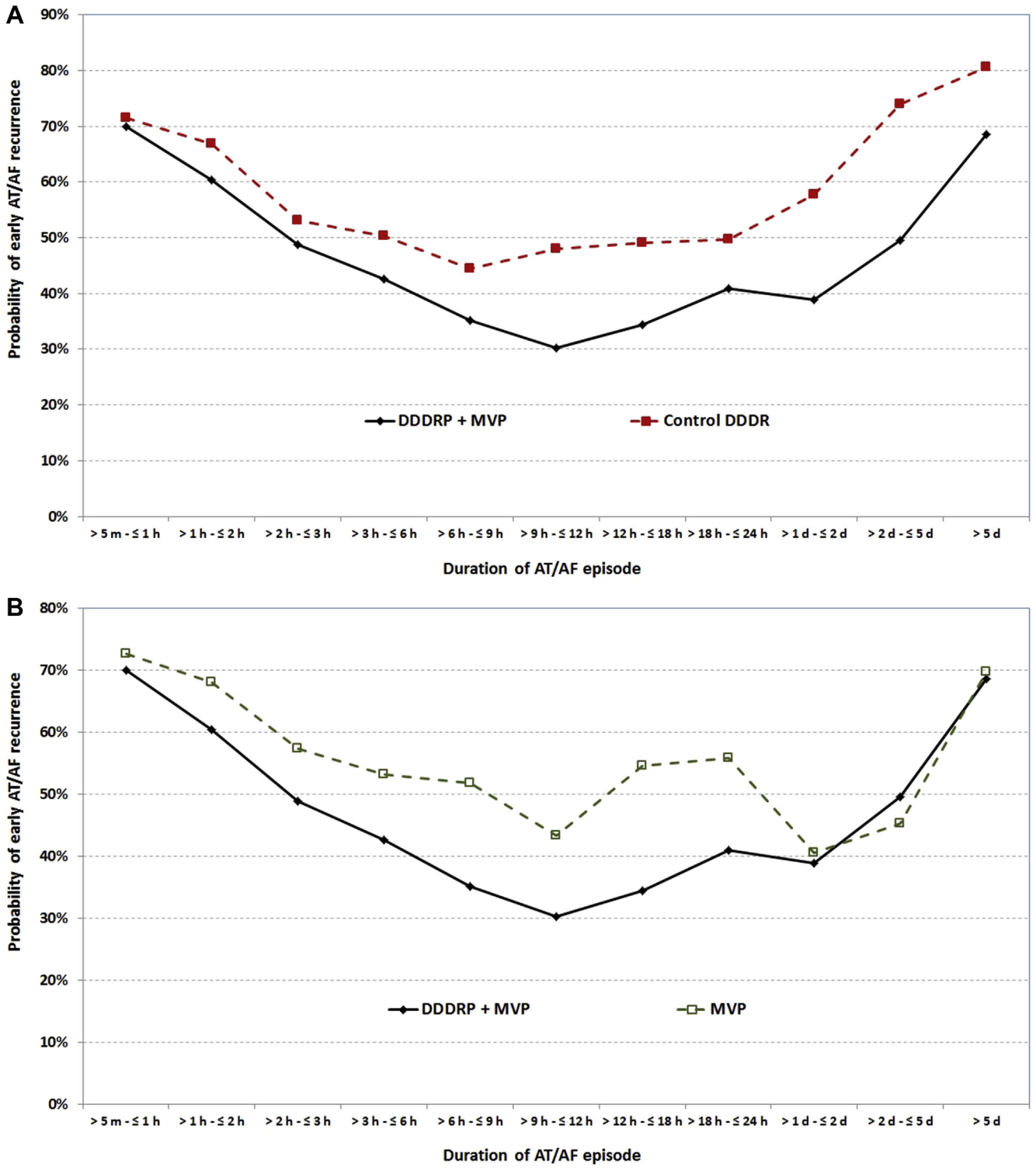

Figure 2 Probability of early recurrence of atrial fibrillation as a function of previous AT/AF duration in the Control DDDR arm and in the DDDRP+MVP arm **(A)** and in the MVP arm and in the DDDRP+MVP arm **(B).** Abbreviations as in Figure 1.

termination of the previous AT/AF episode, show higher percentages of patients with ERAF, even when limiting the analysis to the group of patients with episodes longer than 7 days and a higher percentage of episodes followed by ERAF, likely because of longer follow-up, improved diagnostics capabilities, and a higher proportion of patients with paroxysmal AF or both paroxysmal and persistent AF in our cohort compared with previous studies.

The data from our study on patients with AT/AF duration longer than 7 days show that in most patients (70%) with AT/AF recurrences, the relapse occurs during the first 5 days after previous episode termination (Figure 4). This

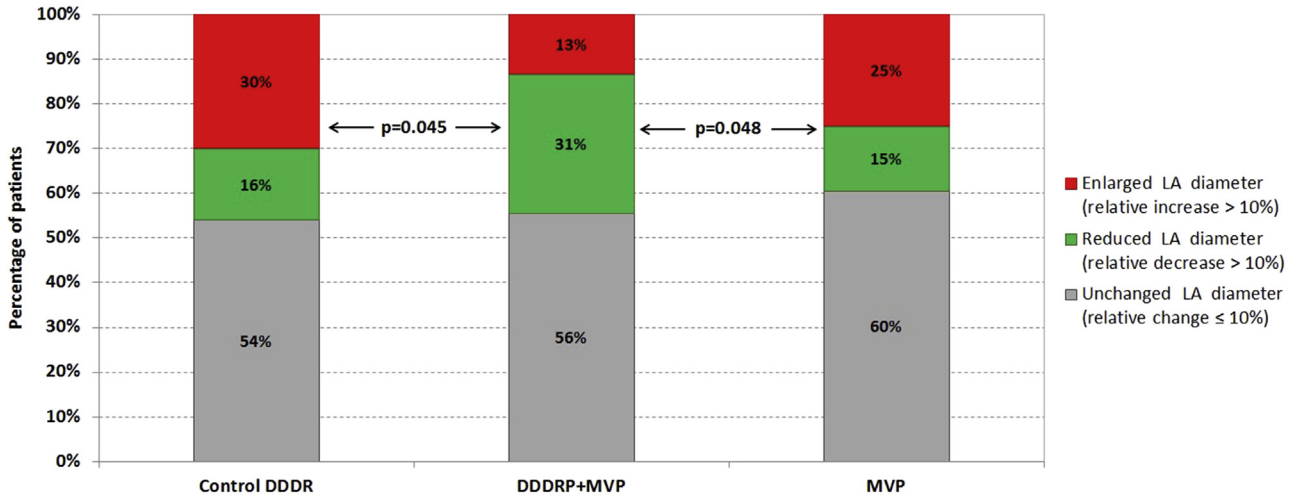

Figure 3 Percentage of patients with unchanged, enlarged, or reduced left atrial (LA) diameter comparing baseline and 24-month echocardiographic data in the 3 study arms. Abbreviations as in Figure 1.

finding, consistent with previous publications, confirms that electrical remodeling of the atria is completely reversible within 5 to 7 days after restoration of sinus rhythm.[2,4,16]

Importantly, multivariable analysis of our data shows that the risk of ERAF was significantly reduced in the DDDRP+MVP arm compared with both Control DDDR and MVP modes. Our analyses show that the percentage of ERAF in the DDDRP+MVP group was significantly lower (20%) after episodes that were successfully terminated by ATP compared with episodes in which ATP was not successful (39%; $P = .004$). The observation that the atrium is less vulnerable to ERAF after ATP-induced termination may be explained by the several hypotheses: (1) the arrhythmia has been interrupted earlier than spontaneous termination, so atrial remodeling has been prevented or diminished; (2) the ATP-induced earlier arrhythmia termination increases the total duration of sinus rhythm during which the effective refractory period may recover; or (3) arrhythmias prone to ATP termination are different from those that do not respond to ATP, and the latter being longer, faster, or more irregular may cause higher vulnerability to ERAF.

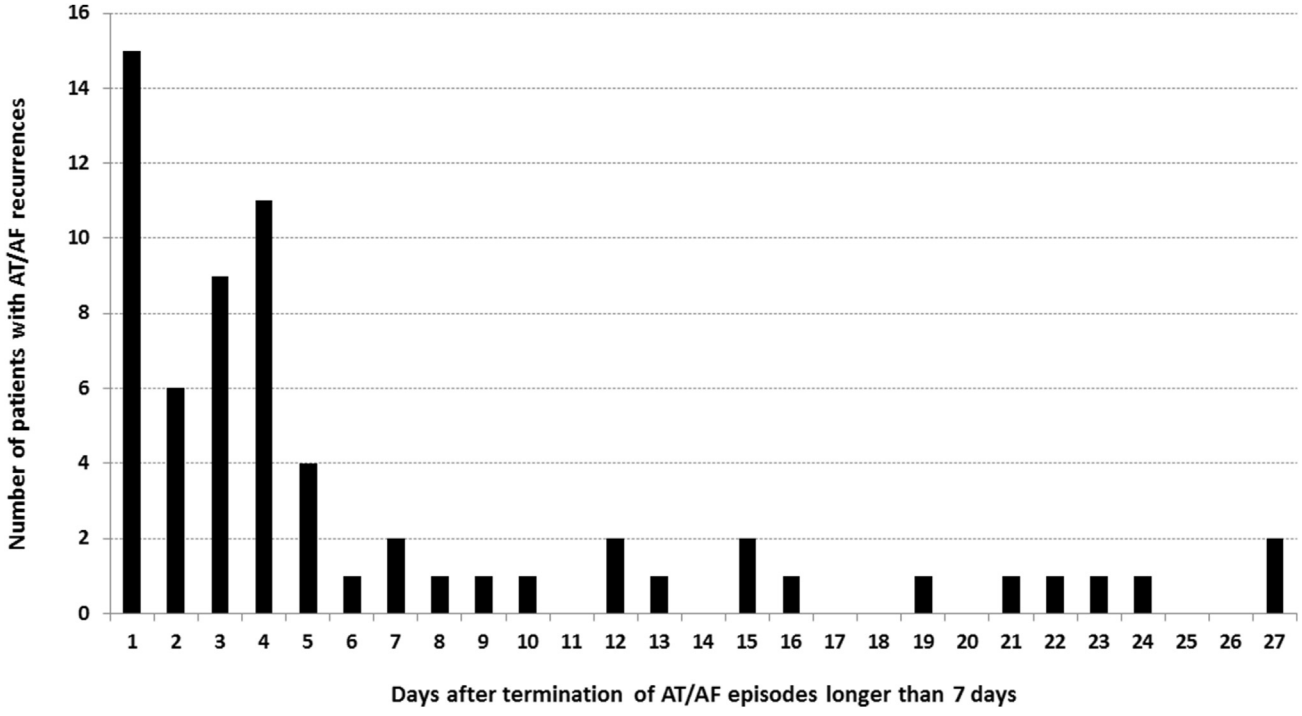

Figure 4 Time distribution of recurrence of AT/AF during 1-month follow-up after AT/AF episodes longer than 7 days. AT/AF = atrial tachycardia/atrial fibrillation.

The observation that the risk of ERAF appeared reduced in all DDDRP+MVP patients (39%) compared with Control DDDR patients (53%; $P < .001$) and with MVP patients (51%; $P < .001$), independently by ATP success may be explained by the fact that reverse electrophysiologic atrial remodeling would occur at the patient level and not at an episode level. Therefore, a patient with some ATP-interrupted episodes may benefit overall in terms of reverse remodeling and lower ERAF risk regardless of the possibility that a few episodes may not be terminated by ATP.

Atrial remodeling: Change in LAD

Long-duration AF is known to cause progressive structural remodeling, myocardial fibrosis, and progressive left atrium dilation.[17] Recently, an ENGAGE-AF (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation) substudy showed that, in AF patients, left atrial structure and function were increasingly abnormal with a greater burden of AF.[18]

Our data show that ATP therapies reduce long-lasting persistent AF and AF burden, and, importantly, the percentage of patients with reduced left atrial dimensions was significantly higher in patients paced in DDDRP+MVP mode compared with patients in standard DDDR pacing or MVP mode.

Clinical implications

Showing that atrial ATP induces reverse atrial remodeling has important clinical implications because atrial structural and electrical remodeling are the hallmarks of AF, and left atrial reverse remodeling is considered an important target in AF treatment. ERAFs have clinical importance because 77% of AT/AF episodes occur in clusters of subsequent ERAF, and up to 88% of the total AT/AF burden is associated with these clusters. Reduction of AF recurrences has clinical relevance because evolution toward persistent or permanent AF has been shown to be an important prognostic marker for death, stroke, or hospital admissions in primary care in several studies. A recent meta-analysis of 12 studies and 99,996 patients confirmed that persistent or permanent AF is associated with a highly significant increase in thromboembolism and death. All these data suggest the need for new therapies to prevent AF progression.[19]

Patients with bradyarrhythmias and associated tachyarrhythmias form an important cohort whose prevalence is expected to increase with an aging population.[20]

Study limitations

Limitations in diagnostics could have caused the underestimation of the number of AT/AF episodes but likely not of the proportion of patients or episodes followed by ERAF because the latter estimations were based on a large sample of collected episodes.

Complete echocardiographic data were available for only 33% of patients because continuous echocardiographic assessment is not common clinical practice in this patient population. We cannot exclude that echocardiograms were obtained in a particular subgroup of patients in whom LAD changes could have been more common than in the entire patient group. However, we believe that the results found in the subgroup of patients with echocardiographic data may be representative of the whole population, first because sensitivity analysis showed no differences in the baseline characteristics of the 2 groups, and second because results regarding the number of ERAFs in the subgroup of patients with echocardiographic data were similar to those of the overall population. In particular, among episodes longer than 3 hours, ERAF occurred in 1061 of 1632 (65%) in the Control DDDR arm, 574 of 1086 (53%) in the MVP arm, and 574 of 1373 (42%) in the DDDRP+MVP arm ($P < .01$ vs other groups). We recognize that left atrial area or volume could have been a better measurement of reverse atrial remodeling compared with LAD, but the study was designed in the early 2000s, and at that time LAD was considered an appropriate measurement.

Findings from the described trial cannot be generalized to all patients implanted with a dual-chamber pacemakers but rather to the subset of patients included in the trial.

Conclusion

Incidence of ERAF as a function of previous AT/AF episode duration suggests that atrial remodeling becomes important after about 12 to 18 hours of continuous arrhythmia. ATP therapies reduce AT/AF recurrences and are associated with more frequent reduction in left atrial diameter, suggesting that termination of AT/AF through ATP may reverse electrical and mechanical remodeling.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrthm.2017.05.023.

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