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Cardiac Rhythm Disorders

Predictors of Non-Pulmonary Vein Ectopic Beats Initiating Paroxysmal Atrial Fibrillation

Implication for Catheter Ablation

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OBJECTIVES The purpose of this study was to investigate the predictor of non-pulmonary vein (PV) ectopic beats initiating paroxysmal atrial fibrillation (PAF).

BACKGROUND Non-PV ectopic beats can initiate PAF in some patients and play an important role in the recurrence of PAF after PV isolation. Information on the predictors of non-PV ectopic beats initiating PAF is unknown.

METHODS This study included 293 patients (215 men and 78 women, age 60 ± 14 years) with clinically documented drug-refractory PAF. Of the 94 patients with non-PV ectopic beats initiating PAF, 38 (40%) patients had superior vena cava (SVC) ectopic beats and 32 (34%) had left atrial posterior free wall (LAPFW) ectopic beats.

RESULTS In a univariate analysis, only female gender was related to the presence of non-PV ($p = 0.016$) and SVC ectopic beats ($p = 0.012$). Right atrial enlargement ($p = 0.005$) and left atrial enlargement ($p < 0.001$) were related to the presence of LAPFW ectopic beats. In a multivariate analysis, female gender ($p = 0.043$; odds ratio 2.00, 95% confidence interval [CI] 1.02 to 3.92) and left atrial enlargement ($p = 0.007$; odds ratio 2.34, 95% CI 1.27 to 4.32) could predict the presence of non-PV ectopic beats. Subgroup analysis showed that female gender could predict the presence of SVC ectopic beats ($p = 0.039$; odds ratio 2.14, 95% CI 1.04 to 4.43). In contrast, left atrial enlargement could predict the presence of LAPFW ectopic beats ($p = 0.002$; odds ratio 3.89, 95% CI 1.62 to 9.38).

CONCLUSIONS The location of non-PV ectopic beats initiating PAF can be predicted by both gender and left atrial enlargement. (J Am Coll Cardiol 2005;46:1054–9) © 2005 by the American College of Cardiology Foundation

Several studies have demonstrated that pulmonary veins (PVs) are the major site of ectopic beats initiating paroxysmal atrial fibrillation (PAF), and isolation of the PVs from the atrial tissue can cure 65% to 85% of patients with PAF (1–3). Non-PV ectopic beats have been proven to initiate PAF in some patients, and the presence of non-PV ectopic beats might play an important role in the recurrence of PAF after PV isolation (4–7). Previous studies have also shown that wide-area left atrial ablation may be more effective than simple PV isolation, because some left atrial posterior free wall (LAPFW) foci might be eliminated and/or isolated during circumferential ablation (8,9). Whether there are predictors of non-PV ectopic beats initiating PAF is unknown. Awareness of this information may be useful in planning the ablation strategy. Therefore, the purpose of the study was to investigate the predictors of non-PV ectopic beats initiating PAF.

METHODS

Electrophysiologic study. This study included 293 consecutive patients (215 men and 78 women, age 60 ± 14 years) with clinically documented PAF, who were refractory to 2 ± 1 antiarrhythmic drug. Furthermore, these patients had more than one episode of PAF per week in the month before the ablation procedure. Each patient underwent an electrophysiologic study in the fasting, non-sedated state after written, informed consent was obtained. All antiarrhythmic drugs except amiodarone were discontinued for at least five half-lives before the study.

We first attempted to locate the spontaneous onset of ectopic beats initiating AF in the baseline state or after infusion of isoproterenol (up to 4 μg/min for 5 min) (2,5,7). If spontaneous AF did not appear, intermittent atrial pacing (8 to 12 beats) with a cycle length of 200 to 300 ms from the high right atrium or coronary sinus (CS) was used to facilitate spontaneous initiation of AF after a pause in the atrial pacing. If spontaneous AF did not occur, burst pacing from the high right atrium or CS was used to induce

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Abbreviations and Acronyms

CS = coronary sinus
CT = crista terminalis
LAPFW = left atrial posterior free wall
LOM = ligament of Marshall
PAF = paroxysmal atrial fibrillation
PV = pulmonary vein
RF = radiofrequency
SVC = superior vena cava

sustained AF. After an episode of pacing-induced AF was sustained for 5 to 10 min, external cardioversion (starting from 50 J and increasing in 50-J increments for each subsequent trial) was attempted to convert the AF to sinus rhythm and observe the spontaneous re-initiation of AF. A bolus of high-dose adenosine (24 to 84 mg) was also used to provoke the spontaneous onset of AF. The onset pattern of spontaneous AF was analyzed, and the earliest ectopic site was considered to be the initiating focus of AF. The method used to provoke spontaneous AF was tried at least twice to ensure reproducibility.

According to our study, the difference in the time interval between the high right atrium and His bundle atrial activation obtained during sinus beats and atrial premature beats was a good method to identify whether the ectopic focus was from the right or left atrium (10). Further, the polarity of the P-wave of the ectopic beat was a useful method to differentiate the location of the ectopic beats (11). Mapping of the PVs was guided by selective PV angiography or the venous phase of selective pulmonary artery angiography, with the first pair of electrodes straddling the ostium. The catheters were first put into superior PVs and then the inferior PVs if the ectopic focus was suspected to be from the inferior PVs. We used two multipolar catheters to perform simultaneous mapping of the PVs and LAPFW, if necessary. If the initiating focus of PAF was considered to be from the right atrium, we put one duodecapolar catheter (1-mm electrode width and 2-mm interelectrode spacing) along the crista terminalis (CT) to reach the top of the superior vena cava (SVC) for simultaneous mapping of the PVs and SVC.

Catheter ablation. Radiofrequency (RF) ablation was not performed in the patients who only had a single ectopic beat without initiating AF during the electrophysiologic study. In the patients with ectopy from the SVC, the atriocaval junction was confirmed by an SVC venogram, intracardiac ultrasound, and electrical signals. Isolation of the SVC was performed at a level about 5 mm below the atriocaval junction (5,7). The SVC-right atrial junction exhibits an eccentric shape, not a round shape; thus, the ablation catheter may not contact the wall well. Application of RF energy at the first or second level of SVC is easier to interrupt the right atrium-SVC myocardial sleeve; however, it may result in a higher risk of SVC narrowing or stenosis (7). For the cases with a high risk of sinus node injury (acceleration of the sinus rate during SVC isolation), we used three-dimensional non-contact mapping to identify the origin and exit site of the sinus node activation, as well as to avoid the application of any energy around that area. For ectopy from the CT, CS ostium, and interatrial septum, a unipolar QS pattern indicated the presumed ablation site.

A unipolar QS pattern also indicated the presumed ablation site for ectopy from the LAPFW. Furthermore, if the ectopic beat was located nearby the PV ostium, we usually extended the ablation lesion from the ostium to encircle part of the posterior wall with a square-shaped (around 1.5 to 2.0 cm on each side) linear lesion to ablate or isolate the ectopy. However, if the ectopic beat is located near the left PV ostium, the possibility of ectopy originating from the ligament of Marshall (LOM) should be considered. In such a case, a discrete, sharp potential preceding the left atrial and PV potentials with "triple potentials" would be observed (5).

The ablation catheter (4-mm tip electrode, Boston Scientific, Watertown, Massachusetts) was connected to an EPT-1000 generator (EP Technologies, Mountain View, California) delivering a 550-kHz sine wave output. Temperature-controlled (target temperature 50°C to 55°C) RF energy was delivered for 20 to 40 s per pulse, but was terminated immediately if the ablation catheter became displaced or the patient complained of burning pain, coughed, or developed severe bradycardia. The ablation end point was the total elimination or marked reduction (<50% of initial amplitude) in the ectopic focus electrogram amplitude. For patients with SVC ectopy, SVC isolation with the disappearance of ectopy and distal SVC potential was the end point. The protocols used to facilitate AF onset before ablation were repeated to assess the effects of RF ablation immediately after and 10 to 15 min after the last application of RF energy. Close clinical follow-up (two weeks, one month, and then every one to three months) was arranged after the ablation (12).

Predictors of the location of ectopic beats initiating PAF. The analyzed variables included gender, age (≥65 or <65 years), a history of documented PAF (≥5 or <5 years), the presence of other cardiovascular disease (e.g., hypertensive cardiovascular disease, coronary artery disease, congestive heart failure, hypertrophic cardiomyopathy, valvular heart disease), the presence of related arrhythmias (e.g., atrial flutter, atrial tachycardia, atrioventricular node reentrant tachycardia, right atrial enlargement, left atrial enlargement), or concurrent drug usage (e.g., beta-blocker, calcium channel blocker, digitalis, angiotensin-converting enzyme inhibitor). Left atrial enlargement was defined as left atrial diameter >40 mm on parasternal short-axis view.

Statistics analysis. Quantitative data are expressed as the mean value ± SD. The chi-square test with Yates' correction was used to analyze the nonparametric data. For comparisons within small groups in which the expected number in any of the four cells was below five, a Fisher exact test was used. Multivariate analysis was performed with

logistic regression to determine the independent predictors of the presence of ectopic beats. Variables selected to be tested in the multivariate analysis were those with $p < 0.1$ in the univariate model. A significant odds ratio was obtained if the 95% confidence interval (CI) exceeded 1.0 and the p value was <0.05. A p value <0.05 was considered statistically significant.

RESULTS

Incidence of PV and non-PV ectopic beats initiating PAF. Of the 293 patients with ectopic beats initiating PAF, 199 (68%) had pure PV, 36 (12%) had pure non-PV, and 58 (20%) had both PV and non-PV ectopic beats initiating PAF. Of the 94 patients with non PV-ectopic beats, 38 (40%) patients had SVC, 32 (34%) had LAPFW, 14 (15%) had CT, 7 (7%) had LOM, 4 (4%) had an interatrial septum, and 1 (1%) had a CS ostium ectopic beat initiating PAF. During a mean follow-up period of 52 ± 21 months, 67% in the patients with pure PV, 76% in those with pure non-PV, and 60% in those with both PV and non-PV ectopic beats initiating PAF were free of AF recurrence without the use of antiarrhythmic drugs.

Predictors of non-PV ectopic beats initiating PAF. Comparisons between the patients with pure PV ectopic beats (n = 199) and those with non-PV ectopic beats initiating AF (n = 94, including patients with PV plus non-PV and patients with pure PV ectopic beats) are shown in Table 1. Univariate analysis revealed that only female gender was related to the presence of non-PV ectopy initiating AF (p = 0.016) (Table 2). Multivariate analysis showed that female gender and left atrial enlargement could predict the presence of non-PV ectopic beats initiating AF.

SVC ectopic beats initiating PAF. Comparisons between the patients with (n = 8) and without (n = 255) SVC ectopic beats initiating AF are shown in Table 1. Univariate analysis showed that only female gender was related to the presence of SVC ectopic beats (p = 0.012) (Table 2). Multivariate analysis demonstrated that only female gender could predict the presence of SVC ectopic beats.

LAPFW ectopic beats initiating PAF. Comparisons between the patients with LAPFW ectopic beats (n = 32) and those without LAPFW ectopic beats initiating AF (n = 261) are shown in Table 1. Univariate analysis revealed that right atrial enlargement (p = 0.005) and left atrial enlargement ($p < 0.001$) were related to the presence of the LAPFW ectopy (Table 2). Multivariate analysis showed that only left atrial enlargement could predict the presence of LAPFW ectopy.

DISCUSSION

Major findings. The present study showed that female gender could predict the SVC ectopic beats initiating PAF and left atrial enlargement could predict the LAPFW ectopic beats initiating PAF. These findings suggest that gender and left atrial enlargement are important predictors of non-PV AF.

Female gender predicts SVC ectopic beats initiating PAF. Sauer et al. (13) reported that women were more likely than men to have non-PV ectopic beats initiating PAF in 343 patients who underwent RF ablation for PAF. The present study also showed that female gender was the only predictor of SVC ectopic beats initiating PAF. These findings suggest that female hormones might play a role in the higher incidence of SVC ectopic beats in women.

Table 1. Patient Characteristics

	Pure PV (n = 199)	Non-PV (n = 94)	SVC (n = 38)	Without SVC (n = 255)	LAPFW (n = 32)	Without LAPFW (n = 261)
Male gender	78%	64%	55%	76%	78%	73%
Age (yrs)	60 ± 14	61 ± 13	57 ± 13	60 ± 14	64 ± 12	60 ± 14
History of PAF (yrs)	5 ± 5	5 ± 5	5 ± 4	5 ± 5	6 ± 5	5 ± 5
Cardiovascular disease	55%	52%	42%	56%	66%	53%
Hypertensive cardiovascular disease	48%	42%	32%	48%	50%	46%
Coronary artery disease	18%	17%	13%	19%	22%	17%
Congestive heart failure	10%	8%	5%	10%	13%	9%
Hypertrophic cardiomyopathy	2%	2%	5%	1%	0%	2%
Valvular heart disease	1%	1%	0%	1%	0%	1%
Related arrhythmias	48%	60%	53%	52%	63%	51%
Atrial flutter	45%	52%	40%	49%	63%	46%
Atrial tachycardia	2%	5%	5%	2%	0%	3%
Atrioventricular nodal re-entrant tachycardia	2%	3%	5%	2%	0%	2%
Right atrial enlargement	15%	17%	9%	17%	34%	13%
Left atrial enlargement	35%	48%	34%	40%	72%	35%
Concurrent drug usage						
Beta-receptor blocker	11%	17%	13%	14%	19%	13%
Calcium channel blocker	21%	19%	13%	21%	26%	19%
Digitalis	1%	5%	6%	2%	7%	2%
Angiotensin-converting enzyme inhibitor	18%	15%	9%	18%	19%	17%

Data are presented as the mean value ± SD or percentage of patients.
LAPFW = left atrial posterior free wall; PAF = paroxysmal atrial fibrillation; PV = pulmonary vein; SVC = superior vena cava.

Table 2. Univariate and Multivariate Analysis for the Presence of Non-Pulmonary Vein, Superior Vena Cava, and Left Atrial Posterior Free Wall Ectopic Beats

	Non-PV (n = 94)				SVC (n = 38)				LAPFW (n = 32)			
	Univariate	Multivariate			Univariate	Multivariate			Univariate	Multivariate		
Variables	p Value	p Value	Odds Ratio	95% CI	p Value	p Value	Odds Ratio	95% CI	p Value	p Value	OR	95% CI
Gender	0.016*	0.043	2.00	1.02–3.92	0.012*	0.039	2.14	1.04–4.43	0.67*	—	—	—
Age	0.96*	—	—	—	0.06*	0.27	—	—	0.20*	—	—	—
History of PAF	0.89*	—	—	—	0.78*	—	—	—	0.78*	—	—	—
Cardiovascular disease	0.74*	—	—	—	0.16*	—	—	—	0.23*	—	—	—
Hypertensive cardiovascular disease	0.40*	—	—	—	0.08*	0.27	—	—	0.77*	—	—	—
Coronary artery disease	0.95*	—	—	—	0.55*	—	—	—	0.71*	—	—	—
Congestive heart failure	0.62*	—	—	—	0.55†	—	—	—	0.52†	—	—	—
Hypertrophic cardiomyopathy	0.66†	—	—	—	0.13†	—	—	—	1.0†	—	—	—
Valvular heart disease	1.0†	—	—	—	1.0†	—	—	—	1.0†	—	—	—
Related arrhythmias	0.09*	0.23	—	—	1.0*	—	—	—	0.28*	—	—	—
Atrial flutter	0.34*	—	—	—	0.37*	—	—	—	0.11*	—	—	—
Atrial tachycardia	0.12†	—	—	—	0.28†	—	—	—	0.60†	—	—	—
Atrioventricular nodal re-entrant tachycardia	0.39†	—	—	—	0.18†	—	—	—	1.0†	—	—	—
Right atrial enlargement	0.76*	—	—	—	0.41*	—	—	—	0.005*	0.19	—	—
Left atrial enlargement	0.08*	0.007	2.34	1.27–4.32	0.66*	—	—	—	<0.001*	0.002	3.89	1.62–9.38
Concurrent drug usage												
Beta-receptor blocker	0.25*	—	—	—	1.0†	—	—	—	0.38†	—	—	—
Calcium channel blocker	0.90*	—	—	—	0.36*	—	—	—	0.58*	—	—	—
Digitalis	0.05†	0.09	—	—	0.14†	—	—	—	0.11†	—	—	—
Angiotensin-converting enzyme inhibitor	0.72*	—	—	—	0.32*	—	—	—	0.79†	—	—	—

*Chi-square test with Yates' correction. †Fisher exact test.
CI = confidence interval; other abbreviations as in Table 1.

However, the effects of female hormones on automaticity were not reported. Furthermore, in the present study, only 1 of 25 premenopausal women had oral contraceptive use and only 8 of 53 postmenopausal women had hormone replacement therapy. Among the postmenopausal women, the incidence of hormone replacement therapy was similar between patients with SVC ectopic beats and those without SVC ectopic beats initiating PAF (10% vs. 19%, $p = 0.66$).

Previous studies have consistently shown that men have higher sympathetic activity and women have higher parasympathetic activity (14,15). Schauerte et al. (16) also showed that high-frequency stimulation of cardiac autonomic nerves in the vicinity of the canine SVC could induce SVC ectopy initiating PAF, and this phenomenon could be abolished by atropine. We also demonstrated that an increase in vagal tone induced by phenylephrine was effective in suppressing focal PAF originating from the PVs but not the SVC (17). These findings suggest that women with higher parasympathetic activity might have a higher incidence of SVC ectopic beats initiating AF.

Left atrial enlargement predicts LAPFW ectopic beats initiating PAF. The present study showed that gender could not predict LAPFW ectopic beats initiating PAF, but that left atrial enlargement could predict LAPFW ectopic beats initiating PAF. Previous studies reported that increased automaticity and increased trigger activity might occur in human diseased atrial fibers (18–20). Thus, it is possible that LAPFW could be the site of spontaneous ectopy in patients with left atrial enlargement. Furthermore, based on the theory of multiple re-entrant wavelets, AF could be more easily induced and maintained in larger atrial sizes (21,22).

Ablation of non-PV ectopic beats initiating PAF. Pulmonary vein isolation can eliminate the triggers and driving mechanisms of PAF that come from the PVs. Oral et al. (8) and Pappone et al. (9) showed that circumferential PV ablation, including LAPFW ablation, had better results than PV isolation in preventing PAF. Circumferential PV ablation may eliminate ectopic foci from the LAPFW and LOM, prevent the rotors and/or spiral waves that drive AF, and encircle some of the left atrial myocardium and limit the atrial area for the AF wavelets in the patients with left atrial enlargements (4,23,24). Previous studies have shown that neural input to the LAPFW and SVC might have some relationship to the triggering of PV foci firing (9,16,17,25). However, further studies are needed to clarify whether vagal denervation produced by circumferential ablation may suppress remote non-PV ectopic beats initiating PAF.

Potential clinical implications. First, isolation of the PVs has been proven to be effective in eliminating ~65% to 85% of PAF. However, non-PV ectopic beats might play an important role in the initiation of PAF in some patients. The present study showed that female gender could predict the presence of SVC ectopic beats initiating PAF. Thus, provoking SVC ectopic beats initiating AF during the electrophysiologic study is important in women. Further studies are needed to clarify the exact effects of female hormones and the autonomic tone on the SVC ectopic beats initiating PAF. Second, the present study showed that left atrial enlargement was a predictor of LAPFW ectopic beats initiating AF; thus, a larger circle ablation to isolate all ectopic beats might be considered in the patients with left atrial enlargement because the LAPFW ectopic beats were difficult to map. Third, the present study showed that the location of non-PV ectopic beats initiating PAF could be predicted by both gender and left atrial enlargement. However, a considerable number of the patients who had SVC ectopic beats initiating PAF were males, and a considerable number of the patients with left atrial enlargement did not have LAPFW ectopic beats initiating PAF. Thus, a detailed electrophysiologic study to find the non-PV ectopic beats initiating PAF is necessary in all patients.

Conclusions. The present study demonstrated that female gender could predict the presence of SVC ectopic beats initiating PAF, and left atrial enlargement could predict LAPFW ectopic beats initiating PAF. These findings suggest the different mechanisms that might be involved in PAF initiated by ectopic beats from different locations.

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