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Early markers of atrial fibrillation recurrence after pulmonary vein isolation

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Abstract

Background: Postprocedural atrial extrasystole (AES) frequency predicts atrial fibrillation (AF) recurrence after pulmonary vein isolation (PVI) in patients with paroxysmal AF. However, the predictive value of preprocedural AES frequency is unknown. We investigate whether preprocedural AES frequency is a feasible marker to predict (timing of) AF recurrence after PVI.

Methods: Patients (N = 684) with paroxysmal or persistent AF undergoing first-time PVI were evaluated for (a) the frequency of AES/day on Holter recordings without AF prior to PVI, (b) AF episodes during the 90 days blanking period, and (c) AF recurrences afterward. The correlation between AES/day and both development and timing of AF recurrences was tested.

Results: Preprocedural AES/day was similar in patients with paroxysmal (66 [20-295] AES/day) and persistent AF (115 [12-248] AES/day, $P = .915$). During the blanking period, 302 (44.2%) patients showed AF episodes. AF recurred in 379 (55.4%) patients at 203 (105-400) days after PVI. AF recurred more frequently in patients with persistent (N = 104 [69.3%]) than in patients with paroxysmal AF (N = 275 [51.5%], $P < .001$). Frequency of AES prior to PVI was not correlated with development ($P = .203$) or timing ($P = .478$) of AF recurrences. AF recurrences occurred both more frequently ($P < .001$) and earlier ($P < .000$) in patients with AF during the blanking period.

Conclusion: AES/day prior to PVI is not correlated with (timing of) AF during the blanking period or AF recurrences, and is therefore not a feasible marker for AF recurrences in patients with PAF. AF during the blanking period is correlated with AF recurrence.

KEYWORDS

atrial extrasystolic beat, atrial fibrillation, blanking period, pulmonary vein isolation, recurrence

1 | INTRODUCTION

Atrial fibrillation (AF) is often triggered by atrial extrasystoles (AES), originating from the pulmonary vein (PV) area.[1] Isolation of these triggers, by means of creating circular lesions around the PVs, is a potential curative treatment modality for AF. Reported 1-year AF-free survival rates after PV isolation (PVI) vary from 50% to 81%.[2] AF recurs more frequently in patients with persistent AF (PeAF) than in patients with paroxysmal AF (PAF).[3] It is generally assumed that in the former group, AF is mediated by an arrhythmogenic substrate, rather than by triggers. Identification of individual patients at risk for AF recurrences remains challenging. Clinical markers associated with AF recurrence include atrial dilatation, valvular heart disease, and type of AF.[4]

The value of daily AES frequency *after* PVI for AF recurrences has been investigated previously in patients with PAF.[5,6] However, it is unknown whether AES frequency *prior to* PVI is a feasible marker to predict AF recurrence after PVI. Advanced atrial remodeling, caused by, for example, AF, might result in increased AES frequency.[7] If AES prior to PVI were to result from non-PV foci, this could relate to AF recurrence after PVI. Since remodeled patients are also more prone to develop recurrences,[3] AES frequency prior to PVI could be a non-invasive clinical marker that allows identification of subjects with a high risk for nonsuccessful PVI outcome.

Hence, AES frequency prior to PVI potentially allow early recognition of patients at risk for AF recurrence. Subsequently, this marker might be used to tailor treatment of AF to the individual patient. The aim of the current study was therefore to investigate whether AES frequency prior to PVI is associated with (timing of) development of AF in the blanking period and (timing of) AF recurrence during long-term follow-up, not only in patients with PAF but also PeAF.

2 | METHODS

This retrospective, observational study is part of the "Arrhythmias predicted by ExtraSystoles" (AES) study. The study was approved by the institutional medical ethical committee (MEC-2016-062) and complies to the Declaration of Helsinki. Written informed consent was not obliged.

Patients undergoing first-time radiofrequency or cryoballoon PVI for drug-resistant PAF or PeAF in the Erasmus MC between 2004 and August 2015, with ≥1 Holter recording prior to or after ablation were evaluated. Exclusion criteria included longstanding PeAF or the absence of Holter registrations. The follow-up period extended until the end of July 2016. Clinical data were obtained from the electronic patient files.

Beta-blockers or other anti-arrhythmic agents were not withheld prior to PVI. Drugs were continued during the first 3 months and thereafter discontinued to discretion of the electrophysiologist.

Patients underwent an endovascular PVI by means of radiofrequency or cryoballoon ablation. Catheter manipulation was either manual or remotely controlled. In case of radiofrequency ablation, catheter navigation was supported by electroanatomical mapping. Immediate procedural success was defined as the presence of an exit block.

All postprocedural rhythms from various rhythm recording devices, such as 12-lead surface ECG, continuous Holter registration, and implantable loop recorders, were evaluated for the presence of AF.[8,9] The amount of AES on Holter recordings was standardized per 24 hours (AES/day). Since AES do not occur during AF episodes, Holter recordings with AF (either paroxysms or continuous) were not included for these calculations. A total AES count could not be retrieved in 13 patients. We defined AF recurrences according to the latest guidelines, hence any documented AF episode after the blanking period.[8,9] Consequently, AF episodes within the 90 days blanking period were not considered AF recurrences. The study endpoint was AF recurrence.

All data were tested for normality. Normally distributed, continuous data are expressed as mean ± standard deviation, whereas dichotomous variables are depicted as number (percentage). Comparison of these data was performed using, respectively, Students t test and χ^2 test. Nonparametric tests (including Kruskal-Wallis and Mann-Whitney U tests) were applied for comparison of continuous, skewed data, which are presented as median (interquartile range). Wilcoxon signed-rank test was performed to compare two related samples of continuous, skewed variables. Spearman's rank (ρ) was applied to test the correlation between non-normally distributed continuous variables and/or categorical parameters. Since the amount of AES/day calculated from baseline Holter recordings is non-normally distributed, data in the amount of AES/day calculated from baseline Holter recordings, patients were categorized into quartiles of AES/day, to evaluate its effect on AF recurrences. AF-free survival after PVI in various patient categories was studied with Kaplan-Meier curves and log-rank testing. A *P*-value of .05 was considered statistically significant.

3 | RESULTS

The total study population consisted of 684 patients (486 [71.1%] males). Clinical baseline characteristics of all patients are depicted in Table 1. The majority of patients underwent cryoballoon ablation (N = 396, 57.9%). In 288 patients (42.1%), ablation was performed with radiofrequency energy, either manually (N = 211) or with magnetic (N = 47) or robotic (N = 30) navigation systems. AF was paroxysmal in 534 patients (78.1%), the remaining 150 patients (21.9%) had PeAF. Prior to PVI, ≥1 anti-arrhythmic drugs were used by 368 (93.3%) patients, as shown in Table 1. Successful isolation of the PVs (criteria according to the recent AF guidelines)[8,9] was achieved in all patients.

Electrophysiological parameters of all Holter recordings are summarized in Table 2. Holter recordings were performed 118 (65-193) days prior to PVI. In 261 (43.6%) patients, the Holter recordings showed either paroxysms or continuous AF: 140 (53.6%) and 121 (46.4%) recordings, respectively. In 326 Holter recordings without AF episodes, a median frequency of 66 (20-295) AES/day was observed on Holter recordings prior to PVI of patients

TABLE 1 Baseline characteristics

	Overall (N = 684)
Age (y)	57.8 ± 9.7
Gender (male, N [%])	486 (71.1)
Type AF (N, [%])	
Paroxysmal	534 (78.1)
Persistent	150 (21.9)
Time since diagnosis (y)	3.0 (1.0-6.5)
Type PVI	
Cryoballoon	396 (57.9)
Radiofrequency	288 (42.1)
Echocardiography	
Left atrial volume index (mL/m^2)	40.8 ± 13.3
Left ventricular function (N, [%])	
Normal[a]	570 (83.3)
Mild impairment[b]	92 (13.5)
Moderate impairment[c]	20 (2.9)
Severe impairment[d]	2 (0.3)
Anti-arrhythmic drug usage	
Class I	259 (37.9)
Class II	288 (42.1)
Class III	312 (45.6)
Class IV	50 (7.3)
Cardiovascular risk factors	
Hypertension (N, [%])	260 (38.0)
Hyperlipidemia (N, [%])	96 (14.0)
Diabetes mellitus (N, [%])	48 (7.0)
Thyroid disease (N, [%])	55 (8.0)
Body mass index (kg/m^2)	27.2 ± 4.1

Abbreviations: AF, atrial fibrillation; BSA, body surface area; PVI, pulmonary vein isolation.

[a]Ejection fraction >50%

[b]Ejection fraction 40%–50%

[c]Ejection fraction 30%–40%

[d]Ejection fraction <30%

TABLE 2 Holter registrations

	Prior to PVI (N = 599)
Average heart rate (bpm)	69 (61-80)
AF on Holter (N, %)	261 (43.6)
Paroxysmal AF	172 (32.2)
Paroxysms	126 (23.6)
Continuous	46 (8.6)
Persistent AF	89 (59.3)
Paroxysms	14 (9.3)
Continuous	75 (50.0)
AES/day (N)	68 (18-289)
Paroxysmal AF	N = 288 66 (20-295)
Persistent AF	N = 38 115 (12-248)

Abbreviations: AES, atrial extrasystole; AF, atrial fibrillation; Bpm, beats per minute; PVI, pulmonary vein isolation.

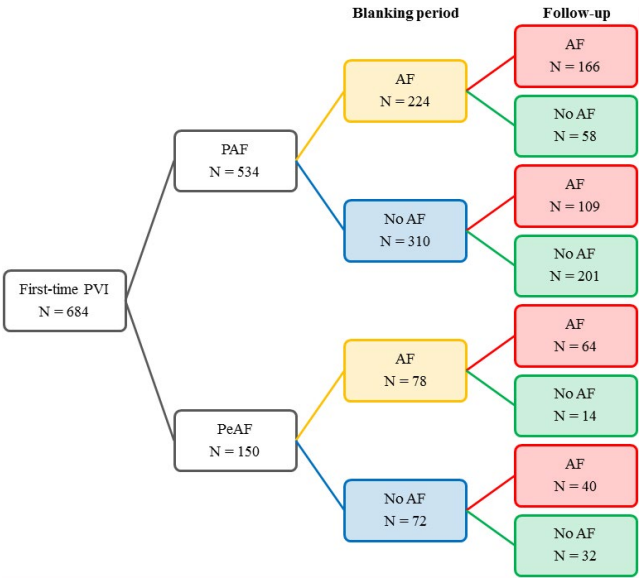

FIGURE 1 AF recurrence after first-time PVI. Flowchart illustrating the amount of patients with AF recurrences per type of AF prior to PVI and for patients with and without AF during the 90 day blanking period. AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; PVI, pulmonary vein isolation

with PAF (N = 288), whereas patients with PeAF (N = 38) had 115 (12-248) AES/day (P = .915). The AES/day frequency was not correlated with anti-arrhythmic drug usage (all classes and digoxin P > .05).

The amount of AES/day weakly correlated with age (ρ = 0.266, P < .001), gender (ρ = −0.137, P = .014), left atrial volume (ρ = 0.212, P = .006), and diabetes (ρ = 0.132, P = .017). There was no correlation between AES/day and time since AF diagnosis, type of AF prior to PVI or left ventricular function, or anti-arrhythmic drug usage (all P > .05). In addition, none of the other known (cardiac) risk factors including BMI, hypertension, hyperlipidemia, and thyroid disease correlated with AES/day (all P > .5).

AF during the blanking period occurred in 302 patients (44.2%), which is depicted in the flowchart in Figure 1. Clinical variables including gender, age, body mass index, hypertension, diabetes mellitus, hyperlipidemia, anti-arrhythmic drug usage, and left ventricular function were not correlated with AF during the blanking period. However, thyroid disease (ρ = 0.105; P = .006) and type of AF (ρ = 0.084; P = .028) correlated (weakly) with AF during the blanking period. First AF episodes were documented 7.0 (2.0-20.0) days after the procedure. Incidence was higher in patients with PeAF (N = 78, 52.0%) than PAF (N = 224, 41.9%) prior to PVI (P = .028). There was no difference in the moment of the first AF episode between patients with PAF and

PeAF: 8 (2-22) vs 5 (2-15) days after procedure (P = .092). The incidence of AES/day prior to PVI was not associated with the presence of AF episodes in the blanking period for both patients with PAF (P = .374) and PeAF (P = .053). Also, AES/day prior to PVI did not correlate with *timing* of AF episodes during the blanking period, in patients with PAF (P = .274) and patients with PeAF (P = .422).

Median follow-up time after PVI was 604 (177-1822) days. Overall, AF recurred after the blanking period in 55.4% of the population (N = 379) at 203 (105-400) days after the procedure. The flowchart in Figure 1 shows the number of patients with AF episodes during the blanking period and AF recurrences for patients with paroxysmal or persistent AF separately. Furthermore, Figure 2 shows the fluctuations in the rhythm outcome per year of procedure for the overall study population (P = .003).

As illustrated in Figure 3, AF recurred more frequently in patients with PeAF (N = 104 [69.3%]) than in patients with PAF (N = 275 [51.5%], P < .001). The majority of recurrences was observed in the first year after PVI and timing of first AF recurrence was similar in both patient groups: 168 (102-355) vs 213 (107-419) days (P = .112). In 218 (31.8%) patients, at least one redo PVI was performed. Reconduction of 543 PVs was observed in 196 (92.9%) patients undergoing redo ablation and occurred equally frequent in patients with PAF or PeAF (P = .886) and equally frequent after cryoballoon or radiofrequency ablation (P = .877). AF recurrence was not correlated with anti-arrhythmic drug usage at baseline.

Kaplan-Meier curves in Figure 4 show the AF-free survival for patients with PAF or PeAF prior to PVI with (solid lines) and without (dashed lines) AF during the blanking period separately. AF recurred more frequently in patients with (N = 230, 76.2%), than in patients without AF during the blanking period (N = 149, 39.0%; P < .001). The curves also show that AF recurrences occurred *earlier* in both patients with PAF and PeAF with AF during the blanking period (P < .001).

Overall, AES/day prior to PVI was not correlated with AF recurrence and time to first recurrence: ρ = 0.071, P = .203 and ρ = −0.055, P = .478. The left panel of Figure 5 shows that AF recurrences in patients with paroxysmal AF prior to PVI occur equally in all four quartiles of AES/day. The right panel depicts AF-free survival for patients with persistent AF. In both patient groups, AES/day prior to PVI did not correlate with either AF recurrence or time to recurrence (Table 3).

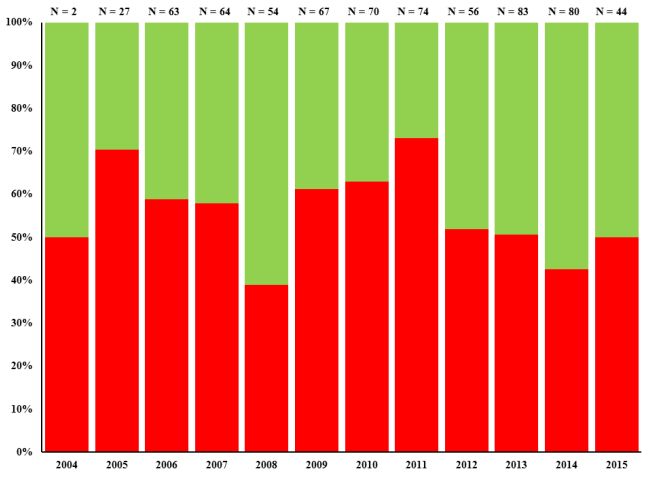

FIGURE 2 AF recurrence per year. Proportion of patients with AF recurrences (red) or without AF recurrences (green) after first-time pulmonary vein isolation, for each year separately. AF, atrial fibrillation

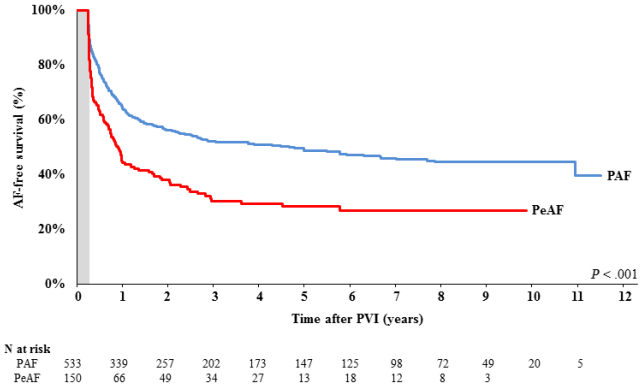

FIGURE 3 AF-free survival per type AF. Freedom from AF recurrences for patients with PAF (blue line) and PeAF (red line) during long-term follow-up. 90 day blanking period is indicated in grey. AF, atrial fibrillation; PAF, paroxysmal AF; PeAF, persistent AF; PVI, pulmonary vein isolation

4 | DISCUSSION

The present study demonstrates that AES/day prior to PVI is not correlated with (timing of) AF in the blanking period or with (timing of) AF recurrence in PAF. As expected, AF recurrences are more

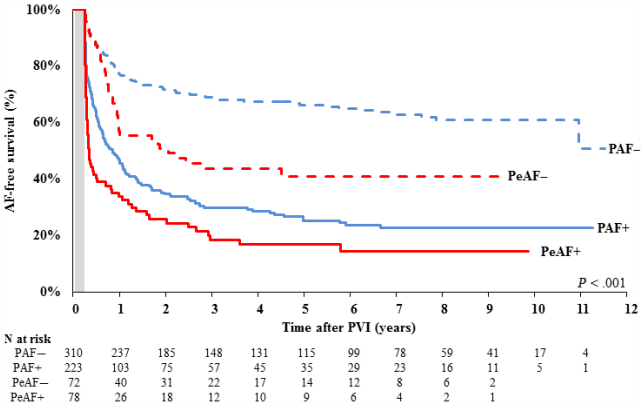

FIGURE 4 Effect of AF during the blanking period on AF-free survival. Dashed blue line: patients with PAF prior to PVI, without AF during the blanking period (PAF-). Solid blue line: patients with PAF prior to PVI, with AF during the blanking period (PAF+). Dashed red line: patients with PeAF prior to PVI, without AF during the blanking period (PeAF-). Solid red line: patients with PeAF prior to PVI, with AF during the blanking period (PeAF+). 90 day blanking period is indicated in grey. AF, atrial fibrillation; PAF, paroxysmal AF; PeAF, persistent AF; PVI, pulmonary vein isolation; –, no AF during blanking period; +, AF during blanking period

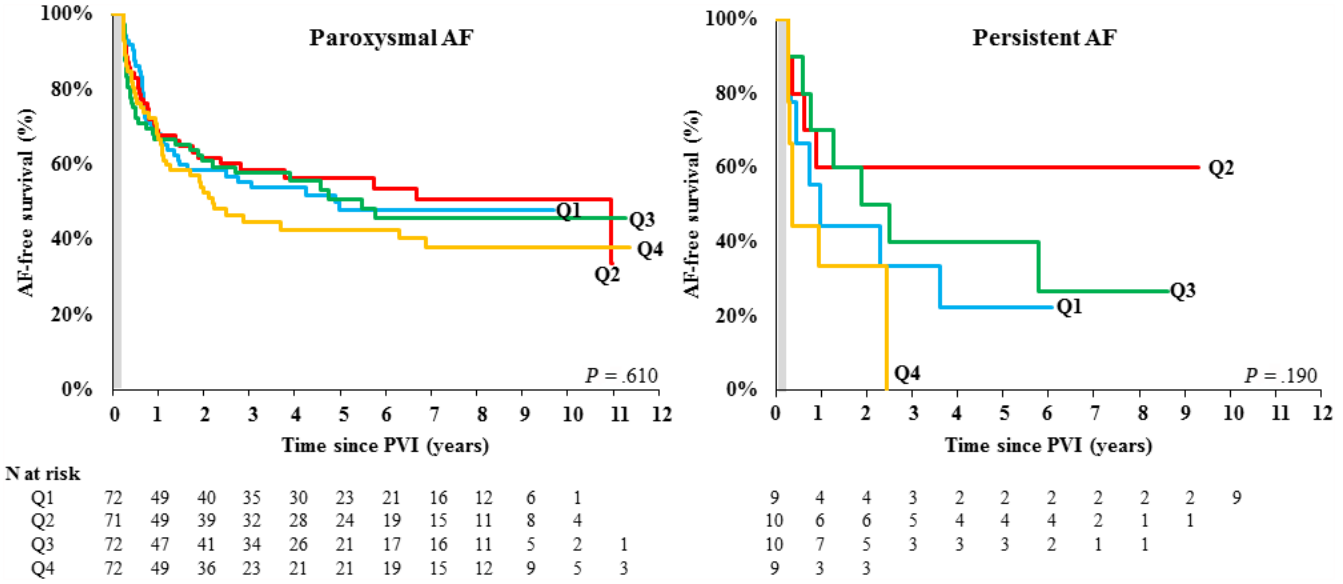

FIGURE 5 AF-free survival per quartile AES prior to PVI. Left panel: freedom from AF recurrences after PVI for paroxysmal AF, patients are categorized according to the number of AES/day at Holter recordings prior to PVI. Blue line: Q1 ≤20 ES/day. Red line: Q2 = 20-66 AES/day. Green line: Q3 = 66-295 AES/day. Yellow line: Q4 ≥295 AES/day. Right panel: freedom from AF recurrences after PVI for persistent AF, patients are categorized according to the number of AES/day prior to PVI. Blue line: Q1 ≤12 AES/day. Red line: Q2 = 12-115 AES/day. Green line: Q3 = 115-248 AES/day. Yellow line: Q4 ≥248 AES/day. 90 day blanking period is indicated in grey. AF, atrial fibrillation; AES, atrial extrasystole; PVI, pulmonary vein isolation

TABLE 3 AES frequency and AF recurrence

	AES/day prior to PVI	Quartile AES prior to PVI
Paroxysmal AF		
AF during blanking period	ρ = 0.053; *P* = .374	ρ = 0.045; *P* = .448
Time to AF during blanking period	ρ = 0.107; *P* = .274	ρ = 0.058; *P* = .552
AF recurrence	ρ = 0.073; *P* = .215	ρ = 0.062; *P* = .293
Time to AF recurrence	ρ = −0.047; *P* = .574	τ = −0.032; *P* = .702
Persistent AF		
AF during blanking period	ρ = 0.316; *P* = .053	ρ = 0.282; *P* = .086
Time to AF during blanking period	ρ = 0.244; *P* = .422	ρ = 0.285; *P* = .345
AF recurrence	ρ = 0.058; *P* = .729	ρ = 0.078; *P* = .640
Time to AF recurrence	ρ = −0.182; *P* = .385	ρ = −0.145; *P* = .490

Abbreviations: AES, atrial extrasystole; AF, atrial fibrillation; PVI, pulmonary vein isolation.

frequent in patients with PeAF than with PAF. As an incidental finding, we showed that development of AF in the blanking period was correlated with AF recurrence afterward.

The predictive value of AES for development of new-onset AF has been widely studied.[10–12] In a large cohort of 1,357 patients with various underlying diseases, Acharya et al[12] demonstrated that patients with ≥100 AES/day have a higher risk for development of new-onset AF (HR 2.97). Recently, this was also confirmed for patients with congenital heart disease.[11] The predictive value of AES for development of AF recurrences was mainly examined *after* PVI in patients with PAF,[5,6] whereas the present study evaluates the value of AES *prior to* PVI in both PAF and PeAF patients. Gang et al[5] showed in a prospective study in 220 patients with PAF that ≥142 AES/day on the 6 months Holter recording was associated with a higher risk of AF recurrences after PVI (HR 2.84). However, the relation between AES prior to PVI and the long-term AF-free survival after PVI was not yet described. In this era of patient-tailored medicine, a more accurate estimation of the expected procedural outcome is desired for selecting the optimal strategy for each individual patient. Therefore, we examined whether a higher incidence of AES prior to PVI is associated with AF recurrences. Since this was not the case, it is most likely not a feasible marker in clinical practice. Although it is generally assumed that AES in patients with AF mainly originate from the PV area, other origins, for example, the superior vena cava, have also been described.[1,13,14] After PVI, AES can either result from non-PV foci or from, for example, reconduction of the initially isolated PVs. In case these AES initiate AF episodes, additional ablation of these non-PVI foci could potentially cure AF in these patients. The group of Lin et al[14] showed that acute success rates of ablation of these foci were highly variable and depend on the origin of ectopy, for example, superior vena cava (96%, N = 27), posterior free wall of the left atrium (63%, N = 5, crista terminalis [100%, N = 10] and interatrial septum [0%, N = 1]). During long-term follow-up, AF recurred in 36.8% (N = 25) patients.[14] At present, additional ablation of non-PV foci (if reproducible) is included as a Class IIa recommendation in clinical guidelines on management of

patients with AF. In the present study, AF also recurred in the absence of PV reconduction. This suggests that AES initiating AF are most likely generated by non-PV foci. Besides the above mentioned non-PV foci, AES might also be generated by other atrial areas. It is generally accepted that AF episodes induce structural and electrical remodeling of the atria.[15,16] As a result, cardiomyocyte hypertrophy, fibroblast proliferation, and deposition of extracellular matrix lead to separation of adjacent bundles of cardiomyocytes and subsequently conduction block.[17] Redistribution of cell-cell connexins and down-regulation of ion channels also cause impaired conduction.[18] Next to these conduction abnormalities, coupling of myofibroblast and cardiomyocytes also facilitates induction of spontaneous ectopic activity.[7] An intracellular calcium overload, caused by atrial stress, may provoke delayed afterdepolarizations, which in turn can produce triggered activity. Altogether, this suggests that (micro)reentry and/or ectopic activity are more likely to occur in remodeled atria, which in turn may lead to an increased number of AES.

A 90 days blanking period after PVI is recommended in both European and American guidelines.[8,9] AF episodes within this window may result from postprocedural inflammation, edema, or recovery phase. Arrhythmias in the blanking period would therefore be nonspecific and not directly related to treatment failure. Nonetheless, episodes of AF or other arrhythmias during this blanking period are frequently reported.[19] In a recent study, Willems et al,[20] examined the value of the 90 days blanking period in 401 patients undergoing first-time PVI for PAF. They show that 1-year freedom from any AT decreased significantly to 28.7% if AF occurred during the blanking period, which was the case in 49.1% of the population. Also, timing of latest symptomatic AT was correlated with time to AF recurrence.[20] The present study confirms the decrease in AF-free survival in patients with not only PAF but also PeAF who have AF during the blanking period. Other AT were not included. In addition, a similar pattern is observed in patients with PeAF.

As a result from the retrospective study design, not all Holter recordings prior to and after PVI were available. Most patients used anti-arrhythmic drugs, this might have influenced AES/day, although there was no difference in the amount of AES in patients with or without anti-arrhythmic drugs, and correlations between AES/day and drug usage were lacking. Asymptomatic and/or short-lasting AF paroxysms might be missed if the patient was not connected to rhythm monitoring devices. AES frequency can vary from day to day and is influenced by, for example, autonomic tone and physical activity. Prolonged recordings might give a more accurate reflection of the AES frequency. For optimal comparison of AES/day between the different types of AF, a larger number of Holter recordings from PeAF patients is most likely required. Origin of AES could not be determined using 3-lead Holter registrations.

5 | CONCLUSION

The amount of AES/day prior to PVI is not correlated with (timing of) AF episodes in the blanking period, or with (timing of) AF recurrences and is therefore not suitable as a biomarker to identify PAF patients at risk for AF recurrences. However, patients with AF episodes during the blanking period develop AF recurrences earlier than patients without early AF episodes.

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DISCLOSURES

The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Committee of Erasmus MC, Rotterdam, The Netherlands, Approval No. MEC-2016-062. Written informed consent was not obliged.

CONFLICT OF INTERESTS

The authors declare no conflict of interests for this article.

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REFERENCES

1. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339(10):659–66.
2. Ang R, Domenichini G, Finlay MC, Schilling RJ, Hunter RJ. The hot and the cold: radiofrequency versus cryoballoon ablation for atrial fibrillation. Curr Cardiol Rep. 2015;17(9):631.
3. Oral H, Knight BP, Tada H, Özaydın M, Chugh A, Hassan S, et al. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. Circulation. 2002;105(9):1077–81.
4. D'Ascenzo F, Corleto A, Biondi-Zoccai G, Anselmino M, Ferraris F, di Biase L, et al. Which are the most reliable predictors of recurrence of atrial fibrillation after transcatheter ablation? A meta-analysis. Int J Cardiol. 2013;167(5):1984–9.
5. Gang UJO, Nalliah CJ, Lim TW, Thiagalingam A, Kovoor P, Ross DL, et al. Atrial ectopy predicts late recurrence of atrial fibrillation after pulmonary vein isolation. Circ Arrhythm Electrophysiol. 2015;8(3):569–74.
6. Yamane T, Date T, Kanzaki Y, Inada K, Matsuo S, Shibayama K, et al. Behavior of atrial ectopic beats before and after pulmonary vein isolation in patients with atrial fibrillation: a reduction in the number and arrhythmogenicity of ectopic firings. Heart Rhythm. 2006;3(12):1421–7.
7. Miragoli M, Salvarani N, Rohr S. Myofibroblasts induce ectopic activity in cardiac tissue. Circ Res. 2007;101(8):755–8.
8. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr,, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64(21):e1–e76.
9. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial

fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37(38):2893–962.
10. Chong B-H, Pong V, Lam K-F, Liu S, Zuo M-L, Lau Y-F, et al. Frequent premature atrial complexes predict new occurrence of atrial fibrillation and adverse cardiovascular events. Europace. 2012;14(7):942–7.
11. Teuwen CP, Korevaar TIM, Coolen RL, van der Wel T, Houck CA, Evertz R, et al. Frequent atrial extrasystolic beats predict atrial fibrillation in patients with congenital heart defects. Europace. 2018;20(1):25–32.
12. Acharya T, Tringali S, Bhullar M, Nalbandyan M, Ilineni VK, Carbajal E, et al. Frequent atrial premature complexes and their association with risk of atrial fibrillation. Am J Cardiol. 2015;116(12):1852–7.
13. Inada K, Matsuo S, Tokutake K-I, Yokoyama K-I, Hioki M, Narui R, et al. Predictors of ectopic firing from the superior vena cava in patients with paroxysmal atrial fibrillation. J Interv Card Electrophysiol. 2015;42(1):27–32.
14. Lin W-S, Tai C-T, Hsieh M-H, Tsai C-F, Lin Y-K, Tsao H-M, et al. Catheter ablation of paroxysmal atrial fibrillation initiated by non-pulmonary vein ectopy. Circulation. 2003;107(25):3176–83.
15. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation. 1995;92(7):1954–68.
16. Brundel BJ, Ausma J, van Gelder IC, et al. Activation of proteolysis by calpains and structural changes in human paroxysmal and persistent atrial fibrillation. Cardiovasc Res. 2002;54(2):380–9.
17. Ausma J, Wijffels M, Thone F, Wouters L, Allessie M, Borgers M. Structural changes of atrial myocardium due to sustained atrial fibrillation in the goat. Circulation. 1997;96(9):3157–63.
18. van der Velden HM, Ausma J, Rook MB, et al. Gap junctional remodeling in relation to stabilization of atrial fibrillation in the goat. Cardiovasc Res. 2000;46(3):476–86.
19. Mugnai G, de Asmundis C, Hünük B, Ströker E, Velagic V, Moran D, et al. Second-generation cryoballoon ablation for paroxysmal atrial fibrillation: predictive role of atrial arrhythmias occurring in the blanking period on the incidence of late recurrences. Heart Rhythm. 2016;13(4):845–51.
20. Willems S, Khairy P, Andrade JG, Hoffmann BA, Levesque S, Verma A, et al. Redefining the Blanking Period After Catheter Ablation for Paroxysmal Atrial Fibrillation: Insights From the ADVICE (Adenosine Following Pulmonary Vein Isolation to Target Dormant Conduction Elimination) Trial. Circ Arrhythm Electrophysiol. 2016;9(8).

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